Adverse Effects of the Atypical Antipsychotics

Collaborative Working Group on Clinical Trial Evaluations

Adverse effects of antipsychotics often lead to noncompliance. Thus, clinicians should address patients' concerns about adverse effects and attempt to choose medications that will improve their patients' quality of life as well as overall health. The side effect profiles of the atypical antipsychotics are more advantageous than those of the conventional neuroleptics. Conventional agents are associated with unwanted central nervous system effects, including extrapyramidal symptoms (EPS), tardive dyskinesia, sedation, and possible impairment of some cognitive measures, as well as cardiac effects, orthostatic hypotension, hepatic changes, anticholinergic side effects, sexual dysfunction, and weight gain. The newer atypical agents have a lower risk of EPS, but are associated in varying degrees with sedation, cardiovascular effects, anticholinergic effects, weight gain, sexual dysfunction, hepatic effects, lowered seizure threshold (primarily clozapine), and agranulocytosis (clozapine only). Since the incidence and severity of specific adverse effects differ among the various atypicals, the clinician should carefully consider which side effects are most likely to lead to the individual's dissatisfaction and noncompliance before choosing an antipsychotic for a particular patient.

(J Clin Psychiatry 1998;59[suppl 12]:17–22)

Adverse effects are important considerations when selecting a drug for a patient. Because most antipsychotics have similar efficacy, a particular side effect may be the deciding factor in the selection of a drug. For this reason, formularies for health networks should be encouraged to approve more than one drug for each diagnosis. Clinicians need the option to choose, for example, an antipsychotic drug suitable for a patient who is worried about weight gain, for a patient who is extremely sensitive to extrapyramidal symptoms (EPS), or for a patient with severe menstrual problems. Virtually all patients with schizophrenia are required to take medication indefinitely to prevent relapse. Therefore, clinicians must address patients' concerns about adverse effects in order to increase compliance. This is an essential part of the effort to improve the quality of life and general health of patients with schizophrenia. Since health problems and personal concerns, such as a heart condition or concern about weight gain, vary among patients, one antipsychotic drug cannot be recommended as the first-line treatment for all patients on the basis of side effects. However, it is important to carefully consider which adverse effects are most likely to lead to a given patient's dissatisfaction and noncompliance.

Examining adverse effects as reported in clinical trials must be approached with caution, however. Different trials may use different terms for adverse effects as well as different methods of assessing them (e.g., patient report vs. investigator questioning). Comparing rates of adverse events between studies is not appropriate because of these differences as well as possible variations in patient populations, study methods, and other variables.

The conventional antipsychotics have unwanted central nervous system effects, particularly EPS and tardive dyskinesia (for more information, see the article[1] in this Supplement about tardive dyskinesia and EPS), sedation, and the potential to impair cognitive function. Other adverse effects of the traditional neuroleptics include cardiac effects, orthostatic hypotension, hepatic effects, anticholinergic side effects, sexual dysfunction, and weight gain. For the conventional agents, the milligram potency is highly correlated with the type of side effects. High-milligram, low-potency agents such as chlorpromazine and thioridazine, which have weak activity at dopamine receptors and strong activity at anticholinergic sites,[2] produce fewer EPS but more anticholinergic side effects, sedation, and hypotension.[3] Low-milligram, high-potency entities such as fluphenazine and haloperidol cause more EPS but fewer anticholinergic effects. Haloperidol is primarily a D_2 antagonist but also has some D_1 and α_1-adrenergic effects. Clozapine has strong anticholinergic effects, but risperidone lacks anticholinergic effects.

Clinical trials data can be used to compare side effects among the different atypicals and between the atypicals

Presented at the closed symposium "Clinical Trial Evaluations and Outcome Measures in Psychiatry" held on November 21, 1997, in Chicago, Illinois, and supported by an unrestricted educational grant from Janssen Pharmaceutica.

A complete list of the collaborators in the Collaborative Working Group on Clinical Trial Evaluations appears at the end of this article.

Reprint requests to: Herbert Y. Meltzer, M.D., Department of Psychiatry, Vanderbilt University School of Medicine, 1601 23rd Avenue South, Suite 306, Nashville, TN 37212.

