EXHIBIT C

(Plaintiffs' Response in Opposition to AstraZeneca's Motion in Limine to Exclude Evidence and Argument About Clinical Investigators' Misconduct)

Seroquel

(quetiapine)

Speakers Slide Kit

March 2001

Contents

- 'Seroquel' - Preclinical overview
- 'Seroquel' - Efficacy in schizophrenia
- Efficacy in other populations
- Safety and tolerability in schizophrenia
- Tolerability in other populations
- Patient acceptability
- Dosing and administration of 'Seroquel'

'Seroquel' - Preclinical overview

Seroquel pharmacology Summary

- Active in standard antipsychotic tests
- Limbic selectivity
- Minimal dystonic liability in haloperidol-sensitised and drug-naive monkeys
- Clozapine-like transient increase in rat plasma prolactin levels
- Clozapine-like in new tests

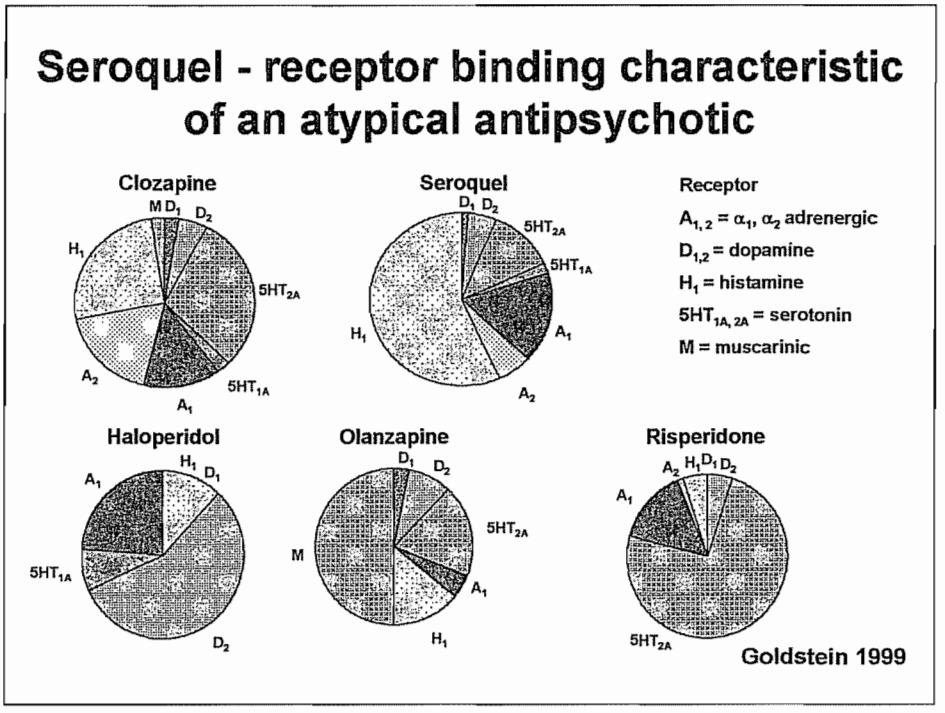
Goldstein and Arvanitis 1995; Goldstein et al 1993; Ellenbroek et al 1996

Seroquel pharmacology - summary

- Seroquel is effective in a number of animal models predictive of antipsychotic activity. For example, Seroquel blocks conditioned avoidance in monkeys,[1] reverses apomorphine- or amphetamine-induced behavioural abnormalities in monkeys, cats and mice[1,2,3] and restores prepulse inhibition in rats[4,5]
- Seroquel is selective for the limbic system,[6,7] the area of the brain where drugs are thought to exert their antipsychotic activity, whereas extrapyramidal symptoms (EPS) adverse events are associated with activity in the striatum. These results predict a low risk of EPS with Seroquel
- In haloperidol-sensitised monkeys, doses exceeding 4.5 times the maximum predicted monkey antipsychotic dose are required before Seroquel produces a 100% incidence of dyskinetic movements.[1] In non-sensitised monkeys, Seroquel produced fewer and much less severe dystonia than haloperidol.[2] These results predict Seroquel should have a low risk of EPS
- Seroquel is clozapine-like in that it produces transient elevation in serum prolactin in animals[2]
- Social isolation paradigms provide animal models of negative symptoms. Standard antipsychotics have no effect on amphetamine-induced social isolation in monkeys, but Seroquel, like clozapine, produces an improvement in social behaviour.[8] Seroquel also reduces the level of phenylcyclidine (PCP)-induced social isolation in rats.[9] Both these results predict that Seroquel has efficacy in improving negative symptoms

References

1. Goldstein JM. In: Holliday SG, Ancill RJ, MacEwan GW, eds. Schizophrenia: *Breaking Down the Barriers*. John Wiley & Sons Ltd, 1996: 177-236.
2. Goldstein J, Arvanitis L. *CNS Drug Reviews* 1995; 1: 50-73.
3. Migler BM et al. *Psychopharmacology* 1993; 122: 299-307.
4. Swerdlow NR et al. *J Pharmacol Exp Ther* 1996; 279: 1290-1299.
5. Swerdlow NR et al. *Psychopharmacology* 1994; 114: 675-678.
6. Goldstein JM et al. *Psychopharmacology (Berl)* 1993; 112: 293-298.
7. Vahid-Ansari F et al. *Eur J Neurosci* 1996; 8: 927-936.
8. Ellenbroek BA et al. *Neuropsychopharmacology* 1996; 15: 406-416.
9. Sams-Dodd F. *Rev Neurosci* 1999; 10: 59-90.

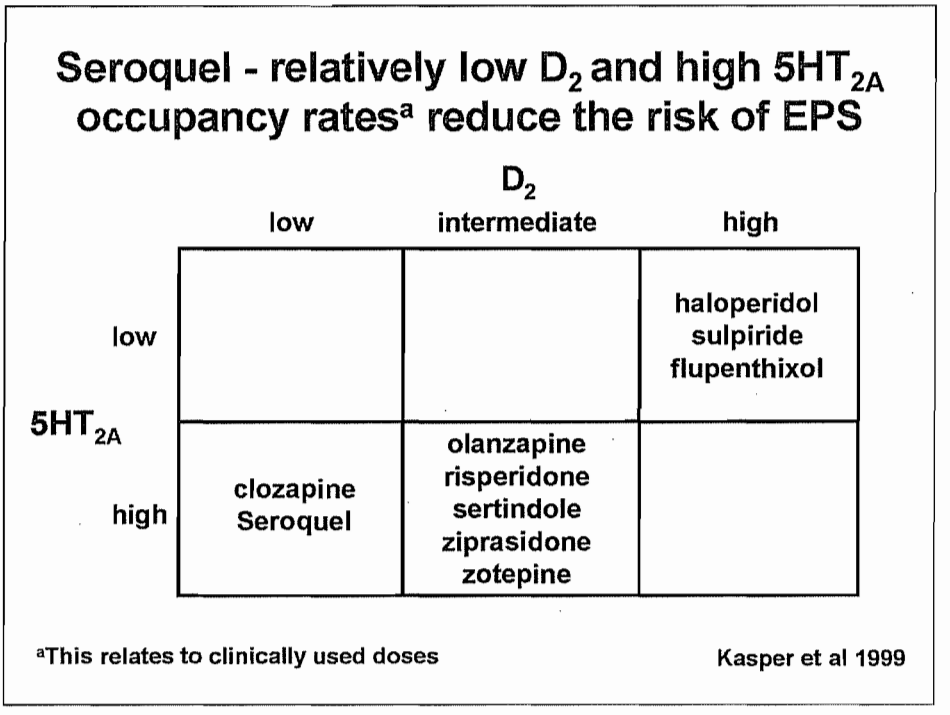


Seroquel – receptor binding characteristic of an atypical antipsychotic

- Seroquel interacts with a broad range of neurotransmitter receptors and this may be responsible for its atypical antipsychotic properties[1]
- Atypical antipsychotics, like Seroquel, clozapine, risperidone and olanzapine, have a higher $5HT_{2A}$ relative to D_2 binding ratio[1]
- By contrast, the standard antipsychotic, haloperidol, has a narrower range of receptor affinities and a higher D_2 relative to $5HT_{2A}$ binding ratio[1]
- Not shown here are binding characteristics to D_3 receptors. Seroquel and clozapine have similar binding to D_3 receptors[2]

References

1. Goldstein JM. *Emerging Drugs* 1999; 4: 127-151.
2. *Goldstein JM. In: Holliday SG, Ancill RJ, MacEwan GW, eds.* Schizophrenia: Breaking Down the Barriers. *John Wiley & Sons Ltd, 1996: 177-236.*



Seroquel – relatively low D_2 and high $5HT_{2A}$ occupancy rates[a] reduce the risk of EPS

- The combination of a relatively high affinity for the $5HT_{2A}$ receptor and a relatively weak affinity for the D_2 receptor may be responsible for minimising motor system disturbances (ie extrapyramidal symptoms, [EPS]) [1]
- Haloperidol and other typical antipsychotics (eg sulpiride, flupenthixol) have a low $5HT_{2A}$ receptor affinity together with a high D_2 affinity, and may be associated with severe EPS[1]
- Some atypical antipsychotics combine a high affinity for the $5HT_{2A}$ receptor with an intermediate affinity for the D_2 receptor which may lead to EPS, particularly at higher doses[1]
- Seroquel and clozapine have the desirable profile of a high $5HT_{2A}$: D_2 receptor affinity ratio, which results in relatively low D_2 occupancy at therapeutic doses and very low placebo-like levels of EPS coupled with efficacy[1]

[a]This relates to clinically used doses.

Reference

1. Kasper S et al. *Eur Arch Psychiatry Clin Neurosci* 1999; 249 (Suppl 4): 83-89.

Seroquel - receptor profile Summary

- Antagonist at multiple receptors
- Moderate affinity for D_2
- Greater $5HT_2$ to D_2 ratio
- High affinity for α_1 and histamine
- No appreciable affinity for muscarinic cholinergic

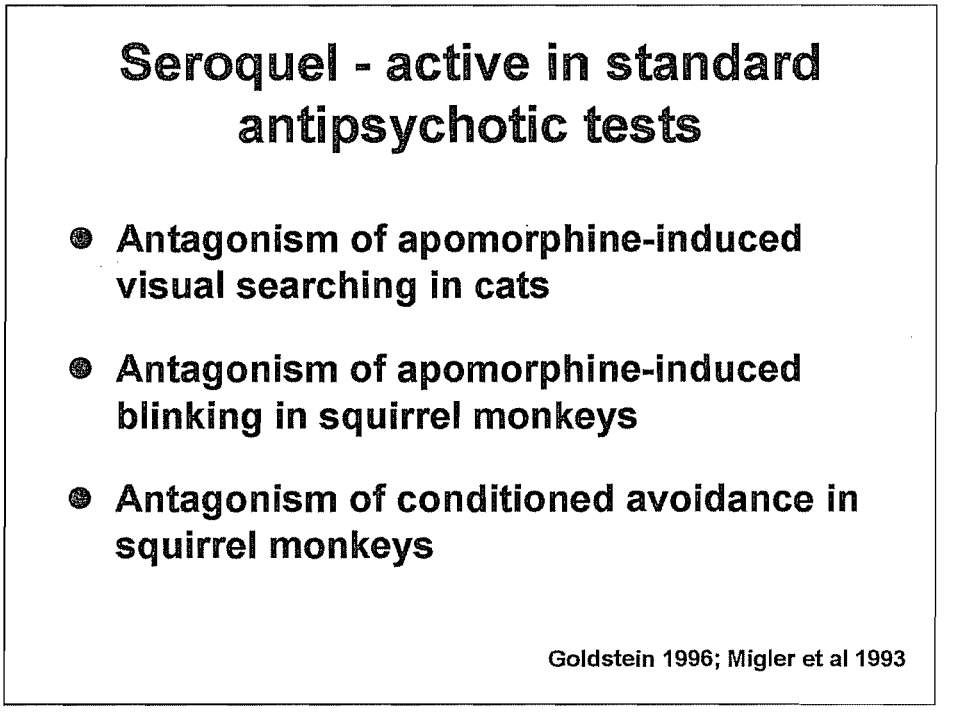
Goldstein 1996; 1999

Seroquel - receptor profile - summary

- Seroquel has the diverse receptor binding profile that is characteristic of an atypical antipsychotic.[1] Receptor binding profiles may be used to predict both the beneficial and adverse effects of drugs
- Seroquel shows only moderate affinity for dopamine D_2 receptors. High levels of D_2 occupancy may be associated not only with therapeutic effects, but also with extrapyramidal symptoms (EPS) and raised prolactin. However, Seroquel binds selectively to limbic D_2 receptors (EPS are associated with D_2 occupancy in the striatum), predicting a therapeutic effect without EPS[2]
- Seroquel binds more readily to 5-HT_2 than to D_2 receptors. This high $5HT_2$ to D_2 binding ratio has been described as the hallmark of the atypical antipsychotics and predicts a low propensity to cause EPS[1]
- Seroquel has high affinity for $alpha_1$ receptors, which may be related to the possible side effects of orthostatic hypotension, dizziness and tachycardia.[2] Seroquel also has high affinity for histamine, which may be related to its sedative effects[1]
- Seroquel's negligible affinity for muscarinic cholinergic receptors explains its lack of anticholinergic side effects[2]

References

1. Goldstein JM. In: Holliday SG, Ancill RJ, MacEwan GW, eds. Schizophrenia: *Breaking Down the Barriers*. John Wiley & Sons Ltd, 1996: 177-236.
2. Goldstein JM. *Emerging Drugs* 1999; 4: 127-151.

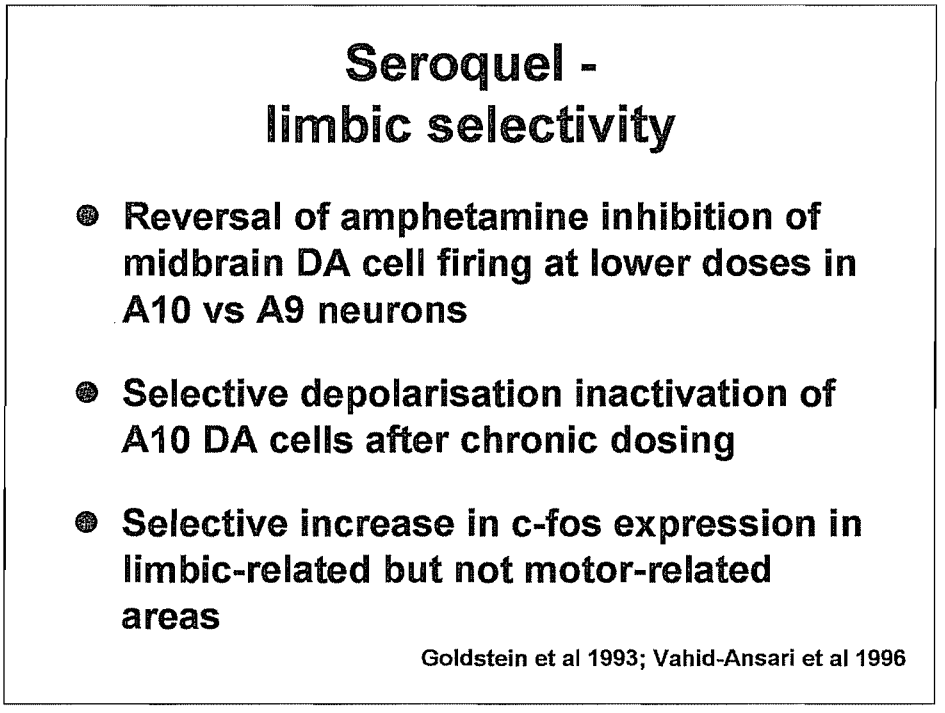


Seroquel - active in standard antipsychotic tests

- These animal models are tests predictive of antipsychotic activity
- In these models, Seroquel produced similar effects to clozapine. These data predict that Seroquel, like clozapine, should be an effective atypical antipsychotic in clinical practice[1,2]

References

1. Goldstein JM. In: Holliday SG, Ancill RJ, MacEwan GW, eds. Schizophrenia: *Breaking Down the Barriers*. John Wiley & Sons Ltd, 1996: 177-236.
2. Migler BM et al. *Psychopharmacology* 1993; 122: 299-307.



Seroquel - limbic selectivity

- Electrophysiological and neurochemical data from these *in vitro* studies provide evidence for the limbic selectivity of Seroquel, which implies antipsychotic activity without extrapyramidal symptoms (EPS)
- Seroquel and clozapine were more active in reversing the inhibitory action of amphetamine on mesolimbic (A10) than nigrostriatal (A9) dopamine (DA)-containing neurons, whereas haloperidol exhibited the opposite selectivity[1]
- After chronic dosing, Seroquel caused depolarisation of A10 DA cells whereas chronic dosing of haloperidol caused a non-selective increase in the number of active A9 and A10 cells[1]
- Chronic dosing with antipsychotics induces the neuronal gene, c-fos, to produce increased levels of its protein, Fos (this process is called 'c-fos expression'). A technique measuring this process is used to 'map' which neurons antipsychotics bind to. Studies have shown that Seroquel, like clozapine, has preferential action on the limbic structures in the brain, which is in contrast to the action of haloperidol in the striatum[2]

References

1. Goldstein JM et al. *Psychopharmacology (Berl)* 1993; 112: 293-298.
2. Vahid-Ansari F et al. *Eur J Neurosci* 1996; 8: 927-936.

Seroquel shows minimal liability to dystonia in drug-naïve monkeys

- Chronic administration more closely simulates dosing conditions in man that produce EPS/TD
- Clozapine does not cause dystonia in this model
- Seroquel has minimal dystonic liability in this model

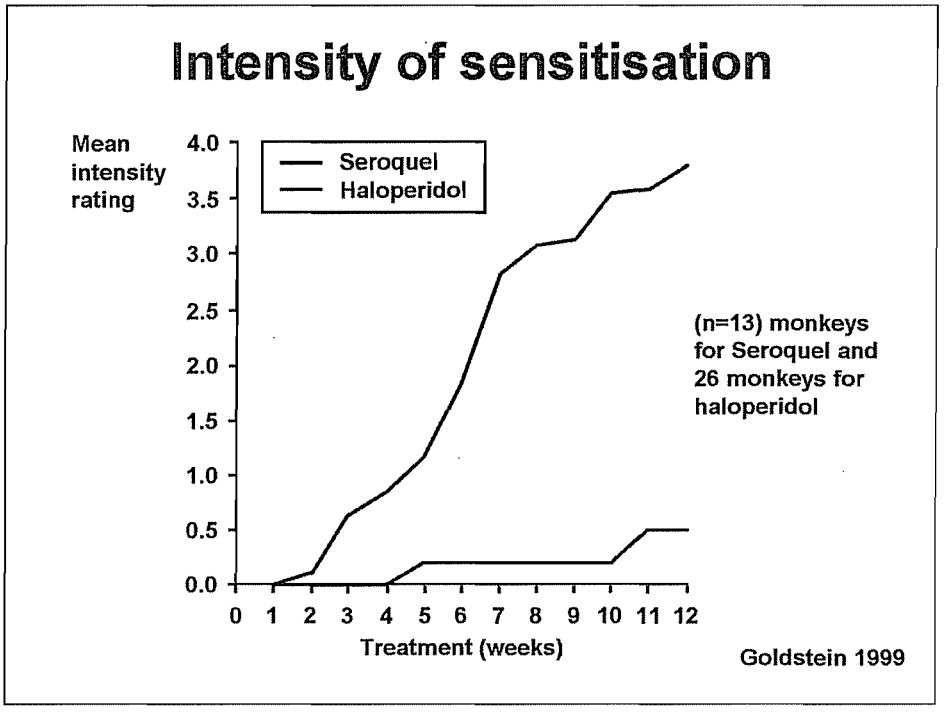
Goldstein 1996

Seroquel shows minimal liability to dystonia in drug-naïve monkeys

- The chronic administration of antipsychotics to previously untreated Cebus monkeys simulates dosing conditions that produce extrapyramidal symptoms (EPS) in humans more closely than does the haloperidol-sensitised monkey model[1]
- Clozapine produces no dystonia in this model. Compared with haloperidol, Seroquel shows a lower rate of sensitisation, producing fewer dyskinesias, which are of lesser severity and of shorter duration[1]
- These data predict that Seroquel, like clozapine, will have a significantly reduced propensity to produce EPS and tardive dyskinesia than standard antipsychotics[1]

Reference

1. Goldstein JM. In: Holliday SG, Ancill RJ, MacEwan GW, eds. Schizophrenia: *Breaking Down the Barriers*. John Wiley & Sons Ltd, 1996: 177-236.

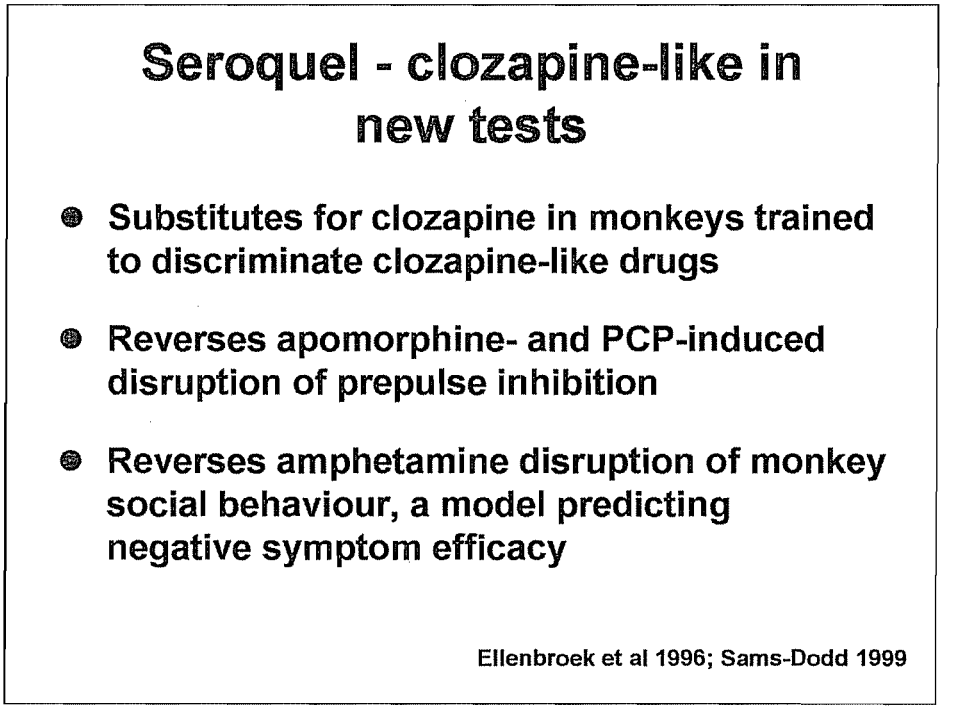


Intensity of sensitisation

- This slide shows the mean intensity rating of dyskinetic responses to Seroquel and haloperidol, exhibited by drug-naive Cebus monkeys, as a function of time[1]
- It was not until Week 5 that the first responses were seen with Seroquel; these remained of low intensity throughout the study[1]
- In contrast, initial reactions with haloperidol were observed from 2 weeks of treatment and the intensity of response increased rapidly over the study period[1]

Reference

1. Goldstein JM. *Emerging Drugs* 1999; 4: 127-151.



Seroquel - clozapine-like in new tests

- Seroquel is clozapine-like in a range of animal tests that are used to predict the antipsychotic activity of potential agents[1]

- Studies in various animal models predict that Seroquel has antipsychotic activity and, furthermore, that it has activity against the negative symptoms of schizophrenia. Activity against negative symptoms is also considered to be a distinguishing characteristic of atypical antipsychotics, and is not shared by the standard antipsychotics[1,2]

References

1. Ellenbroek BA et al. *Neuropsychopharmacology* 1996; 15: 406-416.
2. Sams-Dodd F. *Rev Neurosci* 1999; 10: 59-90.

Seroquel - preclinical findings predict atypical antipsychotic profile

- **Antipsychotic activity**
  - inhibits conditioned avoidance in primates
  - reverses effects of dopamine agonists in rodents
  - elevates levels of dopamine metabolites (a measure of functional response to dopamine receptor blockade)
  - reverses amphetamine-induced asocial behaviours
  - substitutes for clozapine in drug discrimination tests in primates
- **Tolerability profile**
  - low propensity for EPS including minimal dystonia
  - minimal propensity for anticholinergic activity
  - no sustained increase in plasma prolactin

Carey and Bergman 1997; Goldstein 1996; 1999

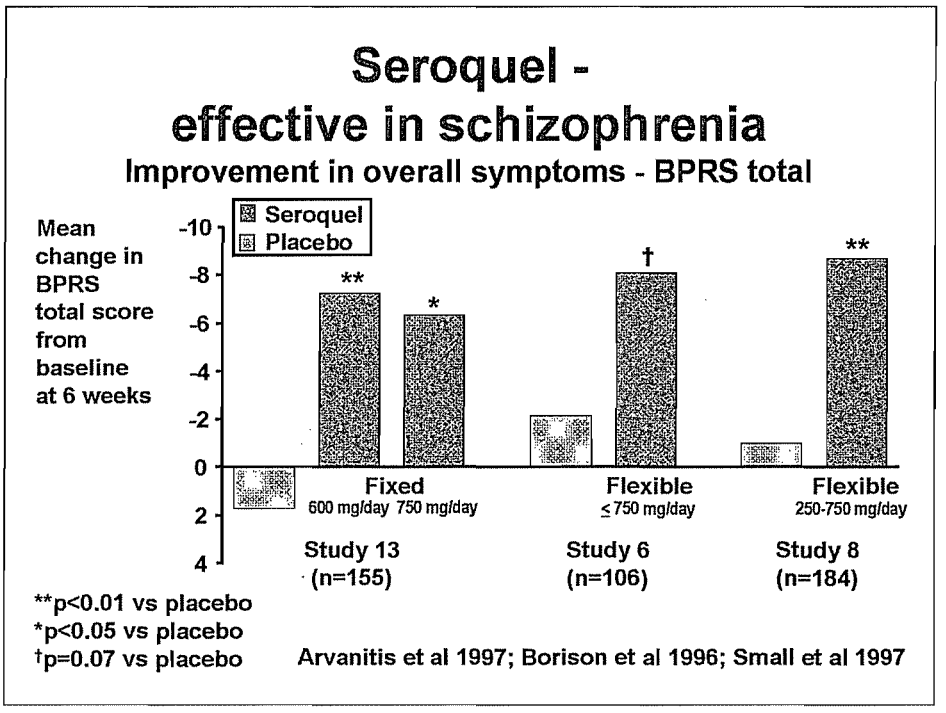
Seroquel - preclinical findings predict atypical antipsychotic profile

- Overall, the preclinical profile[1-7] of Seroquel suggests that it would be clozapine-like in terms of a broader antipsychotic activity than standard antipsychotics. Like clozapine, Seroquel will also be less likely to cause extrapyramidal symptoms (EPS) and tardive dyskinesia than the standard antipsychotics[6]. Furthermore, Seroquel is unlikely to be associated with hyperprolactinaemia, which is a common side effect of standard antipsychotics[2]

References

1. Goldstein JM. In: Holliday SG et al, eds. *Breaking Down the Barriers.* London: John Wiley & Sons Ltd; 1996: 177-236.
2. Saller CF, Salama AL. *Psychopharmacology* 1993; 112: 285-292.
3. Ellenbroek BA et al. *Neuropsychopharmacology* 1996; 15 (4): 406-416.
4. Carey G, Bergman J. *Behav Pharmacol* 1994; 1: 114.
5. Migler BM et al. *Psychopharmacology* 1993; 112: 299-307.
6. Carey G, Bergman J. *Psychopharmacology* 1997; 132: 261-269.
7. Goldstein JM. *Lancet* 1995; 346(8972): 450. (Letter)

'Seroquel' - Efficacy in schizophrenia

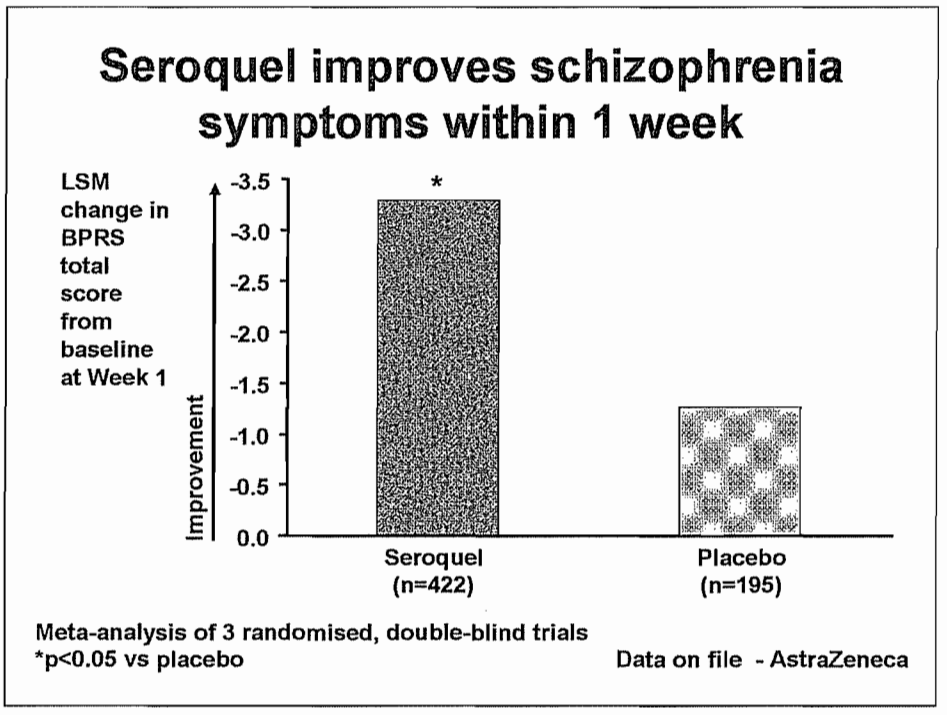


Seroquel – effective in schizophrenia

- Studies 13, 6 and 8 were 6-week randomised, double blind, placebo-controlled trials of Seroquel in patients with schizophrenia[1,2,3]
- This slide presents the consistently observed and statistically significant improvement compared with placebo in the Brief Psychiatric Rating Scale (BPRS) total score reported for study 6 and for subsets of patients from studies 13 and 8
- In study 13, patients (n=361) were randomised to treatment with placebo, Seroquel (75 mg/day, 150 mg/day, 300 mg/day, 600 mg/day or 750 mg/day) or haloperidol 12 mg/day. A subset of trial last value carried forward (LVCF) data is shown in this slide and these data were available from 51 patients receiving placebo, 51 patients receiving Seroquel 600 mg/day (fixed dose) and 53 patients receiving Seroquel 750 mg/day (fixed dose)[1]
- In study 6, patients (n=109) were randomised to treatment with either placebo or Seroquel (75-750 mg/day). The LVCF data shown were evaluated in 53 patients who had received placebo and in 53 patients who had received Seroquel (flexible dose). Patients received Seroquel 58-526 mg/day and the mean daily dose administered was 307 mg/day[2]
- In study 8, patients (n=286) were randomised to treatment with placebo, low-dose Seroquel (flexible dose up to 250 mg/day) or high-dose Seroquel (flexible dose up to 750 mg/day). The subset of LVCF data shown were evaluated in patients receiving placebo (n=92) or high-dose Seroquel (n=92). The high-dose Seroquel patients received a mean dose of 360 mg/day Seroquel (range 50-566 mg/day). For high-dose Seroquel patients who completed the trial, the mean daily dose was 488 mg/day[3]

References

1. Arvanitis LA et al. *Biol Psychiatry* 1997; 42: 233-246.
2. Borison RL et al. *J Clin Psychopharmacol* 1996; 16 (2): 158-169.
3. Small JG et al. *Arch Gen Psychiatry* 1997; 54: 549-557.



Seroquel improves schizophrenia symptoms within 1 week

- Meta-analysis of three 6-week, randomised, double-blind, placebo-controlled trials (trials 6[1], 8[2] and 13[3]). All patients had schizophrenia. A total of 422 patients treated with Seroquel and 195 patients who received placebo were included in the meta-analysis

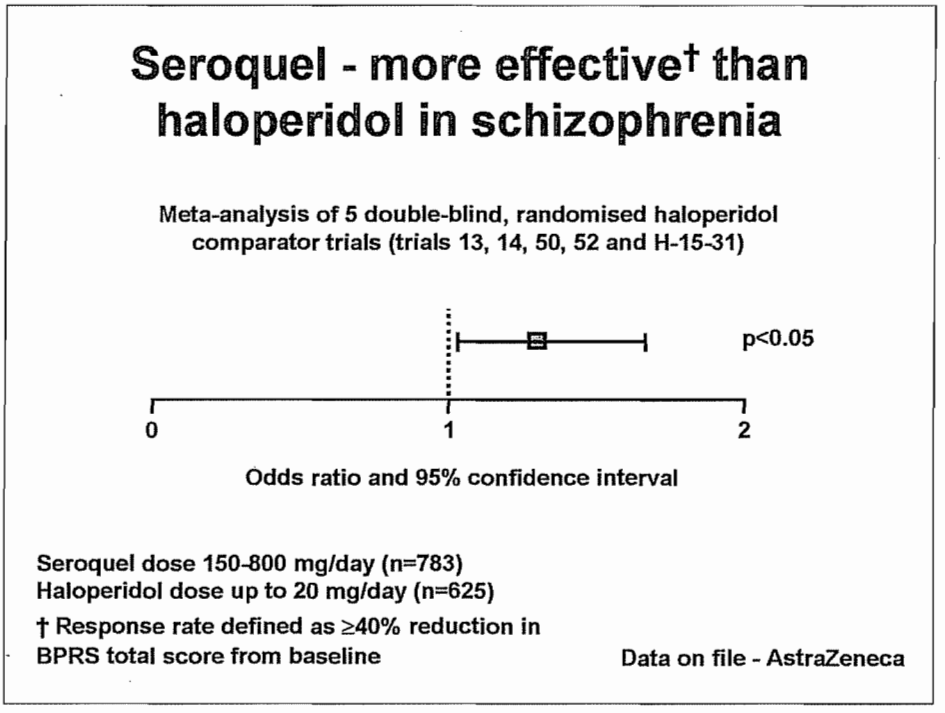
- Patients received Seroquel up to 750 mg/day in trial 6, up to 250 or 750 mg/day in trial 8 and fixed doses (75 mg/day, 150 mg/day, 300 mg/day, 600 mg/day, and 750 mg/day) in trial 13

- This graph shows an analysis of covariance for change in Brief Psychiatric Rating Scale (BPRS) total score (least squares mean) from baseline to Week 1 (observed cases)

- Seroquel shows a statistically significant improvement in BPRS total score, compared with placebo[4]

References

1. Borison RL et al. *J Clin Psychopharmacol* 1996; 16: 158-169.
2. Small JG et al. *Arch Gen Psychiatry* 1997; 54: 549-557.
3. Arvanitis LA et al. *Biol Psychiatry* 1997; 42: 233-246.
4. Data on file – AstraZeneca.

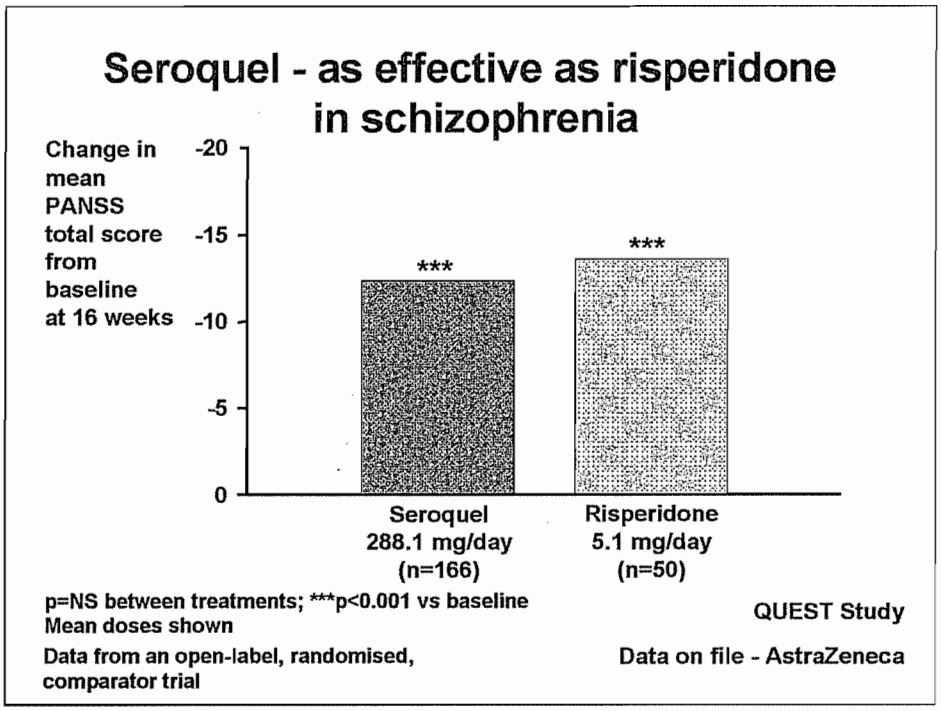


Seroquel - more effective than haloperidol in schizophrenia

- Meta-analysis of five randomised, double-blind, haloperidol-controlled trials (trials 13,[1] 14,[2] 50[3], 52[4] and H-15-31[5])
- In trial 13, patients received Seroquel fixed doses (75 mg/day, 150 mg/day, 300 mg/day, 600 mg/day and 750 mg/day) or haloperidol 12 mg/day. In trial 14, patients received Seroquel up to 800 mg/day or haloperidol up to 16 mg/day. In trial 50, patients received Seroquel up to 600 mg/day or haloperidol up to 20 mg/day. In trial 52, patients received Seroquel up to 600 mg/day or haloperidol up to 20 mg/day. In trial H-15-31, patients received flexible dosing of Seroquel (up to 600 mg/day, n=100) and haloperidol (up to 18 mg/day, n=97)
- Response rates were defined as a ≥40% reduction in total Brief Psychiatric Rating Scale (BPRS) score from baseline to end of treatment
- These data include patients with schizophrenia only. This slide shows the adjusted odds ratio for combined analysis and the 95% confidence limits. Odds ratios greater than 1 indicate a significantly higher rate of response compared with either placebo or haloperidol[3]

References

1. Arvanitis LA et al. *Biol Psychiatry* 1997; 42: 233-246.
2. Copolov DL et al. *Psychol Med* 2000; 30: 95-105.
3. Data on file – AstraZeneca.
4. Emsley RA et al. *Int Clin Psychopharmacol* 2000; 15(3): 121-131.
5. Murasaki M et al. *Int J Neuropsychopharmacol* 2000; 3(S1): 150.

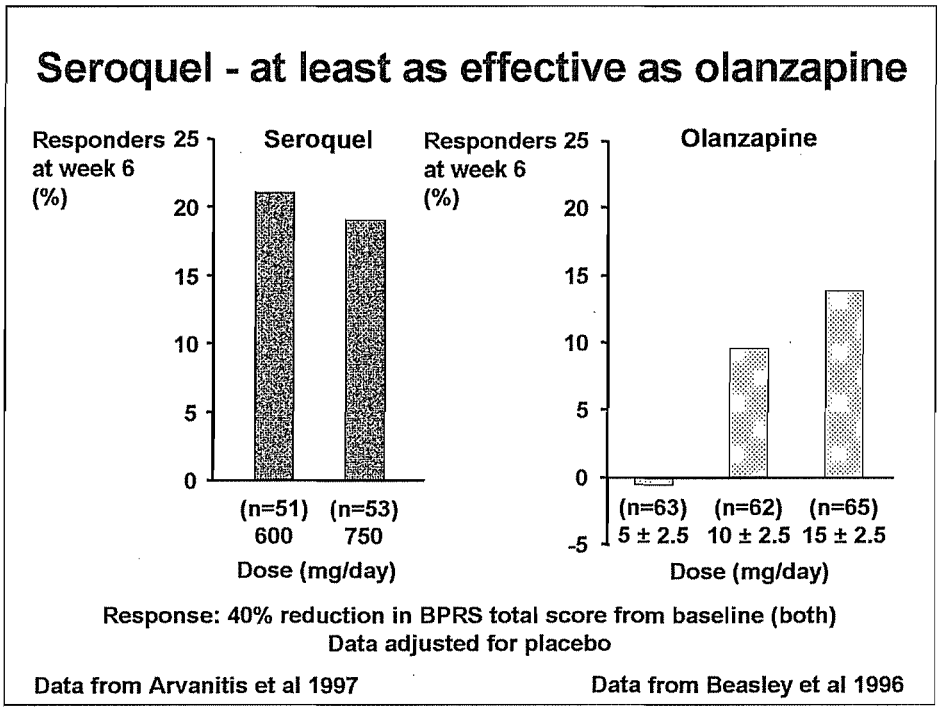


Seroquel - as effective as risperidone in schizophrenia

- QUEST (**Q**uetiapine Experience with **S**afety and **T**olerability) was a 16-week, open-label trial comparing Seroquel and risperidone in 751 adult outpatients with mixed psychotic disorders[1]
- This slide presents the subanalysis of the schizophrenia cohort within QUEST where patients received Seroquel mean dose 288.1 mg/day (n=191) or risperidone mean dose 5.1 mg/day (n=60)[2]
- This slide details the improvement in mean Positive and Negative Syndrome Scale (PANSS) total score from baseline at 16 weeks in patients on Seroquel (n=166) and risperidone (n=50)[2]
- Seroquel is as effective as risperidone in improving the PANSS total score in patients with schizophrenia[2]

References

1. Reinstein M et al. Poster presented at the American Psychiatric Association Annual Meeting, Washington DC, 1999.
2. Data on file – AstraZeneca.



Seroquel – at least as effective as olanzapine

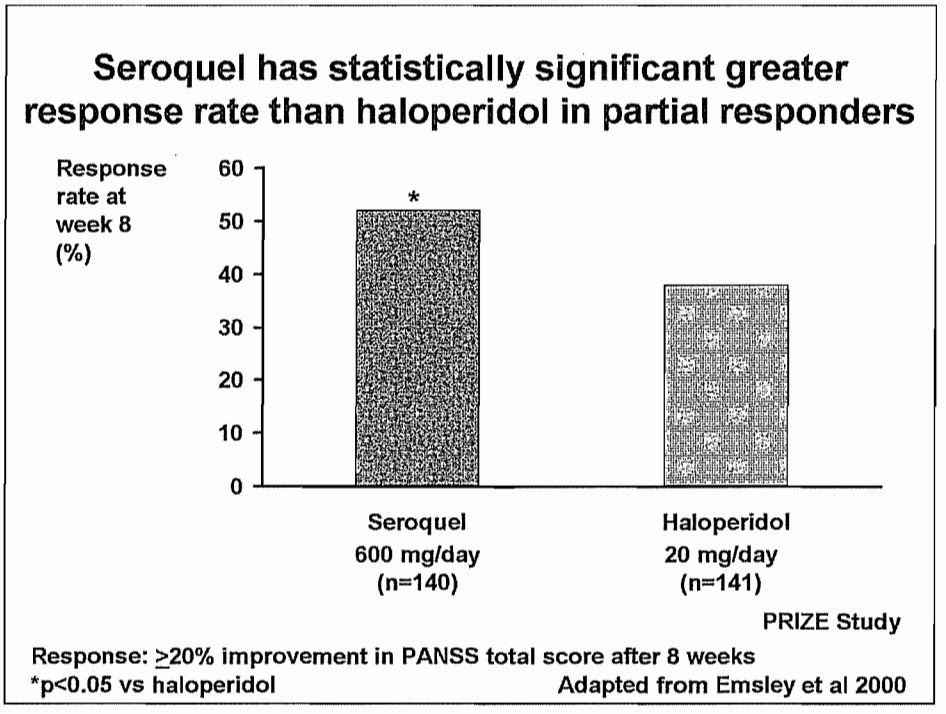
- These data are from two 6-week, randomised, double blind, placebo-controlled trials in patients with schizophrenia. Both trials used several definitions of response. This slide shows the response data that were defined as a ≥40% improvement in the Brief Psychiatric Rating Scale (BPRS) total score from baseline at endpoint[1,2]

- In a study of Seroquel, patients (n=361) were randomised to treatment with placebo, Seroquel (75 mg/day, 150 mg/day, 300 mg/day, 600 mg/day or 750 mg/day) or haloperidol 12 mg/day. The Seroquel analysis shows a subset of the response rates at endpoint (last value carried forward [LVCF]), adjusted for placebo (n=51), in patients receiving Seroquel 600 mg/day (n=51) and 750 mg/day (n=53)[1]

- The olanzapine analysis shows the response rates (LVCF), adjusted for placebo (n=62), in patients receiving olanzapine 5 ± 2.5 mg/day (n=63), 10 ± 2.5 mg/day (n=62) or 15 ± 2.5 mg/day (n=65)[2]

References

1. Arvanitis LA et al. *Biol Psychiatry* 1997; 42: 233-246.
2. Beasley CM et al. *Neuropsychopharmacology* 1996; 14 (2): 111-123.



Seroquel has statistically significant greater response rate than haloperidol in partial responders

- The PRIZE (Partial Responders International schiZophrenia Evaluation) multicentre, double-blind study compared the efficacy and tolerability of 8 weeks' treatment of Seroquel 600 mg/day with haloperidol 20 mg/day in patients with schizophrenia, who had a history of partial response to typical antipsychotics and displayed a partial or no response to 1 month of fluphenazine (20 mg/day) treatment[1]

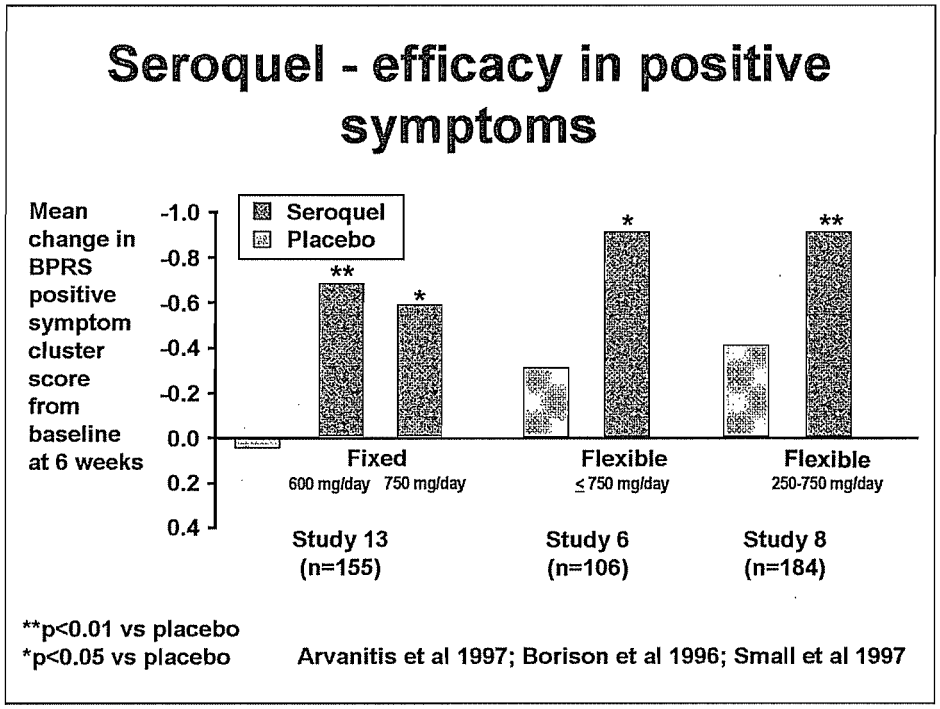
- 365 patients entered the fluphenazine run-in (4 weeks) and, of these, 143 patients were randomised to 8 weeks' treatment with Seroquel and 145 to 8 weeks' treatment with haloperidol

- Positive and Negative Syndrome Scale (PANSS) scores were evaluated in 140 Seroquel patients and 141 haloperidol patients (LVCF analysis)

- Partial responders are the population of patients most commonly seen by psychiatrists in clinical practice

Reference

1. Emsley RA et al. *Int Clin Psychopharmacol* 2000; 15: 121-131.

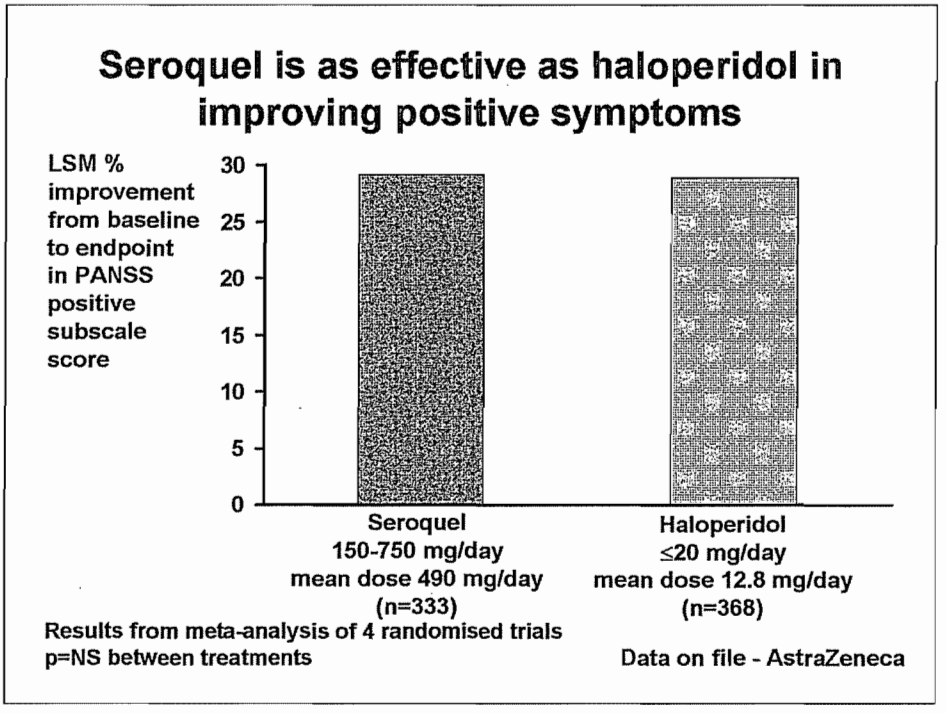


Seroquel – efficacy in positive symptoms

- Studies 13, 6 and 8 were 6-week randomised, double blind, placebo-controlled trials of Seroquel in patients with schizophrenia[1,2,3]
- This slide presents the statistically significant improvement in the positive symptom cluster score of the Brief Psychiatric Rating Scale (BPRS) reported for study 6 and for subsets of patients from studies 13 and 8 compared with placebo
- In study 13, patients (n=361) were randomised to treatment with placebo, Seroquel (75 mg/day, 150 mg/day, 300 mg/day, 600 mg/day or 750 mg/day) or haloperidol 12 mg/day. A subset of trial last value carried forward (LVCF) data is shown in this slide and these data were available from 51 patients receiving placebo, 51 patients receiving Seroquel 600 mg/day (fixed dose) and 53 patients receiving Seroquel 750 mg/day (fixed dose)[1]
- In study 6, patients (n=109) were randomised to treatment with either placebo or Seroquel (75-750 mg/day). The LVCF data shown on the slide were evaluated in 53 patients who had received placebo and 53 who had received Seroquel (flexible dose). Patients received Seroquel 58-526 mg/day and the mean daily dose administered was 307 mg/day[2]
- In study 8, patients (n=286) were randomised to treatment with placebo, low-dose Seroquel (flexible dose up to 250 mg/day) or high-dose Seroquel (flexible dose up to 750 mg/day). The subset of LVCF data shown were evaluated in patients receiving placebo (n=92) or high-dose Seroquel (n=92)[3]

References

1. Arvanitis LA et al. *Biol Psychiatry* 1997; 42: 233-246.
2. Borison RL et al. *J Clin Psychopharmacol* 1996; 16: 158-169.
3. Small JG et al. *Arch Gen Psychiatry* 1997; 54: 549-557.

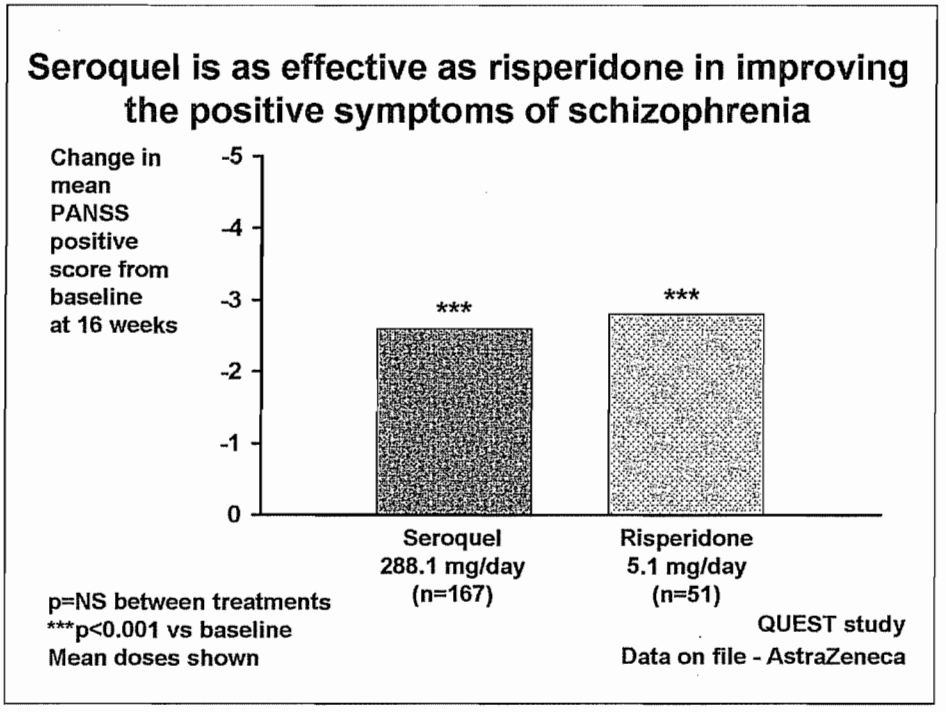


Seroquel is as effective as haloperidol in improving positive symptoms

- Meta-analysis of schizophrenic patients in four randomised, double-blind, haloperidol-controlled trials (trials 14,[1] 50,[2] 52[3] and H-15-31[4]). Trial 14 was 6 weeks in duration, trial 50 data up to Week 12 only (ie the acute phase) has been included, and trials 52 and H-15-31 were of 8 weeks' duration. A total of 333 patients treated with Seroquel and 368 patients treated with haloperidol were included in the meta-analysis[2]
- Patients receiving Seroquel were given a mean dose of 455 mg/day in trial 14, 364 mg/day (data up to Week 12 only) in trial 50, 600 mg/day in trial 52 and 600 mg/day (maximum dose) in trial H-15-31. Patients receiving haloperidol were given a mean dose of 8 mg/day in trial 14, 10 mg/day (data up to Week 12 only) in trial 50, 20 mg/day in trial 52 and 18 mg/day (maximum dose) in trial H-15-31
- The slide details the percentage improvement from baseline in Positive and Negative Symptoms Scale positive subtotal score. This data set included only patients who were dosed with 150-750 mg/day Seroquel and shows efficacy comparable to haloperidol in positive symptoms

References

1. Copolov DL et al. *Psychol Med* 2000; 30: 95-105.
2. Data on file – AstraZeneca.
2. Emsley RA et al. *Int Clin Psychopharmacol* 2000; 15: 121-131.
3. Murasaki M et al. Poster presented at the 11th World Congress of Psychiatry, Hamburg, 1999.

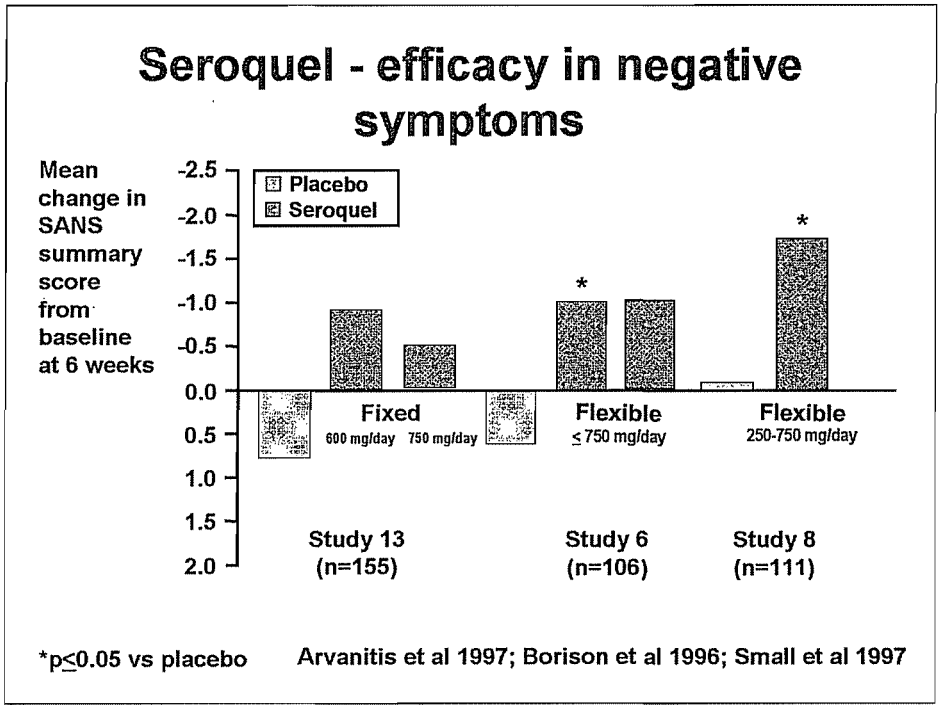


Seroquel is as effective as risperidone in improving the positive symptoms of schizophrenia

- QUEST (**Q**uetiapine Experience with **S**afety and **T**olerability) was a 16-week, open-label trial comparing Seroquel and risperidone in 751 adult outpatients with mixed psychotic disorders[1]
- This slide presents data from the subanalysis of the schizophrenia cohort within QUEST ([n=251]; Seroquel [n=191] and risperidone [n=60]), where patients received Seroquel mean dose 288.1 mg/day or risperidone mean dose 5.1 mg/day[2]
- The Positive and Negative Syndrome Scale (PANSS) was a primary efficacy measure[2]
- This slide details the improvement in mean PANSS positive score from baseline at 16 weeks in patients on Seroquel (n=167) and risperidone (n=51)[2]
- Seroquel is as effective as risperidone in improving the PANSS positive score in patients with schizophrenia[2]

References

1. Reinstein M et al. Poster presented at the American Psychiatric Association Annual Meeting, Washington DC, 1999.
2. Data on file – AstraZeneca.

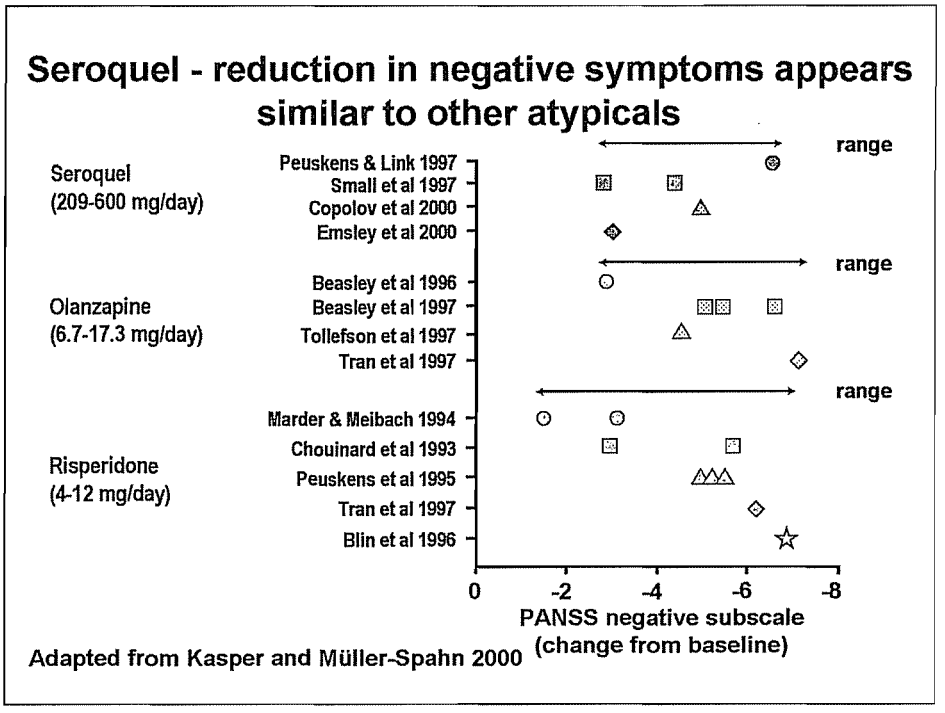


Seroquel – efficacy in negative symptoms

- Studies 13, 6 and 8 were 6-week randomised, double-blind, placebo-controlled trials of Seroquel in patients with schizophrenia
- This slide presents the statistically significant improvement compared with placebo in the Scale for Assessment of Negative Symptoms (SANS) score reported for study 6 and for subsets of patients from studies 13 and 8
- In study 13, patients (n=361) were randomised to treatment with placebo, Seroquel (75 mg/day, 150 mg/day, 300 mg/day, 600 mg/day or 750 mg/day) or haloperidol 12 mg/day. A subset of last value carried forward (LVCF) data is shown in this slide and these data were available from 51 patients receiving placebo, 51 patients receiving Seroquel 600 mg/day (fixed dose), and 53 patients receiving Seroquel 750 mg/day (fixed dose)[1]
- In study 6, patients (n=109) were randomised to treatment with either placebo or Seroquel (75-750 mg/day). The LVCF data shown were evaluated in 53 patients who had received placebo and in 53 patients who had received Seroquel (flexible dose). Patients received Seroquel 58-526 mg/day and the mean daily dose administered was 307 mg/day[2]
- In study 8, patients (n=286) were randomised to treatment with placebo, low-dose Seroquel (flexible dose up to 250 mg/day) or high-dose Seroquel (flexible dose up to 750 mg/day). The subset of LVCF data shown in the slide were analysed in patients receiving placebo (n=56) or high-dose Seroquel (n=55) who were evaluable for SANS score

References

1. Arvanitis LA et al. *Biol Psychiatry* 1997; 42: 233-246.
2. Borison RL et al. *J Clin Psychopharmacol* 1996; 16: 158-169.
3. Small JG et al. *Arch Gen Psychiatry* 1997; 54: 549-557.

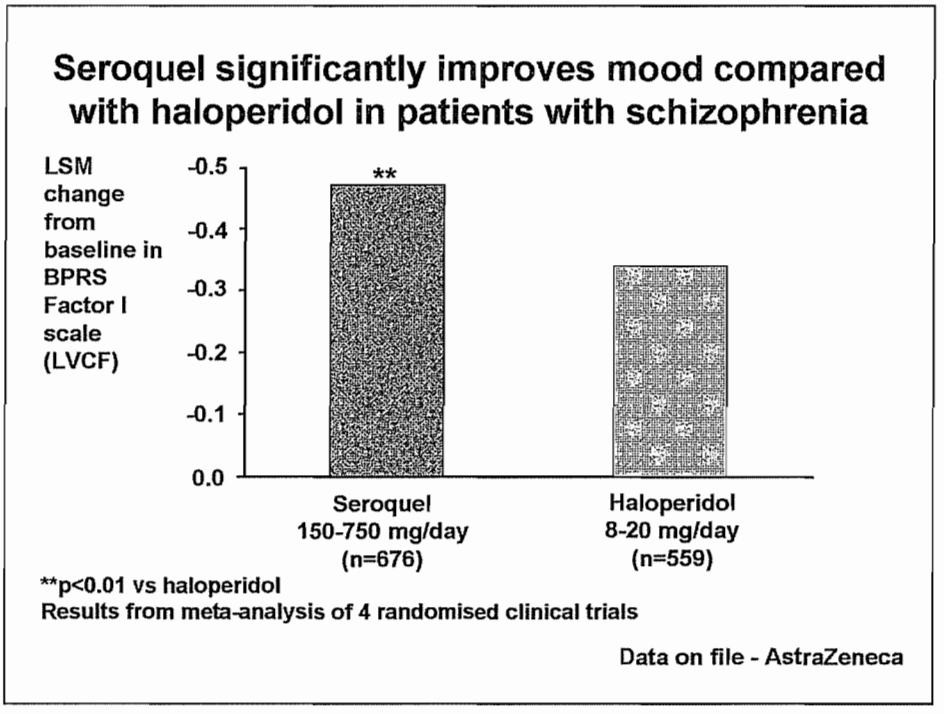


Seroquel - reduction in negative symptoms appears similar to other atypicals

- In a series of 6-week, double-blind, prospective, randomised studies in schizophrenia, the magnitude of change in negative symptoms from baseline with Seroquel, as measured by Positive and Negative Syndrome Scale (PANSS) score, was similar to the changes seen with either olanzapine or risperidone[1-12]

References

1. Peuskens J, Link CCG. *Acta Psychiatr Scand* 1997; 96: 265-273.
2. Small J et al. *Arch Gen Psychiatry* 1997; 54: 549-557.
3. Copolov DL et al. *Psychol Med* 2000; 30: 95-105.
4. Emsley RA et al. *Int Clin Psychopharmacol* 2000; 15: 121-131.
5. Beasley CM et al. *Psychopharmacology* 1996; 124: 159-167.
6. Beasley CM et al. *Eur Neuropsychopharmacol* 1997; 7: 125-137.
7. Tollefson G et al. *Am J Psychiatry* 1997; 154: 457-465.
8. Tran P et al. *J Clin Psychopharmacol* 1997; 17: 407-418.
9. Marder SR, Meibach RC. *Am J Psychiatry* 1994; 151: 825-835.
10. Chouinard G et al. *J Clin Psychopharmacol* 1993; 13: 25-40.
11. Peuskens J. *Br J Psychiatry* 1995: 166: 712-726.
12. Blin O et al. *J Clin Psychopharmacol* 1996: 16: 38-44.
13. Kasper and Müller-Spahn. *Exp Opin Pharmacother* 2000; 1(4): 783-801.

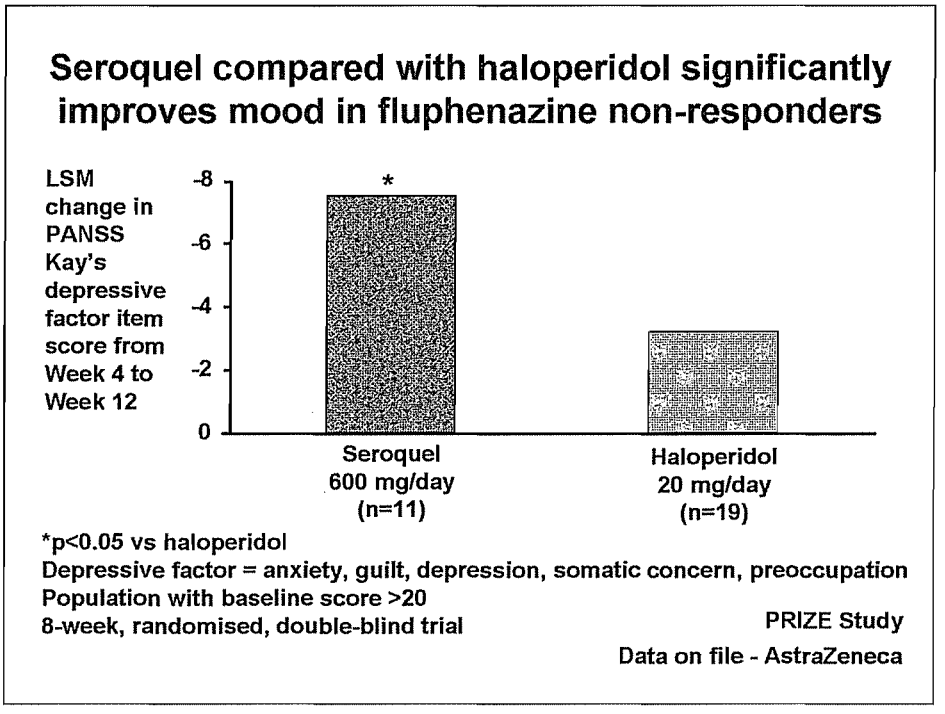


Seroquel significantly improves mood compared with haloperidol in patients with schizophrenia

- These data were obtained from a meta-analysis of four haloperidol comparator trials (studies 13, 14, 50 and 52)[1]
- Least squares mean (LSM)change from baseline in Brief Psychiatric Rating Scale (BPRS) Factor I is shown for Seroquel (n=676) vs haloperidol (n=559) [last value carried forward values][1]
- Only patients with schizophrenia receiving 150-750 mg/day Seroquel or 8-20 mg/day haloperidol were included in this analysis[1]

Reference

1. Data on file – AstraZeneca.



Seroquel compared with haloperidol significantly improves mood in fluphenazine non-responders

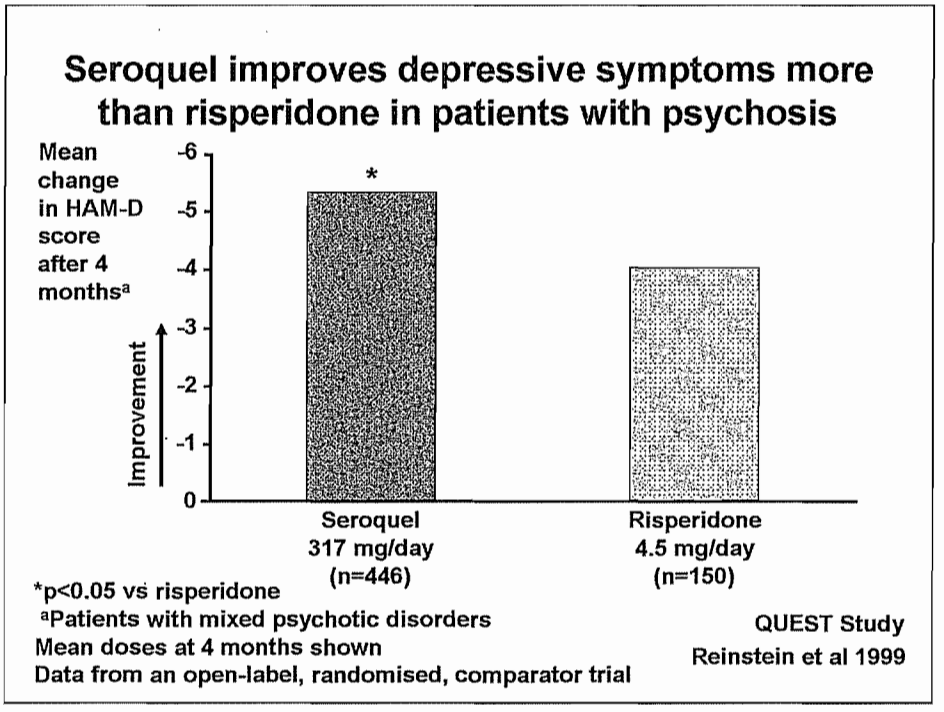
- These data are from an 8-week, multicentre, double-blind randomised trial (PRIZE – Partial Responders International schiZophrenia Evaluation) comparing Seroquel (600 mg/day) and haloperidol (20 mg/day) in schizophrenic patients with a history of partial response to conventional antipsychotic therapy, and who did not experience a sufficient response to 4 weeks' treatment with fluphenazine[1]

- Supplemental efficacy analysis was carried out on the PRIZE data. This enabled comparison of a number of parameters between treatments. This slide shows the change from baseline (last observation carried forward values) in Kay's Depressive Factor (Kay performed a factor analysis on the 30 Positive and Negative Syndrome Scale items which yielded 5 domains including the depressive domain which comprised the 5 items: anxiety, guilt, depression, somatic concern and preoccupation). This population had a baseline score ≥20 for the sum of these items[1]

- Seroquel shows a significantly greater improvement in mood compared with haloperidol ($p=0.015$)[1] Shown as $p<0.05$ on slide to follow convention.

Reference

1. Data on file – AstraZeneca.

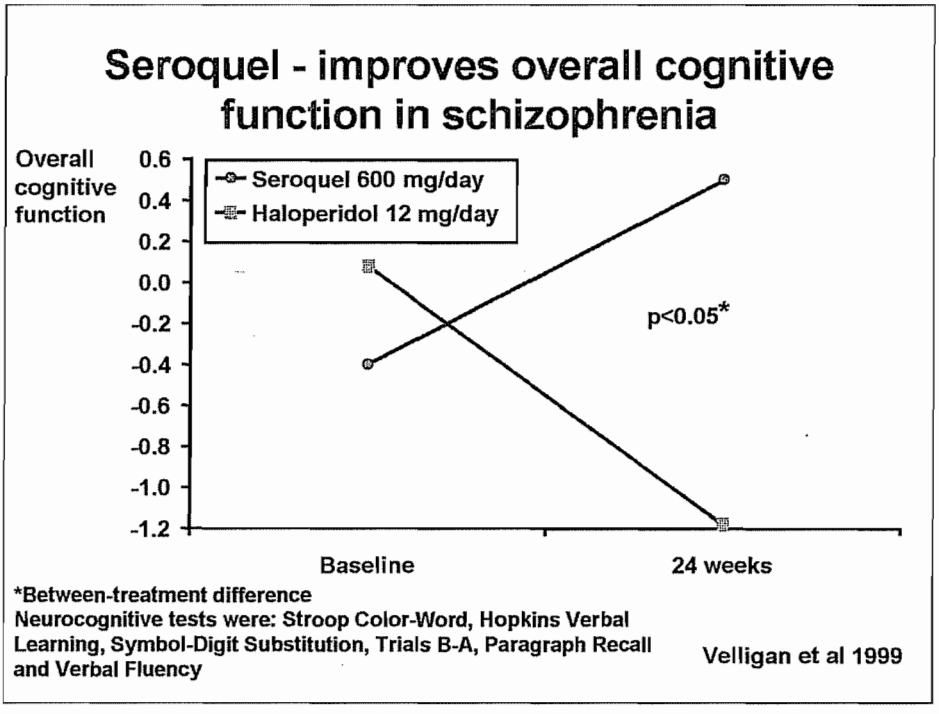


Seroquel improves depressive symptoms more than risperidone in patients with psychosis

- These data are from a 16-week, multicentre, open-label trial (QUEST – **Q**uetiapine Experience with **S**afety and **T**olerability) comparing Seroquel and risperidone in adult outpatients with mixed psychotic disorders[1]
- The mean dose at Week 16 was 317 mg/day for Seroquel and 4.5 mg/day for risperidone[1]
- The slide details the improvement in the Hamilton Rating Scale for Depression (HAM-D) during the trial in 446 Seroquel-treated patients and 150 risperidone-treated patients. The baseline mean HAM-D score was 15.5 for both treatment groups[1]

Reference

1. Reinstein M et al. Poster presented at the American Psychiatric Association Annual Meeting, Washington DC, 1999.

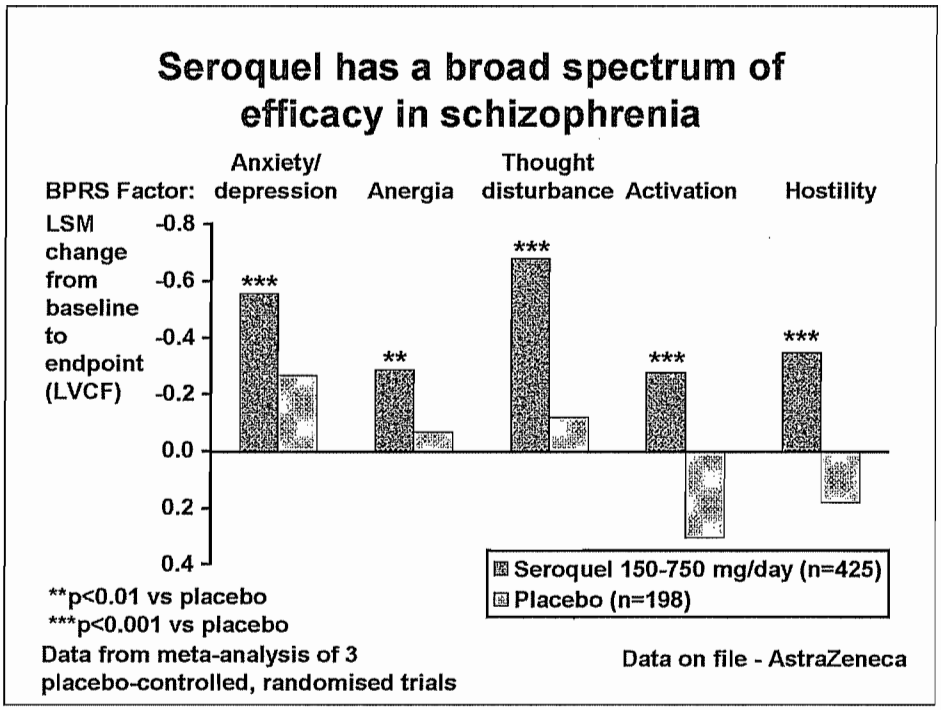


Seroquel – improves overall cognitive function in schizophrenia

- Over 24 weeks, cognitive function improved in patients treated with Seroquel (600 mg/day) and declined in those receiving haloperidol (12 mg/day)[1]
- Cognitive function was measured using a battery of six neurocognitive tests (Stroop Color-Word, Hopkins Verbal Learning, Symbol-Digit Substitution, Trials B-A, Paragraph Recall and Verbal Fluency). The combined scores of these tests provided the measure of overall cognitive function[1]
- Cognitive deficits cause difficulty in living in the community. Seroquel treatment may help alleviate this by improving some aspects of cognitive function[1]
- The between-treatment difference is statistically significant ($p<0.03$ – although shown as <0.05 to follow slide convention)

Reference

1. Velligan DI et al. Poster presented at the American Psychiatric Association Annual Meeting, Washington DC, 1999.

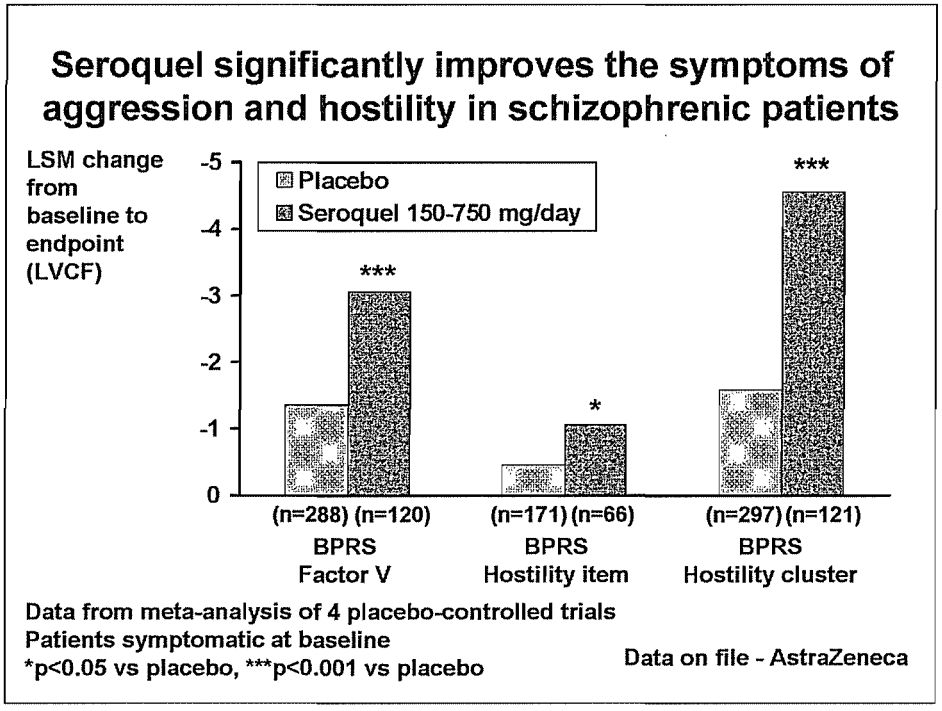


Seroquel has a broad spectrum of efficacy in schizophrenia

- These data are from a meta-analysis of three 6-week, randomised, double-blind, placebo-controlled trials (trials 6[1], 8[2] and 13[3]) in patients with schizophrenia
- Study 5077IL/0006 contained one Seroquel dose group (flexible-dose up to 750 mg/day), and the mean Seroquel dose was 307 mg/day (n=109)[1]
- Study 204636/0008 contained two Seroquel dose groups, one allowing flexible dosing up to 250 mg/day and the other allowing flexible dosing up to 750 mg/day. Data from patients who received less than 150 mg/day have not been included in this meta-analysis. The mean Seroquel dose in the patients included from each dose group was 219 mg/day and 402 mg/day, respectively (n=286)[2]
- Study 5077IL/0013 contained five fixed-dose Seroquel groups (75 mg/day, 150 mg/day, 300 mg/day, 600 mg/day and 750 mg/day). Data from patients in the 75 mg/day group have not been included in this meta-analysis (n=361)[3]
- This slide details the significant improvements in all factors of the Brief Psychiatric Rating Scale (BPRS) for Seroquel (n=425) compared with placebo (n=198). The BPRS factors were: I (anxiety/depression), II (anergia), III (thought disturbance), IV (activation) and V (hostility). The data set included only patients who received 150-750 mg/day Seroquel[4]

References

1. Borison RL et al. *J Clin Psychopharmacol* 1996; 16: 158-169.
2. Small JG et al. *Arch Gen Psychiatry* 1997; 54: 549-557.
3. Arvanitis LA et al. *Biol Psychiatry* 1997; 42: 233-246.
4. Data on file – AstraZeneca.

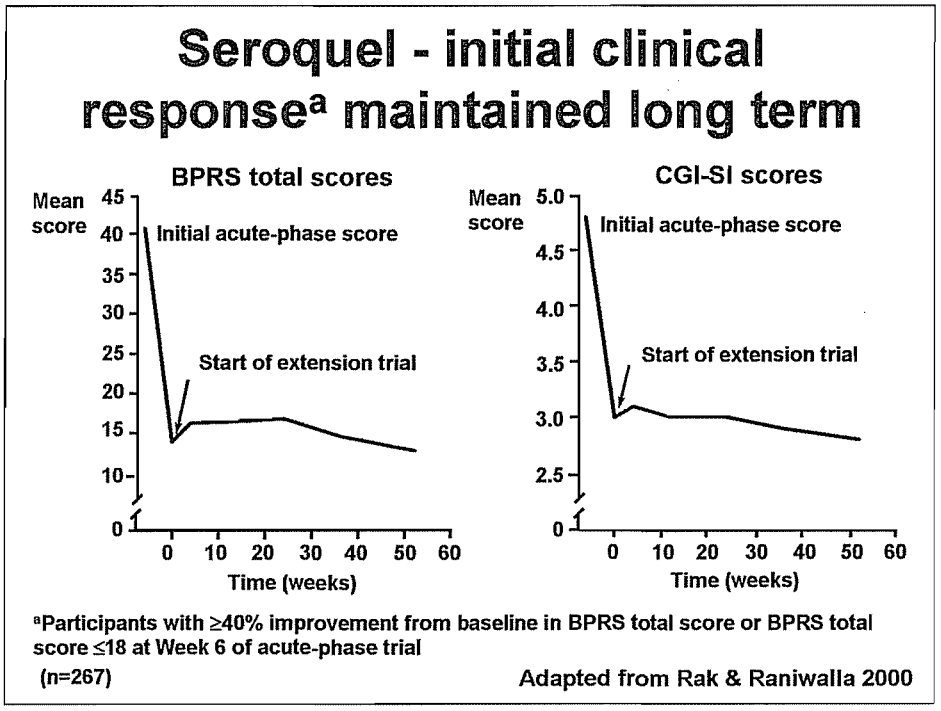


Seroquel significantly improves the symptoms of aggression and hostility in symptomatic schizophrenic patients

- The data in this slide were derived from a meta-analysis of four acute, randomised, double-blind, placebo-controlled studies in patients with schizophrenia[1]
- The Seroquel dose ranged from 150-750 mg/day[1]
- Hostility/aggression was assessed on three parameters: score on the hostility item of the Brief Psychiatric Rating Scale (BPRS); score on the hostility cluster of the BPRS (sum of the scores for the items anxiety, tension, hostility, suspiciousness, uncooperativeness and excitement); and score on Factor V of the BPRS (sum of the scores for the items hostility, suspiciousness and uncooperativeness) [1]
- Only patients who were symptomatic on a given parameter at baseline were included in the analysis for that parameter. The thresholds for inclusion were as follows: hostility item baseline score of 3 or more; hostility cluster baseline score of 12 or more; Factor V baseline score of 6 or more[1]
- A pooled treatment effect was calculated by combining the treatment effects from the four studies, weighted according to study size and within-study variation. Data were analysed using a last value carried forward approach[1]
- The numbers of patients included in each analysis were: hostility item, Seroquel 171/placebo 66; hostility cluster, 297/121, Factor V, 288/120[1]
- Seroquel was significantly more effective than placebo at improving these symptoms of aggression and hostility in patients with schizophrenia[1]

Reference

1. Data on File – AstraZeneca.



Seroquel – initial clinical response[a] maintained long term

- These data are from a subset of patients (n=267), who had previously responded to Seroquel in three 6-week placebo-controlled trials before entering the 52-week open-label extension trial (OLE) of Seroquel in patients with schizophrenia[1]

- Patients received up to 800 mg/day Seroquel in the OLE studies. Two OLE studies evaluated fixed doses of Seroquel and one used flexible dosing[1]

- The observed number of patients evaluated by the Brief Psychiatric Rating Scale (BPRS) Total score and Clinical Global Impression (CGI) severity of illness score, at 0 and 52 weeks were n=266 and 90 and n=267 and 91, respectively[1]

[a]Response was defined as a ≥40% decrease from baseline in the BPRS total score or a BPRS total score of ≤18 at Week 6 of the acute-phase trial[1]

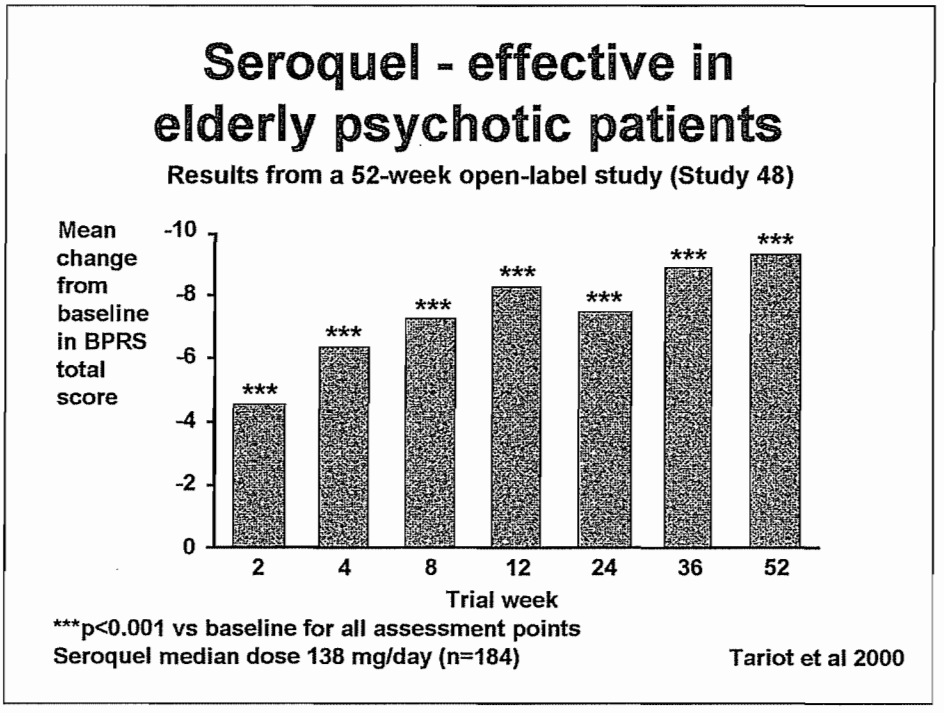
Reference

1. Rak I, Raniwalla J. Poster presented at the Winter Workshop, Davos, 2000.

Seroquel - efficacy in schizophrenia

- Efficacy comparable to or greater than other antipsychotics
- Efficacy in both positive and negative symptoms
- Improves depressive symptoms
- Improves cognitive function
- Reduces aggression and hostility
- Efficacy in 'partial responders'
- Efficacy maintained long term (52 weeks)

Efficacy in other populations



Seroquel – effective in elderly psychotic patients

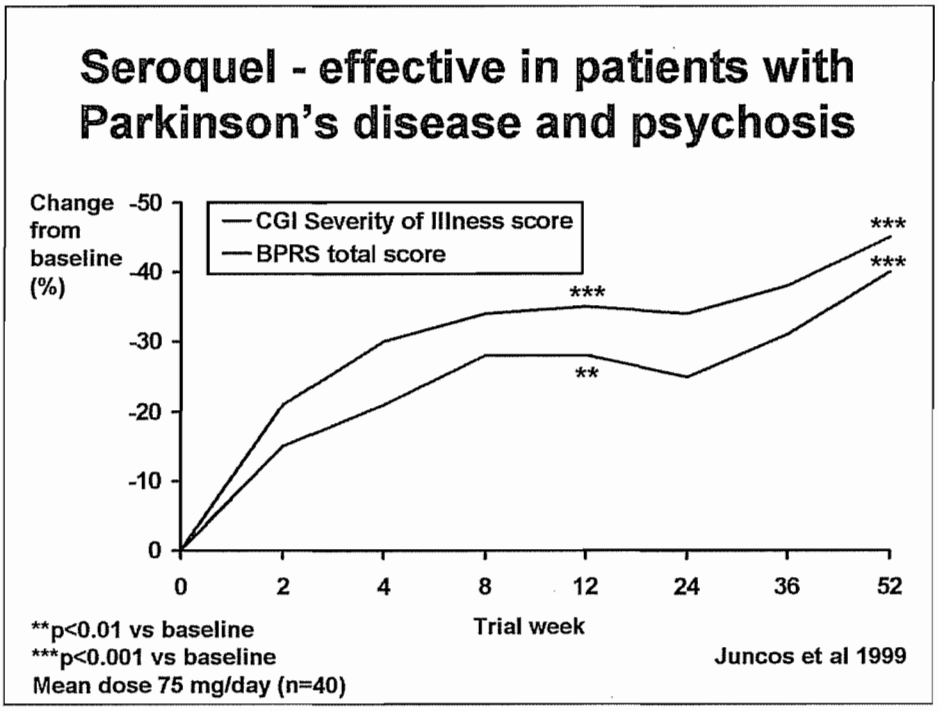
- Results from this 52-week, open-label, multicentre trial involving 184 elderly patients with psychosis showed that, at a median dose of 138 mg/day, Seroquel was effective at all timepoints. Patients had a mean age of 76 years (range 54-94 years) and 53% of the patients were female[1]

- During the study, there was a progressive improvement from baseline in the Brief Psychiatric Rating Scale (BPRS) total score. Improvements from baseline in BPRS total score were significant at all timepoints sampled ($p<0.0001$ vs baseline) [1]

- The median duration of treatment for all patients was 348 days (range 2-428 days) [1]

Reference

1. Tariot et al. *Clin Ther* 2000; 22: 1068-1084.



Seroquel - effective in patients with Parkinson's disease and psychosis

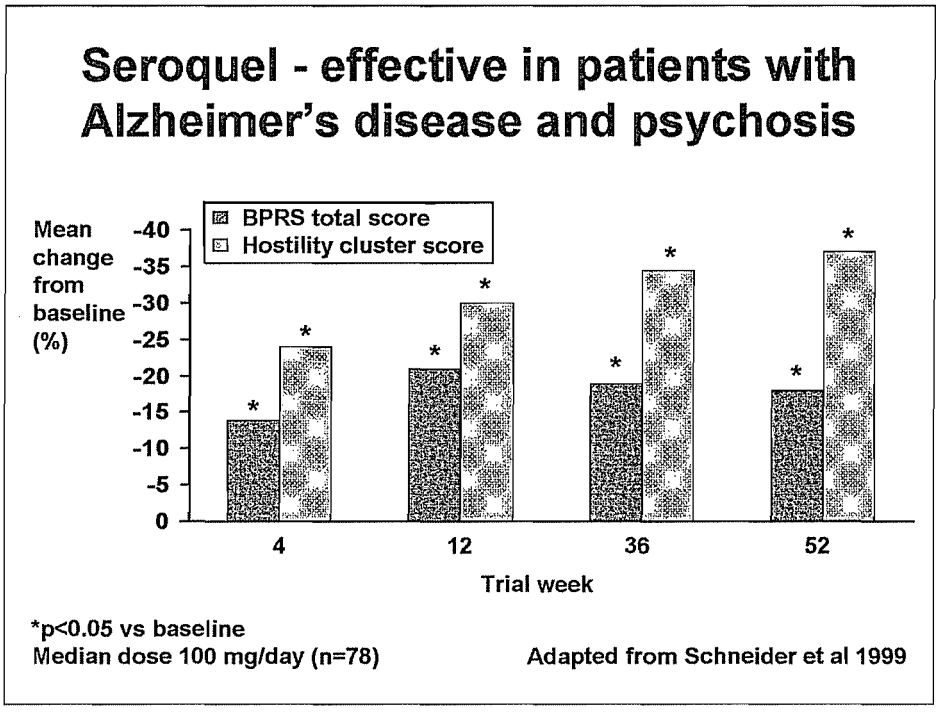
- A subset analysis[1] was carried out on 40 elderly psychotic patients diagnosed with advanced Parkinson's disease (PD) who participated in a 52-week, open-label multicentre trial of Seroquel in elderly psychotic patients (n=184).[2] The patients in the PD subset ranged in age from 54 to 89 years and 45% of the study population were female[1]

- Patients were flexibly dosed, starting with a 25 mg dose (qd or bid). The dose was then increased by 25-50 mg increments every 1-3 days up to 800 mg/day depending on clinical response and tolerability. The mean dose was 75 mg/day[1]

- Seroquel produced continuous improvements in psychotic symptoms up to 12 weeks as assessed by improvements (mean % change) from baseline in the Brief Psychiatric Rating Scale (BPRS) total score and Clinical Global Impression (CGI) Severity of Illness score. Improvements in the BPRS total score were significant at Week 12 ($p<0.0001$), as were improvements in the CGI score ($p=0.0033$). This clinical improvement was subsequently maintained over the 52 weeks[1]

References

1. Juncos J et al. Poster presented at the American Psychiatric Association Annual Meeting, Washington DC, 1999.
2. Tariot P et al. Poster presented at the American Psychiatric Association Annual Meeting, Washington DC, 1999.



Seroquel – effective in patients with Alzheimer's disease and psychosis

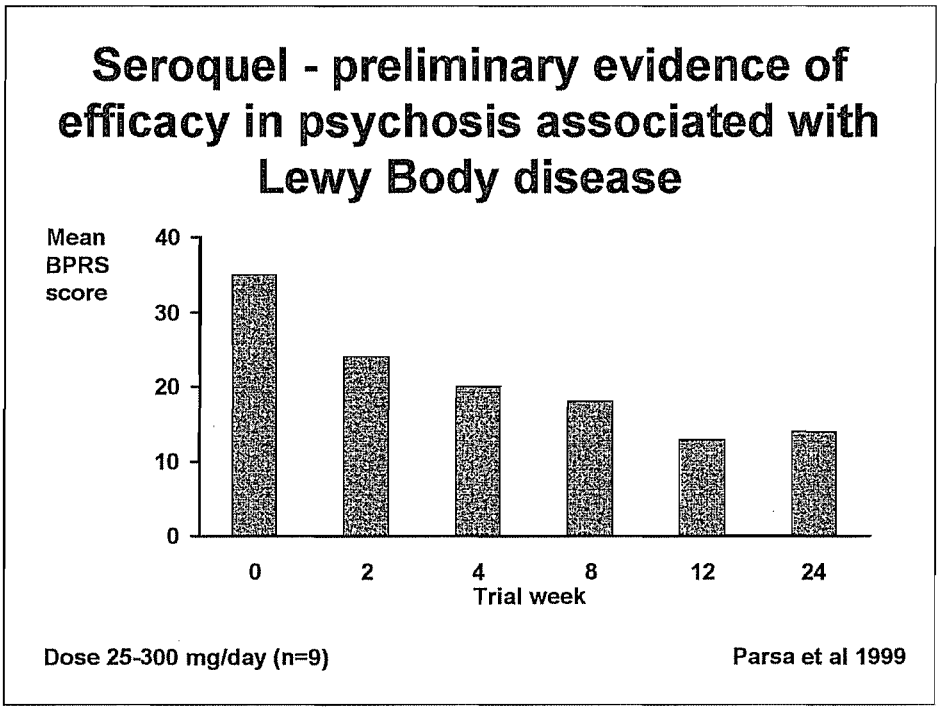
- A subset analysis[1] was carried out data from 78 elderly psychotic patients diagnosed with Alzheimer's disease (AD) who had participated in a 52-week, open-label, multicentre trial of Seroquel in elderly psychotic patients (n=184)[2]

- The patients in this AD subset ranged in age from 62 to 92 years (mean 78 years) and 54% of the study population were female. The median Seroquel dose received by these patients was 100 mg/day[1]

- Significant ($p<0.05$) improvements from baseline scores in BPRS Total and Hostility Cluster scores were noted for Alzheimer's patients treated with Seroquel at all time points analysed (Weeks 2, 4, 8, 12, 24, 36, 52 and LOCF, excluding Week 2 for Factor V and Weeks 2 and 12 for Hostility Item)[1]

References

1. Schneider L et al. Poster presented at the American Psychiatric Association Annual Meeting, Washington DC, 1999.
2. Tariot et al. *Clin Ther* 2000; 22: 1068-1084.

