EXHIBIT 8

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QUETIAPINE

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QUETIAPINE

Introduction:

Seroquel (quetiapine fumarate, ICI 204,636), which was ~~developed~~ discovered in 1984 in the Zeneca (formerly ICI)Wilmington DE laboratories, is a dibenzothiazepine derivative with preclinical indications of antipsychotic activity without neurological side effects or elevations in prolactin. The structural formula is shown in Figure 1. Quetiapine exhibits binding properties similar to clozapine(1,2). Receptor data in animals showed quetiapine's greater affinity for 5-HT2 and 5-HT6 relative to D2 receptors. ~~although recent human evidence suggests that D2 binding may have been underestimated~~. Like clozapine, ~~Quetiapine, clozapine and other atypical neuroleptics occupy high levels of brain D2 receptors but are~~ quetiapine is loosely bound and readily displaced from the D2 receptor, particularly in the striatum(3), providing a mechanism for its low EPS liability~~.~~ It is selective for the A10 mesolimbic but not A9 nigrostriatal dopamine neurons. Unlike clozapine quetiapine has minimal affinity for M1 or D4 but binds strongly to the sigma receptor(4).

In this review clinical data from the pivotal placebo controlled

studies preceding the 1997 marketing of Seroquel and additional reports will be considered under headings of clinical efficacy, safety and tolerability, adverse events including movement disorders, laboratory abnormalities, pharmacokinetics and drug interactions, and therapeutic potential.

Clinical Efficacy:

Several thousand patients have been treated with quetiapine. Although all studies required DSM-III-R diagnoses of acute exacerbation of chronic or subchronic schizophrenia, all subjects typically had long histories of psychotic illness, multiple hospitalizations and previous treatment with standard and sometimes atypical antipsychotic drugs as well. Thus despite manifestations of acute psychosis, most patients could be regarded as chronically ill and relatively treatment resistant. Many of the trials were conducted in tertiary-care teaching centers. Moreover, women of child bearing potential were mostly excluded as were those unwilling to give consent. Hence they were a select group not truly representative of patients routinely encountered in clinical practice. Another consideration is that all conclusions available thus far are derived from industry supported studies without the benefit of confirmation by independent investigators(5).

There have been three placebo controlled pivotal Phase II and III

trials of quetiapine that utilized a substantial number of patients, randomized double-blind treatment assignment and trial durations of six weeks. The first was by Borison et al.(6) who studied 109 patients. Quetiapine was generally superior to placebo in an average dose of 307 mg. Small et al.(7) published results of a multicenter trial of 286 patients on low or high dose quetiapine OR placebo. The average low dose of 209 mg was no better than placebo but the mean high dose of 360 mg was superior to placebo. Arvanitis et al.(8) studied multiple doses of quetiapine compared with haloperidol and placebo. Dosages ranging from 150 to 750 mg were superior to placebo and equivalent to 12 mg of haloperidol. The lowest dose of 75 mg was ineffective. Another study by Peuskins and Link (9) compared quetiapine to chlorpromazine in 201 patients. The two drugs were therapeutically equivalent in mean doses of 407 mg of quetiapine and 384 mg of chlorpromazine. More details about each of these studies follow:

In the Borison et al., study overall therapeutic efficacy favored quetiapine. Although there were statistically significant differences between the treatment groups ($p <$ or equal to 0.05) in favor of quetiapine at various times throughout the trial, differences at end point were not significant on the Brief Psychiatric Rating Scale (BPRS)(10) total score ($p=0.07$) or the anxiety/depression, anergia, thought disturbance, and hostile/suspiciousness factors. Differences in the BPRS positive

symptom cluster approached significance (p=0.06). The end of study Clinical Global Impression (CGI) rating (11) was likewise not significant (p=0.07). Statistical comparisons included all randomized patients who had efficacy data for at least one time interval after baseline with last observation carried forward (LOCF) for determinations at end point. More significant differences were observed earlier in the study in the quetiapine treated patients who improved steadily throughout the six week period whereas placebo subjects remained unchanged. BPRS total scores were significantly different on days 14, 28, and 35 as was the positive symptom cluster. Factor 3 - thought disturbance - was significantly better for quetiapine on days 28 and 35. CGI ratings showed significant differences between treatments on days 21, 28, and 35. The Scale for Assessment of Negative Symptoms (SANS) (12) showed significant group differences from day 21 onwards.

In the study by Small et al., comparing low and high dosage ranges of quetiapine with placebo, the low dose group and placebo were equivalent on global ratings and positive and negative symptoms. The high dose group at end point was significantly more improved on the CGI, the BPRS positive symptom cluster, and the SANS but not the Positive and Negative Syndrome Scale (PANSS)(13). These conclusions were also drawn from LOCF analyses.

Arvanitis et al., studied five fixed doses of quetiapine compared

with 12 mg of haloperidol and placebo. The lowest dose of 75 mg was not different than placebo whereas the quetiapine and haloperidol groups were equivalent at end point for the total BPRS scores and the positive symptom cluster and the CGI. Only the 300 mg dose of quetiapine and placebo scores were significantly better than haloperidol on the SANS. Based on this experience and the previous studies the optimal doses of quetiapine appear to range from 300 to 600 mg. However preferred amounts for management of primary negative symptoms and cognitive impairments to promote the best possible quality of life remain to be ascertained.

Additional randomized double blind trials without placebo conditions have been published. Peuskens and Link compared flexible doses of quetiapine with chlorpromazine showing that quetiapine was as effective as chlorpromazine on measures of both positive and negative symptoms. Sixty-five percent of quetiapine patients and 53% of chlorpromazine subjects achieved at least a 50 percent improvement in total BPRS total score at some point during the study, a statistically significant difference ($p = 0.04$) favoring quetiapine. In other trials dosing frequency was examined comparing two or three times daily schedules. Outcomes with bid and tid dosing were equivalent, corresponding with time courses of PET studies of decline in D2 and $5HT_2$ receptor occupancy but not plasma half-life(14).

