Treatment of the Refractory Schizophrenic Patient

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As antipsychotic treatment evolves toward a broader range of efficacy and more benign side effect profiles, our criteria for treatment-refractory schizophrenia may become more subtle. Unidimensional concepts of treatment resistance may be replaced by multiaxial descriptions of the target symptoms, side effects, and compliance issues that limit the ultimate goals of enhanced psychosocial function and quality of life. Augmentation strategies, increasing insight into dose response relationships, and atypical agents may benefit patients who failed to respond to or tolerate previous therapies. The advantages of newer agents in treatment-resistant schizophrenia may arise in part from their preferential targeting of mesolimbic compared with motor and tuberoinfundibular dopaminergic pathways.

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Approximately 1% of the population of the United States will develop schizophrenia. The indirect and direct costs of treating schizophrenia in the United States are estimated to exceed $40 billion each year.[1] Impairment in adaptive function is a core diagnostic criteria for schizophrenia in the current *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV). Moreover, in schizophrenia, chronic course, repeat exacerbations and hospitalizations, and inability to maintain normal occupational or social function are the norm rather than the exception.[2] This lack of full recovery, despite neuroleptic treatment, may be understood in light of a growing body of cytoarchitectural, gross anatomical, and biochemical evidence suggestive of abnormal brain development in schizophrenia.[3–6] Analysis of ventricular enlargement by using monozygotic twin pairs discordant for schizophrenia and mixture distribution statistical methods are consistent with the notion that in schizophrenia, enlarged ventricles, presumed to be an anatomical manifestation of an early neurodevelopmental insult, are virtually ubiquitous.[7,8] This may explain, in part, the limited, compensatory, therapeutic role for conventional neuroleptics in the treatment of schizophrenia. For example, clozapine, considered to be the gold standard in efficacy of the new generation of serotonin-dopamine antagonist antipsychotics (SDAs), returns only a very small minority of schizophrenic patients to the level of function that would have been expected of them without schizophrenia.[9,10] Despite dramatic progress, we are far from a treatment for schizophrenia that would completely eliminate psychotic symptoms and restore normal psychosocial function for most patients. Instead, perhaps, analogously to antihypertensives in the treatment of essential hypertension, antipsychotic treatment compensates downstream for a mysterious unknown etiology. The effects seen on the heart (i.e., ventricular hypertrophy) in hypertension and brain (i.e., enlarged ventricles) in schizophrenia may be manifestations of the disease that are only distantly related to the primary, core, causative pathology.

CLINICAL APPROACHES

In selecting a clinical strategy, attempts to dichotomize patients as treatment resistant by unidimensional undichotomous criteria may be less useful than a context-specific nomenclature for *treatment resistance* that identifies the dimensions targeted for intervention. Multiaxial classification of treatment resistance avoids the semantic pitfalls of pigeonholing a clinically heterogeneous disease along a single dimension: treatment-resistant versus non-treatment-resistant. Nomenclature for treatment resistance may have bearing on eligibility for more sophisticated, toxic, or expensive drugs; disability determination decisions; eligibility for interpretation of clinical trials; and selection of adjunctive treatments. A multiaxial classification of treatment resistance that focuses attention on specific target symptoms may be helpful in directing treatment (Table 1). The context of the earliest attempts to standardize a definition of treatment resistance dealt with justification of a potentially hematologically toxic drug—clozapine. The original labeling to prescribe clozapine required failure of two adequate trials of different classes of conventional antipsy-

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Table 1. Multiaxial Classification May Direct Treatment of Refractory Schizophrenia

I. Rule out misdiagnosis/comorbidity
II. Major dimensions of treatment resistance
1. Positive symptoms
2. Negative (deficit) symptoms (including impairment in work and in social and independent living functions)
3. Agitation and/or insomnia
4. Treatment intolerance
a. Motor side effects (parkinsonian, akathisia, tardive dyskinesia)
b. Sedative side effects
c. Anticholinergic effects
d. Weight gain
e. Sexual dysfunction
f. Other (specify)
5. Poor compliance
a. Intolerance of side effects
b. Poor insight

Table 2. Medical Differential Diagnosis of Schizophrenia

Any systemic disorder causing encephalopathy
Endocrine (pituitary, thyroid, parathyroid, adrenal, diabetic)
Nutritional (vitamin B_{12}, folic acid, niacin, thiamine)
Collagen vascular disease (lupus cerebritis, other vasculitis)
Infection
Organ failure (uremia, hepatic encephalopathy, electrolyte disturbance)

Table 3. Neurologic Differential Diagnosis of Schizophrenia

Any cerebral disorder that disturbs reality testing
Neoplasm
Cerebral infection
Cerebral trauma, i.e., Wilson's disease, Huntington's chorea, Parkinson's disease, Alzheimer's disease
Developmental disorders, i.e., mental retardation, cerebral palsy, metachromatic leukodystrophy
Demyelinating disorder, i.e., multiple sclerosis