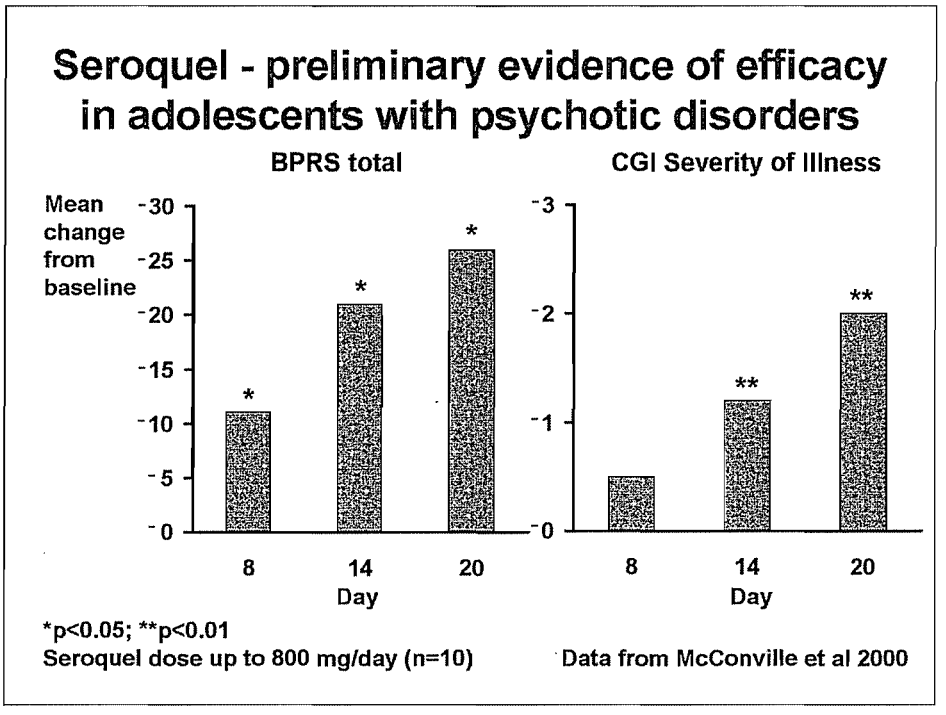


Seroquel - preliminary evidence of efficacy in psychosis associated with Lewy Body disease

- A 24-week, open-label trial evaluated the efficacy and tolerability of Seroquel in 9 elderly psychotic patients with Parkinson's disease and dementia who met the criteria for Lewy Body disease. The patients' mean age was 76 years (range 63-88 years) and 56% of the study population were female[1]
- Seroquel was flexibly dosed (25-300 mg/day) and the mean peak dose administered was 107 mg/day[1]
- All 9 patients with Lewy Body disease and psychosis who received Seroquel showed marked improvements in psychosis, as assessed by improvements in the Brief Psychiatric Rating Scale (BPRS) scores from baseline to endpoint[1]
- Preliminary data suggest that Seroquel is effective in improving psychosis in patients with Parkinson's disease and dementia who meet the criteria for Lewy Body disease[1]

Reference

1. Parsa MA et al. Poster presented at the World Psychiatric Association Annual Meeting, Hamburg, 1999.



Seroquel – preliminary evidence of efficacy in adolescents with psychotic disorders

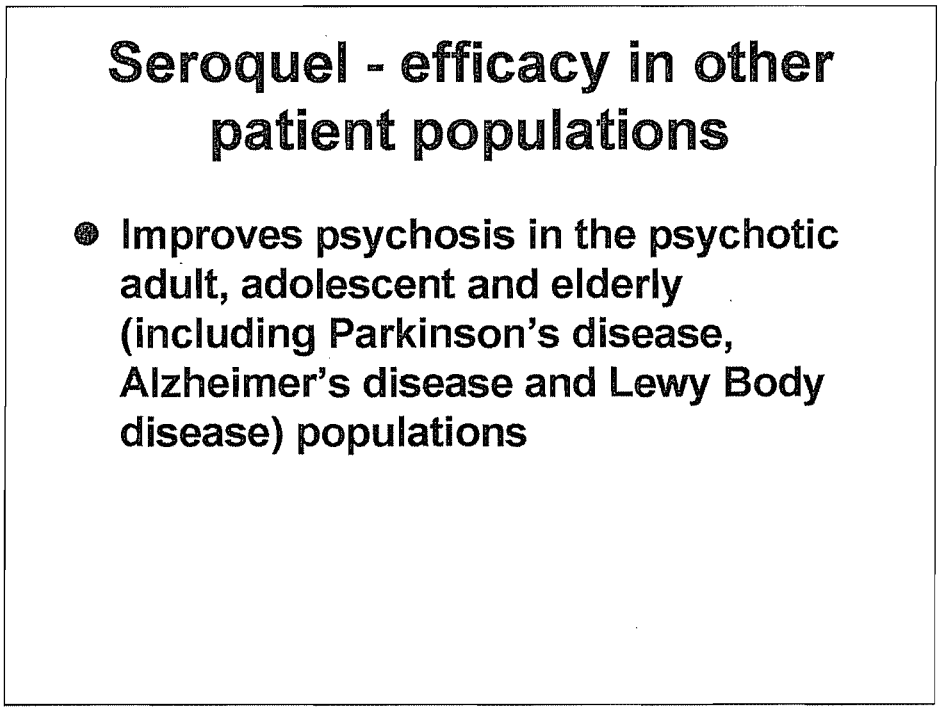
- These preliminary data are from an open-label, 23-day, dose-escalation trial. Patients discontinued all other antipsychotic treatment on Day 1 and started Seroquel 25 mg bid on Day 3, which was increased in a stepwise manner over the following 18 days to reach 400 mg bid on Day 21. A final dose of 400 mg was given on the morning of Day 23. Patients who were unable to tolerate this titration schedule were given up to 6 extra days to reach the maximum dose[1]

- The study evaluated 10 patients. Their mean age was 13.6 years (range 12.3-15.9 years) and 50% of the population were female. Their diagnoses were either schizoaffective disorder (n=7) or bipolar disorder with psychotic features (n=3)[1]

- The slide details improvement in the Brief Psychiatric Rating Scale (BPRS) total score and Clinical Global Impression (CGI) Severity of Illness score during the trial[1]

Reference

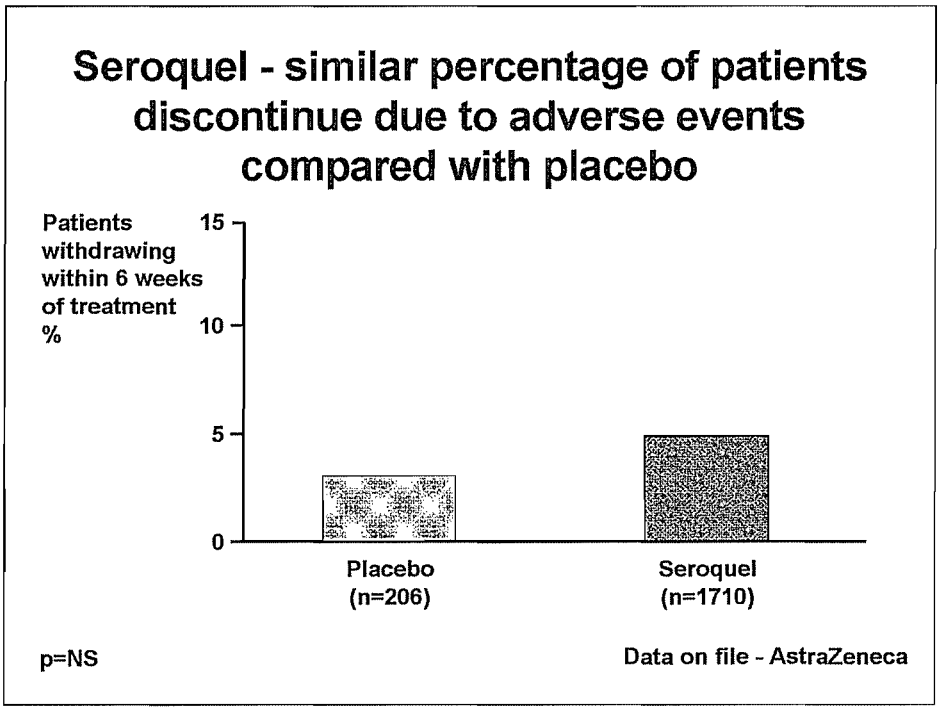
1. McConville BJ et al. *J Clin Psychiatry* 2000; 61: 252-260.



Seroquel - efficacy in other patient populations

Summary slide

Safety and tolerability in schizophrenia

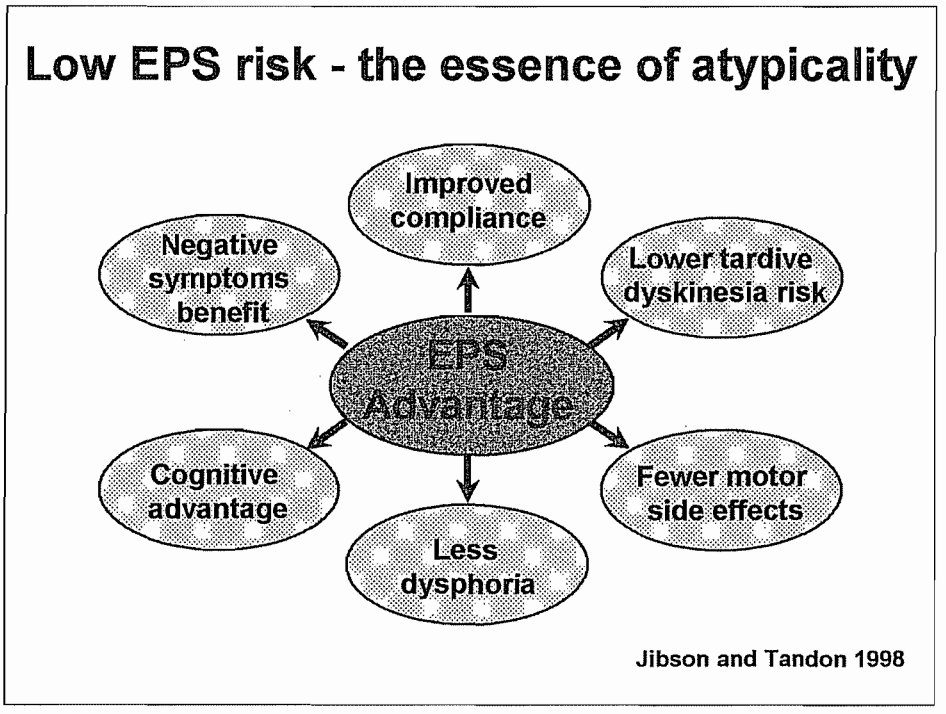


Seroquel - similar percentage of patients discontinue due to adverse events compared with placebo

- In an analysis of Phase II/III controlled trials of Seroquel, the percentage of patients withdrawn from Seroquel treatment (5.0%) was similar to that with placebo (2.9%; p=NS)[1]
- 1710 patients received Seroquel and 206 placebo[1]

Reference

1. Data on file – AstraZeneca.



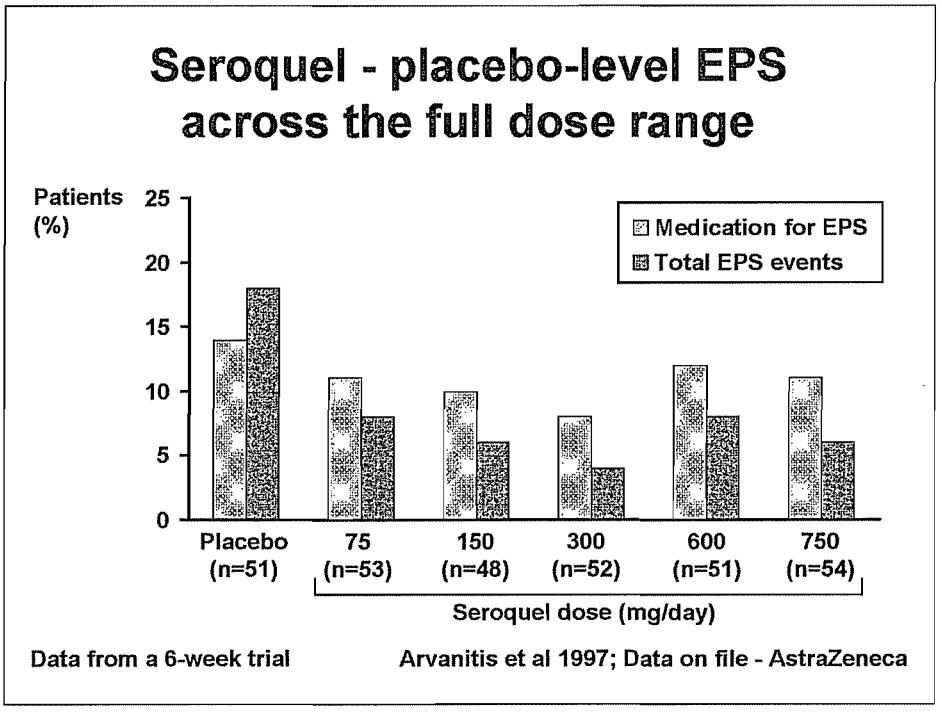
Low EPS risk – the essence of atypicality

- As an atypical antipsychotic, Seroquel is characterised by being at least as effective as standard antipsychotics with a much lower risk of extrapyramidal symptoms (EPS)

- This relative lack of EPS with atypical antipsychotics may have a favourable effect on cognition, compliance and patients' subjective experience of treatment

Reference:

Jibson MD and Tandon R. *J Psychiatr Res* 1998; 32:215-228.

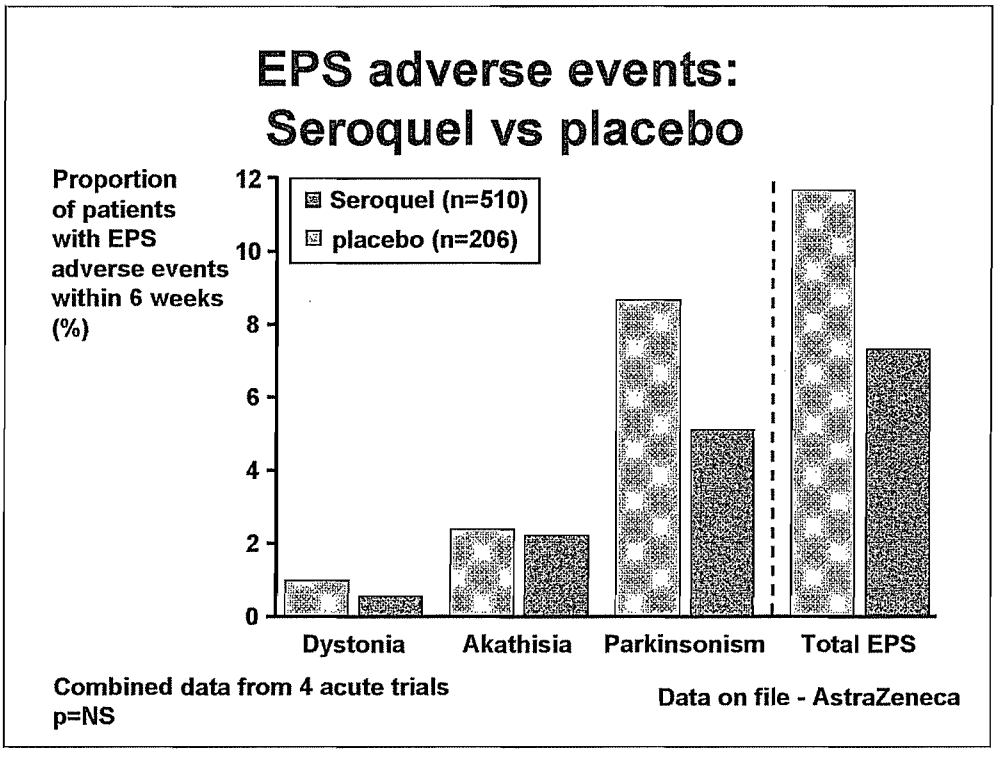


Seroquel – placebo-level EPS across the full dose range

- These data are from a 6-week randomised, double blind, placebo-controlled trial of Seroquel in patients with schizophrenia (361 patients were randomised to treatment)[1]
- Evaluable patients for extrapyramidal symptoms (EPS) and anticholinergic medication are: (Seroquel 75 mg/day [n=53], 150 mg/day [n=48], 300 mg/day [n=52], 600 mg/day [n=51] or 750 mg/day [n=54]) or placebo [n=51][1,2]
- These data show the proportion of patients reporting one or more EPS adverse events (akathisia, parkinsonism or dystonia)[1] and those requiring benztropine during the trial[2]

References

1. Arvanitis LA et al. *Biol Psychiatry* 1997; 42: 233-246.
2. Data on file – AstraZeneca.

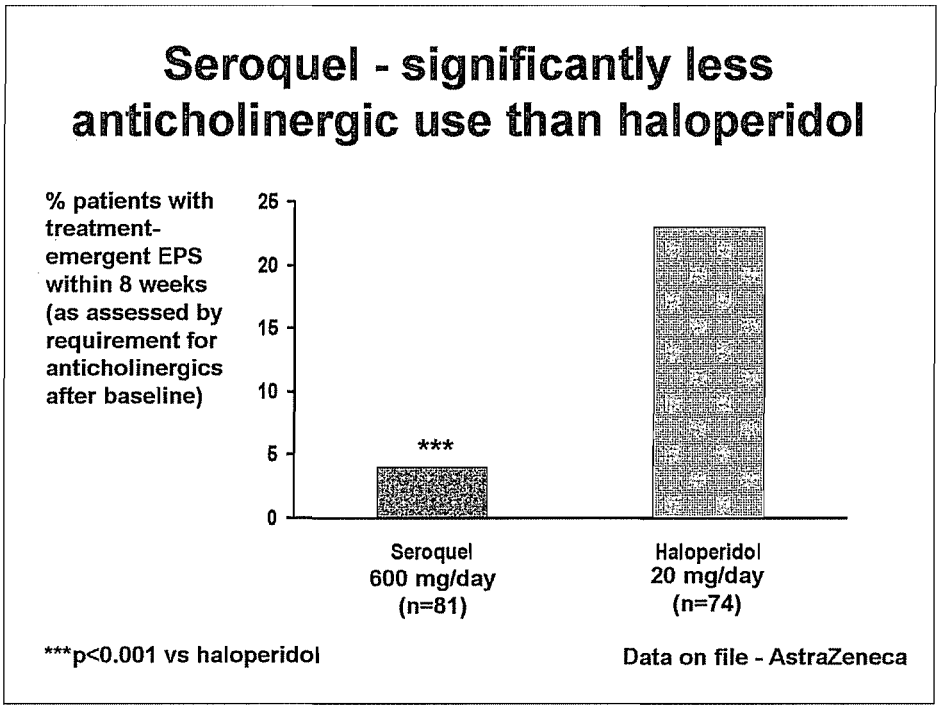


EPS adverse events: Seroquel vs placebo

- These data are from four double-blind, placebo controlled studies (4[1], 6[2], 8[3] and 13[4]) comparing Seroquel with placebo in patients with schizophrenia in the short-term (3 weeks for study 4, 6 weeks for studies 6, 8 and 13)
- In study 4, patients (n=12) were randomised to treatment with either placebo or increasing doses of Seroquel (25-250 mg/day). Doses were increased in increments of 25-50 mg until the final dose of 250 mg/day was reached[1]
- In study 6, patients (n=109) were randomised to treatment with either placebo or Seroquel (75-750 mg/day). Patients received Seroquel 58-526 mg/day and the mean daily dose administered was 307 mg[2]
- In study 8, patients (n=286) were randomised to treatment with placebo, low-dose Seroquel (≤250 mg/day) or high-dose Seroquel (≤750 mg/day). The low dose group received a mean dose of 209 mg/day Seroquel (range 50-267 mg/day), and for those that completed the trial the mean daily dose was 248 mg. The high-dose group of the study received a mean dose of 360 mg/day Seroquel (range 50-566 mg/day). For high-dose Seroquel patients who completed the trial, the mean daily dose was 488 mg[3]
- In study 13, patients (n=361) were randomised to treatment with placebo or fixed dose Seroquel (75 mg/day, 150 mg/day, 300 mg/day, 600 mg/day or 750 mg/day)[4]
- This slide details the combined percentage of total patients from these 4 studies who had acute EPS adverse events during the trials (Seroquel n=510, placebo n=206)[5]
- The Total EPS group = combined data from the three subgroups presented in the slide. The Parkinsonism subgroup = hypertonia, neck rigidity, cogwheel rigidity, tremor, akinesia, hypokinesia and EPS; the akathisia subgroup = akathisia and the dystonia subgroup = dystonia, oculogyric crisis and torticullis[5]
- For this population, significance tests showed there was no difference between Seroquel and placebo in terms of incidence of EPS in the Total EPS data set and in each of the EPS subgroups[5]
- Seroquel has placebo-like EPS levels at doses used in schizophrenia[5]

References

1. Fabre LF et al. *Clin ther* 1995; 17: 366-378.
2. Borison RL et al. *J Clin Psychopharmacol* 1996; 16: 158-169.
3. Small JG et al. *Arch Gen Psychiatry* 1997; 54: 549-557.
4. Arvanitis LA et al. *Biol Psychiatry* 1997; 42: 233-246.
5. Data on file – AstraZeneca.



Seroquel – significantly less EPS than haloperidol

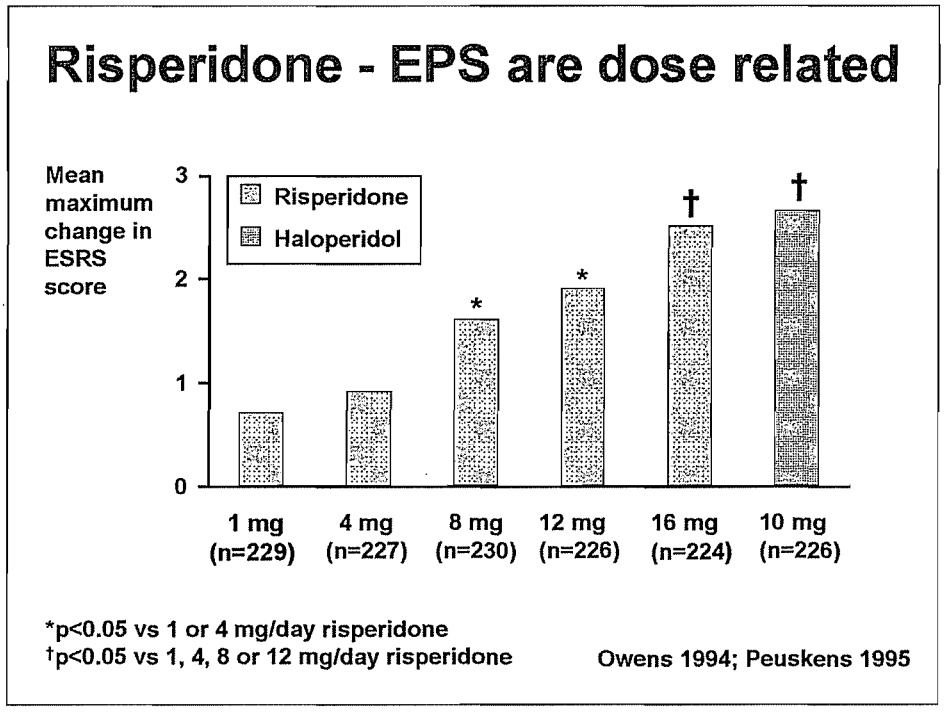
- The PRIZE study (Partial Responders International schiZophrenia Evaluation) compared the efficacy of 8 weeks' Seroquel treatment (600 mg/day) with haloperidol (20 mg/day) in 288 patients who had a history of partial response or non-response to conventional antipyschotics[1]

- After a 4-week run-in period with fluphenazine (20 mg/day), patients with a reduction in Positive and Negative Syndrome Scale (PANSS) total score of <30% and a PANSS positive score of ≥15 (ie partial responders) were randomised to treatment with Seroquel or haloperidol

- Patients treated with Seroquel had significantly less treatment-emergent extrapyramidal symptoms (EPS) (as measured by the number of patients requiring anticholinergics after baseline) than those treated with haloperidol: 3 of 81 patients on Seroquel required anticholinergics after baseline compared with 17 of 74 patients on haloperidol ($p<0.001$)[2]

References

1. Emsley RA et al. *Int Clin Psychopharmacol* 2000; 15: 121-131.
2. Data on file – AstraZeneca.

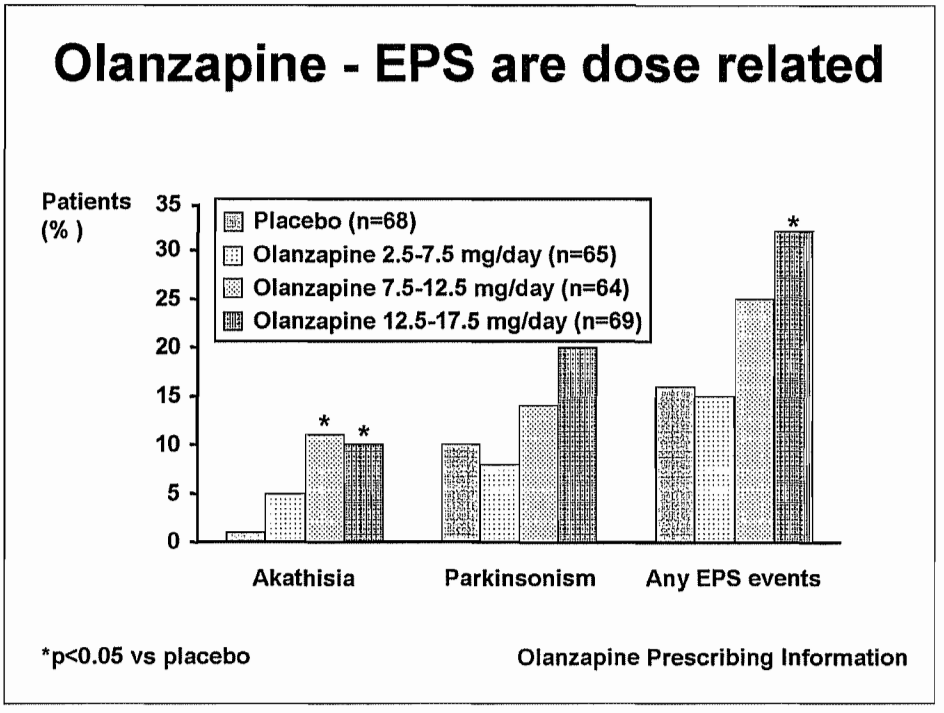


Risperidone – EPS are dose related

- These data are from a multinational, parallel-group, double-blind study of 8 weeks' treatment of risperidone (1-16 mg/day) versus haloperidol 10 mg/day in patients with chronic schizophrenia[1]
- EPS were assessed using the Extrapyramidal Symptom Rating Scale (ESRS)[1]
- EPS with risperidone were evaluated in 1136 patients (1 mg/day, n=229; 4 mg/day, n=227; 8 mg/day, n=230; 12 mg/day, n=226; 16 mg/day, n=224) and EPS with haloperidol 10 mg/day were evaluated in 226 patients[2]

References

1. Owens DGC. *J Clin Psychiatry* 1994; 55 (Suppl 5): 29-35.
2. Peuskens J et al. *Br J Psychiatry* 1995; 166: 712-726.

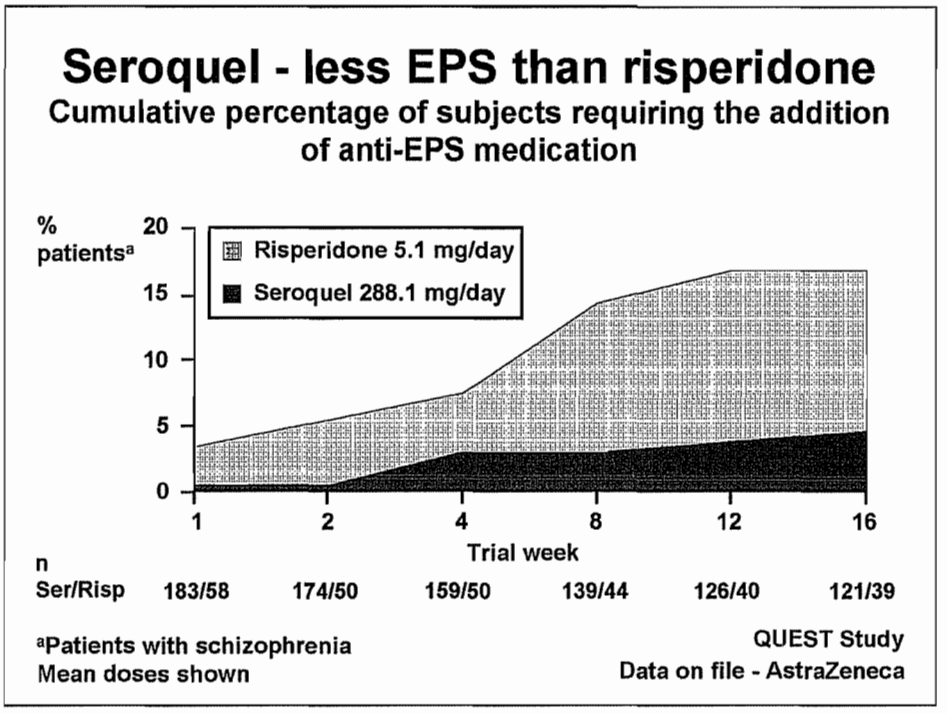


Olanzapine – EPS are dose related

- These treatment-emergent extrapyramidal symptoms (EPS) data were obtained during the acute phase of a fixed dose range placebo-controlled clinical trial[1]
- The fixed dose ranges of olanzapine and the numbers of evaluable patients within these groupings are: (2.5-7.5 mg/day [n=65], 7.5-12.5 mg/day [n=64] and 12.5-17.5 mg/day [n=69]), with placebo (n=68)[1]
- The average daily dose of olanzapine for the treatment of schizophrenia in the UK is 16 mg/day[2]
- Significant differences in treatment-emergent EPS compared with placebo were seen at dosages commonly used in clinical practice

References

1. Olanzapine Prescribing Information, 1998.
2. UK Medicare, 1999.

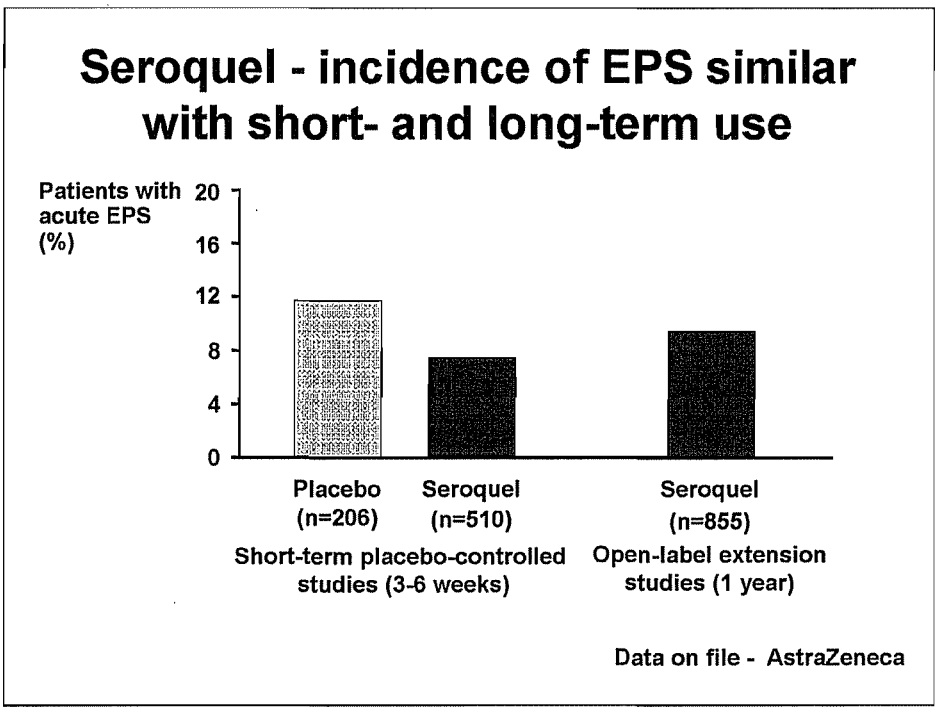


Seroquel – less EPS than risperidone

- QUEST (**Q**uetiapine Experience with **S**afety and **T**olerability) was a 16-week, open-label trial comparing Seroquel and risperidone in 751 adult outpatients with mixed psychotic disorders[1]
- This slide presents data from the subanalysis of the schizophrenia cohort within QUEST ([n=251]; Seroquel [n=191] and risperidone [n=60]), where patients received Seroquel (mean dose 288.1 mg/day) or risperidone (mean dose 5.1 mg/day[2])
- This slide details the cumulative percentage of patients who received adjunctive therapy for extrapyramidal symptoms (EPS) during the 16-week trial. The number of patients in each treatment group who were evaluable for this parameter are: Week 1: 183 Seroquel/58 risperidone; Week 2: 174/50; Week 4: 159/50; Week 8: 139/44; Week 12: 126/40; Week 16: 121/39[2]
- Approximately half of the patients beginning the trial reported baseline EPS (Seroquel 59.7% [n=114/191]; risperidone 51.7% [n=31/60])[2]

References

1. Reinstein M et al. Poster presented at the American Psychiatric Association Annual Meeting, Washington DC, 1999.
2. Data on file – AstraZeneca.



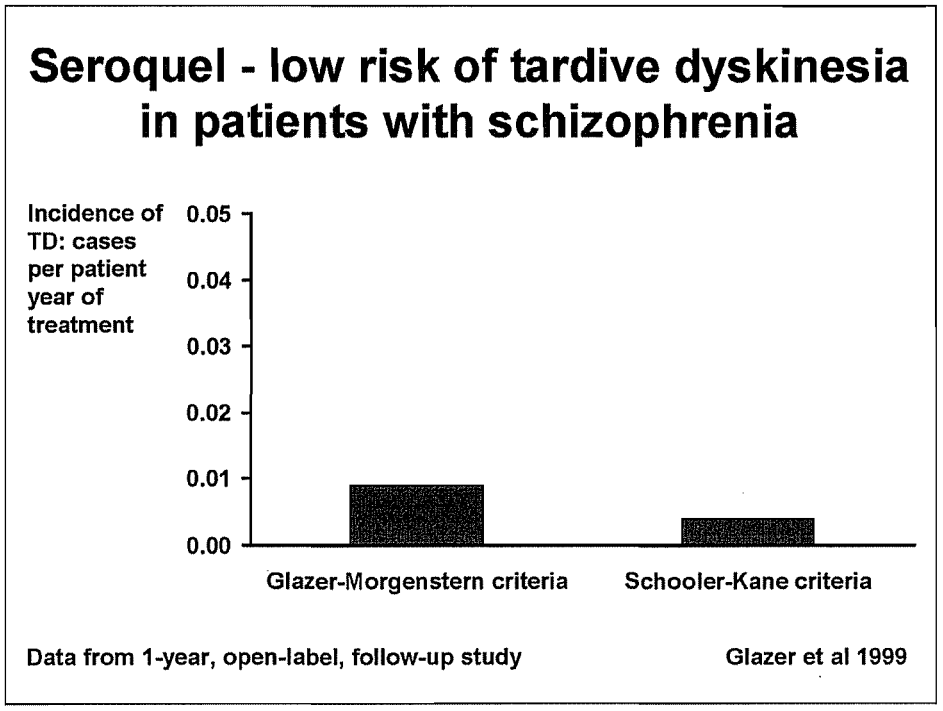
Seroquel – incidence of EPS similar with short- and long-term use

- The two left-hand columns show data[1] from four short-term double blind, placebo-controlled trials (6-week[2,3,4] and 3-week[5]) in patients with schizophrenia who received Seroquel 75-750 mg/day

- An open-label extension (OLE) trial[6] has evaluated the long-term (52-week) safety of Seroquel in 855 patients with schizophrenia. Patients were recruited directly after completing at least 2 weeks of randomised treatment (Seroquel, haloperidol or placebo) in one of three short-term trials. In this OLE trial patients could receive up to 800 mg/day Seroquel on a flexible-dose basis, although the mean dose administered was 490 mg/day

References

1. Data on file – AstraZeneca.
2. Arvanitis LA et al. *Biol Psychiatry* 1997; 42: 233-246.
3. Borison RL et al. *J Clin Psychopharmacol* 1996; 16: 158-169.
4. Small JG et al. *Arch Gen Psychiatry* 1997; 54: 549-557.
5. Fabre LF et al. *Clin Ther* 1995; 17: 366-378.
6. Data on file – AstraZeneca.



Seroquel – low risk of tardive dyskinesia in patients with schizophrenia

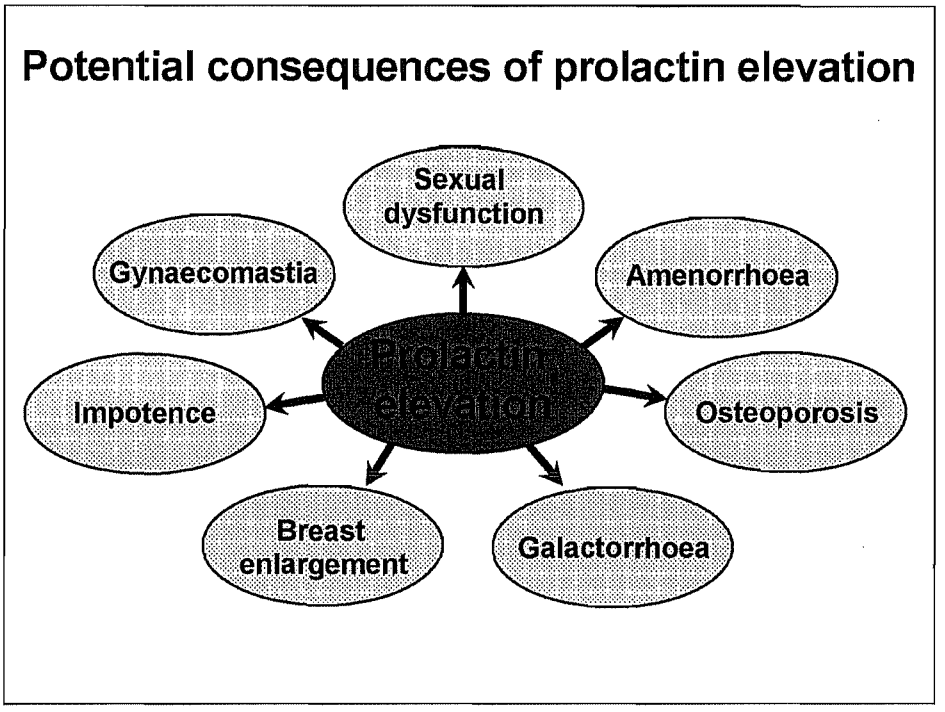
- It is thought that there is an association between extrapyramidal symptoms (EPS) and the development of tardive dyskinesia (TD). Atypical antipsychotics that have a minimal propensity to cause EPS, such as Seroquel, should be therefore less likely to be associated with TD

- Data on TD have been summarised from 3 Phase III Seroquel studies (6-week double-blind phases followed by 2-year+ open-label extensions) involving 301 patients aged 18-65 years with schizophrenia[1]

- Abnormal Involuntary Movement Score (AIMS) assessments, analysed using both Glazer-Morgenstern and Schooler-Kane criteria, showed that Seroquel was associated with a very low risk of TD: 0.009 and 0.004 cases per patient year, respectively

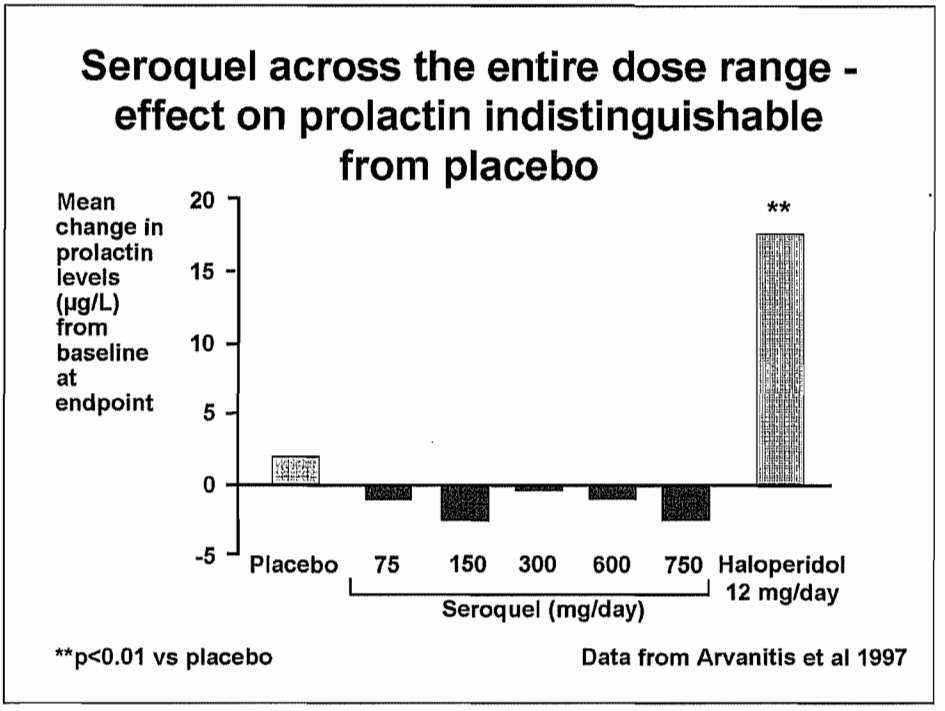
Reference

1. Glazer WM et al. Poster presented at the Annual Meeting of the American College of Neuropsychopharmacology, Acapulco, 1999.



Potential consequences of prolactin elevation

Conventional antipsychotics increase serum prolactin through blockade of the inhibitory effect of dopamine on prolactin release from the pituitary. This may lead to a range of symptoms, including amenorrhoea, galactorrhoea, breast enlargement and osteoporosis in women, and impotence, gynaecomastia and occasional galactorrhoea in men. Sexual dysfunction, including alterations in the quality of orgasm and erectile or ejaculatory dysfunction can occur in up to 60% of patients on standard antipsychotics.



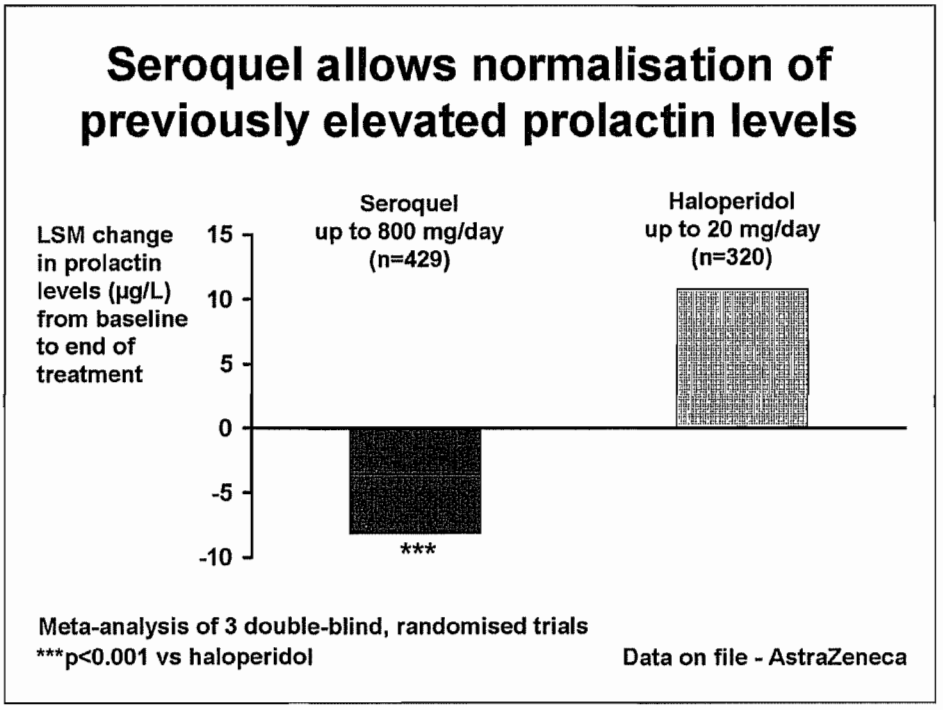
Seroquel across the entire dose range - effect on prolactin indistinguishable from placebo

- These data are from a 6-week randomised, double-blind, placebo-controlled trial of Seroquel 75-750 mg/day in patients with schizophrenia (361 patients were randomised to treatment)[1]

- The bar chart shows the mean change in prolactin from baseline at endpoint. Evaluable patients: (Seroquel 75 mg/day [n=19], 150 mg/day [n=25], 300 mg/day [n=31], 600 mg/day [n=28] or 750 mg/day [n=28] mg/day), haloperidol (12 mg/day [n=24]) or placebo [n=19]

Reference

1. Arvanitis LA et al. *Biol Psychiatry* 1997; 42: 233-246.

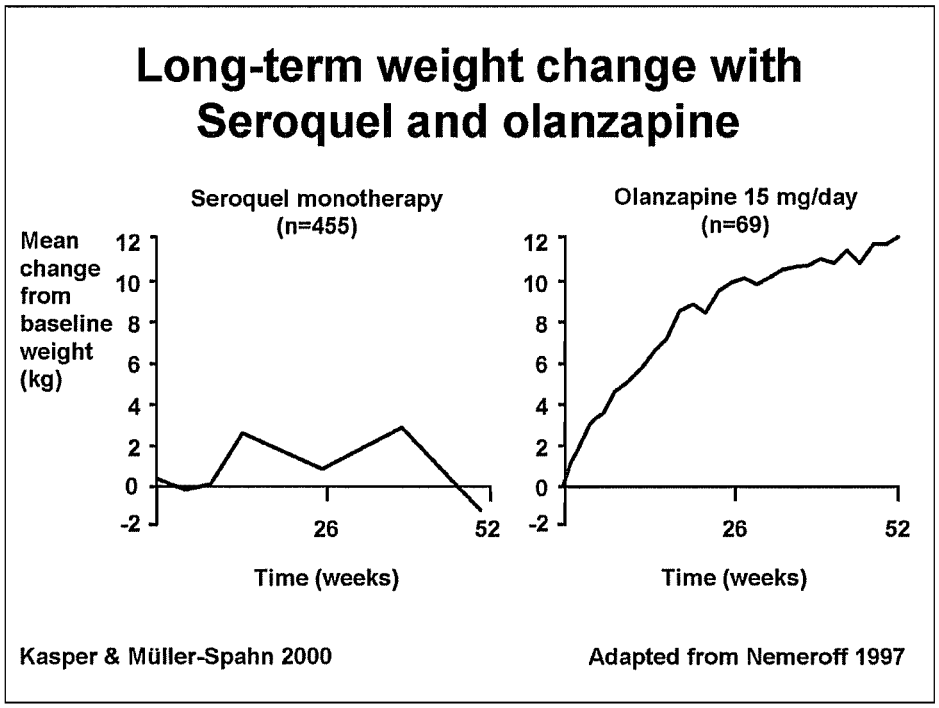


Seroquel allows normalisation of previously elevated prolactin levels

- This is a meta-analysis[1] from three double-blind studies (6-week[2,3] and 8-week, in partial responders[4]) in which patients with schizophrenia received Seroquel (up to 800 mg/day; n=429) or haloperidol (up to 20 mg/day; n=320). These data are from a last value carried forward analysis

References

1. Data on file – AstraZeneca.
2. Arvanitis LA et al. *Biol Psychiatry* 1997; 42: 233-246.
3. Copolov DL et al. *Psychol Med* 2000; 30: 95-105.
4. Emsley RA et al. *Int Clin Psychopharmacol* 2000; 15: 121-131.



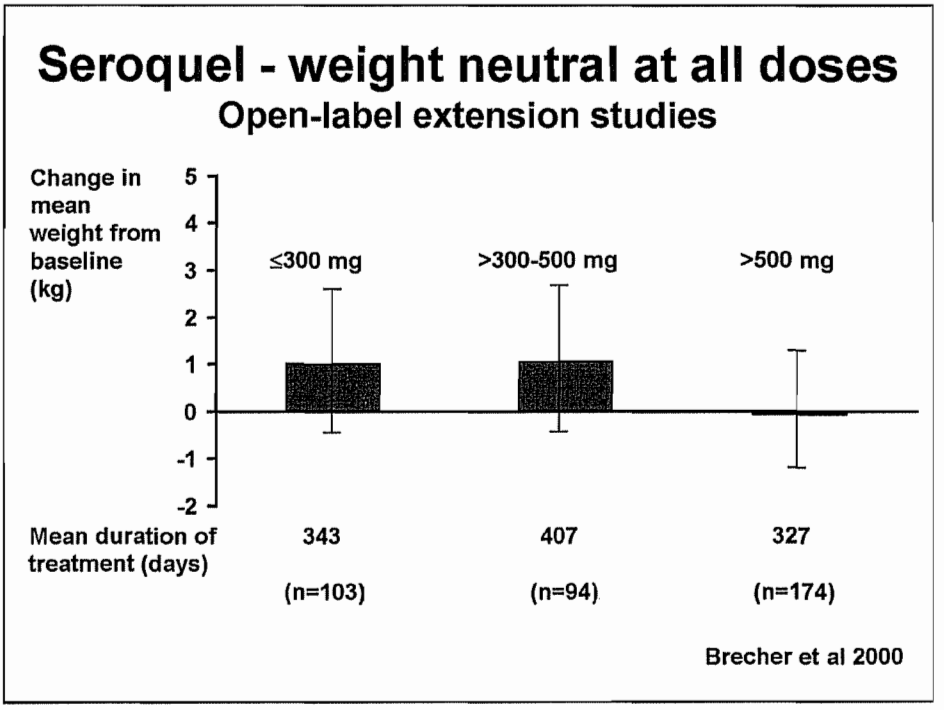
Long-term weight change with Seroquel and olanzapine

- The left-hand graph shows changes in weight observed with seroquel monotherapy during controlled, uncontrolled and open-label extension trials (n=455) over 52 weeks in patients with schizophrenia.[1] Patients received a mean dose of quetiapine 475 mg/day at completion of the trial (156 weeks)[2]

- The right-hand graph shows weight changes observed during a maintenance trial of olanzapine. In this trial, 69 patients received 15 mg/day olanzapine[3]

References

1. Kasper S and Müller-Spahn F. *Exp Opin Pharmacother* 2000; 1: 783-801.
2. Jones AM et al. Poster presented at the Winter Workshop, Davos, 2000.
3. Nemeroff CB. *J Clin Psychiatry* 1997; 58 (Suppl 10): 45-49.



Seroquel – weight neutral at all doses

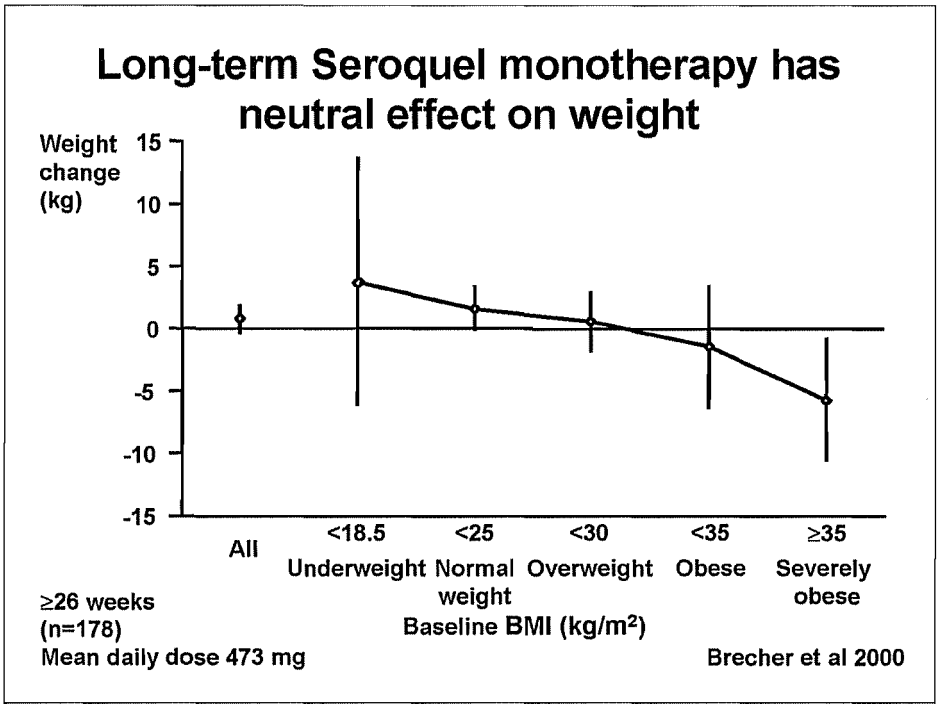
- Study 51 was an open-label extension study of Seroquel in patients who had participated in Phase IIIb clinical trials (approximately 500 patients entered the trial).[1] These data are from a subset of patients with schizophrenia who received Seroquel up to 800 mg/day in Study 51[1]

- For each dose group, the change in mean weight from baseline at endpoint presented in this slide was obtained from the same cohort of patients.[1] Endpoint was defined as the final weight value that was taken for each patient.[1] Dose groups were calculated using the modal dose value for the time period when the last weight value was recorded[1]

- It can be seen that the 95% confidence limits for the mean changes in weight from baseline at each dose include 0; therefore Seroquel has a neutral effect on weight at all doses

Reference

1. Brecher et al. *Int J Psych Clin Pract* 2000; 4: 287-291.

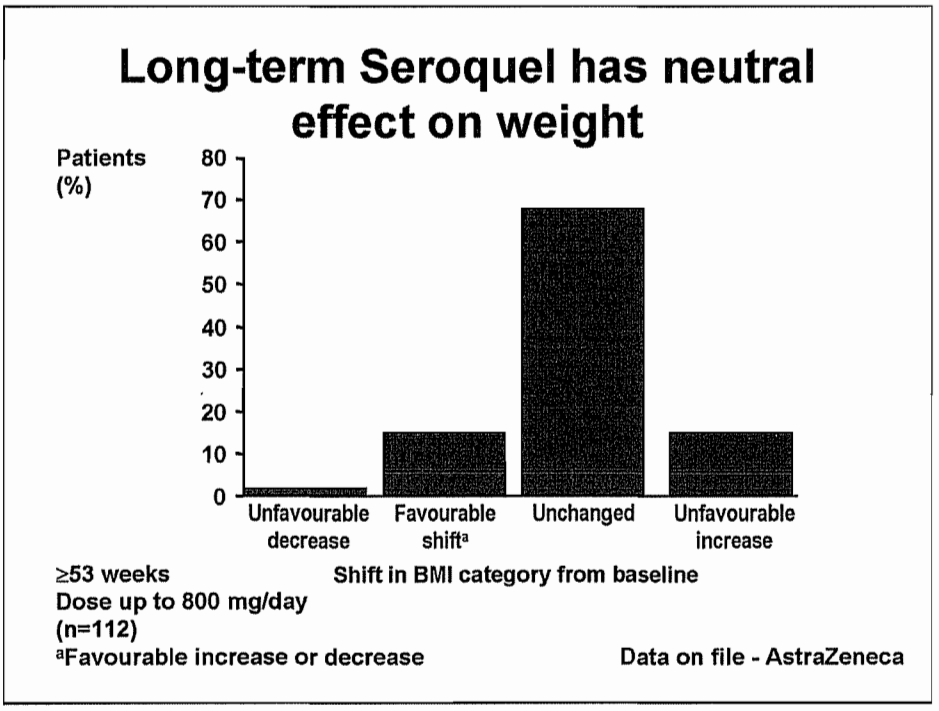


Long-term Seroquel monotherapy has neutral effect on weight

- The slide shows the mean and 95% confidence intervals (CI) change in weight from baseline to endpoint for 178 patients enrolled in an open-label extension (OLE) study[1]
- All patients had a diagnosis of schizophrenia and had completed at least 4 weeks of Seroquel treatment in one of six Phase IIIb clinical trials before entering the OLE
- Seroquel was flexibly dosed up to 800 mg/day. The mean dose was 473 mg/day. The mean duration of OLE Seroquel monotherapy was 18.6 months
- Patients were stratified into five categories according to their BMI at baseline.[2] Seroquel monotherapy was weight-neutral across all the categories (95% CI includes 0), except for the most severely obese group (BMI of 35 or more), in whom the mean weight decreased slightly

References

1. Brecher et al. *Int J Psych Clin Pract* 2000; 4: 287-291.
2. National Heart, Lung and Blood Institute. Clinical Guidelines on the identification, evaluation and treatment of overweight and obesity in adults – executive summary. Bethesda, MD: National Institute of Health; June 1998.

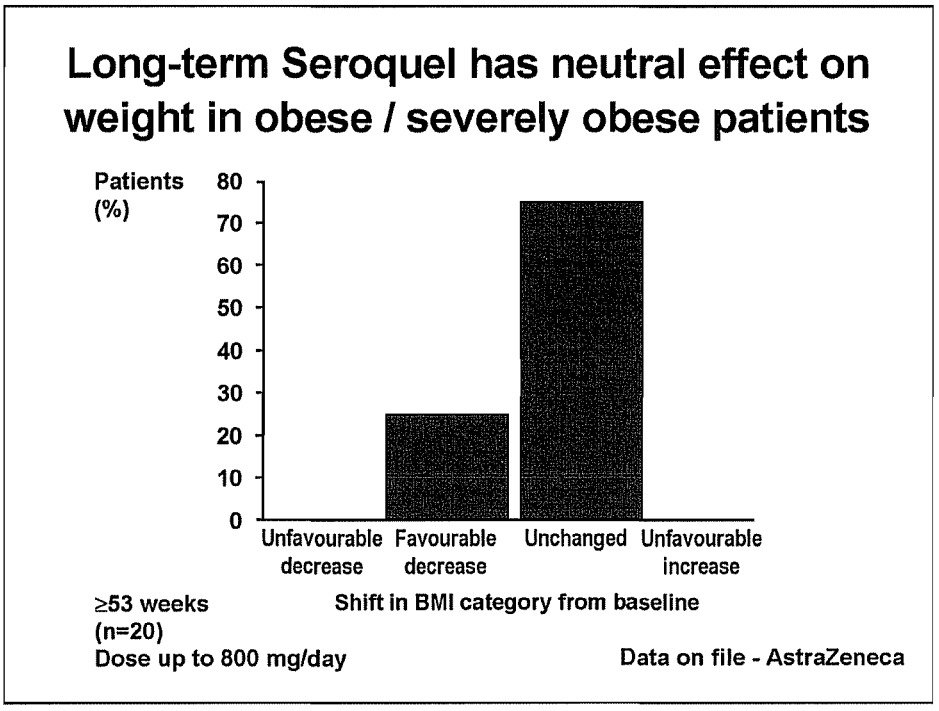


Long-term Seroquel has neutral effect on weight

- Patients who had completed at least 4 weeks of treatment in one of six Seroquel Phase IIIb trials could participate in an open-label extension study (OLE)
- All patients had schizophrenia. Seroquel was flexibly dosed up to a maximum of 800 mg/day
- The slide shows data from 112 patients who completed at least 53 weeks of OLE Seroquel monotherapy[1]
- Patients were stratified according to their BMI at baseline into five categories: underweight (BMI <18.5); normal weight (BMI 18.5-25); overweight (BMI 25-30); obese (BMI 30-40); and severely obese (BMI 40 or more)[2]
- The majority of patients did not change BMI category during Seroquel monotherapy

References

1. Data on File – AstraZeneca.
2. National Heart, Lung and Blood Institute. Clinical Guidelines on the identification, evaluation and treatment of overweight and obesity in adults – executive summary. Bethesda, Md: National Institute of Health; June 1998.



Long-term Seroquel has neutral effect on weight in obese / severely obese patients

- Patients who had completed at least 4 weeks of treatment in one of six Seroquel Phase IIIb trials could participate in an open-label extension study (OLE)
- All patients had schizophrenia. Seroquel was flexibly dosed up to a maximum of 800 mg/day
- The slide shows data from 20 patients who completed at least 53 weeks of OLE Seroquel monotherapy, and who were obese or severely obese (BMI of 30 or more) at the beginning of treatment[1]
- Patients were stratified according to their BMI at baseline into five categories: underweight (BMI <18.5); normal weight (BMI 18.5-25); overweight (BMI 25-30); obese (BMI 30-40); and severely obese (BMI 40 or more)[2]
- Three-quarters of obese or severely obese patients did not change BMI category during Seroquel monotherapy. All those who did change showed a favourable decrease in BMI category
- None of the obese or severely obese patients showed an unfavourable change in BMI category during Seroquel treatment
- Patients is the severely obese category cannot show an unfavourable change in BMI

References

1. Data on File – AstraZeneca.
2. National Heart, Lung and Blood Institute. Clinical Guidelines on the identification, evaluation and treatment of overweight and obesity in adults – executive summary. Bethesda, MD: National Institute of Health; June 1998.

Seroquel - no clinically significant effect on cardiac repolarisation (QT interval)

- **Seroquel causes an increase in heart rate (HR) and a shortening of QT interval**
- **Bazett's heart rate correction overestimates QTc interval for drugs which increase heart rate**
- **No dose-related increase in QT interval (corrected for HR) with Seroquel**
- **No potentially clinically significant outliers (QTc >60 msec change from baseline, QTc >500 ms)**

Pfizer Study 54, FDA Psychopharmacological Drug Advisory Committee 19th July 2000

Seroquel – no clinically significant effect on cardiac repolarisation (QT interval)

- Bazett's heart rate correction formula has been conclusively shown to overestimate the effects on cardiac repolarisation (QTc interval) when heart rates are increased[1,2]
- The conclusions presented in the slide are based on data that were considered by the European regulatory authorities[3] and the FDA during the approval process of Seroquel and in the FDA review of Pfizer Study 054
- In addition, these data are now independently confirmed by the Pfizer study 54, which was conducted at the FDA's request.[4] In this study, the effect of Seroquel on the QT interval was examined across a 2 order of magnitude range of plasma concentration in the presence of a potent CYP 450 3A4 metabolic inhibitor. The absence of a dose- (or concentration-) related effect on QTc interval was confirmed for Seroquel. Of the antipsychotic drugs assessed, Seroquel was the only antipsychotic that demonstrated such a clear shortening of the QT interval and no prolongation of the QT interval (appropriately corrected) across a wide plasma concentration range[4] The plasma concentration extended over a 2 order of magnitude range (10^2 to 10^4 ng/ml)

References

1. Karjalainen J et al. *J Am Coll Cardiol* 1994; 23: 1547-1553.
2. Funck-Bentano C and Jaillon P. *Am J Cardiol* 1993; 72: 17B-22B.
3. Mutual Recognition Procedure No. NL/H/156/01-03, Reference Member State: The Netherlands, Assessment report for Seroquel (film-coated tablets containing quetiapine fumarate) August 1999.
4. FDA Background on Zeldox TM (ziprasidone hydrochloride capsules) Pfizer, Inc. Psychopharmacological Drugs Advisory Committee 19 July 2000. Overview Memo by Thomas Laughren, M.D.; Cardio Review, Maryann Gordon, M.D. http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3619b1b.pdf

Effect of antipsychotic drugs on QTc (steady state)

QTc change from baseline (msec)

	Ziprasi-done	Risperi-done	Olanza-pine	Seroquel	Halo-peridol	Thiorid-azine
Baseline correction	15.9	3.6	1.7	5.7	7.1	30.1
Bazett's correction*	20.3	9.1	6.8	14.5	4.7	35.6
FDA-proposed correction	16.5	4.3	2.3	6.9	6.8	30.8
Fridericia correction	15.5	3.0	1.1	4.8	7.3	29.6
Hodges correction	14.9	3.3	2.5	7.5	7.4	28.7
Framingham correction	14.9	3.7	1.6	4.4	6.1	28.5
Linear Baseline correction	14.6	3.3	1.2	3.8	6.3	28.1

*Bazett's has consistently been found to be inaccurate

Funck-Brentano and Jaillon 1993

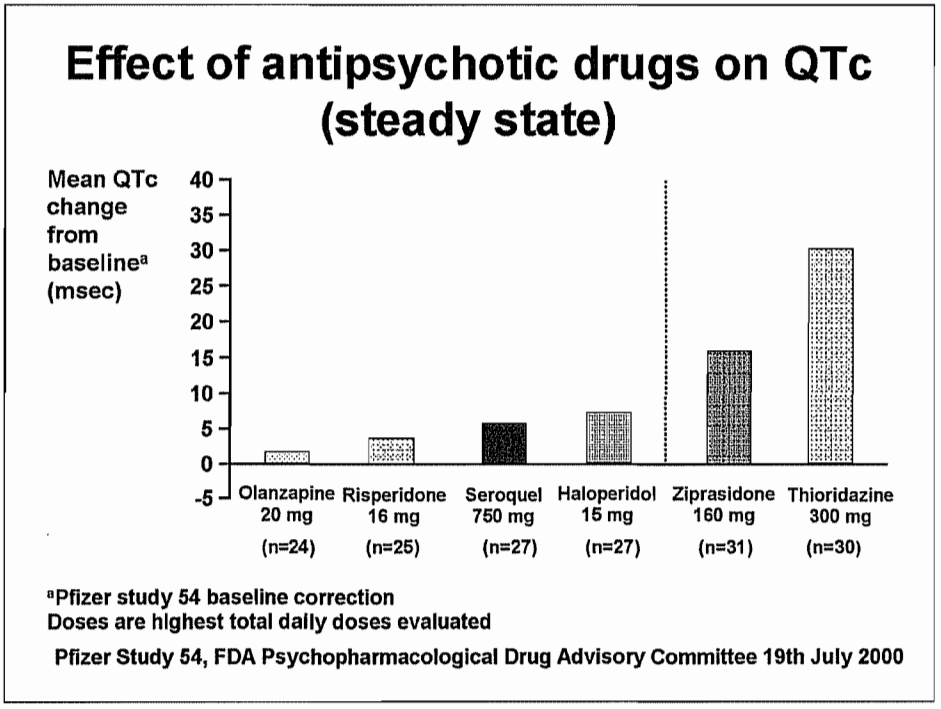
Pfizer Study 54, FDA Psychopharmacological Drug Advisory Committee 19th July 2000

Effect of antipsychotic drugs on QTc (steady state)

- The Pfizer Study 54[1] compared the effects of antipsychotic drugs using 7 formulae including a Baseline heart rate correction formula. This approach was recommended by the FDA in preference to using a 'standard' heart rate correction formula such as Bazett's or Fridericia. The FDA recommended calculating a dataset-specific heart rate correction formula for each drug's baseline dataset. This Baseline heart rate correction formula was, by definition, the best correction formula for the 'baseline' QT interval and heart rate data. The Baseline heart rate correction formula appropriate for each drug's dataset was then applied to the QT intervals during drug treatment. This approach ensures a meaningful comparison across all drugs in spite of their differing effects on heart rates[1]
- Antipsychotics were evaluated over the following dose ranges: ziprasidone (20-80 mg twice-daily); risperidone (1-8 mg twice-daily); olanzapine (5-20 mg once-daily); Seroquel (25-375 mg twice-daily), thioridazine (25-150 mg twice-daily) and haloperidol (2-15 mg once-daily)
- The Bazett's formula has been criticised as it overestimates the QTc interval when heart rates are increased and underestimates it when heart rates are decreased. The Bazett's formula is therefore likely to bias results when comparing drugs that affect heart rate to different extents. This is demonstrated by the data shown on this slide. The effects on QTc interval of the compounds associated with an increase in heart rate (ziprasidone, risperidone, olanzapine, Seroquel and thioridazine) appear largest with the Bazett's formula, while the heart rate lowering effects of haloperidol result in a lower apparent QTc effect with this correction formula than with any of the others[2]
- Haloperidol is considered to have a placebo-like effect, therefore any compound showing a smaller or equivalent change to haloperidol has no clinically significant effect on QTc interval.
- Risperidone, olanzapine and Seroquel showed no effect on appropriately corrected QTc intervals. Use of Bazett's formula is inappropriate due to the dissimilar effects of these drugs on heart rates
- The increases in heart rate with Seroquel are not clinically significant but are sufficient to bias QTc calculations using the Bazett's formula

References:

1. FDA Background on Zeldox TM (ziprasidone hydrochloride capsules) Pfizer, Inc. Psychopharmacological Drugs Advisory Committee 19 July 2000. Advisory Committee Briefing Document. http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3619b1a.pdf
2. Funck-Bentano C and Jaillon P *Am J Cardiol* 1993; 72: 17B-22B.



Effect of antipsychotic drugs on QTc (steady state)

- The Pfizer Study 54[1] compared the effects of antipsychotic drugs using 7 formulae including a Baseline heart rate correction formula. This approach was recommended by the FDA in preference to using a 'standard' heart rate correction formula such as Bazett's or Fridericia. The FDA recommended calculating a dataset-specific heart rate correction formula for each drug's baseline dataset. This Baseline heart rate correction formula was, by definition, the best correction formula for the 'baseline' QT interval and heart rate data. The Baseline heart rate correction formula appropriate for each drug's dataset was then applied to the QT intervals during drug treatment. This approach ensures a meaningful comparison across all drugs in spite of their differing effects on heart rates[1]
- Antipsychotics were evaluated over the following dose ranges: ziprasidone (20-80 mg twice-daily); risperidone (1-8 mg twice-daily); olanzapine (5-20 mg once-daily); Seroquel (25-375 mg twice-daily), thioridazine (25-150 mg twice-daily) and haloperidol (2-15 mg once-daily)
- Thioridazine has received a black box warning in the US for risk of sudden death related to its effects on cardiac repolarisation (QT interval). The warning states that a Pfizer study found that "the mean increase in QTc from baseline for ziprasidone ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine,and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine".[2] Although Seroquel was clearly associated with a decrease in QT interval across a wide plasma concentration range, the effects of Seroquel, risperidone and olanzapine on QTc interval appear to be indistinguishable from each other. The effect of haloperidol on the QTc interval is considered to be equal to that of placebo[1]

Reference

1. FDA Background on Zeldox TM (ziprasidone hydrochloride capsules) Pfizer, Inc. Psychopharmacological Drugs Advisory Committee 19 July 2000. Advisory Committee Briefing Document http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3619b1a.pdf
2. NDA 20-825 Approval letter and labeling http://www.fda.gov/cder/foi/label/2001/20825lbl.pdf

Seroquel - no requirement for cardiac monitoring

- **No statistically significant Seroquel / placebo differences in proportion of patients experiencing potentially important changes in ECG parameters in placebo-controlled trials**
- **Review of post-marketing data (death, sudden death, cardiovascular death, QT prolongation, TdP, syncope) demonstrates no signal of increased risk (as of 30th June 2000)**
- **No requirement for cardiac monitoring with Seroquel**

Seroquel Prescribing Information

Seroquel - no requirement for cardiac monitoring

- The first bullet point is a conclusion based on data that were reviewed by the FDA during their consideration of the New Drug Application for Seroquel, resulting in US approval in September 1997. This conclusion remains in the US label for Seroquel[1]
- The second bullet point summarises data reviews that were considered and agreed by the Dutch College during the Mutual Recognition Review Procedure and were published in a report dated August 1999.[2] The absence of a signal indicating increased risk has been recently reaffirmed

References

1. Seroquel Prescribing Information.
2. Mutual Recognition Procedure No. NL/H/156/01-03, Reference Member State: The Netherlands, Assessment report for Seroquel (film-coated tablets containing quetiapine fumarate) August 1999.

Seroquel - laboratory and safety findings

- **No clinically significant cardiac arrhythmias or alterations in cardiac intervals**
  - **no requirement for ECG monitoring**
- **No clinically significant laboratory findings**
  - **no requirement for blood monitoring**
  - **no requirement for thyroid or liver monitoring**

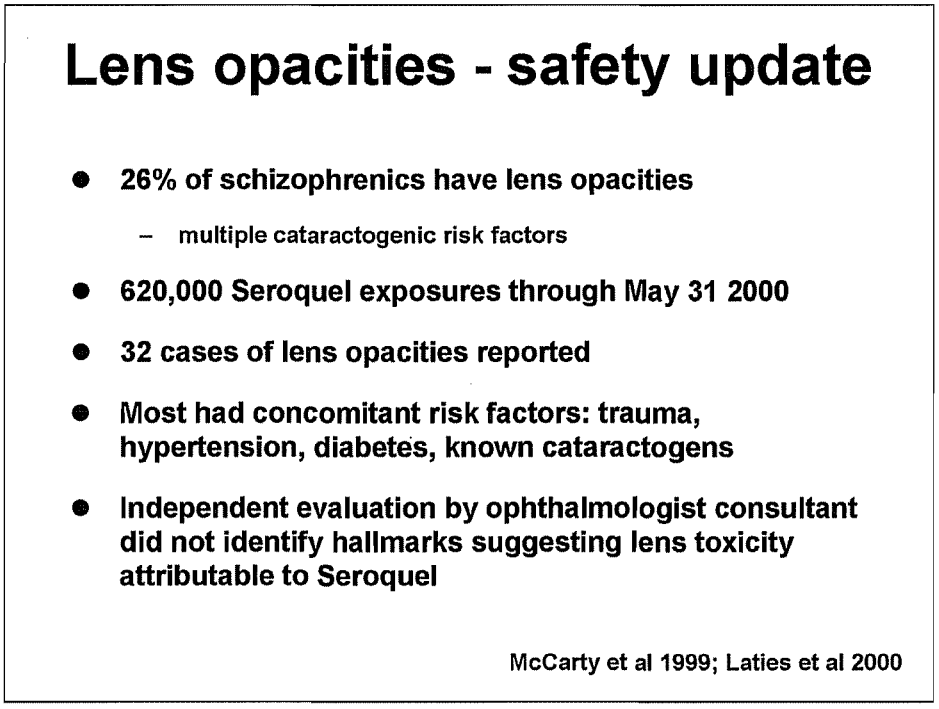
Meats 1997; Data on file - AstraZeneca

Seroquel - laboratory and safety findings

- No requirement for ECG monitoring[1]
- Analysis of phase II/III trials reveal no requirement for monitoring blood pressure or routine monitoring for neutropenia or leucopenia[1]
- A lack of clinically significant laboratory findings means that there is no requirement for thyroid or liver monitoring[2]

References

1. Data on file – AstraZeneca.
2. Meats P et al. *Int J Psych Clin Prac* 1997; 1: 231-239.



Lens Opacities - safety update

- 26% of schizophrenic patients exposed to psychotropic medication from a community mental health service had lens opacities[1]

- Of 620,000 patients in the US (cases reported between September 1997 and 31 July 2000) treated with Seroquel, lens opacities have developed in only 32 patients. These 32 reported cases are a global composite, making the reporting rate even less[2]. The mean age of these cases was 42.6 years; male:female ratio was 1:1.2. Most of the reported cases had risk factors for lens opacities and some cases had cataracts at baseline[2]

- No conclusive evidence of direct linkage between Seroquel and ocular changes has been found[2]

References

1. McCarty CA et al. *Ophthalmology* 1999; 106: 4 683-7.
2. Laties AM et al. Poster presented at the American College of Neuropsychopharmacology Annual Meeting, Puerto Rico, 2000.

Seroquel - tolerability in schizophrenia

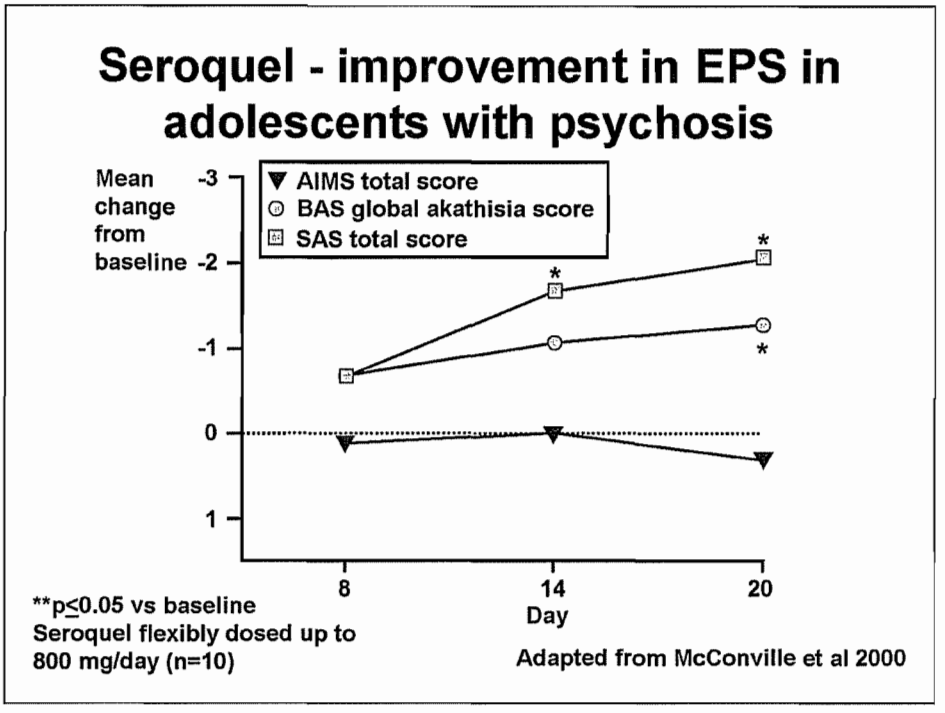
Unique tolerability profile

- Incidence of EPS no different to placebo across the full dose range
- Significantly less EPS than haloperidol, even at higher doses
- Incidence of EPS does not increase with long-term use
- Low risk of tardive dyskinesia
- Low level of sexual dysfunction (prolactin levels equivalent to placebo across all doses)
- Significantly lower prolactin levels than standard antipsychotics
- Weight neutral in long-term monotherapy
- No clinically significant effect on QT interval - ECG monitoring not required

Seroquel - tolerability in schizophrenia

Summary slide

Tolerability in other populations



Seroquel – improvement in EPS in adolescents with psychosis

- These preliminary data are from an open-label, 23-day, dose-escalation trial. Patients discontinued all other antipsychotic treatment on Day 1 and started Seroquel 25 mg bid on Day 3, which was increased in a stepwise manner over the following 18 days to reach 400 mg bid on Day 21. A final dose of 400 mg was given on the morning of Day 23. Patients who were unable to tolerate this titration schedule were given up to 6 extra days to reach the maximum dose[1]

- The study evaluated 10 patients. Their mean age was 13.6 years (range 12.3-15.9 years) and 50% of the population were female. Their diagnoses were either schizoaffective disorder (n=7) or bipolar disorder with psychotic features (n=3)[1]

- The observed mean change from baseline in Abnormal Involuntary Movement Scale (AIMS) total score, Barnes Akathisia Scale (BAS) score and Simpson-Angus Scale (SAS) total score are presented at 3 planned timepoints (n=10; except for baseline SAS assessment where n=9)[1]

Reference

1.McConville BJ et al. *J Clin Psychiatry* 2000; 61: 252-260.

Seroquel - low incidence of EPS adverse events in the elderly

Results from a 52-week, open-label study (n=184)

Adverse event	n (%)
Akathisia	6 (3)
Tremor	6 (3)
Dyskinesia	5 (3)
Abnormal gait	3 (2)
Inco-ordination	2 (1)
Choreoathetosis	1 (1)
Movement disorder	1 (1)
Neck rigidity	1 (1)
Extrapyramidal syndrome	1 (1)
Total	23 (13)

Seroquel median dose 138 mg/day

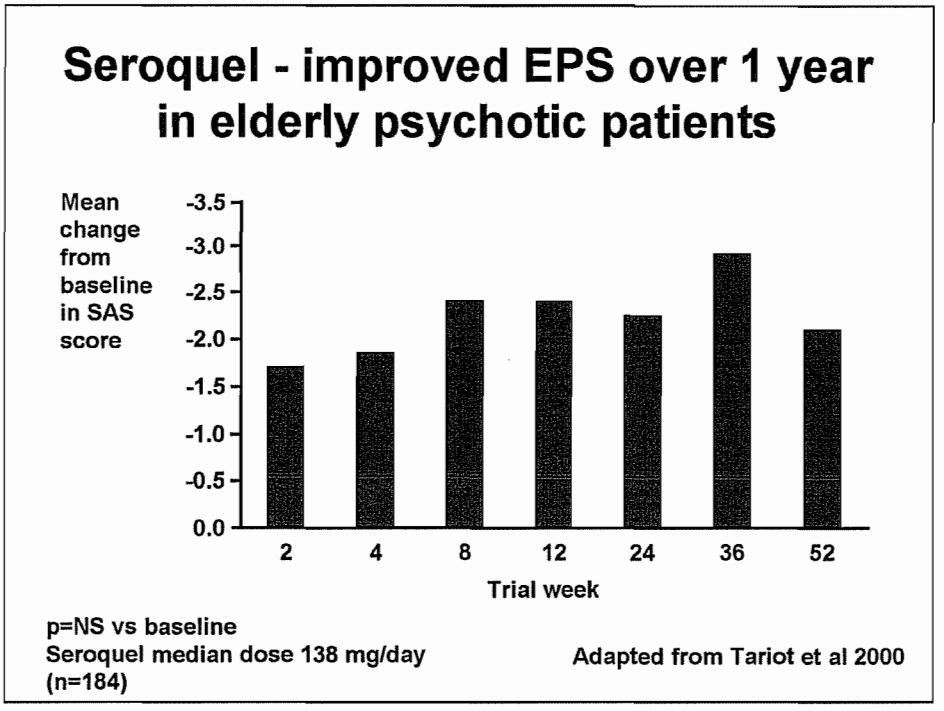
Tariot et al 1999

Seroquel – low incidence of EPS adverse events in the elderly

- This 52-week, open-label, multicentre trial involved 184 elderly patients with idiopathic psychoses (28%) and organic psychoses (72%).[1] Patients had a mean age of 76 years (range 54-94 years) and 53% of the patients were female[1]
- The trial was flexibly dosed with patients started on Seroquel 25 mg (qd or bid) and escalated to 800 mg/day, depending on clinical response and tolerability. The median daily dose was 138 mg/day[1]
- The incidence of extrapyramidal symptoms (EPS) in the elderly is similar to that seen in placebo-controlled Seroquel trials, where EPS were reported in 7% of patients receiving Seroquel and 12% of those on placebo[1]
- In this study only 13% of patients experienced EPS adverse events [1]

Reference

1. Tariot P et al. Poster presented at the American Psychiatric Association Annual Meeting, Washington, 1999.



Seroquel – improved EPS over 1 year in elderly psychotic patients

- This 52-week, open-label, multicentre trial involved 184 elderly patients with idiopathic psychoses (28%) and organic psychoses (72%).[1] Patients had a mean age of 76 years (range 54-94 years) and 53% of the patients were female[1]

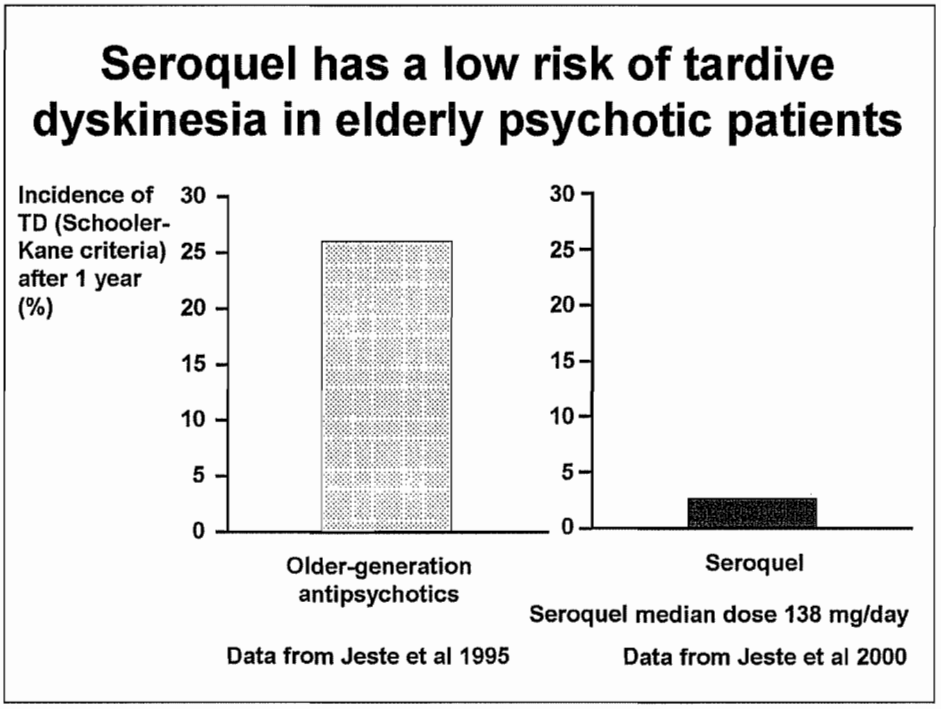
- The trial was flexibly dosed with patients started on Seroquel 25 mg (qd or bid) and escalated to 800 mg/day, depending on clinical response and tolerability. The median daily dose was 138 mg/day[1]

- Extrapyramidal symptoms (EPS) did not worsen during the course of the 52-week trial of Seroquel. In fact, there was a trend towards improvement in EPS as indicated by a progressive decline in the mean Simpson-Angus Scale (SAS) score. At Week 52, the analysis was on observed cases[1]

- Improvement in the SAS score was noted within 2 weeks[1]

Reference

1. Tariot et al. *Clin Ther* 2000; 22: 1068-1084.



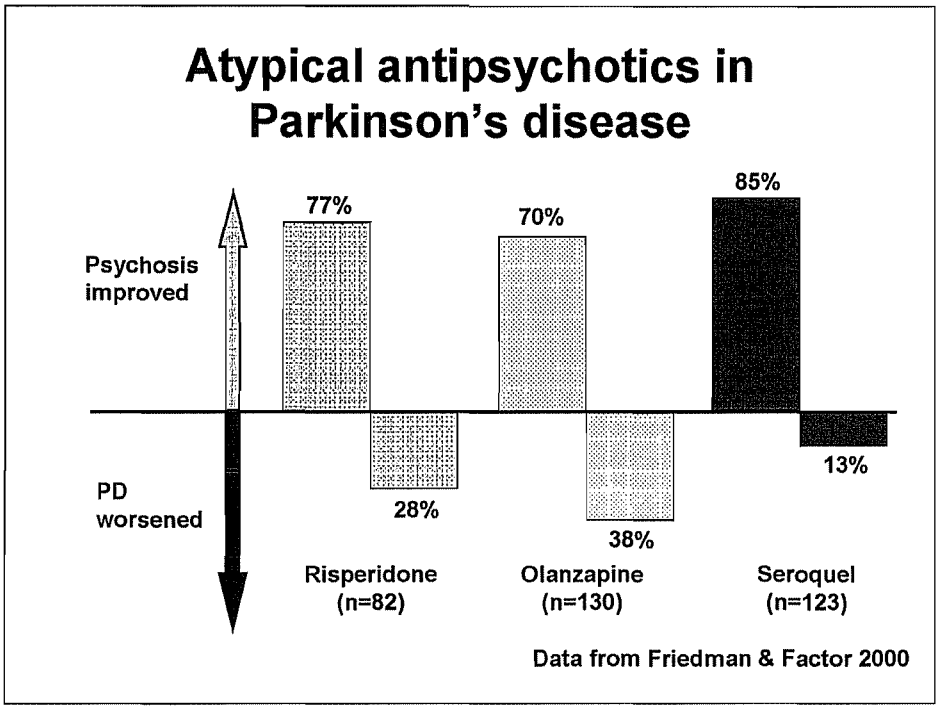
Seroquel – low risk of tardive dyskinesia in elderly psychotic patients

- The data for the older-generation antipsychotics are from a prospective longitudinal study of 266 outpatients who were >45 years old, had psychosis or other severe behavioural symptoms and had a median exposure of 21 days of total lifetime neuroleptic exposure. During the study, most patients received either a high-potency or low-potency neuroleptic and were maintained on relatively low doses (typically <150 mg/day chlorpromazine equivalent). Cumulative incidence of tardive dyskinesia (TD) in this population was 26% after 1 year (Schooler-Kane criteria)[1]

- The data for Seroquel are from a subanalysis[2] of 52-week data in elderly psychotic patients.[3] Eighty-five patients (mean age 77 years; range 54-95 years) with mixed psychotic disorders were included in the subanalysis.[2] These patients had no TD or history of TD at baseline and had not withdrawn from the trial due to TD during the first 4 weeks of the trial. They received a mean dose of Seroquel 172 mg/day. The 1-year persistent TD risk in these 85 patients was estimated to be 2.7% (Schooler-Kane criteria)[2]

References

1. Jeste DV et al. *Arch Gen Psychiatry* 1995; 52: 756-765.
2. Jeste DV et al. Poster presented at the Winter Workshop, Davos, 2000.
3. Tariot P et al. Poster presented at the American Psychiatric Association Annual Meeting, Washington DC, 1999.



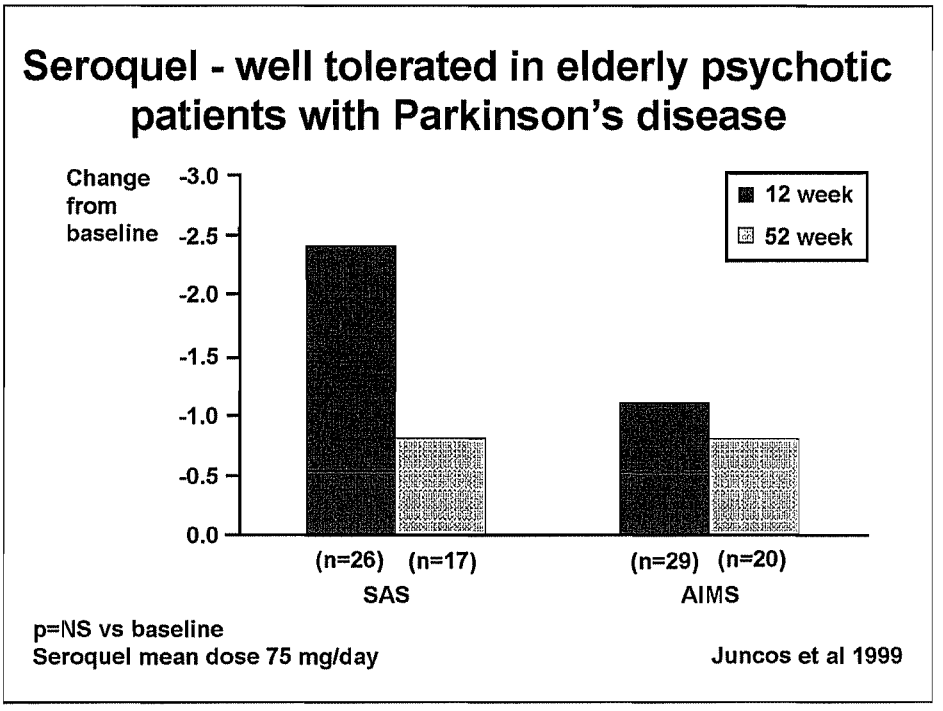
Atypical antipsychotics in Parkinson's disease

- This slide summarises the results of published open-label studies, available from Medline and supplemented by presentations at meetings, with risperidone, olanzapine and Seroquel in Parkinson's disease. These data suggest Seroquel to be well tolerated with less worsening of motor function than risperidone and olanzapine[1]

- Psychosis was measured by Clinical Global Impression scale (CGI), the Brief Psychiatric Rating Scale (BPRS) and Survey Assessment of Positive Symptoms (SAPS). Motor function was measured by the motor scale of Unified PD Rating Scale (UPDRS)[1]

Reference

1. Friedman JH, Factor SA. *Mov Disord* 2000; 15: 201-211.

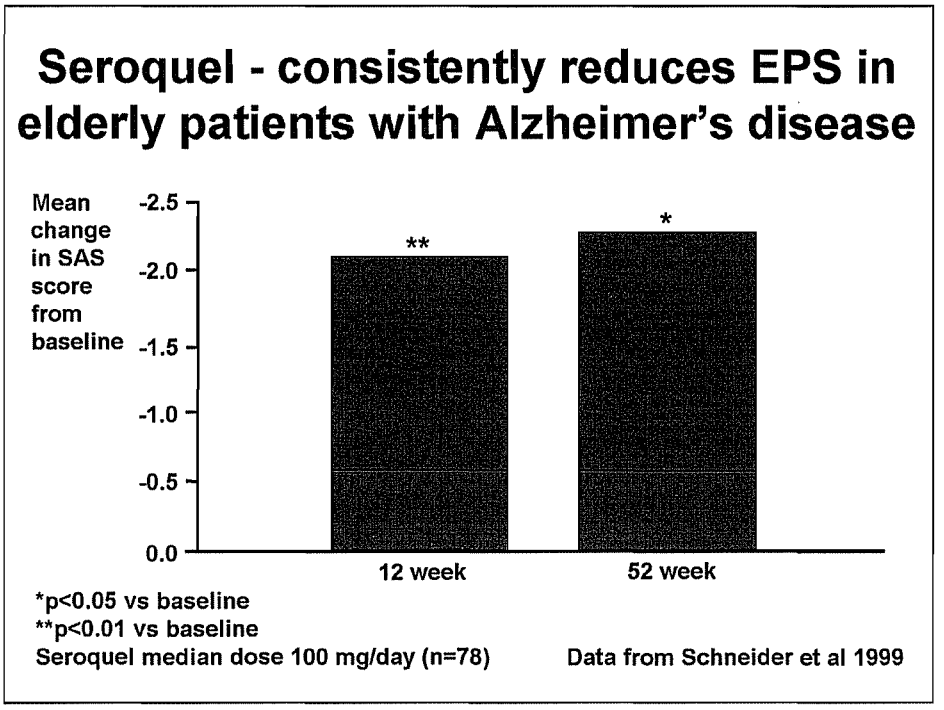


Seroquel - well tolerated in elderly psychotic patients with Parkinson's disease

- A subset analysis[1] was carried out on 40 elderly psychotic patients diagnosed with advanced Parkinson's disease (PD) who participated in a 52-week, open-label multicentre trial of Seroquel in elderly psychotic patients (n=184).[2] The patients in the PD subset ranged in age from 54 to 89 years and 45% of the study population were female[1]
- Patients were flexibly dosed, starting with a 25 mg dose (qd or bid). The dose was then increased by 25-50 mg increments every 1-3 days up to 800 mg/day depending on clinical response and tolerability. The mean dose was 75 mg/day[1]
- Extrapyramidal symptoms (EPS) and abnormal involuntary movements were assessed by the Simpson-Angus Scale (SAS) and the Abnormal Involuntary Movement Scale (AIMS), respectively[1]
- There were no significant changes from baseline in the SAS and AIMS scores at Week 12 and Week 52[1]
- Seroquel did not worsen the motor symptoms of Parkinson's disease[1]

References

1. Juncos J et al. Poster presented at the American Psychiatric Association Annual Meeting, Washington DC, 1999.
2. Tariot P et al. *Clin Ther* 2000; 22: 1068-1084.