Other evidence of therapeutic efficacy of quetiapine can be inferred from uncontrolled studies and case reports. Favorable results in two patients with psychosis and Parkinson's Disease were reported in which mental symptoms improved and Parkinsonism was not adversely affected(15). Another study examined the effectiveness of quetiapine in psychotic geriatric patients(16). An interim analysis was done in 150 patients after twelve weeks of treatment with average dosages of 75 to 100 mg. BPRS total scores and CGI global ratings improved progressively during the course of the trial with significant decreases from baseline. Results were comparable in patients with idiopathic or organic psychoses.

Cognitive impairment is another core feature of schizophrenia which may be benefited more by atypical than standard neuroleptics(17). Performance by schizophrenics and normal controls on a continuous performance test was studied before and after quetiapine therapy in the patients(18). They were significantly worse than normals at baseline but by the end of two months of treatment did not differ significantly from controls. The trial involved 10 patients who received quetiapine as part of other multicenter trials and a comparison group of twelve matched normal volunteers. More comprehensive trials with full neuropsychological test batteries have yet to be reported with quetiapine.

Since marketing of quetiapine abstracts, letters and case reports

about individual experiences have appeared at scientific meetings, in journals and on the Internet. Favorable results were reported in an adolescent with childhood onset schizophrenia who had not responded satisfactorily to other atypical neuroleptics i.e., risperidone and olanzapine(19). Cognitive improvement accompanying treatment with Seroquel was described in a man with chronic schizophrenia(20). Positive comments have appeared on the Internet, mentioning advantages with quetiapine mostly due to fewer side effects(21). Recent presentations have included therapeutic benefits in Alzheimer's disease associated with psychosis,(22) in adolescent patients,(23) and in schizophrenic patients displaying hostility, aggressive behavior and affective symptoms(24). Surveys of caretaker and patient satisfaction indicated a high rate of acceptability of atypical neuroleptics in general and quetiapine in particular with improved quality of life(25,26). Another study was presented indicating beneficial results with quetiapine in Parkinsonian patients on both psychotic and motor abnormalities(27). Comparative studies of quetiapine with other atypical antipsychotic drugs are beginning to appear. An open-label four month trial comparing quetiapine and risperidone in 751 outpatients (28) showed improvement on both drugs with advantages for quetiapine on depression ratings and the CGI. There were no statistically significant differences on ratings of positive or negative schizophrenic symptomatology.

To summarize the data on therapeutic efficacy: relief of positive symptoms appears comparable to standard neuroleptics, primarily haloperidol. Effects on negative symptoms are less robust but they appear to resolve to a greater extent than with placebo or standard neuroleptics. Data on cognitive dysfunctions and quality of life issues are sparse. It must be kept in mind that the bulk of the information about efficacy is limited to six weeks of treatment with few controlled observations for longer time periods. Moreover information in schizoaffective and bipolar disorders, the elderly and pediatric populations and medically compromised patients is minimal and no data are published to date on first episode or refractory schizophrenia.

Safety and Tolerability:

Quetiapine has a good overall safety and tolerability profile with few patients discontinuing from studies due to adverse effects. It has an especially low incidence of extrapyramidal side effects (EPS) with values comparable to placebo and no evidence of a dose response curve. This was also reflected in the minimal use of concomitant anticholinergic medications. The primary reason for early dropouts from pivotal studies was treatment failure as would be expected in chronically ill, hospitalized schizophrenic patients. Correspondingly, the most frequently reported adverse events were common accompaniments of schizophrenic exacerbations

such as agitation and sleep disturbances.

The controlled trials yielded similar adverse event profiles with quetiapine with most complaints rated as mild or moderate. Agitation, somnolence, and headache were the most commonly reported side effects. Somnolence was more common with quetiapine than placebo but similar for quetiapine and low to moderate doses of chlorpromazine. Postural hypotension was encountered infrequently with quetiapine in the placebo controlled trials, occurring three times more often with the chlorpromazine comparator. Other less frequently encountered events included constipation, dry mouth, and tachycardia. Case reports of quetiapine overdoses also attest to its safety(29,30). Sinus tachycardia and sedation were the major effects of acute overdosages from 4700 to over 10,000 mg which resolved uneventfully with supportive care.

Adverse Events:

There is a wide spectrum of potential adverse events with antipsychotic drug therapy. Neurological side effects are the major category which includes Parkinsonism, dystonia, akathisia, tardive dyskinesia, neuroleptic malignant syndrome, seizures and epileptiform EEG features. Impaired cognition, psychotic, decompensation, abnormalities in mood, behavioral worsening and obsessive compulsive manifestations are other CNS effects. Further

all antipsychotics can produce adverse withdrawal symptoms if suddenly or rapidly discontinued with psychotic decompensation, cholinergic rebound, emergent dyskinesias, and general malaise. Early relapse may be more problematic with atypical than standard neuroleptics because of loose binding and rapid release from D2 receptor occupancy in the former(31).

Significant endocrinological abnormalities may develop due to hypogonadism produced by hyperprolactinemia with galactorrhea, menstrual irregularities, sexual dysfunctions and long term risks of osteoporosis, breast cancer and heart disease. Disturbances in glucose regulation may accompany atypical neuroleptic therapy. Asymptomatic deviations in thyroid function tests have also been reported. Weight gain is a common problem. Other side effects involve cardiovascular events such as prolonged QTc interval, postural hypotension, tachycardia and other arrhythmias. Decreased bowel motility, cholestatic jaundice and other gastrointestinal problems can occur. Transient elevations in hepatic transaminase activity have been observed, generally without clinical manifestations.