Table 4. Compliance

May be compromised by
Side effects
Lack of insight
Complicated regimen
Loose follow-up
Poor patient-physician rapport
Postpsychotic depression

Table 5. Approaches to Recalcitrant Positive and Negative Symptoms

Positive Symptoms
Lithium (affective symptoms not required)
Carbamazapine
Benzodiazepines (anxiety)
Risperidone or olanzapine prior to clozapine
Risperidone, olanzapine, or clozapine plus targeted augmentation
Combination of atypical antipsychotic plus second antipsychotic
ECT? (catatonia, prominent affective symptoms)
Reserpine?
Alone: 8–12 mg/d
Adjunct: 1–5 mg/d
Negative Symptoms
Treat motor side effects
Lower antipsychotic dose
Risperidone or olanzapine prior to clozapine
Stimulants
TCA; SSRIs (consider pharmacokinetic interactions); nefazodone?

chotics. This early operational definition of treatment resistance may have been influenced by the seminal trial that established clozapine's effectiveness in treatment-resistant schizophrenia. It required failure of two previous antipsychotic trials and a prospective trial of haloperidol.[10] Now that it is better understood how clozapine may be safely administered and newer, potentially effective and less toxic atypical antipsychotic agents are becoming available, less restrictive definitions of treatment resistance may be needed.

In schizophrenia, as in any medical disorder, when the patient does not respond to treatment as expected, the differential diagnosis should be reexamined. As shown in Tables 2 and 3, almost any medical or neurologic disorder that disturbs the normal environment of the brain may cause psychosis or exacerbate a preexisting psychotic tendency. Multifactoral (psychiatric plus medical-neurologic) etiologies of psychosis may be difficult to recognize. A common trap in investigating medical contributions to psychosis is to assume patients have only one or the other. Comorbidity with drugs of abuse and toxic side effects of approved drugs are more common complicating factors in interpreting both positive and negative symptoms of schizophrenia.

Poor compliance is widespread in schizophrenia and a major cause of ostensible neuroleptic nonresponsiveness. Examples of issues that may contribute to noncompliance or partial compliance are listed in Table 4. Economic factors that promote infrequent short visits with physicians may be a poor substrate for the development of an adequate physician-patient alliance. Medical contexts for poor compliance (i.e., hypertension, diabetes) in patients with normal brains abound.

Compared with medical contexts, in schizophrenia noncompliance is compounded by cognitive impairment, poor insight, paranoia, and complicated medication regimens requiring secondary medications to treat unpleasant side effects of the antipsychotic. Adequate time and rapport with the patient and caregivers are essential, as is an acknowledgment of and sensitivity to the discomforts and inconveniences of side effects.

As shown in Table 5, there are numerous somatic strategies for augmentation of conventional antipsychotics in the treatment of both positive and deficit symptoms. Double-blind evidence may be strongest to support a role for lithium augmentation in a significant minority of patients (with or without a strong affective component), but carbamazepine and valproate (particularly in the context of impulsivity and mood lability) may also be useful.[11,12]

Benzodiazepines may be particularly useful as adjuncts to neuroleptics in acute treatment, but their value in longer term treatment is less clear.[11–13] Behavioral disinhibition is a possibility in some schizophrenic patients taking benzodiazepines.

Comorbid depressive symptoms are common in schizophrenia. The phenomenology and pathophysiology of depressive syndromes in schizophrenia and the role of tricyclic and serotonin selective reuptake inhibitor (SSRI) antidepressants in their treatment have yet to be clearly defined. In combination, SSRI antidepressants and antipsychotic agents sometimes exacerbate motor side effects.[14] The mechanism may be increased blood neuroleptic levels,[15,16] or pharmacodynamic interactions that diminish dopaminergic tone.[17,18] Limited experimental evidence suggests that in some patients with schizophrenia, dopaminergic and noradrenergic agents, including stimulants, may improve deficits in prefrontal activation of cerebral blood flow,[19,20] and some aspects of cognitive function and deficit symptoms.[19,21] However, interventions that increase dopaminergic tone in schizophrenia have the potential to exacerbate psychosis.

Recent evidence suggests that measuring blood drug levels could play a limited role in safer and more effective dose-finding with conventional neuroleptics. It appears that a putative therapeutic window with haloperidol may be in a lower-than-expected dose range. Higher doses and blood drug levels increase risks for motor side effects, neuroleptic-induced deficit symptoms, and sedation, without improving efficacy. Levels ranging from 5 to 15 to 24 ng/mL have been discussed. The wide degree of individual variation in response and plasma levels from a given dose requires flexibility in dosage.[22] Measuring blood antipsychotic levels is not a routine part of clinical practice, but may be useful in evaluating compliance, treatment nonresponsiveness, and unexpected toxicity.