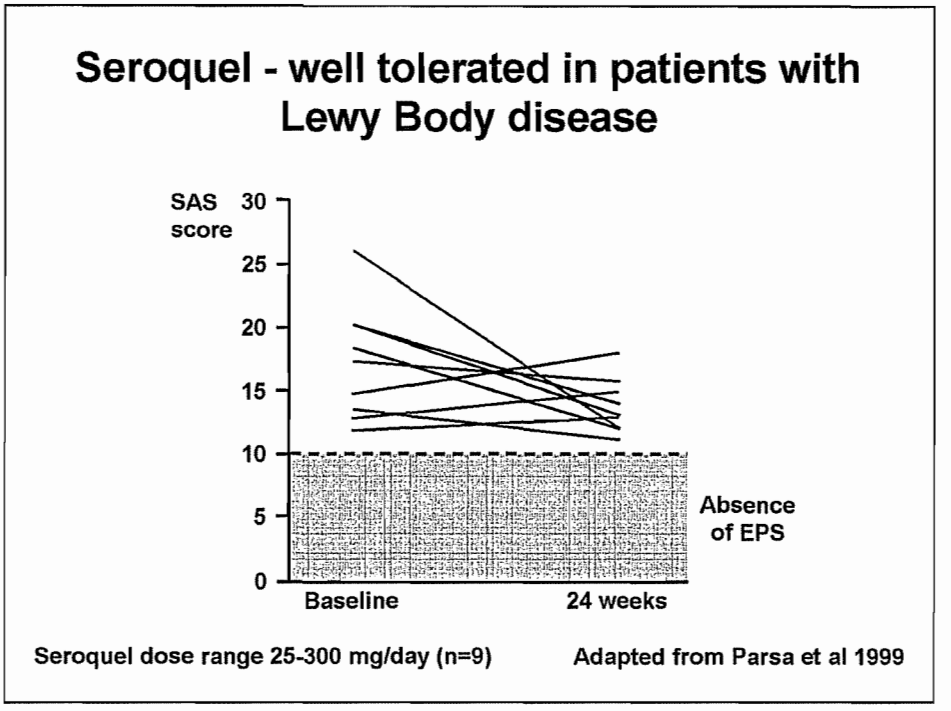


Seroquel – consistently reduces EPS in elderly patients with Alzheimer's disease

- A subset analysis[1] was carried out data from 78 elderly psychotic patients diagnosed with Alzheimer's disease (AD) who had participated in a 52-week, open-label, multicentre trial of Seroquel in elderly psychotic patients (n=184)[2]
- The patients in this AD subset ranged in age from 62 to 92 years (mean 78 years) and 54% of the study population were female. The median Seroquel dose received by these patients was 100 mg/day[1]
- The Simpson-Angus Scale (SAS) data were assessed in observed cases at Weeks 12 and 52[2]

References

1. Schneider L et al. Poster presented at the American Psychiatric Association annual meeting, Washington DC, 1999.
2. Tariot et al. *Clin Ther* 2000; 22: 1068-1084.



Seroquel – well tolerated in patients with Lewy Body disease

- A 24-week, open-label trial evaluated the efficacy and tolerability of Seroquel in nine elderly psychotic patients with Parkinson's disease and dementia who met the criteria for Lewy Body disease. The patients' mean age was 76 years (range 63-88 years) and 56% of the study population were female[1]
- Seroquel was flexibly dosed (25-300 mg/day) and the mean peak dose administered was 107 mg/day[1]
- The Simpson-Angus Scale (SAS) scores at baseline and endpoint for each of the nine patients are shown. These nine patients did not show significant worsening of motor abnormalities as measured by SAS over the course of the trial[1]
- Motor function improved in six of the nine patients[1]
- These preliminary results suggest that Seroquel maintains or improves motor function in patients with Lewy Body disease[1]

Reference

1. Parsa MA et al. Poster presented at the World Psychiatric Association Annual Meeting, Hamburg, 1999.

Seroquel - tolerability in other patient populations

- Low risk of EPS in vulnerable populations:
  - the elderly
  - patients with Alzheimer's disease, Parkinson's disease or Lewy Body disease
  - adolescents
- Better risk:benefit than olanzapine or risperidone indicated in EPS-vulnerable patients

Seroquel – tolerablity in other patient populations

Summary slide

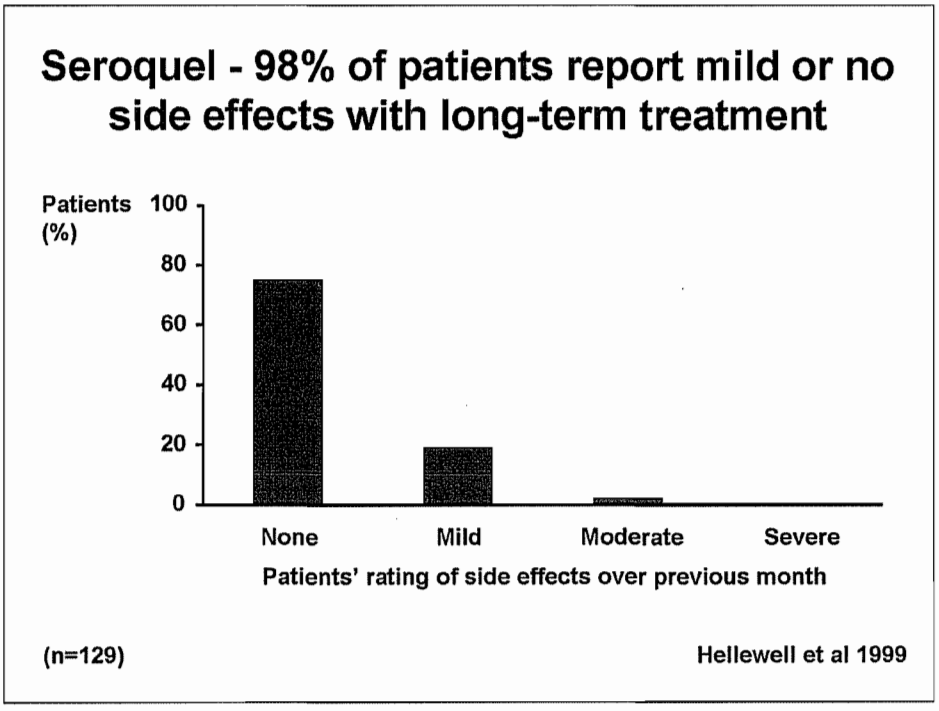
Seroquel - efficacy & tolerability

- Broad spectrum efficacy
- At least as effective as other antipsychotics
- Responses maintained long term
- Unique tolerability profile
- Placebo-level EPS across the full dose range
- Minimal sexual dysfunction
- Weight neutral in long-term monotherapy
- No blood / CV monitoring

Seroquel – efficacy and tolerability

Summary slide

Patient acceptability

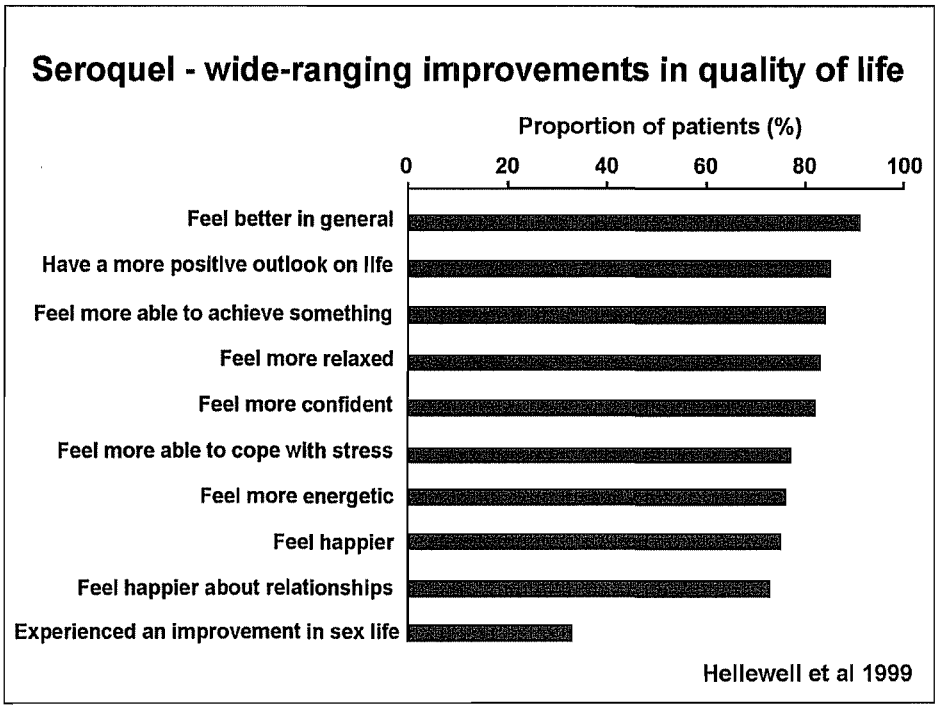


Seroquel – 98% of patients report mild or no side effects with long-term treatment

- In this study, 129 patients with either schizophrenia (68%), functional psychoses (10%), organic psychoses (19%) or affective disorders (3%) who had received Seroquel for ≥6 months in open-label extension trials were asked to complete a patient satisfaction questionnaire[1]
- The questionnaire was designed following a review of published work and input from expert opinion. It was completed by both the investigator and the patient[1]
- The mean duration of Seroquel treatment was 19.9 months (range 6.1-47.2 months); the mean age was 51.3 years (range 18-91 years) and 46.5% of the patients were female[1]
- The majority of patients (98%) reported that they had had no or mild side effects over the previous month of treatment with Seroquel. No effects n=96, mild effects n=30, moderate effects n=3, severe effects n=0[1]
- Patients in open-label extension trials were flexibly dosed with Seroquel up to a maximum of 800 mg/day[2]

References

1. Hellewell JSE et al. *Int J Psychiatr Clin Pract* 1999; 3: 105-113.
2. Data on file – AstraZeneca.

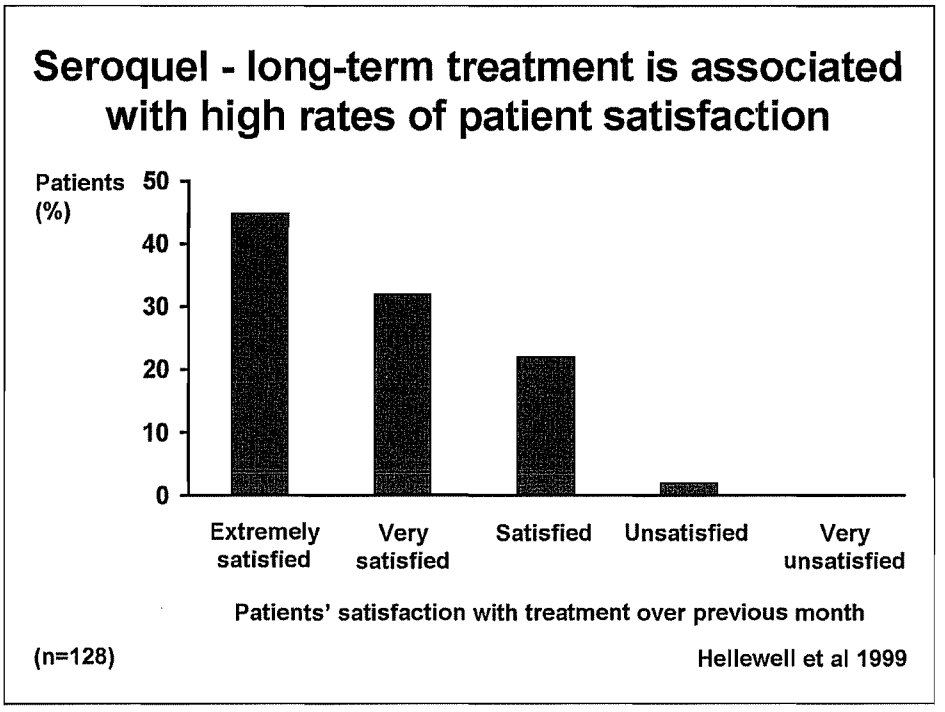


Seroquel – wide-ranging improvements in quality of life

- In this study, 129 patients with either schizophrenia (68%), functional psychoses (10%), organic psychoses (19%) or affective disorders (3%) who had received Seroquel for ≥6 months in open-label extension trials were asked to complete a patient satisfaction questionnaire[1]
- The questionnaire was designed following a review of published work and input from expert opinion. It was completed by both the investigator and the patient[1]
- The mean duration of Seroquel treatment was 19.9 months (range 6.1-47.2 months); the mean age was 51.3 years (range 18-91 years) and 46.5% of the patients were female[1]
- Patients were asked if they had noticed any benefits, during the last 6 months of treatment with Seroquel, in the specific aspects of quality of life listed on the slide[1]
- Patients in open-label extension trials were flexibly dosed with Seroquel up to a maximum of 800 mg/day[2]

References

1. Hellewell JSE et al. *Int J Psych Clin Pract* 1999; 3: 105-113.
2. Data on file – AstraZeneca.

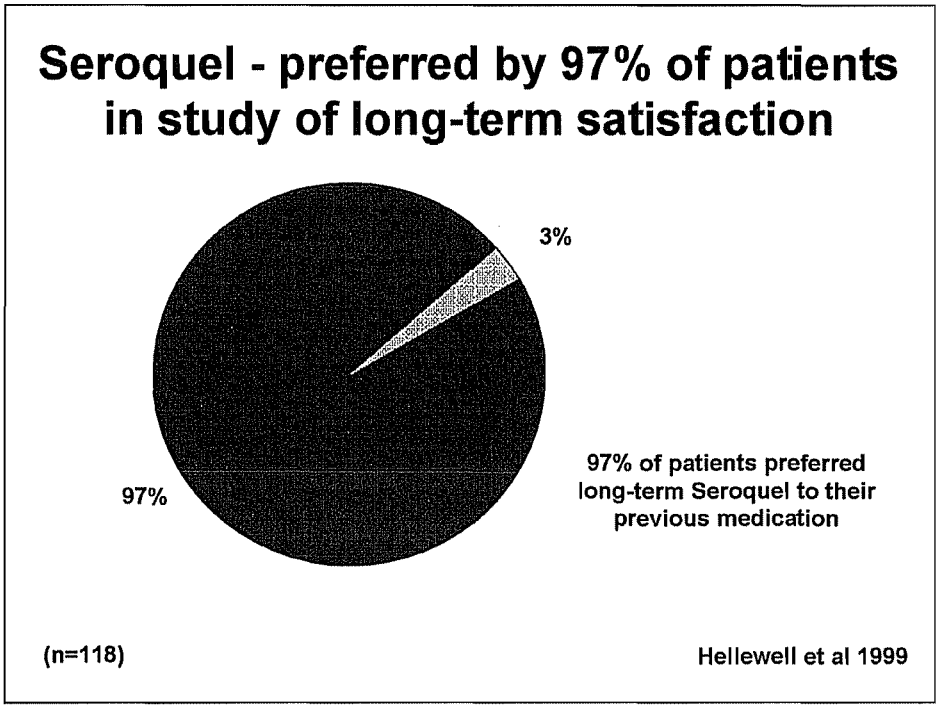


Seroquel – long-term treatment is associated with high rates of patient satisfaction

- In this study, 129 patients with either schizophrenia (68%), functional psychoses (10%), organic psychoses (19%) or affective disorders (3%) who had received Seroquel for ≥6 months in open-label extension trials were asked to complete a patient satisfaction questionnaire[1]
- The questionnaire was designed following a review of published work and input from expert opinion. It was completed by both the investigator and the patient[1]
- The mean duration of Seroquel treatment was 19.9 months (range 6.1-47.2 months); the mean age was 51.3 years (range 18-91 years) and 46.5% of the patients were female[1]
- These data are from 128 patients who responded to the question "During the past month, how satisfied have you been with your antipsychotic medication?" Extremely satisfied n=57, very satisfied n=40, satisfied n=29, unsatisfied n=2[1]
- Patients in open-label extension trials were flexibly dosed with Seroquel up to a maximum of 800 mg/day[2]

References

1. Hellewell JSE et al. *Int J Psych Clin Pract* 1999; 3: 105-113.
2. Data on file – AstraZeneca.



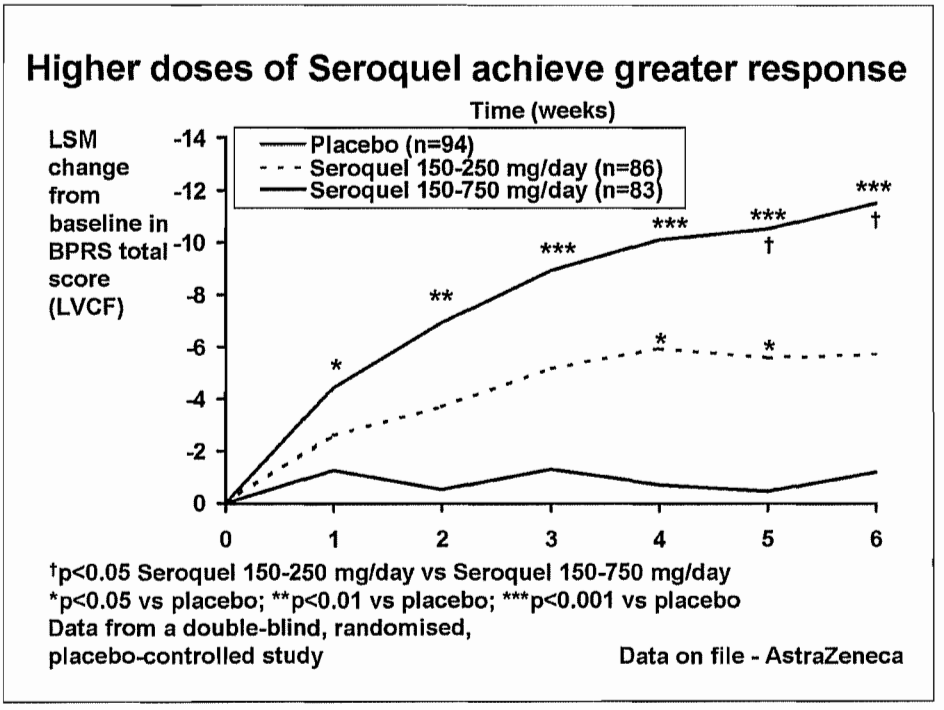
Seroquel – preferred by 97% of patients in study of long-term satisfaction

- In this study, 129 patients with either schizophrenia (68%), functional psychoses (10%), organic psychoses (19%) or affective disorders (3%) who had received Seroquel for ≥6 months in open-label extension trials were asked to complete a patient satisfaction questionnaire[1]
- The questionnaire was designed following a review of published work and input from expert opinion. It was completed by both the investigator and the patient[1]
- The mean duration of Seroquel treatment was 19.9 months (range 6.1-47.2 months); the mean age was 51.3 years (range 18-91 years) and 46.5% of the patients were female[1]
- 114 of the 118 patients (97%) who had received previous treatment reported that they preferred Seroquel to previous medications[1]
- Patients in open-label extension trials were flexibly dosed with Seroquel up to a maximum of 800 mg/day[2]

References

1. Hellewell JSE et al. *Int J Psychiatr Clin Pract* 1999; 3: 105-113.
2. Data on file – AstraZeneca.

Dosing and administration of 'Seroquel'

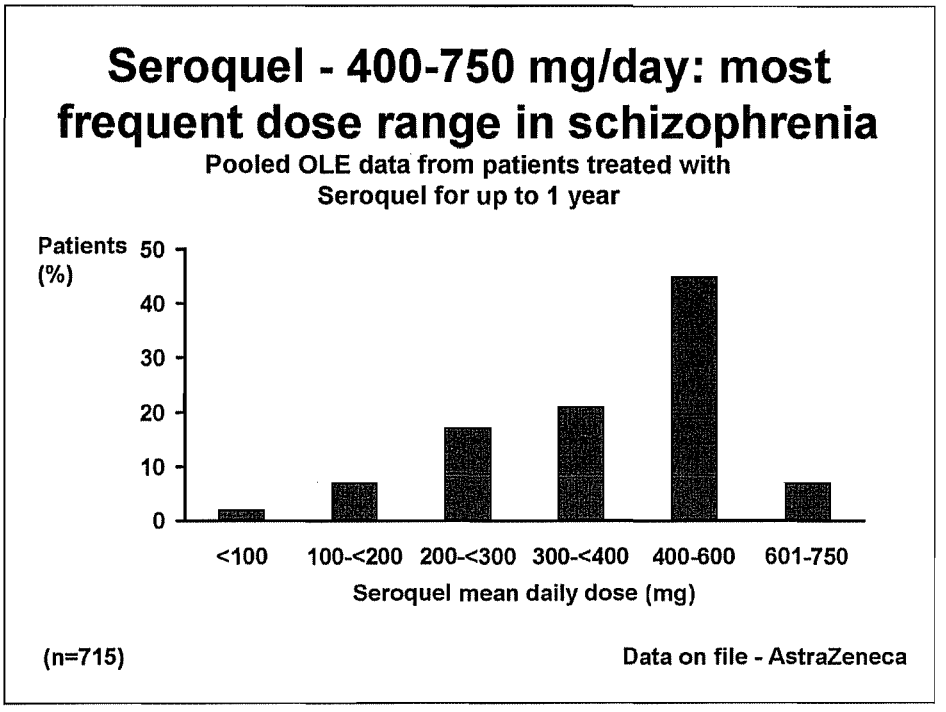


Greater response to higher doses of Seroquel

- Trial 8[1] was a double-blind, placebo-controlled study comparing low and high dosage regimens of Seroquel in patients with schizophrenia
- Patients received up to 250 mg/day or up to 750 mg/day. Mean doses were 218.9 mg/day for the low dose group and 401.8 mg/day for the high dose group.
- The slide details the mean change from baseline in the Brief Psychiatric Rating Scale total score (last value carried forward). This data set includes only patients who were dosed with Seroquel 150-250 mg/day or 150-750 mg/day[2]

References

1. Small JG et al. *Arch Gen Psychiatry* 1997; 54: 549-557.
2. Data on file – AstraZeneca.

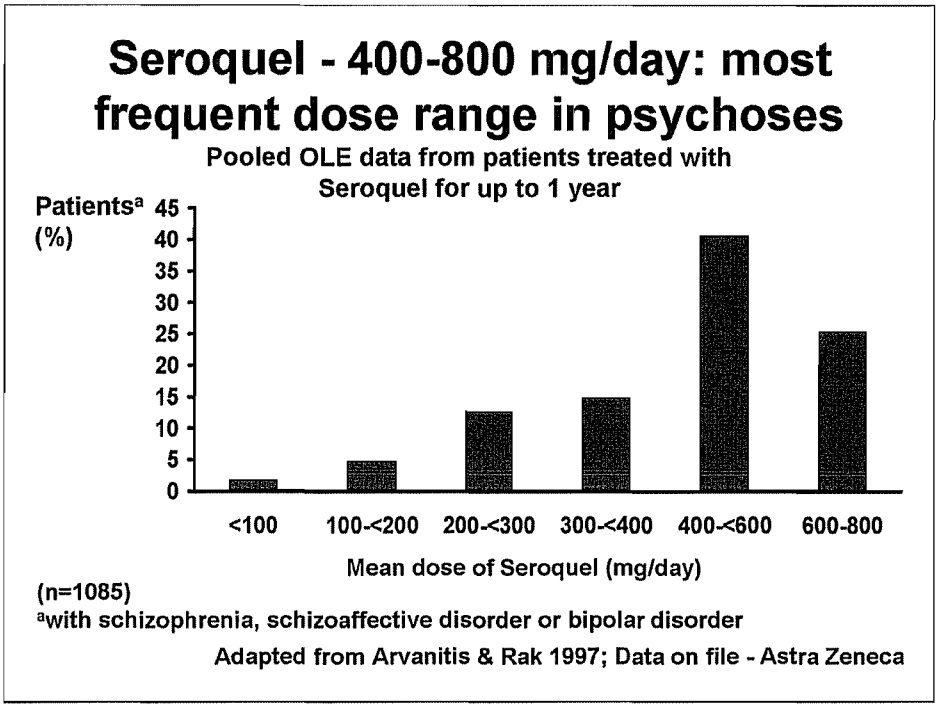


Seroquel - 400-750 mg/day: most frequent dose range

- For 45% of patients the most effective dose of Seroquel was between 400 and 750 mg/day[1]
- Dose levels were based on clinical response and tolerability. The slide details the percentage of patients who received a particular Seroquel dose for up to 1 year. This data set (n=715) excludes patients receiving >750 mg/day Seroquel and includes only patients meeting the DSM-IIIR or DSM-IV criteria for schizophrenia[1]
- These data are derived from pooled open-label-extension (OLE) trials[2] (trials 12, 13, 14, 15, 17 and 35) in which patients with schizophrenia, schizoaffective disorder or bipolar disorder (n=1085) received ≤800 mg/day Seroquel for up to 2 years

References

1. Data on file – AstraZeneca.
2. Arvanitis LA, Rak IW. *Schizophrenia Research* 1997; 24: 196-197.



Seroquel - 400-800 mg/day is the most frequently used effective dose range in the long term treatment of psychoses

- These data are an analysis of 1085 patients who were participating in the open-label extension (OLE) studies of Seroquel. The diagnositic citeria for entry into the OLE studies was schizophrenia, but patients enrolled into these studies could also have a diagnoses of schizoaffective disorder or bipolar disorder[1]

- The data presented show that the most common mean daily dose was 450-600 mg/day (29.9% of patients). The next most common doses were 600-800 mg/day (25.2%) and 300-450 mg/day (24.4%)

- Only 1 in 5 patients (20.5%) received less than 300 mg/day

- Patients entered the OLE studies from one of 11 Phase III clinical or clinical pharamcology trials

References

1. Adapted from Arvanitis LA, Rak I. Poster presented at International Congress on Schizophrenia Research, Colorado Springs, 1997.
2. Data on file – AstraZeneca.

Seroquel in schizophrenia - dosage and ease of administration

- **Initiating therapy: *'Go to 4.. then explore'***
  - initial dose 25 mg bid
  - titrate to dose of 400 mg/day by Day 5
- **Pharmacokinetic considerations**
  - no adjustment to titration and dose usually necessary
  - with or without food
  - dose not dependent on gender or smoking status
  - consider adjustment in elderly and hepatically impaired patients
- **Target dose 400-750 mg/day**
  - >50% of responders maintained long term on 400-750 mg/day

Seroquel in schizophrenia - dosage and ease of administration

- Seroquel is effective across the range 150-750 mg/day.[1] However, the full clinical effect is generally observed at 400-750 mg/day (or up to 800 mg/day in US)[2]
- It is recommended in the prescribing information that Seroquel should be administered twice-daily, at a starting dose of 50 mg/day, increasing to 400 mg/day by Day 5[3]
- Seroquel may be administered with or without food[3]
- Changes to the rate of titration and dose are rarely needed but may be considered in selected populations[3]
- Seroquel is associated with few drug-drug interactions[3]

References

1. Arvanitis LA, Miller BG, and the Seroquel Trial 13 Study Group. *Biol Psychiatry* 1997; 42: 233-246.
2. Small JG et al. *Arch Gen Psychiatry* 1997; 54: 549-557.
3. Seroquel Prescribing Information.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-639 S-048

AstraZeneca Pharmaceuticals LP
Attention: Kathryn Bradley
Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Bradley:

We acknowledge receipt of your supplemental new drug application dated and received December 4, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel (quetiapine fumarate) tablets.

This "Changes Being Effected" supplemental new drug application provides for revised labeling to include new safety information for both adult and pediatric patients.

We have no objection to your submission of the new safety information pertaining to the clinical trials as a CBE supplement. However, the Division is requesting that you reformat the information for better integration in the overall label prior to your intended implementation on January 4, 2009. Specifically:

1. Place the pediatric safety information in the relevant sections of labeling with the adult data rather than separately in sections 5.19 and 8.4. For example, the proposed pediatric data in the section 8.4 subtitled "Changes in Thyroid Function Tests" should be placed at the end of section 5.10 (Warnings and Precautions: Hypothyroidism). The same principle applies to other pediatric safety information that already has adult data included prominently.
2. The weight gain signal is significant for both adult and pediatric populations and should be elevated to the Warnings and Precautions section rather than the vital signs section (the latter section could refer back to the information in Warnings and Precautions section) with inclusion of data for both populations. In fact, the data for weight change, glucose changes, and lipid changes from the clinical trials, both adult and pediatric, need to be elevated to the Warnings/Precautions section of labeling. Please see the format used in the currently distributed label for another antipsychotic drug, i.e., Zyprexa, for the correct format for this information.
3. The safety data for Increases in Blood Pressure is an unexpected signal and there is currently no similar adverse event signal for the adult population. Because of this unexpected and clinically significant signal that may be specific to the pediatric population, this safety data should be included in a separate section in Warnings and Precautions. Please offer your rationale for this unusual finding.

4. For each section describing pediatric safety signals, the following statement should be included "Safety and effectiveness of SEROQUEL have not been established in pediatric patients and SEROQUEL is not approved for patients under the age of 18 years".
5. Please replace your proposed Hyperprolactinemia statement with the standard language now used for more recently approved atypical antipsychotic agents, e.g., Invega. Any actual clinical trials data regarding prolactin elevation should, of course, be data for quetiapine, including the pediatric data.
6. All pediatric safety data and the other changes we are requesting for Seroquel should be included in revised labeling for Seroquel XR as well.

The above requested changes should be implemented immediately, and they should be submitted as an amendment to your pending supplemental application to the Seroquel NDA and as an original supplemental application to the Seroquel XR NDA, 22-047, within 30 days from the date of this letter, or notify FDA that you do not believe these changes are warranted, and submit a statement detailing the reasons. If you wish to have our prior comment on your alternative proposal in response to these requests, we would be happy to provide such comment.

Please note that your proposed labeling language in the above referenced CBE is under continuing review by the Agency. Please also note that the Division is currently reviewing your metabolic data submission and the pediatric efficacy supplements submitted under this NDA (S-045 and S-046). We will be providing further labeling comments, if any, and will take final action on these submissions when reviews are completed.

If you have any questions, call Kimberly Updegraff, M.S., Regulatory Project Manager, at 301-796-2201.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
12/18/2008 04:06:08 PM

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE: Seroquel Products Liability Litigation

MDL DOCKET NO. 1769

This document relates to:

Linda Guinn	6:07-cv-10291
Janice Burns	6:07-cv-15959
Richard Unger	6:07-cv-1581 2
Connie Curley	6:07-cv-15701
Linda Whittington	6:07-cv-10475
Eileen McAlexander	6:07-cv-10360
~~Sandra Carter~~	~~6:07-cv-13234~~
~~Clemmie Middleton~~	~~6:07-cv-10949~~
~~Hope Lorditch~~	~~6:07-cv-12657~~
David Haller	6:07-cv-15733
~~Charles Ray~~	~~6:07-cv-11102~~
~~William Sarmiento~~	~~6:07-cv-10425~~

DECLARATION OF LAURA M. PLUNKETT, PH.D., DABT

My name is Laura M. Plunkett. I am over twenty-one years of age, am of sound mind, have never been convicted of a felony, and am otherwise competent to make this Declaration. I have personal knowledge of all factual statements contained herein and all such factual statements are true and correct as outlined herein in this declaration-report.

A. Qualifications and Expertise

I am board-certified as a Diplomate of the American Board of Toxicology, a pharmacologist and United States Food and Drug Administration (FDA) regulatory specialist. I have over twenty years of experience in the areas of pharmacology[1] and

[1] Pharmacology is the study of how substances interact with living organisms to produce a change in function. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 6th edition.

toxicology[2] and have worked in both government and academic research and taught pharmacology and toxicology at the undergraduate and postgraduate levels.

I received a B.S. degree in 1980 from the University of Georgia, and a Ph.D. in pharmacology from the University of Georgia, College of Pharmacy, in 1984. My doctoral research was focused in the area of cardiovascular pharmacology and specifically dealt with delineating neurochemical mechanisms responsible for the cardiac toxicity of digitalis glycosides. From June of 1984 through August of 1986, I was a Pharmacology Research Associate Training (PRAT) fellow at the National Institute of General Medical Sciences, Bethesda, Maryland. I worked in a neurosciences laboratory of the National Institute of Mental Health and my research there focused on neurochemical systems that control body functions, including dopaminergic and serotonergic systems. From September 1986 to June 1989 I was an Assistant Professor of Pharmacology and Toxicology in the medical school at the University of Arkansas for Medical Sciences, Little Rock, Arkansas where I performed basic research in the areas of neuropharmacology and toxicology as well as cardiovascular pharmacology and toxicology. I taught courses for both medical students and graduate students in pharmacology and toxicology as well as the neurosciences. From December of 1989 to August of 1997 I worked for ENVIRON Corporation, first in the Arlington, Virginia office and then in the Houston, Texas office. At ENVIRON I was a consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy with a focus on products regulated by the U.S. Food and Drug Administration (FDA). Since forming my own company in 1997, I have consulted for a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy with a focus on products regulated by the U.S. Food and Drug Administration.

B. Responses to Particular Astra-Zeneca Statements

I have reviewed the brief of Astra Zeneca that criticizes my opinions and methodology and I believe it is important to respond.

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[2] Toxicology is the study of the adverse effects of xenobiotics, or chemicals, on living organisms. It is the study of symptoms, mechanisms, treatments and detection of poisoning, especially the poisoning of people. *Casarett & Doull's Toxicology: The Basic Science of Poisons*, 7th edition.

1. Use of a Non-Scientific Method

Astra-Zeneca (AZ) has suggested that I have employed a method for assessing causation that is "non-scientific". Contrary to AZ's suggestion, I have employed a method that is routinely used by scientists when examining the possible cause-and-effect relationship between exposure and a disease or condition, namely weight-of-the-evidence. This method is based on use of a series of considerations or guidelines first articulated by Sir Austin Bradford Hill in 1965 in a speech before the Royal Society of Medicine and will be referred to hereafter as the "Bradford Hill" considerations[3]. These considerations or guidelines, there are nine of them outlined[4], have been used for decades by scientists as a tool for organizing and classifying evidence to support a weight-of-the-evidence assessment for causation. As discussed in the speech and paper, all nine are not necessary for causation to be established. In order to understand how the author himself meant for these nine considerations to be used it is best to examine his own statements:

> "Here then are nine different viewpoints from all of which we should study association before we cry causation. What I do not believe – and this has been suggested – is that we can usefully lay down some hard-and-fast rules of evidence that *must* be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?" (from page 299, left column, second full paragraph of Hill, A.B. 1965. The environment and disease: association or causation? *Proc. Royal Soc. Med.* 58:295-300).

Clearly, in order to be consistent with the Bradford Hill methodology, the nine points are used as guidelines to assess the body of literature and evidence that is available for any one situation being investigated. However, no one of the nine considerations should be

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[3] The "Bradford Hill" guidelines or considerations are described in the 1965 publication (Hill, A.B. 1965. The environment and disease: association or causation? *Proc. Royal Soc. Med.* 58:295-300).

[4] The nine viewpoints or considerations described by Sir Austin Bradford Hill were: 1) strength; 2) consistency; 3) specificity; 4) temporality; 5) biological gradient (dose-response); 6) plausibility; 7) coherence; 8) experiment; and 9) analogy.

viewed as an absolute requirement, consistent with the Bradford Hill method as described by Sir Austin Bradford Hill himself.

Therefore, in my current weight-of-the-evidence assessment for Seroquel and diabetes, I employed the Bradford Hill method as a guide in my assessment (see my expert report which is attached to this Declaration and which I affirm contains my scientific opinions in this matter). My use of the Bradford Hill method and weight-of-the-evidence assessment in the Seroquel litigation are consistent with my use of these same tools in my practice as a pharmacologist throughout the years, and has also been accepted by courts in other litigations including phenylpropanolamine (PPA) products, diet drugs known as "Fen-phen", and Zyprexa. It should also be pointed out that a number of the defense experts have also employed a similar method for causation analysis.

AZ has asserted that my use of the Bradford Hill method and weight-of-the-evidence assessment are "non-scientific" because I have limited my discussion only to studies and evidence that support my position, ignoring studies that do not support my position. This is totally false. As in any weight-of-the-evidence assessment, there may be studies that both support a causation opinion and studies that do not. What is important to show is that both types of studies have been considered. In my reference list provided to defense counsel and during my deposition I discussed the fact that indeed studies do exist that I have not cited and that may not support my position. However, also, as discussed in my report and my deposition, it is the totality of the evidence that is important to my eventual finding that Seroquel can cause hyperglycemia and diabetes as well as weight gain. Although I have not given detailed rebuttals of each paper in my expert report, I was prepared to discuss those papers at my deposition and in some cases they were discussed while in other cases defense counsel chose not to discuss certain published studies. Therefore, contrary to the defense's assertions I have not "cherry-picked" studies but have considered all of the studies available and concluded that the totality of the evidence supports a weight-of-the-evidence assessment that Seroquel can cause hyperglycemia and diabetes as well as weight gain.

I have used a method that is based on sound science and considers more than just observational study data. It includes a consideration of the totality of available evidence,

which is consistent with the Bradford Hill method and would include experimental data in cells, animals, and humans (experimentation and biologic plausibility under Bradford Hill), data collected in chemically similar compounds (analogy under Bradford Hill), epidemiological data, case reports, AZ clinical study data, and any other data or information that I felt was relevant to the question of Seroquel and metabolic effects. Although defense counsel attempt to discount the value of *in vitro* and animal studies, I believe that all types of data (animal, *in vitro*, and human) are relevant to a cause and effect assessment of diabetes risk and Seroquel use. Indeed, much of the data submitted by AZ to the FDA as part of the drug approval process was animal experiments AZ performed to assess safety and efficacy of Seroquel. It is curious that the company in this litigation context now chastises the very type of data it values in the drug approval context.

I have also included case reports within my weight-of-the-evidence assessment because, as described by Bradford Hill, such data are a type of experiment where there is a component of challenge/dechallenge, where challenge refers to administration of a drug, in this case Seroquel, and dechallenge refers to the situation where the drug is removed. It should be noted that in the case of Seroquel, there are several case reports that show that with dechallenge of a patient that developed hyperglycemia or diabetes while taking Seroquel, the hyperglycemia or diabetes improved (*e.g.*, Sobel *et al.* 1999[5]; Domon and Cargile 2002[6]; Sneed and Gonzalez 2003[7]; Takahashi *et al.* 2005[8]; Marlowe *et al.* 2007[9]). These type of case reports are consistent with the type of experimentation described by Bradford Hill and are validly used in a weight-of-the-evidence causation assessment.

I testified throughout my deposition, and explained in my expert report, that I have relied on a variety of different types of data (*in vitro* data, animal data, clinical data,

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[5] Sobel, M. et al. 1999. New-onset of diabetes mellitus associated with the initiation of quetiapine treatment. *J. Clin. Psychiatry* 60:556-557.

[6] Domon, S.E. and C.S. Cargile. 2002. Quetiapine-associated hyperglycemia and hypertriglyceridemic. *J. Am. Acad. Child Adolesc. Psychiatry* 41: 495-496.

[7] Sneed, K.B. and E.C. Gonzalez. 2003. Type 2 diabetes mellitus induced by an atypical antipsychotic medication. *J. Am. Board Fam. Pract.* 16:251-254.

[8] Takahashi, M. et al. 2005. Rapid onset of quetiapine-induced diabetic ketoacidosis in an elderly patient. *Pharmacopsychiatry* 38:183-184.

[9] Marlowe, K.F. et al. 2007. New onset diabetes with ketoacidosis attributed to quetiapine. *South. Med. J.* 100:829-831.

epidemiological data, and statements in authoritative texts or by authoritative bodies) to support my opinions regarding the adverse metabolic effects and human health risks associated with Seroquel. Therefore, the method I have used is consistent with methodology routinely used by scientists to assess causation and I have considered all of the evidence before forming my opinion. The fact that after I formed my causation opinions some studies were identified or published that when considered individually may not support my findings is not sufficient evidence to suggest that my method was non-scientific. In fact since then, there have also been new positive studies reflecting the diabetogenic potential of Seroquel (*e.g.*, Savoy et al. 2008[10]; DuMouchel et al. 2008[11]; Meyer et al. 2008[12]). I have not put more weight on papers that support my opinions; I have simply listed those papers in my expert report in order to fully define the evidence that I have relied on.

2. AZ Counsel Suggest It Is Inappropriate to Consider Data on Drugs Chemically Similar to Seroquel In a Weight-of-the-Evidence Assessment

In performing the weight-of-the-evidence causation assessment relating to Seroquel, I used the Bradford Hill method, a standard, well recognized methodology (discussed above) to guide my evaluation of the body of published literature. As already discussed, these nine areas listed by Bradford Hill are not meant to be strictly applied but instead used to guide the health professional. Several of the nine considerations, however, have become an integral part of causation analysis. One such criterion is "analogy" (see Hill 1965). As I discussed in my expert report and my deposition, analogy is the process of examining a potential cause and effect relationship by looking for chemically similar compounds, or other compounds with similar physical or chemical properties, that may or may not have produced similar adverse effects. This is the same

[10] Savoy, Y.E. et al. 2008. Differential effects of various typical and atypical antipsychotics on plasma glucose and insulin levels in the mouse: evidence for the involvement of sympathetic regulation. *Schizophr. Bull.* Aug 14 [Epub ahead of print].

[11] DuMouchel, W. et al. 2008. Antipsychotics, glycemic disorders, and life-threatening diabetic events: a Bayesian data-mining analysis of the FDA adverse event reporting system (1968-2004). *Ann. Clin. Psychiatry.* 20:21-31.

[12] Meyer, J.M. et al. 2008. Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE schizophrenia trial: prospective data from phase 1. *Schizophr. Res.* 101:273-286.

way that textbooks of pharmacology and toxicology are organized. Classes of compounds or drugs are discussed together in terms of the similarities in both their toxicological and pharmacological profiles. Although any two chemically similar substances may differ quantitatively in terms of the doses required to produce certain effects in animals and humans, the qualitative aspects of a pharmacological and toxicological profile of chemically similar compounds are usually very similar. In any event, as a pharmacologist I carefully reviewed the pharmacological similarities and differences of the agents. In fact, to ignore chemical classes would be contrary to fundamental teachings of pharmacology.

To evaluate Seroquel, I thought it was important to look for chemically similar compounds to predict the likely toxicological and pharmacological profile of Seroquel, since it has been known for decades that anti-psychotic drugs, including the atypical anti-psychotics, have effects to alter metabolism that can lead to weight gain and effects on glucose metabolism (see any standard textbook of pharmacology such as Baldessarini, R.J. 1980. In: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 6th edition,* A.G. Gilman et al. (eds.), chapter 19, McMillan Publishing Co.: New York). In these standard textbooks of pharmacology, it is taught that clozapine and olanzapine (Zyprexa) are the two most chemically similar compounds to Seroquel. This is seen by inspecting the ring structures of the compounds and the types of chemical groups attached. Therefore, in these textbooks, the effects of clozapine are used as a standard for comparison of the other chemically similar atypical anti-psychotics, including Zyprexa and Seroquel. As a result, using the Bradford Hill methods of causation analysis, I have used data on clozapine and Zyprexa as part of my weight-of-the-evidence assessment for causation. Never have I only used data on chemically similar compounds. The clozapine and Zyprexa data are only used as supporting information that demonstrate that there was some predictability surrounding the effects of Seroquel on metabolic parameters and its likely propensity to induce diabetes. It is a standard practice for a pharmacologist and toxicologist to perform a causation assessment and to use chemical analogy.

In my deposition and my expert report, I discussed my reasons for concluding that clozapine and Zyprexa data were relevant to the Seroquel assessment. I noted that the drugs were "chemically similar" and they had similar potencies on dopamine and

serotonergic receptors which, for efficacy and likely safety, is an important part of the pharmacological profile of the drugs. Therefore, I believe I have provided valid scientific reasons and used valid scientific methodology for utilizing clozapine and Zyprexa data as part of the body of evidence supporting my conclusions about Seroquel. Therefore, although other scientists may challenge my interpretation of the data, the use of chemically similar compounds in my causation analysis is based on well-accepted principles of pharmacology and toxicology.

3. AZ Counsel Suggest Three Things Are Needed to Establish Causation and These Three Things Are Not Provided for Seroquel

Defense counsel has suggested that three things are needed in order to establish causation: 1) biologic mechanism; 2) dose-response effect; and 3) general acceptance. Defense counsel then suggests that I have failed to provide all three of these necessary supports for causation in my opinions. I strongly disagree with both of defense counsel's suggestions.

First, as discussed in detail above in section 1 of my declaration, there are NOT three absolute requirements for establishing causation. Instead, consistent with the method of Sir Austin Bradford Hill, there are nine considerations that should be applied to the available data for any given situation and two of those nine do include plausibility and biologic gradient. Plausibility is usually interpreted to mean biologic plausibility. As the 1965 paper states: "It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand." (see page 298 of Hill, A.B. 1965. The environment and disease: association or causation? *Proc. Royal Soc. Med.* 58:295-300). This does not mean that it is necessary to completely understand any mechanism of injury only that the cause-and-effect between the injury in question and the agent being examined is based on some type of plausible mechanism. As discussed below, I have addressed this issue in my opinions. More importantly, however, general acceptance is NOT one of the nine considerations for establishing causation. Therefore, defense counsel is simply wrong in its suggestions.

Regardless, my expert report clearly outlines evidence that would support each of these three areas, or provides reasons why certain aspects of all three areas cannot be

provided based on currently available data. I will briefly point out the evidence I have identified for each of these three areas.

With respect to biologic mechanism, I have stated in my expert report and my deposition that no one knows the exact molecular mechanism in any one individual that is responsible for the metabolic effects of Seroquel, including its effects to induce hyperglycemia, weight gain, and diabetes. In fact, AZ's package insert for Seroquel states in the Clinical Pharmacology Section 12.1 that "the mechanism of action of SEROQUEL, as with other drugs having efficacy in the treatment of schizophrenia and bipolar disorder, is unknown." Instead, the insert goes on to discuss proposed mechanisms that may explain its actions. Thus, not knowing with certainty the precise mechanism of action of a therapeutic or an adverse effect does not mean that there is not evidence for a likely biologic mechanism. Nor does it mean that you must need to know the precise mechanism. If that was the case, Seroquel and many drugs, which are recognized to have certain intended therapeutic effects, yet the precise mechanism is not precisely understood, would not be approved for human use, if one applied the same standards is AZ is suggesting should be applied here. Moreover, often in medicine and pharmacology, there can be more than one mechanism underlying therapeutic and adverse drug effects.

In paragraphs 35-40 of my report, I discuss the likely mechanisms underlying the adverse metabolic effects of Seroquel. Then, in my deposition I discussed these mechanisms in even more detail.

I would first like to respond to defense counsel's statements regarding two specific studies, Henderson *et al.* 2006[13] and Melkersson *et al.* 2005[14]. Melkersson *et al.* (2005) is a study of insulin release *in vitro* from rat pancreatic cells and the authors reported that at the doses of Seroquel tested (10^{-6} M), there was no statistically significant increase in insulin release, indicating that the drug did not directly stimulate insulin release in rat pancreas under the conditions of the assay. Interestingly, in a similar study

[13] Henderson, D.C. et al. 2006. Glucose metabolism in patients with schizophrenia treated with olanzapine or quetiapine: a frequently sampled intravenous glucose tolerance test and minimal model analysis. *J. Clin. Psychiatry* 67:789-797.

[14] Melkersson, K.I. et al. 2005. The atypical antipsychotics quetiapine, risperidone, and ziprasidone do not increase insulin release in vitro. Neuroendocrinol. Lett. 26:205-208.

reported in 2001 (Melkersson *et al.* 2001[15]), clozapine but not olanzapine exhibited the ability to directly stimulate insulin release in this experimental system. Given the well-accepted relationship between olanzapine (Zyprexa) and diabetes (see labeling from Physicians' Desk Reference, 2008; ADA Consensus statement 2004[16]), it is clear that this experimental model is not a sensitive indicator of the diabetogenic potential of anti-psychotic drugs in humans. Now considering the paper cited by the defense counsel known as Henderson *et al.* (2006), this study reports results of testing in non-obese schizophrenic patients where measures of insulin resistance in 7 patients taking Seroquel was compared to 8 patients taking Zyprexa or 9 normal controls (not schizophrenic). Although only Zyprexa was associated with statistically significant decreases in insulin sensitivity index as compared to controls (where decreased insulin sensitivity is thought to be associated with Type II diabetes), the insulin sensitivity index in Zyprexa-treated patients was not statistically significant from the index value reported for Seroquel-treated patients. In most endpoints measured in the study, Seroquel treatment affected insulin and glucose homeostasis in the same direction as did Zyprexa, although Zyprexa showed greater diabetogenic potential. This result is actually consistent with my opinions as I have identified Zyprexa as having a greater diabetogenic potential than Seroquel, although the weight-of-the-evidence shows both drugs are capable of causing hyperglycemia and diabetes.

I would also like to respond to defense counsel's concerns that some available studies have shown that Seroquel lacks certain specific activity under the conditions of the assay being tested (*e.g.,* Henderson *et al.* 2006; Melkersson *et al.* 2005) by pointing out that there are peer-reviewed published studies that do provide basic mechanistic or biologic mechanism data specific to Seroquel (*e.g.,* Dwyer and Donohoe 2003[17]; Savoy *et al.* 2008[18]; Vestri *et al.* 2006[19]; Cope *et al.* 2005[20]). The following is a brief discussion of

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[15] Melkersson, K.I. et al. 2001. Different effects of antipsychotic drugs on insulin release in vitro. *Eur. Neuropsychopharmacology* 11:327-332.

[16] American Diabetes Association et al. 2004. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care.* 27:596-601.

[17] Dwyer, D.S. and D. Donohoe. 2003. Induction of hyperglycemia in mice with atypical antipsychotic drugs that inhibit glucose uptake. *Pharm. Biochem. Behav* 75:255-260.

[18] Savoy, Y.E. et al. 2008. Differential effects of various typical and atypical antipsychotics on plasma glucose and insulin levels in the mouse: evidence for the involvement of sympathetic regulation. *Schizophr. Bull.* Aug 14 [Epub ahead of print].

these papers and how they contribute to the potential or likely biologic mechanism of Seroquel to produce metabolic effects including weight gain, hyperglycemia, and diabetes.

Cope *et al.* (2005) provides a basis for a plausible and scientifically-based mechanism that underlies the metabolic effects of Seroquel. The authors report development of a mouse model to evaluate the effects of anti-psychotic drugs on food consumption, body weight, and body composition. This model development was undertaken in order to assist in understanding the known effects of some anti-psychotic drugs to induce significant weight gain in patients undergoing pharmacological treatment. The authors report that 4 weeks treatment with olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone, or risperidone caused significant weight increases in mice but only olanzapine and quetiapine were associated with significantly increased food intake. The authors also conclude that their mouse model of anti-psychotic-induced weight gain resembled the human experience with these medications. It should be noted that animals treated with quetiapine showed a dose-response effect on food consumption (see page 611 of Cope *et al.* 2005). Therefore, the results of this paper provide evidence for a biologic mechanism of Seroquel-induced weight gain that is related to increased caloric intake.

Dwyer and Donohoe (2003) also provide a basis for a plausible and scientifically-based mechanism that underlies the metabolic effects of Seroquel. The authors report use of the same mouse strain used by Cope *et al.* (2005), C57BL/6J mice, of the same age range but a different sex (Cope *et al.* used only female animals while Dwyer and Donohoe employed only male animals). Interestingly, using only a single dose of 10 mg/kg/day of Seroquel (a dose that would be equivalent to giving 700 mg to a 70 kg human; a dose within the therapeutic range for humans), the authors reported statistically significant increases in blood glucose levels at both 30 minutes and 3 hours after dosing. The authors also reported that inhibition of glucose transport was correlated with the hyperglycemic responses seen in the animals. It is the inhibition of glucose transport that

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[19] Vestri, H.S. et al. 2007. Atypical antipsychotic drugs directly impair insulin action in adipocytes: effects on glucose transport, lipogenesis, and antilipolysis. *Neuropsychopharmacology* 32:765-772.

[20] Cope, M.B. et al. 2005. Antipsychotic drug-induced weight gain: development of an animal model. *Int. J. Obesity.* 29:607-614.

is proposed as an underlying biologic mechanism for Seroquel as well as the other drugs shown to have similar activity (*e.g.,* risperidone, clozapine)[21]. Therefore, the results of this paper provide evidence for a biologic mechanism of Seroquel-induced hyperglycemia.

Vestri *et al.* (2006) is another paper that provides a basis for a plausible and scientifically-based mechanism that underlies the metabolic effects of Seroquel. The authors report results of *in vitro* testing to examine the effects of anti-psychotics, including Seroquel, to exert direct cellular effects on insulin action and substrate metabolism in adipocytes (fat cells). The cell lines used are ones routinely used to examine adipocyte functions. The authors reported that quetiapine treatment significantly reduced the lipolytic response to insulin in these cells; normally insulin stimulates lipolysis, or fat breakdown. The effect of quetiapine was similar to the effect seen with olanzapine and clozapine, in terms of potency. Quetiapine also reduced the basal rate of lipolysis in the cells, again similar in potency in producing this effect as compared to olanzapine and clozapine. The authors conclude that they have shown that drugs like quetiapine directly modulate insulin action and metabolic processes, *"and the results are relevant to the high risk of obesity and diabetes conferred by these medications"* (see page 6, left column of Vestri *et al.* 2006). Therefore, the results of this paper provide evidence for a biologic mechanism of Seroquel-induced weight gain and diabetes.

Finally, Savoy *et al.* (2008) is another paper that provides a basis for a plausible and scientifically-based mechanism that underlies the metabolic effects of Seroquel. The authors report on the effects of anti-psychotic drugs, including Seroquel, on plasma glucose and insulin levels *in vivo* in mice. Again, it is important to note that the dose of Seroquel administered to the mice was 10 mg/kg, which if given to a 70 mg human would be approximately 700 mg (in the therapeutic range). The authors report that quetiapine produced statistically significant increases in plasma glucose (produced hyperglycemia) but did not significantly increase plasma insulin levels in the mice; a similar effect was reported for olanzapine and clozapine. It is also reported that the strain of mice had an intact glucose-insulin homeostatic mechanism as evidenced by their

[21] It should be noted that there is published literature available which supports the link of these two drugs to hyperglycemia and diabetes as well.

responses seen following glucose administration. The authors reported that the lack of change in insulin levels in the mice with quetiapine treatment indicates that this drug is blocking the acute insulin secretory compensation mechanism that is usually apparent with hyperglycemic responses, an effect that is in agreement with other studies showing inadequate insulin secretion in dogs treated with olanzapine. The authors further suggest that the glucose response seen following treatment with quetiapine, as well as drugs such as olanzapine and clozapine, is driven by activation of the sympathetic nervous system via a central mechanism. Therefore, the results of this paper provide evidence for a biologic mechanism of Seroquel-induced hyperglycemia and diabetes.

Clearly, contrary to the defense counsel's assertions, I have provided a biologic mechanism that is plausible and scientifically-based for the metabolic effects of Seroquel, including a likely mechanism that could be acting independent of the additional weight gain mechanism.

Now, with respect to dose-response assessment and review of the studies I have cited as support for the weight-of-the-evidence, there are a variety of studies in cells, animals and humans, studies that often examine different endpoints. As a result, there is often a lack of dose-response information in any one study. However, as mentioned above with respect to the study by Cope *et al.* (2005), some studies do specifically provide dose-response data. The study by Cope *et al.* (2005), for example, provides dose-response information for weight gain and food consumption in mice, a model for the effects of Seroquel in humans. The AZ clinical trials for Seroquel also provide data on dose-response for weight gain in patients. However, due to the design of most epidemiological studies, such dose-response information is generally not available, a fact that is not an indicator of the lack of an effect for Seroquel but due to the fact that design of such a study would require enormous resources in order to recruit patients at both low and high doses of the drug, across diseases. For example, since higher doses of Seroquel are generally needed in order to treat schizophrenia, much lower doses of Seroquel may be used for less difficult to treat psychiatric conditions. Comparing doses across disease states is thus almost impossible with the epidemiological data currently available due to the way the drug is used by physicians.

There are, however, data from several AZ clinical trials that can be used to examine the dose-response of metabolic effects with Seroquel treatment. For example, data from AZ clinical trial 125 provides evidence that Seroquel treatment produces statistically significant adverse effects on glucose metabolism. Study 125, the AZ study that was supposedly designed to examine the adverse metabolic effects of Seroquel, was a 24 week, open label study comparing effects of glucose metabolism and insulin sensitivity in patients taking Seroquel (mean dose of 607 mg/day), and its closest market competitors, Zyprexa and Risperdal. It was not a blinded study, nor was it placebo-controlled, two important features of well-designed trials. The design of the study did attempt to control for factors which might confound indicators of glucose dysregulation: it was conducted in primarily white Eastern Europeans, with average baseline BMI of 24, and was intended to exclude patients with history of diabetes or recent atypical antipsychotic use. In other words, the study population was, in general, metabolically healthy; this population is not representative of the general population that is exposed to Seroquel. The study report shows that there were statistically significant increases in both mean fasting blood glucose (3.19 mg/dl) and the marker HbA1c (0.122%), indicating that Seroquel may have disrupted the body's ability to regulate glucose in a fasting state. Fasting C-peptide (a measure of endogenous insulin production) also increased, indicating that the patients were now producing more insulin in a fasting state: a marker for insulin resistance. Further, patients taking Seroquel experienced a mean weight gain of 3.65 kg (8 pounds) in just 24 weeks, a large amount of weight increase in a short period of time. The results of Study 125 provide evidence that Seroquel at doses in the range of 600 mg/day causes adverse metabolic effects, and that it may do so by increasing body weight and/or by inducing insulin resistance.

Other AZ clinical studies also provide dose-response information relating to adverse metabolic effects. Data from AZ Clinical Trial Report 50771L0015 reveals that the company observed a dose-response effect of Seroquel on weight gain across the dose range of 75 mg, 300 mg, and 600 mg Seroquel (see Table 45 of report). These effects are supported by data from a recent June 2008 FDA submission by AZ in response to a specific request by FDA to provide detailed analysis of clinical trials with metabolic data. In this recent submission, which I received after my report and deposition transpired, AZ

reported that in placebo-controlled trials with Seroquel, there was a significant increase in fasting blood glucose levels in patients taking Seroquel for a median time of only 55 days, with a significant number of the patients having fasting levels in the range of diabetes (greater than 126 mg/dL; see Table 339 of the report; attached to the Plaintiffs' exhibit submission). Inspection of data in Table 400 of this same report, also attached to the Plaintiffs' exhibition submission accompanying the opposition to the Daubert motion, reveals that in all trials, a list that did not include trials 41 and 49, despite the fact that they did not appear to meet the exclusion criteria, there was still a significant shift to diabetic levels of fasting blood glucose (*i.e.*, greater than 126 mg/dL) with Seroquel treatment after a median treatment time of only 71 days. While AZ does not explicitly articulate in the submission that the findings are statistically significant, it is clear from the reading of the tables and considering the confidence interval that they are, in fact, statistically significant. This is seen when one performs the relative risk (RR) calculation which AZ neglected to include. I calculate that this data resulted in a RR of 1.73 (95% confidence intervals 1.05-2.85) when quetiapine-treated patients from placebo-controlled trials are compared with placebo-treated patients. In addition to the striking consistency among the data in terms of seeing these effects (hyperglycemia that reaches levels indicative of diabetes) across trials, the median time to appearance of the effects are short, in days, characteristic of drug-induced effects, which can occur in days and weeks. I believe the analysis of this totality of clinical trial data itself supports the dose-response nature of the adverse metabolic effects of Seroquel.

It is also important to point out that the dose-response information available for Seroquel and adverse metabolic effects such as weight gain, hyperglycemia and diabetes indicates that these effects of Seroquel can be seen even at low doses. For example, inspection of the tables from the AZ June 2008 FDA submission reveals that data from Table 450 provide evidence for effects of Seroquel to produce hyperglycemia and diabetic level fasting blood glucose at low doses. In Table 450 it is seen that with Seroquel treatment there was a statistically significant increase in the number of patients exhibiting fasting blood glucose levels indicative of diabetes (> 126 mg/dL) as compared to patients receiving placebo, with the average dose of Seroquel administered being only 180 mg for about 56 days of exposure (median exposure duration). The RR can be

calculated to be 2.15 (95% confidence intervals 1.02-4.56) for Seroquel treatment. Further support for the adverse effects of Seroquel even at low doses is found in the paper by Buse et al. (2003)[22]. In this retrospective analysis of a patient claims database, the authors reported that at a mean dose of only 80 mg quetiapine (Seroquel) was associated with a statistically significant increase in the hazard ratio (HR) for development of diabetes with Seroquel treatment to 1.7. Both of these studies provide evidence that the effects of Seroquel to produce adverse metabolic effects are not limited to high doses of the drug.

Finally, defense counsel has suggested that the weight-of-the-evidence opinions I have expressed, that Seroquel can cause adverse metabolic effects that include weight gain, hyperglycemia and diabetes, are not generally accepted. I strongly disagree. In my deposition I discussed with counsel the fact that there are review articles available on diabetes risk and anti-psychotic drugs that state that Seroquel is associated with an increased risk of weight gain as well as diabetes. I would point to the 2004 consensus statement by the American Diabetes Association (ADA 2004) where they conclude by stating that *"These three adverse conditions [obesity, diabetes, and dyslipidemia] are closely linked, and their prevalence appears to differ depending on the SGA [second generation anti-psychotic] used. Clozapine and olanzapine are associated with the greatest weight gain and highest occurrence of diabetes and dyslipidemia. Risperidone and quetiapine appear to have intermediate effects. Aripiprazole and ziprasidone are associated with little or no significant weight gain, diabetes, or dyslipidemia, although they have not been used as extensively as the other agents."* (see page 600, far right column of ADA 2004). Therefore, this panel of experts has singled out certain anti-psychotics as being of greater risk than others in terms of weight gain and diabetes, with quetiapine being one listed has having a greater risk than some of the others. This is again consistent with my opinions where olanzapine would pose a greater risk than Seroquel.

Similarly, I would point the Court to the most authoritative and widely relied upon treatise in the field of pharmacology, *Goodman & Gilman's: The Pharmacological*

[22] Buse, J.B. et al. 2003. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. *J. Clin. Epidemiol.* 56:164-170.

Basis of Therapeutics, a resource that is available at every hospital formulary and the resource that I used when teaching pharmacology to medical students. This text notes:

> *"**Weight Gain and Metabolic Effects**. Weight gain and its associated long-term complications can occur with extended treatment with most antipsychotic and antimanic drugs. Weight gain is especially prominent with clozapine and olanzapine; somewhat less with quetiapine; even less with fluphenazine, haloperidol, and risperidone; and is very low with aripiprazole, molindone, and ziprasidone (Allison et al., 1999). Adverse effects of weight gain likely include increased risk of new-onset or worsening of type 2 diabetes mellitus, hypertension, and hyperlipidemia. Only some of these consequences are explained by risk factors associated with major psychiatric disorders themselves."*[23]

In addition to this authoritative pharmacology text, there are other textbooks that describe the adverse metabolic effects of anti-psychotic drugs, including Seroquel. The fact that this discussion is found in textbooks is proof of the general acceptance of the fact that Seroquel can cause adverse metabolic effects including weight gain, hyperglycemia, and diabetes. For example, in a textbook entitled "Applied Therapeutics: The Clinical Use of Drugs" it is stated that *"Among the atypical agents, weight gain is most common with clozapine and olanzapine, lowest with ziprasidone and aripirazole, and intermediate with risperidone and quetiapine."*; further that *"The issue of weight gain has important clinical implications in light of the link with impaired glucose tolerance and type II diabetes, hyperlipidemia, and increased mortality."*; further that *"Patients who had no weight gain due to atypical antipsychotics can still develop diabetes mellitus."*[24] In another textbook entitled "Pharmacotherapy Principles & Practice" it is stated that in the case of quetiapine, *"Mild weight gain and minor elevations in triglycerides can occur."*; under the section for antipsychotics that *"As a group, however, they are more likely [than conventional agents] to cause metabolic side effects such as weight gain, glucose dysregulation, and dyslipidemia."*; and further that

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[23] See page 480 of Baldessarini, R.J. and F.I. Tarazi. 2006. Pharmacotherapy of psychosis and mania. *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th edition.* L.L.

[24] Koda-Kimble, M.A. et al. 2009. *Applied Therapeutics: The Clinical Use of Drugs*, 9th edition. Lippincott Williams & Wilkins: Philadelphia, PA.

"Among the atypical antipsychotic drugs approved for treatment of bipolar disorder, olanzapine is more likely to cause metabolic side effects. Quetiapine and risperidone cause fewer metabolic effects than olanzapine. Aripiprazole and ziprasidone are neutral in effects on weight, glucose, and lipids."[25] These statements provide further support for the fact that the adverse metabolic effect profile of Seroquel is generally accepted by the medical community.

Moreover, the above statements from these medical texts reflect to me, clear general acceptance.

I hold additional relevant opinions as set forth in my expert report in this matter, which is attached and incorporated by reference.

I declare under penalty of perjury that the foregoing is true and correct. Executed this 22 day of November 2008.

Laura M. Plunkett, Ph.D, DABT

[25] Chisholm-Burns, M.A. et al. 2008. *Pharmacotherapy Principles & Practice*. McGraw-Hill: New York.

IN THE SUPERIOR COURT OF THE STATE OF DELAWARE

IN AND FOR NEW CASTLE COUNTY

IN RE: SEROQUEL LITIGATION C.A. No.: 07C-SER-1

THIS DOCUMENT RELATES TO:

ALL CASES IN FIRST HALF OF INITIAL TRIAL GROUP

EXPERT REPORT AND DECLARATION OF LAURA M. PLUNKETT, PH.D., DABT

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE: Seroquel Producst Liability Litigation
MDL DOCKET NO. 1769
This Document Relates to ALL CASES

EXPERT REPORT OF
Laura M. Plunkett, Ph.D., DABT
September 6, 2008

I. Training and Qualifications

1. I am a pharmacologist, toxicologist, United States Food and Drug Administration (FDA) regulatory specialist and principal of a consulting company known as Integrative Biostrategies, LLC. Integrative Biostrategies, based in Houston, Texas, is a consulting firm that works at the interface of biological science, regulatory affairs and business decisions to provide its clients with science-based solutions to issues associated with product development and stewardship. Before joining Integrative Biostrategies in 2001, I was head of the consulting firm known as Plunkett & Associates.

2. I am board-certified as a Diplomate of the American Board of Toxicology. I am a member of several professional organizations and have authored or co-authored numerous scientific publications. I have over twenty years of experience in the areas of pharmacology and toxicology and have worked in both government and academic research. I have taught pharmacology and toxicology at the undergraduate and postgraduate levels.

3. I received a B.S. degree in 1980 from the University of Georgia and a Ph.D. in pharmacology from the University of Georgia, College of Pharmacy in 1984. My doctoral

research was focused in the area of cardiovascular pharmacology and specifically dealt with delineating neurochemical mechanisms responsible for the cardiac toxicity of digitalis glycosides.

4. From June 1984 through August 1986, I was a Pharmacology Research Associate Training (PRAT) fellow at the National Institute of General Medical Sciences, Bethesda, Maryland. I worked in a neurosciences laboratory of the National Institute of Mental Health. My research focused on the role of various brain neurochemical systems involved in the control of autonomic nervous system and cardiovascular function.

5. From September 1986 to June 1989 I was an Assistant Professor of Pharmacology and Toxicology in the medical school at the University of Arkansas for Medical Sciences, Little Rock, Arkansas, where I performed basic research in the areas of neuropharmacology and toxicology as well as cardiovascular pharmacology and toxicology. I taught courses for both medical students and graduate students in pharmacology and toxicology as well as the neurosciences. During this time, I studied drugs of all classes that affect brain function, including anti-psychotic drugs. As a pharmacologist, my work was directed towards understanding the biologic mechanisms of drug actions. Much of my focus was on drugs that affect brain function, which includes anti-psychotics.

6. From December 1989 to August 1997, I worked for ENVIRON Corporation, first in the Arlington, Virginia office and then in the Houston, Texas office. I worked specifically within the health sciences group and most of my projects dealt with issues surrounding products or processes regulated by the FDA. During my consulting career (ENVIRON, Plunkett & Associates, and Integrative Biostrategies), I have worked on a variety of projects dealing with the regulation of products by the FDA, including human drugs, veterinary drugs, biologics, medical devices, consumer products, dietary supplements and foods. I have advised my clients on regulatory issues and strategies for their products (relating to both Canadian and American regulations), designed preclinical and clinical studies for both efficacy and safety, advised clients on issues related to statements regarding efficacy and warnings for their products based on the current labelling regulations and generally acted as a regulatory affairs staff for small companies

in their early stages of product development. A tool common to all work my work as a consultant would be risk assessment, including many projects where risks and benefits of human therapeutics were at issue. Attached here in Appendix A is a copy of my curriculum vitae.

II. Information Reviewed

7. During the course of work on this case, I have reviewed the following materials:

a) scientific literature relating to the pharmacology and toxicology of anti-psychotic drugs in general and quetiapine (Seroquel) in particular;

b) labelling for Seroquel as provided by the Physician's Desk Reference; and

c) regulations of the U.S. Food and Drug Administration (FDA) relating to the development, approval, labelling and marketing of prescription drug products.

III. Summary of Bipolar Disorder and Schizophrenia

8. Schizophrenia is a major mental illness described by the Diagnostic and Statistical Manual of Mental Disorders ("DSM IV") as a psychotic disorder that is a chronic, severe and disabling brain disease. The hallmark of schizophrenia is disordered thought and perception. Typical symptoms include delusions and hallucinations. While most people diagnosed with schizophrenia are not gainfully employed, a substantial minority do have gainful employment.

9. Bipolar disorder is described by the DSM IV as a mood disorder. Bipolar disorder is a major mental illness, the hallmark of which is manic episodes marked by a euphoric, irritable or expansive mood. Patients with bipolar disorder usually also experience major depressive episodes.

IV. Atypical Anti-psychotics

10. The primary class of drugs used to treat symptoms of schizophrenia and bipolar disorder is known as anti-psychotics. Additionally, mood stabilizers or anti-depressants may also be used to treat bipolar disorder.

11. Anti-psychotics fall into two general categories: the newly developed atypical anti-psychotics and the older, conventional or typical anti-psychotics. The term "atypical" is

applied to the newer drugs mainly because of the lower risks of adverse neurological effects known as extrapyramidal effects. As a general rule, because many atypical anti-psychotics (including Seroquel) still have patent protection, generic versions are not available and as such they are more expensive to purchase and, as a result, more profitable to the manufacturer.

12. Conventional, or typical, anti-psychotics as a group include drugs of a number of different chemical classes. These drugs have efficacy to treat both bipolar disorder and schizophrenia but also often exhibit significant side effects, including risk of acute and long-term neurological side effects, including extrapyramidal effects.

13. Atypical anti-psychotic drugs are considered as having less of a risk of producing extrapyramidal side effects, the unwanted neurological effects that are characterized by changes in movement. In fact, the goal of introducing atypical anti-psychotics to the marketplace was to provide an effective treatment that also improved the quality of life of the patient. While the exact mechanisms responsible for the pharmacological differences between typical and atypical anti-psychotics have not yet been clearly defined, differences have been identified in the pattern of brain neurotransmitter receptor systems affected by the various drugs, effects that can be seen in responses elicited in animal models and/or effects that relate to the pharmacological and toxicological responses in humans.

14. Anti-psychotics will only treat the symptoms of schizophrenia and bipolar disorder; there is no "cure" for such disorders. The etiology of schizophrenia and bipolar disorder also remains to be elucidated, although genetics appears to play some role in these disorders.

15. Quetiapine, marketed in the U.S. under the trade name of Seroquel, is a widely prescribed prescription drug product that was approved by the FDA in 1997 for the treatment of schizophrenia. Seroquel was subsequently approved for management of acute manic episodes associated with bipolar disorder in 2004. I believe that Seroquel is also widely prescribed for off-label uses, including the treatment of sleep disorders, control of agitation, anxiety, aggression and behavioural disturbances.

16. The psychotic symptoms treated with atypical anti-psychotic drugs such as Seroquel include disordered thought processes, disorganized and/or irrational behaviour, and degrees of altered mood, from severe agitation to severe withdrawal. Other drugs that have been or are used in the treatment of psychotic disorders include phenothiazines (*e.g.*, chlorpromazine, also known as Thorazine; thioridazine, also known as Mellaril), thioxanthines (*e.g.*, chloprothixene, also known as Taractan; thiothixene, also known as Navane), haloperidol (Haldol), clozapine (Clorazil), aripiprazole (Abilify), loxapine (Loxitane), molindrone (Moban), pimozide (Orap), olanzapine (Zyprexa), riperidone (Risperdal), and ziprasidone (Geodon). The optimum therapy for treating schizophrenia and bipolar disorder is chosen for each patient based on the patient's medical history, including any risks of known side effects of the drug, and the patient's response to the drug in relation to the drug's efficacy and adverse events.

17. The pharmacology of Seroquel and other similar anti-psychotic drugs is described in many textbooks and review articles (*e.g., Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th edition.* 2006. Brunton, L.L. et al. (eds.), McGraw-Hill: New York, chapter 18). Seroquel produces its therapeutic and adverse effects through its activity on various receptor systems in the brain and throughout the body. Seroquel is known to be an antagonist of D_1, D_2, 5-HT_{1A}, 5-HT_{2A}, H_1, α_1, and α_2 receptors. The efficacy of Seroquel and other atypical anti-psychotic drugs has been linked to dopaminergic and serotonergic system antagonist activity. However, the exact mechanism by which atypical anti-psychotic drugs produce their effects in schizophrenia and bipolar disorders is not known.

V. Seroquel and Associated Health Risks

18. Seroquel is well absorbed following oral administration, with peak concentrations achieved in the blood within 1.5 hours, and an elimination half-life in the range of 6 hours. It is widely distributed in the body and steady state blood levels are achieved within a few days. Following oral administration, Seroquel is extensively metabolized although the major metabolites are not pharmacologically active.

19. Seroquel use has been associated with deaths that have been attributed to severe liver, kidney, and pancreatic damage. Its adverse effects include, but are not limited to,

ketoacidosis, pancreatitis, diabetes mellitus, weight gain, hyperglycemia, blindness, increased thirst, and hypoglycemia. Other serious injuries associated with Seroquel use include: a potentially fatal condition known as neuroleptic malignant syndrome (NMS); tardive dyskinesia, which can cause potentially irreversible, involuntary movements; and other serious health problems associated with the onset of diabetes including heart disease, blindness, coma, seizures and death. These adverse health effects have been reported following both short-term and longer-term use of Seroquel.

20. Some of the adverse health effects associated with Seroquel use have been attributed to activity of the drug on certain receptor systems in the body. For example, orthostatic hypotension seen in some patients administered Seroquel is thought to be attributed to α_1-adrenergic antagonist activity of the drug while somnolence has been attributed to antagonism of histamine type 1 (H_1) receptors by Seroquel.

21. While Seroquel is similar in basic pharmacological profile to other atypical anti-psychotic drugs, including olanzapine and risperidone, the potency of Seroquel as an antagonist at D_2 and 5-HT_{2A} receptors is less than either olanzapine or risperidone. Differences in potency as an antagonist at certain receptor types may explain some of the differences observed among the various atypical anti-psychotics in terms of both efficacy and toxicity.

22. It has been known for decades that many anti-psychotic drugs have effects to alter metabolism that can lead to weight gain and effects on glucose metabolism (*e.g.*, Baldessarini, R.J. 1980. Drugs and the treatment of psychiatric disorders. In: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 6th edition.* A.G. Gilman et al. (Eds.), chapter 19, MacMillan Publishing Co.: New York). However, it has been recognized more recently (since about 1999) that there appear to be differences among the various anti-psychotic drugs in terms of their propensity for inducing weight gain and changes in glucose metabolism, as well as the onset of diabetes (*e.g.*, Melkersson, K. and M-L. Dahl. 2004. *Drugs* 64:701-723; American Diabetes Association et al. 2004. *Diabetes Care* 27:596-601; Allison, D.B. et al. 1999. *Am. J. Psychiatry* 156:1686-1896; Bobes, J. et al. 2003. *Schizophr. Res.* 62:77-88; Wetterling, T. 2001. *Drug Saf.* 24:59-73; Buse, J.B. et al. 2003. *J. Clin. Epidemiol.* 56:164-170). Moreover, it has

now been recognized that clinically significant hyperglycemia and diabetic complications can occur during anti-psychotic treatment both with and without changes in body weight (Newcomer, J.W. et al. 2002. *Arch. Gen. Psychiatry* 59:337-345; Newcomer, J.W. 2005. *CNS Drugs* 19(S1):1-93). Because of the differences apparent among different anti-psychotic agents in terms of risks of diabetes and weight gain, the effects of Seroquel cannot be considered simply a "class" effect for atypical anti-psychotic drugs (Newcomer, J.W. 2005. *CNS Drugs* 19(Suppl. 1):1-93). Different anti-psychotic drugs, including the second generation atypical anti-psychotic agents, have different toxicological profiles.

23. Between January 1997 and July 2002, numerous adverse drug event reports were submitted to the FDA. These reports indicated that patients consuming Seroquel experienced significant adverse health effects, including hyperglycemia, diabetes, exacerbation of pre-existing diabetes, ketoacidosis, and death. These adverse event reports were discussed in an article by Koller *et al.* (2004. *J. Clin. Psychiatry* 65:857-863). The authors concluded that use of Seroiquel may unmask or precipitate hyperglycemia in patients.

24. Case reports linking Seroquel use with hyperglycemia and/or diabetes appeared in the published literature as early as 1999 (*e.g.*, Sobel *et al.* 1999. *J. Clin. Psychiatry* 60:556-557).

25. A large study involving the U.S. Veterans' Administration (Sernyak, M.J. *et al.* 2002. *Am. J. Psychiatry* 159:561-566) was performed in 1999 where records from all patients being treated nationally with anti-psychotics were examined. The authors reported that there was an increased risk of diabetes with exposure to certain anti-psychotic drugs. One of the drugs shown to be associated with an increased risk was Seroquel.

26. At a conference in Europe in 2002, Lambert and colleagues reported the results of a matched case-control study of California Medicaid claims data from 1997 through 2000. They found that there was an increased risk of developing type II diabetes in patients exposed to Seroquel (Lambert *et al.* 2002. *Eur. Neuropsychopharmacol.* 12:S307).

27. In or about August of 2003, a report in the *Wall Street Journal* showed that a study of 19,878 U.S. military veterans between October 1998 and October 2001 indicated that

Seroquel and other members of the new class of anti-psychotic drugs posed a higher risk of diabetes. The article stated that effects were most pronounced with Seroquel.

28. At a conference of the *International Society for Pharmacoepidemiology* held in Philadelphia on August 23 and 24, 2003, study data were reported that showed that patients on Seroquel had 3.34 times as many cases of diabetes as those on older antipsychotic drugs.

29. When considered as a whole in a weight-of-the evidence assessment, the available scientific data indicate that Seroquel can cause physiological effects known to be risk factors for diabetes, including increased body weight and other metabolic effects, and can cause diabetes itself. The scientific data include case reports published on an ongoing basis since 1999 (Sobel, M. et al. 1999. *J. Clin. Psychiatry* 60:556-557; Procshyn, R.M. et al. 2000. *Can. J. Psychiatry* 45:668-669; Wilson, D.R. et al. 2002. *Schizophr. Res.* 59:1-6; Domon, S.E. and C.S. Cargile. 2002. *J. Am. Acad. Child Adolesc. Psychiatry* 41: 495-496; Sneed, K.B. et al. 2003. *J. Am. Board Fam. Pract.* 16:251-254), clinical data (*e.g.*, Borison, R. et al. 1996. *J. Clin. Psychopharmacol.* 16:158-169; Small, J.G. et al. 1997. *Arch. Gen. Psychiatry* 54:549-557; Arvanitis, L.A. and B.G. Miller. 1997. *Biol. Psychiatry* 42:233-246; Peuskens, J. and C.G. Link. 1997. *Acta Psychiatr, Scand.* 96:265-273; Copolov, D.L. et al. 2000. *Psychol. Med.* 30:95-105; Brecher, M. et al. 2000. *Int. J. Psych. Clin. Pract.* 4:287-291; Wirshing, D.A. et al. 2002. *J. Clin. Psychiatry* 63:856-865; Nasrallah, H. 2003. *Psychoneuroendocrinology* 28:83-96; the product insert for Seroquel in 2005, *Physician's Desk Reference*, pp. 662-667), a survey of adverse drug reports (Koller, E.A. et al. 2004. *J. Clin. Psychiatry* 65:857-863), epidemiological data assembled since 1999 (Sobel et al. 1999. *J. Clin. Psychiatry* 60:556-557; Sernyak, M.J. et al. 2002. *Am. J. Psychiatry* 159:561-566; Ollendorf, D.A. et al. 2004. *MedGenMed* 6:5; Citrome, L. et al. 2004. *Psychiatr. Serv.* 55:1006-1013; Leslie, D.L. and R.A. Rosenheck. 2004. *Am. J. Psychiatry* 161:1709-1711; Feldman, P.D. et al. 2004. *J. Am. Med. Dir. Assoc.* 5:38-46; Sacchetti, E. et al. 2005. *Int. Clin. Psychopharm.* 20:33-37; Lambert, B.L. et al. 2006. *Am. J. Epidemiol.* 164:672-681; Guo, J.J. et al. 2006. *J. Clin. Psychiatry* 67:1055-1061; Guo, J.J. et al. 2007. *Pharmacotherapy* 27:27-35), and animal data (Cope, M.B. et al. 2005. *Int. J. Obesity* 29:607-614). Each source of information is important in the analysis of the risks associated with

use of Seroquel, and is consistent with accepted methods for establishing causation in a weight-of-the-evidence analysis (Hill, A.B. 1965. *Proc. Royal Soc. Med.* 58:295-300).

30. I believe that the available scientific data demonstrate that Seroquel consumption and use can cause adverse metabolic effects that include, but are not limited to an increased risk of clinically significant body weight gain, hyperglycemia, altered glucose metabolism, and an increased risk of diabetes and diabetes-related complications.

31. It is also important to remember that although clinical trials had been performed with Seroquel as part of the drug development process, such trials are limited in their ability to identify risks associated with drug use by the general population. This is because such drug development clinical trials are performed in either healthy volunteers or in patients that have often been pre-screened for the propensity to develop adverse effects such as hyperglycemia or diabetes, with such patients then usually excluded from studies. It is only after a drug has been placed on the market, and wider exposure is seen, that a true picture of the adverse effects associated with a drug can be observed. As a result, I believe that companies have the duty to carefully monitor their drugs after approval and during marketing for either the existence of new adverse events or a higher than expected incidence of known adverse effects.

32. Scientific studies have established that there are apparent differences among anti-psychotic drugs in terms of risks of diabetes, weight gain and other adverse health effects discussed above. As a result of these differences, and differences in toxicological profiles, I believe that side effects arising through the consumption of Seroquel cannot be described as a "class effect" for all atypical anti-psychotic drugs.

33. Finally, when considering the adverse health effects associated with use of Seroquel, it is important to realize that Seroquel is not unique in terms of its efficacy. Studies have shown that other anti-psychotic drugs have similar effectiveness to Seroquel but have less risk for hyperglycemia, weight gain, metabolic disturbances and diabetes. Therefore, there are safer alternative therapies that could be used that would also provide for effective treatment but with fewer side effects.

34. For example, in the CATIE Schizophrenia Trial, a trial sponsored by the National Institute of Mental Health which is the largest trial conducted to date comparing efficacy and safety of some of the most prescribed anti-psychotic drugs, it was shown that clozapine was more effective than other atypical anti-psychotics (*i.e.*, Seroquel, Zyprexa, Risperdal). Further, when all of the atypical agents studied were examined, including Seroquel, none of the agents was more effective or better tolerated than the typical anti-psychotic, perphenazine (Manschreck, T.C. and R.A. Boshes. 2007. *Harv. Rev. Psychiatry* 15:245-258; Nasrallah, H.A. 2007. *J. Clin. Psychiatry* 68:5-11).

VI. Mechanisms Underlying the Adverse Effects of Seroquel

35. Although the exact molecular mechanisms responsible for the metabolic effects of Seroquel have not been established, there are data that describe the basic mechanisms that lead to the effects of Seroquel on body weight gain and altered glucose metabolism, and eventually diabetes. However, weight gain is not a prerequisite for atypical anti-psychotic drug-induced effects on glucose metabolism and induction of type II diabetes (Newcomer, J.W. 2004. *Clin. Ther.* 26:1936-1946; Newcomer, J.W. 2005. *CNS Drugs* 19(S1):1-93; Dwyer, D.S. and D. Donohoe. 2003. *Pharm. Biochem. Behav.* 75:255-260; Ardizzone, T.D. et al. 2001. *Brain Res.* 923:82-90; Dwyer, D.S. et al. 1999. *Prog. Neuro-Psychopharmacol. Biol. Psychiat.* 23:69-80; Newcomer, J.W. et al. 2002. *Arch. Gen. Psychiat.* 59:337-345; Koller, E.A. and P. Murali. 2002. *Pharmacotherapy* 22:841-852; Koller, E. et al. 2001. *Am. J. Med.* 111:716-723; Ebenbichler, C.F. et al. 2003. *J. Clin. Psychiat.* 64:1436-1439).

36. Clinically significant body weight gain is often seen with administration of Seroquel to patients (Borison, R. et al. 1996. *J. Clin. Psychopharmacol.* 16:158-169; Small, J.G. et al. 1997. *Arch. Gen. Psychiatry* 54:549-557; Arvanitis, L.A. and B.G. Miller. 1997. *Biol. Psychiatry* 42:233-246; Peuskens, J. and C.G. Link. 1997. *Acta Psychiatr, Scand.* 96:265-273; Copolov, D.L. et al. 2000. *Psychol. Med.* 30:95-105; Brecher, M. et al. 2000. *Int. J. Psych. Clin. Pract.* 4:287-291; Nasrallah, H. 2003. *Psychoneuroendocrinology* 28:83-96). The effects of atypical anti-psychotics on weight gain have been shown to be attributable to both increased caloric intake (increased appetite) and decreased energy expenditure (Gothelf, D. et al. 2002. *Am.*

J. Psychiatry 159:1055-1057; Virkkunen, M. et al. 2002. *Pharmacopsychiatry* 35:124-126). These mechanisms for increased body weight gain are consistent with the fact that Seroquel has effects on neurotransmitter systems in the brain that affect appetite and mood. It is well-established in the medical literature that a clinically significant increase in body weight is a risk factor for diabetes (*e.g.*, Foster, D.W. 1994. Diabetes mellitus. In: *Harrison=s Principles of Internal Medicine, 13th edition.* K.J. Isselbacher et al. (Eds.), chapter 337, McGraw-Hill: New York). Therefore, any effect of Seroquel to increase body weight is a significant risk for the development of diabetes.

37. As discussed above, Seroquel administration to patients has been linked to an increased risk of type II diabetes (see the weight of the evidence discussion above). The mechanisms responsible for development of type II diabetes have been examined in both animals and humans. Type II diabetes is a disorder that is characterized by normal or high levels of insulin in blood at the same time that glucose levels in blood are elevated. The condition is sometimes referred to as insulin resistance. Insulin normally acts to promote transport of glucose across cell membranes (reducing blood glucose levels) and to inhibit lipolysis. Resistance to the activity of insulin leads to hyperlipidemia and eventually to hyperglycemia and even development of diabetes. Although increased weight gain has been discussed as a likely factor in the development of insulin resistance and drug-induced diabetes, there are data that demonstrate Seroquel-induced effects on glucose metabolism and insulin resistance that are independent of weight gain.

38. Observational data has shown that atypical anti-psychotics that are structurally similar to Seroquel (*i.e.,* clozapine and olanzapine) can exert direct effects on glucose-insulin homeostasis by induction of hyperinsulinemia (Melkersson, K.I. et al. 2003. *Psychopharmacology* 170:157-166; Melkersson, K.I. et al. 2000. *J. Clin. Psychiatry* 61:742-749). The increased levels of insulin lead to decreased insulin sensitivity in tissues and could lead to an insulin-resistant state (Melkersson, K. and M-L. Dahl. 2004. *Drugs* 64:701-723). *In vitro* data have shown that olanzapine stimulates insulin release from pancreatic islet cells (Melkersson, K. 2004. *Eur. Neuropsychopharmacology* 14:115-119). Regardless of the exact molecular changes that may occur in any one patient treated with Seroquel, these data indicate

that atypical anti-psychotics that are pharmacologically and chemically similar to Seroquel have direct and indirect effects on glucose metabolism that are consistent with the development of insulin resistance, hyperglycemia and potentially type II diabetes. Considered together, the mechanistic data provide evidence for both direct and indirect effects that can lead to disturbances in glucose metabolism and development of type II diabetes. These findings are supported by findings with atypical anti-psychotic drugs, including data specific to Seroquel, that have linked the drugs to induction of diabetes, apart from the induction of weight gain (Dwyer, D.S. and D. Donohoe. 2003. *Pharm. Biochem. Behav.* 75:255-260; Ardizzone, T.D. et al. 2001. *Brain Res.* 923:82-90; Dwyer, D.S. et al. 1999. *Prog. Neuro-Psychopharmacol. Biol. Psychiat.* 23:69-80; Newcomer, J.W. et al. 2002. *Arch. Gen. Psychiat.* 59:337-345; Koller, E.A. and P. Murali. 2003. *Pharmacotherapy* 22:841-852; Koller, E. et al. 2004. *J. Clin. Psychiatry* 65:857-863; Ebenbichler, C.F. et al. 2003. *J. Clin. Psychiat.* 64:1436-1439).

39. The data indicate that administration of Seroquel can cause diabetes and/or the effects on glucose metabolism that can lead to diabetes. The data also indicate that Seroquel poses a greater risk for hyperglycemia and diabetes, both with and without body weight gain, than some other anti-psychotic drugs.

40. Although available studies have focused on the association of type II diabetes with Seroquel treatment, as well as treatment with other atypical anti-psychotic drugs, the toxicity of these drugs, which includes altered glucose metabolism, obesity, and hyperglycemia, would also be significant risk factors for individuals with undiagnosed type I diabetes or a genetic predisposition for type I diabetes. Type I diabetes is characterized by a loss of insulin secretion capacity due to the loss of beta cells in the pancreas. The loss of insulin secretion capacity means that type I diabetics would need to rely on exogenous sources of insulin to control blood glucose levels. Therefore, it is only common sense that any effects of a drug such as Seroquel to affect glucose metabolism or blood glucose levels would be a greater risk for individuals who already are at risk of type I diabetes or who are not yet exhibiting clinical signs and symptoms of type I diabetes.

VII. Warning of Health Risks

41. Despite the findings of the studies discussed above, AstraZeneca failed to warn the FDA, physicians, other health practitioners, and patients of the adverse metabolic effects associated with the consumption of Seroquel at the time these risks were first identified.

42. A review of the most recent product labelling for Seroquel that is available to health professionals demonstrates that, in my opinion, the warnings related to risks of hyperglycemia and diabetes in particular are not adequate to convey the risks posed by Seroquel itself. The discussion of hyperglycemia and diabetes is put forth as an effect of anti-psychotics in general only.

43. At the time that the Seroquel labelling failed to adequately warn physicians of the risks associated with use of the drug, other international regulatory bodies were requiring specific changes to product labelling related to the risks of hyperglycemia and diabetes that were associated with Seroquel, not anti-psychotics in general. For example, in Japan, physicians were being specifically warned to not use Seroquel in patients with a history of diabetes and to monitor patients for development of glucose abnormalities during treatment with Seroquel, regardless of their medical history. Additionally, in 2005 permission to market Seroquel in France had been denied due in part to the risk of hyperglycemia and diabetes associated specifically with Seroquel, again not anti-psychotics in general. Accordingly, I believe that the physicians in the U.S., and as a result their patients, were not being supplied with adequate risk information related to hyperglycemia and diabetes even though actions had been taken in other countries to warn physicians and patients of these risks.

44. As a result, I believe that the product warnings were wholly inadequate to warn physicians and their patients of the significant adverse metabolic effects associated with the consumption of Seroquel. Nonetheless, Seroquel was marketed heavily as safe and effective for the treatment of bipolar disorder and schizophrenia, promising fewer side effects than other similar treatments including the other atypical anti-psychotics on the market. Further, Seroquel was being prescribed by physicians for treatment of conditions other than bipolar disorder and schizophrenia (off-label use), which use I believe was known by Astra-Zeneca.

VIII. Conclusion

45. In conclusion, based on my training and experience as a pharmacologist, toxicologist, and risk assessor, it is my opinion that Seroquel can cause hyperglycemia and diabetes. The adverse health effects, including these adverse metabolic effects, associated with the consumption and use of Seroquel were predictable based on the known pharmacological profile of the drug and would have been predicted prior to the approval of Seroquel based on the known effects of other structurally similar anti-psychotic drugs. Moreover, the adverse health effects associated with Seroquel consumption and use can be serious, life-threatening conditions and were recognized in the published medical literature soon after the drug was approved. All opinions expressed in this report are based on a reasonable degree of scientific certainty.

IX. Compensation

46. My compensation by plaintiff's attorney in this matter is at the rate of $300.00 per hour for review of documents and materials related to the case and $400.00 per hour for testimony.

X. Previous Testimony

47. A list of my previous testimony for the past four years is included in Appendix B.

I certify that the foregoing statements made by me are true and correct. Executed this 6th day of September 2008 at Houston, Texas.

LISA GONZALES
MY COMMISSION EXPIRES
February 15, 2009

Laura Plunkett, Ph.D., D.A.B.T.

STATE OF TEXAS)

) ss.

COUNTY OF HARRIS

Subscribed and sworn to me

Before this 6th day of Sept 2008.

Signature of Notary Public

My Commission Expires February 15, 2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

James L. Gaskill, PharmD
Director
Promotional Regulatory Affairs
AstraZeneca
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Mailstop D1C-715
Wilmington, DE 19803-8355
Fax (302) 886-2822

Schwartz
EXHIBIT NO. 63
AM 1/11/08

RE: NDA # 20-639
Seroquel® (quetiapine fumarate) Tablets
MACMIS ID # 14670

Dear Dr. Gaskill:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a professional sales aid (238110) for Seroquel® (quetiapine fumarate) tablets (Seroquel) submitted by AstraZeneca under cover of Form FDA 2253. This piece is false or misleading because it minimizes the risk of hyperglycemia and diabetes mellitus and fails to communicate important information regarding neuroleptic malignant syndrome, tardive dyskinesia, and the bolded cataracts precaution. Thus, the promotional material misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(6)(i). The promotional material raises significant public health and safety concerns through its minimization of the risks associated with Seroquel.

Background

According to its FDA-approved product labeling (PI), Seroquel is indicated for the treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex and for the treatment of schizophrenia.

The PI includes important warnings and precautions. It states (in pertinent part):

WARNINGS

Neuroleptic Malignant Syndrome (NMS)
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical

EXHIBIT
116

manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

Tardive Dyskinesia
A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing

a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome.

Hyperglycemia and Diabetes Mellitus
Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including Seroquel. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

Orthostatic Hypotension
SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period. SEROQUEL should be used with particular caution in patients with known cardiovascular disease, cerebrovascular disease or conditions which would predispose patients to hypotension.

Cataracts
Examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment.

Seizures
As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold.

* * *

After reviewing the available data pertaining to the use of atypical antipsychotic medications and diabetes mellitus adverse events, FDA asked all manufacturers of atypical antipsychotics to include a warning in their PI regarding this risk on September 11, 2003. FDA believes that the safe use of Seroquel can be enhanced by informing prescribers and patients about these events and increased attention to the signs and symptoms of diabetes mellitus may lead to earlier detection and appropriate treatment and thus reduce the risk for the most serious outcomes. The PI including the hyperglycemia and diabetes mellitus warning for Seroquel was approved on January 12, 2004.

Misleading Presentation

Page two of the professional sales aid starts with a prominent header, which states "Diabetes Information," and then presents the following five bullets:

- Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL
- The relationship of atypical use and glucose abnormalities is complicated by the possibility of increased risk of diabetes in the schizophrenic population and the increasing incidence of diabetes in the general population
- The results of retrospective studies of SEROQUEL and diabetes have been discrepant
- Postmarketing reports of diabetes or diabetes-related events are very rare (<0.01%) with SEROQUEL. These reports were confounded by preexisting or coexisting risk factors and/or had limited information
- SEROQUEL is an atypical that has had over 16 million patient exposures worldwide since its approval in 1997. AstraZeneca believes that the available scientific and medical data do not establish that SEROQUEL causes diabetes

The first two bullets contain information from the Warning in Seroquel's PI regarding Hyperglycemia and Diabetes Mellitus concerning the observed hyperglycemic events and the areas of uncertainty about the glucose abnormality findings. While the agency acknowledges that it has not been established whether Seroquel causes diabetes, you fail to include information regarding the increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics. The increased risk may be due to confounding factors and is not completely understood, but a warning about it was recently added to Seroquel's PI to enhance the safe use of Seroquel and protect public health. Because your bullets about the relationship between the use of Seroquel and hyperglycemia leave out this information, the bullets are misleading and undermine the warning.