Unlike the case with clozapine, agranulocytosis and other hematologic abnormalities are not frequently associated with standard or other atypical antipsychotic agents. Nonetheless all of these drugs can impact adversely on multiple organ systems

giving rise to ophthalmologic, dermatologic, allergic and other complications.

Neurological Effects:

Extrapyramidal side effects (EPS) did not distinguish between quetiapine and placebo in the three placebo controlled trials cited previously as measured by Simpson-Angus Scale (SAS) (32) scores at endpoint. This was also reflected in the minimal use of anticholinergic agents for treatment emergent EPS. In the Arvanitis et al. study twelve percent of patients on quetiapine were given anticholinergic drugs for control of EPS compared to 14% on placebo and 48% on haloperidol. The incidence of akathisia measured by the Barnes Scale (33) was the same for quetiapine as with placebo. In the quetiapine - chlorpromazine comparison there were low levels of EPS in both treatment groups. Among the chlorpromazine subjects one patient was withdrawn because of an acute dystonic reaction and more anticholinergic medications were prescribed. Quetiapine and placebo Barnes scores tended to improve from baseline, more with higher quetiapine doses, whereas the haloperidol group worsened. It can be concluded that quetiapine rarely produces EPS. However two cases who experienced EPS with relatively low doses of quetiapine were reported on the Internet(21). One was an Asian woman and the other a man diagnosed as bipolar.

Seroquel has not been available long enough to ascertain its liability for producing tardive dyskinesia (TD). Judging from data on other atypical neuroleptics, the risk can be predicted to be substantially less than with standard neuroleptics. It is also not yet clear whether quetiapine will suppress abnormal involuntary movements. Likewise the risks of neuroleptic malignant syndrome are unknown although cases with several other atypical antipsychotic agents have been reported.

Seizures are another complication of neuroleptic therapy, particularly with clozapine(34). With some exceptions the incidence of seizures is directly proportional to the degree of sedation associated with the drug as well as other factors such as dosage and speed of titration, seizure threshold, concomitant medications, etc.(35). The incidence of seizures with clozapine has been reported as 1.1% whereas clinical trial data for olanzapine yielded 0.9%, risperidone 0.3% and quetiapine 0.8% (36). Epileptiform EEG features in association with clozapine treatment may warn of impending seizures if the dosage continues to increase. However they may also be a favorable prognostic sign(37).

Other research has involved quantitative EEG (QEEG). Studies examining waking EEG and sensory evoked potentials before and after single doses and chronic intake of standard neuroleptics have been

accomplished in schizophrenic patients. QEEG changes have been reported in specific EEG frequency bands with significant associations with plasma neuroleptic levels and indications of therapeutic response.(38,39) QEEG investigations with atypical agents are in progress. Small et al.(40) reported significant negative rank order correlations between D2 receptor affinities and spectral energy in the theta band (4 to 8 Hertz (Hz)) with lowest amplitudes after 4-6 weeks of optimal therapeutic doses for haloperidol followed by risperidone, olanzapine, quetiapine, and clozapine. However these determinations were based upon animal data which are not directly applicable to humans. There were positive associations between the purported degree of histamine receptor binding of the four atypical neuroleptics with highest amplitudes in the fast beta-2 band (18-30 Hz) with quetiapine followed by olanzapine, clozapine, and risperidone.

Other CNS adverse effects include a range of impairments that can be encompassed under the rubric "behavioral toxicity". These reactions may be idiosyncratic or related to dose and timing. Atypical neuroleptics are particularly prone to induce or expose obsessive-compulsive features(41,42). This has not yet been reported with quetiapine but has been observed by the author. Receptor data suggest that withdrawal symptoms would be likely to occur with quetiapine. However abrupt withdrawal of quetiapine

with switchover to standard neuroleptics was associated with psychotic relapse in only 2 of 50 patients studied by Goldstein without associated physical problems(43). Higher than optimal dosages can be associated with increased agitation and other indications of psychotic worsening as well as other side effects. Sleep disturbances with either sedation or insomnia may accompany drug therapy but may also be features of underlying psychosis.

Endocrinological effects:

There were no significant elevations in serum prolactin in the pivotal trials described previously and in some instances quetiapine was associated with reduced levels from baseline. Prolactin levels were significantly higher with both chlorpromazine and haloperidol. There were no significant differences between quetiapine and placebo in either men or women. In the absence of hyperprolactinemia problems such as gynecomastia, menstrual irregularities, impotence, etc. would not be expected although most trial durations were not long enough to evaluate these issues. Likewise reproductive and neonatal difficulties have not been reported to date.

However weight gain was an adverse event experienced by two percent of quetiapine patients in the placebo controlled studies. Clinically significant weight gain, that is more than 7 percent

increase in body weight, was seen more with quetiapine than placebo - 24 percent compared with four percent in the Borison et al. study. Weight gain appeared to be dose related in the Small et al. and Arvanitis et al., trials ranging from five percent for placebo, fifteen percent for low dose and twenty-four percent with high dose quetiapine in the former. Likewise weight gain in the Arvanitis et al. study was proportional to dosage and exceeded amounts with haloperidol and placebo. Twenty-seven percent of quetiapine treated patients had significant weight gain compared with eighteen percent with chlorpromazine reported by Peuskens and Link.

Adverse effects of atypical antipsychotics upon glucose regulation have been recognized recently mostly with clozapine. Hägg et al.(44) compared clozapine patients with those on depot standard neuroleptics and found hyperglycemia in thirty-three percent with clozapine and nineteen percent with traditional antipsychotics (p=.07). Non-insulin-dependent diabetes mellitus or impaired glucose tolerance occurred in twenty-one percent of the clozapine patients versus 9.5 percent of those taking standard neuroleptics (p=.06). Likewise the incidence for clozapine was over three times the expected number of cases based on population surveys. New onset diabetes has also been reported with olanzapine(45). It appears that atypical neuroleptics may promote weight gain, insulin insensitivity and glucose intolerance by virtue of their antagonism of histamine and serotonin receptors. African-Americans are

particularly vulnerable to these effects and individuals with personal or family histories of diabetes mellitus or obesity. As clozapine, olanzapine and quetiapine cause the most weight gain, these drugs may be most likely to induce diabetes. Case reports with quetiapine have not appeared so far.

