

# **EXHIBIT**

**6**

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From: Birkett, Geoff

Sent: Tuesday, March 04, 2003 7:44 PM

To: Bierczynski, Vicky B

Subject: FW: Schizo SSF 3.04

Attachments: Schizo SSF 3.04.ppt

pls do neat colour copy for tomorrow

-----Original Message-----

From: Wilkie, Alison M

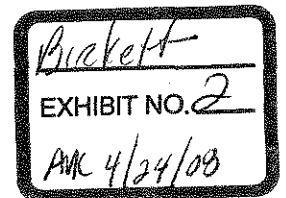
Sent: Tuesday, March 04, 2003 2:28 PM

To: Birkett, Geoff

Cc: Bierczynski, Vicky B

Subject: Schizo SSF 3.04

Geoff




Here is the 'tweaked' version for John tomorrow - please let me know if you have any questions.

thanks

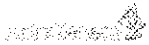
Alison

*In schizophrenia*



*First-line efficacy and tolerability for clinically effective therapy patients can stay with*

- *Delivers unsurpassed efficacy at the right dose*
- *Dose-independent tolerability permits dose escalation to optimise efficacy*
- *Initial target dose of 600 mg/day*



The following pages represent a **core detail flow** and **backup data** that support our current position for Seroquel in the treatment of schizophrenia.

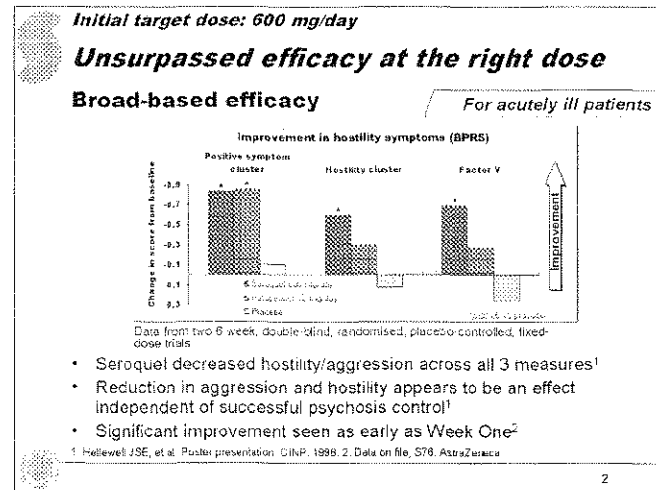
#### **The detail flow**

The detail flow presents a succinct summary of the strongest data from our best studies to support Seroquel as the **only unsurpassed efficacy antipsychotic at the right dose** with:

- Dose-independent tolerability that permits dose escalation to optimise efficacy
- At the right dose—starting with an initial target of 600 mg/day—Seroquel offers unsurpassed clinical effectiveness
- The target 600-mg/day dose is flagged on every page showing efficacy data

#### **Backup data**

Backup data are supplied so that local markets can either expand on the data in the core detail or substitute data approved for marketing purposes.



The symptom spectrum for schizophrenia includes aggression and hostility, which need to be controlled without worsening other primary symptoms.

#### Key communication

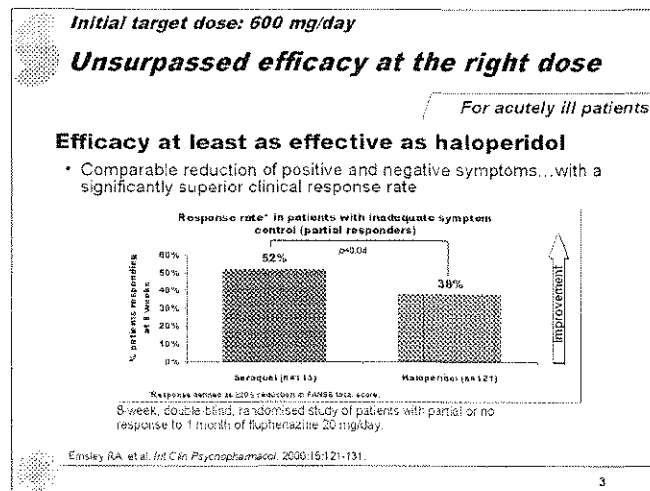
In addition to managing positive and negative symptoms, Seroquel effectively controls aggressive/hostile symptoms.

#### On this page

- The graph shows Seroquel efficacy in controlling symptoms compared to haloperidol and placebo
- The second bullet notes that, although Seroquel controlled positive and negative symptoms in these studies, improvement in aggression/hostility was an independent effect
- The third bullet emphasises the rapid onset of symptom control

#### About the study

- Data from two 6-week, well-controlled trials. One trial compared 5 different doses of Seroquel to haloperidol 12 mg/day or placebo. The other trial compared low doses (up to 250 mg/day), and high doses (up to 750 mg/day) to placebo
- Seroquel 600 mg/day was associated with the most consistent improvement
- Seroquel produced greater improvement than haloperidol, but differences were not statistically significant. In addition, changes vs placebo were significant at certain points for Seroquel, but not for haloperidol



Seroquel and haloperidol have been compared in a number of studies. The Emsley study compares these agents in patients with partial treatment failure on other medication.

#### Key communication

Head to head with haloperidol, Seroquel offers the same—or better—efficacy, and the added advantage of a significantly better clinical response.