Furthermore, the fourth bullet claims that the percentage of diabetes or diabetes-related events in post-marketing reports is "very rare (<0.01%) with Seroquel." In light of the voluntary nature of post-marketing adverse event reporting by healthcare professionals and patients, it is infeasible to obtain an accurate percentage of all diabetes or diabetes-related

adverse events associated with Seroquel based upon these reports. Therefore, quantifying post-marketing adverse events in this manner is misleading.

Omission of Material Facts

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. Specifically, the professional sales aid fails to include relevant risk information about the Warnings and Precautions that it presents. While the professional sales aid states that "Prescribing should be consistent with the need to minimize the risk of tardive dyskinesia," it fails to reveal that the risk of developing the condition and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered increase. The sales aid also fails to mention that the syndrome may partially or completely remit if antipsychotic treatment is withdrawn. Additionally, the professional sales aid states that "A rare condition referred to as neuroleptic malignant syndrome has been reported with this class of medications, including SEROQUEL." This statement is misleading in that it fails to reveal that NMS is a potentially fatal symptom complex associated with the administration of Seroquel. Furthermore, the professional sales aid fails to convey the important information from the PI regarding the clinical manifestations of NMS and that management of NMS should include immediate discontinuation of antipsychotic drugs.

The professional sales aid states that "Precautions include the risk of seizures, orthostatic hypotension, and cataract development." This statement is misleading because it omits material facts from the PI about these risks. In particular, it fails to mention important information from the bolded cataracts precaution recommending that physicians examine all patients at initiation of Seroquel treatment or shortly thereafter, and at six month intervals during chronic treatment, to detect cataract formation.

Conclusion and Requested Action

For the reasons discussed above, the professional sales aid misbrands Seroquel in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(6)(i).

DDMAC requests that AstraZeneca immediately cease the dissemination of violative promotional materials for Seroquel such as those described above. Please submit a written response to this letter on or before November 30, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for Seroquel the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, or facsimile at 301-796-9878. In all future correspondence regarding this matter, please refer to MACMIS # 14670 in addition to the NDA number. We remind you that only written communications are considered official. If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Seroquel comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Robert Dean, MBA
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Dean
11/16/2006 08:56:28 AM

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE: Seroquel Products Liability Litigation

MDL DOCKET NO. 1769

This document relates to:

Linda Guinn	6:07-cv-10291
Janice Burns	6:07-cv-15959
Richard Unger	6:07-cv-1581 2
Connie Curley	6:07-cv-15701
Linda Whittington	6:07-cv-10475
Eileen McAlexander	6:07-cv-10360
~~Sandra Carter~~	~~6:07-cv-13234~~
~~Clemmie Middleton~~	~~6:07-cv-10949~~
~~Hope Lorditch~~	~~6:07-cv-12657~~
David Haller	6:07-cv-15733
~~Charles Ray~~	~~6:07-cv-11102~~
~~William Sarmiento~~	~~6:07-cv-10425~~

DECLARATION OF WILLIAM WIRSHING, M.D.

My name is William C. Wirshing. I am over twenty-one years of age, am of sound mind, have never been convicted of a felony, and am otherwise competent to make this Declaration-Report. I have personal knowledge of all factual statements contained herein and all such factual statements are true and correct as outlined herein in this declaration-report.

Qualifications and Expertise

1. I graduated in 1978 from the College of Engineering at the University of California at Berkeley with highest honors and a Bachelors of Science degree in Electrical Engineering and Computer Science (minor in bioelectric systems). I received my M.D. from the University of California at Los Angeles in 1982, receiving the Sandoz Award for "Excellence in the Behavioral Sciences." I remained at UCLA for both my rotating

internship, during which I focused on internal medicine, neurology, and pediatrics and for my three-year residency training in psychiatry. My final year of residency was at the West Los Angeles Veterans Affairs Medical Center where I was Chief Resident in Geropsychiatry. Over the next two years, I was a Post Doctoral Research Scholar at UCLA, a fellowship position through the National Institute of Mental Health during which I learned and applied clinical research techniques for the study of persons with severe schizophrenia.

2. I am the Vice-President in charge of research and continuing medical education for Exodus Inc. in Culver City, California and also Clinical Director of Exodus Real Recovery in Agoura Hills, California. In my clinical psychiatric practice, I see approximately 325 new patients in a typical month; supervise nearly a dozen psychology doctoral candidates; and teach over a dozen nursing, social work, and nurse practitioner students.

3. Over the decades between 1986 and 2006, both my clinical work and research focus remained on the treatment of persons with schizophrenia. I was the Chief of the Schizophrenia Treatment Unit at the VA Medical Center during the vast bulk of this time frame, and was also the Co-Chief of the Schizophrenia Outpatient Research Clinic during the last ten years.

4. Given my expertise in the treatment of schizophrenia, I have had occasion to prescribe Seroquel and the other antipsychotic agents and have extensive first hand clinical and academic experience with the medication. I was invited to be one of nineteen experts who presented their findings and opinions at the consensus development conference in November 2003 before the American Diabetes Association; the American Psychiatric

Association; the American Association of Clinical Endocrinologists and the North American Association for the Study of Obesity. It was the findings of this conference that resulted in the February 2004 Consensus Statement in the journal *Diabetes Care*, cited by counsel.

5. I have also been involved in litigation regarding another anti-psychotic agent, olanzapine (Zyprexa). I was found qualified to testify before the MDL court in that litigation. Moreover, as a lead witness for the State of Alaska in litigation involving Zyprexa, Eli Lilly did not challenge my qualifications and I presented my opinions in that recent trial which settled before verdict.

6. I have attached my *curriculum vitae* and the report I submitted to counsel for Plaintiffs in this litigation, and I incorporate those documents by reference herein. I also incorporate my deposition testimony.

Definitions

7. I have been asked to provide some basic definition of some salient medical terms : OGTT, two hour and fasting glucose and HbA1c.

> OGTT is a standard test of glucose metabolism wherein a patient in a fasting state is administered a standard oral glucose load (usually 75gm) and has his/her blood glucose measured at standard intervals out to two hours.
>
> Two hour glucose: The plasma glucose measured two hours after the oral glucose load in the OGTT
>
> Fasting glucose: Plasma glucose measured in the fasting state (i.e., at least 8 consecutive hours of fasting--though sometime the definition is extended to 12 hours.
>
> HbA1C: This is glycosolated hemoglobin. It is a measure of the percentage of the hemoglobin (the oxygen carrying molecule of red blood cells) that has an attached glucose element. It is integrated

summary of the severity of glucose elevations a person has had over the preceding 60 days. It integrates both the severity of the elevated glucose and the amount of time such elevations occurred. It does not though distinguish between levels and time (i.e., low elevations over a protracted period and high levels over a briefer epoch will both result in an elevated HbA1c).

Responses to Particular AstraZeneca Statements

8. I have reviewed the brief of AstraZeneca that criticizes my opinions and methodology and I believe it is important to respond.

9. AZ lawyers state "Dr. Wirshing has no scientifically reliable basis for extrapolating from weight gain allegedly related to Seroquel to diabetes. Dr. Wirshing ignores the data that contradict his opinion and relies instead on the cherry-picked weight gain data." I respond as follows:

10. The fact that Seroquel induces significant and sometimes massive increases in adiposity is indisputable. The data supporting this have been available to the company since before launch. The data are so compelling in fact that the company recently (July 2008, Jeffries & Alam) proposed that weight gain be changed to a "very common" undesirable side effect in their labeling. There are literally hundreds of studies to support this observation. Among the more recent of these studies carried out and reported by AstraZeneca (July 2008, Jeffries & Alam Weight Gain in Adolescents) concerns the impact on weight gain in adolescent populations treated from three to 26 weeks. In the 3-week trial a jaw dropping 12% gained in excess of 7% of their body weight (FDA definition of clinically significant for pharmaceutical studies) versus 0% in the placebo group (on average 1.7kg vs. 0.4kg). During the 26-week study patients gained an average of 4.4kg with a startling 45% gaining

more than 7% of their body weight.

11. I have personally treated in excess of 3000 patients with quetiapine over the last decade. Of these, several hundred have developed diabetes and I have been responsible for delivering their endocrinologic care over the years. I have designed, implemented, and currently run programs to help my patients control and loose the weight gain associated with quetiapine and other related psychoactive compounds. For me, weight gain and diabetes are not abstract constructs to be sifted from the voluminous data of trials but stark daily clinical realities. The weight gain in my patients is at least as resistant to weight reduction techniques as the "normal" weight gain. It requires diligence, focus, and consistency over a protracted period of time which is difficult for any group of people, nevertheless those with mental illness.

12. The causal relationship between weight gain and diabetes is established, robust, and unarguable. The connection between Seroquel and diabetes has become generally accepted in the medical community. It is referenced not just in multiple peer reviewed journals, but also in numerous recognized text books, including Harrison's *Internal Medicine*; Goodman and Gillman's *The Pharmacological Basis of Therapeutics* and psychiatry texts including Schatzberg, MD, Alan F., Charles B. Nemeroff, MD, PhD, The American Psychiatric Publishing Textbook of Psychopharmacology. 3rd Ed. Arlington, VA: American Psychiatric Publishing, Inc.

13. Indeed the defense's own expert stated in his report that the causal connection between excessive weight (obesity) and diabetes is larger than the causal impact of smoking on lung cancer. Dr. Koplan however, seeks to draw an artificial line between the risk and

import of obesity, or pre-existing BMI and added weight gain, suggesting that because obesity is such an important risk factor, any other risk factors pale by comparison and are thus epidemiologically and clinically inconsequential.

14. As a clinical and academic physician practicing with this patient population, I was surprised by such an incorrect and flippant approach to the very real risk of the Seroquel induced weight gain in this already high risk population. Dr. Koplan disregarded an abundance of literature that establishes the risk. For example, the Fontaine study, *Estimating the Consequences of Anti-Psychotic Induced Weight Gain on Health and Mortality Rate,* used the Framingham Heart Study's public use data set and national statistics on population demography to estimate the expected effect of weigh gain on number of deaths and incident cases of IGT [Impaired Glucose Tolerance] and HTN [hypertension] for a 10 year period. Critically "results indicated that the estimated deleterious effects of weight gain were greater for people with higher BMI's at baseline, for greater degrees of weight gain." Indeed, the study found that the relationship of impaired glucose tolerance with BMI is "monotonically increasing." Pages 277-278. In the discussion, Fontaine et. al., noted that the impact of weight gain would be even more deleterious amongst the schizophrenic population, precisely because of their increased baseline risk:

> [i]t seems likely that additional weight gain from atypical agents will increase both the prevalence and severity of elevated BMI, as well as further increase the medical diseases that are associated with weight gain and higher BMIs (Henderson et.al., 2000). This will cause the BMI distribution from the Framingham sample, a sample of primarily non- schizophrenic individuals, to result in conservative estimates when extrapolated to the schizophrenic population. Fontaine, *ibid.*, at 283.

15. I was also surprised to see Dr. Koplan's Declaration minimizing the import of

weight gain superimposed on underlying elevated BMI in light of the fact that he was a co-author of a paper by Mokdad and others entitled *The Continuing Epidemics of Obesity and Diabetes in the United States*, JAMA 2001: 286910. In that study, Dr. Koplan and his co-authors note that "**Both** BMI and weight gain are **major** risk factors for diabetes....For every 1-kg increase in measured weight, the risk of diabetes increased by 4.5% in a national sample of adults." (bold added for emphasis) Mokdad at 1197.

16. Similarly, Resnick, HE et. al. suggest in the article *Relation of Weight Gain and Weight Loss on Subsequent Diabetes Adults,* Journal of Epidemiology and Community Health; (Aug 2000; 54,8) that many overweight people have not reached a threshold at which additional weight gain fails to increase diabetes risk reflecting that an increased weight for that population, which pushes them over that threshold, will have obvious deleterious clinical consequences including of course, diabetes. Finally, the literature on this issue is ever growing. Just this week the New England Journal of Medicine published a study from Sweden entitled *Clinical Risk Factors, DNA Variants and the Development of Type 2 Diabetes* by Lysenko N. Engl. J. Med 2008:359:2220-32. This study looked at risk factors beyond obesity and weight gain, and considered genetic risk factors as well. Lysenko notes "[w]e also evaluated whether genetic risk factors would further increase the risk imposed by an increase in the BMI...There was a stepwise increase in diabetes risk with an increasing number of risk alleles and increasing quartiles of BMI or a disposition index above or below the median..." Lysenko at 2229.

17. The above data reflect a fundamental premise of clinical medicine – that each incremental risk factor can worsen outcomes and can be contributory, or in legal parlance,

are substantial contributing factors. The Koplan analysis which disregards the import of incremental drug induced weight gain in an already obese person is incorrect and plainly contrary to good medicine and science. Obviously all these risks are important and hence they are all substantial contributing factors in assessing the etiology of the diabetes.

18. Indeed, the ADA Consensus Conference developed important clinical guidelines including baseline monitoring (including for personal and family history of obesity, etc.) and measurements of weight, blood pressure, fasting plasma glucose and fasting lipid profile prior to inception of antipsychotic medication and thereafter follow-up monitoring at specific intervals. Moreover, the consensus tells physicians that "if a patient gains greater than or equal to five percent of his or her initial weight at any time during therapy, one should consider switching the SGA." The data reflect that Seroquel causes such an appreciable weight gain or higher in a significant number of patients. These recommendations would be superfluous if the Koplan view of the evidence was correct since if the underlying obesity or other underlying or "confounding" risk factors already exist, the incremental weight gain independently related to Seroquel would be immaterial. Of course, it is highly material to real patients in the clinical setting and hence those guidelines are well founded. Even AZ has recognized their validity in the additional recommendations in the later package inserts.

19. It has been and continues to be my opinion that quetiapine induces its most deleterious impact on endocrinologic functioning (i.e., glucose regulation) largely through its impact on weight gain. Diabetes, though, is but one of the many possible downstream consequences of excessive adiposity. Additionally, though weight gain is a large and often

times dominant causal factor for Type II diabetes, it is by no means the only one. Other established risk factors include family history, smoking status, ethnicity, and hepatic functioning (Lyssenko et al, 2008), as well as emerging specific genetic factors (Meigs, et. al., *Genotype Score in Addition to Common Risk Factors for Prediction of Type 2 Diabetes*Meigs, et. al., N. Engl. J. Med 2008; 359:22008-19. 2008.

20. Thus, while the defense is correct in stating that "on average" it can take an extended time for the deleterious impact of excessive weight to exert its ultimate effect on diabetes, there is enormous variance in this figure. In patients, for example, who were obese at baseline, and had several of these additional clinical factors, quetiapine induced weight gain would be expected to have a much more rapid impact on glucose metabolism and ultimately the expression of frank diabetes.

21. In addition to the well-established and recurrently documented connection between quetiapine induced weight gain and diabetes, there is a growing body of evidence to suggest that quetiapine may have an additional deleterious impact on glucose metabolism. For example, Studies 126 and 127, which formed the basis for the recent changes in the adverse experiences section, suggested that quetiapine use resulted in a several fold increase in new onset diabetes over an extremely brief period of time. While there were only a small percentage of patients who developed diabetes, the brevity of exposure suggests that quetiapine was exerting this toxicity through "extra-adiposity" avenues. It is not known exactly what these mechanisms might be (hepatic, neurogenic, and pancreatic have all been suggested), however such an effect could easily account for the many rapid onset diabetes cases that have been reported. It would also account for the few cases I have personally seen

where discontinuing the quetiapine caused a remediation of the diabetes and reintroduction resulted in additional diabetic decompensation. In any event, even though I believe that the weight gain adiposity is the most obvious, if not predominant mechanism, it does not exclude other co-occurring mechanisms. In medicine, the development of disease is frequently multifactorial and there are often multiple mechanisms that explain how a drug causes an effect. In any event, one does not need to fully appreciate the mechanism of action to accept that a certain adverse or salutary response is related to a medication's ingestion. We still do not fully understand the mechanism of action as to how the SGA's, including Seroquel, have a beneficial effect on certain mental illnesses and the same is true for many medications, if not the majority of all medications. Nevertheless certain adverse drug reactions are widely appreciated.

22. Study 125 further highlights this latter point. This study is touted by AstraZeneca as the only study designed to examine the question of whether Seroquel may cause diabetes. On the contrary, Study 125 was actually designed NOT to detect certain important markers for Seroquel-induced glucose dysregulation. Significantly, despite the design limitations, proper interpretation of the results of Study 125 provides evidence that Seroquel does indeed cause diabetes by inducing insulin resistance.

23. Study 125 was a 24 week, open label study comparing effects of glucose metabolism and insulin sensitivity in patients taking Seroquel, and its closest market competitors, Zyprexa and Risperdal. It was not a blinded study, nor was it placebo-controlled, two very important features of well-designed trials. The design of the study did attempt to control for factors which might confound indicators of glucose dysregulation: it

was conducted in primarily white Eastern Europeans, with average baseline BMI of 24, and intended to exclude patients with history of diabetes or recent atypical antipsychotic use. In other words, the study population was (generally speaking) metabolically healthy. As explained below, it is for precisely this reason that the primary endpoint of the study fails to properly measure Seroquel's diabetic potential.

24. The primary endpoint of the study was the change at 24 weeks of the "area under curve" in a 2 hour oral glucose tolerance test (OGTT). The OGTT is a standard clinical measure to detect abnormalities in glucose metabolism. Indeed, a peak blood sugar exceeding 200mg/dl following a glucose load is part of the definition of DM. It is, though, a decidedly down stream effect in a person with Type II DM. Area under curve values such as those identified as the primary endpoint of this study would be very unlikely to shift in an endocrinologically healthy group in but 24 weeks time, even with the significant weight gain that occurred in Study 125. Given what we know about DM, one would not expect a population of increasingly obese patients to manifest an average shift in OGTT for years (though marked individual variation would be expected—see above). A much more sensitive measure of glucose regulation are so-called clamp studies (gold standard) or calculating a HOMA index (less rigorous and more variable). These tests are able to detect subtle changes is glucose regulation well before the insensitive OGTT.

25. The primary endpoint used in Study 125 measures how well a patient's body disposes of glucose immediately following a glucose load; essentially, whether these generally healthy patients were able to produce enough insulin to meet the load. Not surprisingly, the results indicated no statistically significant change from baseline to Week 24

in these metabolically healthy patients. The primary endpoint of this study does NOT measure the body's regulation of glucose in the fasting state, nor does it measure insulin resistance. In other words, the primary endpoint will NOT reveal whether Seroquel has increased insulin resistance in these patients, whether the pancreas must now produce more insulin in order to meet the glucose load, or whether Seroquel has produced a disturbance in fasting blood glucose levels.

26. What is truly important and informative about the results of Study 125 are the statistically significant positive findings in the secondary parameters, particularly taken in the context of the small sample size (110 patients completing the study in the Seroquel arm) and relatively short duration (24 weeks). There were statistically significant increases in both mean fasting blood glucose (3.19 mg/dl) and HbA1c (0.122%), indicating that Seroquel may have disrupted the body's ability to regulate glucose in a fasting state. Fasting C-peptide (a measure of endogenous insulin production) also increased, indicating that these patients were now producing more insulin in a fasting state: a marker for insulin resistance. Further, patients taking Seroquel experienced a mean weight gain of 3.65 kg (8 pounds) in just 24 weeks. All of these findings were statistically significant despite the fact that the study was powered to look at another (less useful) primary endpoint. The results of Study 125 provide additional evidence that Seroquel causes diabetes, and that it may do so by inducing insulin resistance, even over a comparatively brief epoch.

27. Overall it appears that there are some additional non-adiposity factors that may be contributing to the diabetes seen with quetiapine use. Though I continue to be of the opinion that the lion's share of the causal equation goes to increases in adiposity, in certain

patients these other factors may in fact predominate.

28. Defendant's make other incorrect comments about my opinions. Defendant claims that I improperly extrapolate from an accepted premise – that obesity can cause diabetes – to an unfounded claim –"that any amount of weight gain over any period of time will cause diabetes." The defendants misstate. I explain that quetiapine leads to weight gain and that weight gain leads to diabetes. I did not say "any weight gain." Rather, I explained, "[u]sing the FDA's definition of clinically pertinent weight gain (i.e., a 7% increase) quetiapine routinely impacted over 25 percent of the treated population."

29. Defendant states that I do not actually offer an opinion that Seroquel causes diabetes. Instead, they claim I opine that Seroquel causes weight gain and, as a result, "it is axiomatic" that Seroquel will lead to diabetes – eventually." The word "eventually" is tacked on by the defendants. I state that "it is axiomatic that increases in obesity will result in subsequent increases in hyperglycemia, frank diabetes, hyperosmolar coma, and even death due to endocrinologic complications." As I explained above, there is a wealth of literature showing that each incremental kg of weight increase correlates to development of diabetes in some.

30.. I hold additional relevant opinions as set forth in my expert report in this matter, which is attached and incorporated by reference. Additional opinions were elaborated in my deposition. The documents I reference in this Declaration-Report are annexed as exhibits to the Declaration of Paul Pennock, Esq.

I declare under penalty of perjury that the foregoing is true and correct.

Executed this 24th day of November 2008.

William C. Wirshing, M.D.

IN THE SUPERIOR COURT OF THE STATE OF DELAWARE

IN AND FOR NEW CASTLE COUNTY

IN RE: SEROQUEL LITIGATION **C.A. No.: 07C-SER-1**

THIS DOCUMENT RELATES TO:

ALL CASES IN FIRST HALF OF INITIAL TRIAL GROUP

EXPERT REPORT AND DECLARATION OF WILLIAM C. WIRSHING, M.D.

William C. Wirshing, M.D.

Educational and Professional Background

Education
I graduated in 1978 from the College of Engineering at the University of California at Berkeley with highest honors (cumulative G.P.A. 3.93) and a Bachelors of Science degree in Electrical Engineering and Computer Science (minor in bioelectronic systems). During my tenure there, I was elected to membership in the Phi Beta Kappa and Tau Beta Pi honor societies. The former is traditionally reserved only for those pursuing a "liberal" educational experience (e.g., College of Letters and Science) and the latter is the equivalent entity for students in the science-intensive curriculum of the School of Engineering. Although I then began medical school at UCLA almost immediately following my undergraduate studies, my education was interrupted when my youngest brother developed and then succumbed to brain cancer during my first and second years. During several lengthy arranged absences from school in southern California, I assisted my mother in caring for my brother and worked as an engineer in Mountain View (i.e., "Silicon Valley") California through the beginning of my third year at UCLA.

I completed my undergraduate medical schooling ("on time", despite my protracted absences from campus) with a 3.97 GPA and was given the Sandoz award for "Excellence in the Behavioral Sciences" at graduation in 1982. In addition, I was elected to the Alpha Omega Alpha Medical Honor Society at the end of my third year. I remained at UCLA for both my rotating internship during which I focused on internal medicine, neurology, and pediatrics and for my three-year residency training in psychiatry. My final year of residency training I was the Chief Resident in Geropsychiatry at the West Los Angeles Veterans Affairs Medical Center. Over the next two years, I was a Post Doctoral Research Scholar at UCLA, a fellowship position through the National Institute of Mental Health during which I learned and applied clinical research techniques for the study of persons with severe schizophrenia. My mentors were Professors Van Putten, Goldstein, and Marder.

Clinical, Research, and Teaching Background
I remained at both UCLA and the affiliated West Los Angeles Veterans Affairs Medical Center until late in 2006. Over the two decades between 1986 and 2006 though, both my clinical work and research focus remained on the treatment of persons with schizophrenia. I was the Chief of the Schizophrenia Treatment Unit at the VA Medical Center during the vast bulk of this epoch, and was also the Co-Chief of the Schizophrenia Outpatient Research Clinic during the last ten years. Though I rose through the traditional academic ranks at UCLA and even reached the level of full Professor over five years ahead of "schedule", I never lost my fascination with clinical care and never traded it for more administrative tasks as my career wandered through the decades. Since leaving the traditional ranks of academia, I have been able to continue and even expand my dual interests in clinical work and teaching. Over the last year I have been Vice President in charge of research and continuing medical education for Exodus Inc. in Culver City, CA and also Clinical Director of Exodus Real Recovery in Agoura Hills.

CA. In a typical month, I now see approximately 325 new patients; supervise nearly a dozen psychology doctoral candidates; and teach over a dozen nursing, social work, and nurse practitioner students. Over the course of my career, I have taken care of over twenty five thousand patients, the vast majority of which have suffered from one or another psychotic illness.

As is usual among clinical academicians, my patient care tasks and research interests dovetailed consistently and have always taken place in a setting with medical trainees at every level of experience. Teaching these persons over the years has been the third major leg of my vocational life. Unlike most of my academic colleagues, I never thought of these teaching duties as an obligation to be tolerated and where possible shunted to my younger colleagues. In fact, it generally occupied the top spot in my personal emotional ranking of our traditional tasks (i.e., teaching, research, and patient care). My teaching has been honored over the years with several awards from both my students and colleagues, including 2006 when I was again nominated for the Golden Apple Award by the graduating medical school class (the highest teaching accolade in the School of Medicine). I currently give over 125 routine lectures per year at my various work sites.

Within the context of these various positions and responsibilities, I have been able to experience, study, and then teach others about the care of seriously mentally ill patients. While I have been most consistently compelled by and fascinated with the prototypic psychotic illness schizophrenia, persons with bipolar illness (i.e., "manic depressive disorder") have taken up a close second place over the years. Like any academician in my area, I have sought and received grants to continue my studies and have published in the peer reviewed literature (with the substantial aide of my colleagues and assistants—see my attached CV for the details). I believe that I have been fortunate in the extreme to have had these professional opportunities. They have permitted me to live an enviable work life that I was never able to master and was therefore neither predictable nor routine.

Experience With Industry

These sundry positions also brought me into contact with the pharmaceutical industry that coincidentally became increasingly interested in the treatment of psychotic persons at the very onset of my career in the mid 1980's. This time marked the beginning of the second significant epoch of pharmacologic treatment of psychosis (The first one having begun in the early 1950's but which had plateaued by the late 1960's). This period saw the development, testing, and subsequent marketing of what came to be known as the "Second Generation" or "Atypical" antipsychotic compounds. Though not truly revolutionary or even novel per se (see below), they did constitute a significant advance in many, though not all, aspects over the older medications. This mutual interest in the treatment of psychosis allowed me to "test" potential medications in my patients under controlled protocol conditions from the beginning of their development by industry. Although not every medication that we tested over the years survived the gauntlet of clinical testing, we were able to test every medication that did receive the approval to market by the Food and Drug Administration.

The approval process for medications is a lengthy one that has become increasingly burdened by regulation and requirements over the years. As a consequence, it can take years for a given compound to move from first testing in patients to full marketing approval. Among the medications that we tested and studied that went on to receive approval have been risperidone (approval 1994), olanzapine (1996), ziprazadone (2000), aripiprazole (2002), and quetiapine (1997). The early and prolonged nature of this experience allowed us to develop a clinical knowledge of the real world effects of these drugs that was often at the very forefront of the entire field. As is usual with pharmacologic compounds, our novel discoveries and observations generally involved the toxic effects rather than the therapeutic impacts of the drugs.

In the early to mid 1990's we were among the very first to report on the curious metabolic effects. In particular, we noticed that many of our patients gained weight when first begun on these drugs and at a rate that was, on occasion, singular in our experience. We also noted that these patients soon began to suffer the usual downstream consequences of gaining weight (e.g., glucose intolerance, frank diabetes, and even severe hyperglycemia with resultant hyperosmolar coma). As is customary in the academic world, we described our experience in the peer reviewed literature and reported it at any number of scientific meetings. In addition, though, we worked with industry to extend, understand, and hopefully find ways to remediate these various toxicities. The increasingly high economic stakes of the field sometimes lead those in industry to confuse the message and the messenger (at least from my perspective). As a consequence, our relationships would, or at least could, sour and blossom suddenly, depending on the details of our latest report. As one might expect, our observations and conclusions were not infrequently challenged by one company only to be embraced and promoted by its competitor.

I did not have any direct dealings with Imperial Chemical Industries, as Zeneca was called prior to their name change, while they were developing their antipsychotic compound ICI 204636 (quetiapine's "name" prior to its receiving a formal designation by the nomenclature committee). I was, however, very familiar with the published preclinical and clinical literature on the drug in the 1980's and early 1990's. Immediately after launch in the United States in 1997, I began to lecture for the company and started negotiations with them to perform a high dose clinical trial in a subpopulation of persons with schizophrenia whose symptoms were unresponsive to other available antipsychotic compounds. While a variety of regulatory, legal, and logistical impediments conspired to ultimately thwart my hopes for such a trial, our interest in and experience with high dose treatment did result in a single publication (Pierre, et al, 2005). I continued to lecture and provide ad hoc consultation at the company's request (the last time was August of 2008), though the frequency of these interactions has diminished considerably over time. I have, however, kept them apprised of my concerns about and observation of their drug, including this last spring when I sent them a prepublication copy of a letter that was recently published in the American Journal of Psychiatry (Murphy, et al, 2008). Through out this lengthy association, I would characterize our relationship as mutually respectful and professionally cordial. In notable contrast to some of their corporate peers in the pharmaceutical industry, Astra Zeneca never treated

me dismissively or disrespectfully simply because I would describe an observed toxicity or express an unflattering opinion about quetiapine's clinical characteristics.

History of Antipsychotic Drugs

It can, I think, be persuasively argued that the origins of the "modern" biological theories of psychiatry can be traced directly to the serendipitous discovery of antipsychotic medications in the early 1950's. During that epoch, a trio of French physicians (psychiatrists Delay and Deniker and neurosurgeon Henri Laborit) determined that the experimental Rhône-Poulenc compound RP 4609 (i.e., chlorpromazine or "Thorazine") had a singular power to reduce psychotic symptoms in chronically and severely ill patients with schizophrenia. Schizophrenia is the prototypic psychotic illness that consistently afflicts 0.9 percent of the population, is life long and incurable, runs in families, and generally has its origins in late adolescence or early adulthood. It is further the exclusive province of the human animal—even our closest primate relatives do not develop schizophrenia. It would be difficult to overstate the magnitude of this pharmacologic discovery, coming as it did at a time when wet wraps, hydrotherapy, and frontal lobotomies were the only "effective" palliative treatments. The pharmacologic efficacy of chlorpromazine, though, came with an apparently obligatory neurotoxicity that developed after about two weeks of treatment. This neurotoxicity, which came to be called extrapyramidal symptoms or EPS, included parkinsonism (i.e., slowed movements and mentation, a specific tremor, and muscular rigidity), akathisia (i.e., an intensely dysphoric sense of restlessness), and dystonia (i.e., sustained, uncontrollable, and functionally disruptive muscular contractions). While these acute EPS could be dramatic and overwhelming, they were transitory and would eventually disappear once the offending agent was discontinued. Unfortunately, there also developed a later, sometimes grotesque disorder of excessive motor movement that was termed tardive dyskinesia (literally "late bad movement"). It was eventually observed that this tardive dyskinesia (TD) would accrue with each passing year of cumulative exposure to the medication at a rate of three to five percent of the treated population per annum. More ominous still was the observation that unlike acute EPS, TD proved to be lifelong and irreversible in a large number of those afflicted (circa 50%), even if the causal agent were permanently discontinued. These neurotoxicities were so consistent, predictable, and uniform that they eventually came to be seen as the hallmark of this class of medications which were termed "neuroleptics" (i.e., "to seize the neuron"). In other words, these antipsychotic medications were defined quite literally by the toxicities they produced.

Though these EPS were the clinical bane of antipsychotic compounds, they were a crucially exploitable characteristic for drug developers. Because there is no animal model for schizophrenia per se, it is not possible to screen potential molecular candidates for this property. There are, however, many excellent animal models for EPS and related behavioral toxicities. It was thus possible to search for potential antipsychotic compounds by simply screening for extrapyramidal liability in one or another of these models. It should come as no surprise then that all antipsychotic medications shared the neurotoxic characteristic—it was this toxicity that allowed them to be discovered in the first place. Arvid Carlsson and colleagues detailed the mechanisms that are believed to underlie this duality (i.e., antipsychotic potential and neurotoxic liability) in the early

1960's. In a series of clever animal experiments and brilliant deductions he proposed that antipsychotics exerted both effects by binding to and blocking dopamine receptors (more specifically the D2 receptor subtype) in the brain. It is of historical note that he shared psychiatry's first Nobel Prize for Medicine in 2000 for these discoveries.

As an ultimate consequence of this process, there came to clinical market an array of often times chemically dissimilar compounds that had equipotent antipsychotic efficacy and were uniformly neurotoxic. They did, of course, vary in a number of secondary characteristics (e.g., anticholinergic potency, sedative potential, tendency to induce orthostatic hypotension, etc.), but their primary efficacies and core toxicities were effectively equivalent. It is important to note that these dopamine receptors are important not only in motor control and psychotic symptoms, but they are also crucial in mediating reward learning. Thus, any antipsychotic molecule that blocks these dopamine receptors will attenuate and possibly destroy an animal's (or a person's) ability to normally experience pleasure. In clinical practice these drugs are notoriously dysphorogenic and exceedingly difficult to subjectively tolerate.

The singular exception to these generalizations about antipsychotics is the compound clozapine. This molecule is a modified structural analog of the tricyclic antidepressant imipramine (a revolutionarily useful and powerful antidepressant medication that has no antipsychotic power whatsoever) and was synthesized by Sandoz Pharmaceuticals in 1959. Though its road to market was torturously long and marred by a number of tragically toxic detours, it ultimately proved itself to be a truly different antipsychotic. It was eventually shown that clozapine had greater antipsychotic power than conventional neuroleptics (as the rest of the antipsychotic market came to be named) and at ordinary antipsychotic doses it failed to cause the EPS that characterized its conventional counterparts. Clozapine then became the prototypic "atypical" antipsychotic in that it alone was a non-neuroleptic antipsychotic: a drug capable of separating antipsychotic efficacy from neurotoxic liability. While a number of often clever and sometimes even compelling explanations of how clozapine is able to exert these clinical behaviors have been elaborated, none have to date been proven. In addition, though the group of more recently developed and marketed antipsychotics (i.e., risperidone, olanzapine, quetiapine, aripiprazole, and ziprazidone) have claimed kinship to clozapine by usurping its "atypical" label, none has matched clozapine's antipsychotic power and all are variably more neurotoxic. This is not to say that as a "class" they have failed to improve upon the conventional compounds, but only that they have not succeeded in truly inheriting clozapine's legacy.

Quetiapine's Development

Imperial Chemical Industries first elaborated what they designated ICI 204636 in the early 1980's. It is a structural analog of clozapine and technically considered a dibenzothiazepine. Its receptor (i.e., the proteinaceous components on the lipid neural membranes of the central nervous system [CNS]) binding profile indicates that it has weak and easily reversible affinity for the classic D2 receptor that Carlsson identified in 1963. It also binds with weak to moderate intensity to a wide spectrum of other receptors in the CNS, but in a pattern that is really unlike any other antipsychotic compound.

including clozapine, upon which its structure is based. These other binding characteristics are conceptualized to account for quetiapine's observed clinical effects. In brief, they confer on quetiapine: sedation, low EPS liability, minimal impact on prolactin, orthostatic hypotension (i.e., a fall in blood pressure when standing), anticholinergic toxicity (i.e., constipation, dry mouth, blurred vision, memory disturbances, and tachycardia), and weight gain liability. All of these ultimately observed characteristics would be expected based only on the neuromolecular characteristics of quetiapine.

Though the knowledge of quetiapine's unique receptor binding profile allowed for the easy prediction of its pattern of toxicity in humans, its low and weak affinity at the critical D2 receptor posed a challenge for protocol designers during its early years of clinical testing. For all conventional compounds the appropriate dose to achieve optimal antipsychotic activity is exactly the dose that also begins to produce EPS. With an "atypical" drug though, the appropriate dose would be an unknown amount lower. Thus, an early hurdle for quetiapine was determining just where the optimal antipsychotic dose range was located. Ultimately quetiapine's FDA registration trials involved multiple doses (five) of quetiapine over a ten fold dosing range compared to single dose of the reference conventional neuroleptic haloperidol. Despite the methodologic asymmetry of this design that markedly favored quetiapine, it failed to beat its conventional comparator at any dose. In fact, the haloperidol arm was generally slightly better (though not statistically so) than any of the five doses of quetiapine. This pattern of being marginally equal to or slightly inferior to comparator drugs has been repeated numerous times over the years of testing. When AZ attempted to perform a meta-analysis (i.e., combining multiple trials to achieve greater statistical power in an effort to show a small effect that is not apparent in any single study) on its accrued dataset, they discovered this very pattern. This disappointing result prompted the marketing personnel within AZ to "spin" these conclusions by touting that quetiapine had "unsurpassed efficacy". While technically correct from a statistical point of view because no single study had shown that any conventional comparator was statistically superior to quetiapine, such hype is clearly disingenuous sophistry.

When considered across many trials involving schizophrenic subjects, quetiapine has been demonstrated to be about 10-20 percent less effective than standard doses of conventional medications. This was shown most clearly in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study that was reported in late 2005. This NIMH funded trial compared four atypical medications (quetiapine, ziprazidone, risperidone, and olanzapine) to a single typical medication (perphenazine) and involved 1460 subjects treated over an 18-month epoch. The primary outcome variable was "time to discontinuation" of the assigned drug. The results revealed that quetiapine was about 20 percent less effective than the conventional agent perphenazine (4.6 vs. 5.6 months) and about 50 percent less effective than olanzapine (9.2 months).

While these efficacy facts were disappointing and clearly contributed to quetiapine's dismal market share when it was first approved for use in 1997, it also suggested to me a tantalizing possibility. Because conventional antipsychotic medications were all

essentially equi-efficacious and seemed to share a single underlying mechanism of action. any drug that had demonstrably less efficacy might possibly work through a dissimilar mechanism. This possibility was a major motivating factor in my wanting to pursue a higher than standard dose experimental trial with the company after the drug was launched. I continue to believe that quetiapine does, in fact work through largely distinct mechanisms. Unfortunately this distinction translates into slightly less pharmacologic power on average than conventional medications. AZ has "oversold" quetiapine's efficacy in their marketing endeavors for years.

Quetiapine's Toxic Metabolic Profile

The dataset that Zeneca had compiled on quetiapine prior to its launch in 1997 clearly indicated that clinically significant weight gain was a common side effect of quetiapine. The data from Zeneca's Phase II/III trials demonstrated a clear dose related impact on weight that compellingly worsened over time. Using the FDA's definition of clinically pertinent weight gain (i.e., a 7% increase), quetiapine routinely impacted over 25 percent of the treated population (somewhat lower for lower doses of quetiapine and somewhat higher with higher quetiapine doses). The average shift in weight was 6.2 lbs over the first six months of treatment and 11 lbs after six months of treatment. This is approximately halfway between the weight gain induced by risperidone and olanzapine—quetiapine's major competitors at launch. Weight gains of this magnitude are impressively large and impact an amazingly large and consistent percentage of patients. Despite these data, which have been available to the company since before launch, the label for quetiapine has never, even to the present day, "warned" of this predictable and serious toxicity. Instead, the label has merely listed in the adverse experiences section that quetiapine is "sometimes associated with increases in body weight". Further, their marketing materials over the years have consistently touted that quetiapine is "weight neutral". This is palpably inappropriate and inadequate at best and deceptively misleading at worst. It is my opinion that this labeling deficiency rises to the legal definition of gross negligence (i.e., "willful disregard for the safety of others"). It is unconscionable that after more than a decade's time that the warnings section is still silent about the single most prominent serious toxic characteristic of the compound.

There are a number of well-known health consequences to increases in adiposity. Among these are increased risks for glucose intolerance and even frank diabetes, increases in total cholesterol and triglycerides in the blood, secondary risks for cardiovascular disease, increased rates of degenerative osteoarthritis, and even increased risks for certain malignancies (e.g., colon cancer). The fact that quetiapine use results in weight gain and therefore causes diabetes in susceptible patients cannot be rationally disputed. This was confirmed by the APA/ADA consensus conference on the metabolic toxicities of the atypical antipsychotics held in 2004. That conference of independent (i.e., non-industry) experts (at which I provided the presentation on the monitoring protocol) concluded that quetiapine use could result in significant weight gain, increased rates of diabetes, and pathologic changes in lipid profiles. Although the current label change implemented in 2007 does direct one to a new section in the adverse events section that documents, to a degree, some of the measured increases in new onset diabetes, it remains inadequate and misleading. Firstly, the "class labeling" warning section on endocrinologic toxicities is

laced with generalities, disclaimers, and distracting verbiage. It fails completely to state the measured increases in new onset diabetes that are specific to quetiapine and that are detailed in the adverse experiences section. Secondly, it fails to make the known connection between increases in adiposity and subsequent changes in glucose regulation. It gives the mistaken impression that the risks of diabetes only apply to a decidedly minor (circa 2-4%) portion of treated patients when, in fact, nearly one third of patients treated with standard doses for as little as a year are at decidedly increased risk of glucose disregulation. The company personnel have opined in depositions that the details of quetiapine's measured risk of diabetes and related endocrinologic disturbances were unknown until the results of these later done studies were completed. Such rhetoric is intellectually and clinically dishonest as it requires one to deny the clinical fact that increases in adiposity that are caused by quetiapine (and were known to the company before launch in 1997) will result in predictable increase in endocrinologic dysfunction. It is axiomatic that increases in obesity will result in subsequent increases in hyperglycemia, frank diabetes, hyperosmolar coma, and even death due to endocrinologic complications. To deny otherwise, as AZ officials continue to do to the present day, is negligently irresponsible.

Additionally, the label is virtually silent (or at least it is decidedly unclear) about quetiapine's ability to induce massive changes in circulating triglycerides and thereby lead to secondary and potentially lethal pancreatitis (i.e., marked inflammation of the pancreatitis). When a person gains significant adiposity, there is a predictable increase in the levels of circulating lipid pools (i.e., triglycerides, VLDL, LDL, etc.) because to body must manage a larger flow of fats from the gut and to and from the tissues. These changes, while potentially of long-term clinical pertinence, are usually of ordinary magnitude. Quetiapine, though, also results in massive acute elevations in triglycerides that can, on occasion, overwhelm the body's fat management system and cause secondary pancreatitis. The precise mechanisms whereby this toxicity is mediated have yet to be elucidated, however, it is likely that interference with one of the early lipid management enzymes in the liver (e.g., lipoprotein lipase A) causes a "backup" of the triglyceride transport vehicle (i.e., chylomicrons) from the gut that leads to the hypertriglyceridemia. This additional metabolic-like toxicity is unrelated to changes in weight, tends to occur during the first several months of treatment, and is markedly more acutely serious than the more pedestrian increases in the sundry lipid pools that predictably follow increases in adiposity. This toxicity has clearly emerged during the post marketing surveillance period, has been reported frequently in the case report literature, and was discussed at length at the consensus conference in 2004.

Addictive Potential

The single most consistent toxic effect of quetiapine is sedation. This property when coupled with quetiapine's low EPS profile has prompted clinicians to use the drug excessively off-label for such conditions as anxiety and insomnia. These characteristics also raise a reasonable concern that quetiapine may have some addictive potential. In fact clinical experience and a number of case reports have suggested that certain patients will abuse, divert for sale, and become physically dependent on quetiapine (Pierre, et al.

2004; Murphy et al. 2008). Despite these facts the label has been virtually silent about this reality.

Off Label Use

Quetiapine has come to dominate the atypical antipsychotic market primarily because it is used excessively off label (current estimates are about two thirds of the prescriptions are off-label). I am of the opinion that primary among the reasons for this disproportionate off label use are the facts that quetiapine is sedating and highly subjectively tolerable and the inaccurate clinical impression that it is also comparatively free of concerning toxicities and devoid of abuse potential. A secondary reason is that quetiapine's share of the on label market is reduced because it is simply not as potent an antipsychotic as other available products. While prescribing a drug for off label use is a common and often clinically reasonable practice, promoting a drug for off label use is illegal. AZ was clearly aware of the excessive off label use of quetiapine over the years. Their officials have stated repeatedly in depositions that AZ endeavored to provide label support of these "passively observed" prescriptive habits by investing heavily in confirmatory studies. Though many such studies were performed, I consider the claim largely dishonest. If true, then it would have been imperative for AZ to study the largest and most excessive off label use, to wit, insomnia. Such a study would have been logistically and economically trivial to perform, at least in comparison to the studies done in mood and psychosis based disorders. There is to date no evidence of any quality that demonstrates that quetiapine decreases sleep latency, increases total sleep time, normalizes sleep architecture, or improves daytime wakefulness. There is, in fact, ample evidence that quetiapine impairs significantly daytime wakefulness. I believe that AZ knew that any real detailed sleep study would ultimately be an indictment of clinical practice and would potentially cut the total use of their product by more than half. It is further my opinion that AZ mischaracterized the true toxic potential of their product and that this behavior has in part prompted clinicians to use their product inappropriately and excessively off label. If clinicians had been aware of the true metabolic toxicities and addictive liabilities of quetiapine then I do not believe that we would have the amount of off label usage we see today. It is my opinion therefore that AZ has been engaged in "indirect" off label marketing. While their behavior may have in fact been technically within the "letter of the law", it was and continues to be irresponsible, improper, and ethically indefensible.

Conclusions/Summary

AZ's marketing of quetiapine has consistently exaggerated the true efficacy of the compound.

AZ has been aware of the true metabolic toxicities of quetiapine since before launch in 1997. Despite this they have engaged in a marketing campaign that has minimized, obfuscated, or frankly denied these metabolic realities. Their product label has been consistently and continuously inadequate in its warnings about the impact on lipid and glucose metabolism, hyperglycemia, and diabetes. Their label continues to be wholly inadequate to the point of being decidedly misleading in its warnings about weight gain.

Additionally, the current label is inadequate regarding quetiapine's ability to markedly disrupt normal lipid metabolism and cause massive hypertriglyceridemia and secondary pancreatitis.

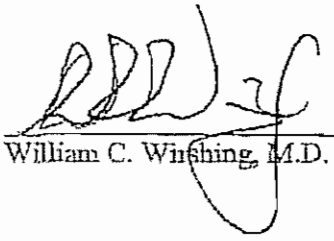
The current label is inadequate in its description about the abuse potential of quetiapine. AZ should have identified and warned of this abuse liability based on the clinical characteristics of quetiapine and the curious and excessive off label use patterns. Further, their tacit acceptance of the excessive use of their product for routine insomnia for the past decade without ever having investigated the effects of their product on sleep, is tantamount to passive marketing for an off label indication. This failure to investigate has been compounded by their insistence that they have behaved responsibly by investing heavily in research to establish on label support for the prescriptive patterns they knew to exist.

AZ's behavior has given prescribing clinicians an inaccurate impression of quetiapine's toxic profile and addictive potential which has robbed physicians of the ability to make informed risk/benefit analysis prior to prescribing quetiapine to a patient. This has led in part to the excessive and inappropriate off label use of the product and to injury and damage to patients who would not have otherwise ever received the medication.

My opinions as stated in this report are based on my education, training, and experience and my review of the relevant literature, internal Astra Zeneca documents, corporate depositions, and public documents and are stated to a reasonable degree of medical probability. It is my understanding that discovery is ongoing and I thus reserve my right to supplement or expound upon my opinions pending review of additional information.

My fees for work in this litigation are $500 per hour.

A list of my testimony for the past 4 years is attached.



William C. Wirshing, M.D.

TESIMONY LIST – DR. WILLIAM C. WIRSHING

I have been asked to supply a list of my deposition and trial testimony for the prior 4 years. The following is a list to the best of my ability to recall:

Alaska V. Lilly 2008

Insurance Carries v. Lilly 2008

Olenic v. Lilly 2008

Class Action case filed in FL against Janssen 2005

In addition, I have given testimony in several small lawsuits involving malpractice question for both the defense and plaintiff whose names and details I no longer have access to.

CURRICULUM VITAE

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Woodland Hills, CA 91303

Tel (310) 413-4200
Home Fax (818) 595-1367

E-mail: WIRSHING@UCLA.EDU

Birthdate 11 June, 1956

Birthplace Palo Alto, CA

Education

1982	M.D. - UCLA
1978	B.S. Electrical Engineering & Computer Science, University of CA, Berkeley

Internship, Residency, & Fellowship

1986-88	Postdoctoral Research Fellowship in Schizophrenia Research, UCLA, Department of Psychology, Los Angeles, CA
1983-86	Resident in Psychiatry, UCLA Neuropsychiatric Institute, Los Angeles, CA
1982-83	Intern in Medicine, UCLA Center for the Health Sciences & Wadsworth VA Medical Center, Los Angeles, CA

Licensure

1983 California License No. G 50986, DEA No. FW0654447

Certification

1991 Added Qualification in Geriatric Psychiatry, American Board of Psychiatry and Neurology (#000479)

1988 Diplomat, American Board of Psychiatry and Neurology (#30125)

Academic Appointments/Positions

2008- Medical Director Real Recovery. Agoura Hills, CA

2007- Vice President in charge of continuing medical education and research Exodus Corp. Los Angeles, CA

1996-06 Professor of Clinical Psychiatry, Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine

1993-06 Chief, Schizophrenia Treatment Unit, West Los Angeles VA Medical Center, Brentwood Division

1993-96 Associate Professor of Clinical Psychiatry, Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine

1987-06 Director, Brentwood Movement Disorders Laboratory, West Los Angeles VA Medical Center

1988-93 Co-Chief, Schizophrenia Treatment Unit, West Los Angeles VA Medical Center, Brentwood Division

1986-93 Adjunct Assistant Professor of Psychiatry, Department of Psychiatry & Biobehavioral Sciences, UCLA School of Medicine

1986-88 Postgraduate Research Scholar, Department of Psychology, UCLA

1986-88 Co-Chief, Geropsychiatry Treatment Unit, West Los Angeles Veterans Administration Medical Center

1985-86 Chief Resident, Geropsychiatry Treatment Unit, West Los Angeles Veterans Administration Medical Center, Brentwood Division

Awards & Honors

2006 Nominated for Golden Apple Award for Clinical years by graduating class of 2006

2003 Award in Recognition of Dedication in Teaching Excellence from the Graduating Class of 2003, David Geffen School of Medicine at UCLA

1999 Departmental Teaching Award, UCLA School of Medicine, Department of Psychiatry & Biobehavioral Sciences

1999 Lucien B. Guze Golden Apple Award for Outstanding Teaching Class of 2001, UCLA School of Medicine

1998 Certificate of Excellence, West Los Angeles Success 98 Award Program, West Los Angeles Veterans Administration Medical Center

1996 Distinguished Educator Award, UCLA School of Medicine, Department of Psychiatry & Biobehavioral Sciences

1994 Departmental Teaching Award, UCLA School of Medicine, Department of Psychiatry & Biobehavioral Sciences

1993 UCLA Medical School. Class of 1995 - Outstanding Teacher Award

1991 Departmental Teaching Award, UCLA School of Medicine, Department of Psychiatry & Biobehavioral Sciences

1988 Travel scholarship to attend the 4th Biannual Workshop on Schizophrenia in Badgastein, Austria.

1982 Sandoz Award for Excellence in the Behavioral Sciences

1982 Alpha Omega Alpha

1978 Tau Beta Pi (Engineering National Honor Society)

1978 Phi Beta Kappa

1978 B.S. Summa Cum Laude

Major Teaching Experience

2007- Weekly Continuing Medical Education Lecture Exodus Urgent Care Center, Culver City, CA.

2000-06 Case Conference: Diagnostic Dilemmas - Psychiatry (#425 Sec. 5) This weekly case conference focuses on differential diagnosis, with an emphasis on the various etiologies of psychotic symptoms including schizophrenia, substance-induced psychosis, malingering,and other disorders.

1995-06 Movement Disorders Seminar - Psychiatry (#446) a weekly, clinical based, interactive seminar focusing on the examination and treatment of patients with a broad range of movement disorders for psychiatry residents,

	neurobehavior fellows, medical students, and research staff (with DA Wirshing, M.D., CS Saunders, M.D., and JM Pierre, M.D.). (1.5 hrs/week)
1992-2004	Course director - Psychopathology (#201) for 2nd-year medical students. (6 hrs/week)
1991-2002	Faculty sponsor - Student Research Program. (1-8 hrs/week)
1990-1992	Faculty advisor for biweekly seminar for psychiatry residents on critical reading of the literature (with Joel Yager, MD, and Alison Doupe, MD, PhD). (1 1/2 hrs/2 weeks)
1989-92	Movement Disorders Seminar (Psychiatry Course #453), a weekly forum for psychiatry residents, neurobehavior fellows, and medical students (with JL Cummings, MD). (1 hr/week)
1988-1991	Class Organizer/Lecturer of "Topics in Geropsychiatry", a weekly seminar for psychiatry residents, medical students, and psychology interns. (1 1/2 hrs/week)
1988-06	Ward teaching supervisor (Psychiatry Course #403) for 1st- and 3rd-year psychiatric residents and for 3rd- and 4th-year medical students on the Schizophrenia Treatment Unit, BVAMC. (9 hrs/week)
1986-06	Off-ward teaching supervisor (Psychiatry Course #403) for 1st-, 2nd-, and 3rd-year psychiatric residents in the UCLA Residency Training Program. (2-4 hrs/week)
1986	Lecturer: "The Psychiatric Hospital in Historical Perspective" (with Dora B Weiner, PhD), a class for undergraduates, College of Letters and Sciences, UCLA.
1985-88	Ward teaching supervisor for first- and second-year psychiatric residents and for first-year geriatric medicine fellows on the Geropsychiatry Ward, WLA/VAMC.
1985	Lecturer: "The Historical Roots of Modern Medicine" (with Dora Weiner, PhD), a class for undergraduates, College of Letters and Sciences, UCLA.

Hospital/University Committees

2005-06	Academic Advancement Committee Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine
2000-02	Academic Advancement Committee Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine
1999-03	Medical Student Education Strategic Planning Committee
1999-02	Human Subjects Protection Committee, Veterans Affairs
1998	Neuroscience Sub Committee, UCLA School of Medicine
1997- 00	Faculty Executive Committee
1997- 01	Voluntary Clinical Faculty Academic Appointments and Adjustments Committee

1996-99	Second Year Curricular Block Planning Committee, UCLA School of Medicine
1995-98	Academic Advancement Committee Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine
1992-94	Ad Hoc Committee for Dementia, UCLA School of Medicine
1992-96	Student Affairs Committee, UCLA School of Medicine
1992-94	Human Subjects Protection Committee, Veterans Affairs
1991-93	Residency Fellowship Nominating Committee, UCLA
1991	Chief of Psychiatry Search Committee, Veterans Affairs
1990-93	Residency Education Curriculum Committee, UCLA
1988-90	Human Subjects Protection Committee, Veterans Affairs
1988-03	Pharmacy and Therapeutics Committee, Veterans Affairs

Grants Awarded

2005-06 "Management of Antipsychotic Medication Associated Obesity"
Co-Principal Investigator Donna A. Wirshing, M.D. PI
VA Merit Review

2005-06 "Relapse Prevention: Long Acting Atypical Antipsychotics"
Co-Investigator , Donna A. Wirshing, M.D. PI
NIMH RO1 (Multicenter Collaborative)

2002-05 Veterans Affairs Merit Review
"Cigarette Smoking by Schizophrenic Patients (Phase II)"
Collaborator. Jarvik Murray, M.D., Ph.D. - P.I.

2000-02 National Institute of Mental Health, MH41573-11A1
"Management for Risk of Relapse in Schizophrenia"
Co-Investigator. Stephen R. Marder, M.D. - P.I.

2000-03 National Institute of Mental Health, MH59750-01A1
"Treatment of Negative Symptoms and Cognitive Impairments"
Co-Investigator. Stephen R. Marder, M.D. - P.I.

1998-00 Veterans Affairs Merit Review
"Brief Hospitalization for Schizophrenia: Strategies to Improve Treatment Outcome"
Co-Investigator. Donna A. Wirshing, M.D. - P.I.

1997-02 Veterans Affairs Merit Review
"Quetiapine vs. Haloperidol Decanoate for the Long-Term Treatment of Schizophrenia and Schizo-Affective Disorder"
Co-Investigator. Stephen R. Marder, M.D. - P.I.

1995-98 National Institute of Health, 1R01-DA09570-01A1
"Dopaminergic Modulation of Nicotine Reinforcement"
Co-Investigator. Murray E. Jarvik, MD, PhD - P.I.

1995-99 National Institute of Health, 1R01-MH46484-01
"New Antipsychotics: Clinical Trials and Naturalistic Follow-up."
Co-Investigator. Stephen R Marder, MD - P.I.

1993-95 Veterans Affairs Merit Review to examine cigarette smoking by schizophrenic patients.
Co-Investigator. Murray E. Jarvik, MD, PhD - P.I.

1993-96 Veterans Affairs Merit Review to examine the risks and benefits of typical and atypical antipsychotic drugs in the treatment of acute psychotic episodes.
P.I.

1992-95 National Institute of Health: MH46484-03
"Clozapine - Treatment Response and Disability."
Co-Investigator.

1990-92 NARSAD (National Alliance for Research on Schizophrenia and Depression) Young Investigators Grant to develop a method of quantifying drug-induced akathisia and to apply this method of determining the relative akathisic liability of the atypical neuroleptic clozapine.

1986-05 National Institute of Health: MH41573
"Management of Risk of Relapse in Schizophrenia."
Co-Investigator. Stephen R Marder, MD and Robert P. Liberman, MD Co-P.I.s

1988-90 Veterans Affairs Merit Review to examine the feasibility of using a battery of electromechanical instruments to prospectively follow patients with tardive dyskinesia.
Co-Investigator. JL Cummings, MD, P.I.

1988-89 NARSAD Young Investigators Grant to continue research on the instrumentation of drug-induced movement disorders.

1987-88 Biomedical Research Support Grant from the Department of Psychiatry, UCLA School of Medicine, to develop a system to measure and analyze the movements of the human larynx.

Industry Sponsored

Investigator Designed and Initiated

1999-03 Janssen Pharmaceutica: Investigator designed protocol.
"Brief Hospitalization for Schizophrenia: Strategies to Improve Treatment Outcome"
Co-Investigator. Donna A. Wirshing, M.D. - P.I.

2000-05 Eli Lilly, Inc.: Investigator designed protocol.
"Olanzapine vs. Risperidone in Treatment Refractory Schizophrenia"
Co-Investigator. Donna A. Wirshing, M.D. - P.I.

Industry Designed and Initiated

1998-99 Merck & Company, Inc.
"A Double-Blind, Active and Placebo-Controlled, Safety Tolerability, and Preliminary Antipsychotic Activity Study of MK-0869 in Hospitalized Schizophrenia Patients"
P.I. William C. Wirshing, M.D.

1998-99 Hoechst Marion Roussel, Inc.
"A Multicenter, Placebo and Active Control, Double-Blind Randomized Study of the Efficacy, Safety and Pharmacokinetics of M100907 (10 and 20 mg/d in Schizophrenic and Schizoaffective Patients."
Co-Investigator. Donna A Wirshing, M.D. - P.I

1997-00 Organon 041002
"A Double Blind, Five-Armed, Fixed Dose, Active and Placebo Controlled Dose-Finding Study With Sublingual ORG 5222 in Subjects With Acute Phase Schizophrenia"
P.I. William C. Wirshing, M.D.

1997-99 Otsuka America: 42,776
"An Open Label Follow-on Study on the Long-Term Safety of Aripiprazole in Patients with Psychosis"
P.I. William C. Wirshing, M.D.

1997-99 Otsuka America: 31-97-202
"A Phase III Double-Blind Study of Aripiprazole and Risperidone in the Treatment of Psychosis"
P.I. William C. Wirshing, M.D.

1997-98 Janssen Pharmaceutica: RIS-USA-112
"A Multicenter, Randomized, Double Blind, Parallel Group Trial Comparing the Safety and Efficacy of Risperidone and Olanzapine in the Treatment of Psychosis in Patients with Schizophrenia and Schizoaffective Disorder."
Co-Investigator. Donna A. Wirshing, M.D. - P.I.

1997-99 Janssen Pharmaceutica: RIS-USA-113
"A Multicenter, Randomized, Double Blind, Parallel Group Trial Comparing the Safety and Efficacy of Risperidone and Olanzapine in the Treatment of Psychosis in Patients with Schizophrenia and Schizoaffective Disorder."
Co-Investigator. Donna A. Wirshing, M.D. - P.I.

1995-98 Hoechst Marion Roussel
"An Open-Label, Follow-Up, Multicenter, Long-Term Maintenance Study of MDL 100, 907 in Patients with Schizophrenia."
Co-Investigator. Donna Ames, M.D. - P.I.

1995-98 Otsuka: 31-95-201
"OPC-14597: An Open-Label Tolerability Study in Schizophrenic Patients."
P.I. William C. Wirshing, M.D.

1995-96 Hoechst Marion Roussel: IND# 47,372
"A Randomized, Double-Blind, Placebo-Controlled, Parallel, Multiple Dose, Multicenter Study to Determine the Safety, Tolerability, Pharmacokinetics, and Biochemical Activity of MDL 100,907 in Patients with Schizophrenia."
Co-Investigator. Donna Ames, M.D. - P.I.

1995-96 Merck & Company, Inc.
"A Double-Blind, Placebo-Controlled, Safety, Tolerability and Preliminary Antipsychotic Activity Study of L-745,870 in Hospitalized Schizophrenic Patients"
P.I. William C. Wirshing, M.D.

1995-96 Otsuka: 31-94-202
"A Dose Ranging Study of the Efficacy and Tolerability of OPC-14597 in Acutely Relapsing Hospitalized Schizophrenic Patients."
P.I. William C. Wirshing, M.D.

1993-97 Eli Lilly Incorporated: F1D-MC-HGAP
"Fixed Dose Olanzapine versus Placebo in the Treatment of Schizophrenia."
Co-Investigator. Donna Ames, M.D. - P.I.

1994-99 Pfizer, Inc.: 128-116B
"A 52-Week, Open Extension Study Evaluating the Safety and Outcome of 40-80 mg BID of Oral Ziprasidone (CP-88,059-1) Daily in the Treatment of Subjects Who Have Participated in Previous Ziprasidone Clinical Trials."
Co-Investigator. Donna Ames, M.D. - P.I.

1993-94 R.W. Johnson: M92-083
"Multi-Center, Randomized, Double-Blind, and Controlled, 4 Week, Multiple Oral Rising Dose Study to Determine Safety Tolerability, Pharmokinetics and Behavioral Activity of RWJ-37796 in Male Schizophrenic Subjects Phase II."
P.I. William C. Wirshing, M.D.

1992-98 Abbott Laboratories - Neuroscience Venture: M92-795
"An Open Label Assessment of the Long Term Safety of Sertindole in the Treatment of Schizophrenic Patients."
Co-Investigator. Donna Ames, M.D. - P.I.

1994-96 Pfizer, Inc.: 128-115
"Phase III, Six Week, Double Blind, Multi-Center, Placebo Controlled Study Evaluating the Efficacy and Safety of Three Fixed Doses of Oral Ziprasidone (CP-88,051-1) and Haloperidol in the Acute Exacerbation of Schizophrenia and Schizo-Affective Disorder."
Co-Investigator. Donna Ames, M.D. - P.I.

1992-94 Glaxo, Inc.: S3B-201
"A Randomized, Double-Blind, Placebo-Controlled, Crossover Evaluation of the Effects of GR68755C on Serum Levels of Haloperidol in Patients with a Diagnosis of Schizophrenia."
Co-Investigator. Stephen R. Marder, M.D. - P.I.

1992-93 Abbott Laboratories - Neuroscience Venture: M92-762
"A Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Sertindole in Schizophrenic Patients."
Co-Investigator. Stephen R Marder, M.D. - P.I.

1992-93 Schering Plough Research Corporation: SCH39166
"Safety, Tolerance and Pilot Efficacy of Rising Multiple Doses of SCH39166: An Open Label Trial."
Co-Investigator. Stephen R Marder, M.D. - P.I.

1988-89 Astra Pharmaceuticals
"Raclopride in Schizophrenia: a Haloperidol-Controlled, Double-Blind, Dose-Finding Clinical Trial."
Co-Investigator. Theodore Van Putten, M.D. - P.I.

1990-91 Sandoz Pharmaceuticals
"A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Multi-Stage, Dose-Finding Study of SDZ HDC 912 in DSM-III-R Defined Hospitalized Schizophrenic Patients."
Co-Investigator. Theodore Van Putten, M.D. - P.I.

Reviewer / Editor

Reviewer:

American Journal of Psychiatry
Archives of General Psychiatry
Biological Psychiatry
Brain Dysfunction
CNS Spectrums
Comprehensive Psychiatry

International Journal of Psychiatry in Medicine
Journal of Clinical Psychiatry
Journal of Psychiatric Research
Journal of Clinical Psychopharmacology
Neuropsychiatry, Neuropsychology, and Behavioral Neurology
Psychiatry Research
Psychopharmacology
Psychopharmacology Bulletin
Psychosomatics
Schizophrenia Bulletin

Invited Presentations

04/07 "Schizophrenia and Related Psychoses" Grand Rounds Northridge Hospital, Northridge CA 15 Apr 2007

08/06 "Tailored Management of Schizophrenia in the Real World: A Naturalistic Approach" Presented at Evansville State Hospital, Evansville, IN, 17 Aug 06

08/06 "The Metabolic Mayhem of Atypicals: The TD of the New Millennium" Grond Rounds Antelope Valley Hospital 11 Aug 06.

08/06 "Use of Atypical Antipsychotics in Bipolar Illness"1 Aug 06 Honolulu, HI.

03/06 "Treatment of Agitation with Behavioral Interventions and Atypical Antipsychotics in Schizophrenia" Presented at American Association for Geriatric Psychiatry, San Juan, Puerto Rico, 11 Mar 06.

02/06 "Addressing Metabolic Disturbances with Antipsychotic Treatments" Presented at San Francisco General Hospital, Dept of Psychiatry, San Francisco, CA, 24 Feb 06

12/05 "Metabolic Impact of Atypical Antipsychotics: The View from Two Decades of Experience" Presented at Eden Medical Center, Castro Valley, CA 7 Dec 2005

11/05 "Clinical Management of Behavioral and Psychological Symptoms in Dementia" Presented at Salem Hospital, Salem, OR, 16 Nov 05

10/05 "Marketing Atypical Antipsychotics and the Opacity of Adiposity" Presented at Grand Rounds, Sepulveda VA, Los Angeles, CA, 26 Oct 05

07/05 "Treatment of Agitation in Elderly Demented Patients" Presented at Grand Rounds, Hawaii State Hospital, Kaneohe, HI, 12 Jul 05

07/05 "Metabolic Disturbances During Antipsychotic Treatment" Presented at Grand Rounds, Castle Medical Center, Kailua, HI, 12 Jul 05

04/05 "Metabolic Disturbances During Antipsychotic Treatment" Presented at Grand Rounds, Battle Creek VA Med Center, Battle Creek, MI, 7 Apr 05

12/04 "Considerations in Long-Term Management of Schizophrenia" Presented at Grand Rounds, Corcoran State Prison, Corcoran, CA 1 Dec 04

12/04 "Management of Associated Comorbidities of Schizophrenia" Presented at Grand Rounds, Atascadero State Hospital, Atascadero, CA 1 Dec 04

09/04 "Pharamacological Treatment of Psychosis and Agitation in Dementia of the Elderly" Presented at Grand Rounds, Scripps Mercy Hospital, San Diego, CA, 7 Sep 04

08/04 "Metabolic Disorder" Presented at Grand Rounds, Kedren Hospital, Los Angeles, CA 16 Aug 04

06/04 "Atypical Antipsychotics in Special Populations" Presented at Grand Rounds Terrell State Hospital, Terrell, TX, 21 Jun 04

06/04 "The Many Faces of 'Wartime' PTSD" Presented at Grand Rounds, Mountain Crest Hospital, Fort Collins, CO, 15 Jun 04

05/04 "Pharmacology Treatment of Psychosis and Agitation in Dementia of the Elderly" Presented at Grand Rounds, Utah State Hospital, Provost, UT, 20 Mau 04

05/04 "Psychiatric Research Ethics" Presented at NIH Neuroscience Center, Bethesda, MD, 17 May 04

05/04 "Lab Science to Clinical Practice: Neurochemical Model of Antipsychotic Effects" Presented at Grand Rounds, Metropolitan State Hospital, Norwalk, CA, 12 May 04

04/04 "New Indications for Antipsychotics for Bi-Polar Disorders" Presented at Grand Rounds, Cedars Sinai, Los Angeles, CA, 29 Apr 04

03/04 "A Century after Bleuler, What Do We Really Know About Schizophrenia, Its Origin, Cause, and Treatment?" Presented at WASP (World Association of Social Psychiatry), 1st Regional Congress of Social Psychiatry in Africa; Johannesburg, Gauteng, 24 Mar 04

03/04 "The Antipsychotics: Their Developmental History, Clinical Limitations, Major Toxicities, and Anticipated Future." Presented at WASP (World Association of Social Psychiatry), 1st Regional Congress of Social Psychiatry in Africa; Johannesburg, Gauteng, 24 Mar 04

02/04 "Consideration in the Long-term Management of Schizophrenia" Presented at Grand Rounds, Stanford University Hospital, Stanford, CA, 19 Feb 04

02/04 "The Marketing of Atypical Antipsychotic Drugs: A War for Our "Loyalties" Moves Into its Guerilla Phase" Presented at Grand Rounds, Sepulveda VA Mental Health Center, Los Angeles, CA, 11 Feb 04

02/04 "Drug Induced Metabolic Symptoms with Antipsychotic Paradigm Shift in an Approach to Patient Care" Presented at Grand Rounds, Atascadero State Hospital, Atascadero, CA, 4 Feb 04

01/04 "Risperdal Consta" Presented at Grand Rounds, Indianapolis VA, Indianapolis, IN, 15 Jan 04

12/03 "Strategies for Controlling Psychotic Symptoms" Presented at Grand Rounds, Riverside County Department of Mental Health, Hemet CA, 9 Dec 03

12/03 "The Side Effects of the Atypical Antipsychotics: Marketing Mischief, Metabolic Mayhem, or Mechanistic Magic?" Presented at Grand Rounds, Castle Medical Center, Kailua, HI, 2 Dec 03

11/03 "Monitoring Patients on Antipsychotic Drugs for Glucose Intolerance and Other Features of the Metabolic Syndrome" Presented at Alexandria, VA, 19-20 Nov 03

11/03 "Antipsychotics: Overcoming Side Effect Treatment Barriers" Presented at Grand Rounds, Long Beach VA Medical Center, Long Beach, CA, 12 Nov 03

11/03 "The Side Effects of the Atypical Antipsychotics: Marketing Mischief, Metabolic Mayhem, or Mechanistic Magic?" Presented at Grand Rounds, Fresno, CA, 11 Nov 03

11/03 "A Broad Spectrum in Psychotropics" Presented at Grand Rounds, Golden Valley Health Center-Corner of Hope, Modesto, CA, 6 Nov 03

10/03 "The Mechanistic Similarities and Distinctions Among Antipsychotics: A Treatment Refractory Model" Presented at Grand Rounds, Hawaii State Hospital Auditorium, Oahu, HI, 24 Oct 03

10/03 "The Side Effects of the Atypical Antipsychotics: Marketing Mischief, Metabolic Mayhem, or Mechanistic Magic?" Presented at Grand Rounds, San Francisco Clinic, San Francisco, CA, 4 Oct 03

10/03 "Kaiser/Group Health Cooperative AP Advisory Board" Presented at San Francisco, CA, 4 Oct 03

10/03 "Improvement in Cognitive Function, Dosing and Titration" Presented at Grand Rounds, Olive View Hospital, Sylmar, CA, 2 Oct 03

09/03 "Strategies for Controlling Psychotic Symptoms" Presented at Grand Rounds, Seattle Hospital, Seattle, WA, 11 Sep 03

08/03 "Neurocognition and Schizophrenia Including Issues on Nicotine Receptors" Presented at Grand Rounds, Ventura County Behavioral Health Inpatient Unit, Ventura, CA, 13 Aug 03

05/03 "Switchover from Clozapine to Quetiapine: Mixed Results" Presented at Biological Psychiatry, San Francisco, CA, 15 May 03

05/03 "Effects of Novel Antipsychotics on Glucose and Lipid Levels" Presented at Grand Rounds, Eugene VA Clinic, Eugene, OR, 13 May 03

05/03 "Effects of Novel Antipsychotics on Glucose and Lipid Levels" Presented at Grand Rounds, VA Medical Center, Portland, OR, 12 May 03

05/03 "Atypical Antipsychotics: Marketing Mischief or Metabolic Mayhem" Presented at Grand Rounds, Harbor-UCLA Medical Center, Torrance, CA, 6 May 03

04/03 "Metabolic Consequences of Antipsychotic Therapy" Presented at Grand Rounds, Atascadero State Hospital, Atascadero, CA, 30 Apr 03

03/03 "Metabolic Toxicities of Atypical Antipsychotic Agents: Speculations, Etiology, and Treatment" Presented at Grand Rounds, RJ Donovan Correctional Facility, San Diego, CA, 12 Mar 03

03/03 "Aripiprazole" Presented at Grand Rounds, Patton State Hospital, Patton, CA, 5 Mar 03

02/03 "Applied Neuropsychopharmacology: The Spectrum of Clinical Outcomes with Atypical Antipsychotics" Presented at the CNS Advisory Summit, Scottsdale AZ, 22 Feb 03

02/03 "The Use of Atypical Antipsychotics in Mood Disorders" Presented at Grand Rounds, Region IV Parole Headquarters, Diamond Bar, CA, 21 Feb 03

01/03 "Metabolic Side Effects of Atypical Antipsychotics" Presented at Grand Rounds, King Drew Medical Center, Los Angeles, CA, 28 Jan 03

01/03 "TD - What if Anything is New?" Presented at Grand Rounds, VA Hospital, Neurology Department, Los Angeles, CA, 24 Jan 03

01/03 "Metabolic Toxicities of Atypical Antipsychotic Agents: Speculations, Etiology, and Treatment" Presented at Grand Rounds, Sepulveda VA, Los Angeles, CA, 22 Jan 03

12-02 "Aripiprazole" Presented at Grand Rounds, Loma Linda University, Redlands, CA 20 Dec 02

12-02 "Aripiprazole" Presented at Grand Rounds, Arrowhead Regional Medical Center, Colton, CA, 17 Dec 02

12-02 "Treatment Emergent Movement Disorders in Current Clinical Practice" Presented at Grand Rounds, Queens Hospital, Honolulu, HI, 13 Dec 02

12-02 "Advancement in Treatment of Schizophrenia" Presented at Grand Rounds, Tripler VA Army Hospital, Honolulu, HI, 11 Dec 02

11-02 "Evolution of Antipsychotic Therapies: A Pathophysiologic Approach" Presented at National Network if Psychiatric Educators, Laguna Niguel, CA, 15 Nov 02.

10-02 "Side Effects Involving Newer Antipsychotic Medications Including Risk of Cardiovascular Disease and Diabetes" Presented at Grand Rounds, Bakersfield Memorial Hospital, Bakersfield CA, 24 Oct 02.

03-02 "The Atypical Antipsychotic Compounds: What is the Crucial Difference Among Them?" Presented at Psychopharmacology Course, Stanford University, Stanford CA, 9 Mar 02.

03-02 "The Relative Metabolic Toxicities Among the Newer Antipsychotic Compounds." Presented at Grand Rounds, Waco, TX, 7 Mar 02

03-02 "The Relative Metabolic Toxicities Among the Newer Antipsychotic Compounds." Presented at Grand Rounds, Dallas VA Medical Center, Dallas, TX, 7 Mar 02

11-01 "Aripiprazole: Is anything Really New in the Wold of Antipsychotic Medications?" Presented at Abilitat Investigators Meeting, Scottsdale, AZ, 29 Nov 01.

09-01 "The Past, Present, and (Near) Future of Antipsychotic Medications: The Under-appreciated Role of Luck!" Presented at The Annual Meeting of the Northern California Psychiatric Society, Saratoga, CA, 19 Sep 01.

07-01 "The Metabolic Side Effects of the Newer Antipsychotic Compounds: The TD of the New Millennium." Presented at Grand Rounds, UC Irvine, Irvine, CA, 17 Jul 01.

05-01 "The Toxicities of the So-Called 'Atypical Antipsychotics'--Focus on Dyslipidemia." Presented at Grand Rounds, Utah Neuropsychiatric Institute, Salt Lake City, Utah, 22 May 01.

04-01 "Prodromal Phase of Schizophrenia: Diagnosis and Treatment." Presented at W. Covina Mental Health Office, W. Covina, CA, 19 April 01.

03-01 "Risperidone: A Clinical Research Update." Presented at Le Royal Meridien, Toronto, Ontario, Canada, 31 Mar 01.

03-01 "Ziprasidone: A New Treatment Option for Schizophrenia." Presented at University Of Tennessee, Memphis, TN, 9 Feb 01

03-01 "Ziprasidone: A New Treatment Option for Schizophrenia." Presented at University Of Arkansas for Medical Science, Little Rock, AR, 8 Feb 01

02-01 "Use of Antipsychotic Drugs on Treatment Approach for Drug Induced Psychosis." Presented at San Quentin State Prison, San Quentin, CA, 21 Feb 01.

01-01 "EPA and TD with Novel Antipsychotics." Presented at Lanterman State Hospital, Pomona, CA, 25 Jan 01.

12-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at VA Hospital, Seattle, WA, 15 Dec 00.

12-00 "Efficacy and Safety Data of the Atypical Antipsychotics." Presented at Atascadero State Hospital, Atascadero, CA, 14 Dec 00.

12-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at Grand Rounds, VA Hospital Outpatient Clinic, Roseburg, OR, 12 Dec 00.

12-00 "Optimal Management of Psychosis and Agitation in the Elderly" Presented at Grand Rounds, USC Ingleside Hospital, Rosemead, CA, 8 Dec 00.

12-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at Grand Rounds, University of Southern California, Los Angeles, CA, 6 Dec 00.

11-00 "Safety and Efficacy Among Atypicals; Treatment Refractory Schizophrenia." Presented at Los Angeles County Jail, Los Angeles, CA, 30 Nov 00.

11-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at Olive View Hospital, Sylmar, CA, 16 Nov 00.

11-00 "Long-Term Outcomes with Antipsychotic Medications: The limitations of Our Current Technology." Presented at Ziprasidone National Consultants Forum, Scottsdale, AZ, 14 Nov 00.

11-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at USC Ingleside Hospital, Rosemead, CA, 9 Nov 00.

10-00 "Newer Antipsychotics: Approaches to Treatment Refractory Patients." Presented at 2000 MIRECC Retreat, Los Angeles, CA, 25 Oct 00.

10-00 "Weight Gain and Atypical Antipsychotic Medications: The TD of the New Millennium?" Presented at MHC of Greater Manchester, Manchester, NH, 12 Oct 00.

09-00 "Side Effects of Typical and Atypical Antipsychotic Agents." Presented at the UCLA Medical Plaza, Los Angeles, CA, 11 Sep 00.

09-00 "Safety and Efficacy Among Atypicals." Presented at Sacred Heart Hospital, Spokane, WA, 12 Sep 00

09-00 "Safety and Efficacy Among Atypicals." Presented at Skagit Valley Mental Health, Mt. Vernon, WA, 13 Sep 00.

09-00 "Update on Atypical Antipsychotics." Presented at Porterville Developmental Center, Porterville, CA, 14 Sep 00.

07-00 "Schizophrenia: Treatment with Risperdal." Presented at the Office of Mental Health, New Orleans, LA, 25 Jul 00.

07-00 "Atypicals and Treatment Resistant Schizophrenia." Presented at Loma Linda Behavior Medicine Center, Redlands, CA, 21 Jul 00.

06-00 "Movement Disorders." Presented at Palacio de Exposiciones y Congresos, Seville, Spain, 16 Jun 00.

06-00 "Tools for Assessing Symptoms: Side Effect Scales." Presented at Palacio de Exposiciones y Congresos, Seville, Spain, 17 Jun 00.

05-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at UC Irvine Medical Neuropsychology Center, Orange, CA, 30 May 00.

05-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at Dave & Buster's, Orange, CA, 24 May 00.

05-00 "The Side Effects of Antipsychotic Compounds." Presented at Kaiser Permanente, Fontana, CA, 17 May 00.

04-00 "Atypical Antipsychotics" Presented at Riverside County Inpatient, Riverside, CA, 27 Apr 00.

03-00 "The Novel Antipsychotics." Presented at Loma Linda University, Loma Linda, CA, 29 Mar 00.

03-00 "The Cardiovascular Liabilities of the Atypical Antipsychotics: The Next 'Big' Thing." Presented at Grand Rounds, University of Hawaii, 24 Mar 00.

03-00 "The New Antipsychotic Compounds Really 'New'?" Presented at Grand Rounds, Contra Costa County Regional Medical Center, Martinez, CA, 14 Mar 00.

03-00 "Treatment Refractory Schizophrenia: Is there a rational approach?" Presented at American Psychiatric Association & Nevada Association of Psychiatric Physicians, Las Vegas, NV, Sat, 4 Mar 00.

02-00 "The Use of Risperidone in Acutely Psychotic Patients." Presented at Italian Society of Psychopathology (V SOPSI Congress), Rome, Italy, 23 Feb 00.

02-00 "The Differential Toxicities Among the Atypical Antipsychotics." Presented at Grand Rounds, Cedars Sinai Medical Center, Los Angeles, CA, 17 Feb 00.

12-99 Visiting Scholar-numerous presentations, Presented at University of Arkansas, Little Rock, AR, 5-8 Dec 99

11-99 "The Novel Antipsychotic Medications." Presented at Anaheim, CA, 12 Nov 99.

11-99 "The Side Effects of Antipsychotic Compounds." Presented at University of Kansas Medical Center, Kansas City, MO, 5 Nov 99.

11-99 "Atypicals Antipsychotics: Efficacy and Side Effects." Presented at The American Restaurant, Kansas City, MO, 4 Nov 99.

11-99 "Side Effects of Antipsychiatric Compounds." Presented at Colmery O'Neil V A M C, Topeka, KS, 4 Nov 99.

11-99 "The Side Effects of Antipsychotic Compounds." Presented at Western Missouri Mental Health South Auditorium, Kansas City, MO, 4 Nov 99.

10-99 "Is Clozaril still relevant?" Presented at Atascadero State Hospital, San Luis Obispo, CA, 14 Oct 99.

10-99 "Interested in Geriatric population & Economics of the drugs." Presented at Grand Rounds, Loma Linda University, Loma Linda, CA, 8 Oct 99.

09-99 "Side Effects of Atypical Antipsychotics: What can we expect in the short and long term?" Presented at Riverside, CA, 30 Sep 99.

09-99 "New Treatment Options in the Acute Management of Psychosis." Presented at New York, NY, 26 Sep 99.

08-99 "How to Choose the Correct Medication Regimen for the Treatment of Psychotic Manifestations." Presented at Lanterman Developmental Center, Pomona, CA, 26 Aug 99.

07-99 "Schizophrenia and Overview Movement Disorders." Presented at UCLA School of Nursing, Westwood, CA, 26 Jul 99.

07-99 "New and Novel Antipsychotics." Presented at Fairview Developmental Center, Costa Mesa, CA, 15 July 99.

06-99 "Schizophrenia-Current and New Treatment Trends." Presented at San Joaquin County Mental Health Services, Sacramento, CA, 24 Jun 99.

05-99 "Research Experience with the Newer Neuroleptics-Grand Rounds." Presented at Kaiser, San Francisco, CA, 25 May 99.

05-99 "New Treatment Options in the Acute Management of Psychosis." Presented at Boston Marriott Long Wharf, Boston, MA, 22 May 99.

05-99 "The Neurophysiology of Schizophrenia: Focus on the action of the Novel Antipsychotics." Presented at Kaiser, Woodland Hills, CA, 12 May 99.

04-99 "The New Generation of Antipsychotic Medications." Presented at Kaiser Sunset Family Practice, Los Angeles, CA, 26 Apr 99.

04-99 "Relative Efficacies and Toxicities of Risperidone and Olanzapine." Presented at Leeds, England, United Kingdom, 9 Apr 99.

04-99 "Relative Efficacies and Toxicities of Risperidone and Olanzapine." Presented at Southampton, England, United Kingdom, 8 Apr 99.

04-99 "The Neurophysiology of Schizophrenia: Focus on the Action of the Novel Antipsychotics." Presented at The Schizophrenic Patient: Profiles, Diagnosis and Treatment Conference, Loma Linda University, Loma Linda, CA, 7 Apr 99.

03-99 "Pharmacological Bases for the Putative Neurocognitive Enhancing Impact of Atypical Antipsychotic Agents." Presented at Neurocognitive Impairment in Schizophrenic and Alzheimer's Disorders: Therapeutic Approaches Workshop, International Academy for Biomedical and Drug Research, Paris, FR, 12-13 Mar 99.

02-99 "Antipsychotic Toxicity in the Elderly." Presented at 9th Annual Geriatric Psychiatry Conference, Dallas, TX, 13 Feb 99.

02-99 "Typical and Atypical Neuroleptics: A Geropsychiatric Perspective." Presented at 9th Annual Geriatric Psychiatry Conference, Dallas, TX, 13 Feb 99.

02-99 "Somatic Treatments of Psychotic Disorders" Given with course entitled "Recovery from Madness", Alex Kopelowicz, MD and Robert Liberman, MD--Course Chairs.

02-99 "The Comparative Toxicities of the New Antipsychotic Medications." Presented at Harbor UCLA, Torrance, CA, 2 Feb 99.

01-99 "The Treatment of Schizophrenia at the Turn of the Millennium: What Have We Learned?" Presented to local lay chapter of the California Alliance for the Mentally Ill, UCLA Medical Plaza, Los Angeles, CA, 14 Jan 99.

01-99 "Treatment Refractory Schizophrenia: The Role of the "New" Antipsychotic Compounds" Presented at Grand Rounds, UCI Medical Center, Irvine, CA, 5 Jan 99.

11-98 "Treatment of Schizophrenia." Presented at Grand Rounds, UC Davis Medical Center, Sacramento, CA, 11 Nov 98.

11-98 "Atypicals and Side Effects." Presented at Sutter Family Practice Residency Program, Sacramento, CA, 11 Nov 98.

11-98 "Treatment of Refractory Patients and Partial Response." Presented at Janssen-Cilag SpA Laboratories, Beerse, Belgium, 6 Nov 98.

10-98 "The Role of Novel Antipsychotics in the Control of the Acute Psychotic Symptoms." Presented at the WPA Symposium, Guadalajara, MX, 30 Oct 98.

10-98 "Efficacy of Risperdal and the Atypical Antipsychotics." Presented at Grand Rounds, Porterville State Hospital, Porterville, CA, 21 Oct 98.

10-98 "Treatment of the Refractory Patient." Presented at the Grand Geneva Resort Symposium, Lake Geneva, IL, 3 Oct 98.

10-98 "Treatment Resistant Schizophrenia" Presented at the APA-IPS Symposium, Los Angeles, CA, 2 Oct 98.

09-98 "Treatment Refractory Schizophrenia." Presented at Grand Rounds, Oregon Health Sciences University Department of Psychiatry, 29 Sep 98.

09-98 "The Second Generation of 'Anti-schizophrenic' Drugs." Presented at the 1998 William Rondeau Memorial Lecture, Oregon Health Sciences University Department of Psychiatry, 28 Sep 98.

09-98 "Movement Disorders in Psychiatry." Presented at VA Hines, IL, 23 Sep 98.

09-98 "The Role of Atypical Antipsychotics." Presented at Napa State Hospital, CA, 19 Sep 98.

09-98 "Atypical Antipsychotics and Schizophrenia." Presented at Grand Rounds, Menlo Park VAMC, Menlo Park, CA, 11 Sep 98.

08-98 "New Treatment Options in Schizophrenia." Presented at ComCare, Phoenix, AZ, 18 Aug 98.

07-98 "Schizophrenia Overview and Movement Disorders." Presented at the Neuropsychiatric Nurse Practitioner Program, UCLA School of Nursing, Los Angeles, CA, 27 Jul 98.

07-98 "New Treatment Interventions for Psychotic Disorders." Presented at San Joaquin County Mental Health Services, Stockton, CA, 16 Jul 98.

07-98 "Strategies for Rapidly Controlling Acute Psychotic Symptoms." Presented at Napa State Hospital, Napa, CA, 3 Jul 98.

06-98 "New Directions in Psychosis." Presented at Grand Rounds, San Francisco General Hospital, San Francisco, CA, 26 Jun 98.

06-98 "The Clinical Choice: Is an Algorithm Possible?" Presented at Riverview Hospital, Vancouver, BC, 12 Jun 98.

06-98 "Treatment of Refractory Psychosis: Is There a Rational Approach?" Presented at Riverview Hospital, Vancouver, BC, 12 Jun 98.

06-98 "Drug Treatment of Schizophrenia" Presented as course number 63 with faculty S Marder, J Davis, P Janicak, at the 151st APA Annual Meeting in Toronto, Canada, 2 Jun 98.

05-98 "New Atypical Antipsychotics: Similarities and Differences" Presented via satellite program for Indio and Riverside County Mental Health Inpatient Treatment Facility, Riverside, CA, 28 May 98.

05-98 "New Advances in the Treatment of Schizophrenia" Presented by CME, Inc. at Sheraton Gateway, Los Angeles, CA, 17 May 98.

05-98 "Psychopharmacology Update: A Comparison of Current Antipsychotic Drugs" Presented at Merritheu Memorial Hospital, Martinez, CA, 12 May 98.

05-98 "Management of Cognitive Disruption in Schizophrenia" Presented at University of Illinois at Chicago Symposium in Bloomingdale, IL, 5 May 98.

05-98 "Neurocognition, Schizophrenia, and the Role of the Novel Antipsychotic Medications" Presented at the Panhellenic Psychiatric Congress, Limnos, Greece, 2 May 98.

04-98 "Neurocognitive and Functional Assessment - Rationale for M100907 Superiority" Presented at second Neuropsychiatry Forum of Hoechst Marion Roussel in Bridgewater, NJ, 24 Apr 98.

04-98 "Treatment Resistant Schizophrenia: Is there a Rational Approach?" Presented at Bergen Pines County Hospital, Paramus, NJ, 23 Apr 98.

04-98 "Treatment Resistant Schizophrenia: Is there a Rational Approach?" Presented at Rockland Psychiatric Center, Orangeburg, NY, 22 Apr 98.

04-98 "Update on Anti-psychotic Medications." Presented at Alaska Psychiatric Association's 5th Annual Spring Education Meeting, Anchorage, AK, 18 Apr 98.

03-98 "Psychopharmacology Update: A Comparison of Current Antipsychotic Drugs." Presented at Washington State Psychiatric Association Spring Meeting in Vancouver, BC, 28 Mar 98.

03-98 "Schizophrenia and Cognitive Function - Approaching the New Millennium" Presented at National Schizophrenia Symposium, Scottsdale, AZ, 27 Mar 98.

03-98 "Challenge: Making the most of Therapy with Atypical Antipsychotics" Presented at Eastern State Mental Hospital, Williamsburg, VA, 20 Mar 98.

03-98 "Past, Present and Future of Antipsychotic Drugs" Presented for the Virginia State Psychiatric Society, Richmond, VA, 21 Mar 98.

03-98 "Pharmacologic Impact on Neurocognitive Deficits in Schizophrenia:" Presented at Grand Round, Long Beach VA Medical Center, 4 Mar 98.

02-98 "Neurocognition in Schizophrenia: Magnitude, Functional Correlates and Pharmacologic Responsivity" Presented at USC School of Medicine Grand Rounds, 10 Feb 98.

02-98 "Biological bases for Schizophrenia" Presented at the seminar course for undergraduates Psychiatry 98P Professional Schools Seminar Program, UCLA, CA, 4 Feb 98.

11-97 "The New Generation of Antipsychotic Medications: Similarities and Differences" - Presented at V.A.Psychiatry Service Grand Rounds, Minneapolis, MI, 21 Nov 97.

11-97 "The New Generation of Antipsychotic Medications: Similarities and Differences" - Presented at HCMC Psychiatry Grand Rounds, MI. 21 Nov 97.

11-97 "Neurocognition in Schizophrenia: Magnitude, Functional Correlates, and Pharmacologic Responsivity" Presented at the Atascadero State Hospital, Atascadero, CA, 19 Nov 97.

11-97 "Pharmacologic Approach to Chronic and Treatment Refractory Schizophrenia" Presented at the Vancouver BCPA Conference, in Vancouver, Canada, 15 Nov 97.

11-97 "New Serotonin/Dopamine Antagonist" - Presented for the Loma Linda Psychiatric Residency Program, Loma Linda, CA, 14 Nov 97

11-97 "The Role of New Generation Antipsychotics in Treatment-Resistant Schizophrenia" - Presented in Grand Rounds at The Chicago Medical School Department of Psychiatry and Behavioral Sciences, Chicago, IL, 6 Nov 97.

10-97 "Beyond Conventional Symptoms" - Presented in Riyadh, Saudi Arabia, 20 Oct 97.

10-97 "Neurocognitive Changes in Schizophrenia" Clinical Pertinence and Impact of Pharmacotherapy" - Presented in Grand Rounds at the University of Nebraska Medical Center, Omaha, NE, 15 Oct 97.

09-97 "Treatment Resistance in Psychosis"- Presented at the Annual Meeting of the Huron Valley Medical Center in in Ypsilanti, MI, 24 Sep 97.

09-97 "Toxic Side Effects of Antipsychotic Medications - Focus on Neuromotor Syndromes" Presented at The Fall 1997 Symposium of Charter Behavioral Health Systems of New England, Nashua, New Hampshire, 20 Sep 97.

09-97 "Risperidone: Efficacy Beyond Conventional Symptoms" Presented at the 10th Annual Meeting of European College of Neuropsychopharmacology, Vienna, Austria, 15 Sep 97.

09-97 "Schizophrenia, Neurocognition, and Antipsychotic Meds" Presented in Grand Rounds at Oregon Health Science University, 9 Sep 97.

09-97 "Past, Present and Future of Antipsychotics" Presented at the Mendota Mental Health Institute Conference Center, Madison, WI, 29 Aug 97.

06-97 "Efficacy: A Clinician's Evidence from Experience" Presented at the Risperdal: Evidence from Experience Interactive Seminars in East Midlands, England, 19 Jun 97.

06-97 "Efficacy: A Clinician's Evidence from Experience" Presented at the Risperdal: Evidence from Experience Interactive Seminars in East Kilbride, England, 18 Jun 97.

06-97 "Efficacy: A Clinician's Evidence from Experience" Presented at the Risperdal: Evidence from Experience Interactive Seminars in Aberdeen, Scotland, 17 Jun 97.

06-97 "Antipsychotics: The Evidence from Experience" Presented at the Janssen Research Foundation in Beerse, Belgium, 16 Jun 97.

06-97 "Atypical Neuroleptics: Newer Antipsychotics" Presented at the Northampton VA Medical Center, Northampton, MA, 4 Jun 97.

05-97 "Beyond Conventional Symptoms: Focus on Risperidone" Presented in Grand Rounds at Vanderbilt University Medical Center, Nashville, TN, 27 May 97.

05-97 "Psychopharmacology in the Geriatric Patient: Utility and Limitations" Presented at the California Society of Internal Medicine annual meeting, San Diego, CA, 24 May 97.

05-97 "The Recognition and Management of Side Effects of Typical and Atypical Neuroleptics" Presented as course number 54 with faculty SR Marder, J Davis, G Simpson, P Janicak at the 150th APA Annual Meeting, San Diego, CA, 17-22 May 97.

05-97 "Overview of Treatment of Psychosis with New Atypical Antipsychotic Medications" Presented at the Psychiatric Institute, Washington, DC, 16 May 97.

05-97 "Overview of Treatment of Psychosis with New Atypical Antipsychotic Medications" Presented at the Commission on Mental Health, Washington, DC, 15 May 97.

05-97 "Practical Applications in Atypical Antipsychotics: Clients with Movement Disorders" Presented at Cambridge Hospital, Boston, MA, 14 May 97.

05-97 "The Newer Antipsychotics: Differences and Applications" Presented at Butler Hospital, Providence, RI, 13 May 97.

04-97 "Risperidone and Neurocognition". Presented at the Annual Meeting of the Dutch Psychiatric Society, Amsterdam, Netherlands, 18 Apr 97.

04-97 "Clozapine vs. Haloperidol: Drug Intolerance in a Controlled Six Month Trial" Presented at the International Congress on Schizophrenia Research, Colorado Springs, CO, 14 Apr 97.

04-97 "Antipsychotic Drug Side-Effects: Objective and Subjective". Presented at the International Congress on Schizophrenia Research, Colorado Springs, CO, 14 Apr 97.

03-97 "An Update on Atypcial Antipsychotics". Presented in Hyannis, MA, 28 Mar 97.

03-97 "An Update on Atypical Antipsychotics". Presented in New Bedford, MA, 27 Mar 97.