THE NEW GENERATION-ATYPICAL ANTIPSYCHOTICS

Although they represented a dramatic improvement over schizophrenic treatment prior to the 1950s, conventional antipsychotics suffer from lack of efficacy against positive symptoms in at least one third of patients; incomplete efficacy against deficit symptoms in most; and a wide array of annoying and toxic side effects owing to anatomical and biochemical nonselectivity. Motor, endocrine, and neuroleptic-induced deficit side effects arise from undesirable dopamine affinity in dorsal lateral striatal, tuberoinfundibular, and prefrontal cortical areas, respectively. Weight gain and severe daytime sedation are also common. Given the impaired insight inherent to a psychotic disorder, it is no surprise that many patients experience the side effects as worse than the symptoms they are treated for. *Atypical antipsychotic* has become a "buzz word" for agents that, unlike *typical* classical neuroleptics, would effectively treat a broad range of schizophrenic symptoms (both positive and negative) without motor side effects, neuroleptic-induced deficit symptoms, or increased prolactin levels. Some *atypical* criteria include efficacy in patients considered treatment refractory.

Clozapine

Clozapine, the prototypic atypical antipsychotic, comes closest to fulfilling this atypical wish list. Clozapine's superiority to conventional neuroleptics in efficacy has been demonstrated in severely treatment-refractory hospitalized schizophrenic patients[10] and, more recently, in partially treatment-resistant outpatients.[23,24] At least seven open-label prospective studies of clozapine in mostly treatment-resistant/intolerant outpatients have demonstrated improvement in quality of life, reduction in utilization of resources (such as hospitalization), or other improvement in function.[25–31] The longer term open-label trials suggest that an adequate trial may require 3 to 4 months and that response rates may approach 50%, with functional measures lagging behind symptomatic measures.[9]

As with conventional neuroleptics, measuring blood levels may be useful in clozapine patients who have insufficient responses or unexpected toxicity. A putative threshold for effectiveness has been described as > 350 ng/mL[32] and > 420 ng/mL,[33] respectively, by different investigators.

Preliminary evidence suggests possible special efficacy for clozapine in other difficult-to-treat situations including polydipsia and intermittent hyponatremia,[34–37] aggression and hostility,[38–41] schizoaffective patients,[42–45] and tardive dyskinesia.[46–48] The issue of whether clozapine has a specific ameliorative effect on tardive dyskinesia, beyond permitting natural restitutive mechanisms to occur, is unresolved.

Clozapine's availability and tolerability remain limited by the need for weekly blood monitoring for agranulocytosis, and a relatively high incidence of daytime sedation, sialorrhea, weight gain, and dose-dependent seizures. Observations that the frequency curve of agranulocytosis diminishes over time have engendered discussion of possible modifications in the blood monitoring schedule.

Mechanistically, clozapine's low incidence of motor side effects and superiority in treatment of negative symptoms are consistent with electrophysiologic,[49] immunohistochemical,[50] and behavioral evidence for anatomical mesolimbic dopamine system specificity, increased dopaminergic function in the prefrontal cortex,[51] and increase in situationally appropriate approach behavior in mice,[52] respectively. The most commonly cited receptor-binding pattern cited to explain clozapine's unique preclinical and clinical profile is its high ratio of serotonin 5-HT_2 to dopamine D_2 antagonism.[53] This is sometimes referred to as the serotonin-dopamine antagonist hypothesis. Clozapine's blend of dopamine D_4 to dopamine D_2 activity, dopamine D_1 to dopamine D_2 activity, muscarinic,

and serotonin 5-HT_6, 5-HT_3, and 5-HT_7 affinities are less commonly cited.[53] The desire to duplicate the success of clozapine in treatment-refractory schizophrenia with a less toxic side effect profile has inspired development of a veritable cornucopia of new atypical antipsychotics, each with its own unique blend of receptor affinities. In this renaissance of antipsychotic development, the most commonly evoked guiding principle of commonality with clozapine is the serotonin-dopamine antagonist hypothesis.

Risperidone

Risperidone is the first of this new generation of SDA antipsychotics to be available in the United States. Unlike clozapine, it lacks anticholinergic effects, does not appear to cause agranulocytosis, and has been approved by the Food and Drug Administration (FDA) for unrestricted use in schizophrenia. It causes relatively few motor side effects compared with conventional antipsychotics and is effective against both positive and negative schizophrenic symptoms.[54,55] This profile has led to a great deal of optimism over risperidone's potential therapeutic role in treatment-resistant/refractory psychosis. Since 1988, a multiplicity of studies in abstract, letter, or journal format have addressed its lower side effect profile by using retrospective case review, open-label, and single- and double-blind designs.[56–73] At least two of the studies compared clozapine and risperidone in a double-blind format. Klieser et al. (1995)[72] compared two parallel groups of acutely exacerbated schizophrenic patients receiving either 4 to 8 mg/day of risperidone (N = 39) or 400 mg/day of clozapine (N = 20) for 28 days. They found significantly greater reduction in total Brief Psychiatric Rating Scale (BPRS) scores at 3 days with risperidone compared with clozapine, but otherwise no significant differences on the total scores or subscales of the BPRS or the Clinical Global Impressions (CGI). The tolerability of risperidone was classified at endpoint as "very good" by 60% of patients receiving 4 mg/day and by 47% of patients receiving 8 mg/day of risperidone. The tolerability of clozapine was considerably lower.