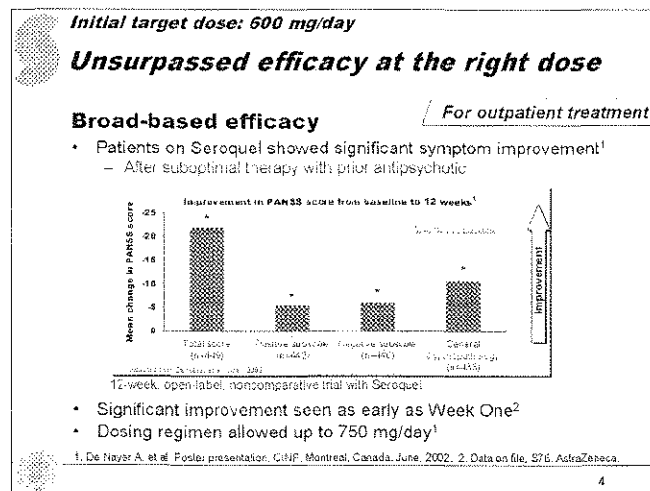
#### On this page

- The graph shows that Seroquel had a significantly better response rate (patients with a  $\geq 20\%$  reduction in PANSS score) than haloperidol
- The bullet highlights the Seroquel advantage—equal efficacy, superior response

#### About the study

- An 8-week, well-controlled trial of 288 patients who had partial response to typical antipsychotics and no response to fluphenazine
- Seroquel showed marked reduction in PANSS scores greater at Week 8 and Week 12 than haloperidol, although these scores did not reach significance

CGP. More patients in the Seroquel group showed a CGI Severity of Illness score  $\leq 3$



The detail flow starts with efficacy. Seroquel efficacy has been proven in numerous well-controlled clinical trials to control a range of schizophrenia symptoms, including 2 of the most critical kind—positive and negative symptoms.

### Key communication

Seroquel significantly improved key symptoms of schizophrenia in patients unsuccessfully treated with another antipsychotic medication

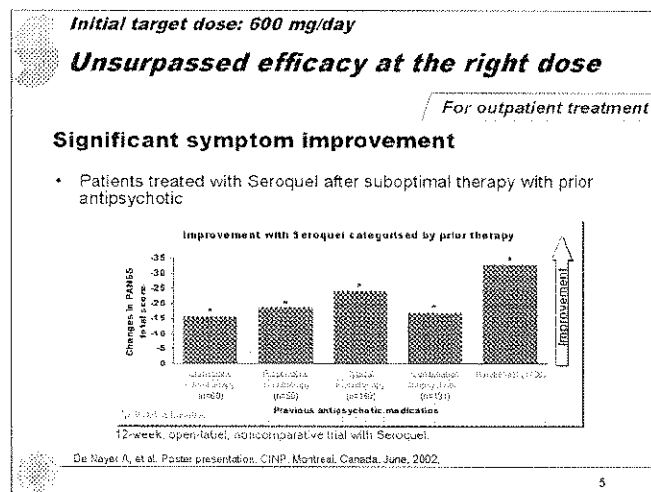
### On this page

- This graph shows data from the SPECTRUM study, illustrating the change in PANSS scores for all patients
- The next page shows improvement categorised by prior suboptimal treatment*
- The second bullet emphasizes rapid onset of improvement—within 1 week
- The third bullet reinforces efficacy at the right dose

### About the study

- SPECTRUM was a 12-week, open-label, noncomparative trial in which 509 patients who failed treatment on or were intolerant to other antipsychotics were switched to Seroquel

PANSS: Positive and Negative Syndrome Scale. SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.



The advantages of switching patients to Seroquel from current therapy support its use as a first-line choice.

#### Key communication

Seroquel improves efficacy, no matter what antipsychotic agent was used prior. So why not start patients on Seroquel, and get the right efficacy from the beginning?

#### On this page

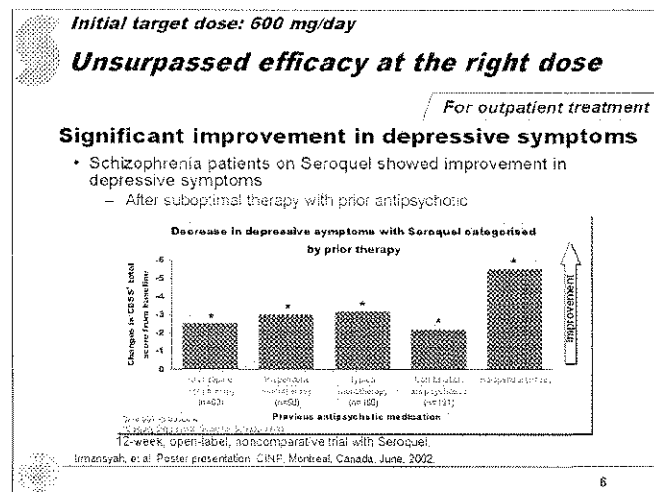
- This graph demonstrates that, no matter which antipsychotic a patient was switched from, Seroquel provided symptom improvement (as measured by PANSS)

#### About the study

- SPECTRUM was a 12-week, open-label, noncomparative trial in which 509 patients who failed treatment on or were intolerant to other antipsychotics were switched to Seroquel
- Study results show that patients who were started on Seroquel due to partial or no response on previous medication showed symptom improvement and a reduction in EPS side effects
- Similarly, patients who were started on Seroquel because of intolerance to the side effects of their previous medication not only showed a reduction in side-effect incidence, but an improvement in efficacy

EPS: Extrapyramidal symptoms. PANSS: Positive and Negative Syndrome Scale. SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.





An antipsychotic that can help treat depression, as well as positive, negative, and other symptoms of schizophrenia, is a valuable treatment choice.

### Key communication

Improvement with a switch to Seroquel includes reduction in depressive symptoms.