Quetiapine was associated with small reductions in mean total T4 and occasionally T3 but these were not associated with concomitant elevations of TSH or any indications of clinical hypothyroidism. Maximal reductions occurred in the first two to four weeks of treatment with no further decline with continued intake. In nearly all instances discontinuation of quetiapine was followed with prompt reversal of effects on both total and free thyroxine.

Cardiovascular, gastrointestinal, and hematologic abnormalities:

Quetiapine exerts some cardiovascular effects such as orthostatic hypotension and dizziness. These usually occur during the initial period of dosage titration and seldom require discontinuation. EKG recordings showed little change in QTc intervals and there was no relationship between plasma levels of quetiapine and the QTc changes. Quetiapine appears to have minimal proarrhythmic activity. However in both reported cases of overdosage there was sustained sinus tachycardia persisting up to 48 hours. A further disclaimer should be added that experience has yet to be obtained

in patients with preexisting heart disease and EKG abnormalities. The major gastrointestinal effects of quetiapine are mild transient, reversible and asymptomatic elevations in serum transaminase (ALT, AST) or gamma-glutamyl/transferase levels. These abnormalities did not exceed five times the upper limits of the normal range for the laboratory assay and were generally reversible despite continued treatment. Constipation was endorsed as a problem in fewer than ten percent of patients, similar to the incidence with placebo. However weight gain was a significant issue as discussed previously.

Hematologic abnormalities are of particular concern in the light of the experience with clozapine. No cases of granulocytopenia have been noted to date nor any deaths that could have been the result of undetected agranulocytosis. Although there appear to be no hematologic problems with quetiapine it should be recognized that patients with preexisting abnormalities or individuals predisposed to these complications were excluded from the systematic trials. Moreover combinations of quetiapine with other agents have yet to be studied.

Ophthalmologic effects:

Quetiapine was associated with the development of cataracts in dogs that received quetiapine at four times the maximum recommended

human dose for six to twelve months. No evidence of cataracts appeared in a comparable study of monkeys at even higher doses and none have been observed in humans. Nevertheless labeling for now recommends that periodic slit-lamp examinations be done before quetiapine treatment and at six month intervals thereafter. Complicating this situation is the high incidence of cataracts in patients with schizophrenia as well as longitudinal changes that occur with advancing chronological age(46).

Pharmacokinetics and Drug Interactions:

The plasma half-life of quetiapine is 6 to 8 hours but the half-life of receptor occupancy may be longer as mentioned earlier. Gefvert et al.(47) compared plasma half-life and D2 and 5-HT2 receptor occupancies finding that the latter declined more slowly than plasma levels, particularly 5-HT2. Fleischhacker et al. (48) compared twice and three times daily dosage regimens of quetiapine and observed a few advantages for twice daily dosing, results supported by PET studies of receptor occupancy.

Quetiapine is rapidly absorbed after oral administration with peak blood levels in 1 to 1-1/2 hours. It appears to be widely distributed in tissues and extensively metabolized in the liver with only a small amount of the parent compound excreted in the urine. The major metabolic pathway involves sulphoxidation by

cytochrome P450 3A4 although CYP 2D6 may also play a role(49). Consequently elevated plasma levels of quetiapine can be anticipated with co-administration of enzyme inhibiting drugs such as ketoconazole, erythromycin, nefazodone, fluvoxamine, and some other antidepressants. 3A4 enzyme inducers such as phenytoin and to a lesser extent thioridazine can increase both clearance and dosage requirements but quetiapine levels will likely rise when the inducer is stopped.

Therapeutic Potential:

Results from randomized, double-blind clinical trials conducted thus far indicate that a wide dosage range of quetiapine is well tolerated and effective in the treatment of positive and negative symptoms of schizophrenic exacerbations. Preclinical and clinical data support its status as an atypical antipsychotic drug with few Parkinsonian, extrapyramidal or other neurological side effects. Although comparative data are not yet available quetiapine may offer the widest dosage range with fewest neurological side effects of all the marketed atypicals. Lack of effects on prolactin predicts few if any sexual dysfunctions and other endocrinological side effects that impinge upon patient compliance. The absence of cardiovascular effects is another desirable feature that may reduce or eliminate the need for dosage titration, although this must be

investigated further. Likewise its weak anticholinergic activity offers potential advantages for patients with cognitive impairments. However weight gain is a significant adverse effect that may limit acceptance as will the required twice daily oral dosing schedule and the ophthalmologic examinations.

Quetiapine's eventual place relative to the other atypical neuroleptics remains to be established. Studies of these applications are appearing rapidly at national and international scientific meetings. Clinical trials in progress include studies of nursing home residents with Alzheimer's dementia and psychosis, studies of psychotic adolescent patients, further investigators of Parkinsonism and combinations of quetiapine and carbamazepine(50).

Data have been already collected from industry supported multicenter trials of treatment refractory schizophrenic patients which should be analyzed and reported in the near future. In this regard an abstract from Japan on refractory patients appeared in a recent program(51). Numerous other investigations are in progress which should soon establish the place of quetiapine in the therapeutic armamentarium.

Figure 1. Structural formula.

01. Hirsch SR, Link CGG, Goldstein JM, and Arvanitis LA:ICI 204,636: A new atypical antipsychotic drug. Br J Psychiatry Suppl. 1996;29:45-56.