and the conventional drugs. The newer atypicals have a lower incidence of EPS and tardive dyskinesia than the conventionals[4–12] but are associated in varying degrees with sedation, cardiovascular effects, anticholinergic effects, weight gain, sexual dysfunction, hepatic effects, lowered seizure threshold (primarily clozapine), and agranulocytosis, as well as effects related to drug interactions.[13] The oldest atypical antipsychotic, clozapine, causes not only hypotension, sedation, and weight gain but also the more serious effects of seizures and agranulocytosis.[14] Clozapine has preferential antagonist activity at 5-HT_2 receptors, some activity at α-adrenergic, muscarinic cholinergic, and histaminic receptors, and relatively slight activity at dopamine D_1 and D_2 receptors, although clozapine also affects other receptor sites.[15,16] Risperidone is mainly a combined D_2 and 5-HT_2 antagonist, and the antagonist activity at the 5-HT_2 site may be the reason for fewer EPS.[15,17] Clinical trials have shown that risperidone causes fewer extrapyramidal symptoms but higher prolactin elevation than typical antipsychotics. Olanzapine, like clozapine, blocks multiple receptor subtypes, with similar activity at 5-HT_2, muscarinic cholinergic, histaminic, α-adrenergic, and dopamine D_1 and D_2 receptors.[18] Quetiapine mainly acts at histaminic and α_1- and α_2-adrenergic receptors.[19] The newest antipsychotic, ziprasidone, which has not been released yet, is mainly a 5-HT_{2A} and 5-HT_{1D} antagonist with strong 5-HT_{1A} agonist properties.[20] This article will review the adverse effects, other than EPS and tardive dyskinesia, of the atypical antipsychotics for which published clinical trials data are available—clozapine, risperidone, olanzapine, and quetiapine (Table 1).[21]

Table 1. Side Effects/Activity of Antipsychotic Agents*

Effects/Activity	Typical Neuroleptics	Clozapine	Risperidone	Olanzapine	Quetiapine
Central nervous system					
Seizures	0	+ to +++	0	+	0
Sedation	+ to +++	+++	0	+	+ to ++
Other					
Cardiovascular effects[a]	+ to ++	+++	+	0 to +	+
Liver transaminase increase	+	+	+	0 to +	0 to +
Anticholinergic	+ to +++	+++	0	+++	0 to ++
Antihistiminic	+	+	0	0	++
Agranulocytosis	0	+++	0	0	0
Prolactin increase	+++	0	+ to +++	0[b]	0
Decreased ejaculatory volume	+	0	0	0	0
Weight gain	+	+++	+	++	+

*Adapted from reference 21. Symbols: 0 = none or not significantly different from placebo; + = mild; ++ = moderate; +++ = marked.
[a]Orthostatic hypotension and prolongation of the QTc interval.
[b]Dose-related increases within the normal range.

ADVERSE CNS EFFECTS

Seizures

Seizures are commonly believed to be caused by neuroleptics, but the studies that suggested this were not well-controlled. Clozapine is associated with a dose-related increase in risk for seizures: doses of clozapine lower than 300 mg/day have a seizure rate of about 1%, between 300 and 600 mg/day have a rate of 2.7%, and above 600 mg/day have a rate of 4.4%.[22] Severe myoclonus may be a forerunner of major motor seizures during clozapine treatment. Adding valproic acid seems to make possible the continuation of clozapine treatment in most patients who develop myoclonus.[23] During premarketing testing, seizures occurred in 22 (0.9%) of 2500 olanzapine-treated patients.[24] Seizures occurred during premarketing testing in 18 (0.8%) of 2387 quetiapine-treated patients and 9 (0.3%) of 2607 risperidone-treated patients.[24] The *Physicians' Desk Reference*[24] and package inserts suggest that atypical antipsychotics should be used with caution in patients with a history of seizures or with conditions such as Alzheimer's disease that potentially lower the seizure threshold.

Sedation

Conventional neuroleptics (especially low-potency agents) are sedating, particularly at high doses, which can be problematic in long-term treatment because of sedation and impaired function.[21] The sedative effects of clozapine can be dose-limiting and may cause some patients to become noncompliant.[14] With the newer atypicals, sedation is seldom problematic in the long-term. In the North American trial of olanzapine, somnolence occurred in 39% of 69 patients taking 15 ± 2.5 mg/day of olanzapine.[25] In a head-to-head study of risperidone and clozapine, clozapine produced more sedation than risperidone.[26] Only when titrated up rapidly is risperidone sedating; the sedation is transient, and only 3% of patients reported somnolence at the optimal dosage of 6 mg/day in a large clinical study.[7]

OTHER ADVERSE EFFECTS

Cardiovascular Effects

Orthostatic hypotension. Any conventional or atypical neuroleptic can cause orthostatic hypotension, the most common cardiovascular side effect.[21] Orthostatic hypotension is correlated with the antagonistic effects of antipsychotics at α_1-adrenergic receptors and is more likely with the high-milligram, low-potency agents[3] such as clozapine, chlorpromazine, and thioridazine and with rapid titration of olanzapine and risperidone. Orthostatic hypotension is of special concern in the elderly, but is usually manageable with careful dose adjustment, and patients frequently become partially or fully tolerant to it.[3]

Of the atypicals, clozapine is most often associated with orthostatic hypotension. The atypical that causes the second highest frequency of orthostatic hypotension is quetia-

pine.[27] Risperidone has shown evidence of hypotension in some patients. Olanzapine and ziprasidone are probably less likely to cause hypotension. In the case of ziprasidone, an intramuscular form of the drug that can be given when oral medication is not acceptable will be available.