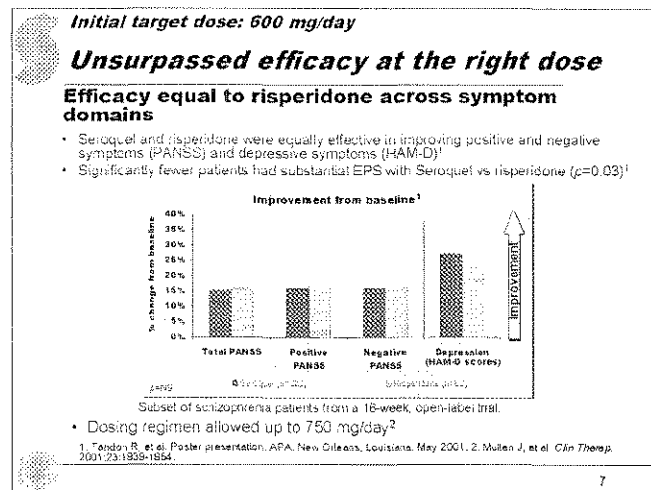
#### On this page

- This graph demonstrates that, no matter what antipsychotic patients were switched from, Seroquel provided improvement in depressive symptoms

#### About the study

- SPECTRUM was a 12-week, open-label, noncomparative trial in which 509 patients who failed treatment on or were intolerant to other antipsychotics were started on Seroquel
- While improvement was seen regardless of whether patients were evaluated as depressed when they started Seroquel, improvement was especially noticeable in patients classified as depressed at baseline

SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.



Data from QUEST compare the symptom relief of Seroquel and risperidone.

### Key communication

Seroquel improved positive, negative, and depressive symptoms significantly better than risperidone.

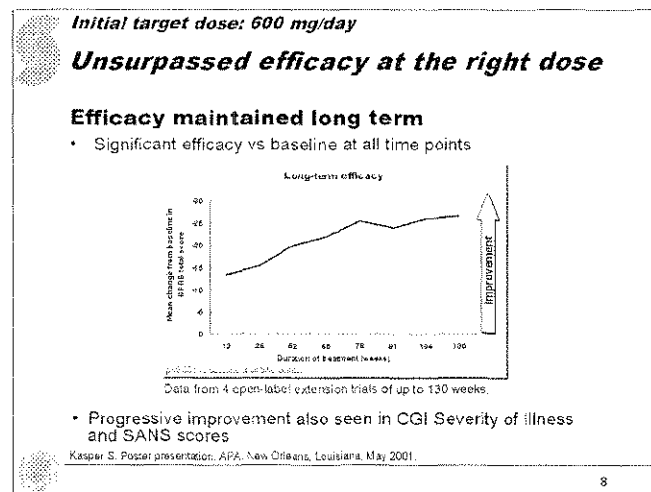
### On this page

- The graph, from the QUEST study, shows improvement in PANSS scores and depressive symptoms in a subset of patients with schizophrenia
- The bullet below the graph notes that dosing went as high as 750 mg/day in this study

### About the study

- QUEST was a 16-week, open-label study comparing efficacy and tolerability in 751 patients with a range of psychoses treated with Seroquel (flexible dosing) or risperidone
- A subset of patients with schizophrenia was also analysed

HAM-D: Hamilton Rating Scale for Depression. PANSS: Positive and Negative Syndrome Scale.  
QUEST: Quetiapine Experience with Safety and Tolerability.



A chronic condition like schizophrenia requires treatment that stays effective long term.

### Key communication

Seroquel maintains effective control of symptoms for the long term.

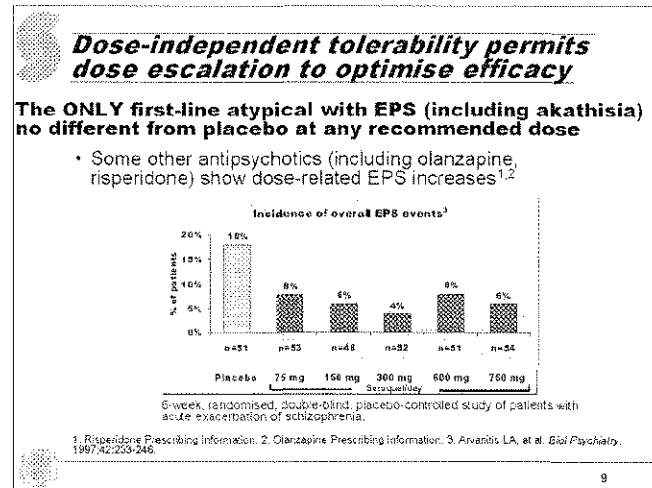
#### On this page

- The graph plots improvement in total BPRS score (which includes positive and negative symptom measures, as well as 16 other items) over 130 weeks
- The second bullet highlights that, in addition to improving BPRS score, Seroquel therapy improved severity of illness, as measured by CGI, and negative symptoms, as measured by SANS

#### About the study

- Data analysis for 674 patients in 4 open-label extension trials lasting up to 130 weeks
- Efficacy and tolerability were assessed

BPRS: Brief Psychiatric Rating Scale. SANS: Scale for the Assessment of Negative Symptoms.  
CGI: Clinical Global Impression.



After efficacy, the detail flow reinforces the well-known Seroquel safety profile, starting with EPS—a side effect of many antipsychotics that interferes with patients’ daily function and compliance. Placebo-level EPS is one of the best-known attributes of Seroquel therapy.

### Key communication

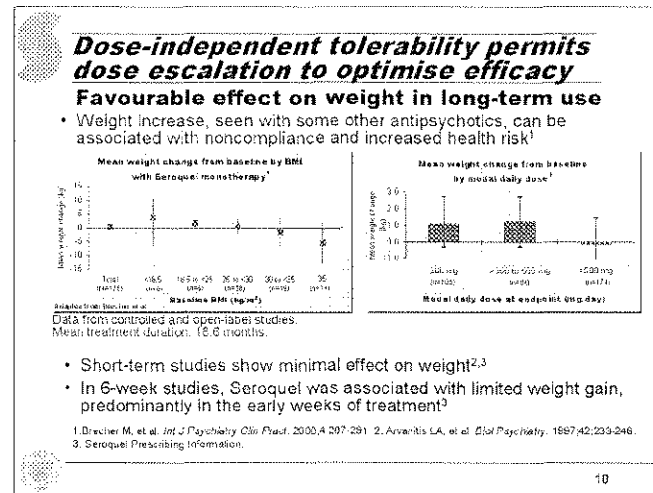
Seroquel is the only first-line atypical with EPS no different than placebo at any recommended dose.