03-97 "The Management of Acute Exacerbations in Chronic Schizophrenia". Presented at Evidence From Experience, Lisbon, Portugal, 21 Mar 97.

03-97 "Beyond the Conventional Symptoms". Presented at Evidence From Experience, Lisbon, Portugal, 21 Mar 97.

03-97 "The Efficacy of Risperidone: The Evidence from the Controlled Clinical Experience". Presented in Beijing, China, 17 Mar 97.

03-97 "The Efficacy of Risperidone: The Evidence from the Controlled Clinical Experience". Presented in Nanjing, China, 15 Mar 97.

03-97 "The Efficacy of Risperidone: The Evidence from the Controlled Clinical Experience". Presented in Shanghai, China, 14 Mar 97.

03-97 "The Efficacy of Risperidone: The Evidence from the Controlled Clinical Experience". Presented in Wuhan, China, 12 Mar 97.

03-97 "The Efficacy of Risperidone: The Evidence from the Controlled Clinical Experience". Presented in Guangzhou, China, 11 Mar 97.

01-97 "Rational Approach to Antipsychotic Medications and Patient Selection". Presented at the Midwinter Program for Psychiatrists, Lake Tahoe, NV, 28 Jan 97.

01-97 "Current Therapy Options: Efficacy and Side Effects". Presented at the Reintegration: Therapeutic Horizons for Psychotic Disorders Symposium in Salt Lake City, UT, 25 Jan 97.

01-97 "Issues in Diagnosis of Schizophrenia". Presented at the Reintegration: Therapeutic Horizons for Psychotic Disorders Symposium in Salt Lake City, UT, 25 Jan 97.

12-96 "The New Generation of Antipsychotic Medications: Similarities & Differences". Presented to the Hawaii Psychiatric Medical Association, Waikiki, HI, 3 Dec 96.

12-96 "The New Generation of Antipsychotic Medications: Similarities & Differences". Presented at Hawaii State Hospital, Kaneohe, HI, 2 Dec 96.

11-96 "Risperidone: The Controlled Clinical Experience". Presented in Newcastle, England.

11-96 "Risperidone: The Controlled Clinical Experience". Presented in Glasgow, Scotland.

11-96 "Risperidone: The Controlled Clinical Experience". Presented in Birmingham, England.

11-96 "Risperidone: The Controlled Clinical Experience". Presented in Manchester, England.

11-96 "Risperidone: The Controlled Clinical Experience". Presented at Kyoto Prefectural University, Kyoto, Japan.

11-96 "Risperidone: The Controlled Clinical Experience". Presented at Hiroshima University, Hiroshima, Japan.

11-96 "Treatment Resistant Schizophrenia: Is There a Rational Approach?" Presented in Kurashiki (Okayama City), Japan.

08-96 "New Solutions to Treatment Resistant Schizophrenia". Presented at the 10th World Congress of Psychiatry, Madrid, Spain, 23 Aug 96.

07-96 "Critical Issues in Psychoses: Dementia, First-Break Patients, Refractory Cases, and Pharmacoeconomics of Schizophrenia". A CME presentation, Costa Mesa, CA.

06-96 "Critical Issues in Psychoses: Dementia, First-Break Patients, Refractory Cases, and Pharmacoeconomics of Schizophrenia". A CME presentation, San Francisco, CA.

06-96 "The New Generation of Antipsychotic Medications: How Are They Different?". A CME presentation, Staunton, VA.

05-96 "Treatment Resistant Schizophrenia" an industry-sponsored symposium presented at the 149th APA Annual Meeting, New York, NY, May 4-9, 1996.

05-96 "The Recognition and Management of Side Effects of Typical and Atypical Neuroleptics" Presented as course number 61 with faculty SR Marder, J Davis, G Simpson, P Janicak at the 149th APA Annual Meeting, New York, NY, May 4-9, 1996.

03-96 "Treatment Resistant Schizophrenia: Is There a Rational Approach?" Presented at Evolving Attitudes Across the Spectrum of Schizophrenia, Amsterdam, Netherlands.

03-96 "The Natural History of the 'Schizophrenias'". Presented at Evolving Attitudes Across the Spectrum of Schizophrenia, Amsterdam, Netherlands.

03-96 "Update on New Antipsychotic Medications". Presented at University of California, Davis, Davis, CA.

03-96 "Special Populations with Psychoses: First Break Patients, Adolescents and Geriatric Patients". A CME presentation, Long Beach, CA.

02-96 "Psychopharmacology in the Elderly: Cognition and Psychosis". Presented at the Area 7 Symposium, Las Vegas, NV.

02-96 "Side Effects of Antipsychotics: Recognition and Treatment". Presented at Grand Rounds, Stanford University Medical Center, Palo Alto, CA.

01-96 "The History and Current Status of Antipsychotic Drug Development". Presented at Grand Rounds, The Palos Verdes Regional Psychiatric Hospital, Tucson, AZ.

01-96 "The Risk Benefit Profiles of the Serotonin-Dopamine Antagonists". Presented at the University of Arizona, Tucson, AZ.

12-95 "Rational Approaches to Antipsychotic Pharmacotherapy". Presented at the Quarterly Meeting of the County of San Diego Mental Health Services, San Diego, CA.

11-95 "Special Populations with Psychosis: Adolescents, Geriatrics, and First Break Patients". A CME presentation, Seattle, WA.

11-95 "Special Populations with Psychosis: Adolescents, Geriatrics, and First Break Patients". A CME presentation, San Francisco, CA.

10-95 "The New Serotonin/Dopamine Antagonists: Are They Really Different?" presented to the Hirosaki University Department of Neuropsychiatry, Hirosaki University, Hirosaki, Japan.

10-95 "The New Serotonin/Dopamine Antagonists: Are They Really Different?" presented to the Akita University School of Medicine Department of Psychiatry, Akita University, Akita, Japan.

10-95 "The New Serotonin/Dopamine Antagonists: Are They Really Different?" presented to the Hokkaido University Department of Psychiatry, Hokkaido University, Hokkaido, Japan.

10-95 "Polypharmacy in the Treatment of Psychosis: Is There a Rational Approach?" presented at the SinYang Park Hotel, KwangJu, Korea.

10-95 "Polypharmacy in the Treatment of Psychosis: Is There a Rational Approach?" presented at the KwangJu Severance Mental Hospital, KwangJu, Korea.

10-95 "Update on Serotonin/Dopamine Antagonists: Are They Really Different?" presented to the Meeting of the Korean Neuropsychiatric Association at the Seoul Education Culture Center, Seoul, Korea.

09-95 "Pharmacologic Treatment of Depression" presented to the Quarterly Meeting of the Hawaii Psychiatric Association, Honolulu, Hawaii.

09-95 "Anti-psychotic Medications & Patient Selection: Is There a Rational Approach?" presented to the Hawaii Medical Association at the University of Hawaii, Honolulu, Hawaii.

08-95 "Side Effects of Antipsychotic Medications" presented at the Quarterly Meeting of the Memphis Psychiatric Association, Memphis, TN.

07-95 "Polypharmacy: When is it Reasonable?" Grand Rounds, Alameda County Psychiatric Hospital, Alameda, CA.

07-95 "Behavioral Skill Training in Schizophrenia: Utility and Limitation" Grand Rounds, Atascadero State Hospital, Atascadero, CA.

06-95 "Side Effects of Antipsychotic Medications" Grand Rounds, Loma Linda VA Hospital, Loma Linda, CA.

06-95 "The Treatment of Psychosis in the Elderly" Los Encinas Hospital Annual Symposium, Pasadena, CA.

06-95 "Update on the New Antipsychotic Medications" presented to the Annual Meeting of the California Department of Corrections Psychiatrists, Diamond Bar, CA.

05-95 "How to do research without an NIMH grant" presented at the 148th Annual Meeting of the American Psychiatric Association, Miami, FL, 20-25 May 95.

05-95 "The recognition and management of the side effects of typical and atypical neuroleptics" presented as Course 69 with Director SR Marder, and Faculty J Davis, G Simpson, Philip Janicek, and myself, at the 148th APA Annual Meeting, Miami, FL, 20-25 May 95.

05-95 "Behavioral Skills Training in Chronic Schizophrenia" presented at the Annual Conference of Western Reserve Psychiatric Hospital, Northfield, OH, 5 May 95.

03-95 "Dopaminergic Modulation of Cigarette Smoking" presented at the Society for Research on Nicotine and Tobacco with Murray E Jarvik, MD, PhD and Nicholas H Caskey, PhD, San Diego, CA.

03-95 "The Safety and Efficacy of Serotonin-Dopamine Antagonists" a Continuing Medical Education presentation, St. Louis, MO.

03-95 "The Safety and Efficacy of Serotonin-Dopamine Antagonists" a Continuing Medical Education presentation, Philadelphia, PA.

02-95 "The Next Generation of Antipsychotic Medications" presented at Grand Rounds, Veterans Affairs Hospital, Tuskegee, AL.

11-94 "Dosing Strategies with Antipsychotic Compounds: Conventional, SDAs, and Atypicals" presented at the Fall Symposium of New Approaches to Treating Schizophrenia, Chicago, IL, 12 Nov 94.

10-94 "Risperidone: Is It Really Different?" presented at the Fall Conference of the California Alliance For the Mentally Ill, San Francisco, CA, 29 Oct 94.

05-94 "The recognition and management of the side effects of typical and atypical neuroleptics" presented as Course 71 with Director SR Marder, and Faculty J Davis, G Simpson, Philip Janicek, and myself, at the 147th APA Annual Meeting, Philadelphia, PA, 24 May 94.

05-94 "Dementia and Movement Disorders in the Elderly," presented as Course 6 with Director JL Cummings, and Faculty WE Reichman, D Sultzer, and myself, at the 147th APA Annual Meeting, Philadelphia, PA, 20 May 94.

04-94 "Risperidone, is it really different?" presented at a Stanford University sponsored symposium on the treatment of schizophrenia Palo Alto, CA.

03-94 "The New Atypical Antipsychotics--Focus on Risperidone" presented to the Utah State Alliance for the Mentally Ill, Salt Lake City, Utah.

02-94 "The New Atypical Antipsychotics--Focus on Risperidone" presented to the Washington State mental health workers (psychiatrists and pharmacists), Seattle, WA.

01-94 "The Real Cost of Neuroleptic Treatments" presented to the California State Legislature, Sacramento, CA.

01-94 "The Rational Use of Neuroleptics" presented at the annual educational meeting of the Los Angeles Chapter of Family Practioners, Santa Monica, CA.

10-93 "The Therapeutic Window--The Role of Subjective Experiences" presented at the Quarterly Meeting of the Royal College of Psychiatrists in London, England.

05-93 "Optimum Dosing in Maintenance Treatment." Marder SR, Van Putten T, Wirshing WC, Lebell MB, McKenzie J, Johnston-Cronk K, presented at the 146th APA Annual

Meeting, San Francisco, CA, 26 May 93. In: 1993 CME Syllabus & Proceedings Summary, p. 238. (No. 87B)

05-93 "Combined Skills Training and Early Intervention." Marder SR, Wirshing WC, Van Putten T, Eckman TA, Liberman RP, presented at the 146th APA Annual Meeting, San Francisco, CA, 24 May 93. In: 1993 CME Syllabus & Proceedings Summary, p. 156. (No. 28D)

05-93 "Clinical Use of Neuroleptic Plasma Levels." presented at the 146th APA Annual Meeting, San Francisco, CA, 25 May 93.

05-93 "Dementia and Movement Disorders in the Elderly," presented as Course 2 with Director JL Cummings, and Faculty WE Reichman and myself, at the 146th APA Annual Meeting, San Francisco, CA, 22 May 93.

01-93 "Hyperkinetic Syndromes in the Elderly" presented at the Geriatric Supercourse in Marina del Rey, CA, 20 Jan 93.

11-92 "Clinical Consequences of Akinesia and Akathisia", presented as first author with T Van Putten and SR Marder at the Association of European Psychiatrists Congress, Barcelona, Spain, 5 Nov 92.

10-92 "The New Atypical Antipsychotics", presented to the South Coast Chapter of the Alliance for the Mentally Ill, Torrance, CA.

06-92 "Impact of Public Opinion and News Media on Psychopharmacology in the 1990's", with Louis Jolyon West, MD, at the College of International Neuropsycho-pharmacology Annual Meeting (CINP), 30 Jun 92, Nice, France.

05-92 "Drug-Induced Movement Disorders in the Elderly," presented at the 145th Annual American Psychiatric Association Meeting, Washington, DC.

03-92 "Fluoxetine-Induced Suicidality: Science, Spurious, or Scientology?" presented at the Daniel X. Freedman Journal Club, UCLA.

01-92 "The Placebo-Controlled Treatment of the Schizophrenic Prodrome," Biannual Winter Workshop on Schizophrenia, Badgastein, Austria.

01-92 "Management of the Neuroleptic-Intolerant Patient," presented with D Ames and T Van Putten at UCLA Grand Rounds, Los Angeles, CA.

01-92 "Akathisia with the New Atypical Neuroleptics," presented at Psychiatry Grand Rounds, UCLA-Harbor Medical Center, Torrance, CA.

12-91 "Management of Risk of Rèlapse in Schizophrenia," presented at the Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico.

10-91 "Extrapyramidal Symptoms and the Atypical Antipsychotics," presented to the Southern California Chapter of the California Alliance for the Mentally Ill, Los Angeles.

06-91 "Neuroleptic-Induced Extrapyramidal Symptoms," presented at the Southern California Psychiatric Society, West Hollywood, CA.

05-91 "Pharmacokinetics of Long-Acting Neuroleptics," presented with SR Marder, T Van Putten, J Hubbard, M Aravagiri, and KK Midha, at the American Psychiatric Association 144th Annual Meeting, New Orleans, LA.

05-91 "Fluphenazine Dose in Chronic Schizophrenia," presented with SR Marder, T Van Putten, M Lebell, J McKenzie, and K Johnston-Cronk, at the American Psychiatric Association Annual Meeting, New Orleans, LA.

05-91 "Early Prediction of Schizophrenic Relapse," presented with SR Marder, T Van Putten, M Lebell, K Johnston-Cronk, and J Mintz, at the American Psychiatric Association Annual Meeting, New Orleans, LA.

04-91 "Instrumental Quantification of Akathisia," presented with T Van Putten, SR Marder, JL Cummings, G Bartzokis, and MA Lee at the International Congress on Schizophrenia Research, Tucson, AZ.

04-91 "Antipsychotic Drugs of the Future: The Legacy of Clozapine," presented at the Annual Meeting of the Southcoast Alliance for the Mentally Ill, Fountain Valley, CA.

02-91 "Free Radicals, Movements Disorders, and their Possible Interrelationship," presented to the College of Pharmacy, University of Saskatchewan, Saskatoon, Canada.

11-90 "Primary and Secondary Effects of the Neuroleptics: An Historical Perspective." California Alliance for the Mentally Ill, Fall Conference, Ventura, CA.

11-90 "Antipsychotic Drugs of the Future: The Legacy of Clozapine." California Alliance for the Mentally Ill, Fall Conference, Ventura, CA.

10-90 "Instrumental Quantification of the Akathisic Liability of Clozapine." 2nd Annual NARSAD Scientific Symposium, Washington, DC.

06-90 "Instrumental Quantification of the Akathisic Liability of Clozapine." Regional Meeting of NARSAD Supporters, Pasadena, CA.

02-90 "Instrumentation of Drug-Induced Movement Disorders." Neurology Grand Rounds, West LA VAMC, Los Angeles, CA.

02-90 "Functional Versus Organic Psychoses." Psychiatry Grand Rounds, UCLA Harbor Medical Center, Torrance.

10-89 "Use of Quantitative Instruments in the Assessment of Neuroleptic-Induced Movement Disorders." Presented to regional representatives of NARSAD.

04-89 "Management of Risk of Relapse in Schizophrenia. "The Annual Spring Scientific Meeting of the Southern California Psychiatric Society, Hollywood, CA.

03-89 "Quantitative Approaches to Drug-Induced Movement Syndromes." Medical Staff of Camarillo State Medical Facility, Camarillo, CA.

01-89 "Social Skills Training in the Chronic Schizophrenic: A Workshop." 2nd Annual Winter Conference of the American Assn. of Community Psychiatrists, Charleston, SC.

11-88 "Instrumentation of Drug-Induced Movement Disorders." Presented to California state legislators, their aides, and advocates of national mental health groups (NAMI and NARSAD).

08-88 "Classical Cases in Schizophrenia", with JA Talbot, MD, Professor and Chair, Department of Psychiatry, University of Maryland. Program produced with an educational grant from Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT.

08-88 "Drug-Induced Extrapyramidal Syndromes in Psychiatric Patients." Texas State Hospital medical staff, Big Springs, TX.

06-88 "Role of Psychopharmacology in the Treatment of the Chronic Mental Patient." Department of Corrections at the California Medical Facility in Vacaville, CA.

04-88 "Psychosocial Rehabilitative Treatment of the Chronic Schizophrenic Patient." Presented to the staff of the Roseburg VA Medical Center, Roseburg, OR.

03-88 "Behavioral Rehabilitation of the Chronic Mental Patient." Workshop presented at the First Annual Winter Conference of the American Society of Community Psychiatrists, Colorado Springs, CO.

01-88 "Electromechanical Characteristics of Tardive Dyskinesia." The Biannual Winter Workshop on Schizophrenia, Badgastein, Austria.

10-87 "Medication/Consent." Symposium with Drs. R Liberman, J Vaccaro, and J Kane, presented at the 1987 Institute on Hospital and Community Psychiatry, Boston, MA.

09-87 "Medication Management and Patient Education." Annual Department of Mental Health Conference at Michigan State University, East Lansing, MI.

05-87 "Quantitative Assessment of Extrapyramidal Symptoms and Involuntary Movement," presented at a symposium on Acute and Chronic Extrapyramidal Symptoms and Tardive Dyskinesia, at the Annual Meeting of the APA, Chicago, IL.

10-86 "The Affective Disorders Spectrum," presented to the Graduate School of Psychology of the California Lutheran College in Thousand Oaks, CA.

04-86 "Unique Issues of Older Adults with Chronic Mental Health Problems, Focus on Schizophrenia." Mental Health and Aging Conference in Los Angeles, CA.

02-86 "The Geriatric Patient with Cardiac and Psychiatric Problems: Pharmacologic Concerns." VA Nursing Service for their Continuing Education Series in Los Angeles, CA.

10-85 "Psychopharmacologic Treatment of the Geriatric Population," presented to the Psychology interns at the VA as part of their Continuing Education Series in Los Angeles, CA.

Publications

Articles

98. Murphy D, Bailey K, Stone M, Wirshing WC. Addictive potential of quetiapine. *Am J Psychiatry*. 2008 Jul;165(7):918.
97. Tabibian JH, Wirshing DA, Pierre JM, Guzik LH, Kisicki MD, Danovich I, Mena SJ, Wirshing WC. Hepatitis B and C among veterans on a psychiatric ward. *Dig Dis Sci*. 2008 Jun;53(6):1693-8.
96. Pierre JM, Peloian JH, Wirshing DA, Wirshing WC, Marder SR. A randomized, double-blind, placebo-controlled trial of modafinil for negative symptoms in schizophrenia. *J Clin Psychiatry*. 2007 May;68(5):705-10.
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91. Pierre JM, Peloian J, Wirshing DA, Wirshing WC, Marder SM. A placebo controlled trial of modafinil for negative symptoms in schizophrenia. *Schizophrenia Bulletin* 2005; 31:501
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84. Pierre JM, Wirshing DA, Wirshing WC: "Iatrogenic malingering" in VA substance abuse treatment. *Psychiatric Services*, 2003, 54(2): 253-4

83. Wirshing DA, Wirshing WC: Aripiprazole: a viewpoint. *CNS Drugs*, 2002,16(11): 779-786

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- Pierre JM, Wirshing DA, Wirshing WC: Reply to: In response to Furst et al, "possible association of QTc interval prolongation with co-administration of quetiapine and lovastatin." *Biological Psychiatry* 2002; 52: 911-915.

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Updated—20 Mar 08

William C. Wirshing, M.D. Date

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-639/S-036
NDA 22-047/S-001

AstraZeneca Pharmaceuticals LP
Attention: Gerald Limp
Director, Regulatory Affairs
1800 Concord Pike, PO Box 8355
Wilmington, DE 19803-8355

Dear Mr. Limp:

We acknowledge receipt of your supplemental new drug applications dated June 22, 2007, and July 25, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel (quetiapine fumarate) tablets (NDA 20-639) and Seroquel XR (quetiapine fumarate) extended-release tablets (NDA 22-047).

We additionally refer to an Agency letter dated January 8, 2008, requesting information on glucose abnormalities.

These applications, submitted as "Changes Being Effected" supplements, provide for the following revisions to product labeling:

20-639/S-036 dated June 22, 2007

- Revisions throughout labeling to provide for new information on quetiapine and hyperglycemia.

22-047/S-001 dated July 25, 2007

- Revisions throughout labeling to provide for new information on quetiapine and hyperglycemia.
- Revisions to the **Adverse Reactions**-Postmarketing Experience section.
- Revisions to the **Drug Interactions**-P450 3A Inhibitors section.

We have completed our review of these supplemental applications, and they are approvable.

In general, the revisions made to the Postmarketing Experience and Drug Interactions sections are acceptable, and these comments were conveyed to you in an Agency letter dated May 13, 2008.

However, we are requesting the following changes to your proposed labeling (double underline font denotes additions and strike through font denotes deletions) before we can take a final action on these supplemental applications.

> *In 2 long-term placebo-controlled randomized withdrawal clinical trials, mean exposure of 213 days for SEROQUEL (646 patients) and 152 days for placebo (680 patients), the exposure-adjusted rate of any increased blood glucose level (≥ 126 mg/dl) ~~for patients more than 8 hours since a meal~~ was 18.0 per 100 patient years for SEROQUEL (10.7% of patients)*

and 9.5 for placebo per 100 patient years (4.6% of patients). The mean change in glucose from baseline was +5.0 mg/dl for SEROQUEL and -0.05 mg/dl for placebo. Because of limitations in the study design of these long-term trials as well as lack of confirmed fasting glucose data, the effects of SEROQUEL on blood glucose may be underestimated.

For the 2 long term placebo-controlled bipolar maintenance trials, we are deleting the statement "more than 8 hours since a meal" from the proposed labeling language. In general, it does indicate fasting, but you indicated that there was still the possibility of caloric intake in the form of liquids or snacks. Therefore, since these subjects may not have been in a fasting state, this phrase should be deleted to reduce confusion.

Since the 2 long-term placebo-controlled bipolar maintenance trials studies were randomized withdrawal trials, there is some bias in that only subjects who were able to tolerate quetiapine in the open-label phase are then randomized. If subjects did not tolerate quetiapine in the open label phase, if they dropped out due to elevations in blood glucose for example, they would not be randomized and the overall effect of the drug on this parameter would be skewed. Therefore, because of this design issue, the overall effect of Seroquel on blood glucose could be underestimated.

In short-term (12 weeks duration or less) placebo-controlled clinical trials (3342 treated with Seroquel and 1490 treated with placebo), the percent of patients who had a fasting blood glucose ≥126 mg/dl or a non fasting blood glucose ≥200 mg/dl was 3.5% for quetiapine and 2.1% for placebo. The mean increase in glucose from baseline was 2.70 mg/dl for SEROQUEL and 1.06 mg/dl for placebo.

For the 24 week active-controlled trial designed to evaluate glycemic status, you included only the LS mean data, and not the mean change from baseline to week 24 for the quetiapine group. Please provide us these data so that it can be incorporated into product labeling.

Based on the PLR regulations, your proposed addition of "Adverse Reactions, Vital Signs and Laboratory Studies, Hyperglycemia (6.2)" under RECENT MAJOR CHANGES in the Highlights should be deleted.

Additionally, we would refer you to our January 8, 2008 letter requesting information on the following glucose data. Please submit these information by the requested due date, June 30, 2008.

- Glucose mean and median change analyses of serum glucose levels by baseline values (baseline to endpoint and baseline to highest measurement for fasting and non-fasting data)
- Fasting serum glucose post-treatment cut-off values are 140 mg/dL, 200 mg/dL, and 300 mg/dL
- Non-fasting serum glucose post-treatment cut-off value level is 300 mg/dL
- Observed case analyses of mean glucose change for the following specified exposure durations - 2 weeks, 4 weeks, 8 weeks, 12 weeks, 24 weeks, and 48 weeks
- Analyses of the proportion of subjects with post-baseline hemoglobin A1c ≥ 6.1%, 8%, 10%, and 12% among patients with baseline hemoglobin A1c values below 6.1%

- Analyses of the proportion of subjects with treatment-emergent glycosuria (defined as any glucose in the urine) for each subject

If you have any questions, call Kimberly Updegraff, Regulatory Project Manager, at 301-796-2201.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
6/25/2008 04:03:23 PM

Unknown

From: Arvanitis Lisa LA
Sent: Wednesday, August 13, 1997 12:30 PM
To: Monyak John JT;Kowalcyk Barbara BB;Scott Mark MS
Cc: Griffett Christopher CR;RUHL Athena M. (MS Mail)
Subject: Weight gain

John, Barbara and Mark

I couldn't attend the Serebral meeting yesterday and haven't been able to catch up with anyone who had in order to hear what the discussion was opposite weight gain (I suspect no one had read the documents) but I did have a chance to look over John's document and have a couple of comments/thoughts. Perhaps we can chat afterward?

The purpose of this analysis is 2-fold:

1) Is there a competitive advantage for SEROQUEL re-weight gain which we can articulate in posters/talks/vis aids? We know we have weight gain but is it limited to the short-term treatment and flattens out over time? Clozapine continues to accumulate.
2) If not #1, then what do we tell the doctors when they ask about long term weight gain?

I recognize that there are a number of interactions/confounds in the analyses John did, but despite this I was really struck by how consistent the data was. Across pools (all trials, 15 alone, all trials - 15), across parameters/measures (mean change from baseline, %change from baseline, proportion with clinically significant weight gain), and across cohorts (various durations of treatment) the results seem to be consistent and show:

Weight gain is more rapid initially

While weight gain slows over the longer term (I only considered to 52 week) there still is weight gain. It doesn't stop...the slope just appears to change.

The magnitude of weight gain at 52 weeks (regardless of pool or cohort) is about 5 kg which is more than the short-term 6 week weight gain.

The proportion of patients with clinically significant weight gain at 52 weeks (regardless of pool or cohort) is about 45% and this is more than the % at 6 weeks.

This was quite surprising to me (not the weight gain but the consistency).

Therefore I'm not sure there is yet any type of competitive opportunity no matter how weak. Quantitative comparisons between compounds (clozapine, olanzapine) not from the same trials are seriously flawed. (Not that I would be giving up on an abstract but it requires more though before making a decision that this something we bally-hoo!) I have yet to re-check out the weight gain over time in the haloperidol group in 15 but comparisons here would be pretty shady!

The other issue of what we tell the sales force is more problematic because of the confounds. I feel the urge to delve more deeply into this but I realize resources are constrained, there are substantial limitations to the database and I'm not sure that the answers will be much different.

Thoughts are:

It appears on the scatterplot with slope marked that patients with lower body weights had a greater weight gain. (Note that Lilly has made this type of an argument stating that patients starting treatment at less than ideal body weight for frame size [they collect height information which we didn't] gained more weight. We can't draw these conclusions so convincingly.). Could the effect of sex be related to baseline weights of men and women? If I recall from CTRs, our women were generally heavier.

Patterson
Exhibit No. 8
6.11.08 C. PERKS

22

[illegible] age be confounded by sex or even baseline weight?

We know that weight gain is dose related. Does the fact that during the first 6 weeks of treatment in many trials many patients were on low doses and when they got into OLE they may have shifted the dose upward (OLE was flexibly dosed) and therefore delayed the appearance of weight gain appearing as an effect of time on drug? Would analysis of Study 14, the only trial with flexibly dosed acute treatment which offered long term OLE be of help here?

The effect of trial isn't surprising. Is it worth repooling like with like? For example, perhaps looking just at Studies 12, 13 and 14 which are 6 week acute studies which offered OLE or adding Studies 6 and 8 as well since the populations were similar (Studies 5, 4, 15, 48 and the clin pharm studies with OLE could be argued as having different populations).

I have to keep asking myself, are we going to go through the motions, using precious resources and not really come up with anything more solid for the sales reps?

Comments? Thoughts? Shold we get together to chat?

Thanks
Lisa

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE: Seroquel Products Liability Litigation

MDL DOCKET NO. 1769

This document relates to:

Linda Guinn	6:07-cv-10291
Janice Burns	6:07-cv-15959
Richard Unger	6:07-cv-1581 2
Connie Curley	6:07-cv-15701
Linda Whittington	6:07-cv-10475
Eileen McAlexander	6:07-cv-10360
Sandra Carter	6:07-cv-13234
Clemmie Middleton	6:07-cv-10949
Hope Lorditch	6:07-cv-12657
David Haller	6:07-cv-15733
Charles Ray	6:07-cv-11102
William Sarmiento	6:07-cv-10425

DECLARATION OF DONNA K. ARNETT, PH.D., M.S.P.H.

My name is Donna K. Arnett. I am over twenty-one years of age, am of sound mind, have never been convicted of a felony, and am otherwise competent to make this Declaration. I have personal knowledge of all factual statements contained herein and all such factual statements are true and correct as outlined herein in this declaration-report.

A. Qualifications and Expertise

I am a cardiovascular epidemiologist with over twenty years of experience in the design, conduct, and analysis of epidemiologic studies. Since 1994, I have worked in leading academic research institutions for cardiovascular epidemiology and I have taught postgraduate (masters and doctoral levels) courses in theory, design, and analysis of epidemiologic studies.

I received a B.S.N. degree in 1981 in nursing (magna cum laude) and an M.S.P.H. degree in 1987 in epidemiology and biostatistics from the University of South Florida. In 1992, I received a Ph.D. in epidemiology from the University of North Carolina and was elected into Delta Omega, the honor society for public health. Prior to my graduate training, I worked as a critical care nurse for 5 years and was CCRN certified (i.e., critical care registered nurse) and as a research coordinator for pharmaceutical clinical trials at the University of South Florida for three years. My doctoral research was focused in the area of cardiovascular epidemiology. In 1992, I was awarded my first peer-reviewed

grant, a post-doctoral fellowship, and worked two years completing the fellowship at the University of North Carolina at Chapel Hill. From October, 1994 through August, 2004, I rose from a tenure-earning assistant professor to a full professor with tenure as well as holding an endowed chair in epidemiology at the University of Minnesota. During that time, I directed large, complex, multi-center epidemiologic studies funded from the National Institutes of Health, as well as a National Institute of Health T32 Training Grant and cardiovascular genetic epidemiology. At the time I left the University of Minnesota, I was ranked in the top 5% of all National Institute of Health researchers. Since 2004, I have served as chairman and a tenured professor of epidemiology at the University of Alabama at Birmingham, where I have maintained a strong research program. I currently am Principal Investigator for five National Institute of Health projects.

As further evidence of my qualifications and expertise in the field of epidemiology, I am an elected fellow of the American Epidemiologic Society, and serve as editor for the highest ranked journal in epidemiology, namely the *American Journal of Epidemiology*. In addition to serving on numerous research peer-review committees for multiple organizations, including but not limited to, the Veterans Affairs, the American Heart Association and the National Institutes of Health, I was named to the prestigious post of chair for the NIH Cardiovascular and Sleep Epidemiology study section for 2006-2008.

B. Responses to Particular Astra-Zeneca Statements

I have reviewed the brief of AstraZeneca that criticizes the veracity of the epidemiologic methodology employed as well as the timing and content of my opinions, and I herein offer a response to these criticisms.

1. AZ Counsel claim that I fail to extensively review the literature and use of flawed methodology

The AstraZeneca (AZ) Counsel state "Dr. Arnett... formed an opinion and submitted her report before she had time to extensively review all of the published literature", "spent at least three days reviewing literature after filing her report in an attempt to bolster her previously submitted litigation opinion", and "her methodology is scientifically flawed".

These assertions by AZ Counsel are incongruent with my expert report, testimony, and experience as an educator of epidemiologic methods and a researcher who employs sound epidemiological principles in her studies. As stated in my expert report[1] and my deposition,[2] my general causation opinions were formed mostly from the placebo-controlled randomized studies conducted as part of the New Drug Application (NDA) for Seroquel, submitted to the Food and Drug Administration in July, 1996. In fact, at least half of my Expert Report was devoted to data derived from the NDA. This approach is in congruence with sound epidemiologic methodology. As stated in my Expert Report:[3]

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[1] Expert Report, page 3
[2] Deposition, page 160, lines 1-4, page 255 line 9-14
[3] Expert Report, page 6

> "Randomized, double-masked, placebo-controlled clinical trials are the optimal design for testing a hypothesized association between an exposure (or treatment) and disease because such studies offer the best control for confounding (i.e., variables that are associated with the disease and associated with the exposure) and provide for the optimal test for temporality (i.e., exposure precedes disease). Placebo controlled studies are the gold standard for evaluating the risks and benefits of a new treatment."

The assertion that the experimental studies, such as the placebo-controlled randomized studies, are the most optimal design to test causal hypothesis is widely held among epidemiologists. Because of randomization of subjects and controlled administration of the agent under study, experiments are considered more useful than observational studies to demonstrate cause-effect relationships.[4] The U.S. Preventive Services Task Force[5] has established a ranking for the evidence about effectiveness of treatment, and has deemed evidence from the randomized controlled trial as the best level of evidence, Level 1. According to sound epidemiological principles, I relied most heavily on Level 1 evidence.

The publications from the earliest AZ clinical trials that I reviewed did not contain adequate information to evaluate the metabolic risks associated with Seroquel.[6] Therefore, I specifically requested the NDA files submitted by AZ with respect to the safety and so that I could fully evaluate the range of metabolic risk factors measured and the placebo-controlled clinical trials, and the impact of Seroquel on these risk factors. In fact, it was not until I evaluated the NDA that I discovered that a wide range of metabolic risk factor data, such as dyslipidemia and glucose were collected in the randomized controlled trials included in the NDA; these data were not readily available in the published literature. The aggregate of these Level 1 evidence data indicate a metabolic toxicity from Seroquel.

Following the review of the NDA, I also evaluated randomized controlled trial study summaries posted on the AZ website. These reports summarized in my expert report[7] demonstrated consistent weight gain findings in comparison to those reported in the NDA Integrated Safety Report. Given the consistent, clinically relevant (as defined by Astra Zeneca as a greater than 7% change in body weight in response to Seroquel treatment), I did not pursue lower levels of scientific evidence from observational epidemiologic studies with respect to weight or other metabolic toxicities, with the exception of type II diabetes. This approach is consistent with sound epidemiological principles.

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[4] Woodward, M. Epidemiology. Study Design and Data Analysis. 2nd Ed 2004. Chapman and Hall/CRC Texts in Statistical Science Series. 2004. Page 337)

[5] www.ahrq.gov/clinic/uspstmeth.htm

[6] Small JG et al, Quetiapine in Patients with Schizophrenia. Arch Gen Psych 1997;54:549-557 and Borison RL et al. ICI 204,636, An Atypical Antipsychotic: Efficacy and Safety in a Multicenter, Placebo-Controlled Trial in Patients with Schizophrenia. J Clin Psychopharmacol 1996; 16:158-169

[7] Expert Report, Page 8

2. AZ Counsel imply that I intentionally did not review the AZ Response to the FDA in June, 2008.

This document was not provided to me prior to my expert report and deposition. It was apparently provided to plaintiffs' counsel around Labor Day and was contained amidst a submission of apparently 15,000 pages and thus it was not promptly recognized as key information that needed to be promptly provided to me. Nonetheless, I have reviewed data regarding the characteristics of the participants that were included in the clinical trials provided in response to the FDA's request. Among the 6,870 adults taking Seroquel in the randomized placebo-controlled trials, 25% were exposed to the drug for 21 days or less, and some were exposed for only 1 day.[8] Most of the drop-outs occurred within the first two weeks of the study as evidenced in Table 16[9] where only 3,779 of the adult subjects in the placebo-controlled clinical trials had a weight measured. Despite the fact that there were so many drop-outs early in the follow-up for this combined analysis, there are statistically significant findings with respect to those who transition from normal to high glucose levels. I have calculated the relative risks and 95% confidence intervals for subjects in placebo controlled trials included in the AZ letter to the FDA. In Table 339, the relative risk of a glucose value $\geq$ 126 mg/dl among those with a glucose value < 100 mg/dl at baseline in Seroquel versus placebo users was 1.73, 95% CI 1.05 - 2.85, p=.03 and the results were stronger for the comparable calculation in the treatment naïve individuals (relative risk = 2.15, 95% CI 1.02 - 4.56, p=0.046, Table 450). Additionally, for Hba1C (Table 341) the relative risk was 1.50 (p=0.016), 95% CI 1.08-2.09, for a shift from a normal Hba1C (<6.1%) to elevated ($\geq$6.1%). These data further support the diabetic potential of Seroquel treatment using the most robust of studies, the placebo-controlled clinical trial.

3. AZ Counsel suggest that Study 125 did not cause a statistically significant change in glucose metabolism as measured by the oral glucose tolerance test and opine that I make no attempt to "explain away these results."

Study 125 was not a placebo-controlled randomized clinical trial, but rather, was an open-label study designed to contrast the effects of Seroquel on a glucose metabolism in comparison to two of their active comparators. Open-label studies fall into the Level II-1 evidence according to the U.S. Preventive Services Task Force[10], a level of evidence that falls below that of the double-blind randomized clinical trial, and one of the reasons I did not include it in my Expert Report. In addition to these limitations, as with other Seroquel randomized, controlled trials, there was a larger drop-out among Seroquel users, 59/168 compared to only 23/169 for olanzapine users and 40/173 for risperidone users, raising the possibility that people who had metabolic side effects could have dropped out more often among the Seroquel users. Nonetheless, even though the primary outcome measure (i.e., the change at 24 weeks of the "area under curve" in a 2 hour oral glucose tolerance test) was not significant, the secondary results indicate statistically significant increases in both mean fasting blood glucose (3.19 mg/dl) and HbA1c (0.122%), showing

[8] Table 2, page 43 and 44, AZ letter to FDA, 6/13/08
[9] AZ letter to FDA, 6/13/08, page 66
[10] See www.ahrq.gov/clinic/uspstmeth.htm

that Seroquel impacted regulation of glucose in a fasting state. Fasting C-peptide (a measure of endogenous insulin production and an indicator of insulin resistance) increased. Further, patients taking Seroquel experienced a mean weight gain of 3.65 kg (8 pounds) in 24 weeks. The observation of the increased insulin production could explain the lack of significance of the primary outcome for this study since it is possible that glucose could be cleared more quickly due to the higher level of insulin from Seroquel. In aggregate, these findings lend Level II-1 evidence in support of the effects of Seroquel on metabolic toxicities, including weight gain and insulin resistance.

4. AZ Counsel states "Dr. Arnett concedes that she is not an expert on the mechanism by which antipsychotics allegedly cause diabetes or weight gain."

This is a misrepresentation of both my Expert Report and my deposition testimony. Pages 3 and 4 of my expert report describe three different biological mechanisms that support the weight gain and diabetic consequences of Seroquel treatment. As stated in my deposition,[11] because of my work in pharmacogenetics I have to understand how drugs work in the body. Additionally,[12] I stated that I had evaluated the literature and had an understanding of how Seroquel worked specifically in relation to weight gain and diabetes.

5. AZ Counsel states "the weight gain mechanism is nothing but pure speculation" and Dr. Arnett indicates there is no correlation between Seroquel weight gain and diabetes.

The relation between weight and weight gain and diabetes is an established risk factor for diabetes. As stated in my Expert Report (page 4), weight gain is also associated with features of the multiple metabolic syndrome, and the metabolic syndrome is an important risk factor for diabetes incidence. Beyond weight gain, Seroquel causes metabolic derangements, such as increased waist size[13] and hypertriglyceridemia.[14] Data from the Atherosclerosis Risk in Communities Study, increasing the number of metabolic risk factors that make up the metabolic syndrome dramatically increases the risk for diabetes in the cohort.[15] Collectively these data point to the importance of Seroquel-induced weight gain and its impact on diabetes risk. Finally, with respect to the correlational analysis between Seroquel weight gain and diabetes I indicated in my deposition that Astra Zeneca has not evaluated the data in that way[16], and therefore, I cannot scientifically offer an opinion regarding that correlation.

6. AZ Counsel states "Dr. Arnett purports to give a dose response opinion, but it amounts to nothing more than a theory based on unsupported extrapolation from

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[11] Deposition, page 53, line 19-20
[12] Deposition, page 55, lines 2-4
[13] Meyer JM et al. Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: prospective data from phase 1. Schizophr Res. 2008;101(1-3):273-86
[14] Expert Report, Page 10
[15] Ballantyne CM et al. Metabolic syndrome risk for cardiovascular disease and diabetes in the ARIC study. *International Journal of Obesity* (2008) **32**, S21–S24.
[16] Deposition, page 209, line 9-10

higher doses" and "Dr. Arnett does not even attempt to evaluate the existence of a dose threshold."

This is a misrepresentation of both my expert report and my deposition testimony. As just one example of several offered in my report, for study 13 alone, low dose Seroquel (75 or 150 mg) versus placebo was associated with a 3.54 greater relative risk of clinically significant weight gain and higher doses (300 or 600 mg) was associated with a 4.77 greater relative risk of weight gain.[17] Additionally, in my deposition[18] I stated the following:

> A. There's a dose response relationship with all of the metabolic parameters that are a part of the diabetic -- Type II diabetes. There's some indication from the observational studies that there is a dose response between diabetes incidence and dose of Seroquel.
> Q. Are you testifying to a reasonable degree of scientific certainty that there's a dose response relationship between Seroquel and diabetes?
> A. Yes.

7. AZ Counsel opines that I filed my reports in this case before my work was completed and I did not properly review or analyze the key clinical trial data, and that I rely instead on confounded observational epidemiology.

This is a ridiculously flawed interpretation of my expert report and a gross misrepresentation of the method by which my opinions in this case were generated. As stated previously under Section 1, my opinion relied heavily on Level 1 evidence, the double-blind, randomized clinical trials. In fact, rather than relying exclusively on observational epidemiology, I painstakingly went through the NDA provided to the Food and Drug Administration to comprehensively evaluate the metabolic impact of Seroquel since all data were not provided in the published literature. As a responsible scientist, I did this even though the data were provided by AZ in a format which did not include an index of the files included, making the task much more difficult than it needed to be. In light of the consistent and significant findings from the Level 1 evidence, I used the observational epidemiologic studies (Level II-B evidence) which support the findings from the randomized controlled clinical trials.

8. AZ Counsel asserts that I reached my conclusions before my review of the relevant scientific evidence, and that I simply "ran out of time."

The assertion that I "ran out of time" is patently absurd and was taken completely out of context from my deposition. In fact, it referred to the section where I described the methods used to evaluate the weight data from the AZ website. In fact, what I referred to in this section[19] was related to the findings regarding

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[17] Expert Report page 5
[18] Deposition, page 210-211, lines 16-25, and 1, respectively
[19] Deposition, page 177-178

weight. What I had observed in the randomized clinical trials from the AZ website is consistent with what I had found in the NDA, namely, that Seroquel was associated with significant increases in weight:

> Q. Your weight chart here, Table 1, you created this based on the clinical trial summaries, right, that were on the Web site?
> A. Yes.
> Q. Am I right that there were many more than just 11 clinical trial synopses on the AstraZeneca Web site?
> A. Yeah. I took them in sequential order from top to Number 11 until I ran out of time.

As indicated previously in Section 1, I principally relied on level 1 evidence from the randomized controlled studies, and supplemented that with evidence level IIb studies regarding Seroquel and diabetes. This does not in any way indicate that I formed my opinions before I completed review of the literature. In fact, it asserts that I used appropriate epidemiologic rigor into writing my opinions.

9. AZ Counsel expressed concern that I did not review the actual study reports.

Because of the method in which the data were provided to me through AZ it was nearly impossible to identify the individual clinical study reports. This is not a concern with respect to the formation of my opinions. The integrated safety report provided by Astra Zeneca to the Food and Drug Administration summarized all Phase I, II and III study safety measurements that were included in the New Drug Application. Therefore, unless Astra Zeneca withheld information from the clinical reports for this Integrated Safety Report, all safety information collected in phase I, II and II studies were reviewed and evaluated in the formation of my opinions.

10. AZ Counsel expressed concern that I did not review the Study 125, the AZ FDA 2008 letter (both discussed previously), and the additional results from the CATIE trial.

Issues related to Study 125, and the FDA 2008 letter, have been previously discussed, as has the important follow-up study from CATIE regarding the metabolic syndrome. I have reviewed the CATIE study publication, and formed my own opinions regarding its scientific merit[20] and its impact on metabolic risk.

11. AZ counsel asserts that statistical significance is the "accepted principle of epidemiology" and that "a non-statistically significant result lies at the heart of Dr. Arnett's opinion."

[20] Expert report, page 12

In my report, I presented numerous statistically significant findings with respect to weight gain, triglyceride increase, measures of insulin sensitivity, waist circumference, and thyroid abnormalities in relation to Seroquel treatment. Additionally, I presented epidemiologic studies that indicated Seroquel was associated with statistically significant increased risk of diabetes. Nonetheless, the assertion that statistical significance is an exclusive requisite for evaluation of causation is a frank misrepresentation of accepted epidemiologic methods. In the recent text, Modern Epidemiology, Third Edition, by Kenneth Rothman at al, page 159 states:[21]

> "Confidence limits and P value functions convey information about size and precision of the estimate simultaneously, keeping these two features of measurement in the foreground, the use of a single P value -- or worse dichotomization at the P value into significant or non-significant -- obscures these features so that the focus of measurement is lost. A study cannot be reassuring about the safety of an exposure or treatment if only a statistical test of the null hypothesis is reported. As we have seen, results that are not significant may be compatible with the substantial effects. Lack of significant alone provides no significance against such effects."

The authors further state that the confidence limits around a point estimate must be interpreted with respect to the point estimate, namely that points nearer to the center of the range are more compatible to the data of them than points farther away from the center. In this particular example from the deposition[22], this would mean that the true effect of Seroquel on diabetes would be nearer to the point estimate of 2.02 rather than from the extremes of the 95% confidence limits. This value is comparable to a range of point estimate derived from the observational epidemiologic studies (e.g., range of 1.15 – 3.02) reported in my expert report.[23]

12. AZ Counsel is concerned that I did not calculate post-hoc power calculations.

In light of the totality of statistically significant data discussed in my export report and deposition concerning the effects of Seroquel on diabetes risk, I did not find it necessary to calculate statistical power in the setting of the consistent and statistically significant findings previously cited. In my twenty years of work in epidemiology, and having served as Chair of the NIH Study Section on Cardiovascular and Sleep Epidemiology Study Section where I routinely evaluate statistical power, I assert that I have a solid understanding of the factors that contribute to statistical power. In the case of the specific calculation requested by AZ Counsel, the idea that the study was inadequately powered (i.e., the error or claiming the null hypothesis is true when indeed it is not) was due to the number

[21] Rothman, Greenland and Lash. Modern Epidemiology, Third Edition, Lippincott Williams and Wilkins 2008, pages 157-159.
[22] Deposition 286:15-287:2
[23] Expert Report, page 11.

of events required for adequate power. Therefore, I did not invest time in calculating the power as it was most assuredly low.

13. AZ Counsel accuses me of "cherry picking" the data.

As stated in my deposition, the method I used to derive the list of observational epidemiologic studies was a PubMed search for studies that contained the words "Seroquel" and "diabetes" in the title or abstract. All published cohort or case-control published manuscripts detected from this search, with the exception of one article from a low-impact journal, were included in my report.

I hold additional relevant opinions as set forth in my expert report in this matter, which is attached and incorporated by reference. Additional opinions were elaborated in my deposition. The documents I reference in this Declaration-Report are annexed as exhibits to the Declaration of Paul Pennock, Esq.

I declare under penalty of perjury that the foregoing is true and correct. Executed this 24th day of November 2008.

Donna K. Arnett

Donna K. Arnett, Ph.D., M.S.P.H.

Expert Report of Donna K. Arnett, Ph.D.

A. Brief Report of Professional Qualifications

I am an epidemiologist with more than 20 years of experience in the design and conduct of experimental and observational epidemiological studies, including clinical trials, family studies, cross-sectional surveys, cohort, and case-control studies. I am Professor and Chair of Epidemiology at the University of Alabama at Birmingham, Department of Epidemiology. I am a Fellow of the American Heart Association and the American College of Epidemiology, and an Elected Member of the American Epidemiology Society. I have served as an Associate Editor for the *American Journal of Epidemiology* since 1996 and as an Editor since 2004. I currently serve as a Guest Editor and as relief Guest Editor-in-Chief for *Circulation*. I am routinely asked to evaluate epidemiological research studies for publication in peer-reviewed journals, including the *New England Journal of Medicine* and the *Journal of the American Medical Association*. I have served on numerous National Institutes of Health (NIH) review panels for epidemiological research. For the past two years, I have served as Chair for the Cardiovascular and Sleep Epidemiology Study Section (CASE) for the National Institutes of Health.

My principle professional interests include cardiovascular and metabolic disease epidemiology, genetic epidemiology, and pharmacogenetics. I have published more than 225 peer-reviewed articles and more than 12 book chapters or invited review papers.

Since 1994, I have designed and taught graduate level courses in fundamental and advanced concepts of epidemiology, methodological and theoretical aspects of epidemiology, and grant writing. From 1998-2001, I served as Chair of the Epidemiology Master's Degree Program at the University of Minnesota and as Director for the National Heart, Lung, and Blood Institute funded Training Program in Cardiovascular Genetic Epidemiology. For the past 10 years, I have taught a two-week summer course in Epidemiology and Prevention to physicians and other health care professionals for the American Heart Association and Centers for Disease Control.

A copy of my curriculum vitae is attached for additional detail.

B. Brief Overview of Principles of Epidemiology

Randomized, double-masked, placebo-controlled clinical trials are the optimal design for testing a hypothesized association between an exposure (or treatment) and disease because such studies offer the best control for confounding (i.e., variables that are associated with the disease and associated with the exposure) and provide for the optimal test for temporality (i.e., exposure precedes disease). Placebo controlled studies are the gold standard for evaluating the risks and benefits of a new treatment. During a clinical trial, four general reasons could explain clinical improvement in a

participant's condition: (1) natural history of the disease; (2) specific effects of the treatment under investigation; (3) regression to the mean; and (4) placebo effect. A study without a placebo control cannot differentiate amongst the prior 3 conditions. Active comparator randomized clinical trials are frequently used once a known treatment is available since withholding treatment from a diseased group could be unethical; however, there are methodological limitations of trials that use an active control. For example, there can be variable responses to drugs in some populations, unpredictable and small effects, and spontaneous improvements which with an active (rather than a placebo) control may mask the full effect of the drug under investigation.

Many epidemiological studies are observational and provide an assessment of a relation between an exposure and disease. Because of the observational nature of these studies, exposures are not "randomly-assigned" to study volunteers, and hence, factors that may be associated with the exposure of interest, and also independent predictors of the disease, may confound the observed relation between the exposure and disease. The best observational design to test a hypothesized association between exposure and disease is a cohort study. Cohort studies can be conducted either prospectively or retrospectively. Cohort studies are similar conceptually to clinical trials in that subjects are followed for the occurrence of endpoints. Therefore, temporality between the exposure and the endpoint can be conclusively evaluated. The availability of large administrative databases has prompted a number of cohort studies to evaluate adverse exposures, including pharmacological exposures, in relation to disease. The benefits of these types of cohort studies include their cost efficiency and ease of implementation. For example, pharmacy records can be linked to clinical records to assess a hypothesized association between a particular drug exposure and disease.

Case-control studies are also hypothesis-testing studies, and they rely on design qualities that, if done correctly, provide for an estimation of the exposure-disease relationship in a cost-efficient way. In a case-control study, diseased individuals are sampled (i.e., cases) as are non-diseased individuals (i.e., controls), and subjects are classified with respect to exposure. The effect measure used is the ratio of the exposure odds in cases compared to the exposure odds in controls. Conceptually, the case-control study can be thought of as nested within a population cohort, and if two important criteria are met, provide a valid estimate of the disease odds ratio. For excellent internal validity, a case-control study requires that exposure must measured in all cases (or a representative sample of cases that reflects the true exposure odds of all cases), and that the sample of the non-diseased members of the source population that generated the cases reflect the exposure odds of the population. If these conditions are met, then the exposure odds ratio will be equal to the disease odds ratio that can be calculated from a cohort study. In practice, these conditions are challenging to meet except in the case of the nested case-control studies, where the exposure odds can be accurately measured using previously collected data and/or specimens. Nested case-control studies overcome two other potential biases common to the case-control studies, namely, temporality and recall bias. Temporality is a concern in non-nested case-control studies because exposure ascertainment is

determined after disease onset. Another potential bias unique to non-nested case-control studies is recall bias, where cases are more likely than controls to recall prior exposures because of their disease.

C. Review of the Evidence for Effects of Seroquel on Metabolic Risk, including Weight Gain, Hypertriglyceridemia, Insulin Resistance, and Diabetes

The basis for my opinions expressed herein is derived from my education, training, research, experience, and review of the Seroquel New Drug Application (NDA) to the Food and Drug Administration, internal Astra Zeneca documents, the peer-reviewed medical literature, and other publicly available documents concerning Seroquel and its relationship to weight gain and other metabolic risks. In developing my opinions in this case, I am relying primarily upon the Astra Zeneca NDA application and the related published literature, published cohort and nested case-control studies, and meta-analyses of published studies. I have spent over 80 hours reviewing literature and documents related to Seroquel.

Based upon my review of the above specified documents, I have developed the following opinions in this case: (1) Seroquel leads to clinically significant and relevant metabolic risk, including weight gain and other metabolic complications, including but not limited to hypertriglyceridemia, insulin resistance, and diabetes; (2) the metabolic risks from Seroquel appear shortly after treatment and throughout treatment; (3) Astra Zeneca should have made the data presentation clearer within the New Drug Approval application and included the data regarding metabolic risk within scientific publications of the Phase II and Phase III randomized clinical trials in order to warn the FDA, future patients and physicians about metabolic risks associated with Seroquel; (4) the metabolic risks associated with Seroquel outweigh the benefits of treatment; and (5) Astra Zeneca promoted Seroquel as metabolically neutral when there was insufficient evidence to support this claim but substantial evidence that the drug in fact caused weight gain and other metabolic derangements (6) Astra Zeneca withheld support for studies that could have demonstrated Seroquel's metabolic risk relative to other atypical antipsychotics. I have developed these opinions utilizing the normal methodology that I exercise as an epidemiologist in the ordinary scope of my practice. Further, I state these opinions to a reasonable degree of scientific certainty.

C.1. Overview: The Effect of Seroquel on Weight Gain and Other Metabolic Derangements

Seroquel causes weight gain and other metabolic toxicities through stimulation of the hypothalamic AMP activated protein kinase (AMPK). AMPK is responsible for maintaining energy balance and the regulation of food intake. Seroquel blocks histamine H1 receptors, the receptors responsible for the inflammatory response which then stimulates AMPK. In addition to the effects on H1 receptors, Seroquel affects insulin action and metabolism directly in the cell, leading to insulin resistance

and alterations in lipogenesis and lipolysis, which ultimately cause progressive lipid accumulation.

Weight gain can lead to reductions in patient compliance with the medication which could lead to poor clinical outcomes. Weight gain is an important concern of Seroquel treatment, and in particular among schizophrenic individuals since there is an association between schizophrenia and Type II diabetes mellitus, and weight gain is an important risk factor for diabetes development. Weight gain is also an important determinant of other metabolic toxicities, such as hypertriglyceridemia, hypertension, and insulin resistance, all part of the metabolic syndrome. Moreover, once weight has been gained, it is challenging to lose, and this is a large concern for schizophrenic patients who are not typically capable of undertaking lifestyle management to maintain or to lose weight.

There is unequivocal and consistent evidence that Seroquel treatment leads to clinically and statistically significant increases in weight, that the onset of the weight gain occurs shortly after the beginning of treatment and progresses with increased duration of treatment, and that the weight gain is proportionate to the dose ingested. Significant weight gain was observed during the Phase II and III trials and subsequently demonstrated throughout the developmental program of Seroquel for other treatment indications. In addition, other components of the metabolic syndrome (i.e., hyperinsulinemia, hypertriglyceridemia) were similarly observed during the development of Seroquel, and increased incidence of diabetes has been observed with Seroquel treatment. The justification for this opinion follows.

C.1.1. Weight Gain in Response to Seroquel Treatment

The New Drug Application for Seroquel was submitted to the FDA in July, 1996. According to the Integrated Safety Report filed as a part of the NDA, weight and vital signs were collected on the same case report form and were summarized together in the safety report to the FDA. In fact, according to the majority of protocols reviewed, weight for the Phase II and III trials was collected at each visit. Results presented in the Integrated Safety Report are restricted to the analysis which required that subjects who were included in the tabulations had both baseline and post-baseline observations available. Clinically significant weight gain was defined by a gain of 7% of the baseline body weight (approximately 10 pounds for a 150 pound individual).

In the Phase II and III trials, the mean age of the trial participants was 38 years, and the mean body weight was normal (76 kg or 168 lbs). A total of 2162 schizophrenic patients were exposed to Seroquel with doses ranging from 50 to 800 mg/day administered between two and four times daily. Of the 2162 subjects, 1710 were from Phase II and III controlled trials and 454 were from new Seroquel exposures from the uncontrolled trials and were available for analysis. As of June 1, 1995, 407 subjects had been exposed to Seroquel for 6 months or longer and only 1 subject for 2 years or longer; 110 subjects were treated for one year or longer. As stated on page

119 of the report, "In the Phase II and III placebo-controlled trials, Seroquel was associated with a statistically significant weight gain (p=0.0471)." Additionally, from the short term placebo-controlled trials, Astra Zeneca stated that the mean weight gain for Seroquel-treated patients was 2.2 kg (4.85 pounds) greater than the mean weight increase for placebo-treated patients. The range of weight gain was markedly higher for the Seroquel treated than the placebo treated patients, indicating that the distribution of weight gain was non-normal. Therefore, median weight change would have been the optimal measure of central tendency, but median weight change was not provided (in contrast to other vital sign measures that were provided as medians). Had the median, rather than the mean, been reported, the findings regarding the differences between Seroquel and placebo would have been even more dramatic. More detail regarding individual studies is provided below.

The following table describes the studies included in the NDA, and the status of vital signs collected in each. Placebo controlled trials are indicated by **bold** type. Uncontrolled trials are indicated by *italics*. Active comparator trials are indicated by underlined text. Trial 0012 was a low dose Seroquel study and limited data were provided in the Integrated Safety report for this study, although the data provided were indicative of weight increases with treatment.

Vital signs and weight assessments by trial (integrated Phase II-III trials)

	0004	*0005*	**0006**	0007	**0008**	0012	**0013**	0014	0015	*0048*	*LTE*
Pulse	X	X	X	X	X	X	X	X	X	X	X
Blood Pressure*		X	X	X	X	X	X	X	X	X	X
Respiratory	X	X	X		X						
Temperature		X	X	X	X	X		X		X	US
Weight	X	X	X	X	X	X	X	X	X	X	X

* All measures were taken while subjects were seated.
* Unless otherwise noted, readings were taken for both supine and standing systolic and diastolic blood pressures.
† Only supine readings were taken for Trial 0007.
** Respiration readings were taken while subjects were in the supine position unless otherwise noted.

Data for studies 0004, 0006, 0008, and 0013 were only provided in summary form. In these trials combined, 89/391 (23%) of Seroquel treated subjects had clinically significant weight gain compared to 11/178 (6%) of placebo-treated subjects. This resulted in a relative risk for clinically significant weight gain with treatment of **3.68** (p<.0001, 95% CI 2.1-6.7).

For Study 13 alone, clinically significant weight gain was observed in 2/51 (6%) for placebo, 2/52 (4%) for haldoperidol, 6/53 (11%), 8/48 (17%), 5/52 (10%), 8/51 (16%), 7/54 (13%) for Seroquel 75 mg, 150 mg, 300 mg, 600 mg, and 750 mg, respectively. In comparing low dose Seroquel (75 or 150 mg) versus placebo, the relative risk of weight gain was **3.54** (p=.06, 95% CI .95-16.1), and contrasting high dose (the dose recommended for schizophrenia), the relative risk of weight gain versus placebo was **4.77** (p=.012, 95% CI 1.34-18.2). This provides strong evidence

for dose response, a criterion frequently invoked to determine causation, and also indicates that Seroquel results in increased risk of clinically significant weight gain.

For Study 0013 and 0014 combined, clinically significant weight gain occurred in 70/354 (19.8%) in the Seroquel treated subjects versus 18/236 (7.6%) in the haldoperidol treated subjects (relative risk **2.61**; 95% confidence interval 1.61 - 2.42, p<.0001).

For Study 0007, clinically significant weight gain occurred in 28/100 Seroquel treated subjects compared to 19/99 of the chlorpromazine treated subjects (**RR=1.47**, p=-0.14, 95% CI 0.88-2.44). This active comparator study indicated that Seroquel's weight gain was greater than that of another atypical antipsychotic. This active comparator was not used again in subsequent trials presented in the NDA.

In summary, for these short-term placebo trials, the relative risk for a clinically significant increase in weight ranged from 2.61 to 4.77, indicating a strong and consistent increased risk, and for the active comparisons, a modest to strong increased risk for weight gain compared to chlorpromazine and haldoperidol.

Study 0015 was the long-term, 52-week study, implemented to evaluate the long-term efficacy and safety of Seroquel compared to haldoperidol for treatment of schizophrenia. In this study, Seroquel was associated with a statistically significant increase in weight gain that was dose-dependent and time-dependent (i.e., the longer the treatment, the greater the weight gain). The difference in the mean weight gain was 3.0 kg between treatment groups (+1.6 kg for Seroquel versus -1.4 kg for haldoperidol). Clinically significant weight gain occurred in 50/209 (23.9%) of the Seroquel participants compared to 4/38 (10.5%) of the haldoperidol-treated subjects (relative risk=2.27, p=0.066, 95% CI=0.94-7.55). As stated in the Integrated Safety Report "In general, mean weight increases from baseline for quetiapine-treated subjects were greater at Week 52 for subjects completing the trial (ranging from 2.05 to 8.52 kg) compared with the increases seen at final evaluation (Week 52 or withdrawal), suggesting a trend for subjects to continue gaining weight over time." Also stated in the Integrated Safety Report "The percentage of subjects with clinically significant increases from baseline in weight increased as the dose level of quetiapine increased (for the 75-, 300-, and 600-mg dose groups, 15.2%, 22.9%, and 32.9% of subjects had significantly high changes)." This dose-response was statistically significant. The findings from this long-term study confirm findings of the short-term studies and also suggest that weight gain continues with treatment duration.

In the uncontrolled trials (0005, 0048, and OLE), 27.5% of Seroquel-treated subjects had a clinically significant high weight gain, comparable to the findings in the controlled trials and the long-term controlled trial for Seroquel-exposed participants (Study 0015 cited previously, i.e., 23.9%).

In addition to these controlled and uncontrolled trials included in the NDA application, there were indications from the long-term extensions of the trials that weight gain was persistent throughout follow-up and increased with time, indicating

that prolonged treatment with Seroquel could lead to substantially increased risk of metabolic toxicity. With increased follow up, data later presented during the observed long-term extensions showed that 37.2% of Seroquel-exposed patients had clinically significant weight gain at some point during follow up. Weight gain increased with increased exposure duration: mean weight change compared to baseline weight increased by 3.8 (± 9.0) kg at week 65, 4.4 (± 9.6) kg at week 104, 5.7 (± 10.9) kg at week 156, and 6.7 to 7.3 (± 9.9-13.1) kg at weeks 208 - 260. If presented as median weight gain, this substantial weight gain would have undoubtedly been much larger.

There are two methodological concerns that, with a degree of scientific certainty, resulted in underestimates of the true effect of Seroquel on weight gain in these studies. First, the studies provided in the NDA had consistently high drop-out rates for Seroquel. This is an important characteristic to define the internal validity of a study. Among the 2162 subjects randomized to (n=1710) or treated in uncontrolled trials (n=454), 80.1% withdrew, and the rate was much higher than the 42% for the active comparators or 61.2% for placebo. This has important implications for the interpretation of results related to weight gain or other metabolic abnormalities. Weight gain is a major contributor to non-compliance, and in aggregate in the Phase II and III program, weight gain was associated with greater drop-outs. Therefore, the result reported from these studies almost surely underestimates the true impact of Seroquel on weight gain. Second, many of the studies conducted restricted weight as an inclusion criterion, generally between 100 and 230 pounds. Had heavier subjects been included, it is likely that the weight gain would have been even greater. Since these subjects were excluded, it is unclear whether Seroquel would have been safe in overweight and obese subjects (i.e., the studies are not generalizeable to these subjects).

A metabolic cause for concern regarding the weight data presented in the NDA is the consistent pattern for reductions in thyroid hormone levels that occurred with Seroquel treatment. Low levels of thyroid hormone are associated with greater body weight. Each trial presented in the Table above collected at least one measure of thyroid function. As stated in the Integrated Safety Report, "Consistent laboratory data suggest that quetiapine treatment tends to reduce thyroid hormone plasma levels, primarily total T4 and free T4 with smaller decreases seen in total T3 and reverse T3... Both total T4 and free T4 mean values are reduced and the incidence of significantly low values is increased in quetiapine-treated subjects compared both to placebo- and haloperidol-treated subjects. Results from Trials 0013 and 0015 indicate that the reductions in thyroid hormone levels are dose-related, that the onset of the reductions may occur within the first few days of treatment." Note that the definition of abnormalities for any of the thyroid hormone levels was less than 0.8 times the lower limits of normal or greater than 1.2 times the upper limit of normal. The Integrated Safety Report dismisses these thyroid changes as clinically irrelevant since the thyroid stimulating hormone did not significantly increase. However, because most of the studies were short term, the design may have precluded the development of an increased TSH.

Finally, weight was measured at almost every visit along with the vital signs. Yet detailed week-by-week data could not be found in the Integrated Safety Results. No data were provided in the published literature across the time course of the studies. This is particularly important given the very large drop-out rates that occurred consistently throughout the studies provided in the NDA. It is likely, given the consistent weight increases seen in every Phase II and III study conducted and summarized in the NDA that weight increased among those that subsequently dropped out, and therefore, findings that included subjects who dropped out could have made the findings even less favorable for Seroquel.

Additional studies from the AZ website conducted after the NDA was submitted were evaluated for weight change (based on data provided only on the AstraZeneca website) and showed the consistent pattern of weight increase seen with studies included in the NDA. Data are only tabulated for the first 11 studies listed on the website since the results were consistent with those observed as part of the NDA.

Table 1. Weight Change in AstraZeneca Studies

Study Number	Start – End Date	Results for Metabolic Risk Factors
0039	03/16/98 – 02/03/00	Clinically significant weight gain in 6% of Seroquel, 5% of haldoperidol, and 2% of placebo treated subjects.
0050	05/02/96 - 05/21/99	6 subjects with hypothyroidism on Seroquel; none on haldoperidol
0099	08/09/00 - 11/26/01	Seroquel-treated patients exhibited a statistically significant (p=0.0031) mean increase of 1.60 kg more than the placebo treated group.
0100	11/08/00 - 01/25/02	Clinically significant weight gain in 10.4% of Seroquel subjects versus 3.9% of placebo subjects (relative risk=2.67)
0104	01/07/01 – 04/25/02	Seroquel subjects gained 2.1 kg versus a loss of 0.1 kg in placebo subjects and a gain of 0.2 kg in haldoperidol subjects
0105	04/03/01 - 05/27/02	Weight gain 3.3 kg in Seroquel vs. 0.3 kg in placebo; clinically significant weight gain in 15% versus 1%, respectively (relative risk=15)
0043	06/28/01 – 09/04/02	Both weight gain and glucose significantly increased (no data provided)
0046	No dates provided	Clinically significant weight gain occurred in 12-15% of Seroquel treated subjects (100-200 mg) versus 15% of placebo treated subjects (relative risk = 0.8 to 1.0)
0049	09/30/02 - 09/17/03	Weight increased 1.7% and 6.1% in 300 and 600 mg Seroquel, respectively, vs. 0.6% in placebo (relative risk 2.8 and 10.2, respectively)
D1447C-0001	08/31/05 - 05/24/07	Seroquel mean weight gain ranged from 0.4 to

		1.3 kg across the doses used compared to placebo (-0.4 kg). Clinically significant weight gain occurred in 12.0 to 15.4% of Seroquel groups compared to 2.9% in the placebo group (relative risk 4.2 – 5.3).
D1447C-0135	06/30/04 - 08/26/05	Weight increased 4.1 kg and 5.4 kg in Seroquel 300 mg and 600 mg treated subjects vs. 1.8 kg in placebo subjects

In aggregate, the evidence from the studies presented in the NDA and the follow-up long-term extensions demonstrate a large effect of Seroquel on weight gain. Based on the placebo-controlled studies using doses recommended for schizophrenia, as much as 90% of the weight gain in Seroquel-treated subjects was caused by the drug.

C.1.2. Glucose Abnormalities and Insulin Resistance in Response to Seroquel Treatment

Increased weight is a major risk factor for elevated glucose, hyperinsulinemia, and Type II diabetes mellitus. Glucose measures were collected in most studies and in every US study completed as part of the NDA. Clinically significant increased glucose was defined to be greater than 13.9 mmol/L or 250 mg/dl. However, limited data were provided in the NDA related to glucose, insulin, or other biochemical indices of metabolic risk.

Studies 126 and 127 were conducted with secondary aims to evaluate more detailed measures of glucose homeostasis. In these two trials, there were 5 cases of diabetes in the Seroquel group (n=646) compared to one in the placebo group (n=689). The difference between Seroquel- and placebo-treated patients was pronounced for glucose values > 200 mg (2.9% and 0.5%, respectively). Among Seroquel-treated subjects, 12.2% of them had at least one glucose value greater than 250 mg/dl compared to only 8.1% of placebo treated subjects. Analyses adjusted for length of follow up and restricted to participants who had fasted for at least 8 hours showed even greater treatment differences with respect to glucose. Seroquel patients had a greater mean increase (5.0 mg/dL) in glucose relative to participants randomized to placebo (-0.05 mg/dL). Elevated HbaIC (> 7.5), a longer term marker of glucose elevation, occurred in 2.1 vs. 0.8 percent of Seroquel versus placebo participants. In aggregate, these data clearly show the excess of glucose abnormalities in subjects randomized to Seroquel.

At the request of the Food and Drug Administration in May, 2000, Astra Zeneca evaluated disturbances in glucose regulation in their Phase I-III program as well as post-marketing surveillance. In the short-term (i.e., less than 6 weeks duration) placebo-controlled studies, only 230 Seroquel treated subjects and 143 placebo-treated subjects had glucose measurements analyzed, and Seroquel treated subjects had higher values of glucose than their placebo counterparts (3.6 (1.52 SE) vs. -0.26 (1.93), p=.12, respectively). Additionally, 3.4% of 323 Seroquel treated subjects

versus 0.7% of 143 placebo-treated subjects had a glucose value in excess of 200 mg/dl during the short term trials (relative risk 4.87, 95% confidence interval 0.83-29.30, p=0.116). In June, 2007, a clinical overview was conducted for the purpose of providing data to support changes to the Core Data Sheet. In that analysis, glucose, insulin, HOMA, and HbA1C were evaluated in the composite of studies that had been conducted. The data indicate that Seroquel is associated with metabolic abnormalities with respect to glucose, insulin resistance, and diabetes. Among the 11,013 Seroquel treated subjects, the mean increase in blood glucose was 0.2 (1.62) mmol/L compared to 0.059 (1.46) mmol/L in 1,592 placebo treated subjects. Differences were much larger for HOMA, a measure of insulin resistance that is sensitive to weight (i.e., subjects who gain weight become more insulin resistant): the difference in means was five fold greater for Seroquel versus placebo [1.26 (9.5) in 2265 Seroquel subjects versus 0.37 (10.83) in 640 placebo subjects]. Not unexpectedly, given these differences in glucose and insulin resistance, the relative risk for diabetes was 2.02 (p=0.49, 95% CI 0.31-12.04).

Since most of the participants in the randomized clinical trials were treated for a short period of time, the actual person-time contributed is small, and may have not yielded sufficient power to detect the excess risk of diabetes associated with Seroquel. However, as early as 1999, Dr. J. Small indicated in her draft for a book chapter for Psychopharmacology of Schizophrenia that "as...quetiapine cause the most weight gain, these drugs may be the most likely to induce diabetes." Once Seroquel was approved by the FDA and administered to large numbers of patients, there was early evidence of an increased risk of diabetes with Seroquel treatment. In 2003, Koller et al published a report using data derived from the FDA Medwatch, a surveillance program for spontaneously reported adverse events. During the period 1/1/97 through 8/15/02, they showed that Seroquel use unmasked or precipitated diabetes, the onset was rapid and severe, and removal of the drug resolved the condition in some cases.

Subsequent observational studies (cohort and case-control) confirmed the excess risk of diabetes with Seroquel. For example, Guo et al, using an integrated, seven-state, Medicaid-managed, care claims database from 1/1/98 through 12/31/02, reported the relative risk of diabetes was 2.5 (95% CI 1.4-4.3) in Seroquel users compared to users of conventional antipsychotics. Other studies have suggested that the diabetes risk increases with greater exposure time. For example, Dr. Lambert and colleagues reported from the Veteran's Affairs database that Seroquel was associated with an increased risk for diabetes compared to conventional antipsychotics (RR 1.67, 95% CI 1.01-2.76) and that the risk increased with greater treatment duration (RR for 52 weeks of treatment 1.82, 95% CI 1.32 – 2.49). Other studies have found relative risks for quetiapine versus conventional antipsychotics to range from 1.17 (95% CI 1.06 - 1.30; Ollendorf et al, 2004) to 3.15 (95% CI 1.63 - 6.09; Citrone et al, 2004), with other studies by Sernyak, Leslie, Lambert, and Guo showing relative risks between these two extremes (see Table 2). However, all studies used conventional treatment as the comparison group rather than non-treatment, which could result in a confounding effect, i.e., attenuation of the effect size of Seroquel, if these treatments also were causally related to diabetes. For example, compared to non-treatment,

Sacchetti et al reported a relative risk of 33.7 (95% CI 9.2 – 123.6) for Seroquel. Most studies reported also have a very limited time window of exposure and a small number of subjects exposed to Seroquel.

Table 2: Observational Studies reporting Relative Risks of Seroquel compared to Conventional Antipsychotic Treatments		
First Author	Year	Relative Risk (95% Confidence Interval))
Semyak	2002	1.31 (1.11 - 1.55)
Citrone*	2004	3.15 (1.63 – 6.09)
Feldman*	2004	NR (1.3 – 2.9)
Ollendorf *	2004	1.17 (1.06 - 1.30)
Leslie*	2004	1.20 (0.99 – 1.44)
Lambert*	2005	1.2 (0.80 -- 1.70)
Guo*	2005	1.8 (1.4 – 2.4)
Lambert*	2006	1.67 (1.01 – 2.76)
Guo*	2007	2.5 (1.4 – 4.3)
* indicates industry support among investigative team members. NR=not reported		

C.1.3. The Effect of Seroquel on Triglycerides and Cholesterol

Seroquel has consistent and detrimental effects on triglyceride values which is congruent with its effects on weight and glucose / insulin abnormalities. As stated in the Integrated Safety Report, clinically significant increased triglycerides were defined as a doubling of triglycerides above the upper limit of normal. In aggregate in the Phase II and III placebo-controlled studies summarized in the Integrated Safety Report, the relative risk for increased triglycerides above the normal range at the end of the treatment was 2.7 (22.3% of Seroquel users versus 8.2% of placebo users). The percentage of participants who had a clinically significantly high triglyceride value at any time during these studies was even greater in Seroquel versus placebo users (26.3% versus 8.2%). Cholesterol values showed a similar pattern.

D. Metabolic Derangements associated with Seroquel outweigh Benefits of Treatment

Given the totality of evidence regarding the increased metabolic risk with Seroquel treatment, the relative benefit of Seroquel compared to other antipsychotic agents is debatable. In fact, in 1997, Dr. L. Arvanitis questioned the competitive advantage of Seroquel. In her review of the data regarding weight gain, she stated "I was really struck by how consistent the data was across pools…across parameters / measures…across cohorts." In her summary, she stated that the weight gain was rapid but continued to increase with continued treatment and that the weight gain was 45% at 52 weeks of treatment. She concluded that she did not see a "competitive opportunity" no matter how weak. Subsequent studies confirmed Dr. Arvantis' concern that Seroquel's benefit / risk profile is not superior to other drugs in the class. In aggregate, the drop out rate in the Phase II and III studies was consistently highest

for Seroquel compared to haloperidol or chlorpromazine. The largest and most carefully done study to address the overall effectiveness across drugs in this class was conducted by the National Institutes of Health, specifically, the National Institute of Mental Health. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study randomized 1493 patients with schizophrenia at 57 U.S. sites to receive olanzapine (7.5 to 30 mg per day), perphenazine (8 to 32 mg per day), quetiapine (200 to 800 mg per day), or risperidone (1.5 to 6.0 mg per day) for up to 18 months; ziprasidone (40 to 160 mg per day) was included after its FDA approval. The primary outcome measured used to define effectiveness was withdrawal from the study for any reason. That study found that the time to the discontinuation of treatment for any cause (i.e., the primary outcome measure) was longer in the olanzapine treated subjects than in the Seroquel treated subjects (hazard ratio, 0.63; P<0.001). Additionally, the time to the discontinuation of treatment for lack of efficacy was longer, and the total duration of successful treatment longer, in the olanzapine treated subjects than in the quetiapine treated subjects (hazard ratio, 0.41; P<0.001 and 0.53; P<0.001, respectively). Finally, another indicator of poorer efficacy is the proportion of patients who take the maximal dose of a drug: a higher proportion of patients assigned to quetiapine received the maximal dose allowed in the study.

E. Astra Zeneca Failed to Warn Future Patients and Physicians about the Metabolic Risk associated with Seroquel

Despite the consistent clinically and statistically significant increases in weight and other metabolic parameters noted in all Phase II and III studies presented in the Integrated Safety Report, none of the weight or metabolic factors were listed in the summary of the risks and benefits provided at the conclusion of that report. Publications of the Phase II and III studies never mentioned increased weight or other metabolic abnormalities in the abstract of the publication (i.e., the summary of a scientific publication that is publicly available through various search engines such as PubMed). Within publications, the weight data were listed at the end of results sections, and in the discussion section, dismissed as expected complication of treatment.

F. Astra Zeneca Promoted Seroquel as Metabolically Neutral

Early publications of Seroquel Phase II and III randomized clinical studies promoted Seroquel as metabolically safe despite the large, consistent, and statistically significant findings of weight gain, reduced T4, and hypertriglyceridemia in the clinical trials included in the NDA application in 1996. Even as late as 5/22/99, Astra Zeneca produced a news release from the APA meeting in Washington stating Seroquel "reduces weight gain" and that the "potential to gain weight and develop diabetes.....can be minimized with Seroquel." This data --- for which a news release was created --- were based on retrospective chart review of a case series of 60 patients. This design is the weakest of all designs in epidemiologic research, and the results from this study were in sharp contrast to the totality of evidence from the gold

standard of research designs, namely, the placebo-controlled randomized clinical trials that comprised much of the data submitted with the NDA.

In 2000, publications supported by the company by Breecher et al; describe Seroquel as having a 'favorable weight profile", consistent with the "recommended vocabulary". In 2003, Seroquel's management team created "key messages" to be used in publication. And again, Seroquel's "favorable weight profile" was a key message of Astra Zeneca. In February, 2005, a document created by Astra Zeneca entitled "Seroquel Vocabulary and Descriptors Summary Document" was finalized. Its purpose was to communicate accepted vocabulary to be used in all publications from Seroquel as well as language to be avoided or not used. With respect to weight, the "recommended" vocabulary to be used in publications was "favorable weight profile" and "minimal weight gain". For diabetes, recommended statements generally highlighted either the increased risk of diabetes in schizophrenic patients or the weaknesses of epidemiological studies and confounding as likely reasons of excess diabetes risk associated with Seroquel treatment. In 2006, the Division of Drug Marketing, Advertising, and Communications of the U.S. Food and Drug Administration ordered Astra Zeneca to "cease the dissemination of violative promotional materials for Seroquel" because of false or misleading statements that minimized the risk of hyperglycemia and diabetes mellitus.

In aggregate, this brief and non-exhaustive list of examples point to a concerted effort to promote Seroquel as safe and metabolically neutral in the context of compelling placebo and active comparator controlled clinical trials indicating the drug was associated with substantial metabolic risk.

G. Astra Zeneca withheld Support for Studies Regarding Seroquel's Metabolic Risk

Astra Zeneca consistently withheld support for studies which could demonstrate Seroquel's lack of safety relative to other antipsychotic agents. As evidenced by an email from Dr. Goldstein, July 18, 2002, an investigator requesting 3 grams of Seroquel to study diabetogenic and hyperlipidemia side effects of Seroquel and other atypical antipsychotics was denied by Astra Zeneca. Dr. Goldstein stated "This would be an interesting study but carries substantial risks that we do not differentiate from olanzapine or clozapine. This would be damaging.....I would not want to enter into a study that could provide any data that could influence regulatory authorities against us." Additional internal communications from Dr. Goldstein reinforce the stance of Astra Zeneca with regard to initiating studies. For example, Dr. Goldstein states in another email "they don't want to introduce studies that could potentially damage Seroquel's comparison against other atypical's."

In 2005, Astra Zeneca promoted a policy that gave "green" or "red lights" to make funding decisions for research proposals brought forward from independent investigators. A "red light" was given for glucose and/or metabolism investigator sponsored studies. Specifically, Astra Zeneca's stated policy for glucose or metabolism studies was "don't bother for red". In light of the totality of data within

their own studies indicating the metabolic derangements associated with Seroquel treatment, and subsequent observational epidemiological studies indicating the diabetes risk associated with treatment, this was an unreasonable approach with respect of patient safety.

As medical literature is consistently being published and new evidence from other sources is emerging in reference to this subject I reserve the right to supplement this

I have participated in two trials involving Vioxx.

Donna K. Arnett, Ph.D., M.S.P.H.

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Formal Education

1981	B.S.	College of Nursing, University of South Florida, Tampa, FL.
1987	M.S.P.H.	Epidemiology, College of Public Health, University of South Florida, Tampa, FL.
1991	Ph.D.	Epidemiology, School of Public Health, University of North Carolina, School of Public Health, Chapel Hill, NC.

Professional Experience

1992 - 1994	American Heart Association Postdoctoral Fellow Department of Epidemiology School of Public Health University of North Carolina
1994 - 1998	Assistant Professor of Epidemiology Division of Epidemiology School of Public Health University of Minnesota
1998 - 2003	Associate Professor of Epidemiology Division of Epidemiology School of Public Health University of Minnesota
2003 – 2004	Mayo Professor of Epidemiology Division of Epidemiology School of Public Health University of Minnesota

2004 – Present	Chair and Professor of Epidemiology Department of Epidemiology School of Public Health University of Alabama at Birmingham

Societies and Organizations

1990 - Present	Fellow, American Heart Association, Council on Epidemiology and Prevention
1992 - Present	Society for Epidemiologic Research
1992 - Present	American Public Health Association
1996 - Present	Minnesota Public Health Association
1996 - Present	The American Society of Human Genetics
1998 - Present	International Genetic Epidemiology Society
2002 - Present	American Society of Hypertension
2004 – Present	Senior Scientist, UAB Comprehensive Cancer Center
2004 – Present	Senior Scientist, UAB Clinical Nutrition Research Center
2005 – Present	Internal Advisor, UAB Center for AIDS Research

Awards and Honors

1981	Graduated magna cum laude
1987	Outstanding Student Faculty Scholarship, College of Public Health, Department of Epidemiology, University of South Florida
1988 - 1991	U.S. Public Health Service Traineeship Award, University of North Carolina, Chapel Hill
1989	Alumni Student Faculty Award for Outstanding Service, School of Public Health, University of North Carolina
1990	Biomedical Research Service Award, University of North Carolina
1992	Delta Omega, Honor Society for Public Health, Theta Chapter
2000	Finalist, Roger Williams Award, American Heart Association, Council on Epidemiology and Prevention, March, 2001
2004	Award of Meritorious Achievement of the American Heart Association

Grant and Contract Support

Title:	GenHAT - Genetics of Antihypertensive Treatments
Funding source/type:	NIH/NHLBI 5 R01 HL63082 $5,263,486
Summary:	Ancillary to the Antihypertension and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), we are investigating whether common polymorphisms of several hypertension candidate genes modify the effect of antihypertensives on long-term outcomes, including mortality, coronary heart disease and stroke.
Period:	8/1/99-7/31/05
Role:	Principal Investigator

Title:	HyperGEN: Genetics of Left Ventricular Hypertrophy
Funding source/type:	NIH/NHLBI 2 R01 HL55673, $3,303,849
Summary:	This 5 year project is recruiting family members with left ventricular hypertrophy and/or hypertension. Genetic analysis will be conducted to identify genomic regions contributing to variation in cardiac size and structure.
Period:	8/1/00-7/31/05
Role:	Principal Investigator

Title:	NHLBI Family Blood Pressure Program-HyperGEN
Funding source/type:	NIH/NHLBI 2 U01 HL54496, $3,558,679
Summary:	This project addresses the genetics of two major complications of hypertension (hypertensive heart disease and hypertension-associated kidney disease). It is a continuation of the first cycle of the NHLBI-FBPP.
Period:	9/16/00-6/30/05
Role:	Co-Investigator

Title:	FHS SCAN
Funding source/type:	NIH/NHLBI, 1 U01 HL67901, $1,171,497
Summary:	As an extension of the NHLBI Family Heart Study, we will re-recruit participants and characterize coronary calcification and inflammatory markers. The goal is to identify genomic regions contributing to inter-individual variation in these traits.
Period:	7/1/01-6/30/05
Role:	Co-Investigator

Title:	Genetic and Environmental Determinants of Triglycerides
Funding source/type:	NIH/NHLBI, U 01 HL72524, $10,147,893
Summary:	This study is characterizing the genetic basis of the variable response of triglycerides (TGs) to two environmental contexts, one that raises TGs (dietary fat), and one that lowers TGs (fenofibrate treatment).
Period:	9/30/02–8/31/06
Role:	Principal Investigator

Title:	Genes and Environmental Determinants of Triglycerides Administrative Supplement
Funding source/type:	NIH/NHLBI, 3 U01 HL72524-0181, $1,000,000
Summary:	The University of Minnesota serves as the Program Administrative Center for the 5 networks participating in the Gene-Environment Collaborative Studies.
Period:	9/30/02-8/31/06
Role:	Principal Investigator

Title:	MESA Family Study
Funding source/type:	NIH/NHLBI, 1 R01 HL071251-01A1, $723,209
Summary:	The goal of this study is to determine the extent of genetic contribution to variation in coronary calcium (EBCT and CT scan) and carotid artery wall thickness (B-mode ultrasound) in non-majority populations.
Period:	8/1/03-6/30/08
Role:	Co-Principal Investigator

Submitted Grants

Status:	Resubmitted
Title:	Identifying Susceptibility Genes for Metabolic Syndrome
Funding source/type:	NIH/NIDDK, $1,651,855
Summary:	The overall goal of this 3-year project is to characterize a 19.5 Mb region on chromosome 2q35-2q37 using linkage disequilibrium (LD) mapping to identify genes influencing susceptibility to the MS.
Period:	4/1/05-3/31/08
Role:	Co-Investigator
Status:	To be resubmitted November, 2005

Title:	Pharmacogenomics of HAART – Induced Lipoatrophy in HIV Patients
Funding source/type:	NIH/HHS/PHS, $5,186,437.00
Summary:	We will use a whole-genome association study to identify loci that predict lipoatrophy among HIV+ patients undergoing highly active antiretroviral therapy (HAART)
Period:	07/01/05-06/30/10
Role:	PI
Status:	To be resubmitted September 2005

Title:	Delta States Center for Genomics and Public Health: A Four-State Partnership
Funding source/type:	CDC/HHS/PHS, $500,000.00
Summary:	Established to develop a strong regional educational and technical assistance program network directed to state and local health departments, K-12 school systems, and the general public.
Period:	09/01/04-08/31/08
Role:	PI
Status:	Not funded; Agency withdrew program

Former Grants

Completed Research

Title:	Colliding Categories: Haplotypes, Race & Ethnicity
Funding source/type:	NIH

Summary:	The aim of this project is to explore the ethical and legal ramifications of the impending collision between biological and regulatory classifications of population subgroups in American society.
Period:	7/1/04-6/30/06
Role:	Consultant

Title:	FHS: Molecular Genetics and Genetic Epidemiology MN
Funding source/type:	NIH/NHLBI, 2 R01 HL56567, $182,025
Summary:	This extends the genome-wide analysis for NHLBI FHS conducted during the initial funding period.
Period:	10/23/01-8/31/04
Role:	Principal Investigator

Title:	Training Grant in CVD Genetic Epidemiology
Funding source/type:	NIH/NHLBI, 1 T32 HI07972, $694,879
Summary:	This proposal funded 3 pre-doctoral and 1 post-doctoral trainees in CVD genetic epidemiology at the University of Minnesota
Period:	7/16/01-7/15/06
Role:	Principal Investigator

Title:	Community Surveillance of Cardiovascular Disease -- Risk Factor Survey (MHS)
Funding source/type:	NIH/NHLBI 5 R01 HL23727, $4,576,444
Summary:	A survey of 5,000 adults, ages 25-74 years, and children ages 8-17 years will be conducted using methodology identical to prior MHS surveys done in 1980-82, 1985-87, 1990-92, and 1995-97.
Period:	3/01/00-2/28/04
Role:	Principal Investigator

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Expert Report of Donna K. Arnett, Ph.D.

A. Brief Report of Professional Qualifications

I am an epidemiologist with more than 20 years of experience in the design and conduct of experimental and observational epidemiological studies, including clinical trials, family studies, cross-sectional surveys, cohort, and case-control studies. I am Professor and Chair of Epidemiology at the University of Alabama at Birmingham, Department of Epidemiology. I am a Fellow of the American Heart Association and the American College of Epidemiology, and an Elected Member of the American Epidemiology Society. I have served as an Associate Editor for the *American Journal of Epidemiology* since 1996 and as an Editor since 2004. I currently serve as a Guest Editor and as relief Guest Editor-in-Chief for *Circulation*. I am routinely asked to evaluate epidemiological research studies for publication in peer-reviewed journals, including the *New England Journal of Medicine* and the *Journal of the American Medical Association*. I have served on numerous National Institutes of Health (NIH) review panels for epidemiological research. For the past two years, I have served as Chair for the Cardiovascular and Sleep Epidemiology Study Section (CASE) for the National Institutes of Health.

My principle professional interests include cardiovascular and metabolic disease epidemiology, genetic epidemiology, and pharmacogenetics. I have published more than 225 peer-reviewed articles and more than 12 book chapters or invited review papers.

Since 1994, I have designed and taught graduate level courses in fundamental and advanced concepts of epidemiology, methodological and theoretical aspects of epidemiology, and grant writing. From 1998-2001, I served as Chair of the Epidemiology Master's Degree Program at the University of Minnesota and as Director for the National Heart, Lung, and Blood Institute funded Training Program in Cardiovascular Genetic Epidemiology. For the past 10 years, I have taught a two-week summer course in Epidemiology and Prevention to physicians and other health care professionals for the American Heart Association and Centers for Disease Control.

A copy of my curriculum vitae is attached for additional detail.

B. Brief Overview of Principles of Epidemiology

Randomized, double-masked, placebo-controlled clinical trials are the optimal design for testing a hypothesized association between an exposure (or treatment) and disease because such studies offer the best control for confounding (i.e., variables that are associated with the disease and associated with the exposure) and provide for the optimal test for temporality (i.e., exposure precedes disease). Placebo controlled studies are the gold standard for evaluating the risks and benefits of a new treatment. During a clinical trial, four general reasons could explain clinical improvement in a

participant's condition: (1) natural history of the disease; (2) specific effects of the treatment under investigation; (3) regression to the mean; and (4) placebo effect. A study without a placebo control cannot differentiate amongst the prior 3 conditions. Active comparator randomized clinical trials are frequently used once a known treatment is available since withholding treatment from a diseased group could be unethical; however, there are methodological limitations of trials that use an active control. For example, there can be variable responses to drugs in some populations, unpredictable and small effects, and spontaneous improvements which with an active (rather than a placebo) control may mask the full effect of the drug under investigation.

Many epidemiological studies are observational and provide an assessment of a relation between an exposure and disease. Because of the observational nature of these studies, exposures are not "randomly-assigned" to study volunteers, and hence, factors that may be associated with the exposure of interest, and also independent predictors of the disease, may confound the observed relation between the exposure and disease. The best observational design to test a hypothesized association between exposure and disease is a cohort study. Cohort studies can be conducted either prospectively or retrospectively. Cohort studies are similar conceptually to clinical trials in that subjects are followed for the occurrence of endpoints. Therefore, temporality between the exposure and the endpoint can be conclusively evaluated. The availability of large administrative databases has prompted a number of cohort studies to evaluate adverse exposures, including pharmacological exposures, in relation to disease. The benefits of these types of cohort studies include their cost efficiency and ease of implementation. For example, pharmacy records can be linked to clinical records to assess a hypothesized association between a particular drug exposure and disease.

Case-control studies are also hypothesis-testing studies, and they rely on design qualities that, if done correctly, provide for an estimation of the exposure-disease relationship in a cost-efficient way. In a case-control study, diseased individuals are sampled (i.e., cases) as are non-diseased individuals (i.e., controls), and subjects are classified with respect to exposure. The effect measure used is the ratio of the exposure odds in cases compared to the exposure odds in controls. Conceptually, the case-control study can be thought of as nested within a population cohort, and if two important criteria are met, provide a valid estimate of the disease odds ratio. For excellent internal validity, a case-control study requires that exposure must measured in all cases (or a representative sample of cases that reflects the true exposure odds of all cases), and that the sample of the non-diseased members of the source population that generated the cases reflect the exposure odds of the population. If these conditions are met, then the exposure odds ratio will be equal to the disease odds ratio that can be calculated from a cohort study. In practice, these conditions are challenging to meet except in the case of the nested case-control studies, where the exposure odds can be accurately measured using previously collected data and/or specimens. Nested case-control studies overcome two other potential biases common to the case-control studies, namely, temporality and recall bias. Temporality is a concern in non-nested case-control studies because exposure ascertainment is

determined after disease onset. Another potential bias unique to non-nested case-control studies is recall bias, where cases are more likely than controls to recall prior exposures because of their disease.

C. Review of the Evidence for Effects of Seroquel on Metabolic Risk, including Weight Gain, Hypertriglyceridemia, Insulin Resistance, and Diabetes

The basis for my opinions expressed herein is derived from my education, training, research, experience, and review of the Seroquel New Drug Application (NDA) to the Food and Drug Administration, internal Astra Zeneca documents, the peer-reviewed medical literature, and other publicly available documents concerning Seroquel and its relationship to weight gain and other metabolic risks. In developing my opinions in this case, I am relying primarily upon the Astra Zeneca NDA application and the related published literature, published cohort and nested case-control studies, and meta-analyses of published studies. I have spent over 80 hours reviewing literature and documents related to Seroquel.

Based upon my review of the above specified documents, I have developed the following opinions in this case: (1) Seroquel leads to clinically significant and relevant metabolic risk, including weight gain and other metabolic complications, including but not limited to hypertriglyceridemia, insulin resistance, and diabetes; (2) the metabolic risks from Seroquel appear shortly after treatment and throughout treatment; (3) Astra Zeneca should have made the data presentation clearer within the New Drug Approval application and included the data regarding metabolic risk within scientific publications of the Phase II and Phase III randomized clinical trials in order to warn the FDA, future patients and physicians about metabolic risks associated with Seroquel; (4) the metabolic risks associated with Seroquel outweigh the benefits of treatment; and (5) Astra Zeneca promoted Seroquel as metabolically neutral when there was insufficient evidence to support this claim but substantial evidence that the drug in fact caused weight gain and other metabolic derangements (6) Astra Zeneca withheld support for studies that could have demonstrated Seroquel's metabolic risk relative to other atypical antipsychotics. I have developed these opinions utilizing the normal methodology that I exercise as an epidemiologist in the ordinary scope of my practice. Further, I state these opinions to a reasonable degree of scientific certainty.

C.1. Overview: The Effect of Seroquel on Weight Gain and Other Metabolic Derangements

Seroquel causes weight gain and other metabolic toxicities through stimulation of the hypothalamic AMP activated protein kinase (AMPK). AMPK is responsible for maintaining energy balance and the regulation of food intake. Seroquel blocks histamine H1 receptors, the receptors responsible for the inflammatory response which then stimulates AMPK. In addition to the effects on H1 receptors, Seroquel affects insulin action and metabolism directly in the cell, leading to insulin resistance

and alterations in lipogenesis and lipolysis, which ultimately cause progressive lipid accumulation.

