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

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- 'Seroquel' - Preclinical overview
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'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

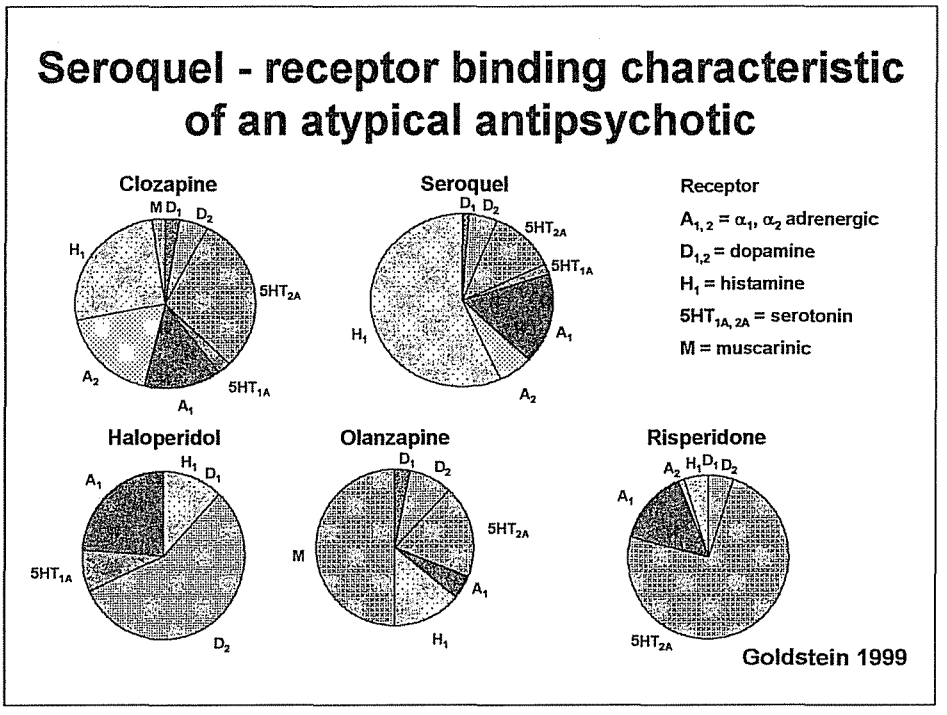
Goldstein and Arvanitis 1995; Goldstein et al 1993; Ellenbroek et al 1996

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.

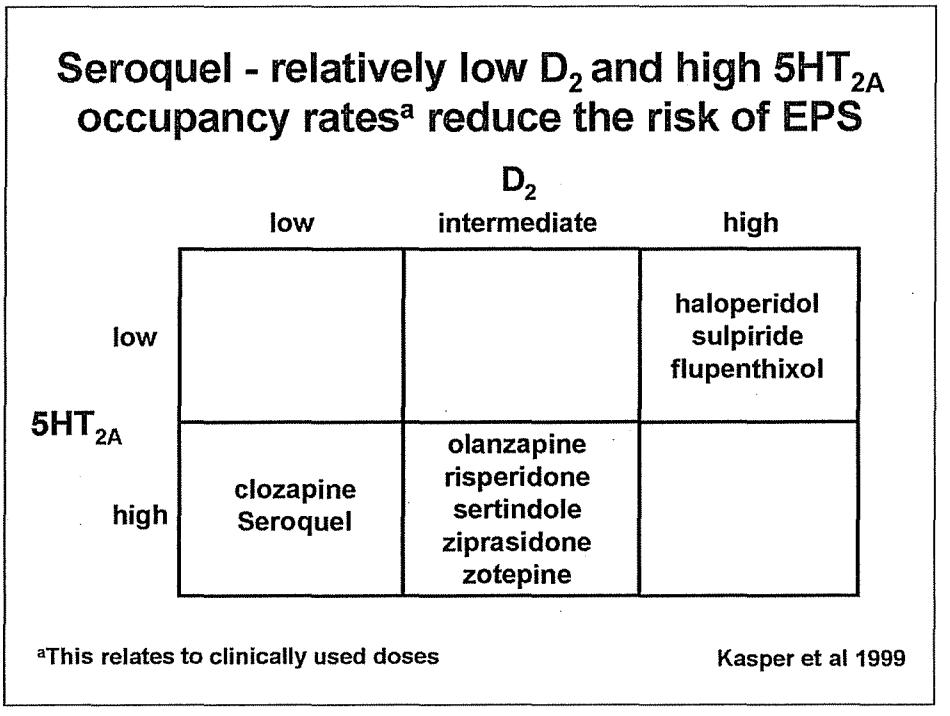


Seroquel – receptor binding characteristic of an atypical antipsychotic

- 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.*



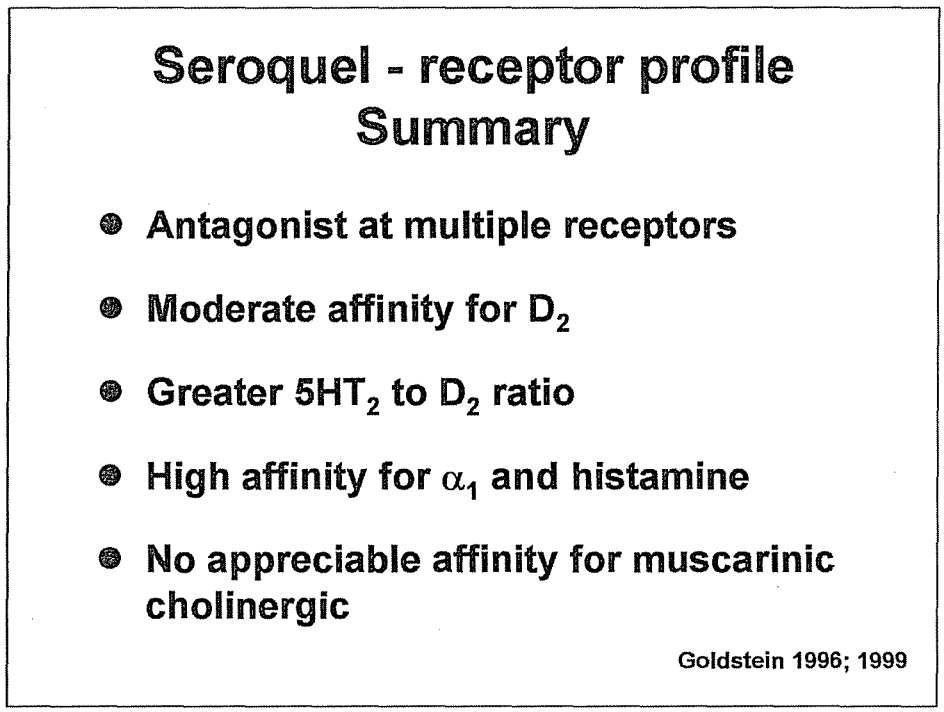
Seroquel – relatively low D_2 and high $5HT_{2A}$ occupancy rates[a] reduce the risk of EPS

- 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.

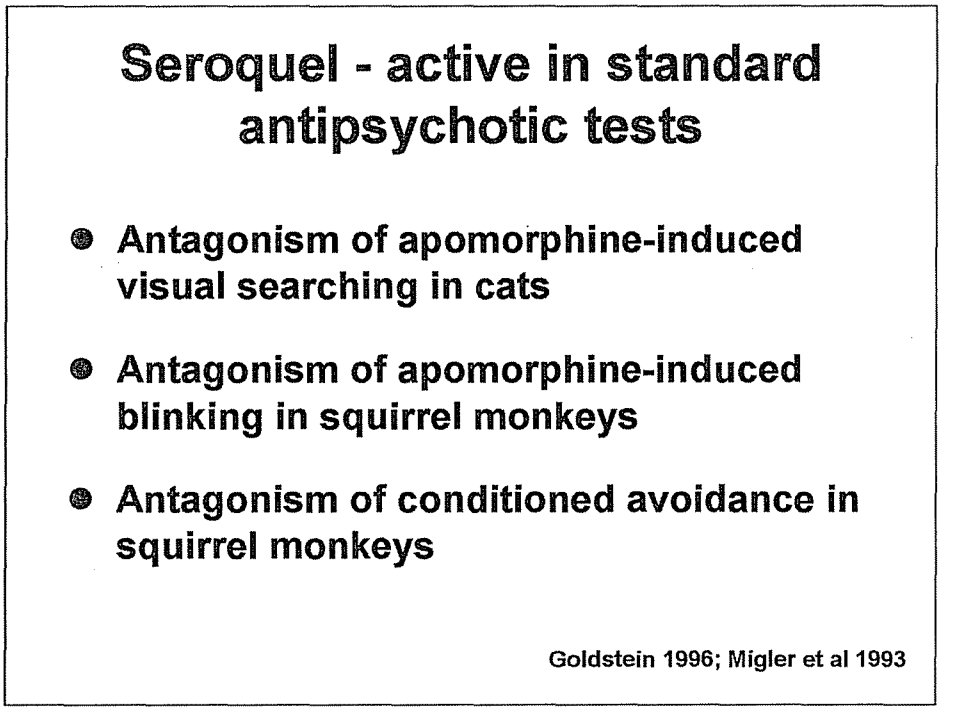


Seroquel - receptor profile - summary

- 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.

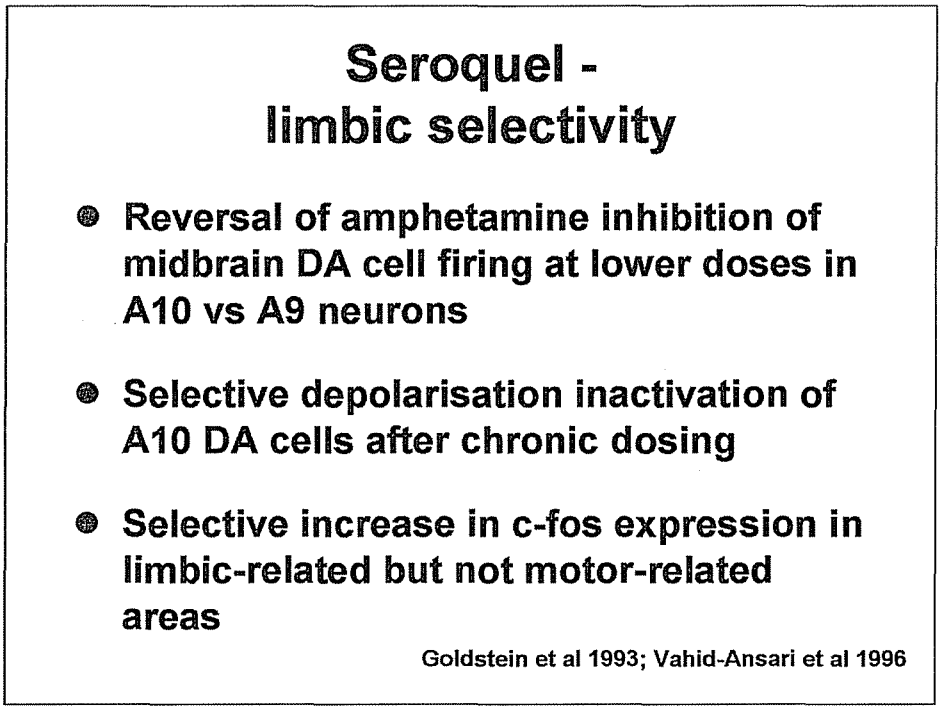


Seroquel - active in standard antipsychotic tests

- 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

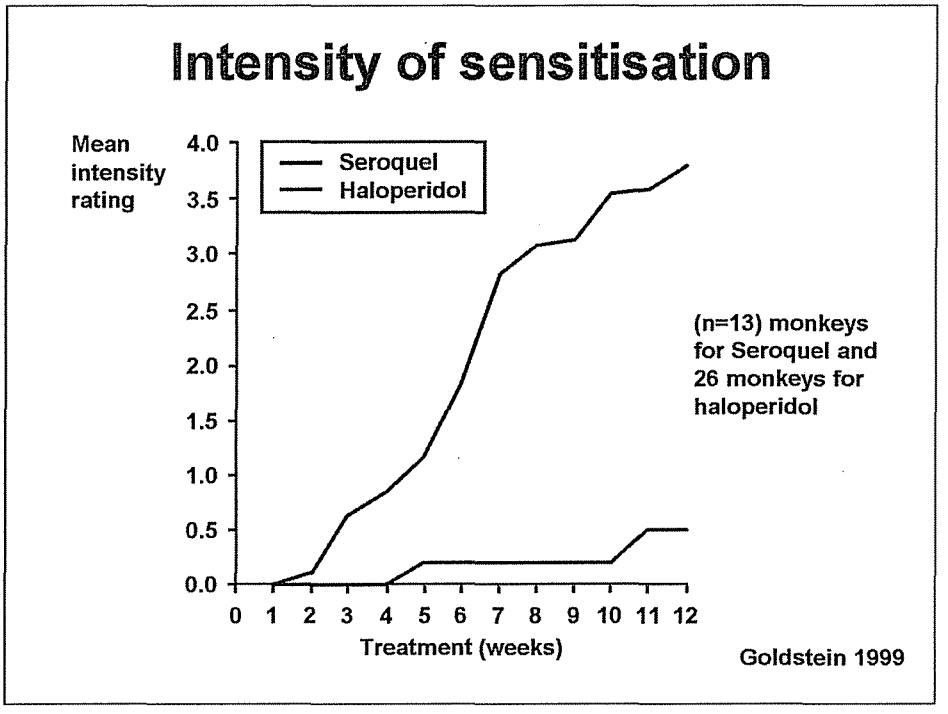
Goldstein 1996

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.

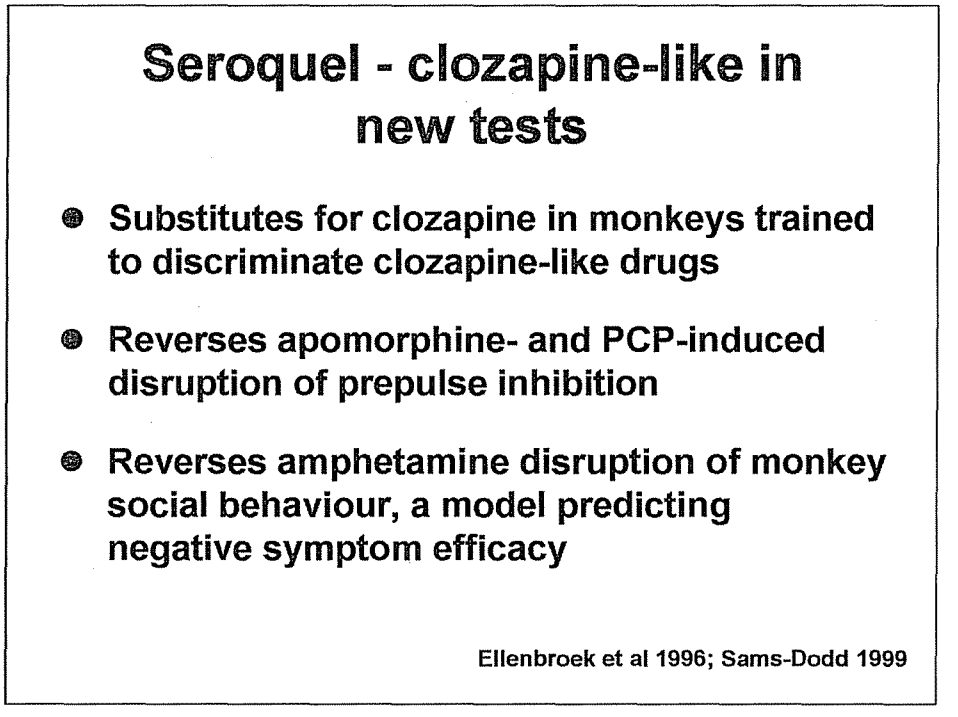


Intensity of sensitisation

- 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

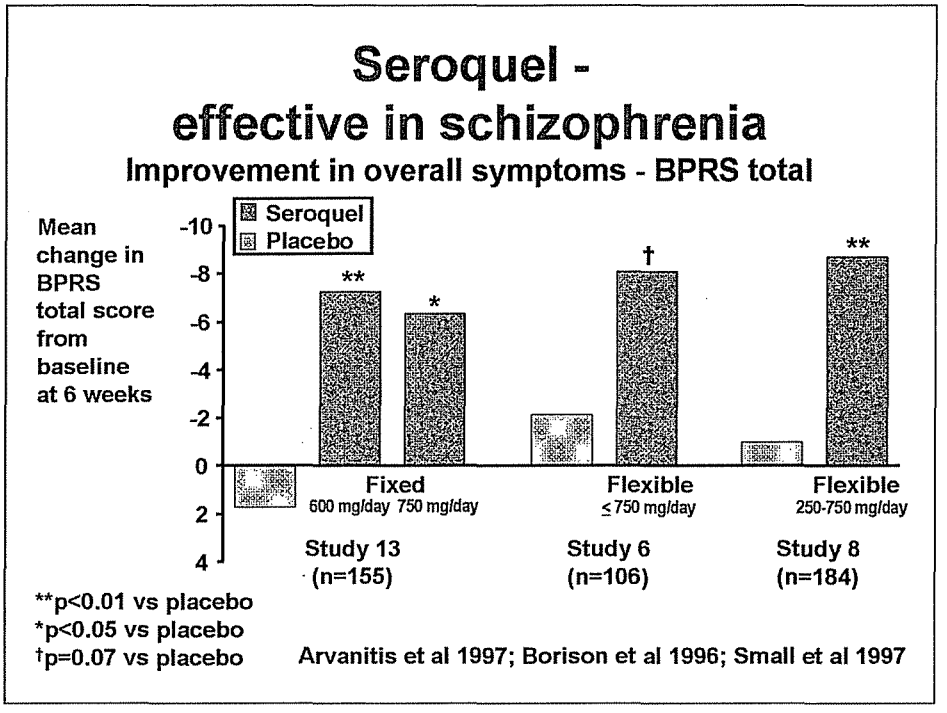
Seroquel - preclinical findings predict atypical antipsychotic profile