### On this page

- The graph shows that incidence of EPS barely changed across Seroquel doses in the study, from the lowest dose (75 mg/day) to the highest dose (750 mg/day)
- The bullet refers to the risperidone and olanzapine PIs, which show increased EPS incidence with increasing doses
- Other EPS-related data can be found in the backup section*

### About the study

- A 6-week, well-controlled study of patients randomised to 1 of 5 fixed doses of Seroquel (n = 255), 12 mg haloperidol (n = 50), or placebo (n = 51)
- EPS evaluation was measured by SAS (modified to include akathisia) and AIMS
- AIMS: Abnormal Involuntary Movement Scale; EPS: Extrapyramidal symptoms; SAS: Simpson-Angus Scale.
- Incidence of EPS-reflective events: Seroquel—4-8%, placebo—18%, haloperidol—37%



Weight gain is a side effect clearly associated with certain antipsychotics, and can be a primary reason for patient noncompliance.

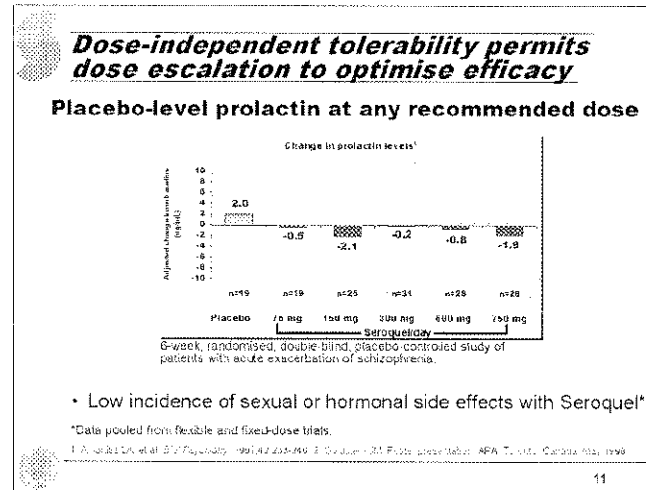
### Key communication

Seroquel, unlike some other antipsychotics, is not associated with meaningful weight gain, either in the short or long term or across the recommended dosing range.

- The left-hand graph evaluates weight gain over a mean treatment duration of 18 months in patients grouped by baseline BMI category
- The right-hand graph shows weight change categorised by 3 dosing ranges
- Overall, there was almost no mean change in weight. Interestingly, in underweight patients (BMI ≤18), there was beneficial weight gain, while the most overweight groups (BMI 30-35) lost weight

### About the study

- Long-term weight-change data for 427 patients were pooled from controlled and uncontrolled studies as well as from their open-label extensions
  - In these studies, Seroquel monotherapy was the only antipsychotic treatment allowed
- BMI: Body Mass Index.



Abnormal prolactin levels are a common adverse event caused by antipsychotic medication.

### Key communication

As with EPS, prolactin levels in patients taking Seroquel are no different than with placebo across the dosing range

### On this page

- The graph shows the minimal change in prolactin levels with Seroquel treatment
- The bullet, from a study by Goldstein, confirms that placebo-level prolactin means minimal risk of sexual or hormonal dysfunction

### About the study

- A 6-week, well-controlled study of patients randomised to 1 of 5 fixed doses of Seroquel (n = 255), 12 mg haloperidol (n = 50), or placebo (n = 51)
- In contrast to Seroquel, the difference in prolactin levels between placebo and haloperidol was significant

EPS: Extrapyramidal symptoms.

**Dose to 600 mg/day by Week 1**

**Dosing initiation**<sup>1-3</sup> *For outpatient treatment*

- Day 1: 50 mg
- Day 2: 100 mg
- Day 3: 200 mg
- Day 4: 300 mg
- Day 5: 400 mg
- Day 7: 600 mg

No dosing adjustments required for differences in gender, race, body weight, or smoking status. May be taken with or without food.

1. Seroquel Prescribing Information. 2. Cutler AJ, et al. *Clin Ther* 2002;24:209-222. 3. Emsley RA, et al. *Int Clin Psychopharmacol*. 2000;15:121-131.

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Standard dosing initiation achieves the initial target dose of 600 mg/day by Day 7.

**Key communication**

Dosing to 600 mg/day is simple and fast.

**On this page**

- Physicians are familiar with the dosing schedule from the Prescribing Information for Seroquel

*(Alternative)*

**Dose to 600 mg/day by Week 1**

*For outpatient treatment*

**Dosing initiation<sup>1\*</sup>**

- Day 1: 100 mg (PM)
- Day 2: 200 mg/day
- Day 3: 300 mg/day
- Day 4: 400 mg/day
- Day 5: up to 600 mg/day
- Day 6: Find most effective dose up to 800 mg/day

No dosing adjustments required for differences in gender, race, body weight, or smoking status. May be taken with or without food.

\*Data from studies in patients with bipolar disorder.