Bondolfi and colleagues (1995)[71] studied treatment-resistant chronic schizophrenic patients (N = 86) receiving risperidone (mean dose = 6.4 mg/day) or clozapine (mean dose = 291.2 mg/day) for 56 days. They found significantly more risperidone than clozapine patients were responders at Days 7 and 14 on the Positive and Negative Syndrome Scale (PANSS) total score. Otherwise, there were no significant differences in CGI or PANSS scores at endpoint. Patients on clozapine treatment reported more asthenia and lassitude and increased fatigue. Mean increase in body weight was significant in the clozapine group but not the risperidone group.

In a single-blind design, 20 treatment-resistant/intolerant chronic schizophrenic/schizoaffective patients who were stable on clozapine treatment at screening entered a single-blind, randomized order, crossover comparison of 6 weeks on each clozapine and risperidone.[73] No difference emerged in PANSS or CGI (severity of illness subscale) scores after 6 weeks within the trial on each drug. Significantly more sedation and subjective cognitive impairment was reported on clozapine therapy; more restlessness and insomnia on risperidone treatment. Better performance was detected on a test of visual memory on risperidone treatment. Significantly more use of antiparkinsonian medication occurred on risperidone therapy. Significantly higher body weight was measured on clozapine treatment. Rapid transition from clozapine to risperidone produced somatic symptoms consistent with cholinergic rebound and loss of sedation in some patients. There was little rebound psychosis.

Although this body of data is far from complete or conclusive, and many of the abstracts and letters offer only scanty details, when viewed as a body, the 17 presentations provide an overall sense of optimism for risperidone's role in treatment-resistant/intolerant patients. Limited conclusions can be drawn from short-term comparisons between clozapine and risperidone. However, on the whole, the similarities in measures of positive and negative symptoms are encouraging. The data also suggest points of differentiation in side effect profiles that may be relevant in drug assignment, particularly among treatment-intolerant patients.

The manner in which treatment-refractory patients are transitioned between their former antipsychotic and risperidone may play a large role in the success of the endeavor. Many clinicians have observed rebound-like effects when a low-potency antipsychotic with marked anticholinergic and sedative effects is rapidly discontinued. When appropriate, a slow taper and overlap along with adjunctive benzodiazepines and anticholinergic medication may enhance the success of the transition. Anticholinergic rebound symptoms may include nausea, vomiting, anorexia, tremor, agitation, and insomnia and can be difficult to distinguish from psychotic relapse or medication side effects.

Olanzapine

Olanzapine is the most recent SDA antipsychotic with a high degree of selectivity for mesolimbic (A10) over nigrostriatal (A9) dopamine tracts to be approved by the Food and Drug Administration. Empirical studies to establish the efficacy of olanzapine in treatment-resistant schizophrenia are not yet available. There is optimism, however, because compared with other antipsychotics, olanzapine is relatively similar to clozapine in its blend of receptor affinities.[74] Extrapolating the biochemical similarities with clozapine to the clinical realm appears, at least in part, borne out by the effectiveness of olanzapine in both positive and deficit symptoms and a superior motor side effect profile compared with haloperidol.[75,76]

Olanzapine may be initiated at a therapeutic dosage and has minimal effects on blood pressure and the electrocardiogram. Sedation, weight gain, and dizziness were reported by a minority of patients.

Other Atypical Antipsychotics

Sertindole, an SDA antipsychotic that recently received an approvable letter from the FDA, lacks anticholinergic and antihistaminergic effects, has minimal effects on prolactin, and does not produce dose-dependent motor side effects within its recommended dose range.[77–79] Nasal congestion, diminished ejaculatory volume, and prolongation of cardiac repolarization time as measured by the electrocardiogram occur in a minority of patients.[79]