Weight gain can lead to reductions in patient compliance with the medication which could lead to poor clinical outcomes. Weight gain is an important concern of Seroquel treatment, and in particular among schizophrenic individuals since there is an association between schizophrenia and Type II diabetes mellitus, and weight gain is an important risk factor for diabetes development. Weight gain is also an important determinant of other metabolic toxicities, such as hypertriglyceridemia, hypertension, and insulin resistance, all part of the metabolic syndrome. Moreover, once weight has been gained, it is challenging to lose, and this is a large concern for schizophrenic patients who are not typically capable of undertaking lifestyle management to maintain or to lose weight.

There is unequivocal and consistent evidence that Seroquel treatment leads to clinically and statistically significant increases in weight, that the onset of the weight gain occurs shortly after the beginning of treatment and progresses with increased duration of treatment, and that the weight gain is proportionate to the dose ingested. Significant weight gain was observed during the Phase II and III trials and subsequently demonstrated throughout the developmental program of Seroquel for other treatment indications. In addition, other components of the metabolic syndrome (i.e., hyperinsulinemia, hypertriglyceridemia) were similarly observed during the development of Seroquel, and increased incidence of diabetes has been observed with Seroquel treatment. The justification for this opinion follows.

C.1.1. Weight Gain in Response to Seroquel Treatment

The New Drug Application for Seroquel was submitted to the FDA in July, 1996. According to the Integrated Safety Report filed as a part of the NDA, weight and vital signs were collected on the same case report form and were summarized together in the safety report to the FDA. In fact, according to the majority of protocols reviewed, weight for the Phase II and III trials was collected at each visit. Results presented in the Integrated Safety Report are restricted to the analysis which required that subjects who were included in the tabulations had both baseline and post-baseline observations available. Clinically significant weight gain was defined by a gain of 7% of the baseline body weight (approximately 10 pounds for a 150 pound individual).

In the Phase II and III trials, the mean age of the trial participants was 38 years, and the mean body weight was normal (76 kg or 168 lbs). A total of 2162 schizophrenic patients were exposed to Seroquel with doses ranging from 50 to 800 mg/day administered between two and four times daily. Of the 2162 subjects, 1710 were from Phase II and III controlled trials and 454 were from new Seroquel exposures from the uncontrolled trials and were available for analysis. As of June 1, 1995, 407 subjects had been exposed to Seroquel for 6 months or longer and only 1 subject for 2 years or longer; 110 subjects were treated for one year or longer. As stated on page

119 of the report, "In the Phase II and III placebo-controlled trials, Seroquel was associated with a statistically significant weight gain (p=0.0471)." Additionally, from the short term placebo-controlled trials, Astra Zeneca stated that the mean weight gain for Seroquel-treated patients was 2.2 kg (4.85 pounds) greater than the mean weight increase for placebo-treated patients. The range of weight gain was markedly higher for the Seroquel treated than the placebo treated patients, indicating that the distribution of weight gain was non-normal. Therefore, median weight change would have been the optimal measure of central tendency, but median weight change was not provided (in contrast to other vital sign measures that were provided as medians). Had the median, rather than the mean, been reported, the findings regarding the differences between Seroquel and placebo would have been even more dramatic. More detail regarding individual studies is provided below.

The following table describes the studies included in the NDA, and the status of vital signs collected in each. Placebo controlled trials are indicated by **bold** type. Uncontrolled trials are indicated by *italics*. Active comparator trials are indicated by underlined text. Trial 0012 was a low dose Seroquel study and limited data were provided in the Integrated Safety report for this study, although the data provided were indicative of weight increases with treatment.

Vital signs and weight assessments by trial (integrated Phase II-III trials)

	0004	*0005*	**0006**	0007	**0008**	0012	**0013**	0014	0015	*0048*	*LTE*
Pulse	X	X	X	X	X	X	X	X	X	X	X
Blood Pressure*		X	X	X	X	X	X	X	X	X	X
Respiratory	X	X	X		X						
Temperature		X	X	X	X	X		X		X	US
Weight	X	X	X	X	X	X	X	X	X	X	X

* All measures were taken while subjects were seated.
* Unless otherwise noted, readings were taken for both supine and standing systolic and diastolic blood pressures.
+ Only supine readings were taken for Trial 0007.
** Respiration readings were taken while subjects were in the supine position unless otherwise noted.

Data for studies 0004, 0006, 0008, and 0013 were only provided in summary form. In these trials combined, 89/391 (23%) of Seroquel treated subjects had clinically significant weight gain compared to 11/178 (6%) of placebo-treated subjects. This resulted in a relative risk for clinically significant weight gain with treatment of **3.68** (p<.0001, 95% CI 2.1-6.7).

For Study 13 alone, clinically significant weight gain was observed in 2/51 (6%) for placebo, 2/52 (4%) for haldoperidol, 6/53 (11%), 8/48 (17%), 5/52 (10%), 8/51 (16%), 7/54 (13%) for Seroquel 75 mg, 150 mg, 300 mg, 600 mg, and 750 mg, respectively. In comparing low dose Seroquel (75 or 150 mg) versus placebo, the relative risk of weight gain was **3.54** (p=.06, 95% CI .95-16.1), and contrasting high dose (the dose recommended for schizophrenia), the relative risk of weight gain versus placebo was **4.77** (p=.012, 95% CI 1.34-18.2). This provides strong evidence

for dose response, a criterion frequently invoked to determine causation, and also indicates that Seroquel results in increased risk of clinically significant weight gain.

For Study 0013 and 0014 combined, clinically significant weight gain occurred in 70/354 (19.8%) in the Seroquel treated subjects versus 18/236 (7.6%) in the hadoperidol treated subjects (relative risk **2.61**; 95% confidence interval 1.61 – 2.42, p<.0001).

For Study 0007, clinically significant weight gain occurred in 28/100 Seroquel treated subjects compared to 19/99 of the chlorpromazine treated subjects (**RR=1.47**, p=-0.14, 95% CI 0.88-2.44). This active comparator study indicated that Seroquel's weight gain was greater than that of another atypical antipsychotic. This active comparator was not used again in subsequent trials presented in the NDA.

In summary, for these short-term placebo trials, the relative risk for a clinically significant increase in weight ranged from 2.61 to 4.77, indicating a strong and consistent increased risk, and for the active comparisons, a modest to strong increased risk for weight gain compared to chlorpromazine and haldoperidol.

Study 0015 was the long-term, 52-week study, implemented to evaluate the long-term efficacy and safety of Seroquel compared to haldoperidol for treatment of schizophrenia. In this study, Seroquel was associated with a statistically significant increase in weight gain that was dose-dependent and time-dependent (i.e., the longer the treatment, the greater the weight gain). The difference in the mean weight gain was 3.0 kg between treatment groups (+1.6 kg for Seroquel versus -1.4 kg for haldoperidol). Clinically significant weight gain occurred in 50/209 (23.9%) of the Seroquel participants compared to 4/38 (10.5%) of the haldoperidol-treated subjects (relative risk=2.27, p=0.066, 95% CI=0.94-7.55). As stated in the Integrated Safety Report "In general, mean weight increases from baseline for quetiapine-treated subjects were greater at Week 52 for subjects completing the trial (ranging from 2.05 to 8.52 kg) compared with the increases seen at final evaluation (Week 52 or withdrawal), suggesting a trend for subjects to continue gaining weight over time." Also stated in the Integrated Safety Report "The percentage of subjects with clinically significant increases from baseline in weight increased as the dose level of quetiapine increased (for the 75-, 300-, and 600-mg dose groups, 15.2%, 22.9%, and 32.9% of subjects had significantly high changes)." This dose-response was statistically significant. The findings from this long-term study confirm findings of the short-term studies and also suggest that weight gain continues with treatment duration.

In the uncontrolled trials (0005, 0048, and OLE), 27.5% of Seroquel-treated subjects had a clinically significant high weight gain, comparable to the findings in the controlled trials and the long-term controlled trial for Seroquel-exposed participants (Study 0015 cited previously, i.e., 23.9%).

In addition to these controlled and uncontrolled trials included in the NDA application, there were indications from the long-term extensions of the trials that weight gain was persistent throughout follow-up and increased with time, indicating

that prolonged treatment with Seroquel could lead to substantially increased risk of metabolic toxicity. With increased follow up, data later presented during the observed long-term extensions showed that 37.2% of Seroquel-exposed patients had clinically significant weight gain at some point during follow up. Weight gain increased with increased exposure duration: mean weight change compared to baseline weight increased by 3.8 (± 9.0) kg at week 65, 4.4 (±9.6) kg at week 104, 5.7 (±10.9) kg at week 156, and 6.7 to 7.3 (±9.9-13.1) kg at weeks 208 - 260. If presented as median weight gain, this substantial weight gain would have undoubtedly been much larger.

There are two methodological concerns that, with a degree of scientific certainty, resulted in underestimates of the true effect of Seroquel on weight gain in these studies. First, the studies provided in the NDA had consistently high drop-out rates for Seroquel. This is an important characteristic to define the internal validity of a study. Among the 2162 subjects randomized to (n=1710) or treated in uncontrolled trials (n=454), 80.1% withdrew, and the rate was much higher than the 42% for the active comparators or 61.2% for placebo. This has important implications for the interpretation of results related to weight gain or other metabolic abnormalities. Weight gain is a major contributor to non-compliance, and in aggregate in the Phase II and III program, weight gain was associated with greater drop-outs. Therefore, the result reported from these studies almost surely underestimates the true impact of Seroquel on weight gain. Second, many of the studies conducted restricted weight as an inclusion criterion, generally between 100 and 230 pounds. Had heavier subjects been included, it is likely that the weight gain would have been even greater. Since these subjects were excluded, it is unclear whether Seroquel would have been safe in overweight and obese subjects (i.e., the studies are not generalizeable to these subjects).

A metabolic cause for concern regarding the weight data presented in the NDA is the consistent pattern for reductions in thyroid hormone levels that occurred with Seroquel treatment. Low levels of thyroid hormone are associated with greater body weight. Each trial presented in the Table above collected at least one measure of thyroid function. As stated in the Integrated Safety Report, "Consistent laboratory data suggest that quetiapine treatment tends to reduce thyroid hormone plasma levels, primarily total T4 and free T4 with smaller decreases seen in total T3 and reverse T3... Both total T4 and free T4 mean values are reduced and the incidence of significantly low values is increased in quetiapine-treated subjects compared both to placebo- and haloperidol-treated subjects. Results from Trials 0013 and 0015 indicate that the reductions in thyroid hormone levels are dose-related, that the onset of the reductions may occur within the first few days of treatment." Note that the definition of abnormalities for any of the thyroid hormone levels was less than 0.8 times the lower limits of normal or greater than 1.2 times the upper limit of normal. The Integrated Safety Report dismisses these thyroid changes as clinically irrelevant since the thyroid stimulating hormone did not significantly increase. However, because most of the studies were short term, the design may have precluded the development of an increased TSH.

Finally, weight was measured at almost every visit along with the vital signs. Yet detailed week-by-week data could not be found in the Integrated Safety Results. No data were provided in the published literature across the time course of the studies. This is particularly important given the very large drop-out rates that occurred consistently throughout the studies provided in the NDA. It is likely, given the consistent weight increases seen in every Phase II and III study conducted and summarized in the NDA that weight increased among those that subsequently dropped out, and therefore, findings that included subjects who dropped out could have made the findings even less favorable for Seroquel.

Additional studies from the AZ website conducted after the NDA was submitted were evaluated for weight change (based on data provided only on the AstraZeneca website) and showed the consistent pattern of weight increase seen with studies included in the NDA. Data are only tabulated for the first 11 studies listed on the website since the results were consistent with those observed as part of the NDA.

Table 1. Weight Change in AstraZeneca Studies

Study Number	Start – End Date	Results for Metabolic Risk Factors
0039	03/16/98 – 02/03/00	Clinically significant weight gain in 6% of Seroquel, 5% of haldoperidol, and 2% of placebo treated subjects.
0050	05/02/96 - 05/21/99	6 subjects with hypothyroidism on Seroquel; none on haldoperidol
0099	08/09/00 - 11/26/01	Seroquel-treated patients exhibited a statistically significant (p=0.0031) mean increase of 1.60 kg more than the placebo treated group.
0100	11/08/00 – 01/25/02	Clinically significant weight gain in 10.4% of Seroquel subjects versus 3.9% of placebo subjects (relative risk=2.67)
0104	01/07/01 – 04/25/02	Seroquel subjects gained 2.1 kg versus a loss of 0.1 kg in placebo subjects and a gain of 0.2 kg in haldoperidol subjects
0105	04/03/01 – 05/27/02	Weight gain 3.3 kg in Seroquel vs. 0.3 kg in placebo; clinically significant weight gain in 15% versus 1%, respectively (relative risk=15)
0043	06/28/01 – 09/04/02	Both weight gain and glucose significantly increased (no data provided)
0046	No dates provided	Clinically significant weight gain occurred in 12-15% of Seroquel treated subjects (100-200 mg) versus 15% of placebo treated subjects (relative risk = 0.8 to 1.0)
0049	09/30/02 – 09/17/03	Weight increased 1.7% and 6.1% in 300 and 600 mg Seroquel, respectively, vs. 0.6% in placebo (relative risk 2.8 and 10.2, respectively)
D1447C-0001	08/31/05 - 05/24/07	Seroquel mean weight gain ranged from 0.4 to

		1.3 kg across the doses used compared to placebo (-0.4 kg). Clinically significant weight gain occurred in 12.0 to 15.4% of Seroquel groups compared to 2.9% in the placebo group (relative risk 4.2 – 5.3).
D1447C-0135	06/30/04 – 08/26/05	Weight increased 4.1 kg and 5.4 kg in Seroquel 300 mg and 600 mg treated subjects vs. 1.8 kg in placebo subjects

In aggregate, the evidence from the studies presented in the NDA and the follow-up long-term extensions demonstrate a large effect of Seroquel on weight gain. Based on the placebo-controlled studies using doses recommended for schizophrenia, as much as 90% of the weight gain in Seroquel-treated subjects was caused by the drug.

C.1.2. Glucose Abnormalities and Insulin Resistance in Response to Seroquel Treatment

Increased weight is a major risk factor for elevated glucose, hyperinsulinemia, and Type II diabetes mellitus. Glucose measures were collected in most studies and in every US study completed as part of the NDA. Clinically significant increased glucose was defined to be greater than 13.9 mmol/L or 250 mg/dl. However, limited data were provided in the NDA related to glucose, insulin, or other biochemical indices of metabolic risk.

Studies 126 and 127 were conducted with secondary aims to evaluate more detailed measures of glucose homeostasis. In these two trials, there were 5 cases of diabetes in the Seroquel group (n=646) compared to one in the placebo group (n=689). The difference between Seroquel- and placebo-treated patients was pronounced for glucose values > 200 mg (2.9% and 0.5%, respectively). Among Seroquel-treated subjects, 12.2% of them had at least one glucose value greater than 250 mg/dl compared to only 8.1% of placebo treated subjects. Analyses adjusted for length of follow up and restricted to participants who had fasted for at least 8 hours showed even greater treatment differences with respect to glucose. Seroquel patients had a greater mean increase (5.0 mg/dL) in glucose relative to participants randomized to placebo (-0.05 mg/dL). Elevated Hba1C (> 7.5), a longer term marker of glucose elevation, occurred in 2.1 vs. 0.8 percent of Seroquel versus placebo participants. In aggregate, these data clearly show the excess of glucose abnormalities in subjects randomized to Seroquel.

At the request of the Food and Drug Administration in May, 2000, Astra Zeneca evaluated disturbances in glucose regulation in their Phase I-III program as well as post-marketing surveillance. In the short-term (i.e., less than 6 weeks duration) placebo-controlled studies, only 230 Seroquel treated subjects and 143 placebo-treated subjects had glucose measurements analyzed, and Seroquel treated subjects had higher values of glucose than their placebo counterparts (3.6 (1.52 SE) vs. -0.26 (1.93), p=.12, respectively). Additionally, 3.4% of 323 Seroquel treated subjects

versus 0.7% of 143 placebo-treated subjects had a glucose value in excess of 200 mg/dl during the short term trials (relative risk 4.87, 95% confidence interval 0.83-29.30, p=0.116). In June, 2007, a clinical overview was conducted for the purpose of providing data to support changes to the Core Data Sheet. In that analysis, glucose, insulin, HOMA, and HbA1C were evaluated in the composite of studies that had been conducted. The data indicate that Seroquel is associated with metabolic abnormalities with respect to glucose, insulin resistance, and diabetes. Among the 11,013 Seroquel treated subjects, the mean increase in blood glucose was 0.2 (1.62) mmol/L compared to 0.059 (1.46) mmol/L in 1,592 placebo treated subjects. Differences were much larger for HOMA, a measure of insulin resistance that is sensitive to weight (i.e., subjects who gain weight become more insulin resistant): the difference in means was five fold greater for Seroquel versus placebo [1.26 (9.5) in 2265 Seroquel subjects versus 0.37 (10.83) in 640 placebo subjects]. Not unexpectedly, given these differences in glucose and insulin resistance, the relative risk for diabetes was 2.02 (p=0.49, 95% CI 0.31-12.04).

Since most of the participants in the randomized clinical trials were treated for a short period of time, the actual person-time contributed is small, and may have not yielded sufficient power to detect the excess risk of diabetes associated with Seroquel. However, as early as 1999, Dr. J. Small indicated in her draft for a book chapter for Psychopharmacology of Schizophrenia that "as...quetiapine cause the most weight gain, these drugs may be the most likely to induce diabetes." Once Seroquel was approved by the FDA and administered to large numbers of patients, there was early evidence of an increased risk of diabetes with Seroquel treatment. In 2003, Koller et al published a report using data derived from the FDA Medwatch, a surveillance program for spontaneously reported adverse events. During the period 1/1/97 through 8/15/02, they showed that Seroquel use unmasked or precipitated diabetes, the onset was rapid and severe, and removal of the drug resolved the condition in some cases.

Subsequent observational studies (cohort and case-control) confirmed the excess risk of diabetes with Seroquel. For example, Guo et al, using an integrated, seven-state, Medicaid-managed, care claims database from 1/1/98 through 12/31/02, reported the relative risk of diabetes was 2.5 (95% CI 1.4-4.3) in Seroquel users compared to users of conventional antipsychotics. Other studies have suggested that the diabetes risk increases with greater exposure time. For example, Dr. Lambert and colleagues reported from the Veteran's Affairs database that Seroquel was associated with an increased risk for diabetes compared to conventional antipsychotics (RR 1.67, 95% CI 1.01-2.76) and that the risk increased with greater treatment duration (RR for 52 weeks of treatment 1.82, 95% CI 1.32 – 2.49). Other studies have found relative risks for quetiapine versus conventional antipsychotics to range from 1.17 (95% CI 1.06 – 1.30; Ollendorf et al, 2004) to 3.15 (95% CI 1.63 – 6.09; Citrone et al, 2004), with other studies by Sernyak, Leslie, Lambert, and Guo showing relative risks between these two extremes (see Table 2). However, all studies used conventional treatment as the comparison group rather than non-treatment, which could result in a confounding effect, i.e., attenuation of the effect size of Seroquel, if these treatments also were causally related to diabetes. For example, compared to non-treatment,

Sacchetti et al reported a relative risk of 33.7 (95% CI 9.2 – 123.6) for Seroquel. Most studies reported also have a very limited time window of exposure and a small number of subjects exposed to Seroquel.

Table 2: Observational Studies reporting Relative Risks of Seroquel compared to Conventional Antipsychotic Treatments		
First Author	Year	Relative Risk (95% Confidence Interval))
Sernyak	2002	1.31 (1.11 - 1.55)
Citrone*	2004	3.15 (1.63 – 6.09)
Feldman*	2004	NR (1.3 – 2.9)
Ollendorf *	2004	1.17 (1.06 – 1.30)
Leslie*	2004	1.20 (0.99 – 1.44)
Lambert*	2005	1.2 (0.80 – 1.70)
Guo*	2005	1.8 (1.4 – 2.4)
Lambert*	2006	1.67 (1.01 – 2.76)
Guo*	2007	2.5 (1.4 – 4.3)
* indicates industry support among investigative team members, NR=not reported		

C.1.3. The Effect of Seroquel on Triglycerides and Cholesterol

Seroquel has consistent and detrimental effects on triglyceride values which is congruent with its effects on weight and glucose / insulin abnormalities. As stated in the Integrated Safety Report, clinically significant increased triglycerides were defined as a doubling of triglycerides above the upper limit of normal. In aggregate in the Phase II and III placebo-controlled studies summarized in the Integrated Safety Report, the relative risk for increased triglycerides above the normal range at the end of the treatment was 2.7 (22.3% of Seroquel users versus 8.2% of placebo users). The percentage of participants who had a clinically significantly high triglyceride value at any time during these studies was even greater in Seroquel versus placebo users (26.3% versus 8.2%). Cholesterol values showed a similar pattern.

D. Metabolic Derangements associated with Seroquel outweigh Benefits of Treatment

Given the totality of evidence regarding the increased metabolic risk with Seroquel treatment, the relative benefit of Seroquel compared to other antipsychotic agents is debatable. In fac, in 1997, Dr. L. Arvanitis questioned the competitive advantage of Seroquel. In her review of the data regarding weight gain, she stated "I was really struck by how consistent the data was across pools…across parameters / measures…across cohorts." In her summary, she stated that the weight gain was rapid but continued to increase with continued treatment and that the weight gain was 45% at 52 weeks of treatment. She concluded that she did not see a "competitive opportunity" no matter how weak. Subsequent studies confirmed Dr. Arvantis' concern that Seroquel's benefit / risk profile is not superior to other drugs in the class. In aggregate, the drop out rate in the Phase II and III studies was consistently highest

for Seroquel compared to haloperidol or chlorpromazine. The largest and most carefully done study to address the overall effectiveness across drugs in this class was conducted by the National Institutes of Health, specifically, the National Institute of Mental Health. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study randomized 1493 patients with schizophrenia at 57 U.S. sites to receive olanzapine (7.5 to 30 mg per day), perphenazine (8 to 32 mg per day), quetiapine (200 to 800 mg per day), or risperidone (1.5 to 6.0 mg per day) for up to 18 months; ziprasidone (40 to 160 mg per day) was included after its FDA approval. The primary outcome measured used to define effectiveness was withdrawal from the study for any reason. That study found that the time to the discontinuation of treatment for any cause (i.e., the primary outcome measure) was longer in the olanzapine treated subjects than in the Seroquel treated subjects (hazard ratio, 0.63; $P<0.001$). Additionally, the time to the discontinuation of treatment for lack of efficacy was longer, and the total duration of successful treatment longer, in the olanzapine treated subjects than in the quetiapine treated subjects (hazard ratio, 0.41; $P<0.001$ and 0.53; $P<0.001$, respectively). Finally, another indicator of poorer efficacy is the proportion of patients who take the maximal dose of a drug: a higher proportion of patients assigned to quetiapine received the maximal dose allowed in the study.

E. Astra Zeneca Failed to Warn Future Patients and Physicians about the Metabolic Risk associated with Seroquel

Despite the consistent clinically and statistically significant increases in weight and other metabolic parameters noted in all Phase II and III studies presented in the Integrated Safety Report, none of the weight or metabolic factors were listed in the summary of the risks and benefits provided at the conclusion of that report. Publications of the Phase II and III studies never mentioned increased weight or other metabolic abnormalities in the abstract of the publication (i.e., the summary of a scientific publication that is publicly available through various search engines such as PubMed). Within publications, the weight data were listed at the end of results sections, and in the discussion section, dismissed as expected complication of treatment.

F. Astra Zeneca Promoted Seroquel as Metabolically Neutral

Early publications of Seroquel Phase II and III randomized clinical studies promoted Seroquel as metabolically safe despite the large, consistent, and statistically significant findings of weight gain, reduced T4, and hypertriglyceridemia in the clinical trials included in the NDA application in 1996. Even as late as 5/22/99, Astra Zeneca produced a news release from the APA meeting in Washington stating Seroquel "reduces weight gain" and that the "potential to gain weight and develop diabetes.....can be minimized with Seroquel." This data --- for which a news release was created --- were based on retrospective chart review of a case series of 60 patients. This design is the weakest of all designs in epidemiologic research, and the results from this study were in sharp contrast to the totality of evidence from the gold

standard of research designs, namely, the placebo-controlled randomized clinical trials that comprised much of the data submitted with the NDA.

In 2000, publications supported by the company by Breecher et al; describe Seroquel as having a 'favorable weight profile", consistent with the "recommended vocabulary". In 2003, Seroquel's management team created "key messages" to be used in publication. And again, Seroquel's "favorable weight profile" was a key message of Astra Zeneca. In February, 2005, a document created by Astra Zeneca entitled "Seroquel Vocabulary and Descriptors Summary Document" was finalized. Its purpose was to communicate accepted vocabulary to be used in all publications from Seroquel as well as language to be avoided or not used. With respect to weight, the "recommended" vocabulary to be used in publications was "favorable weight profile" and "minimal weight gain". For diabetes, recommended statements generally highlighted either the increased risk of diabetes in schizophrenic patients or the weaknesses of epidemiological studies and confounding as likely reasons of excess diabetes risk associated with Seroquel treatment. In 2006, the Division of Drug Marketing, Advertising, and Communications of the U.S. Food and Drug Administration ordered Astra Zeneca to "cease the dissemination of violative promotional materials for Seroquel" because of false or misleading statements that minimized the risk of hyperglycemia and diabetes mellitus.

In aggregate, this brief and non-exhaustive list of examples point to a concerted effort to promote Seroquel as safe and metabolically neutral in the context of compelling placebo and active comparator controlled clinical trials indicating the drug was associated with substantial metabolic risk.

G. Astra Zeneca withheld Support for Studies Regarding Seroquel's Metabolic Risk

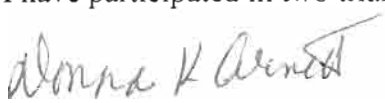
Astra Zeneca consistently withheld support for studies which could demonstrate Seroquel's lack of safety relative to other antipsychotic agents. As evidenced by an email from Dr. Goldstein, July 18, 2002, an investigator requesting 3 grams of Seroquel to study diabetogenic and hyperlipidemia side effects of Seroquel and other atypical antipsychotics was denied by Astra Zeneca. Dr. Goldstein stated "This would be an interesting study but carries substantial risks that we do not differentiate from olanzapine or clozapine. This would be damaging.....I would not want to enter into a study that could provide any data that could influence regulatory authorities against us." Additional internal communications from Dr. Goldstein reinforce the stance of Astra Zeneca with regard to initiating studies. For example, Dr. Goldstein states in another email "they don't want to introduce studies that could potentially damage Seroquel's comparison against other atypical's."

In 2005, Astra Zeneca promoted a policy that gave "green" or "red lights" to make funding decisions for research proposals brought forward from independent investigators. A "red light" was given for glucose and/or metabolism investigator sponsored studies. Specifically, Astra Zeneca's stated policy for glucose or metabolism studies was "don't bother for red". In light of the totality of data within

their own studies indicating the metabolic derangements associated with Seroquel treatment, and subsequent observational epidemiological studies indicating the diabetes risk associated with treatment, this was an unreasonable approach with respect of patient safety.

As medical literature is consistently being published and new evidence from other sources is emerging in reference to this subject I reserve the right to supplement this

I have participated in two trials involving Vioxx.



Donna K. Arnett, Ph.D., M.S.P.H.

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as of Sunday, November 23, 2008

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Id :	i.m.ef7cf616d7186ac5efcbeaababe006bb
CN :	SQ1ED01608498
Date :	Friday, March 18, 2005 8:00:00 AM GMT
From :	Owen, Richard T
To :	Lowe, Matthew
Cc :	Leong, Ronald
Subject :	RE: data on low dose quetiapine and metabolic disturbances
Custodians :	Leong, Ronald

From:
Owen, Richard T

Sent:
Friday, March 18, 2005 3:39 PM

To:
Lowe, Matthew

Cc:
Leong, Ronald

Subject:
RE: data on low dose quetiapine and metabolic disturbances

Dear Matthew

I don't believe we can state that metabolic disturbances are absent (or even minimal) at low doses. Even if we could, we know that the majority of schizophrenia and mania patients would not get substantial efficacy at doses <200mg/day.

Regards

Richard.

Dr Richard T.Owen

Global Medical Affairs Manager-Seroquel

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MACCLESFIELD

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England.

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tel: +44 (0) 1625 514740

fax: +44 (0)1625 515682

mobile: 07747-768531

-----Original Message-----

From:
Lowe, Matthew

Sent:
Thursday, 17 March, 2005 20:07

To:
Owen, Richard T

Cc:
Leong, Ronald

Subject:
RE: data on low dose quetiapine and metabolic disturbances

Hi Richard,

The query came from an academic clinician who commented that if there was not metabolic disturbances with low dose Seroquel, we could be onto something big. In NZ, there is a lot of Seroquel use at low doses (not necessarily in the elderly but also in the general population) for agitation with dementia, generalised anxiety and sleeplessness. Most physicians are using quite a bit of Seroquel in these situations and this particular individual was interested if any metabolic disturbances had been found at low doses.

Regards,

Matthew

-----Original Message-----

From:
Owen, Richard T

Sent:
Tuesday, 15 March 2005 11:04 p.m.

To:
Lowe, Matthew

Cc:
Leong, Ronald

Subject:
RE: data on low dose quetiapine and metabolic disturbances

Dear Matthew

I think it would be difficult to do a search on metabolic disturbances by dose. However the sort of population that would be likely to require doses of <200mg/day would be the elderly-whether suffering from schizophrenia, dementia, mania etc. The evidence to date does not suggest any particular signal for metabolic disturbance in the elderly if one looks at studies such as those by Tariot et al (Clin Ther 2000; 22: 1068-1084), and the results of the STAR trial (see STAR FAQ on PKT)-in terms of blood glucose levels.

I've copied Ron Leong in Drug Safety who may be able to comment on any dose relationship (or lack of it) regarding Seroquel and metabolic disturbances.

I wondered if your query stemmed from a physician who thought he might be able to avoid metabolic disturbance by using a low dose, or did a patient on low dose Seroquel experience a metabolic disturbance?

Regards

Richard.

Dr Richard T.Owen

Global Medical Affairs Manager-Seroquel

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tel: +44 (0) 1625 514740

fax: +44 (0)1625 515682

mobile: 07747-768531

-----Original Message-----

From:
Lowe, Matthew

Sent:
Monday, 14 March, 2005 23:03

To:
Owen, Richard T

Subject:
data on low dose quetiapine and metabolic disturbances

Hi Richard

Do we have any data available on the use of low dose quetiapine (doses < 200 mg/day) and metabolic disturbances?

Many thanks in advance.

Matthew

Document ID: i.m.54ac68db67b61ee532c73364a8133902

Printed on : Saturday, November 22, 2008 @ 5:12:45 PM GMT
Printed by : Yommy Chiu
Item count : 1 (0 Attachments)

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as of Saturday, November 22, 2008

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CN :	S339-E00635654
Date :	Friday, May 23, 2003 7:00:00 AM GMT
From :	Duff, David J
To :	Gilchrist, Kim A (HEOR); Goldstein, Jeffrey M; Pesa, Jacqueline; Tumas, John A; Williams-Hughes, Celeste
Subject :	RE: Gianfrancesco work
Custodians :	Duff, Dave

From:
Duff, David J

Sent:
Friday, May 23, 2003 6:43 PM

To:
Goldstein, Jeffrey M; Tumas, John A; Gilchrist, Kim A (HEOR); Pesa, Jacqueline; Williams-Hughes, Celeste

Subject:
RE: Gianfrancesco work

I agree - we should hold off if Frank is not 100% confident of a positive outcome. We have other abstracts we can submit with confidence, right? (i.e. 104, 105, etc).

Dave

-----Original Message-----

From:
Goldstein, Jeffrey M

Sent:
Friday, May 16, 2003 9:50 AM

To:
Tumas, John A; Gilchrist, Kim A (HEOR); Pesa, Jacqueline; Williams-Hughes, Celeste; Duff, David J

Subject:
RE: Gianfrancesco work

I think we should defer submitting until we are sure of the outcome, especially if Frank is also uneasy.

-----Original Message-----

From:
Tumas, John A

Sent:
Friday, May 16, 2003 9:13 AM

To:
Gilchrist, Kim A (HEOR); Pesa, Jacqueline; Williams-Hughes, Celeste; Goldstein, Jeffrey M; Duff, David J

Subject:
Gianfrancesco work

Hi All,

I've just spoken with Frank and wanted to touch base with those of you who were at his presentation last week. Frank seems uncomfortable submitting an abstract on the preliminary data we saw on diabetes incidence (see attached abstract) and wants to do a full study along the lines of his previous work. I'm not in a position to judge whether his concerns are valid or not, but I wanted to pass this on to you.

The plan was to go ahead with submitting the attached abstract to ASCP (abstract deadline 5/23/03) and IPS (abstract deadline 6/2/03) and do additional analyses for the poster. Frank thinks there is a possible risk that the full analysis could look different than what we have now. I've gone ahead and circulated it for review and am waiting for ATP approval. Please let me know if you think we should hold off from submitting this to ASCP and IPS. There is also the issue with Frank's contract and whether he can even agree to submit the abstract.

Thanks,

John

<< File: Type2Diabetes.FGedit2.5-15-03.doc >>

IN THE UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

- - -

IN RE: SEROQUEL PRODUCTS LIABILITY LITIGATION	:	CASE NO. 6:06-md-01769-ACC-DAB
MDL Docket No. 1769:		

- - -

May 7, 2008

- - -

C O N F I D E N T I A L

- - -

Videotape deposition of WAYNE K. GELLER, M.D. taken pursuant to notice, was held at the offices of Golkow Technologies, Inc., One Liberty Place, 51st Floor, 1650 Market Street, Philadelphia, Pennsylvania 19103, commencing at 9:00 a.m., on the above date, before Linda Rossi Rios, RPR, CCR and Notary Public.

- - -

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short-term clinical trials, which again captures the spirit of significant. Secondly, it was providing long-term clinical study data which they up to that point in time did not have in their possession.

Q. You, yourself -- you, yourself, knew that there was discrepancies with what you told the FDA as opposed to what you had written internally. You, yourself, knew that, didn't you?

A. No, sir, that's not correct.

Q. You didn't. Okay.

- - -

(Exhibit Geller-16, 10/31/00 E-mail, was marked for identification.)

- - -

BY MR. ALLEN:

Q. Let's look at Geller-16. And let's go to the -- this is a series of e-mails, some of which you wrote. This is where I discovered, sir, that you

were the man that allowed the inadvertent data to go out to the Dutch authority. You probably reviewed this e-mail chain in Exhibit 16 in preparation for the deposition, didn't you?

A. I believe I did, sir.

Q. You did?

A. I believe I did.

Q. Yes, sir. As a matter of fact, I want to go to page 6 of this document, Exhibit 16.

By the way, without -- without reviewing this document in preparation for your deposition, you recall these events fairly well, do you not, sir?

A. Yes.

Q. In fact, you were so concerned about the release of data that was internal only to the Dutch authorities that was inconsistent with what you had told the FDA, that you were staying at work late to work on how to correct this problem, weren't you?

A. When you say "work late," sir, I don't recall how long I was working on that, so I can't agree or disagree with you on working late.

Q. Do you normally work until 11:15 at night?

A. Not under most circumstances, but we'll say that it does occasionally happen.

Q. What you were going to say is not under normal circumstances, the word "normal"? Do you use the word "normal" in your everyday life?

MR. RABER: Objection to form.

BY MR. ALLEN:

Q. Do you use that word?

A. Sure.

Q. Do you use the word "limited" in your everyday life?

A. I typically try to avoid using the term "limited."

Q. How about the word "neutral," do you ever use that in your

everyday life?

A. I've used the word -- I used at least on one occasion of my life each of those terms.

Q. Neutral means not positive, not negative, no effect. Right? Isn't that what neutral means?

MR. RABER: Objection to the form.

THE WITNESS: It really depends upon the context.

BY MR. ALLEN:

Q. Okay. How about "minimal," you use that word all the time, don't you?

A. I wouldn't characterize myself as using that term all the time, no.

Q. Minimal means not very much, not to any great extent, no big deal, doesn't it?

MR. RABER: Object to the form.

BY MR. ALLEN:

Q. Doesn't it?

A. I mean, I can't disagree that those are some of the meanings of minimal, but I can't say that everyone interprets minimal exactly the same way.

Q. That's right, sir.

Do you have children?

A. Yes.

Q. Would you want them to come home with a problem and if you asked and inquired about that problem, would you want them to minimize that problem to you or would you want them to tell you the whole truth?

A. I always seek the truth from my kids, as I do from others, sir.

Q. Do you want them to minimize the truth?

A. Minimize the truth by doing what, sir?

Q. What does minimize the truth mean? It means not to tell the whole truth, right?

A. I guess that's one way of

interpreting it.

Q. If you said you always seek the truth from your children, would you want them to limit your information of the truth, to limit it, or would you want them to give you whole truth?

MR. ALLEN: Objection to form.

THE WITNESS: Sir, my children and I have an open enough relationship and dialogue that I would -- I trust in most circumstances that they tell me truth.

BY MR. ALLEN:

Q. That means they should not limit it, minimize it or neutralize it. Is that true?

MR. RABER: Object to the form.

BY MR. ALLEN:

Q. You don't want them to do that, do you?

A. I guess I'm really having

difficulty understanding the context of your question, sir.

Q. Well, I'm -- okay, sir. If you look at page 6 of this Exhibit 16, this is an e-mail you prepared from Wayne Geller, October 23, 2000 at 11:18 p.m. Isn't that right, sir, 23:18?

A. I'm sorry, what page are we on again here?

Q. Page 6. I'll get it. It's on your screen. It's also on the screen about 18 inches from you.

A. Yes.

Q. Is it on -- do you see it on the screen?

MR. RABER: In fairness to the witness, the whole page isn't on the screen 18 inches from him. It's a little snippet of it.

MR. ALLEN: Okay. Well, the jury can see it.

MR. RABER: You keep saying that.

MR. ALLEN: The jury can see

it. And all I was asking, did he write this e-mail October 23, 2000 --

MR. RABER: You did more than that. You said it's just 18 inches away from you.

BY MR. ALLEN:

Q. Yes, sir, is this screen -- can you read the screen, sir? Can you read the screen is my question?

A. Yes.

Q. Okay. What time did you write this e-mail?

A. At 23:18.

Q. And what time is that?

A. That would be 11 -- roughly 11:18 p.m.

Q. Yes, sir. And you wrote it to Martin Brecher and Russell Giddins. Who is Russell Giddins?

A. Russell was the global regulatory affairs director.

Q. He was Vikram Dev's boss. Is that right?

A. That's not correct, sir.

Q. Okay. Never mind. I'm not going to go over the rest of it -- all of it. Subject: Seroquel and diabetes. The importance level that you put on this e-mail was what, sir, high, high importance?

A. Yes.

Q. Now, I'm just going to ask you whether or not you can agree with me, without having to go over this entire e-mail string, whether or not the information that your company had internally had discrepancies from what it told the FDA in August of 2000, whether or not there were discrepancies, I'm just going to ask you that?

MR. RABER: Objection to form.

THE WITNESS: Discrepancies between which documents?

BY MR. ALLEN:

Q. Well, let's ask if there was a discrepancy -- let's take, for example,

was there discrepancies between the Seroquel safety position paper on diabetes and related disorders and what your company told the FDA?

MR. RABER: Objection to form.

THE WITNESS: What was sent to the MEB, the Dutch regulatory authority, was a template of a position paper predicated upon a draft of a discussion document for the June SERM. Within that document was contained language which was not the final language used in the discussion document at the June SERM as it represented my view of glucose dysregulation and Seroquel therapy. And I fully acknowledge having made the mistake of using a document which was a draft document, number one. Number two, which was not an official position paper and was sent to the MEB, the Dutch

regulatory authority.

MR. ALLEN: Objection. Nonresponsive.

BY MR. ALLEN:

Q. Was what your company had in its Seroquel safety position paper, discrepant -- did it have discrepancies from what your company told the FDA?

MR. RABER: Object to the form. No foundation.

MR. ALLEN: Sure it is. He uses the word twice in this e-mail.

BY MR. ALLEN:

Q. Didn't you specifically state in this e-mail --

MR. RABER: There is no foundation.

BY MR. ALLEN:

Q. Let me ask it again after your lawyer has interrupted.

MR. RABER: I'm entitled to object. An objection -- a well-founded objection is not an

interruption, sir.

BY MR. ALLEN:

Q. Isn't it true that there was discrepancies with what you told the FDA, you at AZ, from what your internal safety position paper on diabetes mellitus was?

MR. RABER: Objection to form. No foundation.

THE WITNESS: The document that was sent to the Dutch, again, was not factually correct. And, in fact, as I indicated just a minute ago, was a mistake that I acknowledge having made. And consequently, I would say that the two documents differ in that regard. However, the FDA document, by virtue of its content, contains the correct information regarding the data as it relates to diabetes mellitus and related disorders.

BY MR. ALLEN:

Q. Including weight gain?

Id : i.m.ba158aee404bc53f368a418249149765
CN : SQ1ED00428426
Date : Tuesday, October 3, 2000 7:00:00 AM GMT
From : Wientjens, Dorothee (temp. employee)
To : Geller, Wayne
Subject : RE: Quetiapine and glucose metabolism disorders
Custodians : Geller, Wayne

From:
Wientjens, Dorothee (temp. employee)

Sent:
Tuesday, October 03, 2000 3:20 PM

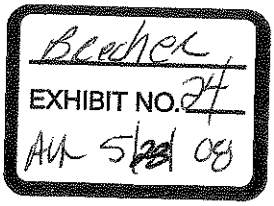
To:
Geller, Wayne

Subject:
RE: Quetiapine and glucose metabolism disorders

Dear Wayne,

Thank you for yoy fax, which I sent to the local authorities.

Best regards,



Drothee PWM Wientjens

DSO

AstraZenecaNL

-----Oorspronkelijk bericht-----

Van:
Geller Wayne

Verzonden:
maandag 25 september 2000 22:38

Aan:
Wientjens Dorothee (temp. employee); Schotel Luci

Onderwerp:
RE: Quetiapine and glucose metabolism disorders

Hi Dorothee,

The document is 11 pages. I can fax a signed copy to you or mail one. If you prefer the latter, please send me your address and I will send it out at once.

Thanks,

Wayne

-----Original Message-----

From:
Wientjens, Dorothee (temp. employee)

Sent:
Monday, September 25, 2000 5:16 AM

To:
Geller, Wayne

Subject:
RE: Quetiapine and glucose metabolism disorders

Dear Wayne,

I think it is ok to send me a hard copy by mail. Then I will send it to the authoroties. From tuesday onwards I will be at a conference, so please contact Luci Schotel, our secretary.

Thank you in anticipation.

Dorothee

-----Oorspronkelijk bericht-----

Van:
Geller Wayne

Verzonden:
vrijdag 22 september 2000 18:25

Aan:
Wientjens Dorothee (temp. employee)

Onderwerp:
RE: Quetiapine and glucose metabolism disorders

Urgentie:
Hoog

Hi Dorothee,

I spoke with our information services department, and it appears that I can not send you a signed PDF-file electronically as you requested. Do you have time for me to send this either as a fax or a signed hard copy?

Please advise. I will not be in the office Monday.

Thanks,

Wayne

-----Original Message-----

From:
Wientjens, Dorothee (temp. employee)

Sent:
Friday, September 22, 2000 11:51 AM

To:
Geller, Wayne

Subject:
Quetiapine and glucose metabolism disorders

Dear Wayne,

Thank you for the safety position paper on seroquel. Would you be so kind as to send me the front page of the paper (as a PDF-file) with your signature and date of report, so I can send it to the local authorities.

Thank you in anticipation

Dorothee P.W.M. Wientjens

dso

Astra ZenecaNL

Id :	i.m.0a2c55e1d81af3b4dc4d550d7bbfe257
CN :	SQ1ED00165892
Date :	Tuesday, February 4, 2003 2:50:00 AM GMT
From :	Ou, Connie
To :	Leong, Ronald
Subject :	RE: re: Re-Challenge of Seroquel
Attachments :	Diabetes (rechallenge).doc
Custodians :	Leong, Ronald

From:
Ou, Connie

Sent:
Tuesday, February 04, 2003 7:39 PM

To:
Leong, Ronald

Subject:
RE: re: Re-Challenge of Seroquel

Attachments:
Diabetes (rechallenge).doc

Ron,

There were limited informatin on reports of glucose dysregulation that described a positive re-challenge.

Please see attached.

Connie

-----Original Message-----

From: Leong, Ronald

Sent: Monday, February 03, 2003 6:20 PM

To: Fontana, Patricia

Cc: Ou, Connie

Subject: RE: re: Re-Challenge of Seroquel

Patricia,

I am forwarding your note to Connie Ou, Seroquel Safety Surveillance Product Manager, to see if we have reports of re-challenge, and the outcomes of re-challenges. Connie has been tracking reports of diabetes related adverse events. I don't recall if there are reports of re-challenge.

Since it may take some time to search our database for reports of re-challenge, I have the following thoughts.

First, it has been the company position that there is insufficient evidence for a causal relationship between Seroquel and diabetes or glucose dysregulation. Accordingly, we are trying to learn as much

about these reports as possible. (See fourth paragraph about useful data for us to have.)

Second, we cannot advise the physician to re-challenge or not to re-challenge the patient. It is the physician's benefit risk judgement. If the physician has tried other antipsychotics, and has the best response to Seroquel, he or she may feel that outweighs the risk of diabetes or hyperglycemia. If the patient develops hyperglycemia or diabetes on re-challenge, the physician may decide to continue Seroquel and use standard treatments for diabetes (e.g. diet, oral hypoglycemic drugs, and possibly insulin). Other atypical antipsychotics, particularly olanzapine, have been associated with diabetes, and some studies have even shown an association with the typical antipsychotics. All the anti-psychotic treatments have some risk, diabetes-related and non-diabetes related. The physician needs to balance the benefit with the risk.

If the physician decides to re-challenge the patient, it would be helpful to obtain the following while the patient is not on Seroquel: date Seroquel was discontinued, weight, height, fasting blood glucose, hemoglobin A1c, other medications. The hemoglobin A1c provides a measure of the average glucose level for the preceding 2-3 months. It would helpful to obtain these data after the patient has been on Seroquel, if he or she decides to re-challenge.

I hope this helps.

Regards,

Ron Leong

-----Original Message-----

From: Fontana, Patricia

Sent: Monday, February 03, 2003 5:30 PM

To: Leong, Ronald

Subject: re: Re-Challenge of Seroquel

Hi Ron,

I had a request from a physician who has a patient who developed DM on Seroquel. The Seroquel was subsequently stopped and the blood sugars have seemed to resolve. The doctor would like to re-start SEROQUEL since the patient did well on it and has tried a number of other medications. I have been checking the literature but at this point I have not found anything on re-challenge in this senario. Do we have any case reports in our databases in this respect or it this really going to be a case of the physician's judgement whether or not to restart the SEROQUEL in this patient? This AE has been reported.

Thanks

Patricia

Patricia Fontana B.Sc. B.Sc Phm

Medical Information Associate

phone (905) 804-4927

fax (905) 277-3556

email: patricia.fontana@astrazeneca.com

IN THE UNITED STATES DISTRICT COURT

MIDDLE DISTRICT OF FLORIDA

ORLANDO DIVISION

- - -

IN RE: SEROQUEL PRODUCTS LIABILITY LITIGATION :CASE NO. :6:06-md-01769-ACC-DAB

MDL Docket No. 1769:

- - -

November 2, 2007
VOLUME II
CONFIDENTIAL

- - -

Videotaped deposition of JAMIE A. MULLEN, M.D. taken pursuant to notice, was held at the offices of Golkow Technologies, Inc., One Liberty Place, 51st Floor, 1650 Market Street, Philadelphia, Pennsylvania, beginning at 9:05 a.m., on the above date, before Ann Marie Mitchell, a Federally Approved Certified Realtime Reporter, Registered Diplomate Reporter and Notary Public for the Commonwealth of Pennsylvania.

- - -

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you remember the movie Carrie? Was it Carrie? What was the name of the movie with the split personality?

Sybil, Sybil.

That's not what schizophrenia is, is it?

A. No, it's not.

Q. By the way, how does Seroquel work? As a fact as opposed to a theory.

A. A fact, we don't know exactly how it works.

Q. All right. You don't know exactly how Seroquel works, do you?

A. No, we don't know exactly how it works.

Q. All right. You nor anybody else in the world, do they?

A. No, we don't know exactly how it works.

Q. By the way, what does Seroquel cure?

A. It treats symptoms. It doesn't cure.

EXHIBIT A

(Plaintiffs' Response in Opposition to AstraZeneca's Motion in Limine to Exclude Evidence and Argument about Ghostwriting)

IN THE UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

- - -

IN RE: SEROQUEL PRODUCTS LIABILITY LITIGATION	CASE NO. 6:06-md-01769-ACC-DAB
MDL Docket No. 1769	

- - -

December 20, 2007
CONFIDENTIAL

- - -

Oral deposition of WAYNE MACFADDEN, M.D. taken pursuant to notice, was held at the offices of Golkow Technologies, Inc., One Liberty Place, 51st Floor, 1650 Market Street, Philadelphia, Pennsylvania, beginning at 9:01 a.m., on the above date, before Ann Marie Mitchell, a Federally Approved Certified Realtime Reporter, Registered Diplomate Reporter and Notary Public for the Commonwealth of Pennsylvania.

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Page 302

yes, it does.
BY MR. ALLEN:
Q. Does it say that above any of the other columns on this page?
A. No.
Q. Okay. Mandatory, where I come from, means it's required.
Is that your same definition of mandatory there at AstraZeneca?
MR. McCONNELL: Objection to form.
THE WITNESS: Mandatory are things that should be done, yes.
BY MR. ALLEN:
Q. Okay. We'll talk -- we are a not going to talk about all of them, but let's look at the second bullet point. It says, "In clinical trials there was no difference in mean change of random glucose measurements between Seroquel and placebo, or between Seroquel and other antipsychotics (if and when available)."
Did I read that correctly?

Page 303

A. Yes.
Q. Is that true?
MR. McCONNELL: Objection, foundation as to time.
THE WITNESS: I don't recall in the participation of this document, and I can't recall if that is an accurate statement when I was with AstraZeneca.
BY MR. ALLEN:
Q. Sir, I want to ask you, as of February the 14th, 2005, when this final version of the vocabulary was sent to you and many other people at AstraZeneca, was it true that in clinical trials there was no difference in mean change of random glucose measurements between Seroquel and placebo or between Seroquel and other antipsychotics if and when available? Was that true?
A. To the best of my recollection, there were no significant differences between Seroquel and other arms of studies.

Page 304

MR. ALLEN: Objection, nonresponsive.
We'll come back and ask that question after the break, contemplate it.
VIDEOTAPE TECHNICIAN: Sorry.
It's eight minutes after 1:00. We're going off the record. This is the end of Tape Number 2.
- - -
(A luncheon recess occurred.)
- - -
VIDEOTAPE TECHNICIAN: The time is 56 minutes after 1:00. This is the beginning of Tape Number 3, and we're back on the record.
BY MR. ALLEN:
Q. Good afternoon, Doctor. How are you?
A. Good.
Q. Scott Allen, again. We're

Page 305

back from our lunch break.
And just to refocus our attention, I put back on the board Exhibit 16, which is the vocabulary and descriptions final version dated February 14, 2005.
Are you with me?
A. I have this document, yes.
Q. Doctor, this is not the first time you have seen in your entire life the Seroquel vocabulary and descriptors documents, is it?
A. I recall there was a document like this around, but I was not familiar with the specifics of it.
Q. Well, in fact, Doctor, you -- there was one for every year, wasn't there?
A. I don't recall that.
Q. And in fact, Doctor, you're on the e-mail chain as one of the individuals who was asked to give feedback concerning the drafting of this document. True?

Page 306

A. It was requested I give -- I was one of the listed people to whom it was sent, asking for feedback, yes.
Q. Right. And the initial request for feedback came from Parexel, who you worked with on the publications. Right?
A. Evidently, Parexel was involved with organizing this document, yes.
Q. And Parexel helped prepare and in fact sometimes prepared entire manuscripts on AstraZeneca's clinical trials. True?
A. AstraZeneca -- excuse me.
Parexel would often draft manuscripts for AstraZeneca to complete.
Q. And Parexel would drafts manuscripts and then contact later authors, "authors," who would then be listed as the actual author of paper that was initially drafted by Parexel. True?
A. Parexel was often engaged in providing first drafts of manuscripts.

Page 307

Q. Yes, sir.
And then if we go --
MR. McCONNELL: Excuse me.
He didn't finish.
BY MR. ALLEN:
Q. Oh, I'm sorry.
Anything else you'd like to say?
A. These manuscripts were then circulated to authors for their comments and reviews.
Q. Okay. Now, go to Bates page 77, the last two names -- numbers, excuse me.
Just so we know what we're talking about here, this is, "Recommended Seroquel Vocabulary & Descriptors for Use in all External Communications."
Did I read that correctly?
A. Yes.
Q. And it says, "Guidance for usage: These terms were identified mainly for the context of publications."
And publications again is

Page 308

what Parexel was involved in. True?
A. That was one of their activities, yes.
Q. Yes.
Tell the jury the other activities, such as slide sets and PowerPoints, advisory committee meetings, preparing poster boards for conventions and abstracts.
Are those the other activities?
A. They would often help with development of slide sets. They would often be present and help organize advisory committees and provide minutes. They would often produce the posters that were presented by AstraZeneca at meetings.
Q. Right. Those would be external communications. Correct?
A. Yes.
Q. Okay. "Guidance for usage: These terms were identified mainly for the context of publications and should

Page 309

therefore be used in all publication activities as much as possible." And then it goes on.
Did I read that correctly?
A. Yes.
Q. Now, we got to diabetes, which is two pages back. And that if -- three pages, 81, four pages. The last two numbers are 81.
And we have mandatory vocabulary language surrounding the issue of diabetes, or at least that's what the document, the final version, says. True?
A. What's the page, please?
MR. McCONNELL: He said 81.
THE WITNESS: There's a column that's entitled "Diabetes - Mandatory vocabulary."
BY MR. ALLEN:
Q. Right.
A. And in the domain, it's listed as "Recommended."
Q. So you're with me under the column that says "Diabetes - Mandatory"

EXHIBIT B

(Plaintiffs' Response in Opposition to AstraZeneca's Motion in Limine to Exclude Evidence and Argument about Ghostwriting)

IN THE UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

- - -

IN RE: SEROQUEL	:	CASE NO.
PRODUCTS LIABILITY	:	
LITIGATION	:	6:06-md-01769-ACC-DAB
	:	
MDL Docket No. 1769:		

- - -

November 1, 2007

- - -

Videotape deposition of JAMIE A. MULLEN, M.D. held in the offices of Golkow Technologies, Inc., One Liberty Place, 51st Floor, 1650 Market Street, Philadelphia, Pennsylvania 19103 commencing at 9:07 a.m., on the above date, before Linda Rossi Rios, RPR, CCR and Notary Public.

- - -

C O N F I D E N T I A L

- - -

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Page 589

any need for it, because it was largely a project delivery and project management database. And secondly, is my understanding was that it was difficult for a layperson to use.

Q. And you were a layperson?

A. In project management, I was considered a layperson, yes.

Q. Yes.

Okay. Then we have several bullet points. Kasper, is that a Dr. Kasper?

A. Yes, it is.

Q. Sir, I've taken depositions of AstraZeneca PSS members and I've reviewed their call notes.

Have you ever reviewed call notes of an AstraZeneca sales representative at any time?

A. I don't recall that I have, no.

Q. Okay. I've seen, and we'll show at trial if need be, call notes indicating that the sales reps utilize

Page 590

the Kasper -- a Kasper reprint in their detailing activities.

Do you know anything about that?

A. I don't know about the use of any manuscript on the ISSs, by the PSSs.

Q. But you know what you do know, though, you do know that part of the purpose of getting these studies published was so that the marketing companies could utilize the studies in their marketing activities.

You know that. Right?

MR. GOODELL: Object to form.

THE WITNESS: They could be used to support their marketing activities, yes.

BY MR. ALLEN:

Q. Yes, sir. And I think you're getting close.

And you knew in your role, the jury will see your resume, they will

Page 591

get to look at your business card, you knew that part of the reason that you hired Parexel medical marketing services company and engaged in activities to get manuscripts published was in order to utilize that information in your marketing of Seroquel. True?

MR. GOODELL: Object to form.

THE WITNESS: Some of the manuscripts that were assisted by Parexel were used in marketing activities.

BY MR. ALLEN:

Q. Yes, sir.

I know they were used. And see, I'm -- I tell you, I'm kind of a student of the English language.

So you've now agreed that some of the articles that were published with the assistance of AstraZeneca were used in marketing activities. Correct?

MR. GOODELL: Object to form.

Page 592

THE WITNESS: With the assistance --

BY MR. ALLEN:

Q. Sir?

A. With the assistance of Parexel.

Q. With the assistance of Parexel.

Because you've agreed some of them have been used in marketing activities. Correct?

A. Correct.

Q. The word "plan," what's a plan?

A. A plan is an understanding of the future and how we're going to get there.

Q. Yeah, that's good.

AstraZeneca had a publication plan, did they not?

A. AstraZeneca as a whole did not have a publication plan, no.

Q. I'm sorry. Tell the jury, see, I'm here on Seroquel, and I keep on

Page 593

forgetting I've got to do a better job. Let me see if I can rephrase the question.

Did the people that were involved with AstraZeneca's product Seroquel have a publication plan for Seroquel?

MR. GOODELL: Object to the colloquy and the question.

THE WITNESS: Yes, there was a publication plan for Seroquel.

BY MR. ALLEN:

Q. That's right.

And the plan was put in place in order to help effectuate strategy that the marketing department had for Seroquel. Correct?

A. Part of the plan was to help provide data that would be used by the marketing companies.

Q. Yeah. So you were helping -- so the publication plan helped effectuate marketing strategies. Correct?

Page 594

MR. GOODELL: Object to form.

THE WITNESS: I don't know about marketing strategies. I wasn't responsible for developing them. I have no idea what fed into them.

BY MR. ALLEN:

Q. Well, the publications helped support the key messages for Seroquel. Right? Isn't that right?

A. Data from clinical trials was used to support, as it's properly done, to support messages.

Q. So just for the jury's understanding, remember things that doctors learn, one of the sources is publication in journals, in scientific and medical journals. Right? It's one of their sources?

A. And you recall, too, that I objected to that diagram.

Q. Sir, I recall your objection. And we're going to let the

Page 595

judge rule on that and that's just the way the system is?

Listen to my question.

You recall that you agreed that one of the sources of doctors' knowledge was publications in journals.

You recall agreeing to that, didn't you?

A. I don't agree to that diagram. I do agree to the fact that publication journals do provide information into their knowledge base, yes.

Q. Yes.

And now you can tell the jury that in the published literature, it was part of a publication plan to support Seroquel marketing at AstraZeneca. Correct?

MR. GOODELL: Object to form.

THE WITNESS: Again, I said before that I don't know what went into the marketing plan. I can

Page 596

say that the publication plan was developed to develop a strategy for publications. And some of those publications were used to support marketing.

BY MR. ALLEN:

Q. And the plan, as you said, a plan.

And you agree there's a publication plan for Seroquel?

A. Yes.

Q. And a plan is where we want to be in the future I think is one of the things you said as a definition. Right?

A. That's correct.

Q. And one of the parts of your plan at AstraZeneca was to have material published that would support the marketing of Seroquel. True?

A. That would support some of the messages in marketing, yes.

Q. Yes, sir. Thank you very much. Very simple. Thank you very much.

MR. GOODELL: Object to the

Page 597

colloquy.
BY MR. ALLEN:
Q. Now, going on down here it says on this Kasper deal, "RS" -- who's RS? I bet I could figure it out.
A. Rod Sayce.
Q. Rod Sayce "has received a draft of the study report from Professor Kasper and will forward to JM."
That's who?
A. That's me.
Q. So the doctors who are involved in the studies forward them to AstraZeneca for comment and thinking. Right?
A. I don't know why it was forwarded to me in this particular context. It may have been because I was a co-author. It may have been because I was one of the reviewers on that review team.
Q. Okay. So by that answer and we'll -- whether you're a co-author or not, your answer concedes that

Page 598

AstraZeneca would have, as part of its review team for published articles, people that's name would not appear on the paper.
In other words, the review team did not consist of all the authors, did it?
A. The review team did not consist of authors, just as review teams at journals do not have authors on them.
Q. Thank you, sir.
"Action," and we're going to get through this. "Action RSIPXL."
What is that? Parexel -- I can't even pronounce that word.
That's Parexel medical marketing services, but --
A. I don't know what the RSI refers to.
Q. Okay. And then action for PXL. And I think there's a bibliography or something.
But PXL we've agreed is Parexel. Right?

Page 599

A. That's correct.
Q. "Provide a data gap analysis for publications so that publication of ISSs can be prioritized."
So it looks like to me Parexel is analyzing some of the data to be utilized by authors of investigator sponsored studies; is that right?
A. No, that's not correct.
Q. What is a data gap analysis?
A. Parexel looked at not the clinical data but looked at the existing literature and determined what was needed in the literature.
Q. Okay. Thank you very much, sir.
Oh, so part of y'all's role, you at AstraZeneca along with your medical marketing services company, Parexel, helped determine what y'all felt was needed in the literature?
MR. GOODELL: Object to form.
BY MR. ALLEN:

Page 600

Q. Is that what you just said?
MR. GOODELL: Object to form.
THE WITNESS: It's not what I said.
BY MR. ALLEN:
Q. Well, I thought I heard the phrase that -- on this data gap analysis there would be an evaluation to determine what was needed in the literature.
Did I not hear that phrase?
A. You did say that -- I did say that.
Q. Yes, sir.
And so who was trying to determine what was "needed in the literature"?
A. Parexel generated a data gap analysis. I don't know what the process was for subsequently looking at that analysis, but Parexel did not determine the priorities.
Q. No. What Parexel did is what you testified to under oath.

Page 601

They helped evaluate "the gaps in the literature." Right?
A. That's correct.
Q. Okay. By the way, you know what, in all fairness to AstraZeneca, what y'all are doing here with Parexel in the medical marketing services, your competitors were doing the same thing, weren't they?
MR. GOODELL: Object to form.
BY MR. ALLEN:
Q. Sir?
A. I have no idea what the competitors are doing.
Q. I mean, Pfizer's doing it with Geodon; Bristol-Myers is doing it with Abilify; Janssen is doing it with Risperdal; and Eli Lilly is doing it with Zyprexa. Is that right?
MR. GOODELL: Object to form.
THE WITNESS: As I said before, I have no idea what the

Page 602

other companies are doing.
BY MR. ALLEN:
Q. So you have no idea.
Is your testimony under oath, your right hand, is you have no idea whether or not the competitive companies of second generation antipsychotics have publication plans and utilize outside consulting services to help author and produce and publish manuscripts in the literature? Is that your testimony?
MR. GOODELL: Object to form.
THE WITNESS: You didn't ask me that before. Are you asking me that now?
BY MR. ALLEN:
Q. Yes, sir.
A. I would imagine they do.
Q. Why would you imagine they do?
A. Because AstraZeneca has done that.

Page 603

Q. So really what the jury sees in Exhibit 29, this is just common everyday industry practice, isn't it?
MR. GOODELL: Object to form.
THE WITNESS: To look at gaps in the knowledge base and try to fill them? Yes.
BY MR. ALLEN:
Q. Sir, I'm sorry.
It's common industry practice for pharmaceutical companies to hire medical marketing services to assist them in the implementation of publication plans, to have manuscripts published in the scientific and medical literature; is that true?
MR. GOODELL: Object to form.
THE WITNESS: Again, I don't know what general practice is. AstraZeneca contracted with Parexel, not to provide medical marketing but to provide

Page 604

assistance with editorial services on the BEST team.
BY MR. ALLEN:
Q. You think the other -- do you think AstraZeneca is out there by themselves in this conduct in this regard, or do you believe or know whether or not the competitors in the pharmaceutical companies -- in pharmaceutical industries do the same thing or approximately the same thing? Do you know?
A. I don't know whether they do the same thing.
Q. Okay. You don't know.
And you're -- how long have you been employed by AstraZeneca or at Zeneca?
A. Nine years.
Q. And you have been involved and you are paid money by the pharmaceutical companies, and you can't tell us -- and you're a board certified psychiatrist. Right?

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original papers

JAMES STONE, RUTH OHLSEN, DAVID TAYLOR AND LYN PILOWSKY

Naturalistic study of the antipsychotic medication review service at the Maudsley Hospital

AIMS AND METHOD

To evaluate the effectiveness of the antipsychotic medication review service (AMRS) at the Maudsley Hospital. Patient notes were analysed from the AMRS and estimates of Global Assessment Scale (GAS) scores were made from entries in the notes. Data on hospital admissions before and during attendance at the AMRS were obtained from the trust-wide computerised patient administration system.

RESULTS

A statistically significant improvement in GAS scores was seen for patients who stayed in contact with the AMRS. Patients who did not respond to the first atypical drug often made a good response to an alternative atypical antipsychotic. Patients attending the AMRS had fewer hospital admissions than they did before attendance, although this was not statistically significant.

CLINICAL IMPLICATIONS

Although more expensive on a dose-by-dose rate, atypical antipsychotics may be cost effective by improving compliance and reducing the number of relapses and hospital admissions. Specialised services with frequent patient contact can be effective in preventing relapse and improving global function.

The antipsychotic medication review service (AMRS) is a specialised service run at the Maudsley Hospital (south London). It was developed initially as a 'test-bed' for atypical antipsychotic drugs so that expertise with these compounds could be gained in order to inform practice throughout the hospital. The AMRS has a broad remit and currently provides drug regime assessment as well as out-patient-based treatment for patients with psychosis. These patients may be partially responsive to or intolerant of typical antipsychotics. The AMRS also accepts referrals of patients with first-episode psychosis. The service aims to minimise drug polytherapy, extrapyramidal symptoms and hyperprolactinaemia while maximising effectiveness through the use of atypical antipsychotic medication as monotherapy. Adjunctive drug treatments and augmentation strategies are not used routinely in the AMRS and formal psychological or psychosocial interventions are not a regular part of treatment, although informal motivational techniques are used. Treatment in the AMRS is underpinned by its emphasis on the formation of an effective therapeutic relationship: efforts are made to share as much information as is available and patients are encouraged to take an active role in choosing their treatment. Patients unresponsive to treatment in the AMRS are referred to the local clozapine clinic.

The study was designed to compare treatment within the AMRS with that previously received by patients. The aims of the study were to verify the usefulness of atypical antipsychotics in a naturalistic setting as well as to evaluate a dedicated clinic as second-line treatment for patients who do not improve with standard out-patient care.

Method

Sample collection

The clinical notes were obtained for all patients who had been referred to the AMRS since its inception in September 1997, up to and including July 2000. The hospital's computer-based patient administration system, which provides data about number and length of treatment episodes, including admissions for all patients within the South London and Maudsley Trust, was searched to provide admission statistics for all patients referred to the AMRS from within sector.

Clinical data collection

The reason for referral, the date of the referral and the length of time seen in clinic were recorded, as was the diagnosis of each patient and whether there was concurrent drug or alcohol misuse. The medication that each patient was on before being admitted to clinic and the change in their medication while they were being seen in clinic were also noted.

Instruments

A psychiatric rater (J.S.) applied the Global Assessment Scale (GAS) to the notes as described by Dill *et al* (1989) for the first assessment in the AMRS and at monthly intervals for the first 6 months. For the second 6 months, ratings were applied at 3-monthly intervals and then 6-monthly up to 2 years. The outcome was recorded for each patient. Outcomes included recovery and referral back to local carers (for patients who made a marked recovery on the new treatment), assessment for medication review (for patients who were referred for review of medication only), continuing treatment (for patients in the clinic who made a response to medication but were still being followed up), non-compliance (with medication or with attendance) and deterioration despite compliance (including patients referred on to the clozapine clinic). The notes were evaluated retrospectively and ratings were independent of the clinical team.

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Statistics

Data were analysed for change in GAS after 1 month, 1 year and 18 months. Tests of significance were made, where appropriate, using student's *t*-test, the χ^2 test and Fisher's exact test. Software package SPSS version 8.0 was used to determine 95% CIs, to calculate significance and to provide a graphical representation of results.

Results

Patient sample

Sixty-three patients had been referred to the service since its inception. Of these, 38 were male and 25 were female; 44 were referred from within the South London and Maudsley Hospitals Trust, 14 were referred from a neighbouring hospital trust and 5 were national referrals. Five patients did not attend following referral.

Clinical characteristics

Of those who attended, the diagnosis was recorded as schizophrenia in 49 cases, with 6 cases of psychosis (unspecified) and 3 of schizoaffective disorder. The reason for referral was fairly evenly spread between treatment resistance (n=24, 41.4%), treatment intolerance (n=20, 34.5%) and first-episode psychosis (n=14, 24.1%). Nine (15.5%) patients had concurrent substance misuse.

Attendance

The mean duration of contact with the clinic was 200 days (n=58, s.d.=245). The mean frequency of attendance (including those referred for review only) was one appointment per 15.7 days of contact with the clinic (n=58, s.d.=11.7).

A total of 13/58 (22%) patients left the clinic before formal discharge. The mean time of contact with the clinic for this group was 47 days (s.d.=42.1).

Medication on referral

The antipsychotic medication regimes on referral are summarised in Fig. 1. Eighty-six per cent of patients were being treated with an antipsychotic at referral (31% on atypical antipsychotics, 41% on typical antipsychotics and 14% on polytherapy). Of those on an atypical antipsychotic at referral, eight were referred because of only having made a partial response, four were intolerant of their medication, five had a first-episode psychosis that was partially treated and one was non-compliant with medication.

Antipsychotic polytherapy

Eight (14%) patients were being treated with more than one antipsychotic at referral but after starting in the clinic and following the crossover period to atypical antipsychotics all but one were on monotherapy. This difference was statistically significant (n=58; χ^2 test, P=0.015; Fisher's exact one-tailed test, P=0.015).

Anticholinergic use

Fifteen (26%) patients were being treated with oral anticholinergics when referred to the clinic but none continued on these while in the clinic (n=58; χ^2 test, $P<0.001$).

Medication started in clinic

A total of 47/58 (81%) patients were treated with an atypical antipsychotic in the clinic. Twenty (42%) patients were started on quetiapine (mean dose 460 mg; s.d. 175.2). Eighteen (38%) were started on olanzapine (mean dose 14.4 mg, s.d. 5.72), five (11%) on sertindole (mean dose 15.8 mg, s.d. 5.22) and four (9%) on risperidone (mean dose 3 mg, s.d. 1.15).

The mean time in clinic before starting on an atypical antipsychotic (or being changed to a new atypical) was 16 days (s.d. 31.0). The mean period of time for which the two antipsychotic drugs were overlapped was 7 days (s.d. 27.3).

Switching between atypical antipsychotic drugs

Twenty-one patients were swapped from one atypical antipsychotic to another while in the AMRS. This was due either to non-response or intolerance of the first atypical tried. The outcome for these cases was that nine cases recovered allowing referral back to their home team, five cases continued in contact with the clinic with good response to the new medication, one deteriorated on the new medication and six were non-compliant with medication or clinic attendance.

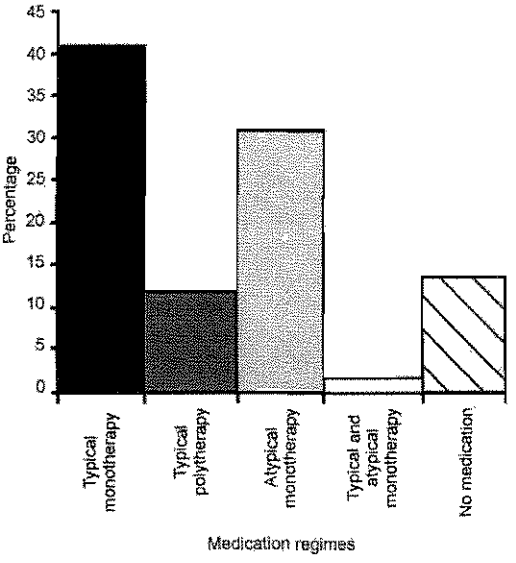

Fig. 1 Medication regimes at referral.

Patients attending clinic who did not receive an atypical antipsychotic

A total of 11/58 patients were not commenced on an atypical antipsychotic medication while attending the clinic. The majority of these (7/11) attended for the purpose of a second opinion and subsequently returned to their local teams. The other four patients discharged themselves before being started on an atypical antipsychotic.

Admission data

The patient administration system covers data on patient admissions exclusively from the South London and Maudsley Trust and so analysis of admission before and during contact with the clinic was limited to this group.

Out of 44 patients referred from South London and Maudsley, four patients did not attend the clinic and so were excluded from the analysis and a further two patients had missing data. Of the remaining group 1 of 38 patients was an in-patient for 18 days while under follow-up by the clinic. In comparison, 5 of the 38 patients were admitted (a total of 182 in-patient days) in the same period of time before their attendance at the clinic (n=38; paired sample t-test, P=0.11; Fisher's one-tailed exact test, P=0.087).

Rating scores

There was a statistically significant improvement in GAS scores. The improvement was significant after 1 month, increasing from 45 to 50 (n=45, $P<0.001$), and this improvement continued for the time that the patients were followed in the clinic. Over 6 months the average GAS score improved from 44 to 58 (n=21, $P<0.001$), and over 12 months the average GAS score improved from 41.4 to 61.2 (n=13, $P<0.001$). Even though there are limited data on patients who stayed in the clinic longer than a year, because many patients were formally discharged from the clinic by this time, the change in GAS score is statistically significant for 18 months, rising from 43 to 56 (n=7, P=0.021).

If data on the patients who self-discharged are included in the analysis of the clinic's effect on the GAS by carrying forward their last recorded GAS score (Fig. 2), the improvement is from 45.1 at time 0 to 52.9 at 6 months (n=58, $P<0.001$). When analysed separately, it is found that the group of patients who self-discharged had a mean GAS score at first contact with the clinic of 46.3 (n=13, s.d.=9.27) and that this had not changed significantly at their last contact (46.5, n=13, s.d.=10.0, P=0.874).

Outcome

Seventeen patients (27%) referred to the clinic recovered and were referred back to their own team for follow-up. Sixteen (25.4%) were non-compliant with treatment and 11 (17.5%) were still under monitoring by the clinic. Of the remaining 19 patients, 13 (20.6%) were referred for medication review only, five (8%) did not attend the clinic and one (2%) deteriorated despite full compliance with treatment (Fig. 3). Substance misuse did not have a significant effect on outcome.

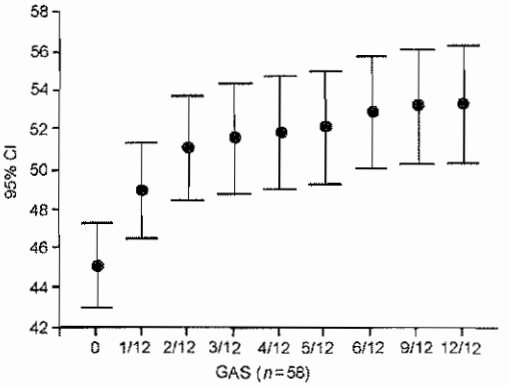

Fig. 2 Change in Global Assessment Scale (GAS) scores with time, with last observation carried forward for 12 months (n=58).

Conclusions

We have performed a retrospective audit of a novel service providing medication review and atypical antipsychotic treatment for patients with psychosis.

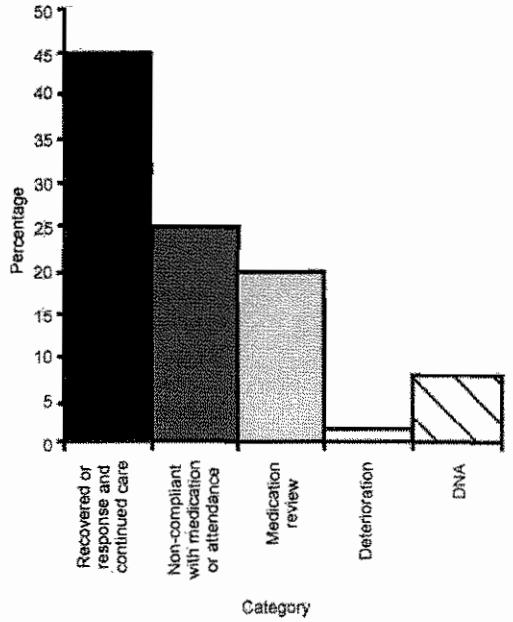

Fig. 3 Outcome showing percentage of cases falling within each category (n=58).
Recovered, marked improvement and referral back to own team; response and continued care, those patients who were still attending the clinic regularly at the time of the study; non-compliant, non-compliance with continued attendance at the clinic, as well as non-compliance with medication; medication review, those patients who attended the clinic in order to assess their medication regime to provide advice to their own team; deterioration, patients who deteriorated despite apparent compliance with treatment; DNA, patients who were referred to the service but failed to attend any appointments.

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Patients who remained in the clinic showed symptomatic improvement, as measured by the GAS. This improvement was maintained for the duration of their contact with the clinic (up to 2 years). Patients who did not respond to the first atypical drug often made a good response to an alternative atypical antipsychotic. In many cases this led to almost complete recovery, allowing referral back to their local carers.

Only one patient who was compliant with attendance and medication at the clinic failed to improve and required referral to the local clozapine clinic. This suggests that the atypical antipsychotics other than clozapine are an effective treatment for the majority of patients with psychosis, including those refractory to treatment with other typical or atypical antipsychotics. It is unclear whether improvement was due solely to the medication used or to some other effect from attendance at the AMRS. It may be that attendance at the AMRS led to increased compliance with medication, possibly through making patients feel more empowered in their choice of treatment, but further work is required to clarify this.

This study has shown that atypical antipsychotic drugs used as monotherapy are an effective treatment for psychosis in patients at various stages of illness. The use of atypicals in the AMRS allowed the discontinuation of anticholinergic medication, the use of which can have a negative effect on cognitive function (Borison, 1996; Mizusawa, 1998). Although more expensive on a dose-by-dose rate, atypical antipsychotics may be cost effective by improving compliance and reducing the number of relapses and hospital admissions. Specialised services such as the AMRS can be a feasible and effective way of maintaining improvement and preventing relapse in patients with psychosis.

A relatively high proportion of patients became non-compliant with medication or failed to attend the clinic after initial assessment. This is not a new finding for patients with psychiatric illness and is not specific to the AMRS (Killaspy *et al*, 2000). The non-compliance rate for the AMRS after initial attendance, although high (25%), compared favourably with data suggesting a 40% rate of non-attendance at follow-up in a general psychiatric clinic (Killaspy *et al*, 2000) and with drop-out rates in clinical trials of 36–50% on a variety of atypical medications (Geddes *et al*, 2000). Factors that may have led to lower drop-out rates than clinical trials or routine adult general psychiatric settings include systematic and formal assessment of patients, with high-quality dialogue between staff and patients concerning choices of medication, and the continuity of involvement of relatively senior psychiatric staff in treatment and follow-up. Both carers and patients were given time to discuss concerns over medication.

The findings of this study are in keeping with previous work, which has demonstrated the benefits of atypical antipsychotics over typical antipsychotics when used in closely controlled but less naturalistic settings (Stanniland & Taylor, 2000; Worrel *et al*, 2000). It is hoped that these data will aid further service development and will assist in defining elements of the AMRS that are transferable to standard community mental health team or depot clinic settings.

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Declaration of interest

D.T. has received unrelated consultancy fees from all manufacturers of atypical antipsychotics. L.P. has received unrelated and unrestricted charitable grants and lecture and consultancy fees from AstraZeneca, Eli Lilly, Novartis, Janssen Pharmaceuticals, Synthelabo and GlaxoSmithKline. She is also a Medical Research Council Senior Clinical Research Fellow.

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Subjects are scanned twice: after placement of nicotine patches and after placement of placebo patches. Order of nicotine/placebo patch administration is random and double blind. During scanning, subjects perform an auditory n-back task with two levels of verbal working memory load and two levels of selective attention load. To date, 10 smokers with schizophrenia and 10 smokers with no psychiatric illness have been studied. Subjects with and without schizophrenia did not differ in age, level of education, estimated IQ, reading achievement, numbers of cigarettes smoked per day, or total smoking exposure (pack-years). fMRI data show a significant interaction between diagnosis, patch condition, and working memory load. Relative to nicotine withdrawal, the presence of nicotine in plasma (active patch condition) is associated with enhanced activation of anterior cortical regions and putamen/insula under high verbal working memory load in smokers with schizophrenia. Smokers with no psychiatric illness do not show this effect. Supported by the Veterans Administration and by NIH grant M01RR00125

AN FMRI PARADIGM TO STUDY RESPONSES TO AVERSIVE STIMULI - A CENTRAL ROLE FOR LIMBIC STRIATUM

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The limbic striatum (ventral striatum in humans, the nucleus accumbens in rats) is critically involved in mediating the motivational salience of appetitive and aversive stimuli. It has been suggested that abnormalities in this system are critical to several neuropsychiatric disorders, most notably, schizophrenia and drug abuse. Several preclinical models have been developed to assess this system, conditioned approach and avoidance among them. The purpose of this study was to develop an fMRI paradigm, analogous to the preclinical models, to examine whether the ventral striatum plays a similarly important role in human motivational salience. Eleven subjects went through a paradigm based on aversive conditioning in an event-related fMRI experiment. As unconditioned stimulus (US) we used aversive electrical stimulations to the index finger where the intensity was titrated to when it was unpleasant but tolerable. Two colored circles were used as neutral stimuli. One (CS+) was paired with the US in 1/3 of the trials while the other colored circle (CS-) was never paired. Twenty-eight slices covering the whole brain were acquired in the axial plane with a GE 1.5 T scanner (TR=2.3s; TE=40ms). Data were realigned, normalized, spatially smoothed and temporally filtered. The main comparison of interest was 30 CS+ trials (in which no electrical stimulation was finally delivered, i.e. 2/3 of CS+ trials) to 30 CS- trials using a random effects analysis in SPM. The analysis showed the CS+ stimuli, even when not accompanied by electrical stimulations on every trial, caused robust activations in five clusters in limbic/paralimbic regions. The regions activated were bilateral anterior insula regions, bilateral ventral striatum and the anterior cingulate/medial frontal region. These findings fit with current theories that suggest a crucial role for the ventral striatum in conditioned motivational salience. This finding is also consistent with several animal models, most notably conditioned avoidance response (CAR), which also critically depends on ventral striatal functioning. Since CAR has a central role in preclinical testing of antipsychotics, we are now exploring whether this fMRI paradigm may serve a similar purpose in human studies.

FUNCTIONAL NEUROANATOMY OF AUDITORY SENSORY MEMORY

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One of the most consistent findings over the past decade in schizophrenia research is a reduction in the amplitude of an early auditory event-related brain potential known as mismatch negativity (MMN). The current study is part of a series of experiments aiming to elucidate the underlying mechanism of MMN reduction in schizophrenia. By means of two functional brain imaging techniques we examined 6 healthy subjects using 15O PET and 10 healthy subjects using fMRI. We measured rCBF (PET) and BOLD contrasts (fMRI) derived from the comparison of blocks of stimuli either presented as a series of standard tones alone versus blocks of rare deviant tones that were interspersed among a series of standard tones (mismatch condition) while subjects were performing a visual distraction task (PET) or were watching a silent movie (fMRI). In addition, attention effects on mismatch processing were assessed in our PET study while possible confounding effects due to scanner noise was assessed by a no tone condition in the fMRI experiment. fMRI data were also analysed by employing an event-related haemodynamic response model. In line with previous EEG source modelling studies, we found temporal lobe and prefrontal cortical activation that was associated with auditory mismatch processing. (Supported by NH&MRC Neuroimaging Consortium, Neuroscience Institute for Schizophrenia and Allied Disorders, (NISAD), University of Western Australia, Small Research Grant, and University of Essen).

EFFECTS OF QUETIAPINE IN FIRST EPISODE SCHIZOPHRENIA. COMPARISON WITH DRUG NAIVE PATIENTS AND HEALTHY CONTROLS

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Introduction We present data suggesting that treatment with the antipsychotic quetiapine in first episode schizophrenia results in an improvement in frontal cortex function. Method Seven drug naive schizophrenic subjects, eight first episode schizophrenic subjects who showed a good therapeutic response to quetiapine treatment and eight normal controls were matched for age and sex underwent a single FMRI scanning session in a 1.5T scanner. During this they completed 1) a blocked periodic overt verbal fluency task (generation of single words in response to a letter cue) 2) passed motor task (random movement of a manual joystick) 3) task involving passive auditory and visual stimulation. Results Comparing the two patient samples the quetiapine treated group exhibited significantly greater power of activation in network of areas that included the inferior frontal cortex (Broca area) and supplementary motor area ($p<0.05$). No significant differences in activation between the patient groups were seen in the passive sensory stimulation task. Despite symptomatic recovery in the quetiapine treated group activation during the two active tasks did not normalise completely compared with the healthy control group. Discussion Quetiapine selectively enhances activation during a cognitive task dependent on frontal cortex function and hence this effect is unlikely to be a general action of quetiapine on cerebral blood flow. Differences in activation between the quetiapine treated and healthy control groups may reflect cognitive

impairments that persist even after good symptomatic recovery in first episode schizophrenia.

FUNCTIONAL CONNECTIVITY OF INNER SPEECH IN SCHIZOPHRENIA

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We explored fronto-temporal connectivity using fMRI of patients and controls generating inner speech. Method The subjects were eight schizophrenic patients in remission recruited from the wards and clinics of the Maudsley Hospital, and 8 controls matched for age, sex and IQ. Diagnosis was made by clinical interview and case-note review, using DSM IV criteria. All subjects were trained to overtly say the word 'rest' once per second and once every four seconds. When they had demonstrated stability of this, they were asked to do the same covertly. Before and after the scan, their silent speech rates were monitored by asking them to tap their finger at each covert speech act. They were then scanned for 5 minutes in a 1.5T GE Signa MRI while covertly repeating the word for alternating 30 second blocks at 1Hz and 0.25Hz in an AB design, without finger tapping. The desired rate was shown to subjects on a screen visible from the scanner. Image analysis was performed using XBAM. All individual maps were then entered into a conjunction analysis that selected only those clusters that were both significant, and whose significance was not due to the effects of the patient group or control group alone. Time series for these clusters were extracted at the individual level, and averaged over the sub-groups of patients and controls. Pearson correlations were calculated between averaged time-series for supra-threshold clusters in the areas of interest. Results The conjunction activation map showed greater left inferior and medial frontal cortex, left and right superior and middle temporal gyrus, at the faster rate, compared with the slower rate, of speech generation. The left inferior frontal lobe activation was significantly correlated with the left superior temporal lobe (0.264, p=0.008) and middle temporal lobe (0.315, p=0.001) in controls. In patients, the left inferior frontal lobe was more weakly correlated with the middle temporal lobe (0.268, p=0.007), but was not correlated with the superior temporal lobe when corrected for multiple comparisons. Discussion This method allows comparison of the same activation areas, selected from patients and controls as groups. Both groups showed widespread activation of the expected areas. Though frontal/superior temporal correlation was weak in the controls, it was not significant in the patients, supporting differential fronto-temporal disconnectivity in schizophrenia.

CONTEXT-PROCESSING DEFICITS AND DECREASED PREFRONTAL CORTEX ACTIVITY: SPECIFIC ASSOCIATIONS WITH UNMEDICATED, FIRST-EPISODE SCHIZOPHRENIA AND WITH DISORGANIZATION SYMPTOMS

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The goals of the research was to examine whether (1) individuals with schizophrenia experiencing their first episode of the disorder and medication naive exhibit both performance deficits and decreased prefrontal cortex activity on a context processing task; (2) context processing deficits were unique to schizophrenia and not associated with other psychiatric disorders; and (3) context processing deficits were uniquely associated with particular symptoms. There were three participant groups: (1) first episode of schizophrenia (n = 18), (2) non-schizophrenia psychoses control (e.g., people with mood disorders, n = 12), and (3) non-psychiatric control (n = 28). During fMRI, participants completed the A-X version of the continuous performance task (A-X CPT). In the A-X CPT, on every trial, participants see a cue and a probe letter, with the only target being an X probe preceded by an A cue. Because the majority of trials consisted of an A cue followed by an X probe, responding to an X as a target becomes a prepotent response. Thus, in this task, demand for cognitive control is increased whenever the cue is not an A (i.e., B trials) because with a B cue participants need to overcome the prepotent response of responding to the X as a target. Thus, fMRI data were analyzed with the general linear model to examine whether people with schizophrenia exhibited decreased prefrontal cortex activity to B cues. The results were that individuals with schizophrenia committed more errors on BX trials than did non-psychiatric controls. In addition, in comparison with both control groups, individuals with schizophrenia exhibited decreased prefrontal cortex activity in response to B cues. Furthermore, decreased prefrontal cortex activity was associated with increased disorganization symptoms. We conclude that individuals with schizophrenia exhibited poor performance and hypofrontality in a context processing task. These deficits are present at the onset of the disorder and are not confounded by the effects of medication or attributable to the effects of psychosis in general. Importantly, the finding of hypofrontality was unique to schizophrenia and was not found in a non-schizophrenia psychiatric control group. Moreover, context processing performance was also specifically associated with disorganization symptoms. Thus, the current results provide further evidence that impaired context processing and decreased prefrontal cortex activity are important aspects of schizophrenia.

FUNCTIONAL CEREBRAL DEFICITS DURING COGNITIVE PERFORMANCE IN FIRST-EPISODE SCHIZOPHRENIA PATIENTS: A MULTI-CENTER FMRI STUDY

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Objective: In the context of this ongoing multi-center project, 44 first-episode schizophrenia patients and 44 healthy controls (matched for gender, age and parental education) were investigated by means of functional Magnetic Resonance Imaging (fMRI) while performing a modified version of the Continuous Performance Test (CPT). Phantom measurements (Siemens standard phantom) are used for quality control. Method: Subjects perform a randomized sequence of 0-back and 2-back tasks, with an intermediate baseline task (fixation). The 0-back task requires attention capacities, while the 2-back task creates a demand on working memory abilities. Group analyses

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Clinical effectiveness in first-episode patients

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Abstract

Managing patients with first-episode schizophrenia is a challenging task for psychiatrists. Early diagnosis and effective intervention are vital to achieving long-term positive clinical outcomes among first-episode patients. Although these patients are the most responsive to treatment, they are also more susceptible to adverse events. The efficacy and improved tolerability associated with the newer atypical antipsychotics means that these drugs can be used successfully in the treatment and long-term management of schizophrenia from the onset of illness. However, as well as managing the symptoms of the disease, pharmacological treatments need to meet the broader requirements of clinical effectiveness that encompass all of the outcome domains associated with schizophrenia. This article will discuss available data on atypical antipsychotics in first-episode patients and present the primary results from the FIRST (Southwark first-onset psychosis) study, which examined the use of quetiapine for the first-line management of schizophrenia as part of a specialist episode psychosis service.

Keywords: First episode; Schizophrenia; Clinical effectiveness; Antipsychotic; FIRST; Quetiapine

1. Introduction

Schizophrenia is a chronic, debilitating disorder and is regarded as the most devastating of all the mental illnesses. It is associated with significant functional impairment and patient mortality, with approximately 10% of patients with schizophrenia committing suicide (Caldwell and Gottesman, 1992). The clinical presentation, course and severity of schizophrenia are complex and this impacts significantly on the effective treatment and long-term management of patients. Early intervention at the onset of illness has been shown to be an important prognostic factor for the subsequent course of schizophrenia (Linszen et al., 1998; Linszen and Dingemans, 2002; McGlashan, 2001; Woods and McGlashan, 2002).

For first-episode patients, as with all patients diagnosed with schizophrenia, successful long-term management relies upon treatment that encompasses the six schizophrenia outcome domains: symptoms of disease, tolerability, everyday functioning, subjective well-being, family/carer burden and treatment adherence, which collectively contribute to the broader concept of clinical effectiveness. Although first-episode patients are generally the most responsive to pharmacological treatment, they frequently have difficulty accepting their diagnosis and fail to engage with their therapy, leading to treatment delay. Early intervention with assertive and effective therapy can potentially enhance the therapeutic alliance, reduce the risk of patient relapse and improve long-term morbidity (DeQuardo, 1998). In some studies, delays in initial treatment have been found to be associated with cognitive impairment, a decreased likelihood of returning to premorbid function and a less successful clinical outcome (Loebel et al., 1992).

The patient's initial experience of treatment also has a significant impact on long-term outcome and adherence.

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First-episode patients are twice as likely to be initially medicated against their will. Supporters of early intervention believe the first episode constitutes a 'critical therapeutic window' for successful care (Birchwood et al., 1998), preventing further potentially traumatic and irreparable damage to psychological, vocational and social support networks.

Even if these patients engage with their treatment regimen and agree to take prescribed medication, many first-episode patients become non-adherent to conventional antipsychotic regimens. Up to one-third of patients may not respond to treatment with conventional antipsychotics (Brenner et al., 1990) which cause many side effects, particularly extrapyramidal symptoms (EPS) such as parkinsonism, dystonia, akathisia and tardive dyskinesia (Levinson et al., 1990). In addition, among first-episode patients the incidence of relapse is high, with >80% of individuals relapsing within 5 years after initial recovery (Robinson et al., 1999). Non-adherence to medication is an important factor in this high rate of relapse.

2. Clinical effectiveness of atypical antipsychotics in first-episode patients

It has been suggested that newer atypical antipsychotic drugs are efficacious and better tolerated treatments for first-episode psychosis than conventional agents. Recent guidelines published in the UK advocate the use of atypical antipsychotic treatment in first-episode psychosis and provide specific guidance advising the continuation of antipsychotic drug therapy for up to 2 years following the onset of psychosis (NICE, 2002). However, there has been limited investigation into the clinical effectiveness of these drugs encompassing the six outcome domains in first-episode patients with schizophrenia. Several studies have highlighted the efficacy and tolerability of atypical antipsychotics (risperidone, olanzapine and quetiapine) in first-episode patients, although these have been primarily over a short-time period (Bobes et al., 2003; Emsley and on behalf of the Risperidone Working Group, 1999; Good et al., 2002; Kopala et al., 1998; Merlo et al., 2002; Montes et al., 2003; Sanger et al., 1999; Tauscher-Wisniewski et al., 2002). Unfortunately, long-term data are lacking on the use of atypical antipsychotic drugs in first-episode, newly treated psychotic patients, although a number of long-term studies are ongoing (Keefe et al., 2004; Lieberman et al., 2003).

2.1. Risperidone

A short-term study by Kopala et al. (1997) assessing the effectiveness of risperidone in 22 patients with first-episode psychosis showed that both low (2–4 mg) and high (5–8 mg) doses of risperidone were efficacious among this patient population. However, patients receiving low-dose risperidone showed significantly greater improvements in Positive and Negative Syndrome Scale (PANSS) positive, negative, general symptoms and total score, compared with patients in the high-dose risperidone group (Kopala et al., 1997). Lane et al. (2001), in a double-blind, fixed-dose, 6-week study comparing the efficacy of low-dose (3 mg/day) and high-dose (6 mg/day) risperidone in first-episode patients (n=24), reported favourable efficacy for both low and high doses of risperidone, although the high-dose group tended to display reduced tolerability to risperidone. In addition to improved PANSS scores, first-episode patients have also shown improvements in overall functioning and depressive symptoms, as measured by Global Assessment of Functioning (GAF) and Clinical Global Impression (CGI) scales, following treatment with risperidone monotherapy (Kopala et al., 1998; Yap et al., 2001). In terms of tolerability, lower doses of risperidone induced fewer EPS in first-episode patients (Emsley and on behalf of the Risperidone Working Group, 1999; Kopala et al., 1997; Lane et al., 2001), compared with patients who were treated with a high dose of risperidone, 32% of whom developed mild akathisia and parkinsonism (Kopala et al., 1997).

When compared with conventional antipsychotics such as haloperidol, risperidone has been shown to display better efficacy in patients with first-episode psychosis (Emsley and on behalf of the Risperidone Working Group, 1999). At endpoint in this double-blind study (n=183), 63% of risperidone-treated patients displayed clinical improvement compared with 56% of haloperidol-treated patients (Emsley and on behalf of the Risperidone Working Group, 1999). Risperidone was also better tolerated than haloperidol in patients, with the severity of EPS and the requirement for antiparkinsonian medication significantly lower in the risperidone group (Emsley and on behalf of the Risperidone Working Group, 1999). Long-term studies comparing the efficacy of risperidone with conventional agents have shown similar efficacy; however, a lower number of patient hospitalisations, shorter hospitalisation times, sustained symptomatic improvements and fewer drug-induced EPS have been reported in patients receiving risperidone (Gutierrez et al., 2002; Malla et al., 2001; Merlo et al., 2002).