1. Data on file, 399, AstraZeneca.

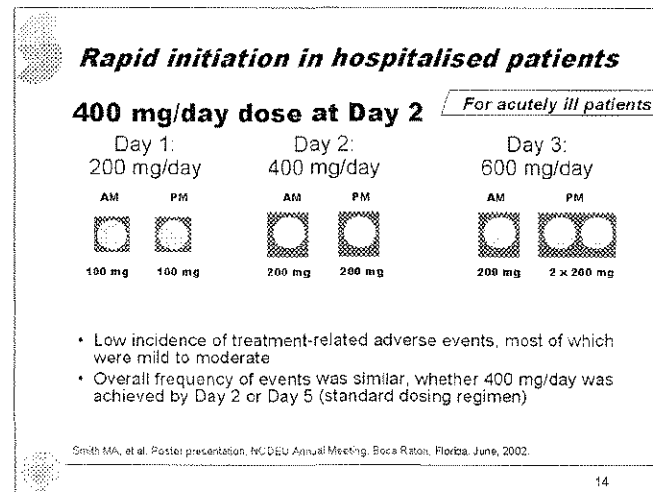
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The “four by four” dosing approved for treatment of bipolar mania gets patients to 600 mg/day at Day 5.

**Key communication**

An accelerated dosing schedule for Seroquel has been proven safe and effective in clinical studies.





For acutely ill patients, an even more rapid target dose initiation has been shown to have a comparable tolerability profile to traditional dosing schedules.

#### Key communication

Seroquel can be dosed up to 600 mg/day in fewer than the standard 5 days with safety and tolerability.

#### About the study

- This was a 5-day, multicentre, double-blind tolerability/safety study of 69 acutely ill schizophrenia patients randomised to 1 of 3 titration arms
- Patients were dosed to 400 mg/day of Seroquel in 5, 3, or 2 days. Patients were hospitalised during their 2-day washout and 5-day treatment periods
- Frequency of adverse events was similar between the 3 groups. Treatment-related events were few, and most were mild to moderate
- Less than 15% of patients experienced somnolence, with the fewest (8%) in the 2-day titration group
- Laboratory values and vital signs were also similar amongst the treatment arms, including for blood pressure and pulse measurements

**Seroquel:**  
***Unsurpassed clinical effectiveness***

**Delivers unsurpassed efficacy at the right dose**

- Proven first-line efficacy in a broad symptom range<sup>1,6</sup>
- Clinical improvement within 1 week, proven efficacy to 130 weeks<sup>4,7</sup>

**Dose-independent tolerability permits dose escalation to optimise efficacy**

- EPS and prolactin no different from placebo across the recommended dosage range<sup>8</sup>
- Favourable weight profile in long-term use<sup>9</sup>

**Initial target dose 600 mg/day**

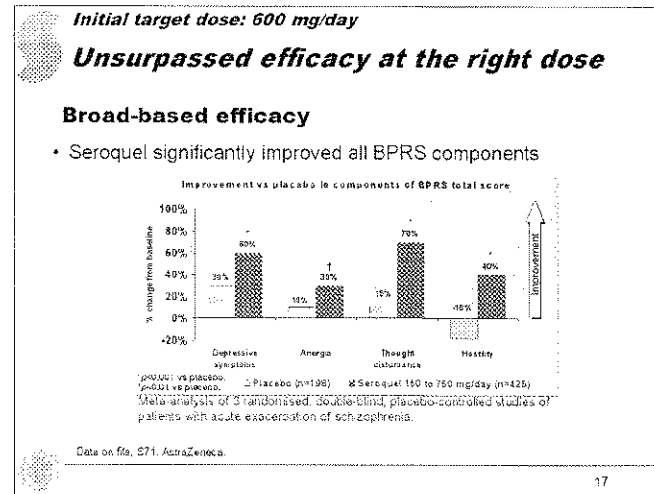
- Can be achieved in 7 days (outpatients)<sup>10</sup>
- Can be achieved in 3 days (inpatients)<sup>9</sup>

1. Kane JM, et al. J Clin Psychiatry. 2002;63(12):1653-1662. 2. Kane JM, et al. J Clin Psychiatry. 2002;63(12):1653-1662. 3. Kane JM, et al. J Clin Psychiatry. 2002;63(12):1653-1662. 4. Kane JM, et al. J Clin Psychiatry. 2002;63(12):1653-1662. 5. Kane JM, et al. J Clin Psychiatry. 2002;63(12):1653-1662. 6. Kane JM, et al. J Clin Psychiatry. 2002;63(12):1653-1662. 7. Kane JM, et al. J Clin Psychiatry. 2002;63(12):1653-1662. 8. Kane JM, et al. J Clin Psychiatry. 2002;63(12):1653-1662. 9. Kane JM, et al. J Clin Psychiatry. 2002;63(12):1653-1662. 10. Kane JM, et al. J Clin Psychiatry. 2002;63(12):1653-1662.

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This page summarises the key communications in the core detail.

*Back-up slides*



Additional material on efficacy includes secondary symptoms of schizophrenia.

### Key communication

Seroquel effectively manages a wide range of symptoms.

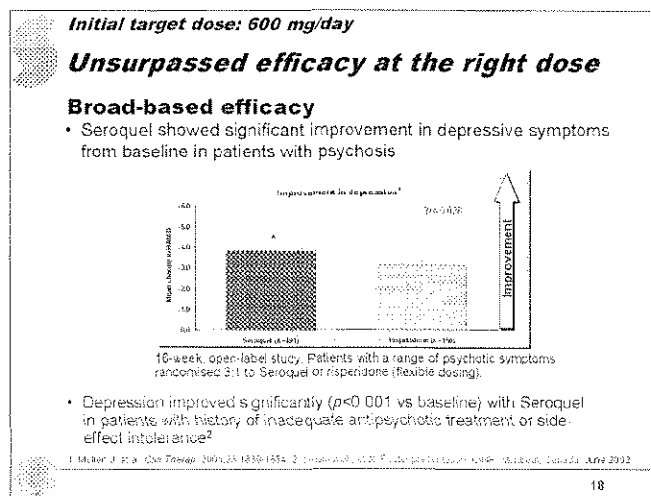
### On this page

- Seroquel efficacy in controlling 4 individual symptoms comprising the BPRS, with significant differences vs placebo for each

### About the study

- Meta-analysis of three 6-week, well-controlled published studies
- Dosing regimens were different for each study

BPRS: Brief Psychiatric Rating Scale.