02. Goldstein JM: Preclinical profile of Seroquel (quetiapine): An atypical antipsychotic with clozapine-like pharmacology. Schizophrenia: Breaking Down the Barriers. Eds. Holliday SG, Ancill RJ and MacEwan GW: 1996 John Wiley & Sons Ltd. city

03. Seeman P and Tallerico T: Antipsychotic drugs which elicit little or no Parkinsonism bind more loosely than dopamine to brain D2 receptors, yet occupy high levels of these receptors. Molecular Psychiatry 1998;3:123-134.

04. Goldstein JM: The New Generation of Antipsychotic Drugs: How atypical are they? In press: Novel Strategies in the Schizophrenic Spectrum and Bipolar Disorders. International Academy for Biomedical and Drug Research. Karger 1999

05. Marder S: Newer antipsychotic in treatment-resistant schizophrenia. Biol Psychiatry 1999;45:383-384.

06. Borison RL, Arvanitis, LA, Miller BG, and the U.S. Seroquel Study Group.: ICI 204,636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. J Clin Psychopharmacol 1996;16:158-169.

07. Small JG, Hirsch SR, Arvanitis LA, Miller BG, Link CGG and the Seroquel Study Group. A high and low-dose double blind comparison with placebo. Quetiapine in patients with

schizophrenia. Arch Gen Psychiatry 1997;54:549-557.

08. Arvanitis LA, Miller BG, and the Seroquel Trial 13 Study Group. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. Biol Psychiatry 1997; 42:233-246.

09. Peuskens J, and Link CGG: A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. Acta Psychiatr Scand 1997;96:265-273.

10. Overall JE, Gorham DR: The Brief Psychiatric Rating Scale Psychol Rep 1962;10:799-812.

11. Guy W: (ed) ECDEU Assessment Manual for Psychopharmacology, rev ed. Rockville, MD: US Department of Health, Education, and Welfare. 1976;Publication ADM:76-338.

12. Andreasen N: Modified Scale for the Assessment of Negative Symptoms. NIMH Treatment Strategies in Schizophrenia Study. Washington, DC: Department of Health and Human Services, Public Health Administration, Publication ADM 9-102.

13. Kay SR, Opler LA, Lindenmayer J-P: The positive and negative syndrome scale (PANSS): rationale and standardisation. Br J Psychiatry 1989;154:155:59-65.

14. Meats P: Quetiapine (Seroquel); An effective and well-tolerated atypical antipsychotic. International Journal of Psychiatry in Clinical Practice 1997;1:231-239.

15. Parsa MA, and Bastani B: Quetiapine (Seroquel) in the

treatment of psychosis in patients with Parkinson's disease. J Neuropsychiatry and Clin Neurosci, 1998;10:216-219.

16. McManus DQ, Arvanitis LA, Kowalcyk BB, and the Seroquel Trial 48 Study Group: "Seroquel" (quetiapine), a novel antipsychotic: experience in elderly patients with psychotic disorder. J of Clinical Psychiatry 1999; (in press)
17. Brier A: Cognitive deficit in schizophrenia and its neurochemical basis. Br J Psychiatry 1999;174:16-18.
18. Sax KW, Strakowski SM, Keck PE: Attentional improvement following quetiapine fumarate treatment in schizophrenia. Schizophrenia Research 1998;33:151-155.
19. Szigethy E, Brent S, Findling RL: Quetiapine for refractory schizophrenia (letter) J Am Acad Child Adolesc Psychiatry 1998;37:1127-1128.
20. Stip E, Lussier I, Babai M, Fabian JL, and Link C: Seroquel and cognitive improvement in patients with schizophrenia (letter) Biol Psychiatry 1996;40:434-435.
21. Currents in Affective Illness: Clinical psychopharmacology on line. Currents 1998;17:18-19.
22. Knesevich JW: Six month findings with quetiapine in three patients with Alzheimer's disease with psychoses. NCDEU Meeting June 1998, FL
23. McConville B, Arvanitis L, Wong J, Yeh C, Wilkinson L, Chaney R, Foster K, Sorter M, Friedman L, and Browne K: Pharmacokinetics, Tolerability, and Clinical Effectiveness of

Quetiapine Fumarate in Adolescents with Selected Psychotic Disorders. NCDEU Meeting June 1998, Florida.

24. Goldstein JM: Quetiapine fumarate: Effects on hostility, aggression and affective symptoms in patients with acute schizophrenia. NCDEU Meeting June 1998, Florida.

25. Hellewell JSE: Attitudes towards the treatment of schizophrenia and perceptions of antipsychotic side effects: a multinational survey of psychiatrists, nurses, patients, and caregivers. 11th ECNP Congress, Paris, 1998.

26. Kalai AH, Hellewell JSE, Goldstein JM, and Langham S: A Multinational Survey of Patient Satisfaction with Long-Term Quetiapine Fumarate Treatment. NCDEU Meeting, June 1998, FL

27. Juncos JJ, Evatt ML, and Jewart D: Long-term effects of quetiapine fumarate in parkinsonism complicated by psychosis. Neurology, 1998; 50:A70-A71.

28. Mullen J, Reinstein M, Bari M, Ginsberg L, and Sandler N Quetiapine and risperidone in outpatients with psychotic disorders: results of the Quest trial. American College of Neuropsycho Pharmacology, 1998 Meeting Puerto Rico, June.

29. Nudelman E, Vinuela LM, and Cohen CI: Safety in overdose of quetiapine: a case report. J Clin Psychiatry 1998;59:433.

30. Harmon TJ, Benitz JG, Krenzelok EP, et al: Loss of consciousness from acute quetiapine overdosage. J Toxicolog-Clin toxicology 1998;36:599-602.

31. Seeman P and Tallerico T: Clozapine and quetiapine: rapid

release from D2 explains low receptor occupancy, early clinical relapse upon drug withdrawal. 1998 Submitted for publication.