- 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

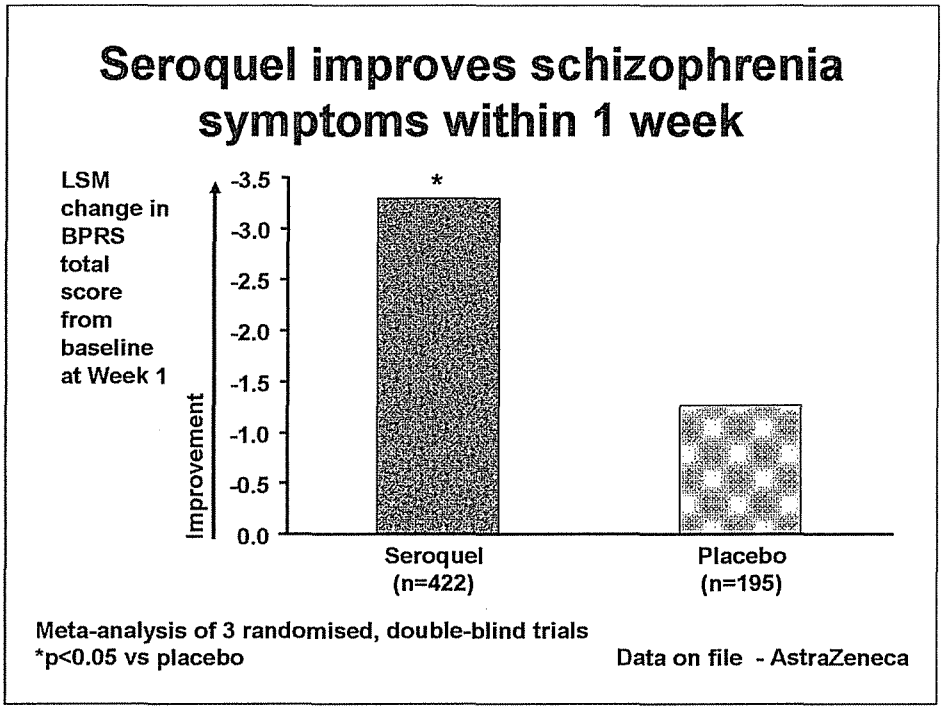


Seroquel – effective in schizophrenia

- 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

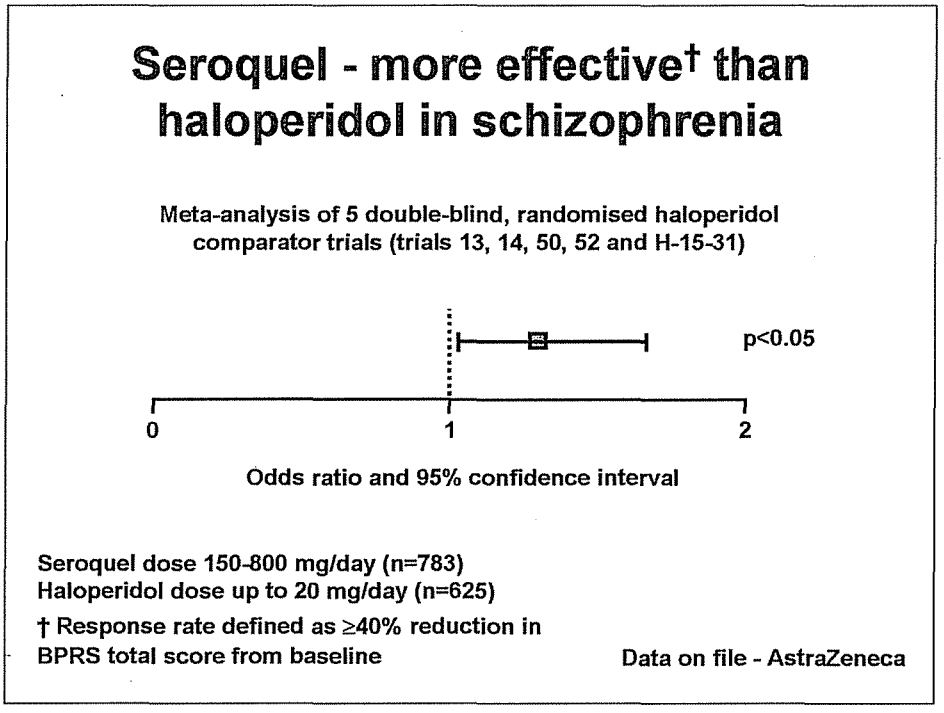
- Patients received Seroquel up to 750 mg/day in trial 6, up to 250 or 750 mg/day in trial 8 and fixed doses (75 mg/day, 150 mg/day, 300 mg/day, 600 mg/day, and 750 mg/day) in trial 13

- 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.

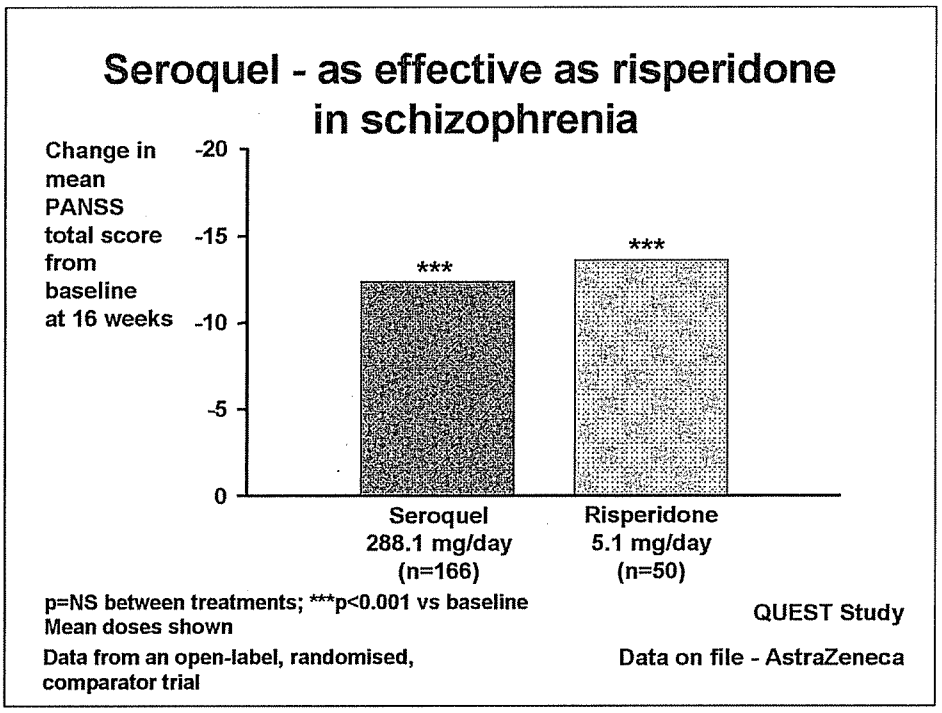


Seroquel - more effective than haloperidol in schizophrenia

- 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.

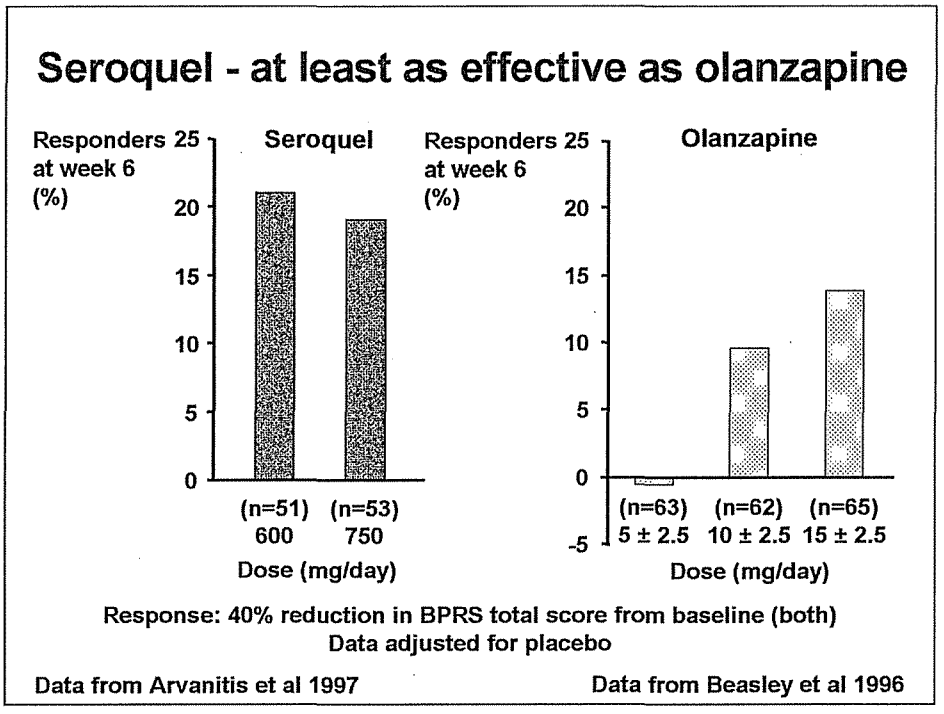


Seroquel - as effective as risperidone in schizophrenia

- 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

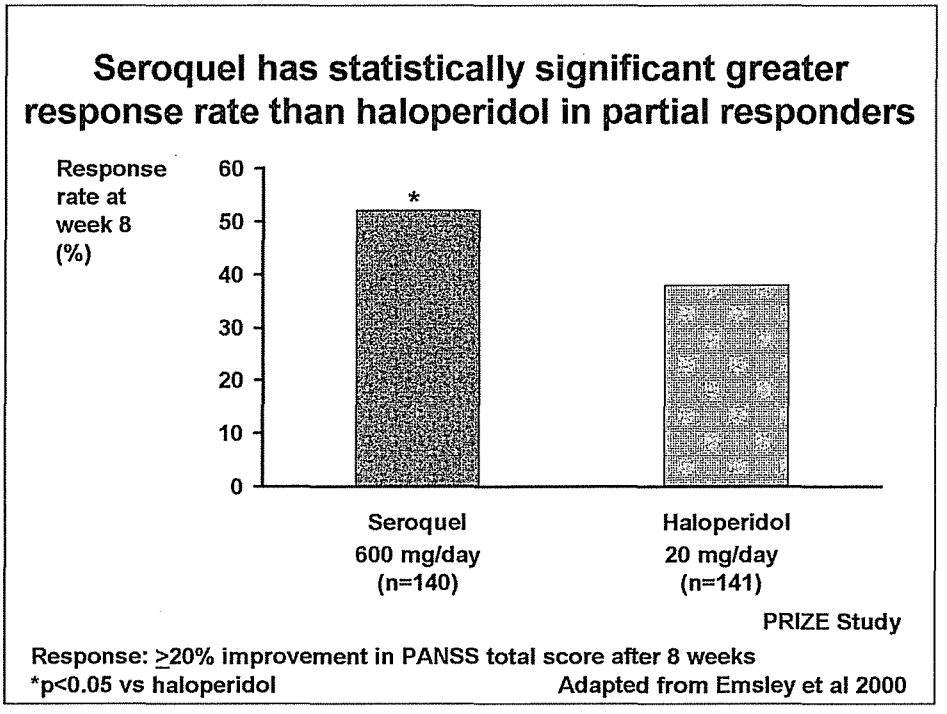
- These data are from two 6-week, randomised, double blind, placebo-controlled trials in patients with schizophrenia. Both trials used several definitions of response. This slide shows the response data that were defined as a ≥40% improvement in the Brief Psychiatric Rating Scale (BPRS) total score from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

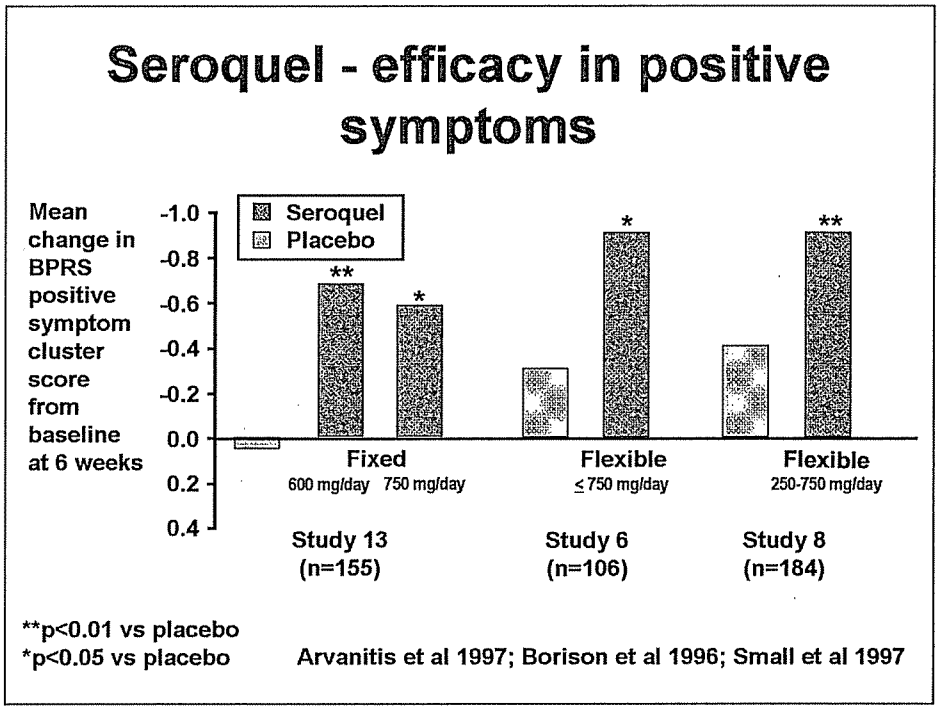
- 365 patients entered the fluphenazine run-in (4 weeks) and, of these, 143 patients were randomised to 8 weeks' treatment with Seroquel and 145 to 8 weeks' treatment with haloperidol

- 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.

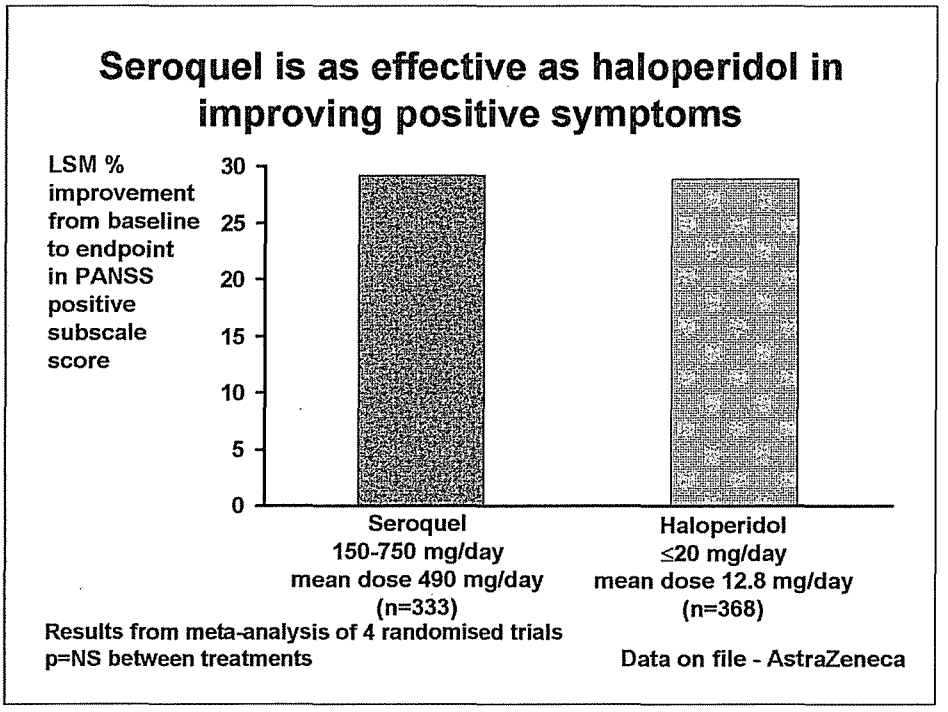


Seroquel – efficacy in positive symptoms

- 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.

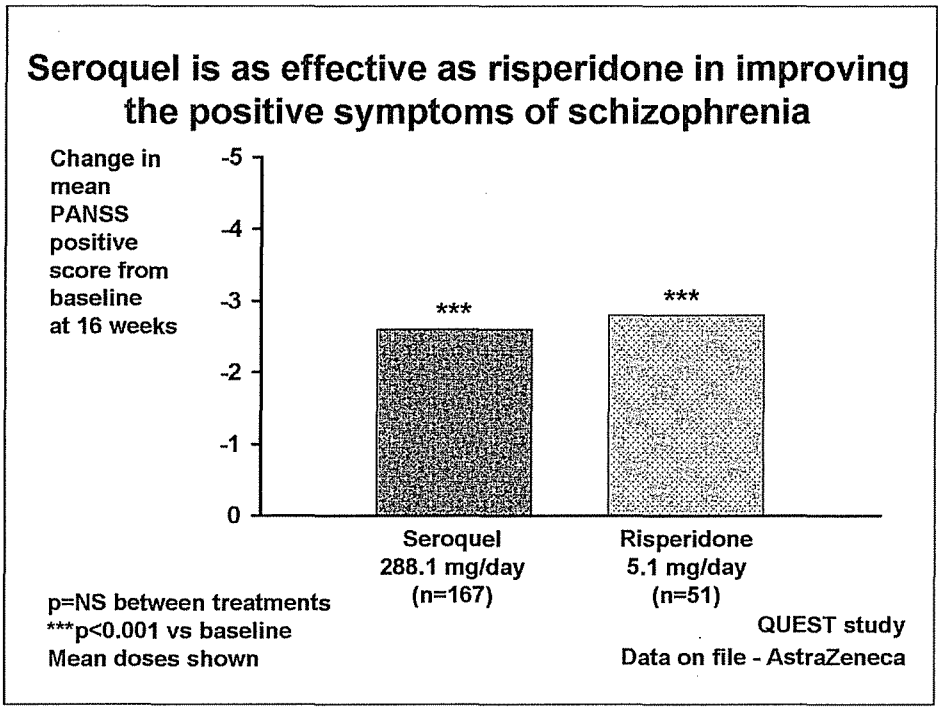


Seroquel is as effective as haloperidol in improving positive symptoms

- 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.