Data from QUEST support the proven relief of depression with Seroquel.

### Key communication

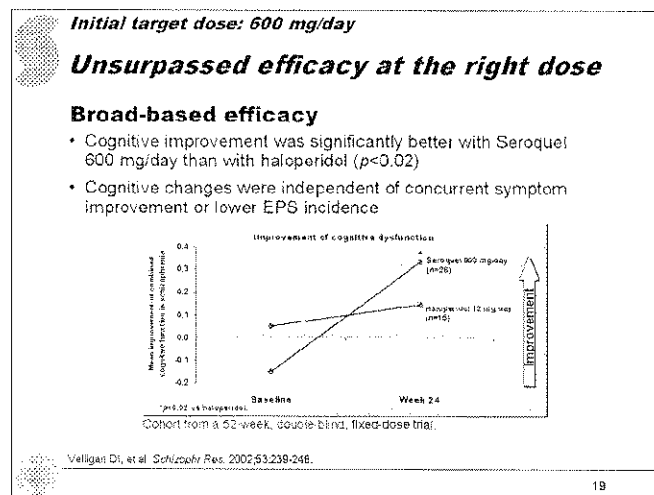
In patients treated for a range of psychosis symptoms, Seroquel improved depressive symptoms significantly better than risperidone.

- The graph, from the QUEST study, shows improvement in depressive symptoms in all patients in the study (ie, all forms of psychosis), measured by change in HAM-D scores
- The bullet below the graph refers to the SPECTRUM study, in which patients with schizophrenia who were unresponsive or intolerant to other antipsychotics were started on Seroquel monotherapy

### About the studies

- QUEST was a 16-week, open-label study comparing efficacy and tolerability in 751 patients with a range of psychoses treated with Seroquel (flexible dosing) or risperidone
- 641 patients from QUEST were evaluated for depressive symptoms
- SPECTRUM was a 12-week, open-label, noncomparative trial in which 509 patients who failed treatment on or were intolerant to other antipsychotics were started on Seroquel flexible dosing

HAM-D: Hamilton Rating Scale for Depression. QUEST: Quetiapine Experience with Safety and Tolerability. SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.



Improvement in cognitive function can help patients recapture functions critical to basic day-to-day tasks.

#### Key communication

Seroquel 600 mg/day improved cognitive function significantly better than haloperidol.

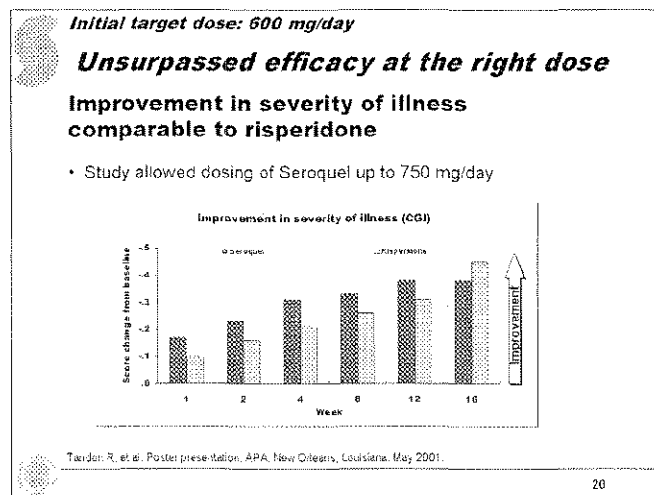
#### On this page

- The graph and first bullet show the difference between Seroquel and haloperidol in restoring some degree of cognitive function
- The second bullet points out that cognitive improvement was independent of the other benefits of Seroquel (improvement in other symptoms, less incidence of EPS)

#### About the study

- This was a cohort from a 52-week study of patients on fixed-dose Seroquel, haloperidol, or placebo

EPS: Extrapyramidal symptoms.



Data from QUEST support the efficacy of Seroquel compared to risperidone.

#### Key communication

Seroquel and risperidone are equally effective in symptom relief.

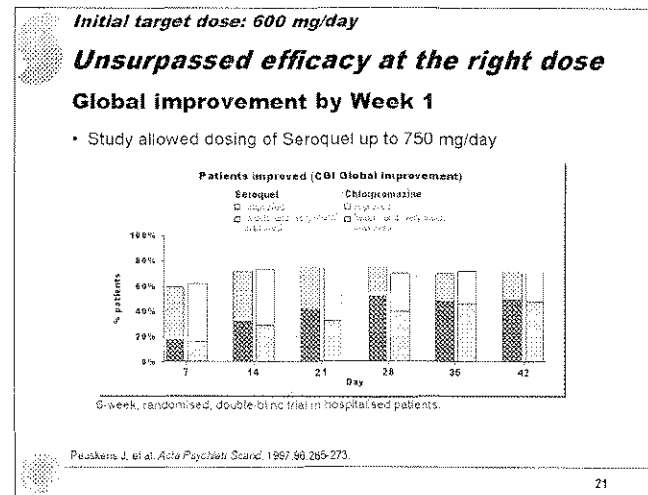
#### On this page

- The graph, from the QUEST study, shows global improvement
- The same study showed that Seroquel produced less substantial EPS than risperidone

#### About the study

- QUEST was a 16-week, open-label study comparing efficacy and tolerability in 751 patients with a range of psychoses treated with Seroquel (flexible dosing) or risperidone

CGI: Clinical Global Improvement. EPS: Extrapyramidal symptoms. QUEST: Quetiapine Experience with Safety and Tolerability. SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.



The CGI scale is a well-known, well-accepted measurement of overall symptom improvement.

#### Key communication

Global improvement—particularly in patients who were “very much” improved—can be seen as early as 1 week and continues to increase throughout treatment.