32. Simpson GM, Angus JW: A rating scale for extrapyramidal side effects. Acta Psychiatr Scand 1970;212:11-19.

33. Barnes TRE: A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672-676.

34. Welch J, Manschreck T, Redmond D: Clozapine-induced seizures and EEG changes. Journal of Neuropsychiatry and Clinical Neurosciences 1994;6:250-256.

35. Oliver AP, Luchins DJ, Wyatt RJ: Neuroleptic-Induced Seizures. An invitro technique for assessing relative risk. Arch Gen Psychiatry 1982;39:206-209.

36. Rehder TL: Communication in Safety Information - Seizures 2-24-99. **NEED A BETTER REFERENCE**

37. Stevens JR, Denney D, and Szot P: Sensitization with clozapine: beyond the dopamine hypothesis. Biol Psychiatry 1997;42:771-780.

38. Czobor P and Volavka J: Level of haloperidol in plasma is related to electroencephalographic findings in patients who improve. Psychiatry Research 1992;42:129-144.

39. Czobor P and Volavka J: Pretreatment EEG predicts short-term response to haloperidol treatment. Biol Psychiatry 1991;30:927-942.

40. Small JG, Milstein V, Malloy FW, and Miller MJ: Quantitative

electroencephalographic frequencies and relative neuroleptic receptor affinities in schizophrenia. Biol Psychiatry 1996;39:986-988.

41. Baker RW, Chengappa KNR, Baird JW, Steingard S, Christ MAG, and Schooler NR: Emergence of obsessive compulsive symptoms during treatment with clozapine. J Clin Psychiatry 1992;53:439-442.

42. Allen RM: Risperidone and Obsessive-Compulsive Disorder. Psychiatric Annals 1995;25:523-524.

43. Goldstein JM: Safety and tolerability of Switching from conventional antipsychotic therapy to quetiapine fumarate followed by abrupt withdrawal from quetiapine fumarate. NCDEU Meeting. June 1998 FL

44. Hägg S, Joelsson L, Mjorndal T, Spigset O, Oja G, Dahlqvist R: Prevalence of diabetes and impaired glucose tolerance in patients treated with clozapine compared with patients treated with conventional depot neuroleptic medications. J Clin Psychiatry 1998;59:294-299.

45. Wirshing DA, Spellberg BJ, Erhart SM, Marder SR, Wirshing WC: Novel antipsychotics and new onset diabetes. Biol Psychiatry 1998;44:778-783.

46. Smith D, Pantelis C, McGrath J, et al: **NEED OTHER AUTHORS** Ocular abnormalities in chronic schizophrenia: clinical implications. Aust N Z J Psychiatry 1997;31:252-256.

47. Gefvert O, Lindstrom L, Langstrom B et al: Time course for

dopamine and serotonin receptor occupancy in the brain of schizophrenic patients following dosing with 150 mg "Seroquel" tid (abstract P-4-65) 1995;5:347.

48. Fleischhacker W, Link C, Horne B: A multicentre, double-blind, randomized comparison of dose and dose regimen of Seroquel in the treatment of patients with schizophrenia. 1995 ACNP Meeting. Tennessee

49. Shen WW: The Metabolism of Psychoactive drugs: A review of enzymatic biotransformation and inhibition. Biol Psychiatry 1997;41:814-826.

50. Focus on Seroquel Winter 1998 **NEED A BETTER REFERENCE**

51. Maeda H, Kotorii T, Nakamura J, Uchimura N: Clinical evaluation of quetiapine (ICI 204636), a novel antipsychotic agent, in treatment-resistant schizophrenic patients. 21st Collegium Internationale Neuropsychopharmacologicum Congress 1998; Glasgow, July 1998.

Seroquel - Quetiapine **ALPHABETICAL**

00. Andreasen N: Modified Scale for the Assessment of Negative Symptoms. NIMH Treatment Strategies in Schizophrenia Study. Washington, DC: Department of Health and Human Services, Public Health Administration, Publication ADM 9-102.

00. Arvanitis LA: Clinical profile of seroquel (quetiapine): An overview of recent clinical studies. Schizophrenia: Breaking Down the Barriers. Edited by S.G. Holliday, R.J. Ancill, and G.W. MacEwan. 1996 John Willey & Sons Ltd.

00. Arvanitis LA, Miller BG, and the Seroquel Trial 13 Study Group. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. Biol Psychiatry 1997; 42:233-246.

00. Bakshi VP, Swerdlow NR, Braff DL, and Geyer MA: Reversal of isolation rearing-induced deficits in prepulse inhibition by seroquel and olanzapine. Biol Psychiatry 1998;43:436-445.

00. Borison RL, Arvanitis, LA, Miller BG, and the U.S. Seroquel Study Group.: ICI 204,636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. J Clin Psychopharmacol 1996;16:158-169.

00. Bowes M: Managing schizophrenia throughout the course of illness. Psychiatric Times Monograph. 1998; December:11-21.

00. Bradford DW, Chakos MH, Sheitman BB, and Lieberman JA:

Atypical antipsychotic drugs in treatment-refractory schizophrenia. Psychiatric Annals 1998;28:618-626.

00. Brier A: Cognitive deficit in schizophrenia and its neurochemical basis. Br J Psychiatry 1999;174:16-18.

00. Casey DE: Extrapyramidal syndromes and new antipsychotic drugs: findings in patients and non-human primate models. Br J Psychiatry Suppl. 1996;29:32-39.

00. Currents in Affective Illness: Clinical psychopharmacology on line. Currents 1998;17:18-19.

00. Czobor P and Volavka J: Level of haloperidol in plasma is related to electroencephalographic findings in patients who improve. Psychiatry Research 1992;42:129-144.