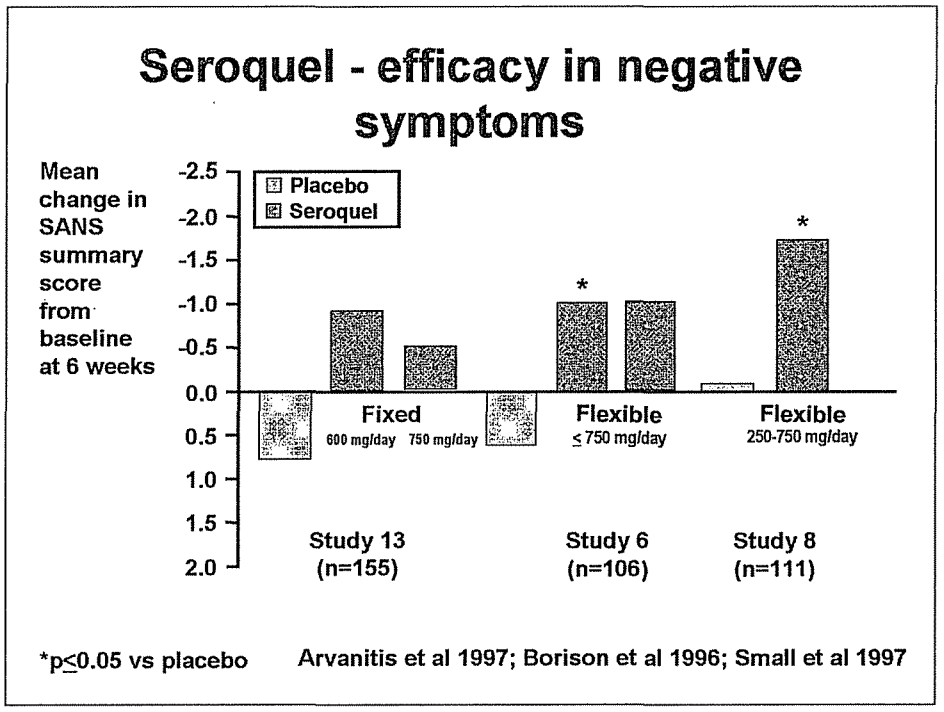


Seroquel is as effective as risperidone in improving the positive symptoms of schizophrenia

- QUEST (Quetiapine Experience with Safety and Tolerability) 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.

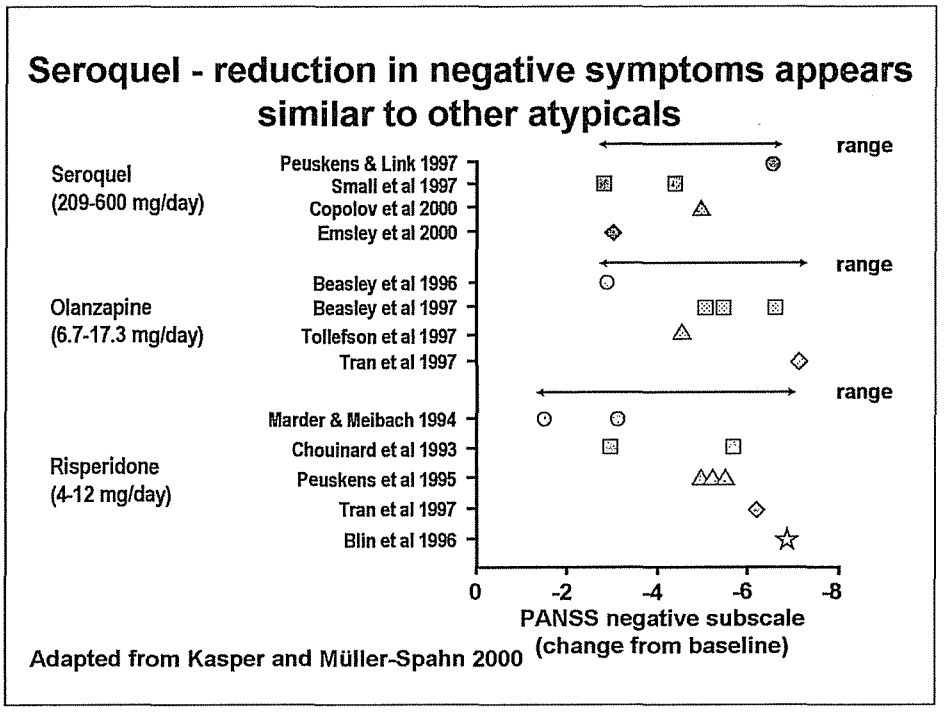


Seroquel – efficacy in negative symptoms

- 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.

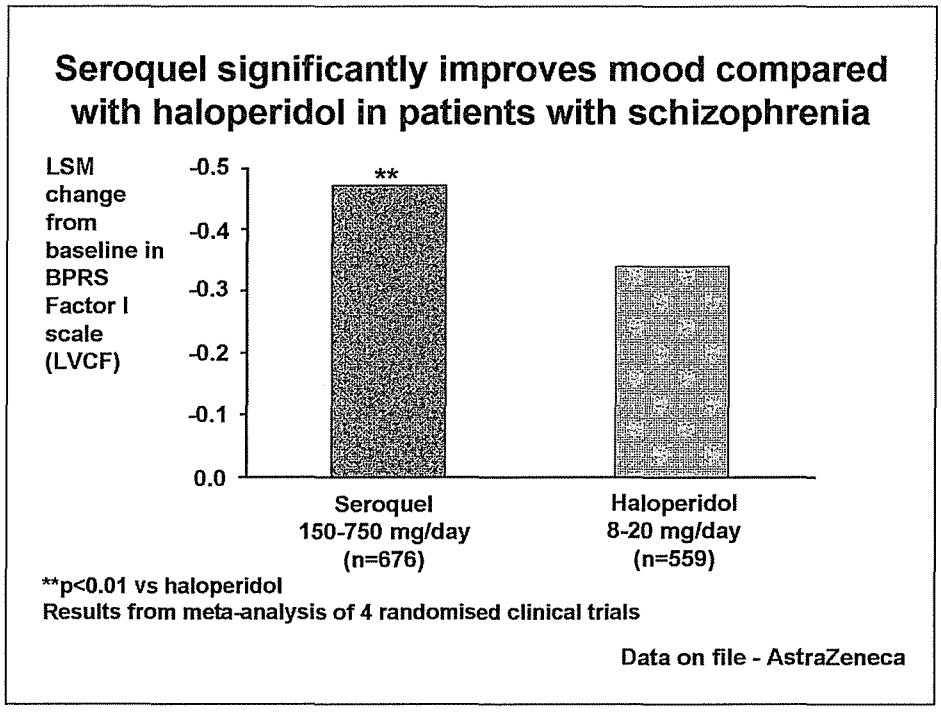


Seroquel - reduction in negative symptoms appears similar to other atypicals

- 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.

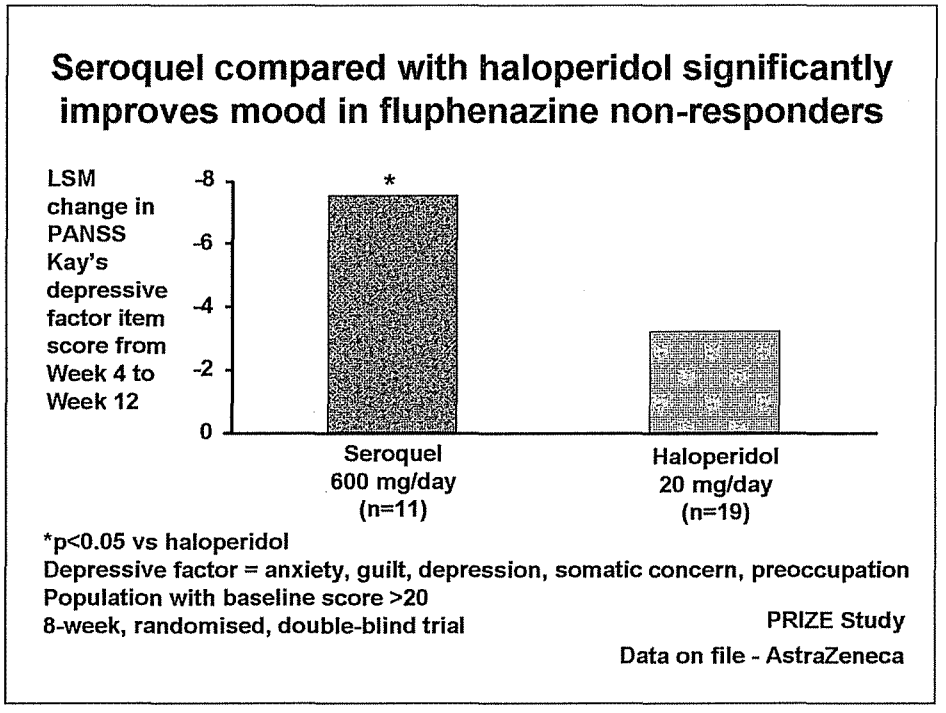


Seroquel significantly improves mood compared with haloperidol in patients with schizophrenia

- 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

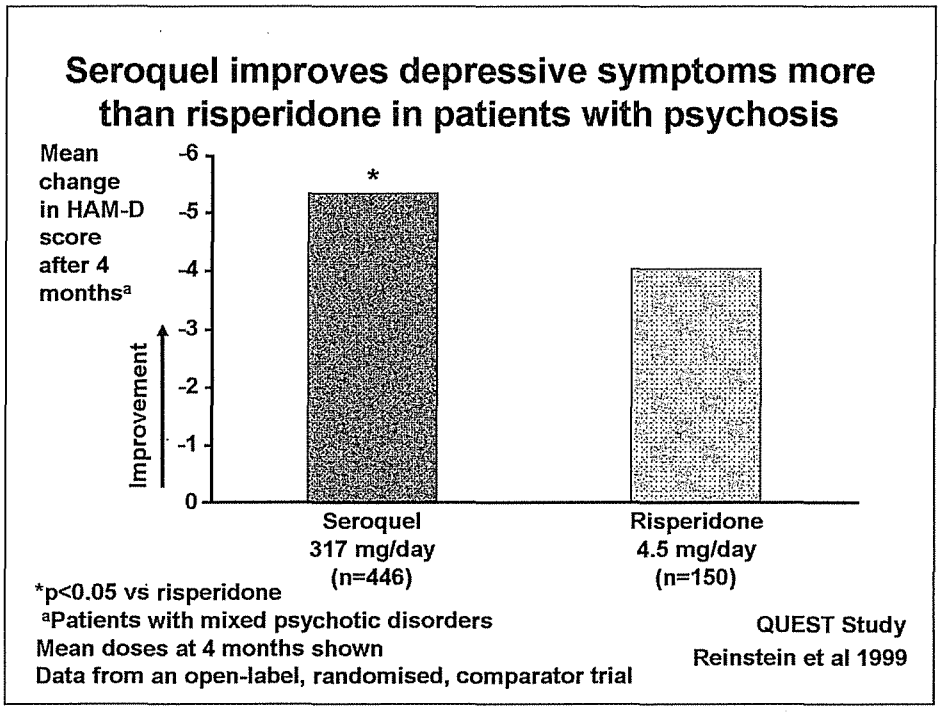
- These data are from an 8-week, multicentre, double-blind randomised trial (PRIZE – **P**artial **R**esponders **I**nternational schi**Z**ophrenia **E**valuation) comparing Seroquel (600 mg/day) and haloperidol (20 mg/day) in schizophrenic patients with a history of partial response to conventional 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.

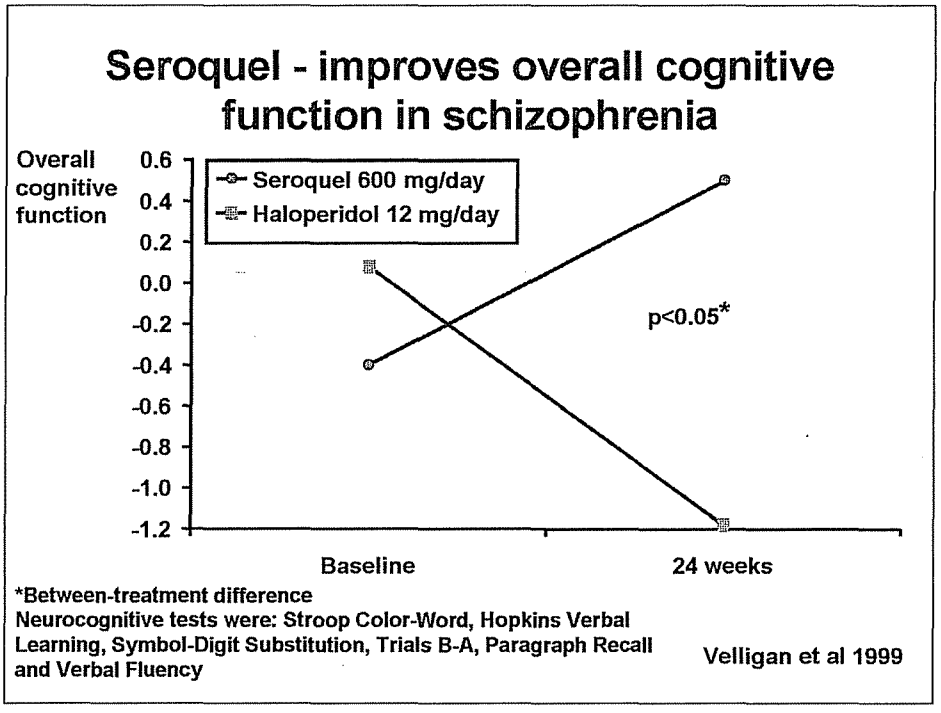


Seroquel improves depressive symptoms more than risperidone in patients with psychosis

- These data are from a 16-week, multicentre, open-label trial (QUEST – Quetiapine Experience with Safety and Tolerability) 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.

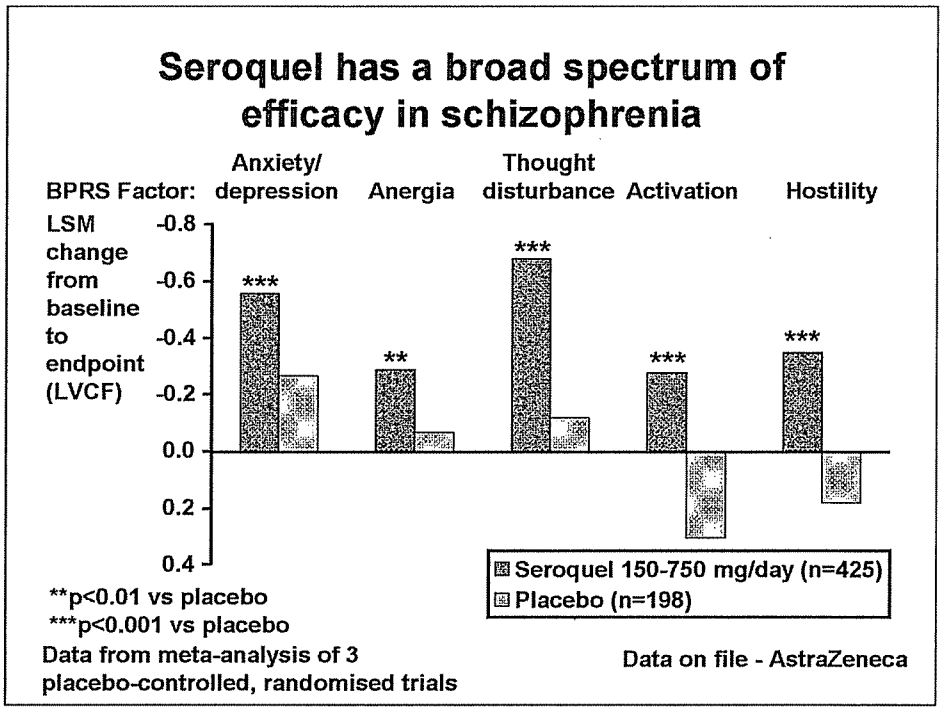


Seroquel – improves overall cognitive function in schizophrenia

- 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.

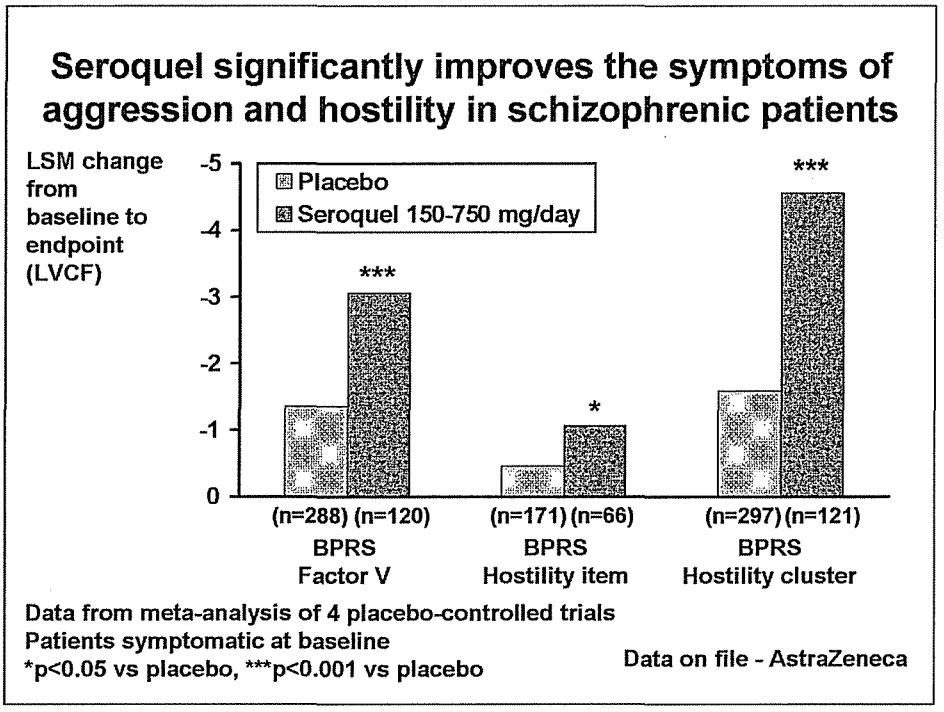


Seroquel has a broad spectrum of efficacy in schizophrenia

- 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.