#### On this page

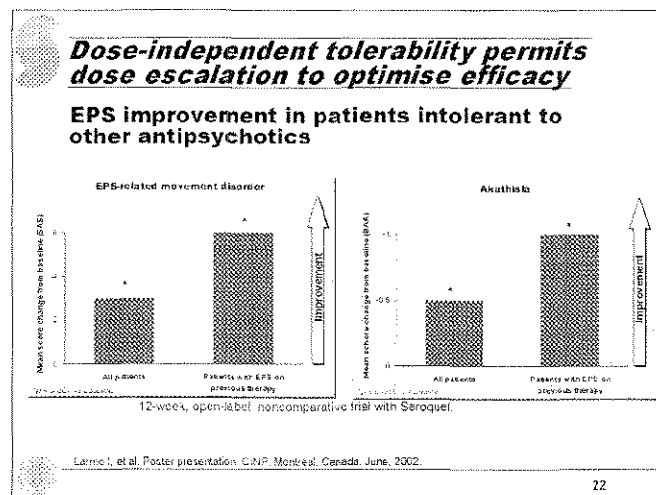
- The graph shows improvement at Day 7, with the ratio of patients “much” and “very much” improved continuing to grow over the 42 days of the study

#### About the study

- This was a 6-week study of patients hospitalised with acute exacerbation of schizophrenia
- Tolerability was also evaluated in this study. Fewer patients in the group on Seroquel had parkinsonian symptoms or akathisia vs those in the chlorpromazine group. Elevated prolactin dropped significantly with Seroquel vs chlorpromazine

CGI: Clinical Global Impression





Data from the SPECTRUM study show that a switch to Seroquel can reduce EPS caused by other antipsychotics.

### Key communication

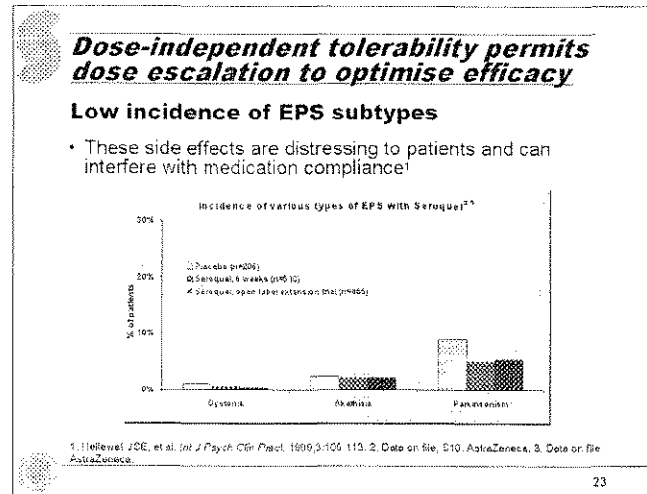
To avoid the EPS caused by other antipsychotics, why not start Seroquel first?  
**On this page**

- The graphs, from the SPECTRUM study, show that the incidence of 2 EPS categories—movement disorder and akathisia—decreased in patients switched to Seroquel from other antipsychotics
- Akathisia is a subset of EPS of particular concern to physicians

### • About the study

- SPECTRUM was a 12-week, open-label, noncomparative trial in which 509 patients who failed treatment on or were intolerant to other antipsychotics were switched to Seroquel
- A total of 506 patients were evaluated for safety
- EPS was measured by the SAS (movement disorders) and BAS (akathisia) scales

EPS: Extrapyramidal symptoms. SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.



More support for placebo-level EPS, by subtype.

#### Key communication

Seroquel shows no more incidence of EPS than placebo when symptoms are broken down by subtype.

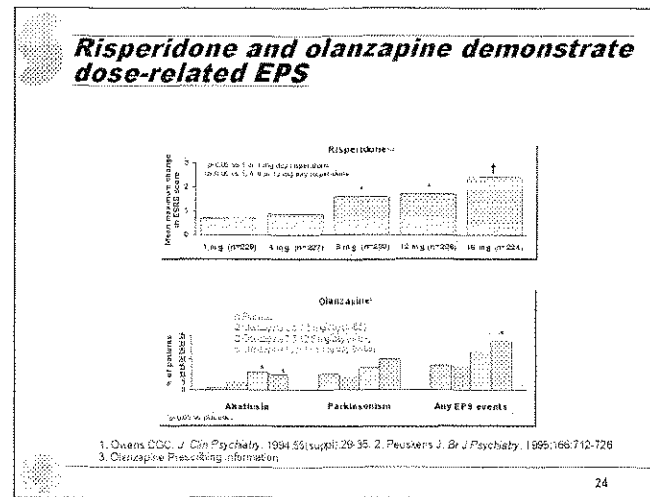
#### On this page

- 2 studies confirm the Seroquel safety profile

#### About the studies

- Data on File S10 showed that Seroquel showed no difference vs placebo in EPS subtypes across a 75-mg to 150-mg dosing range
- (Second DOF info to come from client)

EPS: Extrapyramidal symptoms.



EPS data for risperidone and olanzapine confirm the difference in safety profiles between these atypicals and Seroquel.

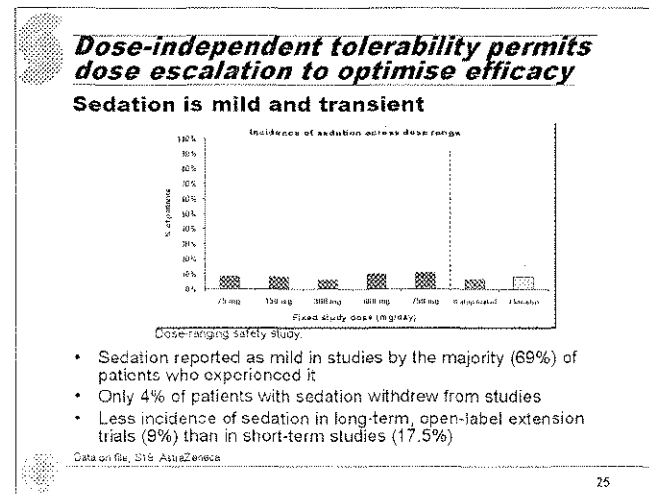
### Key communication

Unlike Seroquel, both risperidone and olanzapine show dose-related increases in EPS.