Quetiapine, which also has serotonin-dopamine antagonist properties and lacks strong antimuscarinic affinity, has filed a new drug application with the FDA.[80] A cornucopia of other SDA antipsychotics are in various stages of development, each with points of differentiation in receptor binding that hypothetically could affect specific niches of the treatment-resistant/intolerant population. Ziprasidone, for instance, combines a high ratio of serotonin 5-HT_{2A} to dopamine D_2 affinity with blockade of reuptake of norepinephrine and affinity at the serotonin 5-HT_{1A} receptor.[81] A new drug application for ziprasidone has been filed with the FDA. Knowledge of the relatively strong affinity of clozapine for dopamine D_4 receptors as well as postmortem studies of dopamine D_4 receptors in schizophrenia has led to interest in both specific dopamine D_4 and serotonin 5-HT_{2A}/dopamine D_4 antagonists as potential antipsychotics. There are insufficient data to predict their ultimate utility at this time. However, preliminary clinical trials with a single dose of a relatively specific dopamine D_4 antagonist and a combined dopamine D_4 antagonist/serotonin antagonist, respectively, have not demonstrated efficacy. An investigational trial with a third dopamine D_4 selective agent is underway. In a twist on the serotonin-dopamine hypothesis of atypical antipsychotic treatment, preclinical testing of a specific 5-HT_{2A} antagonist is consistent with an atypical antipsychotic profile.[82,83]

CONCLUSION

Conventional neuroleptic treatment, while profoundly useful, returns few schizophrenic patients to their premorbid level of function. The neurotransmission imbalances that appear to result from apparently altered cerebral development in schizophrenia are apparently too complex to be fully remediated by untargeted dopamine D_2 antagonism, the primary therapeutic activity of the conventional neuroleptic. In the limbic system, the shell region of the nucleus accumbens seems to be an area in which both typical and atypical antipsychotics share activity in modulating dopaminergic activity.[50] It appears that serotonin-dopamine antagonists, by complex feedback interactions among the two neurotransmitter systems, exert relatively selective effects on limbic dopaminergic systems critical to psychosis, with lesser affinity for nigrostriatal, cortical, and tuberoinfundibular dopamine systems associated with typical neuroleptic side effects. Comparative studies of the therapeutic efficacy of atypical antipsychotics in treatment-resistant schizophrenia are in their infancy. Although predictive factors for assigning patients among the atypical agents are likely to remain elusive for efficacy in the near future, side effect profiles may be a more attainable guide for the present. In treatment resistance, reexamination of differential diagnosis, possible comorbidity, and compliance issues are essential. Antipsychotic augmentation strategies such as lithium carbonate may ultimately prove as useful in combination with atypical agents as with conventional neuroleptics. However, additional neurotransmitter interactions will be involved and empirical data to guide practice are currently scanty.

Drug names: carbamazepine (Tegretol and others), clozapine (Clozaril), haloperidol (Haldol), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), sertindole (Serlect).

REFERENCES

1. Meltzer HY. Cost-effectiveness of clozapine treatment. J Clin Psychiatry Monograph: 1996;14(2):16–17
2. Moller HJ, von Zerssen D. Psychopathometric study of the prognostic significance of psychopathologic findings and premorbid personality for discharge of neuroleptic treated patients with schizophrenic psychoses. Nervenarzt 1985;56:498–505
3. Akbarian S, Bunney WE Jr, Potkin SG, et al. Altered distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase cells in frontal lobe of schizophrenics implies disturbances of cortical development. Arch Gen Psychiatry 1993;50:169–177
4. Akbarian S, Vinuela A, Kim JJ, et al. Distorted distribution of nicotinamide adenine dinucleotide phosphate-diaphorase neurons in temporal lobes of schizophrenics implies anomalous cortical development. Arch Gen Psychiatry 1993;50:178–187
5. Altshuler LL, Casanova MF, Goldberg TE, et al. The hippocampus and parahippocampus in schizophrenic, suicide, and control brains. Arch Gen Psychiatry 1990;47:1029–1034
6. Benes FM. Evidence for neurodevelopmental disturbances in anterior cingulate cortex of post-mortem schizophrenic brain. Schizophr Res 1991;5: 187–188
7. Suddath RL, Christison GW, Torey EF, et al. Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. N Engl J Med 1990;322:789–794
8. Daniel DG, Goldberg TE, Gibbons RD, et al. Lack of a bimodal distribution of ventricular size in schizophrenia: a Gaussier mixture analysis of 1056 cases and controls. Biol Psychiatry 1991;30:887–903
9. Umbricht DS, Leiberman Kane JM. The clinical efficacy of clozapine in the treatment of schizophrenia. Rev Contemp Pharmacotherapy 1995;6: 165–186
10. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988;45:789–796
11. Christison GW, Kirch DG, Wyatt RJ. When symptoms persist, choosing among alternative somatic treatments for schizophrenia. Schizophr Bull 17; 2:2217–2245
12. Schulz SC, Buckley PF. Treatment resistant schizophrenia. In: Hirsch SR, Weinberger DR, eds. Schizophrenia. Oxford, England: Blackwell Science Ltd; 1995:469–480
13. Wolkowitz OM, Pickar D. Benzodiazepines in the treatment of schizophrenia: a review and reappraisal. Am J Psychiatry 1991;148:714–726
14. Daniel DG, Linnoilia M, Randolph C, et al. Coadministration of fluvox-