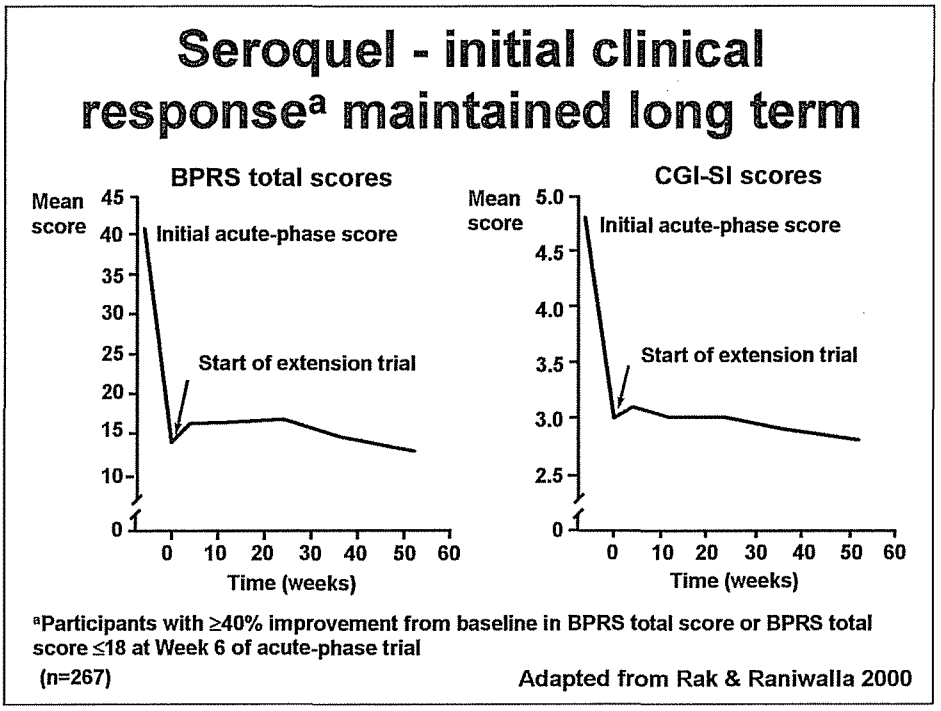


Seroquel significantly improves the symptoms of aggression and hostility in symptomatic schizophrenic patients

- 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]

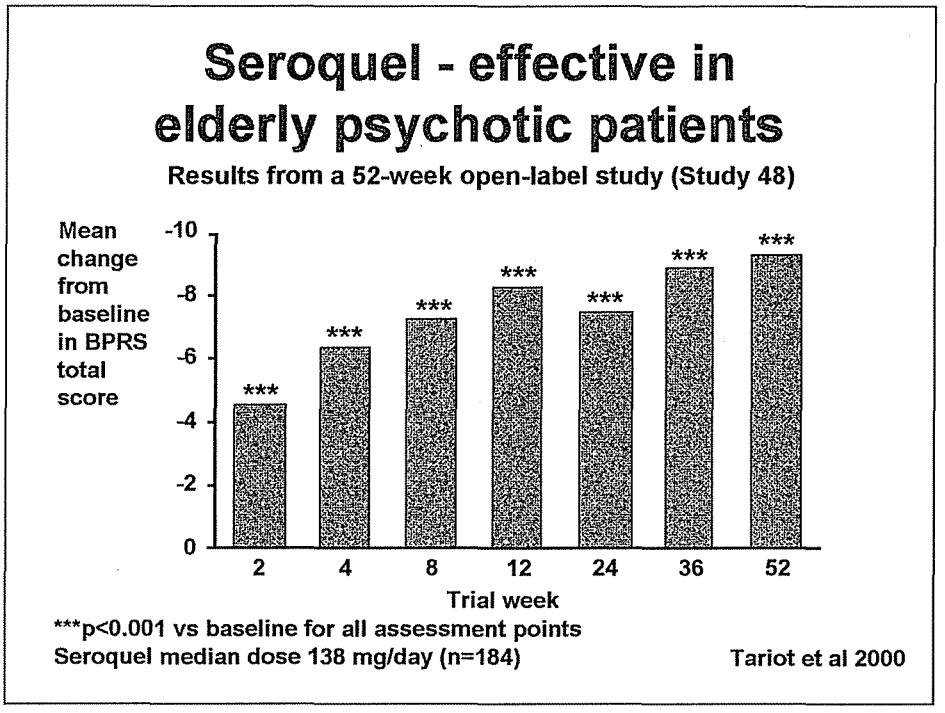
Reference

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

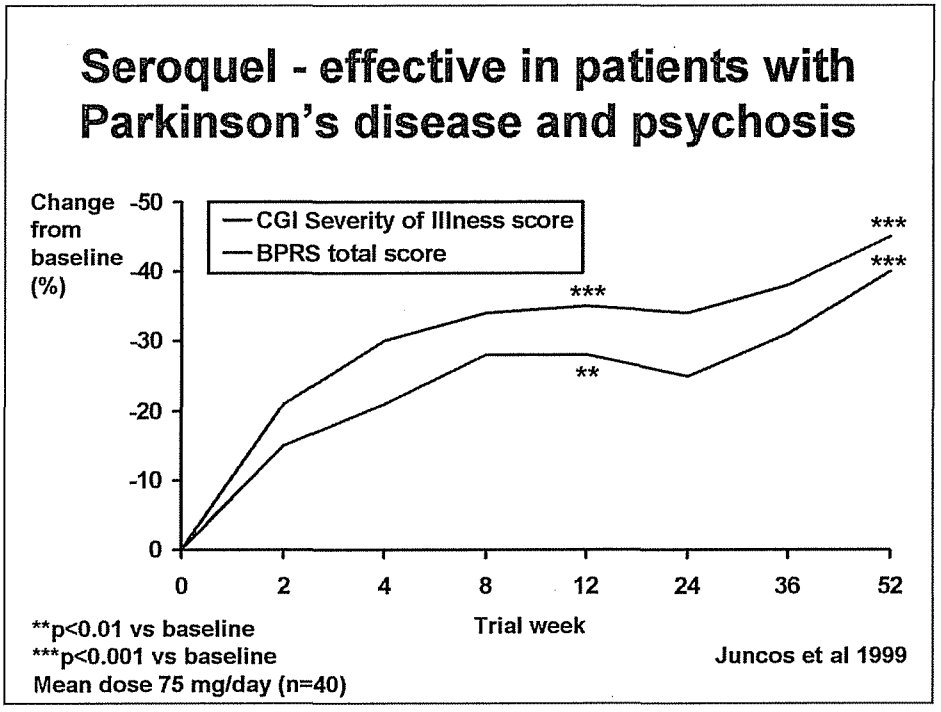
- Results from this 52-week, open-label, multicentre trial involving 184 elderly patients with psychosis showed that, at a median dose of 138 mg/day, Seroquel was effective at all timepoints. Patients had a mean age of 76 years (range 54-94 years) and 53% of the patients were female[1]

- 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

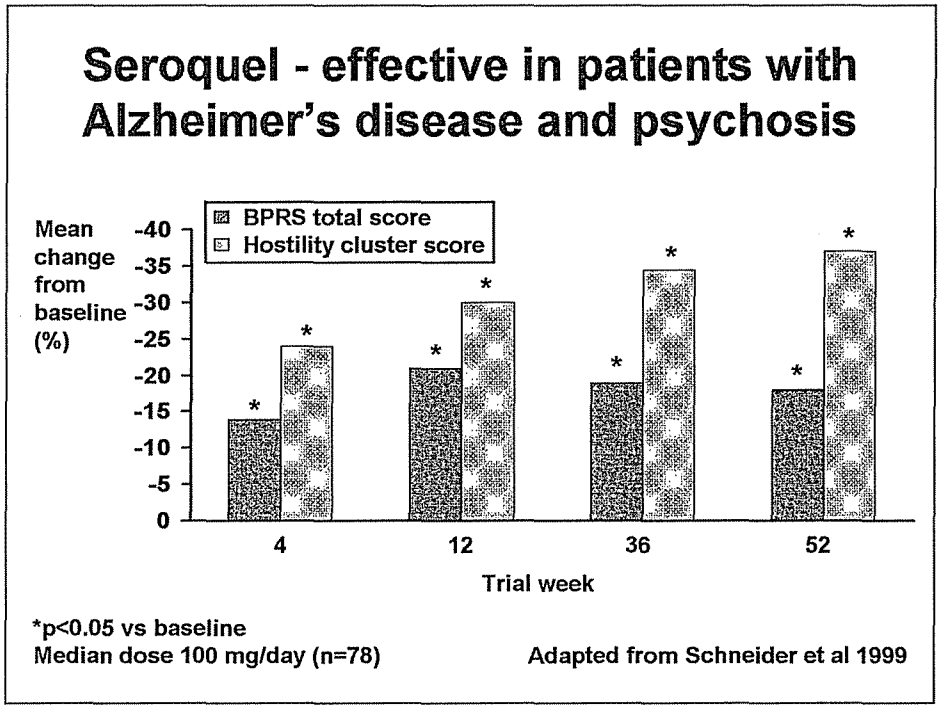
- A subset analysis[1] was carried out on 40 elderly psychotic patients diagnosed with advanced Parkinson's disease (PD) who participated in a 52-week, open-label multicentre trial of Seroquel in elderly psychotic patients (n=184).[2] The patients in the PD subset ranged in age from 54 to 89 years and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

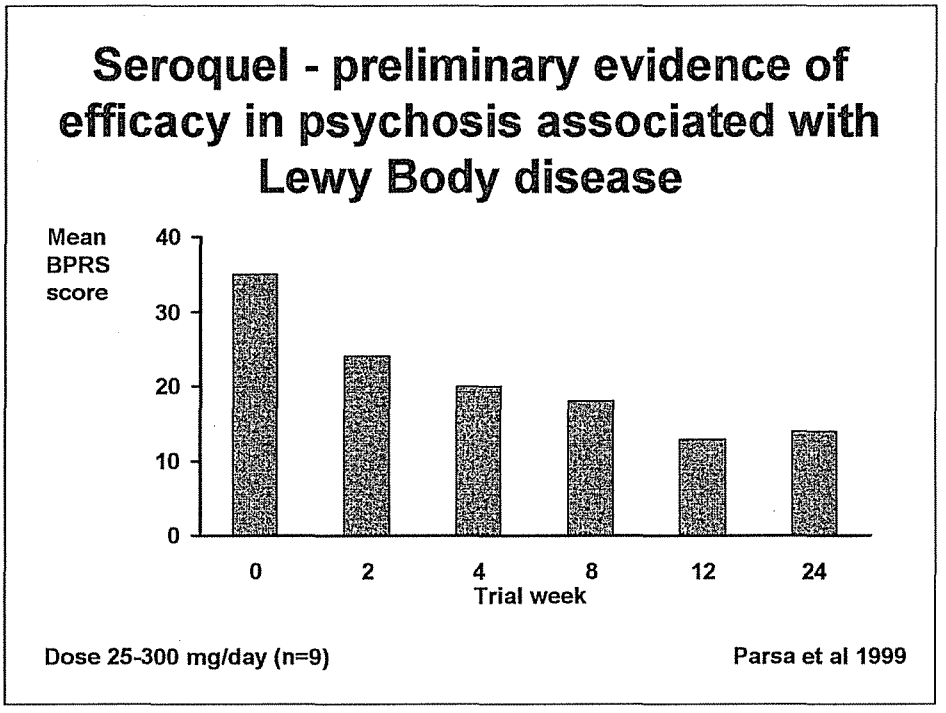
- A subset analysis[1] was carried out data from 78 elderly psychotic patients diagnosed with Alzheimer's disease (AD) who had participated in a 52-week, open-label, multicentre trial of Seroquel in elderly psychotic patients (n=184)[2]

- 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.

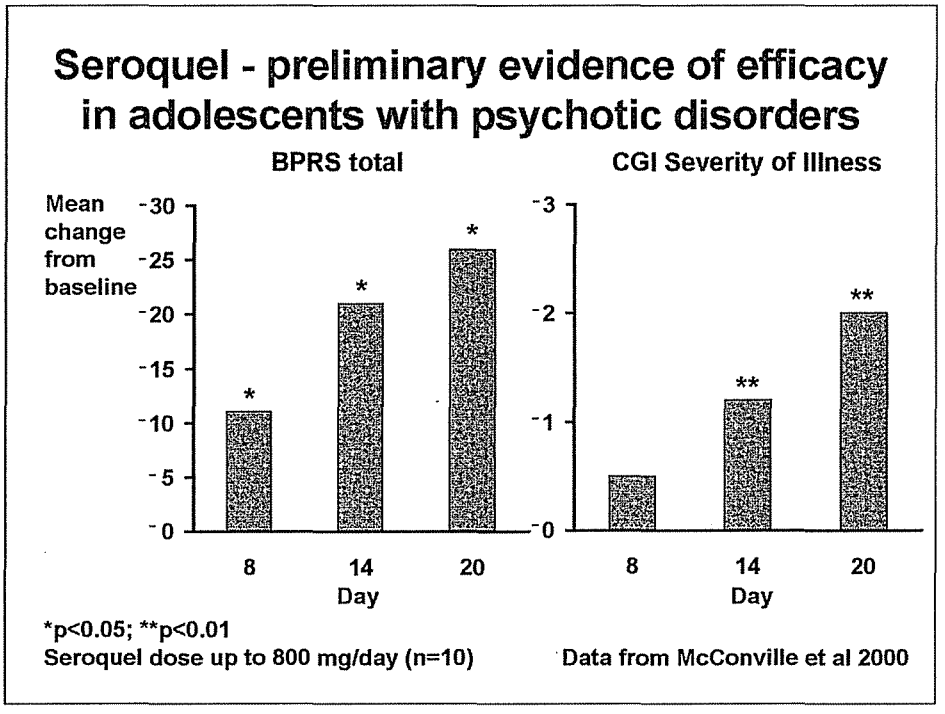


Seroquel - preliminary evidence of efficacy in psychosis associated with Lewy Body disease

- 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

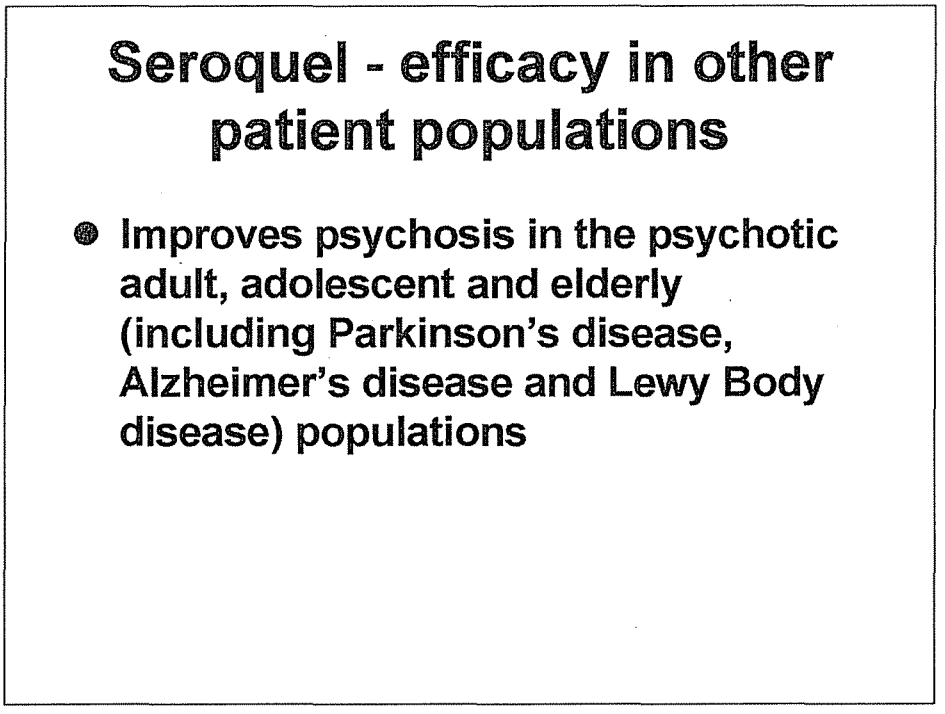
- These preliminary data are from an open-label, 23-day, dose-escalation trial. Patients discontinued all other antipsychotic treatment on Day 1 and started Seroquel 25 mg bid on Day 3, which was increased in a stepwise manner over the following 18 days to reach 400 mg bid on Day 21. A final dose of 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

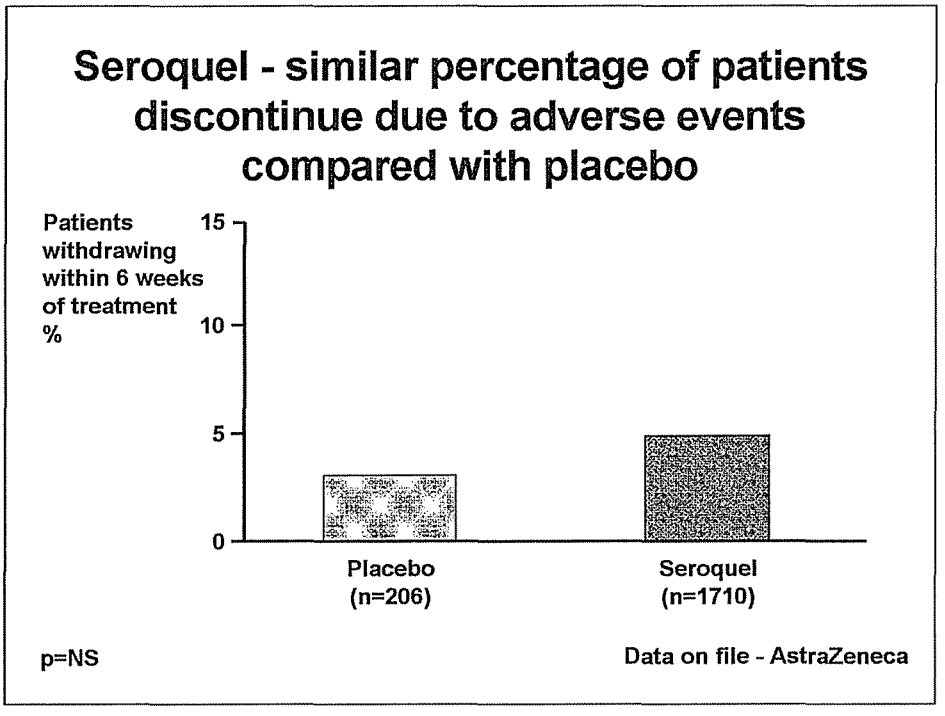
1. McConville BJ et al. *J Clin Psychiatry* 2000; 61: 252-260.