00. Czobor P and Volavka J: Pretreatment EEG predicts short-term response to haloperidol treatment. Biol Psychiatry 1991;30:927-942.

00. Fenton WS, and McGlashan TH: Antecedents, symptom progression, and long-term outcome of the deficit syndrome in schizophrenia. Am J Psychiatry 1994;151:351-356.

00. Fleischhacker W, Link C, Horne B: A multicentre, double-blind, randomized comparison of dose and dose regimen of Seroquel in the treatment of patients with schizophrenia. 1995 ACNP Meeting. Tennessee

00. Gefvert O, Lindstrom L, Langstrom B et al: Time course for dopamine and serotonin receptor occupancy in the brain of schizophrenic patients following dosing with 150 mg "Seroquel"

tid (abstract P-4-65) 1995;5:347.

00. Ghaemi SN: Atypical antipsychotic agents in the treatment of bipolar and schizo-affective disorders. Part II-olanzapine, extrapyramidal symptoms, tardive dyskinesia. International Drug Therapy Newsletter 1998;33:49-53.

00. Goldstein JM: The new generation of antipsychotic drugs: How atypical are they? Novel Strategies in the Schizophrenic Spectrum and Bipolar Disorders. International Academy for Biomedical and drug Research. 1999 Karger (in press)

00. Goldstein JM: Preclinical profile of Seroquel (quetiapine): An atypical antipsychotic with clozapine-like pharmacology. Schizophrenia: Breaking Down the Barriers. Eds. Holliday SG, Ancill RJ and MacEwan GW: 1996 John Wiley & Sons Ltd. city

00. Goldstein JM: Quetiapine fumarate: Effects on hostility, aggression and affective symptoms in patients with acute schizophrenia. NCDEU Meeting June 1998, Florida.

00. Goldstein JM: Preclinical tests that predict clozapine-like atypical antipsychotic actions. In: Brunello N, Racagni G, Langer SZ, Medlewicz J (eds): Critical issues in the treatment of schizophrenia. Int Acad Biomed Drug Res. Basel, Karger 1995;10:95-101.

00. Goldstein JM, Cantillon M: Low incidence of reproductive/hormonal side effects with Seroquet (quetiapine) is supported by its lack of elevation of plasma prolactin concentrations. Internationale Collegium

Neuropsychopharmacologicum Congress 1998;228 Abs PT07093. Abstracts from the 21st CINP Congress, Glasgow, 1998;Jul:12-16.

00. Gunasekara NS and Spencer CM: Quetiapine: A review of its use in schizophrenia. CNS Drugs 1998;3.

00. Gunn KP, Harrigan EP, and Heym J: The safety and tolerability of ziprasidone treatment. In: Brunello N, Racagni G, Langer, SZ, Medlewicz J. (eds): Critical issues in the treatment of schizophrenia. Int Acad Biomed Drug Res. Basel, Karger 1995; 10:171-177.

00. Gunther W, Baghai T, Naber D, et al: EEG alterations and seizures during treatment with clozapine. A retrospective study of 2843 patients. Pharmacopsychiatry 1993;26:69-74.

00. Guy W: (ed) ECDEU Assessment Manual for Psychopharmacology, rev ed. Rockville, MD: US Department of Health, Education, and Welfare. 1976;Publication ADM:76-338.

00. Hägg S, Joelsson L, Mjorndal T, Spigset O, Oja G, Dahlqvist R: Prevalence of diabetes ad impaired glucose tolerance in patients treated with clozapine compared with patients treated with conventional depot neuroleptic medications. J Clin Psychiatry 1998;59:294-299.

00. Harmon TJ, Benitz JG, Krenzelok EP, et al: Loss of consciousness from acute quetiapine overdosage. J Toxicolog-Clin toxicology 1998;36:599-602.

00. Hirsch SR, Link CGG, Goldstein JM, and Arvanitis LA:ICI

204,636: A new atypical antipsychotic drug. Br J Psychiatry Suppl. 1996;29:45-56.

00. Juncos JJ, Evatt ML, and Jewart D: Long-Term Effects of Quetiapine Fumarate in Parkinsonism Complicated by Psychosis. Neurology, 1998; 50:A70-A71.

00. Kapur S, Zipursky RB, and Remington G: Clinical and theoretical implications of 5-HT_2 and D_2 receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. Am J Psychiatry 1999;156:286-293.

00. Kay SR, Opler LA, Lindenmayer J-P: The positive and negative syndrome scale (PANSS): rationale and standardisation. Br J Psychiatry 1989;154:155:59-65.

00. Lieberman JA: Understanding the mechanism of action of atypical antipsychotic drugs. Br J Psychiatry 1993;163:7-18.

00. Maeda H, Kotorii T, Nakamura J, Uchimura N: Clinical evaluation of quetiapine (ICI 204636), a novel antipsychotic agent, in treatment-resistant schizophrenic patients. Collegium Internationale Neuropsychopharmacologicum Congress 1998;339:Abs PT07099. Abstracts from the 21st CINP Congress, Glasgow, 12-16 July 1998.

00. Marder S: Newer antipsychotic in treatment-resistant schizophrenia. Biol Psychiatry 1999;45:383-384.

00. McManus DQ, Arvanitis LA, Kowalcyk BB, and the Seroquel Trial 48 Study Group: "Seroquel" (Quetiapine), a novel antipsychotic: experience in elderly patients with psychotic

disorder. J of Clinical Psychiatry 1998; (in press)

00. Meats P: Quetiapine (Seroquel); An effective and well-tolerated atypical antipsychotic. International Journal of Psychiatry in Clinical Practice 1997;1:231-239.

00. Meltzer HY: Pre-clinical pharmacology of atypical antipsychotic drugs: a selective review. Br J Psychiatry Suppl. 1996;29:23-31.