2.2. Olanzapine

To date, four studies have evaluated the efficacy and safety of olanzapine in first-episode patients with schizophrenia (Bobes et al., 2003; Lieberman et al., 2003; Montes et al., 2003; Sanger et al., 1999). Sanger et al. (1999) examined a subgroup of first-episode patients (n=83) from a large prospective, multicentre, international study comparing olanzapine and haloperidol. A significantly higher clinical response (>40% reduction in Brief Psychiatric Rating Scale [BPRS] total score) was reported for the olanzapine-treated patients (67.2%) than for the haloperidol

group (29.2%). In addition, significantly fewer EPS were reported in the olanzapine group (Sanger et al., 1999). Similarly, in a recent study of first-episode patients (n=158) from a large prospective open trial of patients with schizophrenia, treatment with olanzapine showed a significantly higher clinical response, with significant lowering of total BPRS and CGI scores compared with conventional antipsychotic therapy. Fewer EPS were also reported with olanzapine compared with conventional antipsychotics (Bobes et al., 2003).

In an observational, naturalistic 24-week study (n=182), olanzapine produced similar improvements to risperidone and conventional antipsychotics on CGI Severity of Illness and GAF scales, although olanzapine and risperidone displayed greater quality of life improvements compared with conventional antipsychotics (Montes et al., 2003). EPS symptoms were also significantly lower in the olanzapine-treated patients than in the risperidone and conventional antipsychotic treatment groups (Montes et al., 2003). Lieberman et al. (2003), reporting the results from the 12-week acute phase of a long-term (2-year), randomised, double-blind trial, demonstrated a therapeutic advantage for olanzapine over haloperidol in first-episode patients (n=263), in terms of symptom reduction and treatment retention. Although olanzapine exhibited a lower incidence of EPS in this study, it was associated with greater weight gain (7.8 kg vs. 2.6 kg) (Lieberman et al., 2003).

2.3. Quetiapine

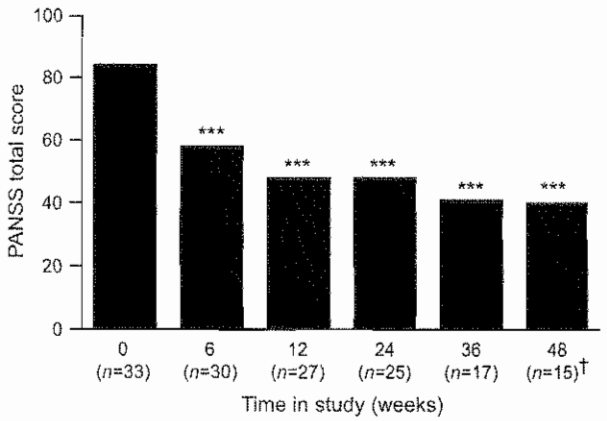
Quetiapine has demonstrated efficacy in acutely relapsed psychotic patients (Arvanitis and Miller, 1997; Borison et al., 1996; Fabre Jr. et al., 1995; King et al., 1998), with a low propensity to induce EPS and tardive dyskinesia. In a recent short-term study of patients (n=14) experiencing a first-episode of schizophrenia, statistically and clinically significant reductions in psychopathology were observed in 71% of patients following treatment with quetiapine (Tauscher-Wisniewski et al., 2002). Improvements in PANSS subscales and significant improvements in cognitive performance have also been reported in an interim analysis of a 2-year, open-label study in young patients (n=34) with first-episode psychosis treated with quetiapine (mean dose 517.9 mg/day) (Good et al., 2002).

The Southwark first-onset psychosis study (F1RST) was designed to provide a detailed audit of the use of quetiapine for first-line management of schizophrenia as part of a specialist first-episode service (outpatient mental health team based in the London Borough of Southwark), and to evaluate clinical effectiveness in a "real-world" setting by assessing most of the outcome domains of clinical effectiveness (disease symptoms, tolerability, functioning/well-being), which encompass everyday functioning and subjective well-being, and treatment adherence.

A total of 33 patients (aged ≥16 years) who had experienced a first episode of psychosis or had been out of contact with services for >6 months with an active illness of <2 years were recruited into the study (22 men, 11 women). The mean age was 29.2 (SD 9.8) years; 54.5% of patients were from ethnic minority groups. Sixty-four percent (n=21) of patients met ICD-10 diagnostic criteria for schizophrenia, 9% (n=3) for delusional disorders and 27% (n=9) for schizoaffective disorder (WHO, 1992). At 1 year, patient discontinuations were attributable to patient dropout (n=4), discharge from service (n=11) and transfer to other services (n=3). Quetiapine was the first-line drug for all participants in the study, and for 66% of patients (n=22) quetiapine was their first exposure to antipsychotic medication. Thirty-three percent of patients (n=11) had experienced brief exposure to other antipsychotics prior to the study, but were switched to quetiapine due to intolerable side effects (hyperprolactinaemia, akathisia) or lack of clinical response. Patients were prescribed quetiapine starter packs, which gradually increased the dose of quetiapine from 50 to 300 mg/day over a period of 4–8 days. Doses were then titrated according to clinical response and tolerability by the treating physicians. The mean dose of quetiapine was 360.4 (SD 148.9) mg/day at week 6 and 431.8 (SD 176.4) mg/day at week 48.

Analysis of quetiapine efficacy in patients showed statistically and clinically significant symptomatic and functional improvements over time on each of three clinical rating scales (PANSS, BPRS and Calgary Depression Scale for Schizophrenia [CDSS]). Treatment with quetiapine resulted in a significant reduction in PANSS total, positive, negative and general psychopathology scores throughout the study (all P<0.001 vs. baseline at weeks 6, 12, 24, 36 and 48) (Fig. 1). There was also a significant improvement in depressive symptoms after 6 weeks of treatment (P<0.05 vs. baseline) (Fig. 2) which was maintained over 1 year.

EPS were rated at each time point using the Simpson-Angus Scale (SAS), Barnes Akathisia Scale (BAS) and



***P<0.001 vs baseline
†Numbers do not reflect drop-out rates

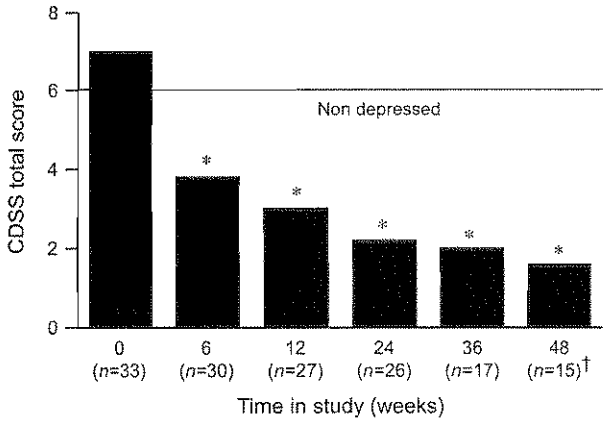
Fig. 1. Mean change in PANSS total score from baseline to weeks 6, 12, 24, 36 and 48.

Abnormal Involuntary Movement Scale (AIMS). There were negligible treatment-emergent EPS and no cases of tardive dyskinesia were seen. Although somnolence was not systematically evaluated in the study, most patients reported a degree of somnolence during the initial stages of quetiapine therapy. However, this was transient and most patients felt less sedated after approximately 3 weeks of treatment. No evidence of clinical hyperprolactinaemia was noted and there were no reports of sexual side effects or amenorrhoea.

In the present study, a statistically significant improvement in overall functioning, as measured by the GAF scale, was observed after 6 weeks and continued throughout 1 year of treatment (Fig. 3). Scores on the Schizophrenia Quality of Life Scale (SQLS), measuring subjective quality of life, indicated a statistically significant improvement in psychological well-being over 1 year of follow up. Scores on the symptoms/side-effect subscale were consistently low at baseline but still indicated an improvement over 1 year of treatment. Similarly, scores on the Drug Attitude Inventory (DAI-10) showed that there appeared to be a general trend towards improvement after 1 year of treatment intervention, suggesting a positive attitude.

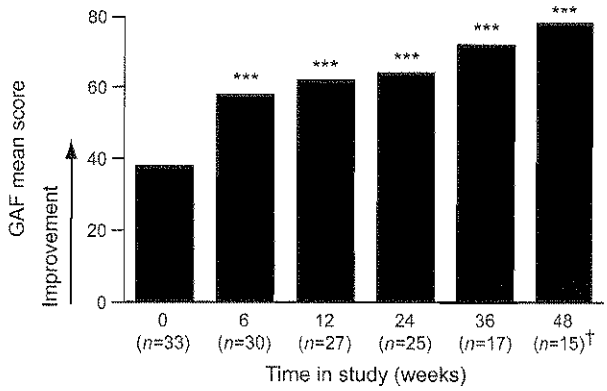
As the study progressed, an increasing number of patients were treated on an outpatient basis. Employing a mirror-image approach, a retrospective comparison between the treatment approach used during the study and a standard treatment approach used in an age- and sex-matched sample was analysed. Reduced patient readmission and higher engagement rates were observed in the FIRST patients compared with the matched patient group.

These findings support the use of quetiapine in the early treatment of first-episode psychosis and reflect previous research evidence (Tauscher-Wisniewski et al., 2002). Given the lack of research in this area, these findings will undoubtedly contribute to the evidence base for the use of better tolerated atypical antipsychotic drugs in the modern management of patients with first-episode psychosis.



*P<0.05 vs baseline
†Numbers do not reflect drop-out rates

Fig. 2. Mean change in CDSS total score from baseline to weeks 6, 12, 24, 36 and 48.



***P<0.001 vs baseline
†Numbers do not reflect drop-out rates

Fig. 3. Mean improvement in global functioning from baseline to weeks 6, 12, 24, 36 and 48.

3. Maximising clinical effectiveness in first-episode patients

3.1. Improved tolerability

There are important differences between antipsychotic medications, and careful selection of an appropriate agent with a good tolerability profile will ensure that minimal problems will arise for both patients and their carers. As described earlier, recent studies have highlighted the improved tolerability profile of atypical antipsychotics compared with conventional antipsychotics, particularly the reduced incidence of EPS in first-episode patients. However, there are differences in tolerability between atypical antipsychotics, such as risperidone when used at high doses (Kopala et al., 1997). One of the most distressing adverse events associated with antipsychotic medication is weight gain, particularly for women. Preventing weight gain in first-episode patients may have significant short- and long-term benefits in terms of minimising morbidity, mortality and the economic impact of obesity (Fontaine et al., 2001). This is important as previous research has shown that standard psychosocial intervention has little impact in patients who are already obese (Ohlsen et al., 2003). Weight gain has been reported in first-episode patients treated with risperidone (Gutierrez et al., 2002; Merlo et al., 2002) and olanzapine (Lieberman et al., 2003; Montes et al., 2003; Sanger et al., 1999). In the 6-week study by Sanger et al. (1999), a significant mean weight increase of 4.1 kg ($P<0.001$) was recorded for patients treated with olanzapine compared with a mean weight increase of 0.5 kg for haloperidol-treated individuals. Similarly, Lieberman et al. (2003) reported a mean weight increase of more than 7.0 kg in first-episode patients treated with olanzapine compared

with a 2.6 kg increase for haloperidol-treated patients ($P<0.001$) during the 12-week acute phase of a long-term study. In the olanzapine group, 61.5% of the patients had a >7% increase in their body weight from baseline, compared with 22.7% of haloperidol-treated patients ($P<0.001$) (Lieberman et al., 2003). Other non-EPS effects, which patients can find distressing, have also been reported following treatment with conventional and atypical antipsychotics. Increased prolactin levels were significantly greater in patients with first-episode psychosis treated with haloperidol compared with those treated with olanzapine (Sanger et al., 1999). Diminished sexual desire and amenorrhoea have also been reported in first-episode patients following treatment with risperidone (Gutierrez et al., 2002; Merlo et al., 2002).

Patients and their carers must be informed of any potential side effects associated with the prescribed medication as this can improve treatment adherence. However, tolerability is only one factor affecting adherence to medication. Other factors, such as poor insight into the disease, need further investigation in this patient group.

3.2. Dosing

In order to ensure an atypical agent is clinically effective, it is important that dosing is adequate. There is a perception that with some atypical antipsychotics the dose used in first-episode patients should be lower than that used in patients with chronic schizophrenia (Emsley and on behalf of the Risperidone Working Group, 1999). In the FIRST study, few tolerability problems associated with the initiation of quetiapine treatment were seen; transient sedation was the only adverse event observed. However, studies examining the efficacy of risperidone in first-episode patients highlighted increased tolerability problems particularly in relation to EPS, that were associated with higher doses of this agent (Emsley and on behalf of the Risperidone Working Group, 1999; Kopala et al., 1997). Quetiapine was initiated up to 300 mg/day within the first week of the FIRST study and the dose was increased over the first 4–6 weeks. Results from this study indicate that the lower dosage requirements observed previously in this patient group may be drug specific. Therefore, drugs that cause dose-dependent EPS, such as risperidone and olanzapine, may be more problematic in first-episode patients and should be investigated further.

3.3. Improving adherence to medication

3.3.1. Treatment adherence

Many first-episode patients hold the view that they have already been treated and therefore do not require further treatment, and that they would not become ill again. Continued treatment adherence is crucial for achieving improved patient outcomes in first-episode patients, particularly when approximately 40% of patients with schizophrenia fail to adhere to their prescribed medication (MacEwan, 1993). Currently, few data are available on adherence rates in first-episode patients treated with atypical antipsychotics; however, a recent study reported that almost 60% of patients ($n=186$) were non-adherent or inadequately adherent after 1 year (Coldham et al., 2002). Despite non-adherence to medication, there is clear evidence for an enhanced treatment alliance as more than 80% of patients were still engaged with the service and were willing to return as soon as 'warning signs', determined collaboratively with patients, appeared. Lieberman et al. (2003) have reported that significantly more patients treated with olanzapine remained in their study compared with patients treated with haloperidol. The authors suggested that as atypical drugs are associated with better long-term adherence, there is a potentially lower risk of symptomatic recurrence, as occurs in patients with chronic disorders.

Developing a therapeutic alliance is integral to promoting adherence and identifying and understanding patient needs and treatment expectations. An equally important component of this alliance is improving the patient's own understanding and acceptance of their illness and the need for adherence to treatment.

3.3.2. Positive attitude to treatment

In a retrospective study by Malla et al. (2001), significant improvements in terms of reduced length of hospitalisation, total number of days spent in hospital subsequent to first admission, number of admissions per year and days spent in the hospital as a proportion of total time in treatment were seen in first-episode patients treated with risperidone compared with patients receiving conventional antipsychotics. In the FIRST study, patients recruited into the FIRST study strongly identified with the study team's approach, goals and philosophies. Interestingly, patients continually emphasised the team's unique and positive approach compared with other treatments of which they were aware. This is reflected by the higher rate of engagement and reduced patient readmission observed compared with similar patients receiving standard treatment.

3.3.3. Family attitudes

Family attitudes can have a significant impact in first-episode patients. Some family members will be devastated by the diagnosis, while others may underestimate the illness severity and requirement for long-term treatment. Although gaining the family or carer view of patient progress would be beneficial, the practicalities of getting carers and family members to fill in rating scales are often difficult and frequently impossible. It is important to educate both the patient and carer about the disease, treatment regimen, tolerability issues and potential signs of relapse. Clear and effective communication between all parties plays a vital role in improving and maintaining treatment adherence.

3.3.4. Continuity of care

The organisation of psychiatric services is also essential for delivering clinically effective treatment in first-episode patients. Continuity of care is important and problems may occur when patients are transferred from an inpatient to an outpatient setting. In addition, more emphasis should be put on successfully reintegrating first-episode patients into their workplace or school and into the wider community. Usually only 15–30% of patients achieve this vocational reintegration so, from an employment perspective, treatment programmes that do not include a specific focus for retraining continue to be less successful (Dickson et al., 2001; Turgay et al., 2002). Including a job coach in the therapeutic alliance may represent one solution to this issue.

4. Conclusions

It is now accepted that patients with schizophrenia and other related psychotic disorders are more responsive to treatment in the early stages of illness. Consequently, the treatment of patients experiencing their first psychotic episode is of critical importance. The longer patients experience symptoms, the more likely that they are to develop persistent cognitive and functional impairment. Although first-episode patients are the most responsive to treatment, they are also the most susceptible to adverse events.

Clinical evidence to date suggests that the atypical antipsychotics (quetiapine, olanzapine and risperidone) are effective treatments in first-episode schizophrenia, with statistically and clinically significant symptomatic and functional improvement being sustained throughout treatment. Improvements are also seen in patients' quality of life, with a reduced or negligible incidence of side effects. Further long-term comparative studies in first-episode patients are needed. However, as well as managing the symptoms of disease, pharmacological treatments need to meet the broader requirements of clinical effectiveness that encompass all of the outcome domains associated with schizophrenia. Rather than giving such prominence to the symptoms traditionally assessed in clinical trials, subjective measures of improvement in first-episode patients should be compared across the different atypical antipsychotics. Whether patients actually want to take their medication should also be considered. Evidence from dedicated early intervention services, such as the F1RST study using quetiapine, support the notion that by addressing issues such as adherence and providing flexibility in contacts with patients and carers, high engagement rates and low hospitalisation rates can be successfully achieved.

Overall, the important issues for achieving clinical effectiveness in first-episode psychosis are a positive treatment experience resulting in maintenance of recovery and relapse prevention, good tolerability, education of the family, continuity of care and reintegration.

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Cortical Effects of Quetiapine in First-Episode Schizophrenia: A Preliminary Functional Magnetic Resonance Imaging Study

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Background: *Quetiapine improves both psychotic symptoms and cognitive function in schizophrenia. The neural basis of these actions is poorly understood.*

Methods: *Three subject groups underwent a single functional magnetic resonance imaging (fMRI) session: drug-naive (n = 7) and quetiapine-treated samples of patients with schizophrenia (n = 8) and a healthy control group (n = 8). The fMRI session included an overt verbal fluency task and a passive auditory stimulation task.*

Results: *In the verbal fluency task, there was significantly increased activation in the left inferior frontal cortex in the quetiapine-treated patients and the healthy control sample compared with the drug-naive sample. During auditory stimulation, the healthy control group and stably treated group produced significantly greater activation in the superior temporal gyrus than the drug-naive sample.*

Conclusions: *Quetiapine treatment is associated with altered blood oxygen level–dependent responses in both the prefrontal and temporal cortex that cannot be accounted for by improved task performance subsequent to drug treatment.*

Key Words: Antipsychotic, first episode, fMRI, schizophrenia, verbal fluency

Quetiapine is a novel, atypical antipsychotic drug, with a broad spectrum of in vitro receptor affinity similar to that of clozapine, although with lower absolute affinities for most important receptor subtypes (Goldstein 1995). Preclinical animal studies show that quetiapine has a greater effect on tests associated with limbic function, such as conditioned avoidance, and a greater physiologic effect on ventral tegmental area dopamine neurons. It also has a low potential to produce extrapyramidal side effects (Goldstein 1995). The functional consequences of this neuropharmacologic profile at the neuronal level are unclear. Functional magnetic resonance imaging (fMRI) techniques now permit assessment of brain activity in living subjects by mapping the blood oxygen level–dependent (BOLD) effect consequent on oxygen extraction from hemoglobin by active neurons.

In addition to its antipsychotic effect, quetiapine appears to improve cognitive functions including verbal fluency (Velligan et al 2003). The neural basis for these actions has not been determined. Because cognitive function is an important predictor of overall functional outcome in schizophrenia (Green 1996), mapping the neuronal response to the drug may help provide a neurobiological basis for these effects and an important surrogate marker of the effectiveness of antipsychotic drugs.

Verbal fluency is robustly impaired in schizophrenia. Functional imaging studies have reported reduced left prefrontal cortex activation in unmedicated and medicated schizophrenic patients compared with healthy control subjects (Curtis et al 1998; Yurgelen-Todd et al 1996). Quetiapine, in contrast to other antipsychotic drugs, may improve this aspect of cognition (Purdon et al 2000; Velligan et al 2003).

We have used fMRI to test the hypothesis that treatment with the atypical antipsychotic drug quetiapine results in a normalization of the BOLD response to a verbal fluency paradigm in frontal cortical areas previously linked to this task (Curtis et al 1998; Yurgelen-Todd et al 1996).

Functional imaging studies of prefrontal cortex function are greatly dependent on task performance (Manoach 2003). For this reason, we decided to use an additional task, auditory stimulation, that is less reliant on task performance and for which deficits in activation are well documented in schizophrenia (Braus et al 2002; Woodruff et al 1997).

Methods and Materials

Ethical approval for the study from the ethical committee of the South London and Maudsley NHS Trust, London, was obtained before the start of the investigation. Subjects were recruited from patients and staff within the South London and Maudsley NHS Trust. After a full explanation of the aims of the study and before inclusion in it, all subjects provided written informed consent.

The patients were selected from a cohort of subjects recruited by a specialist service dealing with first-episode psychosis. All patients recruited to this service were offered treatment with quetiapine as a first-line antipsychotic. None of the patients scanned when drug-naive was included in the quetiapine-treated sample. Initial clinical diagnosis was made using DSM-IV and a diagnosis of schizophrenia confirmed 6 months later. The quetiapine-treated patients exhibited no significant motor side effects at the time of scanning as measured by standard rating scales for extrapyramidal side effects and akathisia (Barnes 1989; Simpson and Angus 1970).

The following inclusion and exclusion criteria were set for the study subjects.

General (for All Groups)

Inclusion Criteria. Capacity to give written informed consent, cooperate with the scanning procedure and perform the

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study tasks; right-handedness as measured by the Annett handedness scale (Annett 1970).

Exclusion Criteria. A history of organic neurologic illness or clinically significant substance abuse; any general contraindications for MRI examination.

Drug-Naive Sample

Inclusion Criteria. Diagnosis of schizophrenia by DSM-IV criteria reconfirmed after 6 months.

Exclusion Criteria. Previous exposure to antipsychotic treatment at any time before initial presentation.

Drug-Treated Sample

Inclusion Criteria. Diagnosis of schizophrenia by DSM-IV criteria; score on the Positive and Negative Syndrome Scale (PANSS) less than 50 to indicate low level of active symptoms; no significant change in symptoms (i.e., <10% difference) for at least 1 month before scan procedure (assessed by trained raters using a well-validated measure of schizophrenic symptomatology; Kay et al 1987); on quetiapine monotherapy for at least 3 months with no change in dose for at least 6 weeks.

After application of these criteria, seven drug-naive subjects, eight stably treated patients on quetiapine, and seven healthy control subjects participated in the study.

Cognitive Tasks

Verbal Fluency. The task was a phonemically cued word generation task, designed for use in functional imaging studies (Abrahams et al 2003). This task has a slow rate of word presentation that appears to be important in patients likely to perform poorly in standard tests of verbal fluency (Abrahams et al 1996). The paradigm used a blocked periodic design. Written and verbal instructions were given to each subject before entering the scanner, and the instructions were repeated when each individual was inside the scanner. Subjects were asked to respond to visual cues presented on a computer screen. The active task involved the overt articulation of a word in response to a single letter. Ten presentations of each letter were given, after each of which the subject was asked to speak a single word aloud. A compressed image sequence was employed to avoid confounds due to head motion during speech production (Amaro et al 2002). The control task involved repetition of the word "REST" displayed on the screen. Subjects were given 5 cycles of 10 presentations of the word REST followed by 10 presentations of a given letter (in this study, the letters used were T, S, L, C, and P). Letters were presented every 6 sec and appeared on the screen for 2 sec. The total experimental run time was 10 min.

Passive Auditory Stimulation. This task involved a blocked periodic AB design. Subjects were presented with passive auditory stimulation that consisted of a list of neutral words spoken through headphones (A) alternated with silence (B). In this auditory task, there were 8 cycles with each lasting 16 sec. Subjects were instructed to remain alert with eyes open but to make no response to either task. This auditory task has previously been well described (Brammer et al 1997; Bullmore et al 1996).

fMRI Scanning

Imaging Parameters. Gradient echo echoplanar MRI data were acquired with a 1.5-T General Electric MR system using a standard quadrature head coil. Head movement was minimized by positioning the subject's head between cushioned supports. T_2*-weighted images depicting BOLD contrast were acquired at each of 16 near-axial 7-mm-thick planes parallel to the anterior–posterior commissural (AC-PC) line (.7 mm interslice gap, echo time [TE] = 40 msec, flip angle 90°). In the verbal fluency task, 100 images were collected (repetition time [TR] = 2 sec). In the auditory–visual stimulation task 144 images were collected (TR = 2 seconds).

An inversion recovery echoplanar imaging (EPI) data set was also acquired to facilitate registration of each individual's fMRI data set to Talairach space (Talairach and Tournoux 1988). This comprised 43 near-axial 3-mm slices (.3-mm gap), which were acquired parallel to the AC-PC line (TE = 73 msec, inversion time [TI] = 180 msec, TR = 12 sec).

Data Analysis

Individual and Group Functional MRI Analysis. Three-dimensional realignment of each image volume was first carried out to correct for head movement during the course of the experiment using a well-validated methodology (Bullmore et al 1999).

The data at each intracerebral voxel were analyzed to detect significant correlations between and the experimental paradigm. This was achieved by convolving the experimental paradigm with two gamma variate functions chosen to model hemodynamic delays of 4 and 8 sec. A weighted sum of these two convolutions will encompass delays in the likely physiologic range of 4- to 8-sec design (Friston et al 1998). Following computation of the best (least-squares) fit of the weighted sum of the two convolutions to the time series at each voxel, a goodness-of-fit statistic was computed (the ratio of the sums of squares due to the model fit and the residuals, or SSQ ratio). Significant values of this statistic were identified by comparison of observed values of SSQ ratio with a null distribution computed by repeating the fitting procedure 10 times at each voxel after wavelet resampling of the data to destroy the relationship between the experimental stimuli and responses (Bullmore et al 2001). Combining the resulting data across all voxels to produce a large distribution (typically 150,000–200,000 values) of the SSQ ratio under the null hypothesis. The critical value of SSQ ratio for any desired type I error level can easily be obtained from this null distribution and used to identify activated voxels at that level of significance.

To facilitate group analysis, the voxelwise SSQ ratios calculated for each subject from the observed data and following wavelet resampling were transformed into the standard space of Talairach and Tournoux (1988) as described previously (Brammer et al 1997). Group activation maps at any desired type I error level were once again obtained by comparing observed median SSQ ratio values at each voxel with the null distribution of median SSQ ratio values computed from the Talairach transformed wavelet resampled SSQ ratio data. Signal-to-noise ratio was improved by smoothing both the observed and wavelet resampled SSQ ratio with a Gaussian filter (full width at half maximum, 7.2 mm).

Group Contrast Analyses

Differences between group responses (H) were inferred at each voxel by regression of the general linear model (GLM), $F = a_0 + a_1H + a_2X + e$, where H codes the individuals for group, X is a covariate (when included), and e is the residual error. Maps of the standardized coefficient (effect size), a_1^*, were tested for significance against a two-tailed distribution generated by repeated randomization of H, representing the null hypothesis of no difference between groups. To improve sensitivity, spatial information was introduced by thresholding the maps of a_1^* such

Table 1. Demographic Data on Schizophrenic Subjects Included in Study

	Age	Gender	PANSS Rating	Quetiapine Dose	Treatment Duration (months)
Drug-Naive					
1	18	m	114		
2	22	m	76		
3	27	m	81		
4	21	m	45		
5	53	f	81		
6	33	m	63		
7	25	m	94		
Quetiapine Treated					
1	21	m	30	450	5
2	23	f	36	200	4
3	38	m	43	400	3
4	22	f	36	300	4
5	21	m	47	500	6
6	38	m	30	300	12
7	24	m	46	400	6

PANSS, Positive and Negative Syndrome Scale.

that only voxels passing a set voxelwise p value (see Results) were retained and contiguous suprathreshold voxels aggregated into three-dimensional clusters. The sum of a_i^* for each cluster was then tested for significance against the identically derived randomization distribution (Bullmore et al 1999). The voxel- and clusterwise type I error rates were set to .05 and .01, respectively. At these levels, the expectation of false positive clusters is <1.

Results

Subject Sample

The drug-naive schizophrenic patients (6 men, 1 woman) had a mean age of 28.4 years (± SD 11.9; Table 1). The quetiapine-treated schizophrenic patients (5 men, 2 women) had a mean age of 26.7 years (SD .8). There was no significant age difference between the patient groups. The treated patients had received quetiapine for an average of 5.7 months (± SD 3 months) at a mean daily dose of 364 mg (± SD 103 mg). Patients were receiving no other antipsychotic treatment. Four of the patients had never received any previous antipsychotic treatment. Two patients had received short courses (less than 3 months) of a single antipsychotic. One patient had previously received a depot antipsychotic (haloperidol, 50 mg, 4 times/week) for 2 years. This patient had been on quetiapine monotherapy for more than 2 years at time of study.

Clinical ratings were performed (HMJ) using the PANSS. The drug-naive sample had a mean score of 79.1 (± SD 22, range 45–114). Only one patient did not exhibit clear positive symptomatology at the time of fMRI scanning; however, this individual was subsequently hospitalized for 8 months during which time it emerged that he had been experiencing positive symptoms throughout his illness. This information was not offered at the initial interview. The stably treated group were chosen to have a low level of current symptoms. They had a mean PANSS total score of 38.2 (± SD 7.1, range 30–47). An independent t test analysis demonstrated the difference in mean PANSS ratings between the patient groups to be significantly different ($p < .001$).

The control group comprised 6 men and 2 women, with a mean age of 27.2 years (± SD 3.7 years).

Verbal Fluency

Each subject group was able to perform the task to an adequate standard. During the task, subjects were asked to produce a maximum of 48 words. The mean number of missed words in drug-naive (3.87) and the quetiapine-treated (4.0) groups was not significantly different ($p = .91$). The mean number of errors in the normal control group was .87 errors which was significantly less than either the two patient samples ($p < .05$).

For each subject group, a group activation map was computed. These maps showed activation during the active task in similar brain regions. These included the left inferior frontal cortex (Brodmann area 44), the left and right premotor cortex/supplementary area (Brodmann area 6), left dorsolateral prefrontal cortex (Brodmann area 9), and left medial frontal lobe (Brodmann area 32). These regions are highly consistent with previous findings (Abrahams et al 2003; Curtis et al 1998).

Comparison of Three Subject Groups

The healthy control group and the stably treated group demonstrated significantly greater activation in the left inferior frontal cortex (Brodmann area 44) than the drug-naive group (see Table 2 and Figure 1). The stably treated patient group demonstrated significantly lower activation in the left orbitofrontal cortex (Brodmann area 11) than either of the other subject groups.

Auditory Stimulation

All subject groups activated a similar group of brain regions, including the right and left superior temporal gyrus (STG; Brodmann area 22) and right and left middle temporal cortex (Brodmann area 21), as would be expected from the task (Table 3). Both the normal volunteer group and quetiapine-treated group demonstrated significantly greater activation in right and left STG compared with the drug-naive subjects. There were also differences between normal volunteers and treated patients in the levels of activation found in other regions of the temporal cortex.

Table 2. Significant Differences in Group Activation During Verbal Fluency Task Across Three Subject Groups

Brain Region (Brodmann Area)	Cluster Size	Talaraich Coordinates			Significant Group Difference
		x	y	z	
Left Inferior Frontal Cortex (44)	24	−43	4	26	Stably treated group > drug-naive sample
Left Inferior Frontal Cortex (44)	45	−40	19	31	Normal volunteers > drug-naive sample
Left Dorsolateral Prefrontal Cortex (9)	59	−40	11	42	Normal volunteers > drug-naive sample
Left Orbitofrontal Cortex (11)	63	−14	56	−18	Normal volunteers and drug-naive subjects > quetiapine-treated sample

Table 3. Significant Differences in Group Activation During Auditory Stimulation Across Three Subject Groups

Brain Region (Brodmann area)	Cluster Size	Talaraich Coordinates			Significant Group Difference
		y	z	x	
Right Superior Temporal Gyrus (22)	31	51	−33	9	Normal volunteers > drug-naive sample
Right Superior Temporal Gyrus (22)	41	58	−11	4	Quetiapine-treated sample > drug-naive sample
Right Middle Temporal Gyrus (21)	47	54	−7	−2	Normal volunteers > drug-naive sample
Right Middle Temporal Gyrus (21)	41	58	−7	−2	Quetiapine-treated sample > drug-naive subjects

Discussion

To our knowledge this is the first study that has used fMRI to evaluate the effects of quetiapine treatment in vivo in schizophrenia. The use of a drug-naive schizophrenic comparator is rare in the imaging literature and is an important advantage of this study in determining disease- or medication-specific neural responses. Quetiapine-treated patients showed increased left inferior frontal cortex activation during a verbal fluency task and increased superior temporal gyrus activation during passive auditory stimulation compared with a matched drug-naive schizophrenic patient sample. Task-specific deficits in cortical activation have previously been reported in schizophrenic subjects (Curtis et al 1998; Woodruff et al 1997; Yurgelun-Todd et al 1996), but the extent to which such deficits may be "normalized" by effective antipsychotic treatment is uncertain. Although this study did not demonstrate significant differences in left inferior cortex activation between the drug-treated and control groups, this may reflect reduced statistical power of the relatively small sample sizes in the study. The data presented here are, however, consistent with both the antipsychotic efficacy and the improvement in verbal fluency performance evident during quetiapine treatment (Velligan et al 2003).

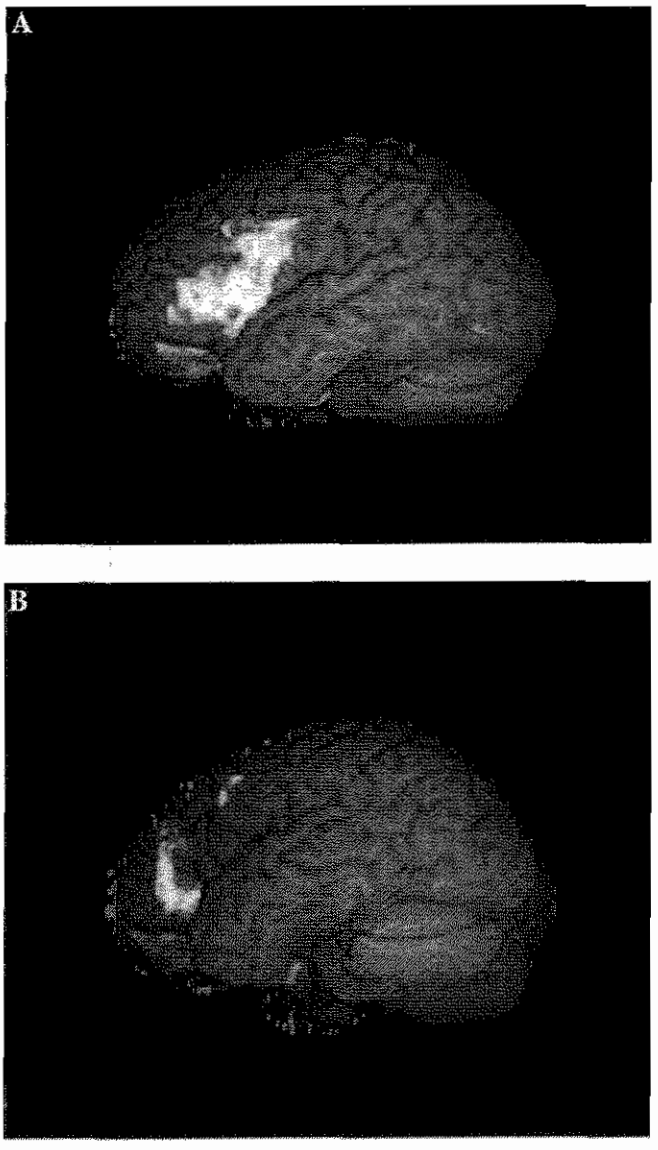

Figure 1. Increased activation in left inferior frontal cortex during verbal task in **(A)** quetiapine-treated (n = 7) compared with **(B)** drug-naive (n = 7) schizophrenic subjects samples.

Methodological Considerations

This study did not use a prospective design to scan the same schizophrenic subjects before and after quetiapine treatment. We were thus unable to assess the functional consequences of the increased BOLD response associated directly with quetiapine treatment. The patients were, however, closely matched in terms of age and gender. Perhaps more important, the subjects in stably treated patient sample were all relatively newly diagnosed with schizophrenia, providing a good match of the patient groups in terms of illness duration.

The reported reduction in orbitofrontal activation during verbal fluency in quetiapine-treated patients should also be treated with caution as representing altered neuronal activity. It is plausible that this reflects a vascular effect of quetiapine treatment. This change is in the opposite direction from that observed in the healthy control sample, and there is no difference in activation in this region between the drug-naive and healthy control groups.

Effects of Quetiapine on Cortical Activation

Verbal fluency is robustly associated with activation of the left inferior frontal cortex during functional imaging studies (Phelps et al 1997). Although there is some uncertainty about the anatomic location of verbal fluency this region is consistently implicated in letter fluency paradigms such as that examined in the current study (Mummery et al 1996). Reduced left inferior frontal cortex activation has been reported in schizophrenic subjects (Curtis et al 1998; Yurgelun-Todd et al 1996). Our finding of increased left inferior frontal gyrus activation in quetiapine-treated subjects provides a plausible neurobiological explanation for recent clinical data that quetiapine, in contrast to older antipsychotic drugs, improves performance on verbal fluency in schizophrenia (Velligan et al 2003).

Reduced left temporal cortex activation during auditory processing tasks in acutely psychotic subjects is well documented (Braus et al 2002; Woodruff et al 1997). There are, however, few reports of the effects of antipsychotic drug treatment on activation in such a task. Here we show that quetiapine treatment is associated with a partial "normalization" of this reduced activa-

tion. It has been suggested (Frith et al 1995) that subtle differences in task performance might underlie changes in activation such as that seen in this study; however, the auditory stimulation task appears less susceptible to such an effect. It was designed to require minimal cognitive effort and may be well suited for studies in acutely ill subjects.

Pharmacologic studies are designed primarily to assess drug action rather than to elucidate the neural mechanisms of cognitive function. There is a significant overlap between cognitive and psychotic symptoms in schizophrenia, and antipsychotic drugs appear to improve both. It may thus be more helpful to consider the reported results as possible surrogate markers predicting clinical improvement rather than relating to specific cognitive processes.

It is now fairly well established that there is a neural basis to the BOLD signal in fMRI (Logothetis 2002), although possible neurovascular confounds may occur with some drug treatments. Changes in activation associated with antipsychotic drug treatment may reflect direct effects of these drugs on synaptogenesis and neural plasticity, thought to underlie the longer-lived changes in symptoms consequent on antipsychotic treatment (Konradi and Heckers 2001).

This study demonstrates the feasibility in using fMRI to assess the effects of antipsychotic treatment in vivo. Our results suggest that quetiapine treatment in schizophrenia may provoke significant improvements in prefrontal and temporal cortical neuronal activity. This methodology could be used more generally to assess in vivo effects of existing and novel antipsychotic drugs. If these findings represent a consistent surrogate marker associated with antipsychotic efficacy, the fMRI approach would make a useful tool for assessing preclinical efficacy of promising novel compounds with good antipsychotic potential and few side effects.

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Id : i.m.c22c37e56740fa1f408e63eba6fa447b
CN : S339-E01167234
Date : Tuesday, December 4, 2007 1:39:49 PM GMT
From : "Rak, Ihor W" <ihor.rak@astrazeneca.com>
To : "Goldstein, Jeffrey M" <jeffrey.goldstein@astrazeneca.com>
Subject : Re: information
Custodians : Goldstein, Jeffrey

From: Rak, Ihor W

Sent: Tuesday, December 04, 2007 1:40 PM

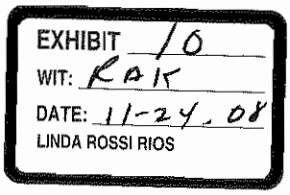
To: Goldstein, Jeffrey M

Subject: Re: information

Jeff

Thanks for reaching out to me - I will look into this and we should discuss. When is your must decide date so I know how much time I have?

Ihor



Sent from my BlackBerry Wireless Handheld

----- Original Message -----

From: Goldstein, Jeffrey M

To: Rak, Ihor W

Sent: Mon Dec 03 19:49:04 2007

Subject: information

Dear Ihor,

I need to make a very difficult decision over the next few weeks and I wanted to reach out to you for advice. A few weeks ago we chatted briefly and I told you that I was anticipating a promotion to Senior Director but things have not progressed as fast as I had hoped, and the recent reorganization may have removed this from peoples radar screens. I was counting on this promotion to bring me to Band 7 and allow the cap on my salary to be removed because over the past three years I have not received a raise. This was because my salary in relation to the MRP for Band 6 is above the accepted limits. Although I have received a lump sum each year in lieu of a raise, it has not figured into my bonus or pension. You can imagine how frustrated I am in view of my excellent performance reviews. I recently did some calculations and if I were to retire at the end of this year the company would have to add 6 weeks of banked vacation plus an additional week that I was allowed to carryover into 2008. That would make 2007 my best grossing year (assuming my bonus is on par with previous years) and my pension would increase. That is a very attractive option for me. However, I am hesitant to act on this urge as I feel I still have a lot to offer this company and my passion for Seroquel has far from ended. And, there is a lot going on with Seroquel under the pretense of science that needs serious review. So to be very frank with you and the reason for this email is to ask the following questions - am I being considered for promotion to Senior Director, when will this likely happen, and will my salary increase appropriately? Sorry if I am putting you in a difficult situation but I need to make a decision very soon and you are the only one who can provide me with the answers to those questions.

I will be traveling this week to Budapest to make 2 Seroquel presentations at IFMAD, and then on vacation for the rest of the year although I am giving up several vacation days to handle urgent matters not the least of which is to continue to meet with the attorneys who are preparing me for my January deposition. I regularly check my email when home (a habit I cannot seem to break) so except for my time in Budapest I will look for a response from you. I would also welcome some time with you to discuss this further if you think that would be best and would happily give up some vacation time to meet at your convenience.

I truly hope that AZ will reward and recognize me with a promotion but more importantly give me the opportunity to take on a more senior leadership role. I truly believe our group needs a senior person to step in and question the science being presented at several levels. I look forward to hearing back from you.

Sincerely,

Jeff

From: Furlong, Stephen T
Sent: Tuesday, October 12, 2004 8:40 AM
To: Rak, Ihor W
Cc: Keith, Rich A; Allen, Robert (R&D TA Pain)
Subject: FW: diabetes/atypicals and metabalomics

Hi Ihor,
Rob Allen suggested that I share with you the attached proposal for a pilot metabalomic study and request that the EPT provide funding. The results from the study have the potential for helping us identify new biochemical biomarkers for schizophrenia useful for understanding the relationship between atypical antipsychotics and diabetes, and possibly, insight that would help new target identification. This proposal is brief so I would be happy to provide more details or explanation.
Thanks
Steve

-----Original Message-----
From: Allen, Robert (R&D TA Pain)
Sent: Tuesday, October 12, 2004 7:35 AM
To: Furlong, Stephen T; Brecher, Martin
Cc: Smith, Mark A (Exp Med)
Subject: RE: diabetes/atypicals and metabalomics

Steve,

Apolgies for delay in getting back on this. This is a sound and reasonable proposal. Suggest you also share directly with Ihor and EPT with request for $$$ support. Would not wait for any clinical reorganization or decisions around DxM budgets to progress this. Glad to further discuss / faciitate as you request.


metabolon-business -case.doc


Proposal for Metabolon Collabo...

Thanks.

Rob

EXHIBIT 11
WIT: RAK
DATE: 11-24-08
LINDA ROSSI RIOS

-----Original Message-----
From: Furlong, Stephen T
Sent: Monday, October 11, 2004 4:20 PM
To: Brecher, Martin
Cc: Smith, Mark A (Exp Med); Allen, Robert (R&D TA Pain)
Subject: diabetes/atypicals and metabalomics

Hi Martin,
Mark mentioned to me that there is renewed interest on the Seroquel team for understanding the nature of the diabetes liability for atypicals so I thought you might be interested in the review paper at the attached link. By the way, the metabalomics approach that we discussed has some real potential for providing some insight here. I'd be interested in talking to you some more about this and/or giving a presentation to the Seroquel about how this approach might help us.
Steve

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15378663

Stephen T. Furlong, Ph.D.

AstraZeneca, 1800 Concord Pike, Wilmington, DE 19850
ph 302-886-8588 mobile 302-898-7207 fax 302-885-3245

Clinical Study

The weight profile of SEROQUEL over the long term

Authors: Brecher M, Rak IW, Melvin K, et al

Title: The long-term effect of quetiapine (Seroquel®) monotherapy on weight in patients with schizophrenia.

Journal: *International Journal of Psychiatry in Clinical Practice* 2000;4:287-291.

Seroquel®
quetiapine fumarate 25 mg, 100 mg, 200 mg & 300 mg tablets

Study design

- Retrospective analysis of SEROQUEL monotherapy in placebo-controlled and open-label extension trials
- 427 patients with schizophrenia received a mean daily dose of 475 mg of SEROQUEL after one year of open-label treatment
  - —178 of the 427 patients were treated with SEROQUEL for a minimum of 6 months (mean duration = 18.6 months)
  - —Weight was recorded at baseline and end point
- Body weight was assessed by baseline body mass index (BMI) categories established by the National Heart, Lung, and Blood Institute of the National Institutes of Health
  - —BMI defines weight relative to height
- All concomitant antipsychotic medication was stopped prior to entry into clinical trials

Favorable weight profile unaffected by higher doses of SEROQUEL in this study

- SEROQUEL did not result in clinically significant mean weight gain at any dose
- No correlation between higher doses and long-term mean weight changes

Minimal treatment withdrawal

- Only 1 patient in 427 (0.22%) withdrew due to weight gain

In short-term studies, only dyspepsia, weight gain, and abdominal pain were reported at a significantly higher incidence with increasing doses of SEROQUEL.

Favorable weight profile over time

- Clinically insignificant weight changes over the long term (mean duration = 18.6 months) demonstrated by BMI categories

Weight changes from baseline to end point* by baseline BMI category

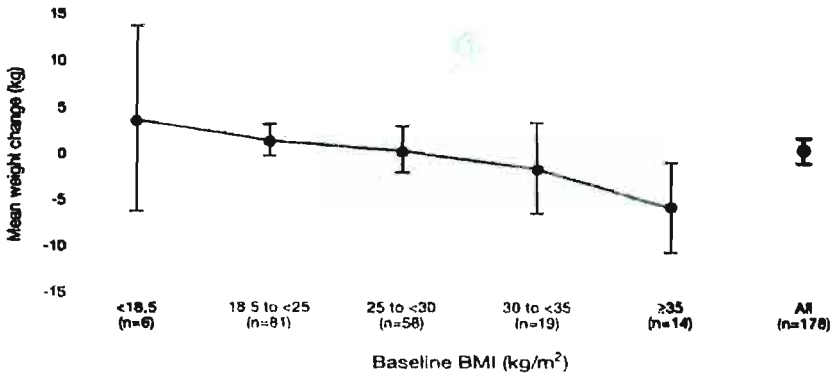
Baseline BMI (kg/m^2)	Number of patients	Mean daily dose at end point (mg)	Mean duration of treatment (days)	Mean weight change (kg)
<18.5	6	443	540	3.75
18.5 to <25	81	468	539	1.6
25 to <30	58	466	607	0.53
30 to <35	19	514	551	-1.53
≥35	14	483	543	-5.76
All	178	473	563	0.41

*[illegible]

Little overall effect on weight across BMI categories

- SEROQUEL demonstrates a favorable weight profile in every weight category (from underweight to obese)

Mean change in weight by baseline BMI category



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The long-term effect of quetiapine (Seroquel™) monotherapy on weight in patients with schizophrenia

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INTRODUCTION: *Quetiapine (Seroquel™) is an atypical antipsychotic drug with demonstrated efficacy and tolerability. In particular, placebo-level extrapyramidal symptoms (EPS) across the entire dose range and a low propensity to cause sexual dysfunction suggest it may be associated with greater patient acceptability than alternative treatments. However, other side-effects, such as weight gain, may also have a significant impact on treatment acceptability.*

METHOD: *We report the long-term weight changes observed in a cohort of 427 patients with schizophrenia from controlled and open-label extension (OLE) trials, in which quetiapine (mean dose 475 mg/day after 1 year) was the only antipsychotic medication during the OLE period.*

RESULTS: *In these patients, there was no overall effect on weight across the body mass index (BMI) spectrum. There were no dose-related effects on weight, and only one patient withdrew from treatment due to an adverse event of weight gain. Quetiapine appeared to have a weight-neutral or 'normalizing' effect, with a tendency towards favourable shifts in bodyweight in underweight patients (BMI* < 18.5 *kg/m*^{2}) and severely obese patients (BMI ≥ 35 kg/m^2).

CONCLUSION: *These results indicate that long-term weight changes with quetiapine monotherapy are minimal and potentially beneficial, and do not appear to raise the medical concerns associated with some other atypical agents.* (*Int J Psych Clin Pract* 2000; 4: 287–291)

Keywords
atypical antipsychotics *quetiapine*
schizophrenia *weight gain*
Body Mass Index *long-term therapy*

INTRODUCTION

Schizophrenia is a chronic and debilitating illness that affects approximately 1% of the population worldwide. Conventional antipsychotic agents have been prescribed extensively over the last 40 years to treat schizophrenia; however, they are associated with undesirable motor symptoms (extrapyramidal symptoms) (EPS) such as akathisia, dyskinesia, bradykinesia and parkinsonism, which are known to contribute to poor compliance with treatment.[1,2] Such adverse effects of the older, typical antipsychotics caused great distress to patients but were tolerated as being inevitable in the treatment of psychotic symptoms. Even so, studies have suggested that 40% of patients stopped taking their medication within 1 year and 75% within 2 years.[3]

Many of the newer, atypical antipsychotic agents have an improved tolerability profile, and are less likely to cause debilitating EPS than are the earlier antipsychotic agents.[1] However, there are marked differences between compounds: quetiapine, for example, has a particularly favourable EPS profile,[4] with an incidence of EPS no different from placebo across the entire dose range.[5]

Quetiapine also has a low propensity to cause hyperprolactinaemia or sexual dysfunction.[4] These properties suggest that quetiapine may be more acceptable to patients than alternative treatments.[6] Other side-effects, including a tendency to induce weight gain, have been observed to varying degrees with most atypical antipsychotics.[7] Weight gain may also adversely affect patients' quality of life and compromise treatment compliance.

The association between antipsychotic medication and weight gain has been recognized for more than 40 years.[8] Historically, weight gain has been linked to efficacy of antipsychotic medication, with increased weight being linked to a positive outcome. However, more recent research suggests this may not be the case.[9,10]

Weight gain is associated with increased morbidity and mortality in a wide range of conditions, including hypertension, coronary heart disease, cerebrovascular disease, type 2 diabetes mellitus, various cancers, sleep apnoea and respiratory problems.[11,12] It is also linked with morbidity related to the disease being treated. Studies have shown that weight gain causes relatively more distress than many of the other side-effects commonly associated with antipsychotic medication.[13,14] If weight gain is considered unacceptable to the patient, then compliance may be compromised, potentially exacerbating the psychotic condition.

The extent to which antipsychotics are associated with weight gain varies considerably.[7,15] Weight gains of 4.45, 4.15, 2.10 and 2.16 kg have been observed following 10 weeks' treatment with clozapine, olanzapine, risperidone and quetiapine, respectively.[15,16] However, the true clinical significance of weight gain is observed in the context of long-term treatment. It is clear that long-term treatment with some antipsychotics (in particular clozapine and olanzapine) is associated with considerable increase in weight.[9,17] Given the growing importance of this issue, the present review assesses weight changes in patients with schizophrenia during long-term treatment with quetiapine monotherapy, focusing particularly on the potential effects exerted by dose or related to Body Mass Index (BMI).

METHODS

Weight data were analysed from controlled and uncontrolled clinical trials of quetiapine and the respective open-label extensions (OLE). Patients with psychotic symptoms were evaluated for eligibility to enter controlled and uncontrolled studies of quetiapine according to the inclusion and exclusion criteria of the particular study. Following the clinical trial, patients were allowed to enter into an open-label extension phase, where appropriate. Data from all patients who had a DSM-IV diagnosis of schizophrenia are included in the current review.

All concomitant antipsychotic medication was stopped prior to entry into the clinical studies, and treatment was with quetiapine monotherapy throughout both the double-blind and OLE periods of all studies.

Weight was assessed at baseline in most patients and at least once during follow-up, which varied across trials, ranging from 6 weeks to beyond 18 months. Consequently, the numbers of patients do not indicate the length of follow-up, and patients were not assessed following withdrawal of therapy. Baseline Body Mass Index (BMI) was available for most patients. For analysis, patients were grouped according to the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute's standard categories for BMI.

STATISTICAL ANALYSIS

Weights were summarized using a last-observation-carried-forward approach within specified time intervals. Since the present exploratory analysis was designed only to highlight apparent contributors to weight change, rather than to provide a definitive analysis of predictors of weight change, no formal statistical analysis was performed on these data.

RESULTS

Weight data were analysed from 427 patients with schizophrenia from controlled and OLE studies in which only quetiapine was allowed as antipsychotic medication throughout the double-blind and open-label extension phase of each study. Patients received a mean daily quetiapine dose of 475 mg after one year of open-label treatment. Patient demographics are presented in Table 1.

Minimal overall weight change was observed over 18 months of treatment with quetiapine. The mean weight change from baseline was: 1.58 kg after 9–13 weeks (n=170); 0.26 kg after 14–26 weeks (n=165); 1.66 kg after 27–39 weeks (n=134); −1.53 kg after 40–52 weeks (n=41); and 1.94 kg after 53–78 weeks (n=146). (Note: patients did not necessarily have weight recorded at all timepoints.)

Table 1
Patient demographics

Number of patients (n)	427
Male/female (n)	277/150
Age, years (mean ± SD)	37.3 ± 10.8
Age distribution (N)	
<65 years	425
≥65 years	2
Weight, kg (mean ± SD)	75.21 ± 15.55
Weight distribution (n)	
Data not collected	28
≤50 kg	5
50–70 kg	171
71–90 kg	164
>90 kg	59

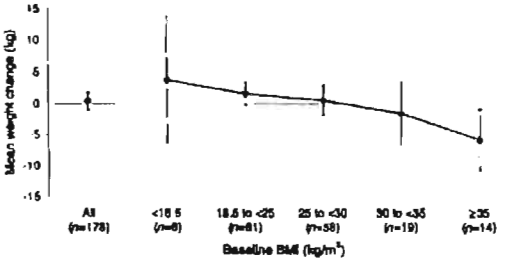


Figure 1
Mean change in weight, and associated 95% CI, from baseline to endpoint by baseline BMI category in patients treated with quetiapine monotherapy for at least 6 months (n=178). Mean treatment duration 18.6 months; mean daily dose 473 mg

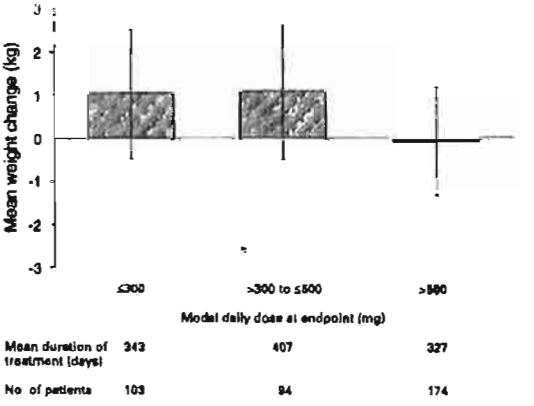


Figure 2
Mean change in weight, and associated 95% CI, from baseline to endpoint by modal daily dose at endpoint in patients receiving quetiapine monotherapy (endpoint is defined as final recorded weight measurement)

Effect of Baseline Body Mass Index

The mean change in weight from baseline to endpoint and associated 95% confidence intervals are shown in Figure 1 for each baseline BMI category for those patients who received at least 6 months' treatment with quetiapine (mean duration 18.6 months), and whose weight was recorded at baseline and endpoint. The mean dosage and duration of treatment are shown in Table 2 for each baseline BMI category. These data indicate that long term treatment with quetiapine has very little overall effect on weight, and the overlap of the 95% CIs with the zero change line allows quetiapine to be characterized as weight-neutral. Moreover, there is a tendency towards beneficial shifts in body weight in patients with BMI <18.5 kg/m^2 and in those with BMI ≥ 35 kg/m^2.

Longitudinal Analysis of Weight Change by Dose

Any effect of quetiapine dose on weight was investigated by analysing weight at baseline and endpoint for each of three dosage groups. The endpoint value was defined for each patient as the final recorded weight measurement that was taken. Patients were included in this analysis only if a baseline weight value had been obtained and if there was at least one other non-baseline value. Weight changes by dose group are presented in Figure 2, using the modal dose value for the last recorded weight value. These longitudinal data and associated 95% confidence intervals (CI) show there is no effect of quetiapine on weight at any dose, nor is there any correlation between increasing dose and mean long-term weight changes. These results are consistent with those from a short-term dose-ranging study reported previously.[5,16]

Effect of Gender

No clinically significantly different changes in weight from baseline to endpoint were observed between male and female patients on long term treatment with quetiapine. Weight changes of -0.58 kg and 1.94 kg were observed in male (n=108) and female (n=70) patients, respectively.

Withdrawals Due to Weight Gain

Only one patient withdrew (0.22%) as a result of an adverse event of weight gain.

DISCUSSION

Results of the present analysis show that, in clinical studies where no other antipsychotic medications were permitted during the OLE phase of treatment, quetiapine was associated with only minimal changes in weight in the short term (8 weeks), and with an overall neutral effect on weight with long-term treatment. By comparison, an increase of approximately 12 kg has been reported after 12 months' treatment with olanzapine 12.5–17.5 mg/day.[17]

BMI is widely accepted as being the most clinically appropriate measure of weight change, since it describes relative weight for height, and our analysis of the weight change profile by baseline BMI shows that in the long term (18 months), weight changes in all but the severely obese (BMI >35 kg/m^2; Obesity Category II) are small, with 95% CIs overlapping the zero change line. Indeed, in this severely obese group, long-term quetiapine therapy was associated with a favourable weight loss. In addition, there was a trend towards beneficial weight gain in underweight patients (BMI <18.5 kg/m^2). Quetiapine appears therefore to be associated with potentially beneficial shifts in body weight towards normal values when individual BMI categories are considered.

Table 2
Weight changes from baseline to endpoint[a] by baseline BMI category in patients treated for at least 6 months with quetiapine monotherapy

Baseline BMI (kg/m^2)	n	Mean daily dose at endpoint (mg)	Mean duration of treatment (days)	Mean change in weight (kg)
All	178	473	563	0.41
<18.5	6	443	540	3.75
≥18.5<25	81	468	539	1.6
≥25<30	58	466	607	0.53
≥30<35	19	514	551	−1.53
≥35	14	483	543	−5.76

[a]Final recorded weight measurement

Weight gain with certain antipsychotics (such as clozapine and olanzapine) has been associated with the development of diabetes.[18] In this context it is interesting to note that the addition of quetiapine to ongoing clozapine therapy in 65 patients significantly improved glycaemic status in the 20% of patients who had developed diabetes while on clozapine monotherapy.[19] Furthermore, these 65 patients had also experienced a 6.5 kg mean increase in weight during 6 months of clozapine monotherapy. Addition of quetiapine to the treatment regimen resulted in a mean weight loss of 4.2 kg over the subsequent 10 months.

Although various theories have been proposed, the precise mechanism(s) involved in the induction of weight gain by atypical antipsychotic agents has not been fully elucidated. It may be a multifactorial process, with involvement of serotonergic, histaminergic and/or adrenergic neurotransmission. Olanzapine and clozapine, which appear to be associated with comparatively large increases in weight,[9,15,18,20] have been shown to increase circulating leptin levels,[21,22] which correlate positively with increased BMI.

Antipsychotics also vary in the time course of their effect on weight gain. Weight changes occurring in the first weeks of treatment, particularly in patients who have previously been untreated, have important implications for compliance with long-term antipsychotic medications.[23] In this regard, therefore, quetiapine would appear to have a significant advantage over other antipsychotics. In a retrospective analysis, risperidone-treated patients reached a weight plateau after approximately 12 weeks, whereas clozapine- and olanzapine-treated patients showed continued increase in weight over a longer period (20 weeks).[7] In contrast, the present analysis demonstrates that quetiapine is associated with only a minimal change in weight that does not appear to be dose-related, does not increase over time, and does not appear to affect compliance. Indeed, in a recent study of patients' satisfaction with quetiapine, the combination of efficacy and a favourable tolerability profile was reflected in high levels of satisfaction and acceptance of long-term treatment, and a normalization of eating habits in 73% of the study population.[6] Given the association of weight gain with increased morbidity and mortality from hypertension and macrovascular disease,[11,12] and its detrimental impact on patients' well-being,[13,14] quetiapine's overall neutral or 'normalizing' effect on weight in the long term may have wider implications for patients' overall health, and associated healthcare costs.

In conclusion, weight changes in patients treated long term with quetiapine when used as monotherapy are neutral and potentially beneficial, and do not appear to raise the medical concerns associated with some other atypical agents. Combined with quetiapine's balanced combination of efficacy and tolerability, the present analysis suggests that quetiapine has a favourable benefit – risk profile as a first-choice antipsychotic in the long-term treatment of schizophrenia.

KEY POINTS

- While the impact of weight gain during long-term antipsychotic therapy is an important consideration when treating patients with schizophrenia, the extent to which individual agents are associated with weight gain varies considerably
- Long-term quetiapine monotherapy showed no overall effect on weight across the BMI spectrum, with 95% CIs encompassing zero weight change in all BMI categories apart from the severely obese (BMI ≥35 kg/m^2), in whom weight loss was observed. Any weight changes with quetiapine therapy showed no association with dose or gender
- Long-term monotherapy with quetiapine is associated with a potentially 'normalizing' effect on weight, with a tendency towards weight gain in underweight patients and weight loss in severely obese patients
- The combination of efficacy, good tolerability and an overall neutral long-term effect on weight suggests that quetiapine should be considered a first-choice antipsychotic in the long-term treatment of schizophrenia.

Id : i.m.1c410850894554945d81f36421b63267
CN : SQ1ED00099292
Date : Saturday, February 26, 2000 6:48:00 PM GMT
From : Murray Michael MF
To : Owens Judith J; Rak Ihor IW; Wilkie Alison AM
Cc : Brecher Martin M; Czupryna Michael MJ; Denerley Paul PM; Gavin Jim JP; Gorman Andrew AP; Holdsworth Debbie D; Jones Martin AM - PHMS; Litherland Steve S; OBrien Shawn SP; Tugend Georgia GL; Tumas John JA; Westhead Emma EK
Subject : RE: Short Report on Weight Gain
Custodians : Jones, Martin

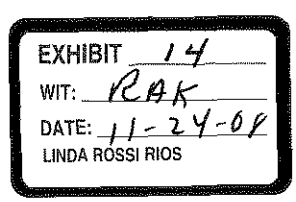
From: Murray Michael MF
Sent: 2/26/2000 10:18:42 AM
To: Owens Judith J; Wilkie Alison AM; Rak Ihor IW
CC: Holdsworth Debbie D; O'Brien Shawn SP; Gavin Jim JP; Litherland Steve S; Jones Martin AM - PHMS; Denerley Paul PM; Westhead Emma EK; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Brecher Martin M
BCC:
Subject: RE: Short Report on Weight Gain

Ihor,
Thank you for your excellent comments!!! Totally on mark. I agree we should be as aggressive as possible on the weight gain issue. You make a great point about us giving up too much with EPS, lets not concede all atypical are the same, they are not.

Ihor should definitely be one of the authors of this paper.

Thanks again for this input.
Mike Murray

Senior Product Strategist, SEROQUEL
1-800-456-3669 ext. 4328
michael.murray@astrazeneca.com



>----------
>From: Rak Ihor IW
>Sent: Friday, February 25, 2000 2:30 PM
>To: Owens Judith J; Wilkie Alison AM
>Cc: Holdsworth Debbie D; O'Brien Shawn SP; Gavin Jim JP; Litherland Steve S; Murray Michael MF;

Jones Martin AM - PHMS; Denerley Paul PM; Westhead Emma EK; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Brecher Martin M

>Subject: RE: Short Report on Weight Gain

>

>Judith

>

>Thank you for the opportunity to comment on this very important paper.

>

>1. I think we are giving away too much of our competitive advantage saying repeatedly that atypical antipsychotics (as a class) have a much reduced tendency to cause EPS. Our competitors have been able to undifferentiate themselves from Seroquel, despite our having the only true no dose related advantage. I would tone down the linkage between less EPS with atypicals leading to greater attention on weight changes.

>

>2. We need to emphasize much more that Seroquel treatment is NOT associated with a mean weight gain in patients where it is used alone (without other antipsychotics). That should be the key message; not that there is a small weight gain in a group of patients who were treated with Seroquel (with and without other antipsychotics). The abstract and paper can mention these data, but then stress that finer analyses and more relevant data tell a far better, and more clinically relevant to Seroquel, story.

>

>3. The last key point in the first section after the abstract: only minimal effects on weight is not strong enough. We showed a mean weight loss in patients treated with Seroquel alone long term!

>

>4. Introduction: 5th paragraph: the weight gains in the Allison paper were NOT estimates. (Only the quetiapine weight gain at 10 weeks in the poster not the paper was an estimate.) Later in that paragraph: "psychotic symptoms other than schizophrenia" is incorrect; should be "disorders" replacing "symptoms".

>

>5. The mean dose (446 mg) for the first study (and 475 mg for the second cohort) and the no dose related effect finding are also important messages and should be included in the abstract.

>

>6. The one patient who withdrew from each study: are we certain that this is not the same patient? If it is, we should say it is the same patient and not count the patient twice in two %. Since the second cohort came from the first, it is possible this is one and the same patient.

>

>7. Discussion: The first sentence"... quetiapine treatment was associated with only a modest mean increase in weight" is not the key message of this work, since that analysis did not separate out patients treated with other antipsychotic medications. The net loss on quetiapine alone is the key message. Stressing the importance of this distinction is key.

>

>8. Last paragraph: Sentence "In conclusion, ..." should read more emphatically favorably for quetiapine: "Weight changes in patients treated long term with quetiapine (alone or in combination with other antispychotics) do not appear to raise potential medical concerns relating to significant weight increases as seen with other atypical antipsychotic agents.">
>
>9. Lastly, I respectfully request that my name be added to the authors, in view of my contribution to understanding this issue, data and poster generation since August 99.
>
>Kind regards
>
>Ihor
>
>
> ----------
> From: Wilkie Alison AM
> Sent: Wednesday, February 23, 2000 7:32 AM
> To: Owens Judith J
> Cc: Holdsworth Debbie D; O'Brien Shawn SP; Gavin Jim JP; Litherland Steve S; Murray Michael MF; Rak Ihor IW; Jones Martin AM - PHMS; Denerley Paul PM; Westhead Emma EK; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Brecher Martin M
> Subject: FW: Short Report on Weight Gain
> Importance: High
>
> Judith
>
> Thanks for the opportunity to comment - I think this is very good. I've suggested amends to the abstract section, attached.>
>
> ALSO: the paper refers to data out to 52 weeks only - therefore table 2 and figure 3 should reflect this - ie be cut at 52 weeks. On this basis, is it possible for us to claim a neutral effect on weight with Seroquel rather than 'minimal'??
>
> <<File: Weight brief report.doc>>
>
>

Unknown

From: Aked Dominic DM
Sent: Thursday, October 26, 2000 9:30 PM
To: Rak Ihor IW
Cc: O'Brien Shawn SP; Shadwell Pamela PG; Holdsworth Debbie D; Jones Martin AM - PHMS
Subject: RE: Data for weight neutral slide

Hi Ihor

Many thanks for this important feedback.

I agree we need to be able to tell a convincing story to our internal and external customers. I'm sure we can do this.

- Re US PI: From what I can see any mention of weight gain in the US PI relates to short-term studies. We may be able to make a clear distinction between this clinical situation and long-term treatment (that is, acutely psychotic relapse versus long-term maintenance). Presumably the latter is what is important clinically given that patients receive long-term treatment.

A promotional claim ***'Seroquel is weight neutral during long-term treatment*** should help to make this distinction.

- There may be a rationale to explain why acutely psychotic patients may gain weight in the short term, following effective therapy. The relief of negative symptoms, apathy etc, disorganised thinking, may result in return to normal activities like having regular meals.

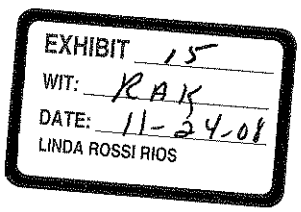
There are useful indicators in the patient satisfaction study to support the view that effective long term therapy with Seroquel helps to normalise eating.

Benefits noticed in last 6 mo by patients on Seroquel
55% patients prepare and cook meals
64% go shopping for food/personalitems
73% eat more normally
Page 25 Figure 4C Clear Perspectives Vol 2 issue 3

One additional comment (where there's a ying there's a yang): if we look at incidence of patients gaining >7% baseline weight, we should also consider looking at patients losing >7% baseline weight, or what would be considered a clinically significant weight loss.

Kind regards

Dom

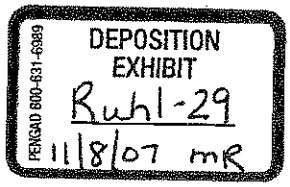


From: Rak Ihor IW
Sent: 25 October 2000 02:16
To: 'Rob Kite'; Holdsworth Debbie D; Jones Martin AM - PHMS
Cc: Shadwell Pamela PG; Ashworth Phillip P; Aked Dominic DM; Gavin Jim JP; O'Brien Shawn SP
Subject: RE: Data for weight neutral slide

All

I had the pleasure of presenting 5 weight slides (from the International Speaker's Training meeting) to the US SEROQUEL Product Team.

The titles of the 5 slides were: SEROQUEL-minimal effect on weight long term; SEROQUEL- neutral effect on weight at all doses; 3 slides-- Long-term SEROQUEL monotherapy has neutral effect on weight (1 with confidence intervals, another n=112 of 53 weeks exposure and longer shifts in BMI category, and another shifts in BMI category in obese/severely obese patients).



3

They had some very good suggestions based on their having to deal with the US label which states that SEROQUEL causes dose related weight gain (NDA dataset).

1. Best to tell a story. Data from clinical trials showed this, but limitations are these. hence another dataset analysed

2. using different datasets raises suspicions if not adequately explained and justified.

3. when selecting a cohort of patients who were treated for 26 or 53 weeks minimum, suspicions are immediately raised about the patients "censored": what was their mean weight change. For both cohorts of patients (those displayed and those censored) how many experienced adverse events (weight gain >7% of body weight), how any discontinued from the OLE due to weight gain, etc

4. BMI shifts not quickly understood; patients can not shift fromtheseverely obese BMI category (already mentioned)

Certainly, the more of these comments that we examine and address, the more confidence we will have in our weight neutral message.

Ihor

From: Jones Martin AM - PHMS
Sent: Friday, October 20, 2000 10:25 AM
To: 'Rob Kite'; Holdsworth Debbie D
Cc: Shadwell Pamela PG; Ashworth Phillip P; Rak Ihor IW; Aked Dominic DM; Gavin Jim JP
Subject: RE: Data for weight neutral slide
Importance: High

Rob

Please find attached a word document containing the data that you need. There are 40 pages in totally. The first 20 refer to all doses, the last 20 to data from within the 150-750 mg dose range.

In yesterday's Communication Planning Team meeting, it was decided to focus on the all dose cohort, for which we have 178 schizophrenic patients, with weight data beyond day 182, with BMI data. This data is slightly different to that previously included in my slide.

The summary data for this cohort starts on page 6, with :

	N	Mean	LCL	UCL	Median	Min	Max	Std Err	t Prob>|t|
All	178	0.410	-0.910	1.742	-0.450	-27.00	27.000	0.991	0.674	0.610	0.729	1.973

From this you should be able to get all the required data. The following page contains mean dose data for the entire cohort.

The next dozen or so pages divide these 178 patients into demographic sub-groups i.e. baseline BMI, gender, age group, race, mean dose group (interesting ?). All the tables should contain data for 178 patients !

The analyses are then repeated for the 150-750 mg group.

Hope this helps.

I am away on holiday next week, but Pamela, or Phill Ashworth may be able to help you with any queries.

Regards

AstraZeneca

Clinical Overview

Drug Name Quetiapine fumarate

Date July 2008

SEROQUEL™ (quetiapine fumarate)
Clinical Overview on Weight Gain in pediatric patients

Authors:

Leigh Jefferies M.D.
Global Safety Physician
Patient Safety, Wilmington, DE

Eva S.K. Alam, M.S., Pharm.D., RPh
Safety Surveillance Team Leader
Patient Safety, Wilmington, DE

TABLE OF CONTENTS PAGE

LIST OF TABLES

1. PRODUCT DEVELOPMENT RATIONALE

1.1 Introduction

The Core Data Sheets for SEROQUEL is to be amended following an internal safety evaluation and review meeting on 09 July 2008. The purpose of this document is to summarize the key information on which the decision to amend the CDS was based, to document the Core Data Sheet amendment and to support changes to local Prescribing Information.

1.1.1 SEROQUEL and SEROQUEL XR

SEROQUEL and SEROQUEL XR are atypical antipsychotic agents, presented as tablets containing quetiapine fumarate, which exhibits affinity for brain serotonin (5HT2) and dopamine D1 and D2 receptors. In addition, SEROQUEL/SEROQUEL XR also have high affinity at histaminergic and adrenergic α1 receptors, with a lower affinity at adrenergic α2 receptors, but no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors.

SEROQUEL was first approved for marketing in the United Kingdom (UK) on 31 July 1997 and was first launched in the UK on 22 September 1997. By 31 March 2008, SEROQUEL has been approved in 89 countries for schizophrenia, 86 countries for bipolar mania, (with Mexico being the first country to approve bipolar mania on 29 May 2003), 26 countries for bipolar depression, (with Czech Republic being the first country to approve bipolar depression on 27 September 2006), and in one country for bipolar maintenance (USA being the first country to approve bipolar maintenance on 14 May 2008). SEROQUEL is presented as tablets delivering a dose of 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 300 mg, or 400 mg of quetiapine free-base. SEROQUEL is not approved for children or adolescents below 18 years of age.

SEROQUEL XR was first approved for marketing in the United States (US) for acute schizophrenia on 18 May 2007 and for maintenance of schizophrenia on 15 November 2007. By 31 March 2008, SEROQUEL XR has been approved in 30 countries for schizophrenia (including 14 countries in the Mutual Recognition Procedure), 7 countries for bipolar mania (with Slovakia being the first country to approve bipolar mania on 28 June 2007), and in one country for bipolar depression (Mexico being the first country to approve bipolar depression in October 2007). SEROQUEL XR is presented as tablets delivering a dose of 50 mg, 200 mg, 300 mg, or 400 mg of quetiapine free-base. SEROQUEL XR is not approved for children or adolescents below 18 years of age.

1.2 Proposed label change

The following text will be added to Section 4.8 *Undesirable effects* of the SEROQUEL CDS under a subheading of *Children and adolescents.*

Children and adolescents

The same ADRs described above for adults apply to children and adolescents. The following table summarizes ADRs that occur in a higher frequency category in children and adolescents patients (10-17 years of age) than in the adult population or ADRs that have not been identified in the adult population.

Weight gain in children and adolescents

In one 6-week, placebo-controlled trial in adolescent patients (13-17 years of age) with schizophrenia, the mean increase in body weight, was 2.0 kg in the quetiapine group and -0.4 kg in the placebo group. Twenty one percent of quetiapine-treated patients and 7% of placebo-treated patients gained $\geq$ 7 % of their body weight.

In one 3-week, placebo-controlled trial in children and adolescent patients (10-17 years of age) with bipolar mania, the mean increase in body weight was 1.7 kg in the quetiapine group and 0.4 kg in the placebo group. Twelve percent of quetiapine-treated patients and 0% of placebo-treated patients gained $\geq$ 7 % of their body weight.

In the open-label study that enrolled patients from the above two trials, 63% of patients (241/380) completed 26 weeks of therapy with quetiapine. After 26 weeks of treatment, the mean increase in body weight was 4.4 kg. Forty five percent of the patients gained $\geq$ 7% of their body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change; 18.3% of patients on quetiapine met this criterion after 26 weeks of treatment.

Since clinical trials in pediatric patients have been conducted with SEROQUEL and not SEROQUEL XR this change applies only to the SEROQUEL CDS.

2. OVERVIEW OF BIOPHARMACEUTICS

This section is not relevant to this document.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

This section is not relevant to this document.

4. OVERVIEW OF EFFICACY

This section is not relevant to this document.

5. OVERVIEW OF SAFETY

5.1 Data summary and discussion

5.1.1 Pediatric clinical trial data

The data presented below is taken from two acute placebo-controlled studies with SEROQUEL in pediatric patients with schizophrenia or bipolar mania and one longer-term open-label study with SEROQUEL. The patients in the longer-term trial were originally enrolled in one of the two acute placebo-controlled trials. The following is a brief description of these three trials.

- D1441C00112: a 6-week, International, Multicenter, Randomized, Double-blind, Parallel group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 800 mg Compared with Placebo in the Treatment of Adolescents with Schizophrenia

- D1441C00149: a 3-week, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 600 mg Compared with Placebo in the Treatment of Children and Adolescents with Bipolar I Mania

- D1441C00150: a 26-week, International, Multicenter, Open-label Phase IIIb Study of the Safety and Tolerability of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg to 800 mg in Children and Adolescents with Bipolar I Disorder and Adolescents with Schizophrenia

5.1.2 Acute placebo-controlled data

5.1.2.1 D144C00112

Mean increase in body weight

In study D144C00112, mean weights were similar at baseline for the three treatment groups. Mean changes in weight from baseline were higher for quetiapine-treated patients at each time point compared to placebo. At Day 42, the mean changes from baseline were 2.2 kg in the 400 mg/day quetiapine group, 1.8 kg in the 800 mg/day quetiapine group, and –0.4 kg in the placebo group (see Table 1).

Table 1 D144C00112: Mean increase in weight from baseline

Change from Baseline	QTP 400 mg	QTP 800 mg	PLACEBO
Day 42	2.2 kg	1.8 kg	-0.4 kg

Patients with ≥7% weight gain

A higher percentage of quetiapine-treated patients (23.21% in the 400 mg/day and 18.18% in the 800 mg/day) had ≥7% weight gain at Day 42 compared to the placebo-treated patients (6.82%) (see Table 2).

Table 2 D144C00112: Patients with ≥ 7% weight gain (Summary safety population)

Visit	QTP 400 mg N=56 n (%)	QTP 800 mg N = 55 n (%)	PLA N = 44 n (%)
Day 42	13 (23.2)	10 (18.2)	3 (6.8)

5.1.2.2 D144C00149

Mean increase in weight

Mean increases in weight from baseline to Day 21 were higher for quetiapine-treated patients at each time point compared to placebo. These increases from baseline were 1.7 kg in the 400 mg quetiapine-treated group, 1.7 kg in the 600 mg quetiapine-treated group and 0.4 kg in the placebo group. Quetiapine-treated patients experienced higher mean increases in weight compared to placebo at Day 21 (see Table 3).

Table 3 D144C00149: Mean increase in weight from baseline

Change from baseline	QTP 400 mg	QTP 600 mg	PLA
Day 21	1.7 kg	1.7 kg	0.4 kg

Patients with ≥7% weight gain

A higher percentage of quetiapine-treated patients (14.47% in the 400 mg/day and 9.88% in the 600 mg/day) had ≥7% weight gain at Day 21 compared to placebo-treated patients (0%) (see Table 4).

Table 4 D144C00149: Patients with ≥7% weight gain (Summary safety population)

Visit	QTP 400 mg N = 76 n (%)	QTP 600 mg N = 81 n (%)	PLACEBO N = 68 n (%)
Day 21	11 (14.5)	8 (9.9)	0 (0)

5.1.3 Longer-term open-label pediatric data

5.1.3.1 D1441C00150

Study D1441C00150 was an open-label extension study designed to assess the safety and tolerability of quetiapine (flexibly dosed at 400 mg/day to 800 mg/day) in adolescents with schizophrenia (continuing from Study D144C00112) and in children and adolescents with bipolar I disorder (continuing from Study D144C00149). There were a total of 380 patients in the safety analysis set, including 175 with schizophrenia and 205 with mania. Sixty-three percent of patients (241) completed 26 weeks of therapy with quetiapine.

All patients treated with quetiapine 50 mg/day on Day 1 then escalated to 400 mg on Day 5. From Day 5, the target dose of 400 mg/day was maintained or increased by no more than 100 mg/day, up to 800 mg/day or adjusted down to 200 mg/day. Patients were treated for up to 26 weeks.

Mean increase in weight

The mean change in weight for schizophrenia and bipolar I patients (who enrolled) from OL baseline as well as DB baseline to final visit are provided in Table 5.

Table 5 **Study D1441C00150: mean changes from baseline to the final visit (safety population)**

	Acute feeder study treatment								
	Prior Placebo (N=129)			All prior QTP (N=251)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
112 DB Baseline									
Final visit (150 OL BSLN)	62	67.4	16.3	113	64.8	19.2	175	65.7	18.2
Change from 112 DB BSLN	62	4.1	8.5	113	4.8	10.8	175	4.6	10.0
Change from 150 OL Baseline	62	4.3	6.9	113	2.8	10.1	175	3.3	9.1
149 DB Baseline									
Final visit (150 OL BSLN)	64	68.3	21.9	136	64.5	18.4	200	65.8	19.6
Change from 149 DB BSLN	64	5.8	6.4	136	5.1	5.7	200	5.3	5.9
Change from 150 OL Baseline	64	5.5	5.8	135	3.2	4.8	199	4.0	5.2
Total 149 and 112 pooled DB Baseline									
Final visit (150 OL BSLN)	126	67.9	19.3	249	64.7	18.7	375	65.7	19.0
Change from DB BSLN	126	5.0	7.50	249	5.0	8.3	375	5.0	8.1
Change from 150 OL Baseline	126	4.9	6.4	248	3.0	7.6	374	3.7	7.3

In patients who completed 26 weeks of therapy with quetiapine (n=241) in Trial D1441C00150, the mean change in weight from OL baseline was 4.4 kg.

Patients with ≥7% weight gain

In the safety population, 134 patients (35.6%) experienced ≥7% weight gain from OL baseline to final visit (see Table 6).

Table 6 **Study D1441C00150: Patients with ≥ 7% weight gain (Summary safety population)**

	Acute feeder study treatment								
	Prior Placebo (N=129)			Prior All QTP (N=251)			Total (N=380)		
	N	n	(%)	N	n	(%)	N	n	(%)
Pooled data 149 and 112									
From DB Baseline	127	58	45.7	249	119	47.8	376	177	47.1
From 150 OL Baseline	127	50	39.4	249	84	33.7	376	134	35.6
Study 112 (schizophrenia)									
From DB Baseline	62	24	38.7	113	43	38.1	175	67	38.3
From 150 OL Baseline	62	19	30.6	113	32	28.3	175	51	29.1
Study 149 (BP I)									
From DB Baseline	65	34	52.3	136	76	55.9	201	110	54.7
From 150 OL Baseline	65	31	47.7	136	52	38.2	201	83	41.3

Of the patients who completed 26 weeks of treatment with quetiapine, 44.8% (108/241) had a ≥7% increase in weight from OL baseline.

5.1.4 Additional analysis of Pediatric data

5.1.4.1 Z-scores

Since body weight and height should increase in children, data showing an increase in weight with time sometimes may not indicate a problem. One convenient way to express body weight is in terms of body mass index (BMI), since with BMI, the weight is adjusted for height (Correll et al 2006).

A better measure of weight change in children and adolescents is to convert the mean weight and BMI to a Z-score taking into consideration the age and gender of the subject. Z-scores are able to show how different a child's weight or BMI is from the average children of the same height (Reyes et al 2006).

One of the criteria proposed to show significant weight gain in children and adolescents is a greater than or equal to an increase in BMI Z-score of 0.5 over any duration of time (Correll et al 2006). This increase represents a change of 0.5 standard deviation from baseline.

BMI Z-scores

The mean BMI Z-scores (for patients who enrolled in study D1441C00150) from the DB baseline for schizophrenia to the final visit and end of treatment are higher for the prior placebo group compared to the prior quetiapine group (see Table 7).

Table 7 Study D1441C00150: Mean values of BMI Z score at baseline, end of treatment and final visit (safety population)

	Acute feeder study treatment								
	Prior Placebo (N=129)			All prior QTP (N=251)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
112 DB Baseline	62	**0.3**	1.2	113	**-0.1**	1.4	175	**0.0**	1.3
Week 26	41	0.4	1.1	86	0.1	1.22	127	0.2	1.2
Final Visit	62	**0.5**	1.0	113	**0.2**	1.3	175	**0.3**	1.2
149 DB Baseline	67	**1.0**[a]	1.0	138	**0.9**[a]	1.1	205	**0.9**[a]	1.0
Week 26	37	1.2	1.0	77	1.2	1.0	114	1.2	1.0
Final Visit	63	**1.2**	1.0	135	**1.0**	1.0	198	**1.1**	1.0
DB Total Baseline	129	**0.6**	1.2	251	**0.4**	1.3	380	**0.5**	1.3
Week 26	78	0.8	1.1	163	0.6	1.2	241	0.7	1.2
Final Visit	125	**0.9**	1.0	248	**0.7**	1.2	373	**0.7**	1.2

[a] The mean BMI Z score at baseline is much higher for the 149 population

Table 8 below shows patients who had a ≥ 0.5 shift in BMI Z-score during trial D1441C00150 from both DB baseline and OL baseline and by indication. Of all patients who completed 26 weeks of treatment with quetiapine, 18.3% (44/241) had a shift of ≥ 0.5 BMI Z-score.

Table 8 **Patients with ≥ 0.5 shift in BMI Z score in Study D1441C00150 by indication**

Occurrence	Schizophrenia to OL 150		BP to OL 150		OL 150
Time/baseline	DB All Quetiapine	DB Placebo	DB All Quetiapine	DB Placebo	OL All - Quetiapine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	N/N (%)
End of Treatment/DB	24/113 (21.2)[a]	17/62 (27.4)[a]	29/135 (21.5)[c]	12/63 (19)[c]	82/373 (22)
End of Treatment/OL	16/113 (14.2)[b]	15/62 (24)[b]	11/133 (8.3)[b]	12/63 (19)[b]	54/371 (14.6)[b]

[a] From double blind baseline of study 112 to end of study 150; [b] From OL baseline of study 150 to end of study 150; [c] From double blind baseline of study 149 to end of study 150

Patients with ≥0.5 shift in standardized BMI Z-score in Study D1441C00150 by age group

A similar percentage of patients ≤12 years of age (who enrolled in study D1441C00150) treated with prior placebo (28% at EOT) had ≥0.5 shift in standardized BMI Z-score compared with prior quetiapine-treated patients (25% at EOT) from the DB baseline (see Table 9).

A higher percentage of patients ≤12 years of age (who enrolled in study D1441C00150) treated with prior placebo (24% at EOT) had ≥0.5 shift in standardized BMI Z-score compared with prior quetiapine-treated patients (8.6% at EOT) from the OL baseline (see Table 9).

A similar percentage of pediatric patients 13-18 years of age (who enrolled in study D1441C00150) treated with prior placebo (22% at EOT) had ≥0.5 shift in standardized BMI Z-score compared to prior quetiapine-treated patients (20.1% at EOT) from the DB baseline (see Table 9).

A higher percentage of pediatric patients 13-18 years of age (who enrolled in study D1441C00150) treated with prior placebo (21% at EOT) had ≥0.5 shift in standardized BMI Z-score compared to prior quetiapine-treated patients (11.7% at EOT) from the OL baseline (see Table 9).

Table 9 **Patients with ≥0.5 shift in BMI Z score in Study D1441C00150 by age group***

Occurrence	≤ 12 years OL 150		13 to 17 years OL 150		OL 150
Time/baseline	DB All Quetiapine	DB Placebo	DB All Quetiapine	DB Placebo	OL All - Quetiapine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
End of Treatment/DB	15/59 (25)	7/25 (28)	38/189 (20.1)	22/100 (22)	82/373 (22)
End of Treatment/OL	5/58 (8.6)	6/25 (24)	22/188 (11.7)	21/100 (21)	54/371 (14.6)

* Study 112 was a six week placebo controlled trial in adolescent patients (13-17 years) and study 149 was a three week trial in children and adolescent patients (10-17 years)

5.1.4.2 Overall summary of pediatric clinical trial data

In trial D1441C00112, the mean increase in body weight was 2 kg in the quetiapine group and -0.4 kg in the placebo group. Twenty-one percent of quetiapine patients and 7% of placebo patients had gained ≥7% of their body weight.

In trial D144C00149, the mean increase in body weight was 1.7 kg in the quetiapine group and 0.4 kg in the placebo group. Twelve percent of quetiapine patients and 0% of placebo patients had gained ≥7% of their body weight.

In trial D1441C00150, where 63% of patients (241/380) completed 26 weeks of therapy with quetiapine, the mean increase in body weight was 4.4 kg. Forty-five percent of the patients had ≥7% increase in body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks, an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change; 18.3% of patients on quetiapine met this criterion after 26 weeks of treatment.

6. BENEFITS AND RISKS CONCLUSIONS

The purpose of this application is to update the SEROQUEL Core Data Sheet and local Prescribing information with current findings in relation to weight gain in patients treated with quetiapine. AstraZeneca believes that these data do not alter the overall safety and tolerability profile of SEROQUEL and SEROQUEL XR and that the benefit/risk profile of SEROQUEL and SEROQUEL XR remains positive.

7. REFERENCES

Correll et al 2006
Correll CU, Carlson HE. Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. J. Am. Acad. Child. Adolesc. Psychiatry. 2006; 45 (7):771-791.

Reyes et al 2006
Reyes M, Croonenberghs J, Augustyns I, Eerdekens M. Long-term use of risperidone in children with disruptive behavior disorders and subaverage intelligence: efficacy, safety and tolerability. J. Child. Adolescent. Psychopharmacol. 2006; 16(3): 260-272.

According to his/her respective qualification the undersigned expert declares hereby to have performed the duties set out in the Article 12 and in accordance with Annex I Part I 1.4 of Directive 2001/83/EC, as amended

CLINICAL:

Name of the expert: Leigh Jefferies, MD
Global Safety Physician
Patient Safety

Signature:

Address:
1800 Concord Pike
Wilmington, DE 19850

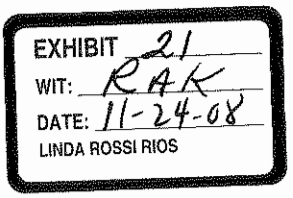
Date:

According to the Annex I of Directive 2001/83/EC as amended, brief information (curriculum vitae) on the educational, training and occupational experience of the expert is attached.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-639/S-036
NDA 22-047/S-001



AstraZeneca Pharmaceuticals LP
Attention: Gerald Limp
Director, Regulatory Affairs
1800 Concord Pike, PO Box 8355
Wilmington, DE 19803-8355

Dear Mr. Limp:

We acknowledge receipt of your supplemental new drug applications dated June 22, 2007, and July 25, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel (quetiapine fumarate) tablets (NDA 20-639) and Seroquel XR (quetiapine fumarate) extended-release tablets (NDA 22-047).

We additionally refer to an Agency letter dated January 8, 2008, requesting information on glucose abnormalities.

These applications, submitted as "Changes Being Effected" supplements, provide for the following revisions to product labeling:

20-639/S-036 dated June 22, 2007

- Revisions throughout labeling to provide for new information on quetiapine and hyperglycemia.

22-047/S-001 dated July 25, 2007

- Revisions throughout labeling to provide for new information on quetiapine and hyperglycemia.
- Revisions to the **Adverse Reactions**-Postmarketing Experience section.
- Revisions to the **Drug Interactions**-P450 3A Inhibitors section.

We have completed our review of these supplemental applications, and they are approvable.

In general, the revisions made to the Postmarketing Experience and Drug Interactions sections are acceptable, and these comments were conveyed to you in an Agency letter dated May 13, 2008.

However, we are requesting the following changes to your proposed labeling (double underline font denotes additions and strike through font denotes deletions) before we can take a final action on these supplemental applications.

> *In 2 long-term placebo-controlled randomized withdrawal clinical trials, mean exposure of 213 days for SEROQUEL (646 patients) and 152 days for placebo (680 patients), the exposure-adjusted rate of any increased blood glucose level (≥ 126 mg/dl) ~~for patients more than 8 hours since a meal~~ was 18.0 per 100 patient years for SEROQUEL (10.7% of patients)*

and 9.5 for placebo per 100 patient years (4.6% of patients). The mean change in glucose from baseline was +5.0 mg/dl for SEROQUEL and -0.05 mg/dl for placebo. Because of limitations in the study design of these long-term trials as well as lack of confirmed fasting glucose data, the effects of SEROQUEL on blood glucose may be underestimated.

For the 2 long term placebo-controlled bipolar maintenance trials, we are deleting the statement "more than 8 hours since a meal" from the proposed labeling language. In general, it does indicate fasting, but you indicated that there was still the possibility of caloric intake in the form of liquids or snacks. Therefore, since these subjects may not have been in a fasting state, this phrase should be deleted to reduce confusion.

Since the 2 long-term placebo-controlled bipolar maintenance trials studies were randomized withdrawal trials, there is some bias in that only subjects who were able to tolerate quetiapine in the open-label phase are then randomized. If subjects did not tolerate quetiapine in the open label phase, if they dropped out due to elevations in blood glucose for example, they would not be randomized and the overall effect of the drug on this parameter would be skewed. Therefore, because of this design issue, the overall effect of Seroquel on blood glucose could be underestimated.

In short-term (12 weeks duration or less) placebo-controlled clinical trials (3342 treated with Seroquel and 1490 treated with placebo), the percent of patients who had a fasting blood glucose ≥126 mg/dl or a non fasting blood glucose ≥200 mg/dl was 3.5% for quetiapine and 2.1% for placebo. The mean increase in glucose from baseline was 2.70 mg/dl for SEROQUEL and 1.06 mg/dl for placebo.

For the 24 week active-controlled trial designed to evaluate glycemic status, you included only the LS mean data, and not the mean change from baseline to week 24 for the quetiapine group. Please provide us these data so that it can be incorporated into product labeling.

Based on the PLR regulations, your proposed addition of "Adverse Reactions, Vital Signs and Laboratory Studies, Hyperglycemia (6.2)" under RECENT MAJOR CHANGES in the Highlights should be deleted.

Additionally, we would refer you to our January 8, 2008 letter requesting information on the following glucose data. Please submit these information by the requested due date, June 30, 2008.

- Glucose mean and median change analyses of serum glucose levels by baseline values (baseline to endpoint and baseline to highest measurement for fasting and non-fasting data)
- Fasting serum glucose post-treatment cut-off values are 140 mg/dL, 200 mg/dL, and 300 mg/dL
- Non-fasting serum glucose post-treatment cut-off value level is 300 mg/dL
- Observed case analyses of mean glucose change for the following specified exposure durations - 2 weeks, 4 weeks, 8 weeks, 12 weeks, 24 weeks, and 48 weeks
- Analyses of the proportion of subjects with post-baseline hemoglobin A1c ≥ 6.1%, 8%, 10%, and 12% among patients with baseline hemoglobin A1c values below 6.1%

- Analyses of the proportion of subjects with treatment-emergent glycosuria (defined as any glucose in the urine) for each subject

If you have any questions, call Kimberly Updegraff, Regulatory Project Manager, at 301-796-2201.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
6/25/2008 04:03:23 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDAs 20-639, 22-047

Gerald Limp
Director, Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike, PO Box 8355
Wilmington, DE 19803-8355

Dear Mr. Limp:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel (quetiapine fumarate) Tablets (NDA 20-639) and Seroquel XR (quetiapine fumarate) Extended-Release Tablets (NDA 22-047).

The Division of Psychiatry Products is evaluating the effects of atypical antipsychotic drugs on metabolic parameters (e.g., weight, lipids, and glucose). We are writing to request analyses from your clinical development program.

Subject Groups to Be Evaluated

In Table 1 below, we outline the subject groups for which we request information. For each analysis discussed subsequently, we request evaluation related to each of the groupings in Table 1 (9 total), unless otherwise noted.