Seroquel - efficacy in other patient populations

Summary slide

Safety and tolerability in schizophrenia

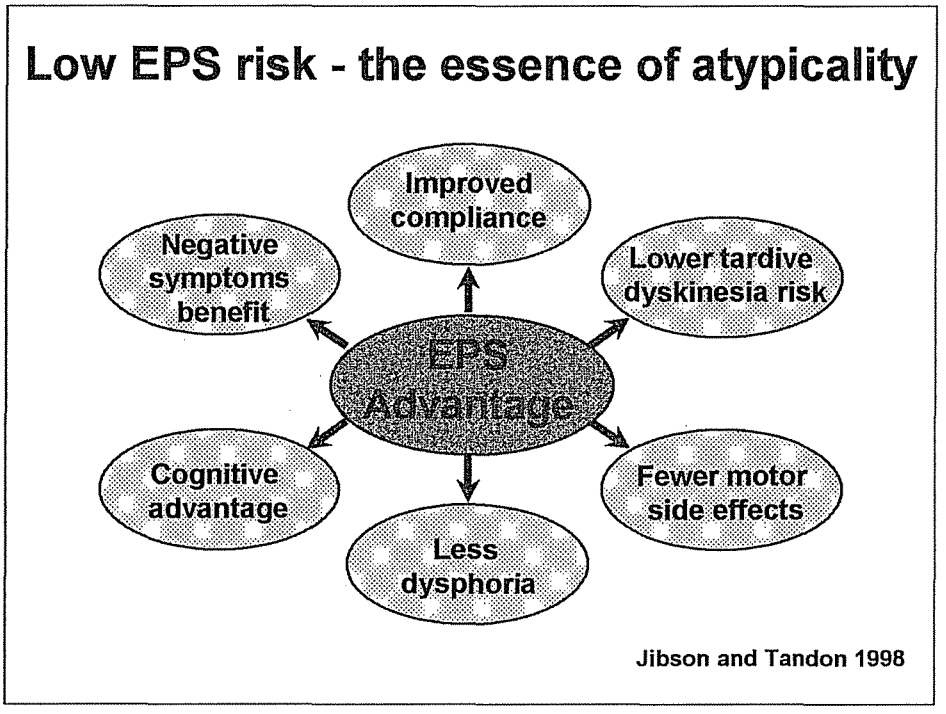


Seroquel - similar percentage of patients discontinue due to adverse events compared with placebo

- 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.



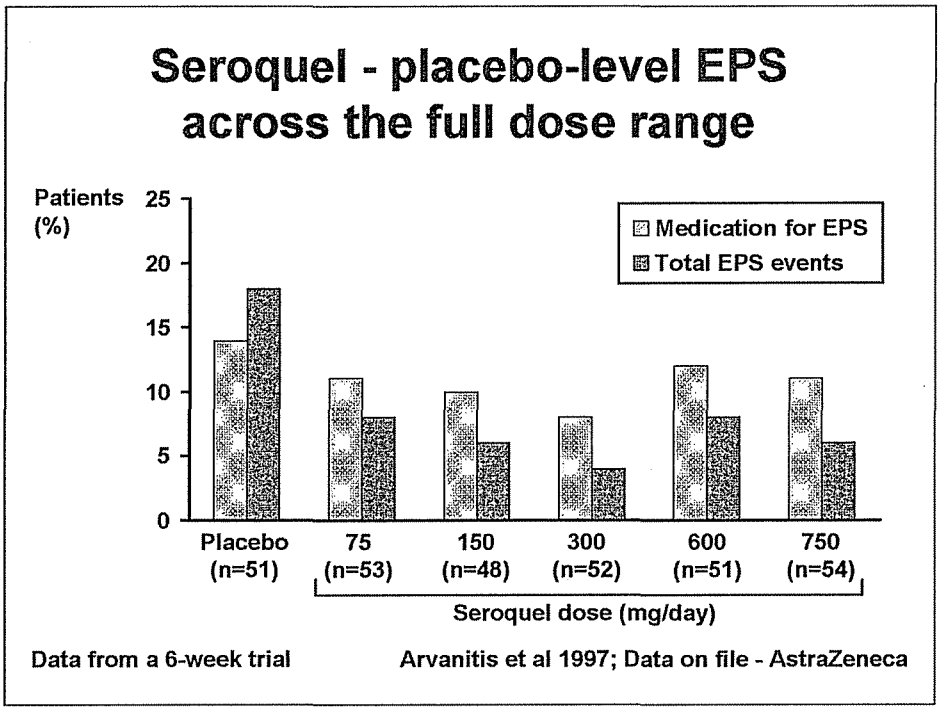
Low EPS risk – the essence of atypicality

- 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

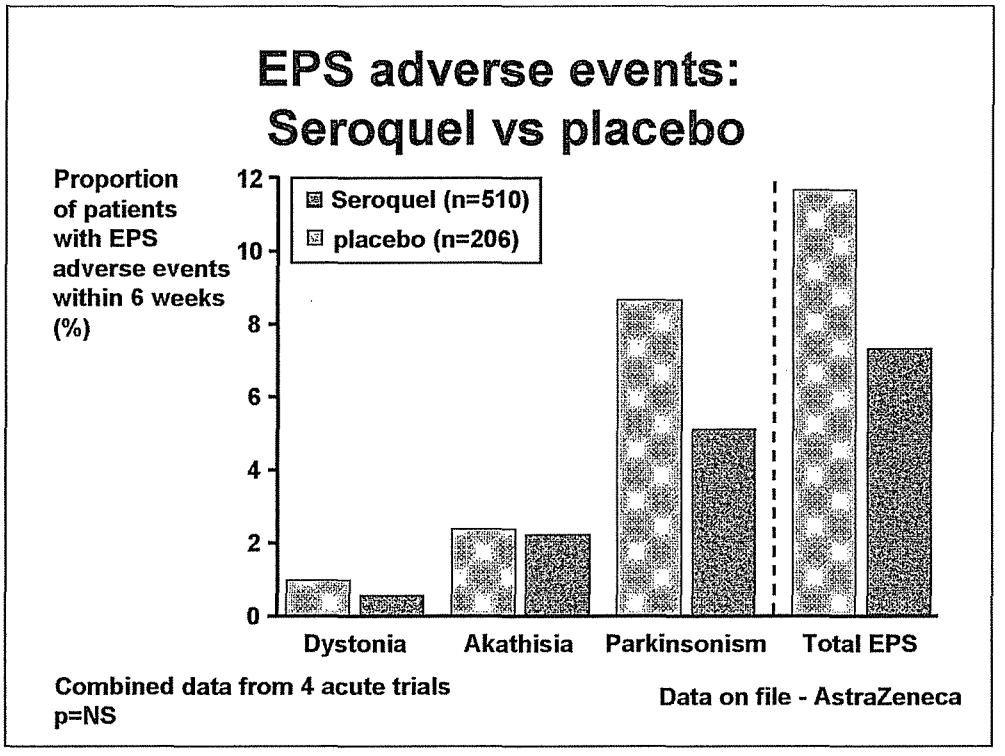
- These data are from a 6-week randomised, double blind, placebo-controlled trial of Seroquel in patients with schizophrenia (361 patients were randomised to treatment)[1]

- 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.

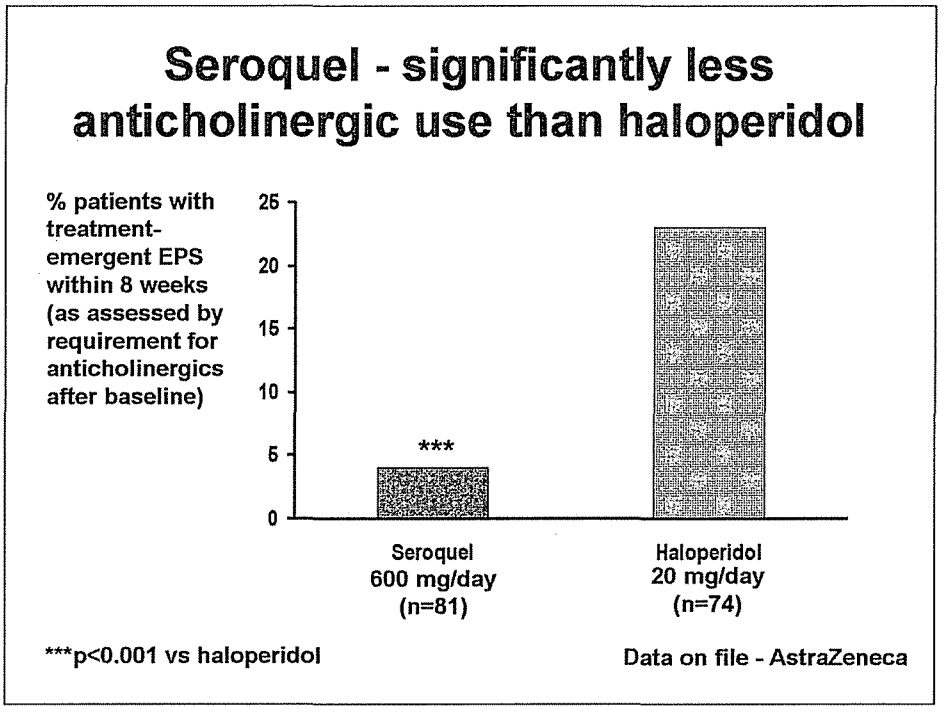


EPS adverse events: Seroquel vs placebo

- 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

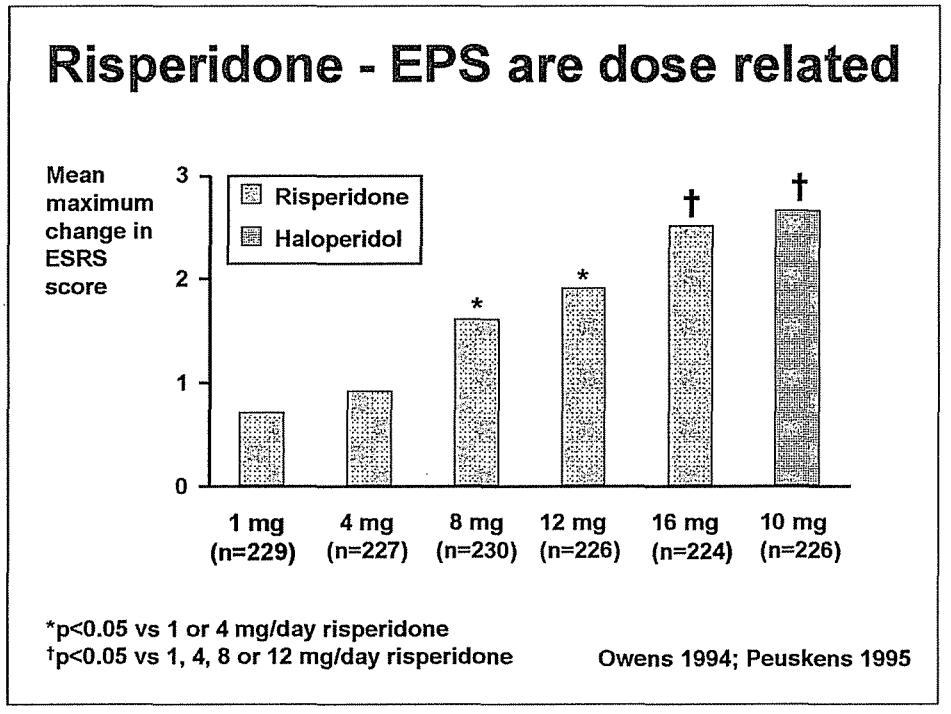
- The PRIZE study (**P**artial **R**esponders **I**nternational schi**Z**ophrenia **E**valuation) compared the efficacy of 8 weeks' Seroquel treatment (600 mg/day) with haloperidol (20 mg/day) in 288 patients who had a history of partial response or non-response to conventional antipyschotics[1]

- 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.

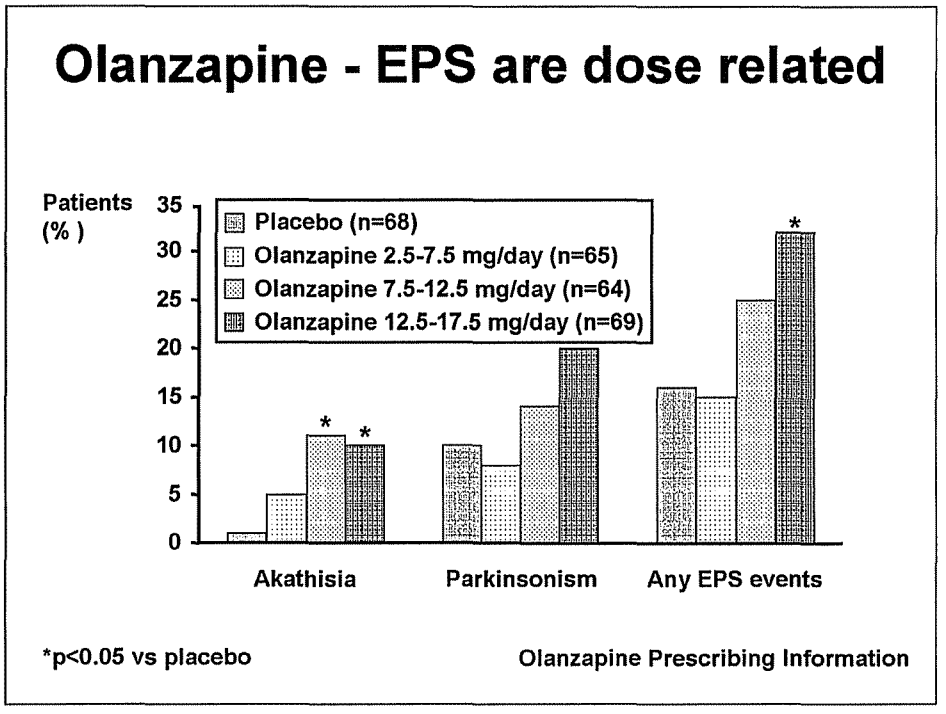


Risperidone – EPS are dose related

- 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.

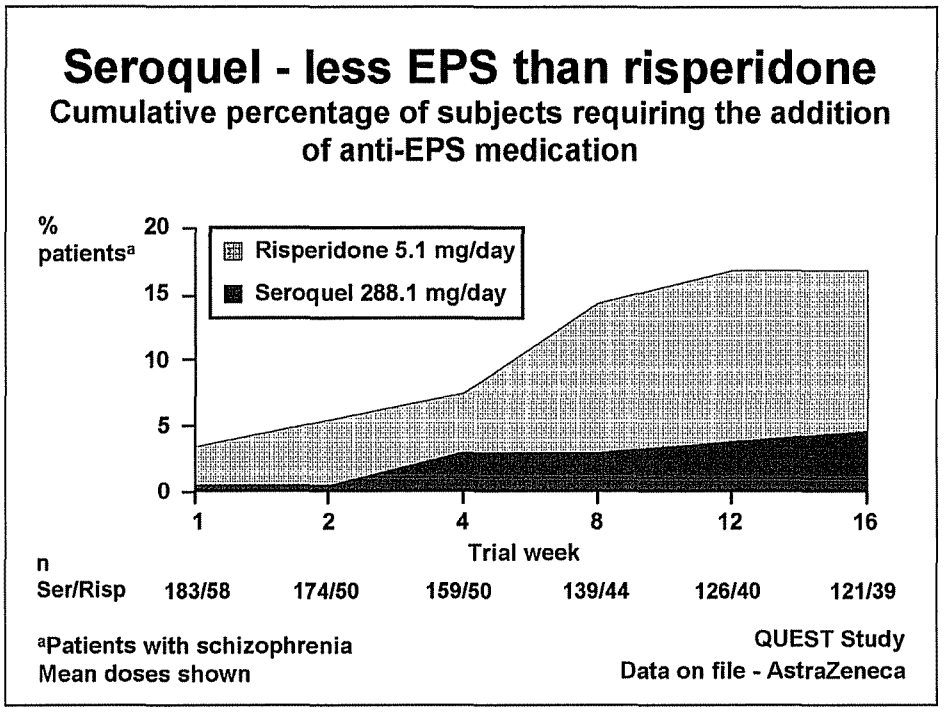


Olanzapine – EPS are dose related

- 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 **E**xperience 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]

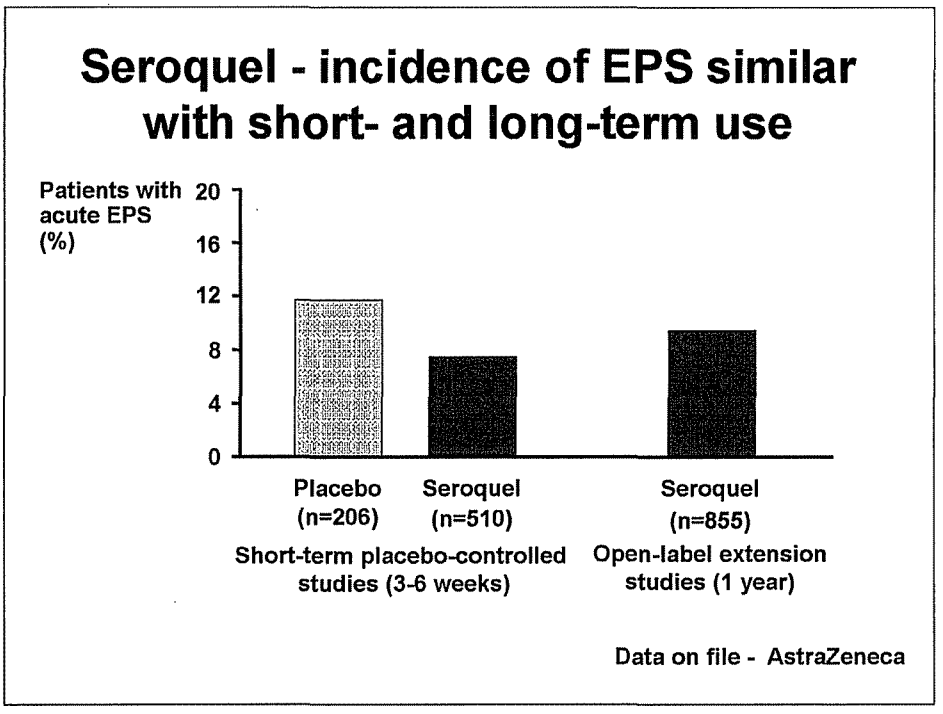
- This slide presents data from the subanalysis of the schizophrenia cohort within QUEST ([n=251]; Seroquel [n=191] and risperidone [n=60]), where patients received Seroquel (mean dose 288.1 mg/day) or risperidone (mean dose 5.1 mg/day[2])

- 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.