amine increases serum concentrations of haloperidol. J Clin Psychopharmacol 1994;14:340–343
15. Crewe HK, Lennard MS, Tucker GT, et al. The effect of selective serotonin re-uptake inhibitors on cytochrome P4502D6 (CYP2D6) activity in human liver microsomes. Br J Clin Pharmacol 1992;34:262–265
16. Daniel DG, Randolph C, Jaskiw G, et al. Coadministration of fluvoxamine increases serum concentrations of haloperidol. J Clin Psychopharmacol 1994;14:340–343
17. Soubrie P, Reisine TD, Glowinski J. Functional aspects of serotonin transmission in the basal ganglia: a review and an in vivo approach using the push-pull cannula technique. Neuroscience 1984;13:605–625
18. Saller CF, Czupryna MJ, Salama AI. 5-HT_2 receptor blockade by ICI 169,369 and other 5-HT_2 antagonists modulates the effects of D_2 dopamine receptor blockade. J Pharmacol Exp Ther 1990;253:1162–1170
19. Daniel DG, Weinberger DR, Jones DW, et al. The effect of amphetamine on regional cerebral blood flow during cognitive activation in schizophrenia. J Neurosci 1991;11:1907–1917
20. Daniel DG, Berman KF, Weinberger DR. The effect of apomorphine on regional cerebral blood flow in schizophrenia. J Neuropsychiatry Clin Neurosci 1989;1:377–384
21. Golberg TE, Bigelow LB, Weinberger DR, et al. Cognitive and behavioral effects of the coadministration of dextroamphetamine and haloperidol in schizophrenia. Am J Psychiatry 1991;148:78–84
22. Darby JK, Pasta DJ, Dabiri L, et al. Haloperidol dose and blood level variability: toxicity and interindividual variability in the nonresponder patient in the clinical practice setting. J Clin Psychopharmacol 15;5:334–340
23. Breier A, Buchanan RW, Kirkpatrick B, et al. Effects of clozapine on positive and negative symptoms in outpatients with schizophrenia. Am J Psychiatry 1994;151:20–26
24. Schooler N, Cain J, Marter J, et al. Efficacy of clozapine versus haloperidol in a long term clinical trial: preliminary findings. In: Abstracts of the 33rd Annual Meeting of American College of Neuropsychopharmacology; Dec 11–16, 1994; San Juan, Puerto Rico. Abstract 223
25. Owen RR, Beake BJ, Marby D, et al. Response to clozapine in chronic psychotic patients. Psychopharmacol Bull 1989;25:253–256
26. Meltzer HJ. Dimensions of outcome with clozapine. Br J Psychiatry 1992; 160(suppl 17):46–53
27. Breier A, Buchanan RW, Irish D, et al. Clozapine treatment of outpatients with schizophrenia: outcome and long-term response patterns. Hosp Community Psychiatry 1993;44:1145–1149
28. Clozapine Study Group. The safety and efficacy of clozapine in severe treatment resistant schizophrenic patients in the UK. Br J Psychiatry 1993; 163:150–154
29. Jalenques I, Coudert AJ. A new therapeutic approach to drug-resistant schizophrenic patients: clozapine. Long term prospective study in 16 patients. Acta Psychiatr Belg 1992;92:323–338
30. Lieberman JA, Safferman AZ, Pollack S, et al. Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome. Am J Psychiatry 1994;151:1744–1752
31. Kane J, Schooler N, Marder S. A six month comparison of clozapine and haloperidol. In: Scientific Abstracts of the 35th Annual Meeting of the American College of Neuropsychopharmacology; Dec 9–13, 1996; San Juan, Puerto Rico. Abstract 65
32. Miller DD, Fleming F, Holman TL, et al. Plasma clozapine concentrations as a predictor of clinical response: a follow-up study. J Clin Psychiatry 1994;55(9, suppl B):117–121
33. Potkin SG, Bera R, Gulasekaram B, et al. Plasma clozapine concentrations predict clinical response in treatment-resistant schizophrenia. J Clin Psychiatry 1994;55(9, suppl B):133–136
34. Lee HS, Kwon KY, Alphs LD, et al. Effect of clozapine on psychogenic polydipsia in chronic schizophrenia [letter]. J Clin Psychopharmacol 1991; 11:222–223
35. Munn NA. Resolution of polydipsia and hyponatremia in schizophrenic patients after clozapine treatment [letter]. J Clin Psychiatry 1993;54: 439–440
36. Henderson DC, Goff DC. Clozapine for polydipsia and hypernatremia in chronic schizophrenia. Biol Psychiatry l994;36:768–770
37. Leadbetter RA, Shutty MS Jr. Differential effects of neuroleptics and clozapine on polydipsia and intermittent hyponatremia. J Clin Psychiatry 1994; 55:(9, suppl B):l10–113
38. Mallya AR, Roos PD, Roebuck-Colgan K. Restraint, seclusion, and clozapine. J Clin Psychiatry 1992;53:395–397