Table 1. Subject Groups to Be Evaluated

I. All Adult Subjects
   1. Adult Subjects in Placebo-Controlled Trials
   2. Adult Subjects in Comparator-Controlled Trials §
   3. All Adult Quetiapine-treated Subject Data, Controlled and Uncontrolled

II. Pediatric and Adolescent Subjects (Age <18 at Time of Enrollment) †
   1. Pediatric and Adolescent Subjects in Placebo-Controlled Trials
   2. Pediatric and Adolescent Subjects in Comparator-Controlled Trials §
   3. All Pediatric and Adolescent Quetiapine-treated Subject Data, Controlled and Uncontrolled

III. Subjects with First Episode Psychosis and Antipsychotic-Naïve Subjects*
   1. Subjects with First Episode Psychosis and Antipsychotic-Naïve Subjects in Placebo-Controlled Trials
   2. Subjects with First Episode Psychosis and Antipsychotic-Naïve Subjects in Comparator-Controlled Trials §

3. All Data for Quetiapine-treated Subjects with First Episode Psychosis and Antipsychotic-Naïve Subjects, Controlled and Uncontrolled

§ For evaluations of comparator-controlled trials, we request separate evaluations for each comparator with data for more than 50 subjects.

† Include all pediatric and adolescent subjects, including subjects in trials that do not enroll only pediatric or adolescent subjects.

* This subject group is comprised of two categories of subjects: subjects with first episode psychosis and antipsychotic-naïve subjects. This group includes subjects from trials with psychiatric indications only and includes adult and pediatric subjects. Include all subjects with first episode psychosis and all antipsychotic-naïve subjects, including subjects in trials that did not enroll these types of subjects exclusively. We define antipsychotic-naïve subjects as those who have received antipsychotic therapy for four months or less prior to study enrollment.

Subject Exclusion Criteria

We request the exclusion of subjects from trials that meet the following criteria:

- Studies without a source drug monotherapy arm
- Studies with duration under 7 days
- Studies with a relapse-prevention study design, in which subjects had source drug exposure prior to randomization
- Studies evaluating the source drug using routes of drug delivery other than oral drug delivery (e.g., intramuscular, intravenous)

Tables Summarizing Clinical Trials for Each Subject Group

We request tables with summary information on clinical trials with metabolic data. For each subject group in Table 1 (9 total) provide a data table with the 18 columns summarized in Table 2. Each row should contain information on a single clinical trial.

Table 2. Clinical Trial Information

Column Number	Column Name	Description	Notes
1	Study	Clinical Trial Name	
2	Indication	Trial Indication	

Column Number	Column Name	Description	Notes
3	Quetiapine N	Number of subjects in the clinical trial who received the source drug	
4	Quetiapine Dose Range	Range of source drug doses used in the clinical trial	
5	Placebo N	Number of subjects in the clinical trial who received placebo. If no subjects received placebo, leave the column blank.	
6	Comparator	Name of the comparator(s) used in the trial. Multiple comparators may be listed.	
7	Comparator N	Number of subjects in the trial who received the comparator. If there are multiple comparators, list comparator N adjacent to the comparator (see example).	<table><tr><td>Comparator</td><td>Comparator N</td></tr><tr><td>Comp 1 Comp 2</td><td>43 55</td></tr></table>
8	Total Cholesterol	If not measured, leave blank. Otherwise, enter one of the following: R (random) NF (non-fasting) F (fasting	
9	HDL Cholesterol	If not measured, leave blank. Otherwise, enter one of the following: R (random) NF (non-fasting) F (fasting	
10	LDL Cholesterol	If not measured, leave blank. Otherwise, enter one of the following:	

Column Number	Column Name	Description	Notes
		R (random) NF (non-fasting) F (fasting	
11	Triglycerides	If not measured, leave blank. Otherwise, enter one of the following: R (random) NF (non-fasting) F (fasting	
12	Glucose	If not measured, leave blank. Otherwise, enter one of the following: R (random) NF (non-fasting) F (fasting	
13	HbA1c	Hemoglobin A1c. If not measured, leave blank. If measured, enter Y for yes.	
14	UA glucose	Urine glucose. If not measured, leave blank. If measured, enter Y for yes.	
15	Weight	If not measured, leave blank. If measured, enter Y for yes.	
16	Duration Controlled	Enter the duration controlled in weeks.	
17	Duration Uncontrolled	Enter the Duration Uncontrolled in Weeks	
18	Notes	Any additional notes about the study (optional).	

Tables Summarizing Subject Demographic Information

We request demographic tables for each of the nine subject groups described in Table 1 with the following information:

- Mean Age
- Gender
- Race
- Treatment Indication
- Mean Modal Dose Received
- Median Time of Exposure to Treatment
- Number of Years Since First Antipsychotic Medication Prescribed (if available)
- Percent Discontinued due to Lack of Efficacy
- Percent Discontinued to Side Effect
- Percent Discontinued Due to Metabolic Side Effect
- Mean Baseline Weight
- Mean Baseline BMI

Tables Summarizing Subject Metabolic Data

Each data table should clearly list:

- The studies from which analyses were derived
- The mean modal dose of treatment received by each subject group
- The median, range, and interquartile range of treatment exposure time for each subject group

We have the following specific requests regarding the analysis plan for weight, lipids, and glucose:

I. Weight

I. A. Weight: Mean Change Analyses

- We request analyses of simple mean changes in weight and in body mass index (BMI) from baseline to last observation carried forward (LOCF) endpoint for all patients in each subject group; we also request similar mean change analyses of subgroups divided according to World Health Organization categories of baseline BMI: Underweight (BMI<18.5), Normal Weight (18.5≤BMI<25), Overweight (25≤BMI<30), and Obese (BMI≥30). We request that treatment effect be assessed based on an analysis of variance (ANOVA) model with terms for protocol and treatment. It is not necessary to perform this analysis on the combined controlled and uncontrolled subject groups.

- We request observed case analyses of mean change for the following specified exposure durations: 2 weeks, 4 weeks, 8 weeks, 12 weeks, 24 weeks, and 48 weeks. For these analyses, mean weight change should be reported for all patients who completed the study time up to the time point specified for that analysis. Comparison between treatment groups should be conducted and p-values reported. We request information on all subject groups in Table 1 for this analysis.

I. B. Weight: Categorical Analyses

To assess for weight gain outliers in each subject group, stratifying by treatment exposure time, we request analyses similar in format to the table below:

Table 3. Combined Weight Data

	6 weeks		6 months		12 months		24 months		36 months	
Weight change (kg)	n	%	n	%	n	%	n	%	n	%
Wt change ≤0	500	10								
0<Wt change≤5	500	10								
5<Wt change≤10	500	10								
10<Wt change≤15	500	10								
15<Wt change≤20	500	10								
20<Wt change≤25	500	10								
25<Wt	500	10								

change≤30										
30<Wt change≤35	500	10								
35<Wt change≤40	500	10								
Wt change>40	500	10								
Total for time point	5000	100		100		100		100		100

- Using this format, we request analyses for all subject groups in Table 1.
- Since changes in weight are sometimes difficult to interpret in pediatric populations, we request additional tables displaying change in BMI. The format is similar to Table 3, except that it substitutes "BMI Change" for "Weight Change." The BMI change categories should be as follows: BMI change ≤0, 0<BMI change≤1, 1<BMI change≤2, 2<BMI change≤3, 3<BMI change≤4, 4<BMI change≤5, 5<BMI change≤6, 6<BMI change≤9, 9<BMI change≤12, 12<BMI change≤15, and BMI change>15.
- Please ensure that analyses have not included individual subjects more than once.

II. Lipids

II. A. Lipids: Mean Change Analyses

- Assess simple mean changes in the following lipid parameters: total cholesterol (combined fasting and non-fasting), fasting triglycerides, non-fasting triglycerides, HDL cholesterol (combined fasting and non-lasting), and fasting LDL cholesterol. We request that treatment effect be assessed based on an analysis of variance (ANOVA) model with terms for protocol and treatment. It is not necessary to perform this analysis on the combined controlled and uncontrolled subject groups. Otherwise, we request analyses for the placebo-controlled and comparator-controlled subject groups in Table 1.
- We request analyses of all subject groups listed in Table 1. Because exposure time is essential to interpreting lipid results, we request for each subject group separate analyses of: 1.) All subjects and 2.) Subjects with at least 12 weeks of exposure 3.) Subjects with at least 24 weeks of exposure.
- We request that median exposure at time of lipid measurement also be listed with each table related to lipids. This is in addition to information on clinical trials included in calculations, drug exposure time, and dose requested earlier in this document.
- Report the mean baseline lipid value, post-treatment lipid value, and magnitude of change.

II. B. Lipids: Categorical Analyses

II. B. 1. Lipid Categorical Analyses: Adult Subjects

- We request analyses of all subject groups listed in Table 1. Because exposure time is essential to interpreting lipid results, we request for each subject group in Table 1 separate analyses of: 1.) All subjects and 2.) Subjects with at least 12 weeks of exposure 3.) Subjects with at least 24 weeks of exposure.
- We request that median exposure at time of lipid measurement also be listed with each table related to lipids. This is in addition to information previously requested on studies included, dose, and treatment exposure time.
- In tables of categorical lipid analyses, report the mean or median baseline, post-baseline, and change in lipid values for each analysis.
- We request the following analyses of treatment-emergent significant changes in lipids listed in Tables 4 and 5.

Table 4. Treatment-Emergent Significant Changes in Lipids: Based on NCEP-based Classifications for Adults*

	Baseline	Postbaseline
Total Cholesterol (Fasting and Non-Fasting)*		
Normal to High	<200 mg/dL	≥240 mg/dL
Borderline to High	≥200 and <240 mg/dL	≥240 mg/dL
Normal/Borderline to High	<240 mg/dL	≥240 mg/dL
Normal to Borderline/High	<200 mg/dL	≥200 mg/dL
LDL Cholesterol (Fasting)		
Normal to High	<100 mg/dL	≥160 mg/dL
Borderline to High	≥100 and <160 mg/dL	≥160 mg/dL
Normal/Borderline to High	<160 mg/dL	≥160 mg/dL
Normal to Borderline/High	<100 mg/dL	≥100 mg/dL
HDL Cholesterol (Fasting and Non-fasting)*		
Normal to Low	≥40 mg/dL	<40 mg/dL
Triglycerides (Fasting)		
Normal to High	<150 mg/dL	≥200 mg/dL
Normal to Very High	<150 mg/dL	≥500 mg/dL
Borderline to High	≥150 and <200 mg/dL	≥200 mg/dL
Borderline to Very High	≥150 and <200 mg/dL	≥500 mg/dL
Normal/Borderline to High	<200 mg/dL	≥200 mg/dL
Normal/Borderline to Very High	<200 mg/dL	≥500 mg/dL

Normal to Borderline/High/Very High	<150 mg/dL	≥150 mg/dL

* The National Cholesterol Education Program (NCEP) Adult Treatment Program Classifications of lipids refer to fasting lipid measurements. However, given that total cholesterol and HDL cholesterol measurements are not significantly changed by fasting status and that the majority of clinical trial lipid data is non-fasting, we elect to include fasting and non-fasting values for total cholesterol and HDL cholesterol in combined analyses.

Table 5. Treatment-Emergent Significant Changes in Lipids: Additional Analyses

	Baseline	Post-baseline
Treatment- emergent very high triglycerides (fasting)	Fasting triglycerides <500 mg/dL	Fasting triglycerides ≥500 mg/dL
Treatment-emergent very high triglycerides (non-fasting and random)	Non-fasting and random triglycerides <500 mg/dL	Non-fasting and random triglycerides ≥500 mg/dL
Treatment-emergent triglycerides >1000 mg/dL (All cases—fasting, non-fasting, and random)	Triglycerides <1000 mg/dL	Triglycerides ≥1000 mg/dL
Change in fasting or non-fasting total cholesterol ≥40 mg/dL at any time post-baseline[1]	Any value	Increased fasting or non-fasting total cholesterol ≥40 mg/dL
Change in fasting LDL cholesterol ≥ 30 mg/dL at any time post-baseline[2]	Any value	Increased fasting LDL cholesterol ≥ 30 mg/dL
Change in fasting or non-fasting HDL cholesterol ≥20 mg/dL at any time post-baseline[3]	Any value	Decreased fasting or non-fasting HDL cholesterol ≥20 mg/dL
Change in fasting triglycerides ≥50 mg/dL at any time post-baseline[4]	Any value	Increased fasting triglycerides ≥50 mg/dL

[1] We also request subgroup analyses based on the following categories of baseline fasting or nonfasting total cholesterol for adults: Normal (<200 mg/dL), Borderline (≥200 and <240 mg/dL), and High (≥240 mg/dL). For pediatric subjects use the total cholesterol categories listed in Table 6.
[2] We also request subgroup analyses based on the following categories of baseline fasting LDL cholesterol for adults: Normal (<100 mg/dL), Borderline (≥100 and <160 mg/dL), and High (≥160 mg/dL). For pediatric subjects use the fasting LDL cholesterol categories listed in Table 6.
[3] We also request subgroup analyses based on the following categories of baseline fasting or non-fasting HDL cholesterol: Normal (≥40 mg/dL) and Low (<40 mg/dL).
[4] We also request subgroup analyses based on the following categories of baseline fasting triglycerides: Normal (<150 mg/dL), Borderline (≥150 and <200 mg/dL), High (≥200 and <500 mg/dL), and Very High (≥500 mg/dL).

II. B. 2. Lipid Categorical Analyses: Pediatric Subjects

Because the National Cholesterol Education Program (NCEP) defines borderline and high cut-off values for LDL cholesterol and total cholesterol differently in pediatric subjects, we request using these criteria in pediatric subject analyses.[1] The LDL cholesterol criteria apply to fasting lipid measurements, and the total cholesterol criteria apply to fasting and non-fasting lipid measurements.

Since NCEP has designated specific pediatric cut-off values for neither HDL cholesterol nor triglycerides, we request using identical categories for clinically significant changes in HDL cholesterol and triglycerides in adult and pediatric subjects (see Tables 4 and 5 above).

Regarding the pediatric and adolescent subject groups only, we request the following categorical lipid analyses (Tables 7) based on the NCEP criteria (Table 6).

Table 6. Criteria for Abnormal Metabolic Values in Pediatric Subjects

Criterion	Abnormal Value in Pediatric Subjects
Normal Fasting LDL Cholesterol Level	<110 mg/dL
Borderline Fasting LDL Cholesterol Level	110-129 mg/dL
High Fasting LDL Cholesterol Level	≥130 mg/dL

[1] NCEP Expert Panel on Blood Cholesterol Levels in Children and Adolescents. National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics 1992; 89(3):495-501.

Normal Total Cholesterol Level	<170 mg/dL
Borderline Total Cholesterol Level	170-199 mg/dL
High Total Cholesterol Level	≥200 mg/dL

Table 7. Pediatric Categorical Analyses: Treatment-Emergent Significant Changes in Lipids

	Baseline	Post-baseline
Normal to borderline total cholesterol level (fasting and non-fasting values)	<170 mg/dL	170-199 mg/dL
Normal to high total cholesterol level (fasting and non-fasting values)	<170 mg/dL	≥200 mg/dL
Borderline to high total cholesterol levels	170-199 mg/dL	≥200 mg/dL
Normal to borderline fasting LDL cholesterol level	<110 mg/dL	110-129 mg/dL
Normal to high fasting LDL cholesterol level	<110 mg/dL	≥130 mg/dL
Borderline to high fasting LDL cholesterol level	110-129 mg/dL	≥130 mg/dL

III. Glucose

III. A. Glucose: Mean Change Analyses

III. A. 1. Glucose: Overall Mean Change Analyses

We request analysis of mean and median changes in serum glucose levels from baseline to endpoint (separate analyses for fasting and non-fasting data). We also request mean and median changes in serum glucose levels from baseline to highest measurement (separate analyses for fasting and non-fasting data).

We also request observed case analyses of mean change for the following specified exposure durations: 2 weeks, 4 weeks, 8 weeks, 12 weeks, 24 weeks, and 48 weeks. For these analyses, mean change in serum glucose from baseline to highest post-baseline measurement should be reported for all subjects who completed the study time up to the time point specified for that analysis. Comparison between treatment groups should be conducted and p-values reported. We request information on all subject groups in Table 1 for this analysis.

III.A. 2. Glucose: Mean Change Analyses by Baseline Values

We request that each of the mean change analyses (baseline to endpoint and baseline to highest measurement for fasting and non-fasting data) described in section III.A.1 also be performed with stratification according to baseline serum glucose measurement for each of the six categories in Table 8, as follows:

Table 8. Categorization of Serum Glucose Levels (Based on American Diabetes Association Criteria)

Fasting Serum Glucose	
Normal	<100 mg/dL
Impaired Fasting Glucose	100-125 mg/dL
Diabetes (High)	≥126 mg/dL
Non-fasting Serum Glucose	
Normal	<140 mg/dL
Borderline	140-199 mg/dL
High	≥200 mg/dL

III. B. Glucose: Categorical Analyses

We request analyses of proportions of subjects with treatment-emergent changes of interest at any time post-baseline as described in Table 9 below. We request that you compare the proportions of subjects with clinically significant changes using Fisher's exact test.

Table 9. Serum Glucose: Criteria for Clinically Significant Changes

	Baseline	Post-Treatment
Fasting Serum Glucose		
Normal to High	<100 mg/dL	≥126 mg/dL
Impaired Fasting Glucose to High	100-125 mg/dL	≥126 mg/dL
Normal/Impaired Fasting Glucose to High	<126 mg/dL	≥126 mg/dL
Change in fasting serum glucose ≥10 mg/dL at any time post-baseline*	Any value	Fasting glucose increased ≥10 mg/dL
Non-Fasting Serum Glucose		
Normal to High	<140 mg/dL	≥200 mg/dL
Borderline to High	140-199 mg/dL	≥200 mg/dL
Normal to Borderline/High	<140 mg/dL	≥140 mg/dL
Normal/Borderline to High	<200 mg/dL	≥200 mg/dL
Change in non-fasting serum glucose ≥20 mg/dL at any time post-baseline*	Any value	Non-fasting glucose increased ≥20 mg/dL

* For these two analyses, we request additional subgroup analyses divided according to baseline glucose levels. Please use the categorizations of fasting serum glucose and non-fasting serum glucose listed in Table 8 to define the subgroups.

In addition to the analyses listed in Table 9, we request similar analyses using the following additional serum glucose cut-off values:

- For fasting serum glucose, we request analyses of the proportion of subjects with post-treatment levels of 140 mg/dL, 200 mg/dL, and 300 mg/dL.
- For non-fasting glucose, we request analyses of the proportion of subjects with post-treatment level of 300 mg/dL.

We request analyses of the proportion of subjects with post-baseline hemoglobin A1c $\geq$ 6.1%,[2] 8%, 10%, and 12% among patients with baseline hemoglobin A1c values below 6.1%.

We also request analyses of the proportion of subjects with treatment-emergent glycosuria (defined as any glucose in the urine) for each subject database listed in Table 1.

Time Frame for Submission to the Division of Psychiatry Products

Responses to this information request may be submitted in stages. Specifically, information from placebo-controlled trials (all subject groups), comparator-controlled trials (all subjects groups), and combined controlled and uncontrolled data (all subjects), may be submitted separately, as they are completed. We expect that the response to all components of this request will be submitted by June 30, 2008.

If you have any questions, call Sonny Saini, Pharm.D., Safety Regulatory Project Manager, at (301) 796-0532.

Sincerely,
{See appended electronic signature page}
Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

[2] Rohlfing, CL, Little RR, Wiedmeyer, HM, et al. Use of GHb (HbA(1c)) in screening for undiagnosed diabetes in the U.S. population; Diabetes Care 2000: 23(2), 187-191.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

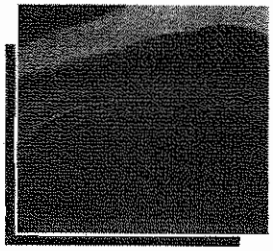
Thomas Laughren
1/8/2008 01:06:01 PM

Managing Weight Gain and Diabetes in Schizophrenia

A Patient Case Study

From the files of
Michael J. Reinstein, MD

Forest Foundation, Inc.
Clinical Research Department
Community Mental Health
Chicago, Illinois



Patient Presentation

- A 49-year-old white male, unemployed, with a long history of psychiatric hospitalizations dating from age 25
- His various diagnoses include acute schizophrenic episode, paranoid schizophrenia, bipolar disorder, and schizoaffective disorder
- The patient also has a history of alcohol abuse

Past Medical/ Psychiatric History

- The patient was first hospitalized in 1976 with religious delusions, auditory hallucinations, and withdrawal
- He was subsequently hospitalized on several different occasions and followed on an outpatient basis after each discharge

Personal History

- There is no family history of psychiatric illness
- The patient was married with a son but has not had contact with either his wife or son for over 20 years
- He has not been gainfully employed for over 15 years
- He lives sporadically with either his mother or in homeless shelters

As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of tardive dyskinesia. If its signs and symptoms appear, discontinuation should be considered.

Mental/Physical Evaluation

- At presentation, the patient was alert and oriented to time, place, and person, maintained good eye contact, and was stable and in a cooperative mood
- Intelligence appeared to be within normal range
- He denied any hallucinations or ideas of reference
- No EPS, rigidity, or ataxia; no suicidal or homicidal ideations were expressed
- Judgment and reality contact were impaired, he appeared to have no insight, and he frequently laughed inappropriately in response to internal stimuli
- The patient answered questions only after considerable pauses—very briefly and in a low tone and volunteered no information whatsoever
- Physical evaluation revealed a patient overweight by approximately 10 lb

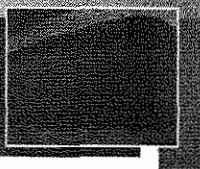
Treatment with SEROQUEL, like other antipsychotics, may result in somnolence, especially during initial dose titration.

Rationale for SEROQUEL Therapy

- Previous treatment with olanzapine 10 mg/day resulted in significant weight gain (10 lb) and subsequent development of type II diabetes (NIDDM)
- Accu-Chek™ was scheduled tid with sliding scale of Humulin® insulin

"This patient demonstrated some classic negative symptoms—blunted affect, emotional withdrawal, poor rapport, lack of spontaneity. Negative symptoms can often be very difficult to treat. We chose SEROQUEL for this patient because in our experience it provides excellent results with negative psychotic symptoms, and weight gain with SEROQUEL hasn't been an issue."

—Michael J. Reinstein, MD



SEROQUEL Dosing Regimen

- Olanzapine therapy was discontinued due to weight gain and the development of diabetes
- SEROQUEL was initiated at 150 mg/day for 1 week
- The SEROQUEL dose was then increased to 300 mg/day where it remains

Response to SEROQUEL

- The patient has shown a positive response to SEROQUEL, becoming more spontaneous, more interested in his surroundings, and has demonstrated improved interactions with others
- Blood glucose levels were brought under control, permitting the substitution of an oral hypoglycemic agent for insulin treatments
- Metabolic stability was maintained, allowing the patient to discontinue the hypoglycemic agent and return to a normal diet
- Not only did the patient not gain weight with SEROQUEL, he lost approximately 8 of the 10 lb gained while on olanzapine

"Our laboratory data revealed a normalization of serum glucose levels which is valid proof of improvement of diabetes and metabolic stabilization. His psychotic symptoms were well controlled, including the negative symptoms. The patient lost weight (8 lb) and is very pleased about this. He is also relieved that he no longer has to take daily insulin injections."

—Michael J. Reinstein, MD

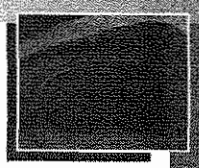
Follow Up

- After 7 months, the patient remains well on SEROQUEL 300 mg/day
- The patient is currently taking part in a research study, where he perceives himself as a partner in a joint endeavor. He has achieved clinical improvement and a better quality of life
- He denies having any side effects and is considered competent to handle his own funds and supervised self-medication

"We have found SEROQUEL to be ideal in patients who have problems with weight gain and, due to this, the development of diabetes. In this patient, once olanzapine was discontinued and SEROQUEL was started, the weight was lost, the diabetes resolved, and the patient was able to stop taking hypoglycemic medication. In our experience, weight gain is not an issue with SEROQUEL, unlike some other antipsychotic medications."

—Michael J. Reinstein, MD

As with all antipsychotic medications, a rare condition referred to as neuroleptic malignant syndrome (NMS) has been reported, and prescribing should be consistent with the need to minimize the risk.



Seroquel®
quetiapine fumarate 25 mg, 100 mg & 200 mg tablets

For a more normal life

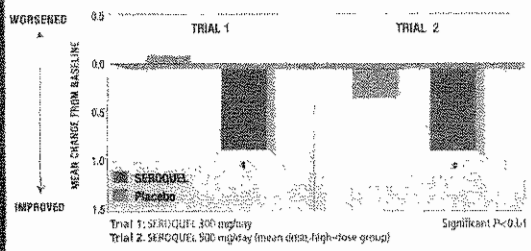
Please see accompanying full prescribing information.

The Strength to Control Both Positive and Negative Symptoms

Across well-controlled trials

Consistent Efficacy in the Treatment of Positive Symptoms[1-4]...

Mean Change in BPRS* Positive Symptom Cluster Scores (LOCF)[1,4†]



- **SEROQUEL significantly reduced positive symptom scores**

SEROQUEL was compared with placebo in the following well-controlled, 6-week, acute-phase, multicenter trials.

Trial 1: fixed doses of 75, 150, 300, 600, and 750 mg/day of SEROQUEL (n=255), placebo (n=51).

Trial 2: titrated doses up to 250 mg/day (low dose, n=94) and up to 750 mg/day (high dose, n=96) of SEROQUEL, placebo (n=96).

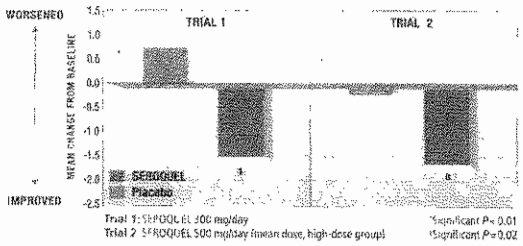
*BPRS: Brief Psychiatric Rating Scale is a clinical assessment tool that measures a combination of 18 individual positive, negative, and general symptom items. The BPRS positive symptom cluster score is the mean of 4 of the 18 individual symptom items for the clinical assessment of conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.

†LOCF: Last Observation Carried Forward.

Precautions listed in the label include orthostatic hypotension and the risk of cataract development.

...and Consistent Efficacy in the Treatment of Negative Symptoms[1,2]

Mean Change in SANS[5] Summary Scores (LOCF)[1-4]



- **SEROQUEL significantly reduced negative symptom scores**

[5]SANS: Modified Scale for the Assessment of Negative Symptoms is used to assess the negative symptoms associated with schizophrenia. The SANS summary score is a total of 5 global items: affective flattening or blunting, alogia, avolition/apathy, anhedonia/asociality, and attention.

The most common adverse events leading to treatment withdrawal were somnolence (0.8%) and hypotension (0.4%).

Seroquel®
quetiapine fumarate 25 mg, 100 mg & 200 mg tablets

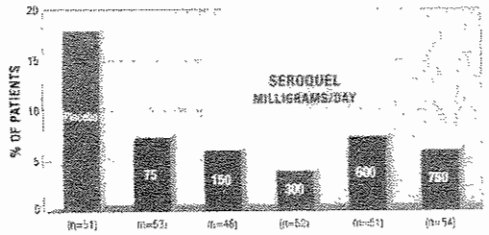
For a more normal life

Please see accompanying full prescribing information.

Outstanding Overall Tolerability Across the Entire Dose Range

Across the entire dose range,* an EPS† profile no different from placebo

EPS Adverse Events by Dose[1‡]

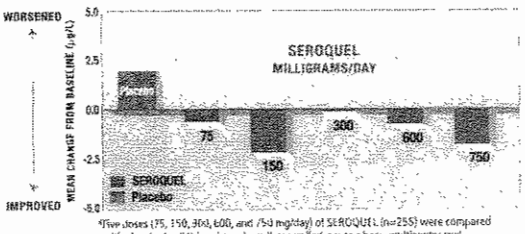


*In a 6-week, acute-phase, placebo-controlled trial
†EPS: Extrapyramidal Symptoms were defined as dystonia, akathisia, and parkinsonism
‡Five doses (75, 150, 300, 600, and 750 mg/day) of SEROQUEL (n=255) were compared with placebo (n=51) in a 6-week, well-controlled, acute-phase, multicenter trial.

- No dose-related EPS were associated with treatment with SEROQUEL® (quetiapine fumarate)[5]

Across the entire dose range, plasma prolactin levels no different from placebo[1§]

Mean Change in Plasma Prolactin Levels[1]



§Five doses (75, 150, 300, 600, and 750 mg/day) of SEROQUEL (n=255) were compared with placebo (n=51) in a 6-week, well-controlled, acute-phase, multicenter trial.

- There were no statistically significant differences in plasma prolactin levels between any group taking SEROQUEL and the placebo group[1]

Minimal Weight Gain

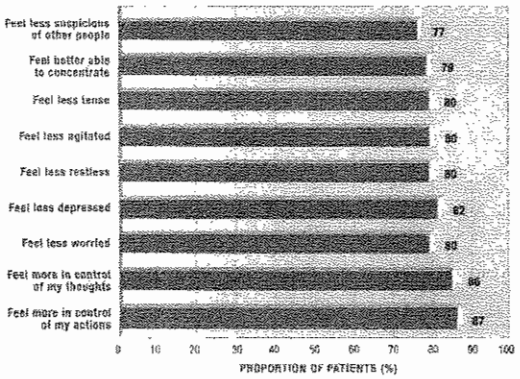
- In a recent open-label study, only 2.5% of patients treated with SEROQUEL (n=553) reported weight gain[6]

Patient Preferred

In a survey of patients (n=129) using SEROQUEL[7]

- 97% reported that they preferred SEROQUEL to previous medications
  - —Two reasons for preferring SEROQUEL were efficacy (29%) and tolerability (41%)[7]
- Benefits noticed in the last 6 months by patients using SEROQUEL

Efficacy-Related Benefits[7]



As with other antipsychotic agents, SEROQUEL has been associated with weight gain. However, in all placebo-controlled clinical trials, weight gain was approximately 5 lb, which occurred mainly during the early weeks of treatment.[5]

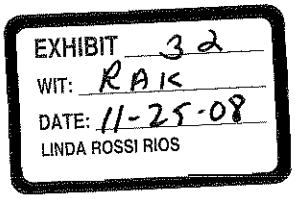
Please see accompanying full prescribing information.

Id :	i.m.c6eeb47556ec043db4b68161227303d2
CN :	SQ1ED00100027
Date :	Monday, February 15, 1999 9:34:00 PM GMT
From :	Owens Judith J
To :	Davies Diane DE - MMCC; Hough Nick NW; Jones Martin AM - PHMS; Lawrence Richard RA; Litherland Steve S; Murray Michael MF; Price Anna AC; Rak Ihor IW
Cc :	Bill Kevin K; Tugend Georgia GL; Tumas John JA
Subject :	ECNP Abstract 'Weight gain & diabetes management'
Attachments :	Management of Weight Gain and Diabetes by Clozapine.doc
Custodians :	Jones, Martin

From: Owens Judith J
Sent: 2/15/1999 8:20:50 AM
To: Davies Diane DE - MMCC; Rak Ihor IW; Litherland Steve S; Jones Martin AM - PHMS; Hough Nick NW; Price Anna AC; Lawrence Richard RA; Murray Michael MF
CC: Tumas John JA; Tugend Georgia GL; Bill Kevin K
BCC:
Subject: ECNP Abstract 'Weight gain & diabetes management'

Dear All
Sorry for the previous e-mail which contained the abstract but no message.
Please find attached an abstract for review. The abstract on the topic of 'management of weight gain and diabetes' is intended for submission to ECNP. The author, Dr Reinstein - a US investigator, has written this article which is reporting on his own study. This abstract has been deemed internationally important by the Communications Planning Team, therefore it is being subjected to international review. Should you have any comments on Dr Reinstein's abstract please forward them directly to John Tumas [you will see that there are some queries which need to be put to the author, these are italicised in the attachment].
Kind regards
Judith Owens
Ext: (2)8235

>----------
>From: Owens Judith J
>Sent: 15 February 1999 13:04
>To: Davies Diane DE - MMCC; Rak Ihor IW; Litherland Steve S; Jones Martin AM - PHMS; Hough Nick NW; Price Anna AC; Lawrence Richard RA; Murray Michael MF
>Cc: Tumas John JA; Tugend Georgia GL; Bill Kevin K
>
><<File: Management of Weight Gain and Diabetes by Clozapine.doc>>
>



Management of Weight Gain and Diabetes by Clozapine-Seroquel Combination Therapy: Preliminary Findings

Author: Reinstein

Objective: To assess changes in weight and diabetes status for patients who initially were treated with Clozapine and then switched to Clozapine-Seroquel combination therapy.

Method: Body weight data were collected for a group of 65 randomly selected schizophrenic patients who were on Clozapine initially *[Author: please supply dose and duration of therapy]* and then had Seroquel *[Author: please supply dose]* added to their therapy. Weights were recorded monthly, and status of diabetes follow-up was also performed. Clozapine dosages were reduced as Seroquel was added proportionally.

Results: Data were extracted from retrospective chart review of 65 patients who were prospectively assigned to Clozapine-Seroquel therapy. All 65 patients showed weight loss ranging from 0 to 23 lbs *[Author: range of weight loss should start above 0 lbs if* ***all*** *patients had weight loss]*, with a mean loss of 3.98 lbs, after the first month of treatment *[Author: change statement to 'the first month of combination treatment'? What was the Seroquel dose at one month?]*. The improvement continued through the study end points. Marked total weight loss ranged from 1 to 41 lbs, with a mean loss of 9.2 lbs over the 10-month study period. Twenty per cent of patients developed diabetes during Clozapine monotherapy and showed significant improvement of diabetes with addition of Seroquel *[Author: did each of these patients with diabetes show significant improvement with Seroquel?]*.

Conclusions: An unusual clinical effect of Seroquel is its apparent propensity to induce weight loss and help with diabetes management in patients who gain weight and develop diabetes on Clozapine. The study's data support the safety and tolerability of Clozapine-Seroquel combination therapy.

This research was supported by Zeneca Pharmaceuticals Inc.

Background: letter from M. Reinstein, et al to D. Brennan, dated Oct. 23, 2001

This group does generate a very significant amount of SEROQUEL sales for us. They run several clinics in the city of Chicago and by all accounts have over 1,000 patients on SEROQUEL. While likely not "the largest prescribers of SEROQUEL in the world", they probably are in the top 5 in the US.

Because of their patient volume they are attempting to establish themselves as a research center.

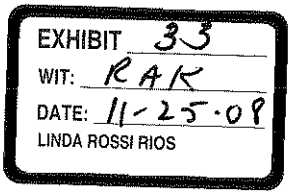
This group, in particular John Sonneberg PhD, Director of Research has been extremely persistent in recent months with demanding research from AZ. Their comments to several AZ employees suggest since they use large volumes of SEROQUEL they should by default be doing research on our behalf. They have further implied that should they not get research funding that they would switch patients currently on SEROQUEL to competitive agent(s).

Our Clinical colleagues have significant and numerous issues in past with the quality of research that this group has produced in the past. Matters such as not getting informed consent from study participants, modification of protocols without permission, etc has made the business understandably reluctant to place studies with this group. There is little confidence that Good Clinical Practices can be adhered to. Their research is often criticized by peers in Psychiatry.

However, in attempts to have a "win-win" for all, we have offered funding for projects such as retrospective chart reviews (as opposed to well-controlled, double blinded trials) that could do little harm but still demonstrate commitment to the customer. The group has not accepted this and they continue to insist on funding to do a high dose SEROQUEL trial (>1600 mg/day) that is addressed in Point 2 of their letter.

Drs. Reinstein and Chasnov are prolific speakers on our behalf and are particularly influential with prescribers outside the Chicago regional area. They get numerous speaking engagements because of their own experience and belief in the brand. (Note: they are generally held in poor regard among their peers in the greater Chicago area).

Because of their importance to our business, they have had an extraordinary amount of attention given to them. A number of AZ personnel from numerous functions have had open, honest but collegial, cordial dialog with Drs. Reinstein and Sonneberg. Contact has been with Sales, Marketing, USDD, and Scientific Commercialization at several levels, including Leadership levels within our organization. All involved have had extremely good communication internally and with the customers to address their interests. Every discussion appeared to be well received at that time. However, actions like this letter and other persistent calls demanding research continue to occur despite our attention to their group, thus disappointment with the "time for new leadership" remark.



From: Hough Nick NW
Sent: 2/24/1999 8:30:56 AM
To: Rak Ihor IW; Litherland Steve S; Jones Martin AM - PHMS; Price Anna AC; Lawrence Richard RA; Murray Michael MF; Owens Judith J; Bill Kevin K; Davies Diane DE - MMCC; Tumas John JA
CC: Tugend Georgia GL
BCC:
Subject: RE: ECNP Abstract 'Weight gain & diabetes management'

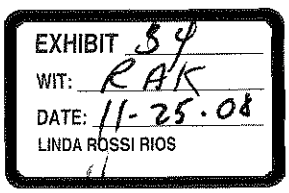
Hi John,

in principle it's the quality of the data, not the source that matters for promo claims etc. - providing, of course, that whatever the message is, that it is consistent with the totality of the data. We must not get too carried away with 'weight loss' when we know the rest of our data appears to point in the other direction, although a specific message related to the special nature of this particular finding might be possible. I need to see a full account of the data in order to be more certain at this stage. In some countries, however, a promotional claim can only be made if the data has been 'published' - usually this means a peer-reviewed journal. In the UK we can use 'data on file', but we must be prepared to supply it to anyone asking for substantiation, and if they don't like it they can complain to the relevant bodies. I guess there are different rules in the US? - as I understand it you can only make promotional claims based on the data/information in your actual labelling; I'd be interested to know more about this.

I hope this helps,

Nick

>----------
>From: Tumas John JA
>Sent: 24 February 1999 13:13
>To: Rak Ihor IW; Litherland Steve S; Jones Martin AM - PHMS; Hough Nick NW; Price Anna AC; Lawrence Richard RA; Murray Michael MF; Owens Judith J; Bill Kevin K; Davies Diane DE - MMCC
>Cc: Tugend Georgia GL
>Subject: RE: ECNP Abstract 'Weight gain & diabetes management'
>
>Actually, this abstract was submitted to APA, which will be the first time it is presented anywhere - that will be May 15 -20. I'm afraid that because it wasn't clear until the last minute if Dr. Reinstein was going to submit this, it never got on our abstract list.
>
>Bye the way, is it possible to make a claim from data that are not the result of a Zeneca trial?
>
> ----------
> From: Davies Diane DE - MMCC
> Sent: Wednesday, February 24, 1999 3:39 AM



> To: Rak Ihor IW; Litherland Steve S; Jones Martin AM - PHMS; Hough Nick NW; Price Anna AC; Lawrence Richard RA; Murray Michae_ MF; Owens Judith J; Bill Kevin K
> Cc: Tumas John JA; Tugend Georgia GL
> Subject: RE: ECNP Abstract 'Weight gain & diabetes management'
>
> Dear Kevin
> If accepted, the abstract will be published at ECNP, which is September 21st 1999.
> To my knowledge this will be the first report of weight loss with seroquel - in this setting.
> kind regards
> Diane
> ----------
> From: Bill Kevin K
> Sent: 23 February 1999 22:52
> To: Davies Diane DE - MMCC; Rak Ihor IW; Litherland Steve S; Jones Martin AM - PHMS; Hough Nick NW; Price Anna AC; Lawrence Richard RA; Murray Michael MF; Owens Judith J
> Cc: Tumas John JA; Tugend Georgia GL
> Subject: RE: ECNP Abstract 'Weight gain & diabetes management'
>
> Is this the first mention of weight loss for SEROQUEL ?>
> If so when does it publish?
>
> ----------
> From: Owens Judith J
> Sent: 15 February 1999 13:20
> To: Davies Diane DE - MMCC; Rak Ihor IW; Litherland Steve S; Jones Martin AM - PHMS; Hough Nick NW; Price Anna AC; Lawrence Richard RA; Murray Michael MF
> Cc: Tumas John JA; Tugend Georgia GL; Bill Kevin K
> Subject: ECNP Abstract 'Weight gain & diabetes management'
>
> Dear All
> Sorry for the previous e-mail which contained the abstract but no message.
> Please find attached an abstract for review. The abstract on the topic of 'management of weight gain and diabetes' is intended for submission to ECNP. The author, Dr Reinstein - a US investigator, has written this article which is reporting on his own study. This abstract has been deemed internationally important by the Communications Planning Team, therefore it is being subjected to international review. Should you have any comments on Dr Reinstein's abstract please forward them directly to John Tumas [you will see that there are some queries which need to be put to the author, these are italicised in the attachment].
> Kind regards
> Judith Owens
> Ext: (2)8235
> <<File: Management of Weight Gain and Diabetes by Clozapine.doc>>
> ----------
> From: Owens Judith J
> Sent: 15 February 1999 13:04

> To: Davies Diane DE - MMCC; Rak Ihor IW; Litherland Steve S; Jones Martin AM - PHMS; Hough Nick NW; Price Anna AC; Lawrence Richard RA; Murray Michael MF
> Cc: Tumas John JA; Tugend Georgia GL; Bill Kevin K
>
> <<File: Management of Weight Gain and Diabetes by Clozapine.doc>>
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>

Distinct advantages of a favorable weight profile

- Weight gain, commonly reported with some other antipsychotics, is associated with particular morbidities:
  —Type 2 diabetes, hypertension, coronary heart disease, cerebrovascular disease, certain cancers, and respiratory problems
- Minimal weight gain may reduce the likelihood that treatment with SEROQUEL will lead to diabetes and other morbidities associated with weight gain.
- Among patients taking antipsychotic medication, weight gain has been shown to cause more distress than other common adverse events

The most common adverse events associated with the use of SEROQUEL are dizziness (10%), postural hypotension (7%), dry mouth (7%), and dyspepsia (6%). The majority of adverse events are mild or moderate.[1]

In premarketing trials, the most common adverse events leading to treatment withdrawal were somnolence (0.8%) and hypotension (0.4%).[1]

As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of tardive dyskinesia, seizures, and orthostatic hypotension.[1]

As with all antipsychotic medications, a rare condition referred to as neuroleptic malignant syndrome (NMS) has been reported.[1]

The safety and effectiveness of SEROQUEL in pediatric patients have not been established.[1]

As with other antipsychotic agents, SEROQUEL has been associated with weight gain. However, in a placebo-controlled clinical trial, weight gain ranged from 0.9 kg to 2.6 kg.[2]

References: 1. SEROQUEL® (quetiapine fumarate) Prescribing Information, AstraZeneca Pharmaceuticals LP, Wilmington, Delaware. **2.** Arvanitis LA, Miller BG, and the Seroquel Trial 13 Study Group. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *Biol Psychiatry.* 1997;42:233-246.

Seroquel®
quetiapine fumarate
25 mg, 100 mg, 200 mg & 300 mg tablets

AstraZeneca

AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 15437
Wilmington DE 19850-5437

7/01 201644

Please see Prescribing Information in pocket of this brochure.

www.SEROQUEL.com

Unknown

From: Gavin Jim JP
Sent: Wednesday, December 08, 1999 12:32 PM
To: De Vriese Geert
Cc: Holdsworth Debbie D;Tumas John JA;Tugend Georgia GL;Czupryna Michael MJ;Gorman Andrew AP;Wilkie Alison AM;Litherland Steve S;Murray Michael MF;Rak Ihor IW;Owens Judith J;O'Brien Shawn SP;Denerley Paul PM;Goldstein Jeffrey JM
Subject: RE: 2 EPS Abstracts for APA

Attachments: jamapubs.pdf

Thanks for this Geert. If I could add my own thoughts in advance of the GPT tomorrow...Certainly any progress on the (selective) use of data from COSTAR would be particularly appreciated, as I'm currently getting mixed messages on whether we use the EPS data from this trial.

I was interested to hear that we are discussiing the recent JAMA article on the reporting of clinical trials (link attached). This article concerns me as it highlights what appears to be an increasing scepticism among journal editors with regards to certain aspects of company-sponsored publications. Janssen have had their fingers burned in the past in this regard, and are consequently cited every time such an editorial appears, something that presumably irritates the hell out of them. Quite apart from any ethical considerations, if they thought we were publishing positive data vs risperidone from QUEST while results from a second trial were being buried, they'd be onto it in a flash. Selectively using (for example) the EPS data from COSTAR is pushing it too far in my opinion, and might prove extremely damaging in the long run (and you can bet Janssen would push it), and would destroy our current high standing in the publishing community.

jamapubs.pdf (112 KB)

Regards
Jim

From: Owens Judith J
Sent: 08 December 1999 09:24
To: Gavin Jim JP
Subject: FW: 2 EPS Abstracts for APA

FYI

From: De Vriese Geert
Sent: 08 December 1999 08:42
To: Baker Kendra; Tumas John JA
Cc: Scanlon Rose Ann RA; Denerley Paul PM; Owens Judith J
Subject: RE: 2 EPS Abstracts for APA

Kendra,
John,

REDACTED

From: Baker Kendra
Sent: 07 December 1999 22:49
To: Owens Judith J; De Vriese Geert
Cc: Tumas John JA; Scanlon Rose Ann RA; Denerley Paul PM
Subject: FW: 2 EPS Abstracts for APA

PRIVILEGED AND CONFIDENTIAL

EXHIBIT 42
WIT: RAK
DATE: 11-25-08
LINDA ROSSI RIOS

REDACTED

Best regards,
Kendra Baker
Attorney
Legal Department
AstraZeneca
Tel. (302) 886-4233 Fax: (302) 886-8221
Kendra.Baker@astrazeneca.com

From: Scanlon Rose Ann RA
Sent: Tuesday, December 07, 1999 2:33 PM
To: Baker, Kendra
Subject: FW: 2 EPS Abstracts for APA

REDACTED

Rose Ann Scanlon
Assistant General Counsel
AstraZeneca
Telephone: 302 886 4009
Fax: 302 886 8221

From: Denerley Paul PM
Sent: December 07, 1999 10:24 AM
To: Scanlon Rose Ann RA
Subject: FW: 2 EPS Abstracts for APA

From: Tumas John JA
Sent: Monday, December 06, 1999 11:45 PM
To: Owens Judith J; Jones Martin AM - PHMS; Litherland Steve S; Gavin Jim JP
Cc: Holdsworth Debbie D; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert; Shadwell Pamela PG
Subject: RE: 2 EPS Abstracts for APA

Please allow me to join the fray.

There has been a precedent set regarding "cherry picking" of data. This would be the recent Velligan presentations of cognitive function data from Trial 15 (one of the buried trials). Thus far, I am not aware of any repercussions regarding interest in the unreported data.

That does not mean that we should continue to advocate this practice. There is growing pressure from outside the industry to provide access to all data resulting from clinical trials conducted by industry. Thus far, we have buried Trials 15, 31, 56, and are now considering COSTAR.

The larger issue is how do we face the outside world when they begin to criticize us for suppressing data. One

could say that our competitors indulge in this practice. However, until now, I believe we have been looked upon by the outside world favorably with regard to ethical behavior. We must decide if we wish to continue to enjoy this distinction.

The reporting of the COSTAR results will not be easy. We must find a way to diminish the negative findings. But, in my opinion, we cannot hide them.

Best regards,

John

From: Gavin Jim JP
Sent: Monday, December 06, 1999 1:59 PM
To: Owens Judith J; Jones Martin AM - PHMS; Litherland Steve S
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert; Shadwell Pamela PG
Subject: RE: 2 EPS Abstracts for APA

Steve's comments are pertinent, as the EPS abstracts (for the APA) and the Scourge of EPS review both emanate from the ECNP symposium, and as such represent a potential transition of COSTAR data from a "closed" mtg to a public forum. Coming in late to the debate, the only directive I have on QUEST/COSTAR (contained in a document compiled by Ihor & Martin in August) suggested using them "as clinically appropriate", but independently.

I believe the newly-formed Commercial Support Team will be considering looking at potential ways of using COSTAR. With regards to the present outputs however, a short-term solution (given the impending APA deadline) is to avoid reference to COSTAR in the proposed APA abstract. Whether or not we discuss it in either the poster or the review subsequently will need to decided by the team, with reference to how we would then need to approach the efficacy story.

Regards
Jim

From: Litherland Steve S
Sent: 06 December 1999 11:51
To: Owens Judith J; Jones Martin AM - PHMS
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Gavin Jim JP; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert
Subject: RE: 2 EPS Abstracts for APA

Martin has drawn our attention to an enduring problem which requires resolution as soon as possible.

- should we publish COSTAR? The disadvantages are obvious, not least that we provide the opposition with potentially damaging data when they calculate p values re the primary efficacy endpoint
- if not, can we extract some information and use this to support our messages? The following is scheduled to appear in Clear Vision (proceedings of the ECNP EPS meeting):

A second study comparing flexible dosing of risperidone (6-10 mg daily) and quetiapine (300-600 mg daily) reported that over 10 weeks significantly more risperidone patients (31.4%) than quetiapine patients (14.1%)In my draft 30.4 and 13.1% ; need to check experienced EPS or akathisia (30.4% and 16.6 15.4 in MR doc%, respectively) ($p<0.001$ for both comparisons) (Data on file).

This was sanctioned for the meeting but when it appears in Clear Vision it will be in the public domain. We can be accused of "cherry picking" and this may fuel demands to see the entire study (Cochrane would be most interested, for example).

- Are we using QUEST promotionally? If so, we could be accused of not telling the complete story

I am concerned that by doing nothing re COSTAR, except to allow details to emerge in dribs and drabs we are not taking control of the situation. An initial step may perhaps be to canvass expert opinion

outside the Company (I know that we have had some feedback but I understand this was conflicting and uncoordinated).

Steve

From: Jones Martin AM - PHMS
Sent: 06 December 1999 10:55
To: Owens Judith J
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Gavin Jim JP; Litherland Steve S; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM
Subject: RE: 2 EPS Abstracts for APA

Judith

I have no real comments on the Juncos abstract, but am concerned about Tandon's.

In Tandon's results section, he refers to a randomised comparative study. This study is COSTAR. I think that we are still not comfortable about communicating the overall results of this study. Whilst this data may have been presented orally in London, I think this abstract would be the first time we have put anything 'down on paper'. Are we sure that this we can present the EPS data in isolation given the nature of the other results ? Will we not create a desire for further information about the study ? Can we not refer to published (non-comparative) data for risperidone, as we must be doing this for olanzapine ? Should we be looking at the ziprasidone data too ? They seem to have dose-response effect as well.

Martin

From: Owens Judith J
Sent: 02 December 1999 17:14
To: Wilkie Alison AM; Gavin Jim JP; Litherland Steve S; Murray Michael MF; Rak Ihor IW; Jones Martin AM - PHMS; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP
Subject: 2 EPS Abstracts for APA
Importance: High

Dear All
Please find attached, for your review, 2 EPS abstracts that are intended for submission to APA. The abstracts are based on presentations at the AstraZeneca symposium 'CLEAR VISION - A fresh look at EPS' held during this year's ECNP.
Please return any comments you may have by midday (UK time) **Monday 6 December**.
Kind regards
Judith
<<File: Juncos abstract.doc>><<File: Tandon abstract.doc>>
Judith Owens
Ext: 24164
11F34 Mereside

AstraZeneca

Clinical Overview

Drug Name Quetiapine fumarate

Date July 2008

SEROQUEL™ and SEROQUEL XR ™ (quetiapine fumarate)

Clinical Overview on Weight Gain

Authors:

Leigh Jefferies M.D.
Global Safety Physician
Patient Safety, Wilmington, DE

Eva S.K. Alam, M.S., Pharm.D., RPh
Safety Surveillance Team Leader
Patient Safety, Wilmington, DE

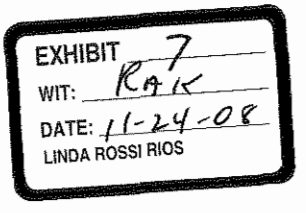


TABLE OF CONTENTS PAGE

LIST OF TABLES

1. PRODUCT DEVELOPMENT RATIONALE

1.1 Introduction

The Core Data Sheets for SEROQUEL and SEROQUEL XR are to be amended following an internal safety evaluation and review meeting on 09 July 2008. The purpose of this document is to summarize the key information on which the decision to amend the CDS was based, to document the Core Data Sheet amendment and to support changes to local Prescribing Information.

1.1.1 SEROQUEL and SEROQUEL XR

SEROQUEL and SEROQUEL XR are atypical antipsychotic agents, presented as tablets containing quetiapine fumarate, which exhibits affinity for brain serotonin (5HT2) and dopamine D1 and D2 receptors. In addition, SEROQUEL/SEROQUEL XR also have high affinity at histaminergic and adrenergic α1 receptors, with a lower affinity at adrenergic α2 receptors, but no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors.

SEROQUEL was first approved for marketing in the United Kingdom (UK) on 31 July 1997 and was first launched in the UK on 22 September 1997. By 31 March 2008, SEROQUEL has been approved in 89 countries for schizophrenia, 86 countries for bipolar mania, (with Mexico being the first country to approve bipolar mania on 29 May 2003), 26 countries for bipolar depression, (with Czech Republic being the first country to approve bipolar depression on 27 September 2006), and in one country for bipolar maintenance (USA being the first country to approve bipolar maintenance on 14 May 2008). SEROQUEL is presented as tablets delivering a dose of 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 300 mg, or 400 mg of quetiapine free-base. SEROQUEL is not approved for children or adolescents below 18 years of age.

SEROQUEL XR was first approved for marketing in the United States (US) for acute schizophrenia on 18 May 2007 and for maintenance of schizophrenia on 15 November 2007. By 31 March 2008, SEROQUEL XR has been approved in 30 countries for schizophrenia (including 14 countries in the Mutual Recognition Procedure), 7 countries for bipolar mania (with Slovakia being the first country to approve bipolar mania on 28 June 2007), and in one country for bipolar depression (Mexico being the first country to approve bipolar depression in October 2007). SEROQUEL XR is presented as tablets delivering a dose of 50 mg, 200 mg, 300 mg, or 400 mg of quetiapine free-base. SEROQUEL XR is not approved for children or adolescents below 18 years of age.

It has been estimated that about 22.8 million patients worldwide have been exposed to SEROQUEL/SEROQUEL XR since launch through the end of February 2008. This estimate is based upon: (1) assumptions as to the number of prescriptions per patient, based upon 2007 United States (US) market research; and (2) projections of prescriptions since launch based upon information available in the US (dispensed prescriptions from retail, long-term care and mail order) and 12 other countries (Australia, Belgium, Canada, Egypt,Germany, Italy, Japan,

Netherlands, Saudi Arabia, Spain, and United Kingdom; written prescriptions from office based physicians) in which SEROQUEL/SEROQUEL XR is marketed.

1.2 Proposed label change

The event of weight gain is to be changed from common to very common in the table in Section 4.8 *Undesirable effects* of the SEROQUEL and SEROQUEL XR Core Data Sheets. In addition, footnote three will be updated as follows (new text: double underline):

Undesirable effects

Frequency	System organ class	Event
Very common (≥10 %)	Investigations	Weight Gain[3]

[3] Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.

2. OVERVIEW OF BIOPHARMACEUTICS

This section is not relevant to this document.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

This section is not relevant to this document.

4. OVERVIEW OF EFFICACY

This section is not relevant to this document.

5. OVERVIEW OF SAFETY

5.1 Data summary and discussion

The frequency of weight gain previously categorized as uncommon was based on adverse event (AE) data from AstraZeneca clinical trials. Beginning in approximately 2001, according to AstraZeneca standard operating procedure (SOP 110-G), abnormal laboratory/vital signs values are not reported as AEs unless the abnormal value fulfils any criterion for a serious AE (SAE), the abnormal value results in the subject's discontinuing from the study (DAE) or the investigator insists that the abnormal value be reported as an AE. Symptoms associated with the abnormal laboratory value are reported as AEs. Thus, since this percentage includes AE reports both before and after the institution of this SOP, the percentage is difficult to interpret.

5.1.1 Acute placebo-controlled trials

The data below are taken from the cumulative clinical trial database (v15 [through 18 June 2008]) for quetiapine. In acute placebo-controlled trials of quetiapine in adult patients (≥18 years of age) the incidence rate in patients with ≥7% weight gain was 9.6% in the quetiapine group and 3.8% in the placebo group. The relative risk estimate was 2.5 (95% CI: 3.00, 2.10) (see Table 1).

Table 1 Incidence and relative incidence for weight gain risk, adult subjects – all Placebo-controlled trials

Risk	QTP incidence rate N=7481	Pla incidence rate N=3501	Relative incidence compared to Pla	Relative incidence 95% CIs	
	n (%)	n (%)	Ratio	Lower	Upper
Weight gain (> 7% increase)	721 (9.6)	134 (3.8)	2.5	2.1	3.0

CI Confidence interval. Pla Placebo. QTP Quetiapine.
Numbers in heading are patients with weight values at baseline and at least one value post baseline.
Note: Patients with multiple adverse events are counted only once.
Note: Percentages are calculated as (n/N)*100.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001and D1447C00134.
Program: Reg-Def\Prolactin May 08 MHRA\...\weigth_inc_pla_ctr.SAS. Programmer: F Strömberg. 2008-06-18 15:23. DB version: 15

5.1.2 All Trials

In all adult quetiapine clinical trials, the incidence of patients who had an increase of ≥7% of their body weight from baseline at any time was 18.2% (see Table 2).

Table 2 Incidence weight gain, adult subjects – all trials

Risk	QTP incidence rate N=22382
	n (%)
Weight gain (> 7% increase)	4070 (18.2)

Number in heading are patients with weight values at baseline and at least one value post baseline.
Note: Patients with multiple adverse events are counted only once.
Note: Percentages are calculated as (n/N)*100.
Program: Reg-Def\Prolactin May 08 MHRA\...\weigth_inc_all.SAS. Programmer: F Strömberg. 2008-06-26 9:14. DB version: 15

5.1.3 Overall summary of adult clinical trial data

In acute placebo-controlled trials of quetiapine in adult patients (≥18 years of age), the incidence rate in patients with ≥7% weight gain was 9.6% in the quetiapine group and 3.8% in the placebo group. In all adult quetiapine clinical trials, the incidence of patients who had an

increase of ≥7% of their body weight from baseline at any time was 18.2%. Therefore, the incidence of weight gain is to be changed from common to very common in the SEROQUEL and SEROQUEL XR Core Data Sheet, which represents the frequency in patients ≥18 years of age. In addition, the frequency will be changed from representing AE reports to actual weight gain data.

6. BENEFITS AND RISKS CONCLUSIONS

The purpose of this application is to update the SEROQUEL and SEROQUEL XR Core Data Sheets and local Prescribing information with current findings in relation to weight gain in patients treated with quetiapine. AstraZeneca believes that these data do not alter the overall safety and tolerability profile of SEROQUEL and SEROQUEL XR and that the benefit/risk profile of SEROQUEL and SEROQUEL XR remains positive.

7. REFERENCES

Correll et al 2006
Correll CU, Carlson HE. Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. J. Am. Acad. Child. Adolesc. Psychiatry. 2006; 45 (7):771-791.

Reyes et al 2006
Reyes M, Croonenberghs J, Augustyns I, Eerdekens M. Long-term use of risperidone in children with disruptive behavior disorders and subaverage intelligence: efficacy, safety and tolerability. J. Child. Adolescent. Psychopharmacol. 2006; 16(3): 260-272.

According to his/her respective qualification the undersigned expert declares hereby to have performed the duties set out in the Article 12 and in accordance with Annex I Part I 1.4 of Directive 2001/83/EC, as amended

CLINICAL:

Name of the expert: Leigh Jefferies, MD
Global Safety Physician
Patient Safety

Signature:

Address: 1800 Concord Pike
Wilmington, DE 19850

Date:

According to the Annex I of Directive 2001/83/EC as amended, brief information (curriculum vitae) on the educational, training and occupational experience of the expert is attached.

From: Eriksson, Hans A
Sent: Monday, July 07, 2008 3:53 PM
To: Rak, Ihor W; O'Dowd, Liza
Subject: FW: Updated Discussion document for the 09July08 Seroquel Peds SERM

Attachments: Weight SERM 09 July 2008.doc

Ihor and Liza,

Hot off the press, additional material for SERM.

Hans

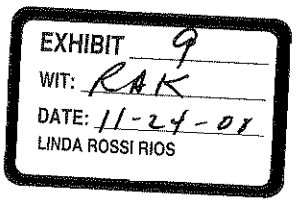
-----Original Message-----
From: Arnold, Karen
Sent: Monday, July 07, 2008 10:45 AM
To: Carey, Eileen; Dev, Vikram J; Arnold, Barry DC; Zander, Judith; Jefferies, Leigh; Leong, Ronald; Manning, Julia; Fors, Susanne (Seroquel); Boornazian, Lisa; Lee, Tara; Rolfe, Deborah; Warner, Linda (Safety); Delillio, Nina DH; Alam, Eva; Forsgren, Joachim; Spiers-Alston, Janet L; Gelman, Michele; Ni, Xiang; Eriksson, Hans A; Simpson, Brandon; Tyler, Robyn C; Åström, Mikael; Sherak, Nina; Walsh, Louisa M; Fullmer, Timothy S; Pathak, Sanjeev; Munro, Magna; Karlsson, Anders F; Patterson, Pat; Sullivan, Tim; Held, Peter; Stankowski, Jill; Nickless, Duncan M

Subject: Updated Discussion document for the 09July08 Seroquel Peds SERM

Dear all,

Additional data has been received for weight gain. An updated discussion document is attached. The new data is highlighted in yellow in the document.

Karen



AstraZeneca

Discussion Document

Drug name Quetiapine fumarate

Date *July 2008*

CONFIDENTIAL

Discussion Document

SEROQUEL/SEROQUEL XR AND WEIGHT GAIN

ALL FINDINGS PRESENTED IN THIS DOCUMENT ARE TO BE SUBJECT TO FURTHER CONSIDERATION AT SERM

Author: Eva S. K. Alam, M.S., Pharm.D.
Safety Surveillance Team Leader
Patient Safety, Wilmington, DE

Leigh Jefferies, MD
Global Safety Physician
Patient Safety, Wilmington, DE

TABLE OF CONTENTS

PAGE

LIST OF TABLES

APPENDICES

APPENDIX A

SUMMARY

Weight gain reported in pediatric patients taking SEROQUEL was identified as a subject for review by pharmacovigilance processes internal to AstraZeneca. In addition, we have reassesed the frequency of adult weight gain from the current clincial trial data. The current Core Data Sheet reference to weight gain is based on adverse evnent report data and not actual weight data.

In two acute placebo-controlled clinical trials with quetiapine in pediatric patients the incidence rate of patients with ≥ 7 % weight gain was 15.68 % respectively in the quetiapine group and 2.68 % in the placebo group. Using an increase of at least 0.5 standard deviation from baseline in BMI as a measure of clinically significant change, X% of patients on quetiapine met this criterion after 26 weeks of treatment.

In acute placebo-controlled trials of quetiapine in adult patients (≥18 years of age) the incidence rate in patients with ≥ 7 % weight gain was 9.6 % in the quetiapine group and 3.8 % in the placebo group. The relative risk estimate was 2.5 (95% CI: 2.10, 3.00). The incidence rate in patients with weight gain ≥ 7 % in all trials was 18.2 %.

The current Core Data Sheet refers to Weight Gain as common in Section 4.8 in the adult population, which is based on AE reports and not actual weight data.

Safety Evaluation and Review Meeting (SERM) is asked to consider whether the SEROQUEL CDS requires amendment with respect to the incidence of weight gain in pediatric and adult patients taking SEROQUEL.

1. INTRODUCTION

The purpose of this document is to review relevant information such as, clinical study data, received by AstraZeneca regarding the association of weight gain in pediatric patients with SEROQUEL treatment and to assess whether the Core Data Sheet for SEROQUEL requires amendment to reflect the company's current understanding of the subject.

2. BACKGROUND

2.1 SEROQUEL / SEROQUEL XR

SEROQUEL and SEROQUEL XR are atypical antipsychotic agents, presented as tablets containing quetiapine fumarate, which exhibits affinity for brain serotonin (5HT2) and dopamine D1 and D2 receptors. In addition, SEROQUEL/SEROQUEL XR also have high affinity at histaminergic and adrenergic α1 receptors, with a lower affinity at adrenergic α2 receptors, but no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors.

SEROQUEL was first approved for marketing in the United Kingdom (UK) on 31 July 1997 and was first launched in the UK on 22 September 1997. By 31 March 2008, SEROQUEL has been approved in 89 countries for schizophrenia, 86 countries for bipolar mania, (with Mexico being the first country to approve bipolar mania on 29 May 2003), 26 countries for bipolar depression, (with Czech Republic being the first country to approve bipolar depression on 27 September 2006), and in one country for bipolar maintenance (USA being the first country to approve bipolar maintenance on 14 May 2008). SEROQUEL is presented as tablets delivering a dose of 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 300 mg, or 400 mg of quetiapine free-base. SEROQUEL is not approved for children or adolescents below 18 years of age.

SEROQUEL XR was first approved for marketing in the United States (US) for acute schizophrenia on 18 May 2007 and for maintenance of schizophrenia on 15 November 2007. By 31 March 2008, SEROQUEL XR has been approved in 30 countries for schizophrenia (including 14 countries in the Mutual Recognition Procedure), 7 countries for bipolar mania (with Slovakia being the first country to approve bipolar mania on 28 June 2007), and in one country for bipolar depression (Mexico being the first country to approve bipolar depression in October 2007). SEROQUEL XR is presented as tablets delivering a dose of 50 mg, 200 mg, 300 mg, or 400 mg of quetiapine free-base. SEROQUEL XR is not approved for children or adolescents below 18 years of age.

It has been estimated that about 22.8 million patients worldwide have been exposed to SEROQUEL/SEROQUEL XR since launch through the end of February 2008. This estimate is based upon: (1) assumptions as to the number of prescriptions per patient, based upon 2007 United States (US) market research; and (2) projections of prescriptions since launch based upon information available in the US (dispensed prescriptions from retail, long-term care and mail order) and 12 other countries (Australia, Belgium, Canada, Egypt,Germany, Italy, Japan, Netherlands, Saudi Arabia, Spain, and United Kingdom; written prescriptions from office based physicians) in which SEROQUEL/SEROQUEL XR is marketed.

2.2 Core Data Sheet for SEROQUEL and SEROQUEL XR

The AstraZeneca CDS presents the company position on the prescribing information for SEROQUEL and provides a reference for consistency of product information documents in individual markets.

The current SEROQUEL/SEROQUEL XR Core Data Sheets contain the following information regarding weight gain in Section 4.8:

"As with other antipsychotics, weight gain, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral edema, have been associated with SEROQUEL".

Frequency	System Organ Class	Event
Common (≥ 1% - < 10%)	Investigations	Weight Gain[3]

[3] Occurs predominantly during the early weeks of treatment.

The current frequency of common is based on AE reports and not actual weight data.

3. THE LITERATURE

Not reviewed for this topic.

4. PRE-CLINICAL DATA

Not reviewed for this topic.

5. CLINICAL STUDY DATA

5.1 Pediatric clinical trial data

The data presented below is taken from two acute placebo-controlled studies with SEROQUEL in pediatric patients with schizophrenia or bipolar mania and one longer term open label study with SEROQUEL. The patients in the longer-term trial were originally enrolled in one of the two acute placebo-controlled trials. The following is a breif description of these three trials.

- D144C00112: A 6-week, International, Multicenter, Randomized, Double-blind, Parallel group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 800 mg Compared with Placebo in the Treatment of Adolescents with Schizophrenia

- D144C00149: A 3-week, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 600 mg Compared with Placebo in the Treatment of Children and Adolescents with Bipolar I Mania

- D144C00150: A 26-week, International, Multicenter, Open-label Phase IIIb Study of the Safety and Tolerability of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg to 800 mg in Children and Adolescents with Bipolar I Disorder and Adolescents with Schizophrenia

5.1.1 Acute placebo-controlled data

5.1.1.1 D144C00112

Adverse event data

Adverse events of weight increased were reported for three patients (4.12%) in the 400 mg/day mg/day quetiapine group, two patients (2.70 %) in the 800 mg/day quetiapine group, and two patients (2.66 %) in the placebo group. All adverse events of weight increased were judged related to the study medication by the investigator, and no adverse event of weight increased led to discontinuation of study treatment.

Mean increase in body weight

In study 112 mean weights were similar at baseline for the three treatment groups. Mean changes in weight from baseline were higher for quetiapine treated patients at each time point compared to placebo. At Day 42, the mean changes from baseline were 2.2 kg in the 400 mg/day quetiapine group, 1.8 kg in the 800 mg/day quetiapine group, and –0.4 kg in the placebo group (see Table 1).

Table 1 D144C00112: Mean increase in weight from baseline

Change from Baseline	QTP 400 mg	QTP 800 mg	PLACEBO
Day 42	2.2 kg	1.8 kg	-0.4 kg

Patients with ≥ 7% weight gain

A higher percentage of quetiapine treated patients (23.21 % in the 400 mg/day and 18.18 % in the 800 mg/day) had ≥ 7% weight gain at Day 42 compared to the placebo treated patients (6.82 %). (see Table 2).

Table 2 D144C00112: Patients with ≥ 7% weight gain (Summary safety population)

Visit	QTP 400 mg N=56 n (%)	QTP 800 mg N = 55 n (%)	PLA N = 44 n (%)
Day 42	13 (23.21)	10 (18.18)	3 (6.82)

5.1.1.2 D144C00149

Adverse event data

Adverse events of weight increased were reported for six patients (6.32 %) in the 400 mg/day quetiapine group, six patients (6.12 %) in the 600 mg/day quetiapine group, and none in the

placebo group. All adverse events of weight increased were judged related to study medication by the investigator and no adverse events of weight increased led to discontinuation of study treatment.

Mean increase in weight

Mean increases in weight from baseline to Day 21 were higher for quetiapine-treated patients at each time point compared to placebo. These increases from baseline were 1.7 kg in the 400 mg quetiapine treated group, 1.7 kg in the 600 mg quetiapine treated group and 0.4 kg in placebo. Quetiapine-treated patients experienced higher mean increases in weight compared to placebo at Day 21 (See Table 3).

Table 3 D144C00149: Mean increase in weight from baseline

Change from baseline	QTP 400 mg	QTP 600 mg	PLA
Day 21	1.7 kg	1.7 kg	0.4 kg

Patients with ≥ 7 % weight gain

A higher percentage of quetiapine treated patients (14.47 % in the 400 mg/day and 9.88 % in the 600 mg/day) had ≥ 7% weight gain at Day 21 compared to placebo treated patients (0 %). (See Table 4).

Table 4 D144C00149: Patients with ≥ 7% weight gain (Summary safety population)

Visit	QTP 400 mg N = 76 n (%)	QTP 600 mg N = 81 n (%)	PLACEBO N = 68 n (%)
Day 21	11 (14.47)	8 (9.88)	0 (0)

5.1.1.3 Pooled Data (Trials 112 and 149)

Adverse events of weight increase in pediatric studies D1441C00149 and D1441C0112 (pooled data)

In the pooled data, from the two acute placebo-controlled clinical trials (study 112 and study 149) with quetiapine in pediatric patients the incidence of reports of weight increased was 5.0 % in the quetiapine group and 1.2 % in the placebo group. The relative risk estimate (quetiapine vs placebo) was 4.13 (95% confidence interval: 0.96, 17.54). When adjusted for duration of exposure the incidence density for quetiapine was 64.8 per 100 patient years and 15.6 per 100 patient years for placebo. The relative incidence density was 4.17 (95% CI: 0.96, 18.03). (See Table 5).

Table 5 Number of patients with adverse events in pediatric studies D1441C00149 and D1441C00112

MedDRA preferred term	Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]	Relative risk QTP vs Pla	95%CI Lower	Upper	Incidence density[d]	Relative incidence density QTP vs Pla	95%CI Lower	Upper
Weight increased	QTP	17 (0)	340	26.2 (27.0)	5.0 (0.0)	4.13	0.96	17.64	64.8 (0.0)	4.17	0.96	18.03
	Pla	2 (0)	165	12.9 (13.0)	1.2 (0.0)				15.6 (0.0)			

[a] Patients must have received at least one dose of trial medication.
[b] Exposure in patient-years, cencored at first event.
[c] 100xtotal number of patients with event/total number of patients.
[d] 100xtotal number of patients with event/total patient-years of exposure.
[e] The number of patients with any of the adverse events. Since a patient can have more than one adverse ecent within the adverse event group, the number does not necessarily equal the sum of the numbers below.

Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Studies included: D1441C00149 and D1441C00112.
Derived from: Pgm: Reg-Def\Pediatric Apr08\...\AE_pla_ctrl. Data version: V15. User: Å Hellqvist. 07MAY08 14:20.

Patients with ≥ 7% weight gain by BMI (pooled data)

A higher percentage of quetiapine treated patients had ≥ 7 % weight gain compared to placebo in the majority of the different BMI categories (30.8 % vs. 9.5 % in the 0-<18.5; 18.6 % vs. 2.2 % in the 18.5 - <25; 5.2 % vs. 0% in the 25 - <30). A higher percentage of quetiapine treated patients had ≥ 7 % weight gain compared to placebo in the age group ≤ 12 year old in the majority of the different BMI categories. (23.8% vs. 0 % in the 0-<18.5, 16.3 % vs. 0 % in 18.5 - <25). Similarly, a higher percentage of quetiapine treated patients had ≥ 7 % weight gain compared to placebo in the age group 13-18 year old in the majority of the different BMI categories (34.1 % vs.14.3 % in the 0-<18.5, 19.4 vs. 2.8 % in 18.5 - <25). (See Table 6).

Table 6 Patients with ≥ 7% weight gain by BMI in pediatric studies D144C00149 and D144C00112 (pooled data)

Weight Cut-offs	BMI group	PLA	All QTP	PLA ≤ 12	All QTP ≤ 12	PLA 13-18	All QTP 13-18
≥ 7 % increase at any visit		N n (%)	N n (%)	N n (%)	N n (%)	N n (%)	N n (%)
	0-<18.5	21 2 (9.5)	65 20 (30.8)	7 0 (0)	21 5 (23.8)	14 2 (14.3)	44 15 (34.1)
	18.5 - < 25	89 2 (2.2)	177 33 (18.6)	17 0 (0)	43 7 (16.3)	72 2 (2.8)	134 26 (19.4)
	25-<30	36 0 (0)	58 3 (5.2)	9 0 (0)	16 0 (0)	27 0 (0)	42 3 (7.1)
	30 - < 40	14 0 (0)	27 0 (0)	2 0 (0)	4 0 (0)	12 0 (0)	23 0 (0)
	≥ 40	2 0 (0)	2 0 (0)	0 0 (0)	0 0 (0)	2 0 (0)	2 0 (0)
	Total	163 4 (2.5)	335 57 (17.0)	36 0 (0)	85 12 (14.1)	127 4 (3.1)	250 45 (18)

Change from baseline in weight and BMI by BMI category (pooled data)

The pooled data for patients with a mean increase in weight and BMI from baseline to end of treatment were higher for quetiapine treated patients compared to placebo in each of the different BMI categories. (See Table 7).

Table 7 Change from baseline in weight and BMI by BMI category in pediatric studies D144C00149 and D144C00112 (pooled data)

BMI category (kg/m^2)		QTP		PLA	
	n	65		24	
Underweight BMI < 18.5		**Weight**	**BMI**	**Weight**	**BMI**
Baseline	Mean (SD)	42.5 (7.5)	17.1 (1.2)	42.3 (10.2)	16.9 (1.2)
End of treatment	Mean (SD)	44.5 (7.9)	17.8 (1.5)	42.8 (10.0)	17.0 (1.3)
Change	Mean (SD)	2.0 (2.3)	0.7 (0.9)	0.5 (1.5)	0.2 (0.6)
Normal weight 18.5 ≤ BMI≤ 25	**n**	**181**		**90**	
		Weight	**BMI**	**Weight**	**BMI**
Baseline	Mean (SD)	57.1 (9.7)	21.5 (1.8)	58.3 (9.6)	21.6 (1.8)
End of treatment	Mean (SD)	58.9 (10.3)	22.0 (2.0)	58.6 (9.8)	21.7 (2.1)
Change	Mean (SD)	1.8 (2.4)	0.6 (0.9)	0.4 (2.5)	0.1 (0.9)
Overweight 25 ≤ BMI≤30	**n**	**60**		**33**	
		Weight	**BMI**	**Weight**	**BMI**
Baseline	Mean (SD)	72.4 (10.7)	27.4 (1.4)	69.5 (8.3)	26.8 (1.3)
End of treatment	Mean (SD)	73.5 (11.0)	27.7 (1.7)	68.8 (7.5)	26.4 (1.3)
Change	Mean (SD)	1.1 (2.6)	0.3 (1.0)	-0.8 (2.7)	-0.3 (0.9)
Obese BMI ≥ 30	**N**	**34**		**18**	
		Weight	**BMI**	**Weight**	**BMI**
Baseline	Mean (SD)	92.4 (14.5)	33.5 (3.1)	96.7 (11.3)	34.8 (3.6)
End of treatment	Mean (SD)	94.9 (16.7)	34.1 (3.4)	97.4 (12.5)	34.9 (3.9)
Change	Mean (SD)	2.5 (3.8)	0.7	0.7 (2.8)	0.1 (1.1)

5.1.2 Longer-term open label pediatric data

5.1.2.1 D1441C00150

Study 150 was an open-label extension study designed to assess the safety and tolerability of quetiapine (flexibly dosed at 400 mg/day to 800 mg/day) in adolescents with schizophrenia (continuing from Study 112) and in children and adolescents with bipolar I disorder (continuing from Study 149). There were a total of 380 patients in the safety analysis set, including 175 with schizophrenia and 205 with mania.

All patients treated with quetiapine 50 mg/day on Day 1 then escalated to 400 mg on Day 5. From Day 5, the target dose of 400 mg/day was maintained or increased by no more than 100 mg/day, up to 800 mg/day or adjusted down to 200 mg/day. Patients were treated for up to 26 weeks.

Adverse event data

Adverse events of weight increased were reported for 51 patients (13.4%) in the safety population, including 24 patients (18.6%) who were treated with placebo during the acute feeder studies and 27 patients (10.8%) who received quetiapine during the acute feeder studies. Nearly all adverse events of weight increased were judged related to study medication by the investigator; three adverse events of weight increased led to discontinuation of study treatment.

Mean increase in weight

The mean change in weight for schizophrenia and bipolar I patients (who enrolled) from OL baseline as well as DB baseline to final visit are provided in Table 8.

The mean change in weight for all schizophrenia patients who enrolled from OL baseline to final visit was 3.3 kg; the increase in weight was greater in patients who were treated with placebo (4.3 kg) compared with quetiapine (2.8 kg) during the acute feeder study. The change in mean weight from DB baseline was 4.6 kg for schizophrenia patients.

The mean change in weight for all bipolar I disorder patients who enrolled from OL baseline to final visit was 4.0 kg; the increase in weight was greater in patients who were treated with placebo (5.5 kg) compared with quetiapine (3.2 kg) during the acute feeder study. The change in mean weight from DB baseline was 5.3 kg for bipolar I disorder patients.

The mean change in weight for all patients who enrolled in trial 150 (n=380) from OL baseline to final visit was 3.7 kg; the increase in weight was greater in patients who were treated with placebo (4.9 kg) compared with quetiapine (3.0 kg) during the acute feeder studies. The change in mean weight from DB baseline was 5.0 kg for the total population. The mean change in weight for patients (from OL baseline) who completed 26 weeks of treatment with quetiapine (n= 241) was 4.4 kg.

Table 8 **Study 150: mean changes from baseline to the final visit (safety population)**

	Acute feeder study treatment								
	Prior Placebo (N=129)			All prior QTP (N=251)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
112 DB Baseline									
Final visit (150 OL BSLN)	62	67.4	16.34	113	64.8	19.18	175	65.7	18.22
Change from 112 DB BSLN	62	4.1	8.46	113	4.8	10.75	175	4.6	9.98
Change from 150 OL Baseline	62	4.3	6.90	113	2.8	10.07	175	3.3	9.08
149 DB Baseline									
Final visit (150 OL BSLN)	64	68.3	21.85	136	64.5	18.43	200	65.8	19.61
Change from 149 DB BSLN	64	5.8	6.42	136	5.1	5.66	200	5.3	5.90
Change from 150 OL Baseline	64	5.5	5.81	135	3.2	4.75	199	4.0	5.21
Total 149 and 112 pooled DB Baseline									
Final visit (150 OL BSLN)	126	67.9	19.26	249	64.7	18.74	375	65.7	18.95
Change from DB BSLN	126	5.0	7.50	249	5.0	8.34	375	5.0	8.06
Change from 150 OL Baseline	126	4.9	6.38	248	3.0	7.64	374	3.7	7.28

In patients who completed 26 weeks of therapy with quetiapine (n=241) in Trial 150, the mean change in weight from baseline was 4.4 kg. In these patients, the average percentiles at baseline and 26 weeks, respectively, were 64.0% and 64.7% for weigh, 49.4% and 49.0% for height, and 66.3% and 67.7% for BMI.

Patients with ≥ 7% weight gain

In the safety population, 134 patients (35.6%) experienced ≥7% weight gain from OL baseline to final visit (see Table 9). The incidence of ≥7% weight gain was higher in patients who were treated with placebo (39.4%) compared with quetiapine (33.7%) during the acute feeder studies.

In the schizophrenia population, 29.1% of patients experienced ≥7% weight gain. The incidence of ≥7% weight gain was similar in patients on quetiapine in the Study 150 who were treated with placebo (30.6%) compared with quetiapine (28.3%) during the acute feeder studies.

In the bipolar I disorder population, 41.3% of patients experienced ≥7% weight gain. The incidence of ≥7% weight gain was higher in patients on quetiapine in the Study 150 who were treated with placebo (47.7%) compared with quetiapine (38.2%) during the acute feeder studies.

Of the patients who completed 26 weeks of treatment with quetiapine, 44.8% (108/241) had a ≥ 7 % increase in weight from baseline.

Table 9 Study 150: Patients with ≥ 7% weight gain (Summary safety population)

	Acute feeder study treatment								
	Prior Placebo (N=129)			Prior All QTP (N=251)			Total (N=380)		
	N	n	(%)	N	n	(%)	N	n	(%)
Pooled data 149 and 112									
From DB Baseline	127	58	45.7	249	119	47.8	376	177	47.1
From 150 OL Baseline	127	50	39.4	249	84	33.7	376	134	35.6
Study 112 (schizophrenia)									
From DB Baseline	62	24	38.7	113	43	38.1	175	67	38.3
From 150 OL Baseline	62	19	30.6	113	32	28.3	175	51	29.1
Study 149 (BP I)									
From DB Baseline	65	34	52.3	136	76	55.9	201	110	54.7
From 150 OL Baseline	65	31	47.7	136	52	38.2	201	83	41.3

5.1.3 Additional analysis of Pediatric data

5.1.3.1 Z-scores

Since body weight and height should increase in children, data showing an increase in weight with time sometimes may not indicate a problem. One convenient way to express body weight is in terms of body mass index (BMI) since in BMI, the weight is adjusted for height. (Correll et al 2006).

A better measure of weight change in children and adolescents is to convert the mean weight and BMI to a Z score taking into consideration the age and gender of the subject. Z scores are able to show how different a child's weight or BMI is from the average children with the same height. (Reyes et al 2006).

One of the criteria proposed to show significant weight gain in children and adolescents is a greater than or equal to an increase in BMI Z score of 0.5 over any duration of time. (Correll et al 2006). This increase represents a change of 0.5 standard deviation from baseline.

BMI Z-scores

The mean BMI Z-scores (for patients who enrolled in study 150) from the DB baseline for schizophrenia to the final visit and end of treatment are higher for the prior placebo group compared to the prior quetiapine group. (See Table 10).

The mean BMI Z-scores (for patients who enrolled in study 150) from the DB baseline for bipolar-I patients to the final visit and end of treatment are similar for the prior placebo group compared to the prior quetiapine group. (See Table 10).

The mean BMI Z-scores (for patients who enrolled in study 150) from the total DB baseline to the end of treatment and final visit were higher in the prior placebo group compared to the prior quetiapine group. (See Table 10).

The mean BMI Z-scores for each visit are plotted over time for the treatment of placebo, quetiapine and total for study 150 (See Appendix A).

Table 10 **Study 150: Mean values of BMI Z score at baseline, end of treatment and final visit (safety population)**

	Acute feeder study treatment								
	Prior Placebo (N=129)			All prior QTP (N=251)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
112 DB Baseline	62	**0.3**	1.20	113	**-0.1**	1.40	175	**0.0**	1.34
Week 26	41	0.4	1.05	86	0.1	1.22	127	0.2	1.17
Final Visit	62	**0.5**	1.03	113	**0.2**	1.25	175	**0.3**	1.19
149 DB Baseline	67	**1.0**[a]	1.01	138	**0.9**[a]	1.06	205	**0.9**[a]	1.04
Week 26	37	1.2	0.97	77	1.2	0.96	114	1.2	0.96
Final Visit	63	**1.2**	0.95	135	**1.0**	1.03	198	**1.1**	1.00
DB Total Baseline	129	**0.6**	1.15	251	**0.4**	1.32	380	**0.5**	1.27
Week 26	78	0.8	1.08	163	0.6	1.22	241	0.7	1.18
Final Visit	125	**0.9**	1.04	248	**0.7**	1.21	373	**0.7**	1.16

[a] The mean BMI Z score at baseline is much higher for the 149 population

Schizophrenia patients with ≥ 0.5 shift in standardized BMI Z score

A higher percentage of quetiapine treated patients (15 % at the end of treatment) had ≥ 0.5 shift in standardized BMI Z score compared to placebo treated patients (3 % at the end of treatment). (See Table 11).

A higher percentage of prior placebo treated patients, who enrolled in study 150, (27.4 % at the end of treatment) had ≥ 0.5 shift in standardized BMI Z score compared to prior quetiapine treated patients (21 % at the end of treatment). (See Table 11).

A higher percentage of prior placebo treated patients, who enrolled in study 150, (24.2 % at EOT) vs. prior quetiapine treated patients (14.2 % at EOT) from the OL baseline for schizophrenia had ≥ 0.5 shift in standardized BMI Z score. (See Table 11).

Table 11 Patients with ≥ 0.5 shift in standardized BMI Z score in Study 112 and patients from study 112 extending into Study 150

Occurrence	Double blind Study 112		Study 112 to OL Study 150		
Time/baseline	All Quetiapine	Placebo	DB All Quetiapine	DB Placebo	OL All - Quetiapine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
End of Treatment /DB	22/147 (15)	2/75 (3)	24/113 (21)[a]	17/62 (27.4)[a]	41/175 (23.4)[a]
End of Treatment /OL			16/113 (14.2)[b]	15/62 (24.2)[b]	31/175 (18)[b]

[a] From double blind baseline of study 112 to end of study 150; [b] From OL baseline of study 150 to end of study 150

Patients with ≥ 0.5 shift in standardized BMI Z score in Study 150 by indication

A higher percentage of schizophrenia patients, (who enrolled in study 150) treated with prior placebo (27.4 % at EOT) had ≥ 0.5 shift in standardized BMI Z-score compared to prior quetiapine treated patients (21.2 % at EOT) from the DB baseline of study 112. (See Table 12).

A higher percentage of schizophrenia patients (who enrolled in study 150) treated with prior placebo (24 % at EOT) had ≥ 0.5 shift in standardized BMI Z-score compared to prior quetiapine treated patients (14.2 % at EOT) from the OL baseline. (See Table 12).

A similar percentage of bipolar patients (who enrolled in study 150) treated with prior placebo (19 % at EOT) had ≥ 0.5 shift in standardized BMI Z-score compared to prior quetiapine treated patients (21.5 % at EOT) form the DB baseline of study 149 (See Table 12).

A higher percentage of bipolar patients (who enrolled in study 150) treated with prior placebo (19 % at EOT) had ≥ 0.5 shift in standardized BMI Z score compared to prior quetiapine treated patients (8.3 % at EOT) form the OL baseline (See Table 12).

Table 12 Patients with ≥ 0.5 shift in BMI Z score in Study 150 by indication

Occurrence	Schizophrenia to OL 150		BP to OL 150		OL 150
Time/baseline	DB All Quetiapine	DB Placebo	DB All Quetiapine	DB Placebo	OL All - Quetiapine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	N/N (%)
End of Treatment/DB	24/113 (21.2)[a]	17/62 (27.4)[a]	29/135 (21.5)[c]	12/63 (19)[c]	82/373 (22)
End of Treatment/OL	16/113 (14.2)[b]	15/62 (24)[b]	11/133 (8.3)[b]	12/63 (19)[b]	54/371 (14.6)[b]

[a] From double blind baseline of study 112 to end of study 150; [b] From OL baseline of study 150 to end of study 150; [c] From double blind baseline of study 149 to end of study 150

Of all patients who completed 26 weeks of treatment with quetiapine, 18.3% (44/241) had a shift of ≥ 0.5 BMI Z-score.

Patients with ≥ 0.5 shift in standardized BMI z score in Study 150 by age group

A similar percentage of ≤ 12 years old patients (who enrolled in study 150) treated with prior placebo (28 % at EOT) had ≥ 0.5 shift in standardized BMI Z score compared to prior quetiapine treated patients (25 % at EOT) from the DB baseline (See Table 13).

A higher percentage of ≤ 12 year old patients (who enrolled in study 150) treated with prior placebo (24 % at EOT) had ≥ 0.5 shift in standardized BMI Z-score compared to prior quetiapine treated patients (8.6 % at EOT) from the OL baseline (See Table 13).

A similar percentage of 13-18 year old pediatric patients (who enrolled in study 150) treated with prior placebo (22 % at EOT) had ≥ 0.5 shift in standardized BMI Z score compared to prior quetiapine treated patients (20.1 % at EOT) from the DB baseline (See Table 13).

A higher percentage of 13-18 year old pediatric patients (who enrolled in study 150) treated with prior placebo (21 % at EOT) had ≥ 0.5 shift in standardized BMI Z score compared to prior quetiapine treated patients (11.7 % at EOT) from the OL baseline (See Table 13).

Table 13 Patients with ≥ 0.5 shift in BMI Z score in Study 150 by age group*

Occurrence	≤ 12 years OL 150		13 to 17 years OL 150		OL 150
Time/baseline	DB All Quetiapine	DB Placebo	DB All Quetiapine	DB Placebo	OL All - Quetiapine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
End of Treatment/DB	15/59 (25)	7/25 (28)	38/189 (20.1)	22/100 (22)	82/373 (22)
End of Treatment/OL	5/58 (8.6)	6/25 (24)	22/188 (11.7)	21/100 (21)	54/371 (14.6)

* Study 112 was a six week placebo controlled trial in adolescent patients (13-17 years) and study 149 was a three week trial in children and adolescent patients (10-17 years)

5.2 Adult clinical trial data

An analysis of SEROQUEL and long-term weight gain was performed. This retrospective study assessed the magnitude and pattern of weight change during long-term treatment with SEROQUEL. Analysis of data collected from patients with schizophrenia, who were treated with SEROQUEL in AstraZeneca clinical trials from July 1993 to May 1999, was performed.

Weight changes were analyzed in patients treated for 12 weeks (± 4 days), 52 weeks (±30 days), and 104 week (±45 days). To be eligible for inclusion in the analyses patients had to have weight measurements recorded at baseline, and at the relevant time points (12, 52, 104 weeks). The primary cohort was the 52-week group.

All concomitant medications were stopped before entry into the trials, but in some concomitant antipsychotic medication was permitted during the open-label extension phases. Data were analyzed for all patients receiving quetiapine, and for the subgroup of patients who received quetiapine monotherapy.

In total, 378 patients with schizophrenia had weight data available after treatment with quetiapine for 12 weeks; of these 340 received quetiapine Monotherapy. Mean (95% CI) weight gain was 1.46 (0.98, 1.95) kg for all patients and 1.48 (0.98, 1.99) kg for the monotherapy group. Median weight gain was 1.15 kg for all patients and 1.36 kg for the monotherapy group.

In total, 352 patients with schizophrenia had weight data available after treatment with quetiapine for 52 weeks; of these 297 received quetiapine Monotherapy. Mean (95% CI) weight gain was 3.19 (2.27, 4.11) kg for all patients and 3.59 (2.57, 4.61) kg for the Monotherapy group.

In total, 166 patients with schizophrenia had weight data available after treatment with quetiapine for 104 weeks; of these, 143 received quetiapine Monotherapy. Mean (95% CI) weight gain was 5.16 (3.62, 6.70) kg for all patients and 5.59 (3.98, 7.20) kg for the Monotherapy group. Median weight gain was 4.1 kg for all patients and 4.5 kg for the Monotherapy group.

Ninety-seven patients with schizophrenia had bodyweight data available at Weeks 12, 26, and 52. These data indicate that during one year of treatment with quetiapine, 69% of the total mean weight gain occurred within the first 12 weeks and 96% in the first 26 weeks. Similarly, data from the 12, 52, 104 week cohort (n = 5) indicated that 62% of the total weight gain occurred in the first 12 weeks of treatment. Furthermore, 99% of weight gain occurred in the first year, with negligible weight change between one and two years.

The results of the analysis show that long-term treatment with quetiapine monotherapy was associated with moderate weight gain in patients with schizophrenia. Most weight gain occurs within the first 12 weeks of treatment and has no clear dose relationship. (Brecher et al 2007)

5.2.1 Acute placebo-controlled trials

The data below is taken from the cumulative clinical trial database (v15) for quetiapine. In acute placebo-controlled trials of quetiapine in adult patients (≥18 years of age) the incidence rate in patients with ≥ 7 % weight gain was 9.6 % in the quetiapine group and 3.8 % in the placebo group. The relative risk estimate was 2.5 (95% CI: 3.00, 2.10). (see Table 14).

The incidence rate in adult patients with weight gain ≥ 7 % in all trials was 18.2 % (see Table 15).

Table 14 Incidence and relative incidence for weight gain risk, adult subjects – all Placebo-controlled trials

Risk	QTP incidence rate N=7481	Pla incidence rate N=3501	Relative incidence compared to Pla	Relative incidence 95% CIs	
	n (%)	n (%)	Ratio	Lower	Upper
Weight gain (> 7% increase)	721 (9.6)	134 (3.8)	2.5	2.1	3.0

CI Confidence interval. Pla Placebo. QTP Quetiapine.
Numbers in heading are patients with weight values at baseline and at least one value post baseline.
Note: Patients with multiple adverse events are counted only once.
Note: Percentages are calculated as (n/N)*100.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001and D1447C00134.
Program: Reg-Def\Prolactin May 08 MHRA\...\weigth_inc_pla_ctr.SAS. Programmer: F Strömberg. 2008-06-18 15:23. DB version: 15

Table 15 Incidence weight gain, adult subjects – all trials

Risk	QTP incidence rate N=22382
	n (%)
Weight gain (> 7% increase)	4070 (18.2)

Number in heading are patients with weight values at baseline and at least one value post baseline.
Note: Patients with multiple adverse events are counted only once.
Note: Percentages are calculated as (n/N)*100.
Program: Reg-Def\Prolactin May 08 MHRA\...\weigth_inc_all.SAS. Programmer: F Strömberg. 2008-06-26 9:14. DB version: 15

6. HOUSE SAFETY DATABASE OR POST-MARKETED USE

The post-marketing data was not reviewed for this topic.

7. DISCUSSION

Weight gain reported in pediatric patients taking SEROQUEL was identified as a subject for review by pharmacovigilance processes internal to AstraZeneca. In addition, we have reassesed the frequency of adult weight gain from the clincial trial data. The current Core Data Sheet reference to weight gain is based on adverse evnent report data and not acutal weight data.

In two acute placebo-controlled clinical trials with quetiapine in pediatric patients the incidence rate of patients with ≥ 7 % weight gain was 15.68 % respectively in the quetiapine group and 2.68 % in the placebo group. Using an increase of at least 0.5 standard deviation from baseline in BMI as a measure of clinically significant change, X% of patients on quetiapine met this criterion after 26 weeks of treatment.

In acute placebo-controlled trials of quetiapine in adult patients (≥18 years of age) the incidence rate in patients with ≥ 7 % weight gain was 9.6 % in the quetiapine group and 3.8 % in the placebo group. The relative risk estimate was 2.5 (95% CI: 3.00, 2.10). The incidence rate in adult patients with weight gain ≥ 7 % in all trials was 18.2 %.

The current Core Data Sheet refers to Weight Gain as common in Section 4.8 in the adult population, which is based on AE reports and not actual weight data.

Safety Evaluation and Review Meeting (SERM) is asked to consider whether the SEROQUEL CDS requires amendment with respect to the incidence of weight gain in pediatric and adult patients taking SEROQUEL.

8. REFERENCES

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