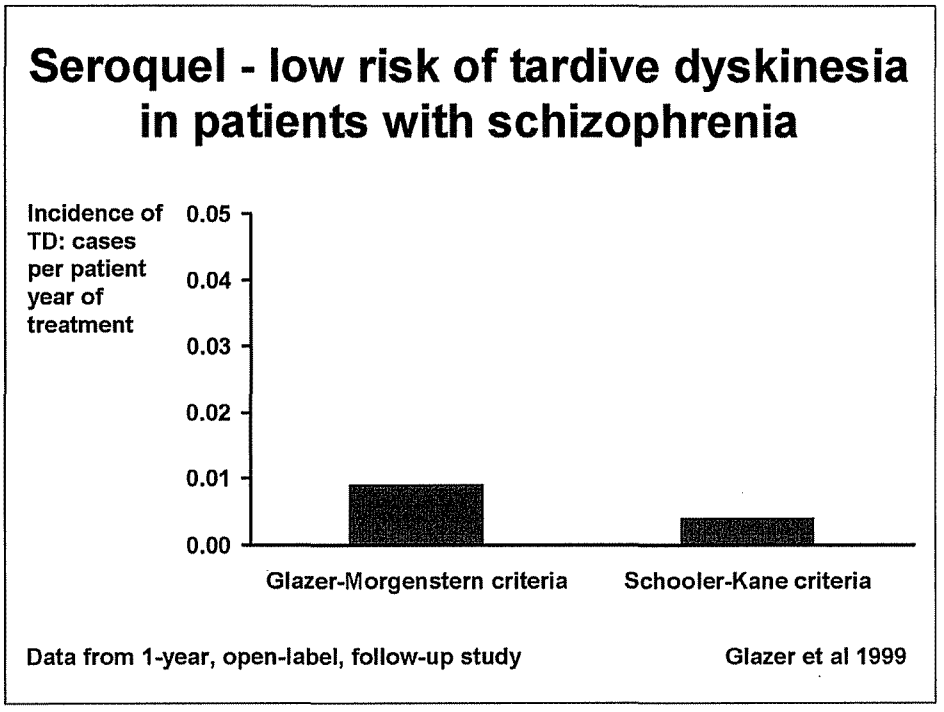
Seroquel – incidence of EPS similar with short- and long-term use

- 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

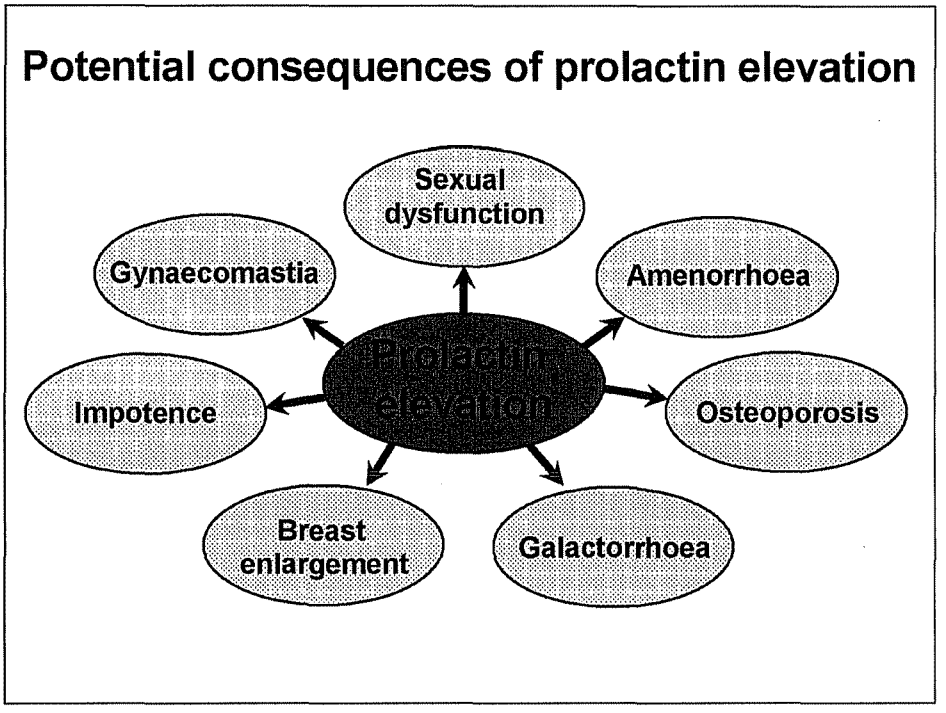
- It is thought that there is an association between extrapyramidal symptoms (EPS) and the development of tardive dyskinesia (TD). Atypical antipsychotics that have a minimal propensity to cause EPS, such as Seroquel, should be therefore less likely to be associated with TD

- 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

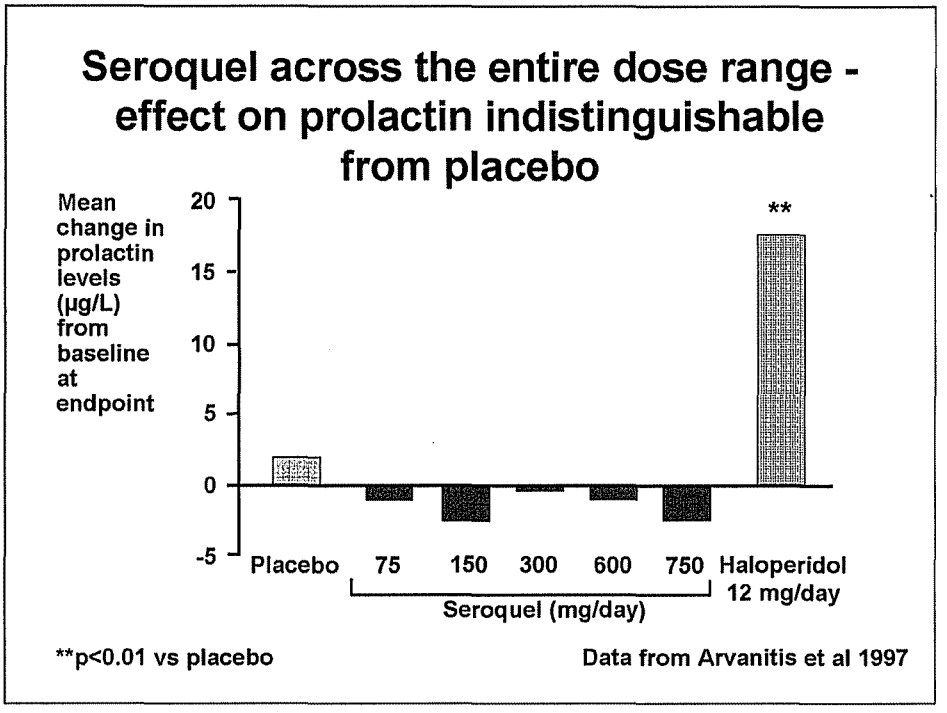
Reference

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.



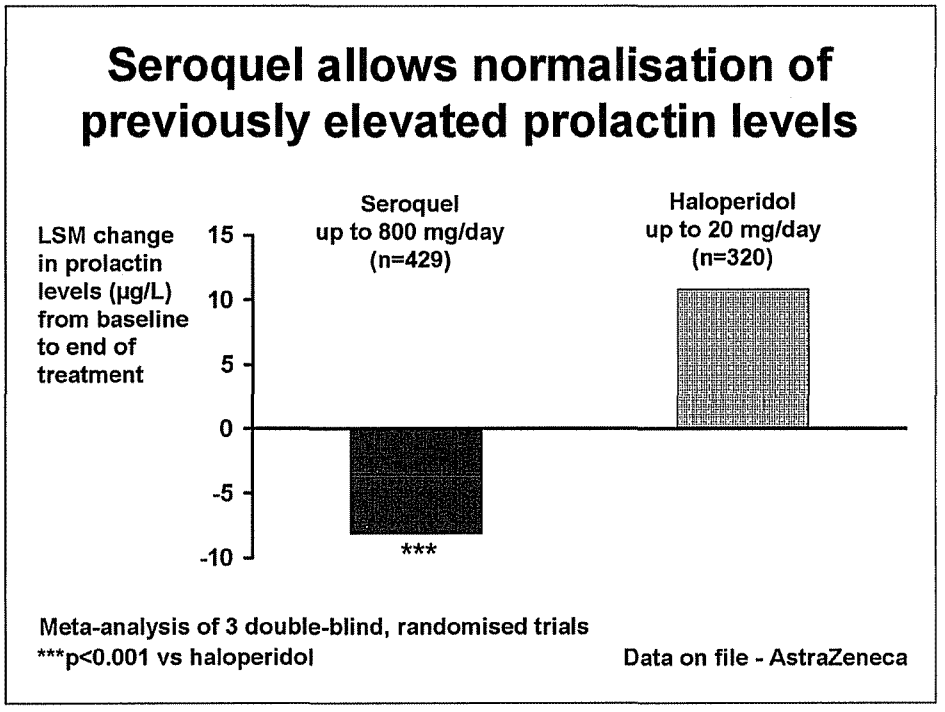
Seroquel across the entire dose range - effect on prolactin indistinguishable from placebo

- 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.

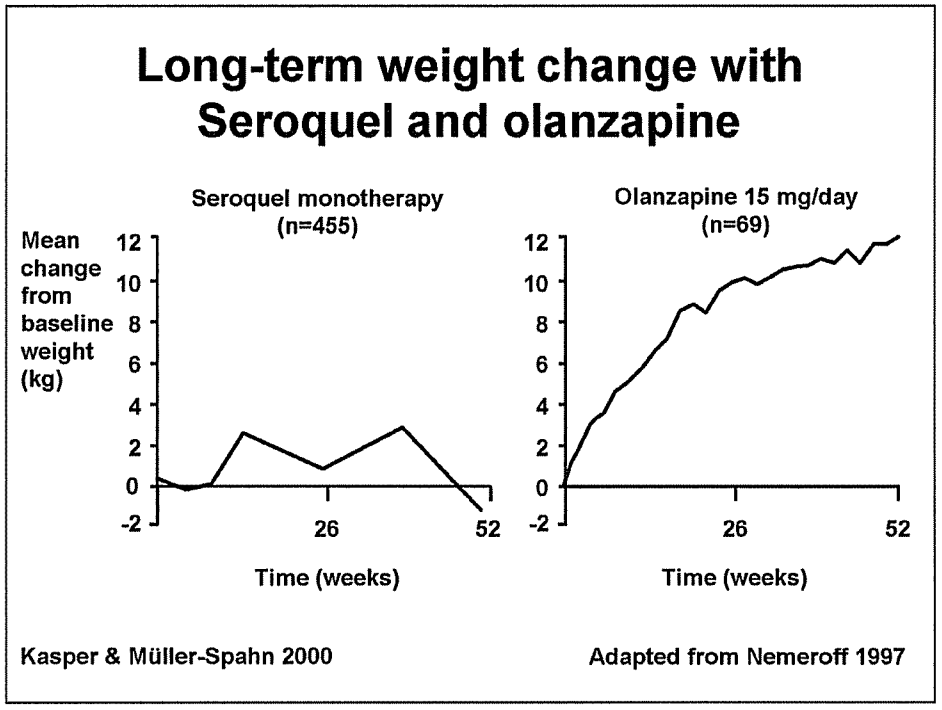


Seroquel allows normalisation of previously elevated prolactin levels

- 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.



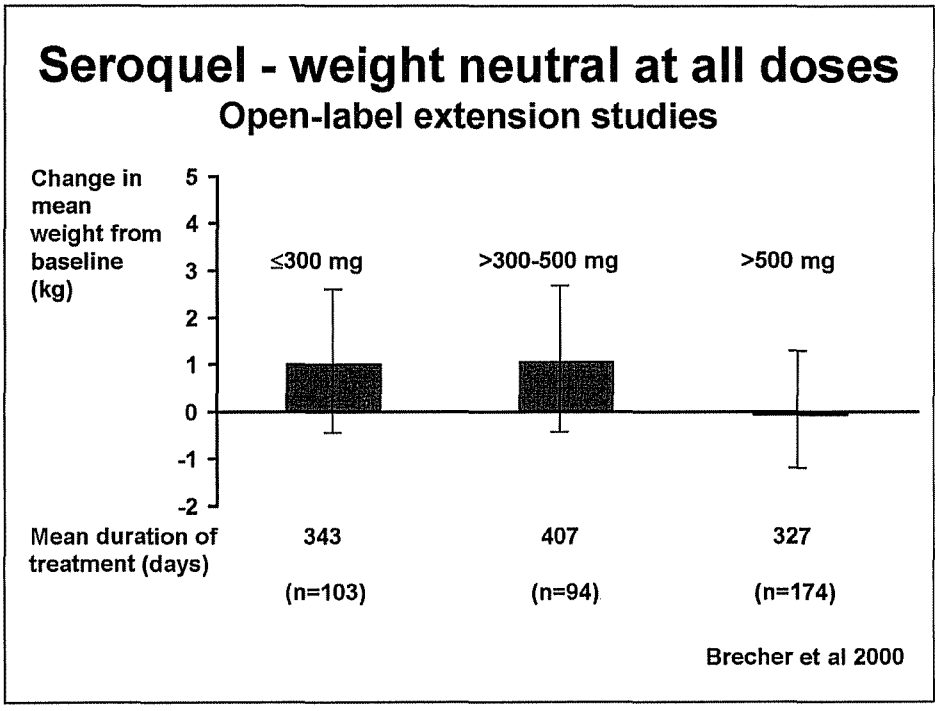
Long-term weight change with Seroquel and olanzapine

- 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

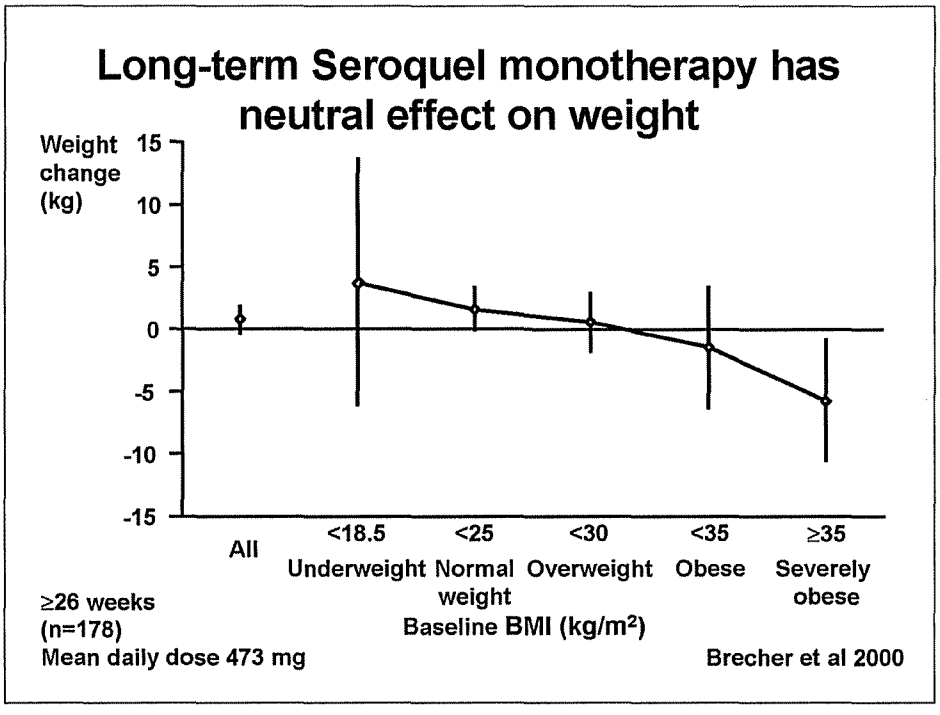
- Study 51 was an open-label extension study of Seroquel in patients who had participated in Phase IIIb clinical trials (approximately 500 patients entered the trial).[1] These data are from a subset of patients with schizophrenia who received Seroquel up to 800 mg/day in Study 51[1]

- 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.

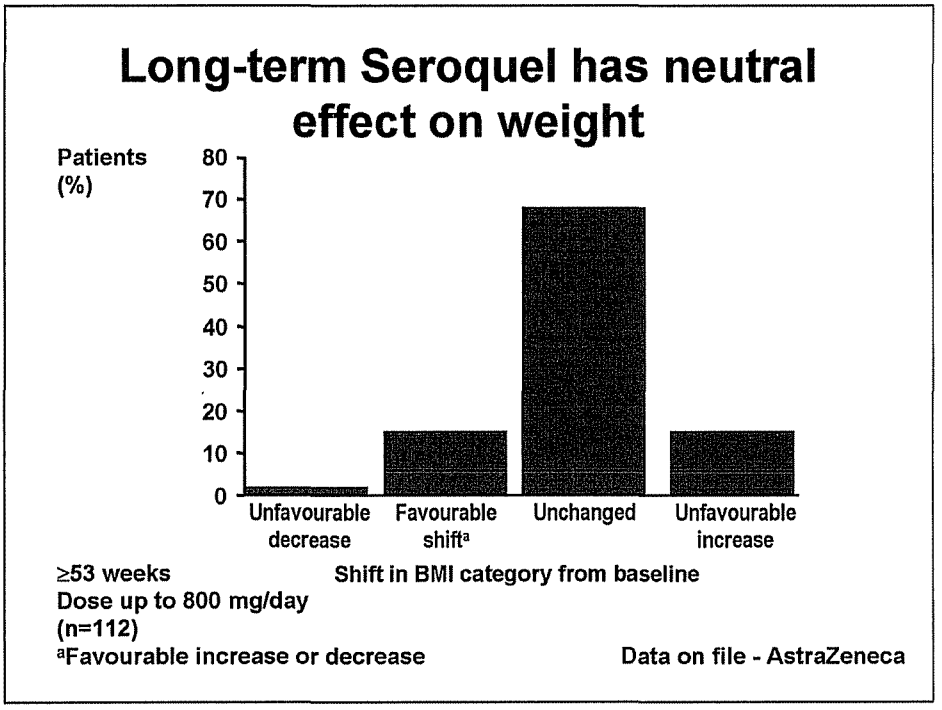


Long-term Seroquel monotherapy has neutral effect on weight

- 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.