39. Volavka J, Zito JM, Vitrai J, et al. Clozapine effects on hostility and aggression in schizophrenia. J Clin Psychopharmacol 1993;13:287–289
40. Ratey JJ, Leveroni C, Kilmer D, et al. The effects of clozapine on severely aggressive psychiatric inpatients in a state hospital. J Clin Psychiatry 1993; 54:219–223
41. Breier A, Buchanan RW, Kirkpatrick B, et al. Effects of clozapine on positive and negative symptoms in outpatients with schizophrenia. Am J Psychiatry 1994;151:20–26
42. Owen RR Jr, Beake BJ, Marby D, et al. Response to clozapine in chronic psychotic patients. Psychopharmacol Bull 1989;25:253–256
43. Naber P, Hippius H. The European experience with the use of clozapine. Hosp Community Psychiatry 1990;41:886–890
44. McElroy SL, Dessain EC, Pope HG, et al. Clozapine in the treatment of psychotic mood disorders, schizoaffective disorder, and schizophrenia. J Clin Psychiatry 1991;52:411–414
45. Banov MD, Zarate CA Jr, Tohen M, et al. Clozapine therapy in refractory affective disorders: polarity predicts response in long-term follow-up. J Clin Psychiatry 1994;55:295–300
46. Leiberman JA, Saltz BL, Johns CA, et al. The effects of clozapine on tardive dyskinesia. Br J Psychiatry 1991;158:503–510
47. Tamminga CA, Thaker GK, Moran M, et al. Clozapine in tardive dyskinesia: observations from human and animal model studies. J Clin Psychiatry 1994;55(9, suppl B):102–106
48. Tamminga CA, Thaker GK, Moran M, et al. Clozapine in tardive dyskinesia: observations from human and animal model studies. J Clin Psychiatry 1994;55(9, suppl B):102–106
49. Gardner EL, Chen J, Paredes W. Clozapine produces potent antidopaminergic effects anatomically specific to the mesolimbic system. J Clin Psychiatry 1994;55(9, suppl B):15–22
50. Fibiger HC. Neuroanatomical targets of neuroleptic drugs as revealed by Fos immunochemistry. J Clin Psychiatry 1994;55(9, suppl B):33–36
51. Moghaddam B. Preferential activation of cortical dopamine neurotransmission by clozapine: functional significance. J Clin Psychiatry 1994;55(9, suppl B):27–29
52. Dixon AK, Huber C, Lowe DA. Clozapine promotes approach-oriented behavior in male mice. J Clin Psychiatry 1994;55(9, suppl B):4–7
53. Meltzer HY. An overview of the mechanism of action of clozapine. J Clin Psychiatry 1994;55(9, suppl B):47–52
54. Chouinard G, Vainer JL, Belanger MC, et al. Risperidone and clozapine in the treatment of drug-resistant schizophrenia and neuroleptic-induced supersensitivity psychosis. Prog Neuropsychopharmacol Biol Psychiatry 1994;18:1129–1141
55. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994;151:825–835
56. Abuzzahab FS, Gillard JM. Clozapine and risperidone in schizophrenia. In: Scientific Abstracts of the 33rd Annual Meeting of the American College of Neuropsychopharmacology; Dec 12–16, 1994; San Juan, Puerto Rico. Abstract 225
57. Roose K, Gelders Y, Heylen S. Risperidone (R64 766) in psychotic patients: a first clinical therapeutic exploration. Acta Psych Belg 1988;88: 233–241
58. Bressa GM, Bersani G, Meco G, et al. One year follow-up study with risperidone in chronic schizophrenia. New Trends in Experimental and Clinical Psychiatry 1991;7(4):169–177
59. Small JG, Miller MJ, Klapper MH, et al. Risperidone versus clozapine in resistant schizophrenia. In: Programs and Abstracts of the 146th Annual Meeting of the American Psychiatric Association; May 27, 1993; San Francisco, Calif. Abstract NR724:241
60. Chouinard G, Vainer JL, Belanger MC, et al. Risperidone and clozapine in the treatment of drug-resistant schizophrenia and neuroleptic-induced supersensitivity psychosis. Prog Neuropsychopharmacol Biol Psychiatry 1994;18:1129–1141
61. Kronig MH, Loebel AD, et al. Risperidone in treatment-resistant schizophrenia and schizoaffective patients. In: Syllabus of the APA 46th (1994) Institute of Hospital and Community Psychiatry; Sept 30–Oct 4, 1994; San Diego, Calif. Abstract 72
62. Evans EG. Risperidone in institutionalized psychotic patients unresponsive to conventional antipsychotic agents. In: New Research Program and Abstracts of the 148th Annual Meeting of the American Psychiatric Association; May 24, 1995; Miami, Fla. Abstract NR491:187
63. Cavallero R, Colombo C, Smeraldi E. A pilot, open study on the treatment of refractory schizophrenia with risperidone and clozapine. Human Psychopharmacology 1995;10:231–243
64. Ibrahim ZY, Buckley PJ, Donenwirth K, et al. Risperidone treatment of