### On this page

- These graphs expand on the points made in the core detail piece and backup

EPS: Extrapramidal symptoms.



Reports of the impact of sedation with Seroquel are greatly exaggerated.

### Key communication

Sedation associated with Seroquel therapy is transient and mild across the dosing range

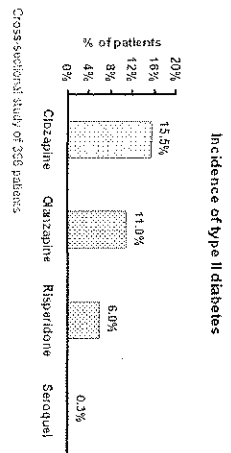
### On this page

- A dosing study shows sedation incidence hardly increases, even at higher doses, and is comparable to haloperidol

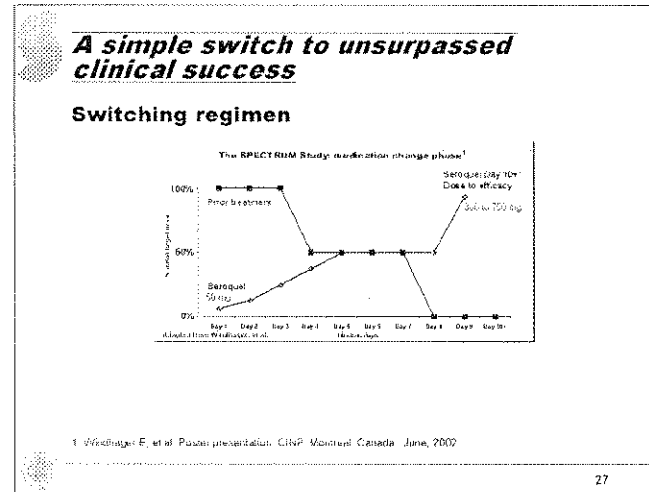
### About the studies

- Data on File S19 is from uncontrolled, placebo-controlled, and haloperidol-controlled studies of almost 3,000 patients taking Seroquel

**Type II diabetes associated with  
atypical antipsychotic use**



Data on file, AstraZeneca. Canadian Guidelines on the Treatment of Diabetes, 1999



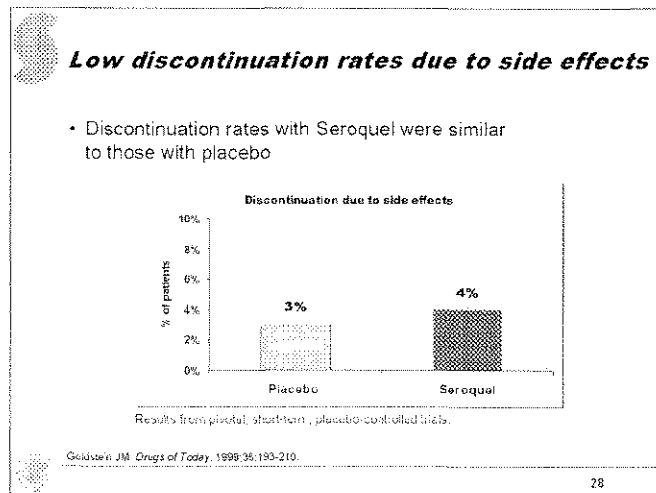
Starting patients who are taking another antipsychotic on Seroquel means simply cutting the current medication in half and increasing Seroquel in a few easy steps.

#### Key communication

Switching patients to Seroquel is simple.

- The schematic shows the switch protocol from the SPECTRUM study, in which patients were switched to Seroquel from a variety of other antipsychotics

SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.



Seroquel tolerability is supported by its low discontinuation rates.

#### Key communication

The percentage of patients stopping therapy with Seroquel due to side effects were essentially the same as with placebo.

#### On this page

- Simple and compelling evidence of Seroquel tolerability

#### About the study

- Pooled data from short-term trials

**Efficacy and safety patients can stay with**

**In a long-term, open-label study,\* patients were highly satisfied with Seroquel therapy**

**76%** were "extremely" or "very" satisfied with therapy

**74%** reported no side effects with Seroquel

- 23% reported mild side effects
- 2% reported moderate side effects
- 0% reported severe side effects

**98%** wanted to continue therapy with Seroquel

\*Minimum duration of therapy: 6 months; Mean duration of therapy: 20 months

Hollnagel JSE, et al. *Int J Psych Clin Pract.* 1999;3:105-113

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The efficacy and unique tolerability profile of Seroquel add up to patient satisfaction, providing therapy that patients can stay with long-term.

#### **Key communication**

The great majority of patients were highly satisfied with long-term Seroquel efficacy and tolerability. Almost all expressed interest in continuing therapy with Seroquel.

- The numbers link patient-reported satisfaction with efficacy and tolerability, with the conclusion that virtually all of them would continue therapy

#### **About the study**

- 129 patients from 12 countries who had been on Seroquel for at least 6 months and currently in open-label studies were asked to complete a questionnaire about satisfaction with therapy
- Mean treatment duration with Seroquel was 19.9 months, with 38% of patients on treatment for 31 to 42 months
- The most common characteristics patients reported that they liked about Seroquel were lack of side-effects or improvement in side effects caused by other medications
- 96% of patients who expressed a medication preference indicated a preference for Seroquel over previous antipsychotics for both efficacy and tolerability