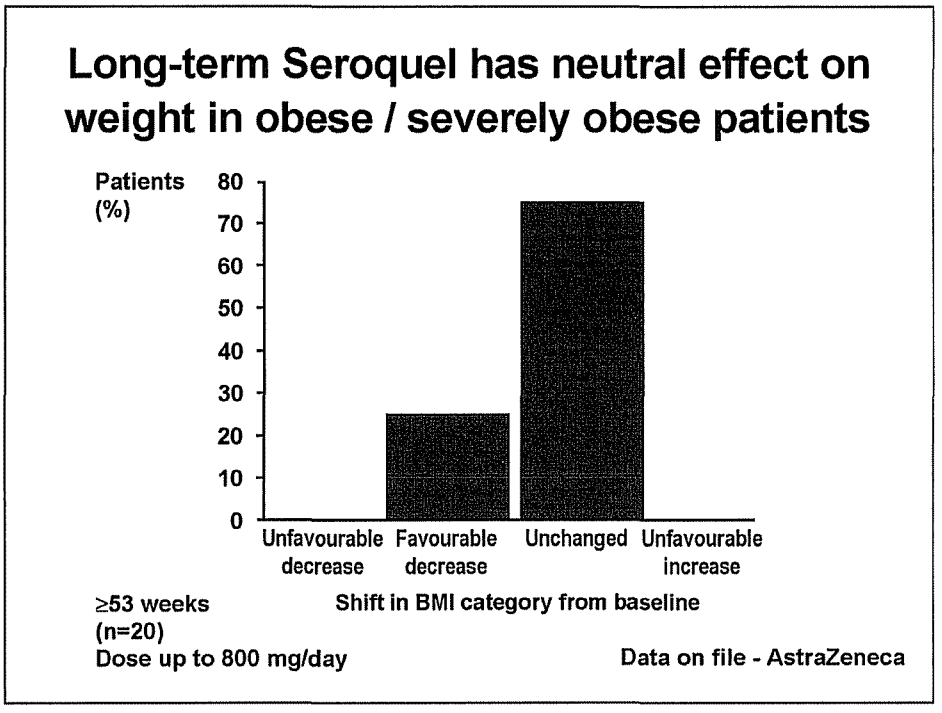


Long-term Seroquel has neutral effect on weight

- 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

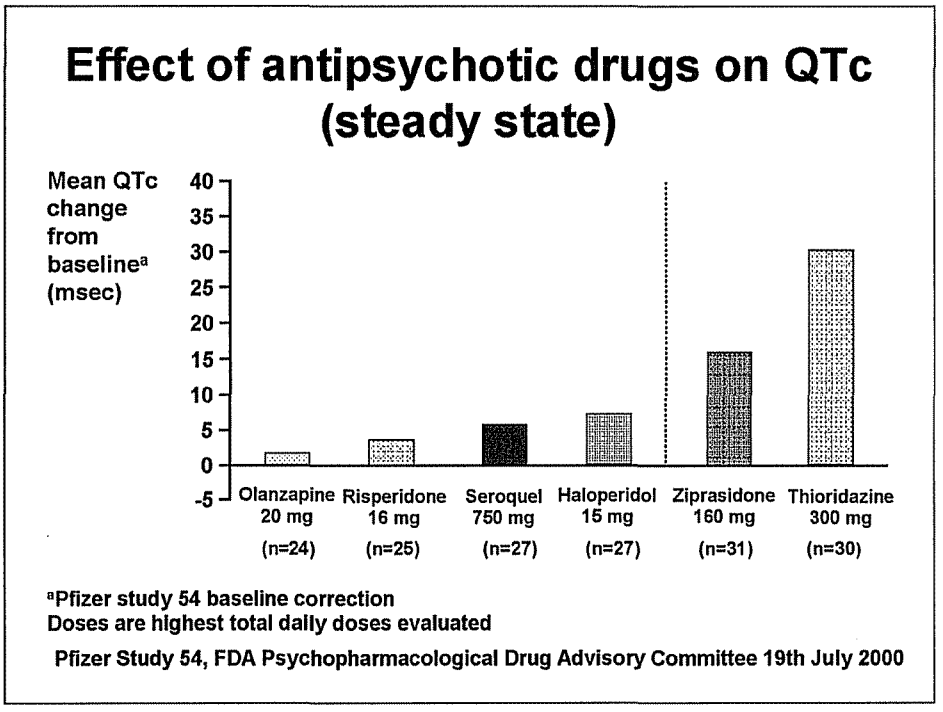
Pfizer Study 54, FDA Psychopharmacological Drug Advisory Committee 19th July 2000

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)

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- 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**

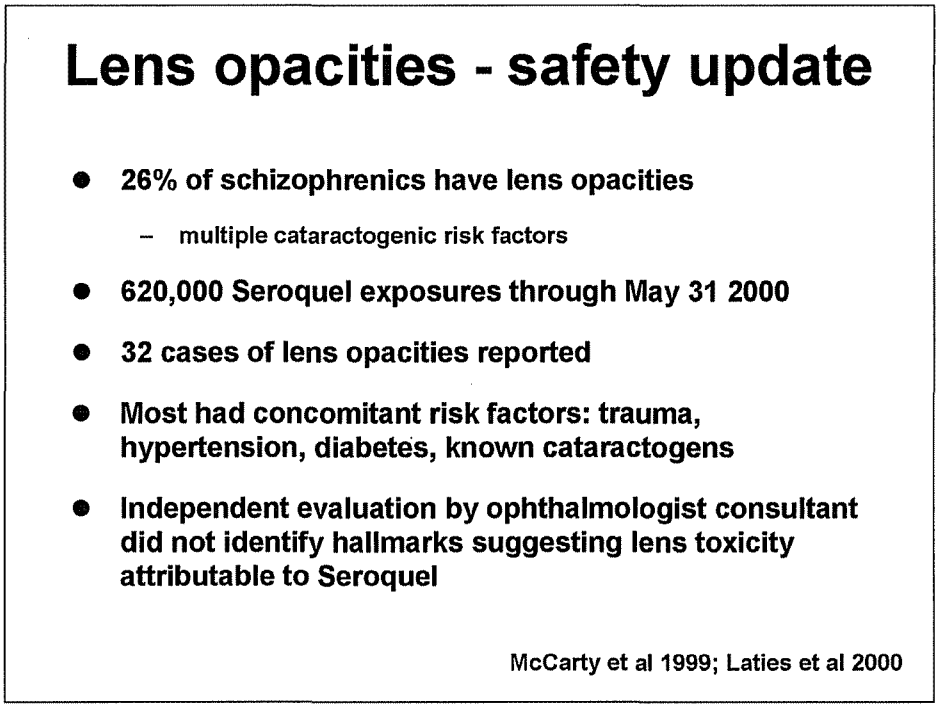
Meats 1997; Data on file - AstraZeneca

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

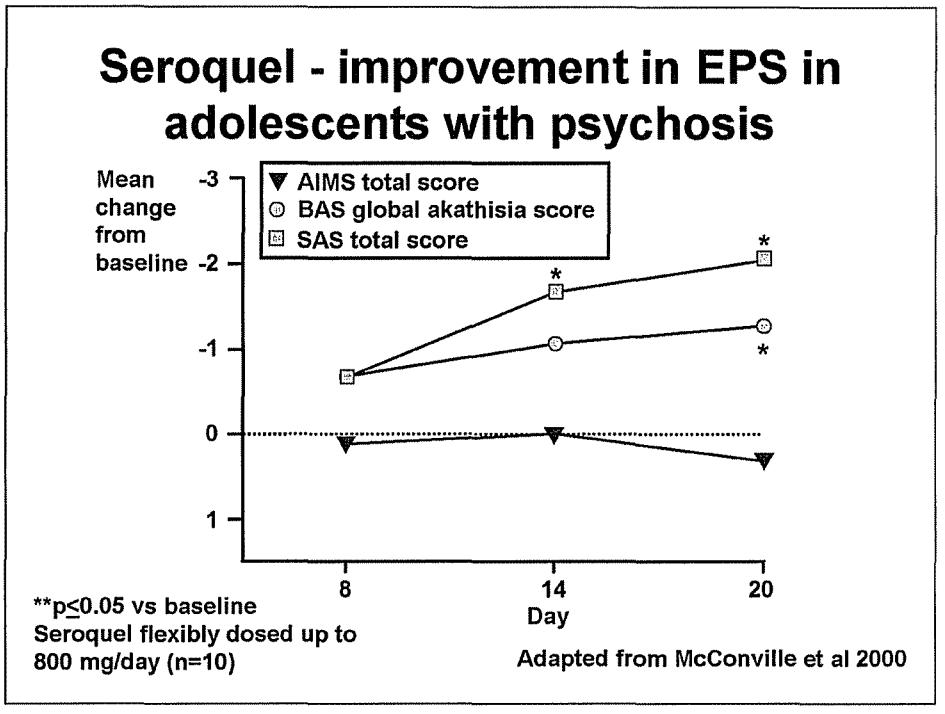
Unique tolerability profile

- 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

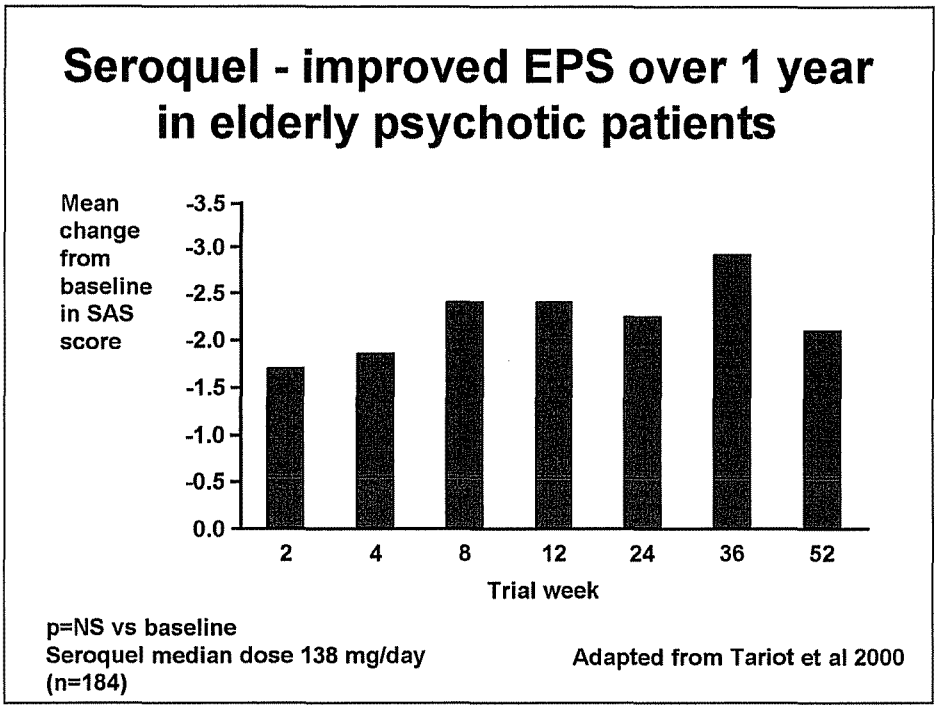
Tariot et al 1999

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]

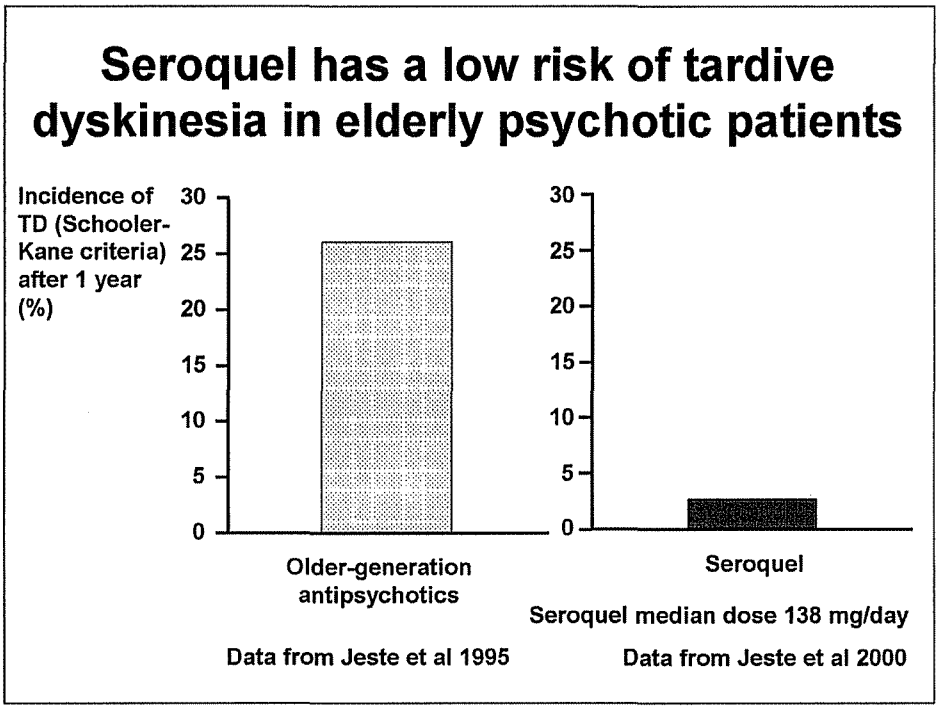
- The trial was flexibly dosed with patients started on Seroquel 25 mg (qd or bid) and escalated to 800 mg/day, depending on clinical response and tolerability. The median daily dose was 138 mg/day[1]

- 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.



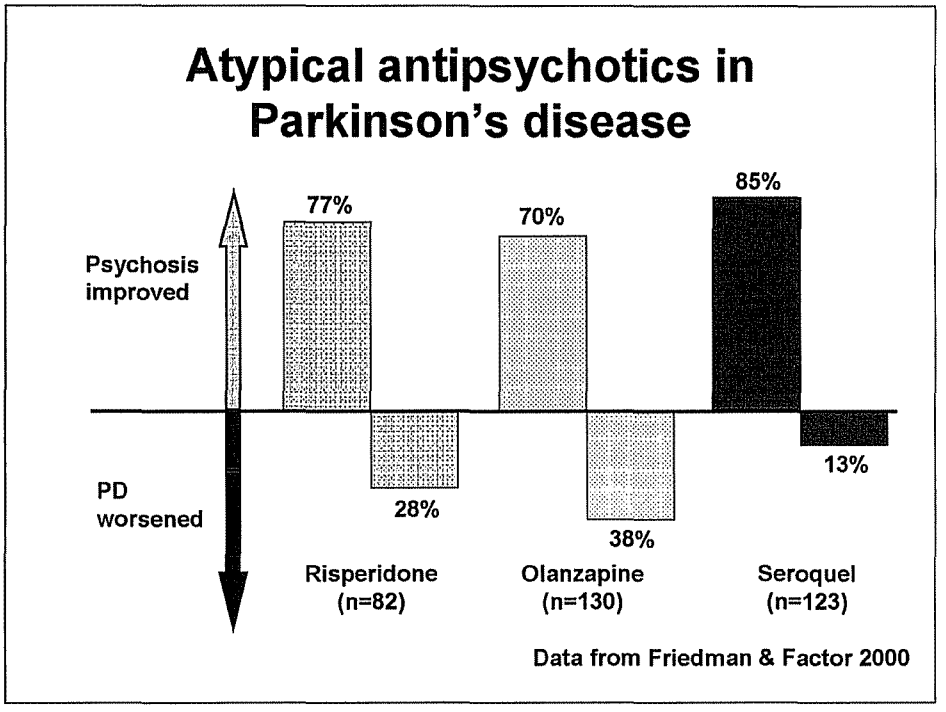
Seroquel – low risk of tardive dyskinesia in elderly psychotic patients

- 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.



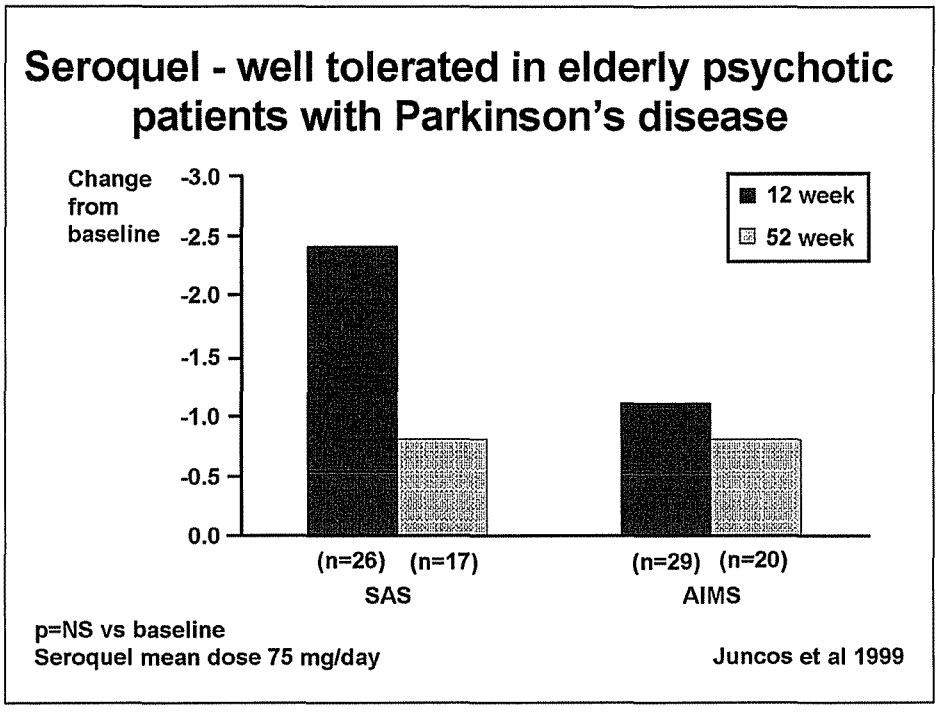
Atypical antipsychotics in Parkinson's disease

- 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.