schizophrenia in a state hospital. In: New Research Program and Abstracts of the 148th Annual Meeting of the American Psychiatric Association; May 23, 1995; Miami, Fla. Abstract NR9:56
65. Lindenmayer J-P, Vital-Herne M, Simon FS, et al. Use of risperidone in neuroleptic refractory schizophrenics in a state psychiatric center. In: New Research Program and Abstracts of the 148th Annual Meeting of the American Psychiatric Association; May 23, 1995; Miami, Fla. Abstract NR208:112
66. Raza A, Ettinger T, Sharif ZA, et al. A comparison of the efficacy of clozapine and risperidone in treatment refractory schizophrenia. In: New Research Program and Abstracts of the 148th Annual Meeting of the American Psychiatric Association; May 23, 1995; Miami, Fla. Abstract NR228: 117
67. Horne RL, Miller F. Outcome in schizophrenic patients switched from clozapine to risperidone. In: New Research Program and Abstracts of the 148th Annual Meeting of the American Psychiatric Association; May 24, 1995; Miami, Fla. Abstract NR447:175
68. Tanner TB, Ganguli R, Reddy R, et al. Risperidone for treatment-refractory schizophrenia [letter]. Am J Psychiatry 1995;152:l233
69. Lacey RL, Preskorn SH, Jerkovich GS. Is risperidone a substitute for clozapine for patients who do not respond to neuroleptics [letter]? Am J Psychiatry 1995;152:1401
70. Bacher NM, Kaup BA. Combining risperidone with standard neuroleptics for refractory schizophrenic patients [letter]. Am J Psych 1996;153:137
71. Bondolfi G, Bauman P, Patris M, et al. A randomized double-blind trial of risperidone versus clozapine for treatment-resistant chronic schizophrenia. In: New Research Program and Abstracts of the 148th Annual Meeting of the American Psychiatric Association; May 24, 1995; Miami, Fla. Abstract NR485:185
72. Klieser E, Lehmann E, Kinzler E, et al. Randomized, double-blind, controlled trial of risperidone versus clozapine in patients with chronic schizophrenia. J Clin Psychopharmacol 1995;15(suppl 1):45S–51S
73. Daniel DG, Goldberg TE, Weinberger DR, et al. Different side effect profiles of risperidone and clozapine in 20 outpatients with schizophrenia or schizoaffective disorder: a pilot study. Am J Psychiatry 1996;153:417–419
74. Bymaster FP, Calligaro DO, Falcone JF, et al. Radioreceptor binding profile of the atypical antipsychotic olanzapine. Neuropsychopharmacology 1996;14:87–96
75. Beasley CM, Tollefson G, Tran P, et al. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology 1996;14:111–123
76. Tollefson GD, Beasley CM, Tran PV, et al. Olanzapine versus haloperidol: results of the multicenter, international trial. Schizophr Res 1996;18:131
77. Hyttel J, Nielsen JB, Nowak G. The acute effect of sertindole on brain 5-HT-2, D-2, and alpha-1 receptors (ex vivo radioreceptor binding studies). J Neural Transm 1991;89:61–69
78. Van Kammen DP, McEvoy JP, Targum SD, et al. A randomized, controlled, dose-ranging trial of sertindole in patients with schizophrenia. Psychopharmacology (Berl) 1996;124:168–175
79. Schulz SC, Mack R, Zborowski J, et al. Efficacy, safety, and dose response of three doses of sertindole in schizophrenia patients. Schizophr Res 1996; 18:133
80. Saller CF, Salama AI. Seroquel: biochemical profile of a potential atypical antipsychotic. Psychopharmacology (Berl) 1993;112:285–292
81. Seeger TF, Seymour PA, Schmidt AW, et al. Ziprasidone (CP-88, 059): a new antipsychotic with combined dopamine and serotonin receptor antagonist activity. J Pharmacol Exp Ther 1995;275:101–113
82. Sorensen SM, Kehne JH, Fadayel GM, et al. Characterization of the 5-HT2 receptor antagonist MDL 100907 as a putatative atypical antipsychotic: behavioral, electrophysiological and neurochemical studies. J Pharmacol Exp Ther 1993;266:684–691
83. Schmidt CJ, Fadayel GM, Sullivan CK, et al. 5-HT2 receptors exert a state-dependent regulation of dopaminergic function: studies with MDL 100.907 and the amphetamine analogue, 3,4-methylenedioxymethamphetamine. Eur J Pharmacol 1992;223:65–74