00. Mullen J, Reinstein M, Bari M, Ginsberg L, and Sandler N Quetiapine and risperidone in outpatients with psychotic disorders: results of the Quest trial. American College of Neuropsycho Pharmacology, 1998 Meeting Puerto Rico, June.

00. Nudelman E, Vinuela LM, and Cohen CI: Safety in overdose of quetiapine: a case report. J Clin Psychiatry 1998;59:433.

00. Nyberg S, Nakashima Y, NÖrdstrom A-L, Halldin C, and Farde L: Positron emission tomography studies of in-vivo binding characteristics of atypical antipsychotic drugs. Review of D^2 and 5-HT^2 receptor occupancy studies and clinical response. Br J Psychiatry Supply. 1996;29:40-44.

00. Oliver AP, Luchins DJ, Wyatt RJ: Neuroleptic-Induced Seizures. Arch Gen Psychiatry 1982;39:206-209.

00. Overall JE, Gorham DR: The Brief Psychiatric Rating Scale Psychol Rep 1962;10:799-812.

00. Parsa MA, and Bastani B: Quetiapine (Seroquel) in the treatment of psychosis in patients with Parkinson's disease. J Neuropsychiatry and Clin Neurosci, 1998;10: (in press)

00. Peuskens J, and Link CGG: A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. Acta Psychiatr Scand 1997;96:265-273.

00. Pickar D: Prospects for pharmacotherapy of schizophrenia. Lancet 1995;345:557-562.

00. Pickar D: Pharmacotherapy of schizophrenia. Lancet 1995;346:450

00. Pies R: New advances in the treatment of schizophrenia. Psychiatric Times Monograph. 1998;December:1-6.

00. Popli AP, Konicki PE, Jurjus GJ, Fuller MA, and Jaskiw GE: Clozapine and associated diabetes mellitus. J Clin Psychiatry 1997;58:108-111.

00. Pulver AE, Bartko JJ, and McGrath JA: The power of analysis: Statistical perspectives. Part I., Psychiatry Res 1987; 23:295-299.

00. Quetiapine for Schizophrenia. The Medical Letter, 1997; 39:117.

00. Quetiapine (Seroquel) A few more points. Seroquel product insert. Biological Therapies in Psychiatry 1998;21:10.

00. Rund BR: A review of longitudinal studies of cognitive functions in schizophrenia patients. Schizophr Bull 1998;24:425-435

0. Sax KW, Strakowski SM, Keck PE: Attentional improvement following quetiapine fumarate treatment in schizophrenia. Schizophrenia Research 1998;33:151-155.

00. Schooler NR: Comparing new anti-psychotic medications: what do the data say? Biol Psychiatry 1998;43:59S.

00. Sedvall G and Farde L: Chemical brain anatomy in schizophrenia. _____ 1995;346:743-749.

00. Seeman P and Tallerico T: Antipsychotic drugs which elicit little or no Parkinsonism bind more loosely than dopamine to brain D2 receptors, yet occupy high levels of these receptors. Molecular Psychiatry 1998;3:123-134.

00. Small JG, Hirsch SR, Arvanitis LA, Miller BG, Link CGG and the Seroquel Study Group. A high and low-dose double blind comparison with placebo. Quetiapine in patients with schizophrenia. Arch Gen Psychiatry 1997;54:549-557.

00. Small JG, Milstein V, Malloy FW, and Miller MJ: Quantitative electroencephalographic frequencies and relative neuroleptic receptor affinities in schizophrenia. Biol Psychiatry 1996;39:986-988.

00. Smith D, Pantelis C, McGrath J, et al:**need other authors** Ocular abnormalities in chronic schizophrenia: clinical implicatins. Aust N Z J Psychiatry 1997;31:252-256.

00. Stevens JR, Denney D, and Szot P: Sensitization with clozapine: beyond the dopamine hypothesis. Biol Psychiatry 1997;42:771-780.

00. Stip E, Lussier I, Babai M, Fabian JL, and Link C: Seroquel and cognitive improvement in patients with schizophrenia (letter) Biol Psychiatry 1996;40:434-435.

00. Szigethy E, Brent S, Findling RL: Quetiapine for refractory schizophrenia (letter) J Am Acad Child Adolesc Psychiatry 1998;37:1127-1128.

00. Tandon R, Harrigan E, and Zorn SH: Ziprasidone: A novel antipsychotic with unique pharmacology and therapeutic potential. Journal of Serotonin Research 1997;4:159-177.

00. Welch J, Manschreck T, Redmond D: Clozapine-induced seizures and EEG changes. Journal of Neuropsychiatry and Clinical Neurosciences 1994;6:250-256.

00. Wirshing DA, Spellberg BJ, Erhart SM, Marder SR, Wirshing WC: Novel antipsychotics and new onset diabetes. Biol Psychiatry 1998;44:778-783.

ADDITIONS

00. McConville B, Arvanitis L, Wong J, Yeh C, Wilkinson L, Chaney R, Foster K, Sorter M, Friedman L, and Browne K: Pharmacokinetics, Tolerability, and Clinical Effectiveness of Quetiapine Fumarate in Adolescents with Selected Psychotic Disorders. Annual NCDEU Meeting June 1998, Florida.

00. Knesevich JW: Six Month Findings with Quetiapine in Three Patients with Alzheimer's Disease with Psychoses. Annual NCDEU Meeting June 1998, Florida.

00. Hellewell JSE: Attitudes towards the treatment of schizophrenia and perceptions of antipsychotic side effects: a multinational survey of psychiatrists, nurses, patients, and caregivers. 11th ECNP Congress, Paris, 1998.

00. Hellewell JSE, Kalaki AH, Langham SJ, McKellar J: Patient satisfaction and acceptability of long-term treatment with SEROQUEL: Results of an international study. Poster

Presentation at the 11th ECNP Congress, Paris, 1998.