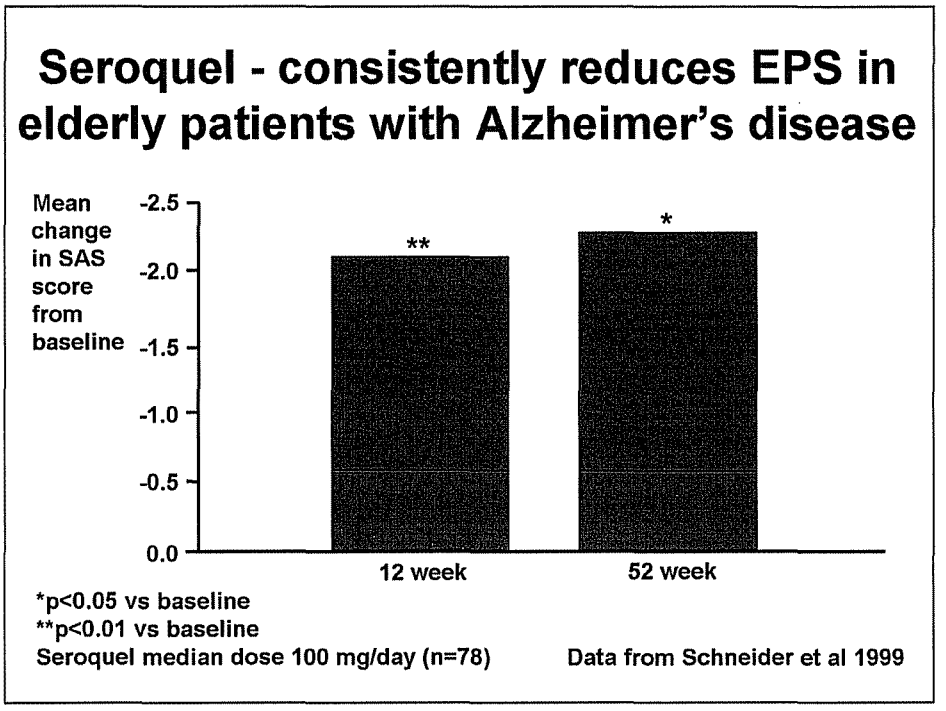


Seroquel - well tolerated in elderly psychotic patients with Parkinson's disease

- 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.



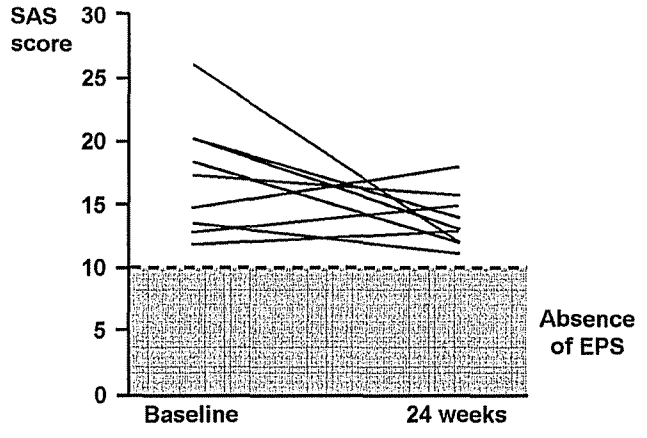
Seroquel – consistently reduces EPS in elderly patients with Alzheimer's disease

- 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



Seroquel dose range 25-300 mg/day (n=9)

Adapted from Parsa et al 1999

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

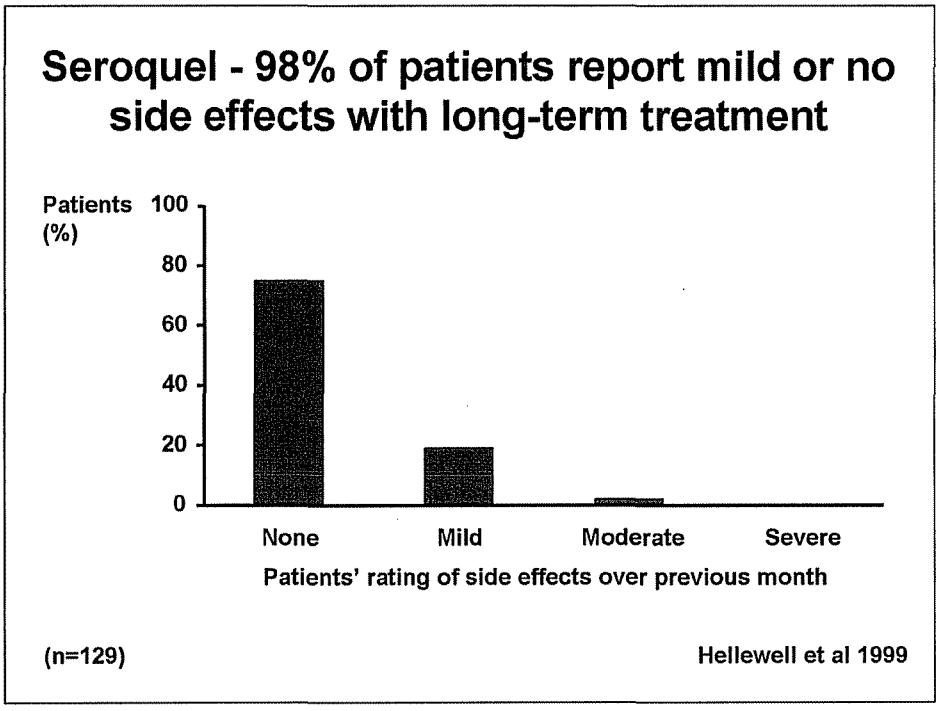
Seroquel - efficacy & tolerability

- 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

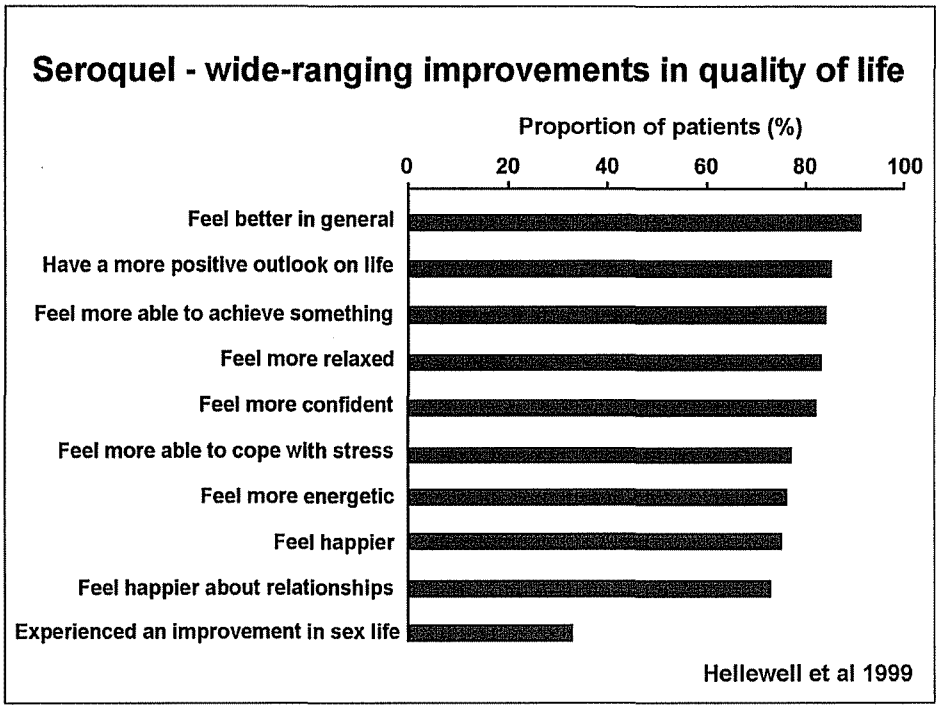


Seroquel – 98% of patients report mild or no side effects with long-term treatment

- 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.

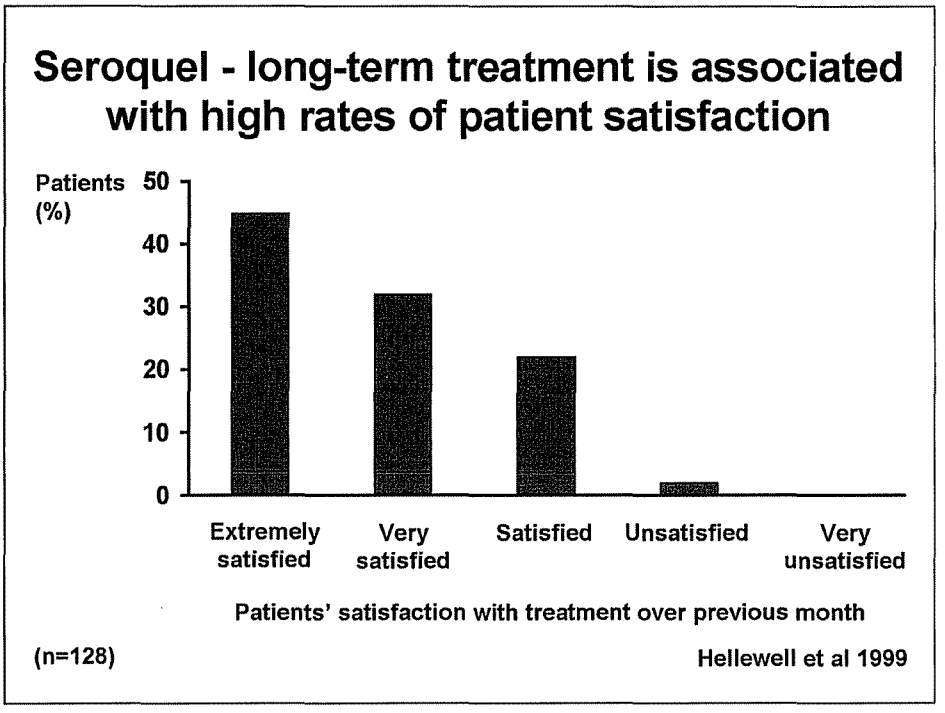


Seroquel – wide-ranging improvements in quality of life

- 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.

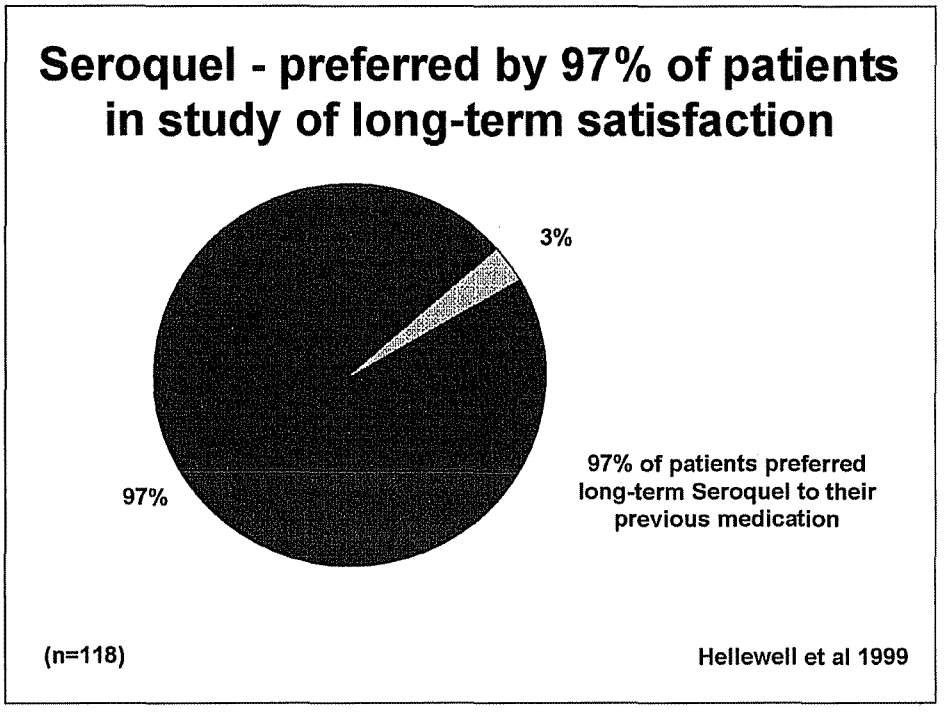


Seroquel – long-term treatment is associated with high rates of patient satisfaction

- 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.



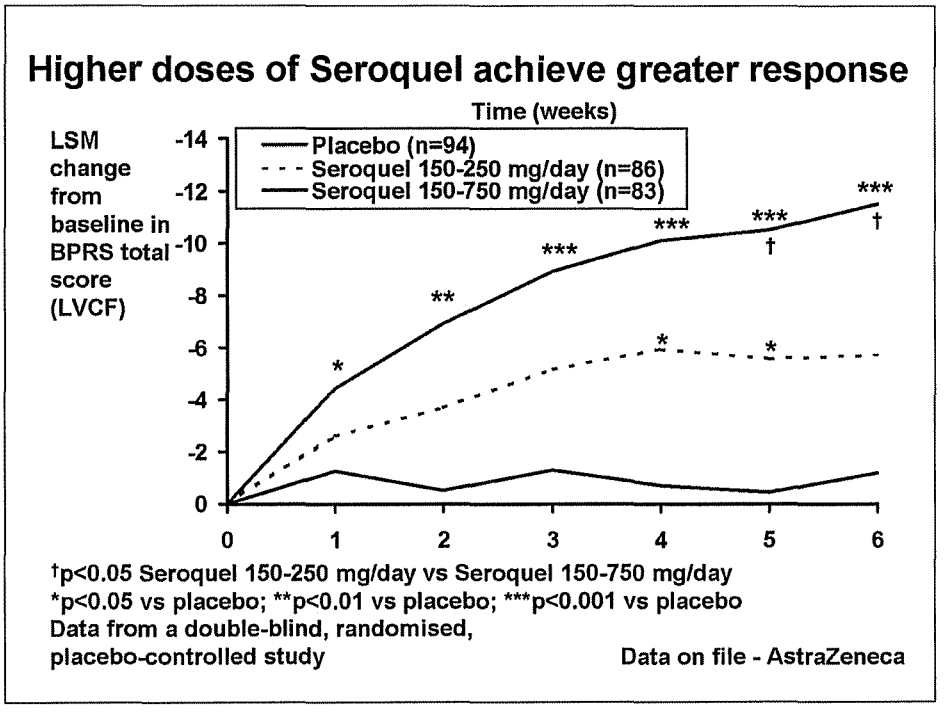
Seroquel – preferred by 97% of patients in study of long-term satisfaction

- 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'

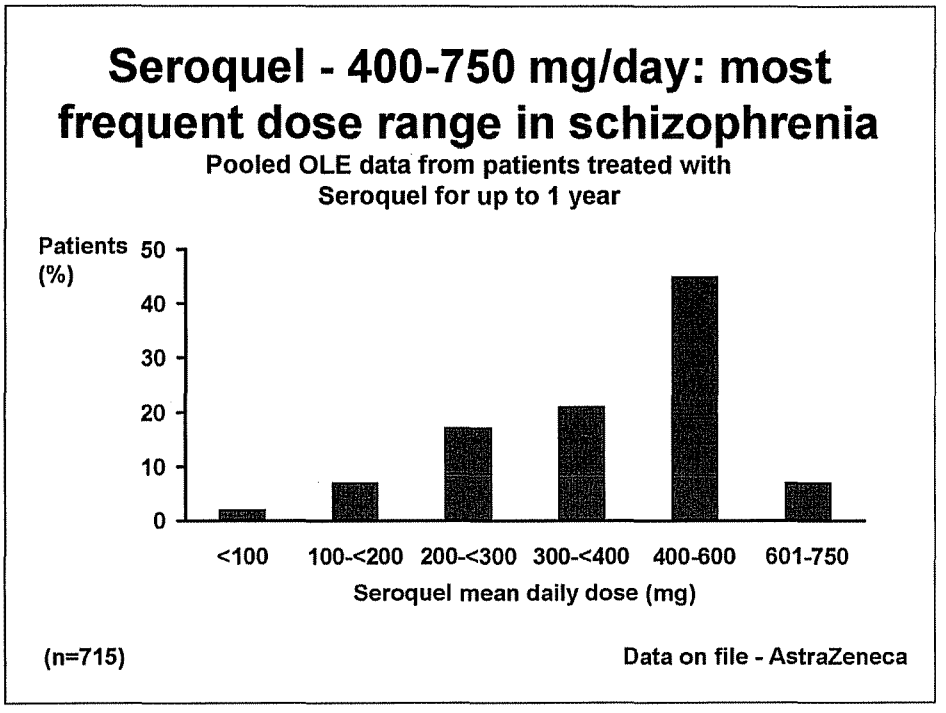


Greater response to higher doses of Seroquel

- 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.

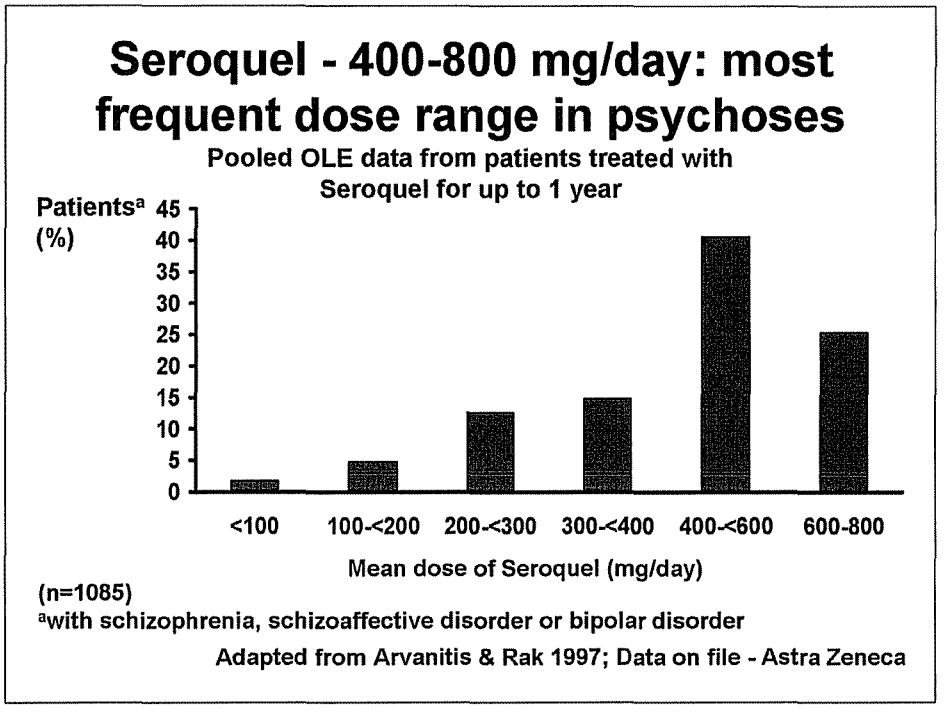


Seroquel - 400-750 mg/day: most frequent dose range

- 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.