Prolongation of the QT interval. Other cardiac effects due to antipsychotic drugs that a patient might experience include tachycardia, arrhythmias, and changes in the electrical conduction of the myocardium. Prolongation of the QT interval, which is sometimes presented as QTc (correction of the QT in relation to heart rate), is the conduction effect most often discussed. It probably occurs because of alternation of ion channels in the myocardium.[28,29] Three short-term double-blind studies and 7 long-term studies of risperidone showed that the QTc changes were negative or minimally positive.[30] No patients in trials of risperidone have had QTc levels above 500, which would be a risk factor for torsade de pointes.[31] In a large study of 3000 patients taking risperidone, no QTc difference from placebo or haloperidol was found.[30] Sertindole recently was withdrawn from application to join the roster of U.S. antipsychotics available, due to the fact that QTc prolongation was higher with it than with any of the other atypicals.

Anticholinergic Side Effects

Most frequently, anticholinergic/antihistaminic side effects occur in patients taking high-milligram, low-potency antipsychotics. These side effects include dry mouth, blurred vision, urinary hesitation, constipation, learning and memory impairment, confusion, and delirium. Some of the atypical antipsychotics are associated with anticholinergic effects.[32] For example, clozapine has a highly anticholinergic receptor-binding profile, and clozapine induces constipation in some patients, but some patients taking clozapine also experience increased salivation, which may be due to M_4 agonism. Clozapine can also cause acetylcholine release.[33] Risperidone, quetiapine, and ziprasidone have low levels of anticholinergic activity.[34,35] Olanzapine has few anticholinergic effects, although peripheral anticholinergic activity is often associated with it. Olanzapine may have more complex muscarinic-receptor activity than is now understood.[21] Quetiapine lacks strong antimuscarinic affinity but has significant antihistaminic effects.[36]

Weight Gain

When chlorpromazine was introduced, most patients who took it gained substantial amounts of weight, and this problem has continued with all the antipsychotic compounds in varying degrees. Patients often become noncompliant due to weight gain. Clozapine can cause substantial weight gain, and clozapine and olanzapine appear to cause the most weight gain among the atypical agents. Weight gain is likely to occur in patients taking risperidone,[7,8] olanzapine,[31] sertindole,[37] and quetiapine,[27] but the problem is clinically significant with clozapine.[21] Weight gain may be the most troublesome problem caused by olanzapine.[31] One study[4] showed that 40% of patients taking olanzapine gained 7% or more of their body weight, compared with 12.4% of those taking haloperidol and 3.1% taking placebo. Patients in clinical trials of quetiapine[27] gained, on average, about 2 to 8 lbs (1–4 kg) during the first 6 to 8 weeks of treatment, and some patients continued to gain weight before stabilizing.

Weight gain is a major public health issue in people with and without schizophrenia. Clinicians must attempt to manage the weight of patients with schizophrenia just as they would manage any other health or quality of life issue, such as smoking or sexual dysfunction. In addition, weight gain should certainly be considered when selecting a drug for any patient who is worried about it. Advice from the clinician about the potential risk and appropriate recommendations about diet and exercise are essential. If a patient who was not underweight at baseline begins gaining substantial weight, switching to an agent other than olanzapine or clozapine may be advisable because of the unhealthy consequences of weight gain.

Sexual Dysfunction

Sexual dysfunction is another side effect that should be considered when selecting a drug for a patient with schizophrenia.[38] Sexual dysfunction may precede antipsychotic treatment; Friedman and Harrison[39] found that 60% of women with schizophrenia had never experienced an orgasm. Aizenberg et al.[40] reported that libido was diminished in untreated patients with schizophrenia and returned with treatment, although erection and orgasm problems developed with treatment. Changes in sexual functioning are supposed to be related to increases in prolactin levels caused by the antipsychotics. These changes include galactorrhea and breast soreness, ejaculatory latency, and lessened lubrication and intensity of climax, as well as changes in menstrual function.[34]

All traditional antipsychotics have been associated with sexual dysfunction, with thioridazine the most problematic (causing retrograde ejaculation).[3] Clozapine has produced an increase in libido and the return of menstrual function, resulting in a fair number of pregnancies; thus, patients starting clozapine treatment should be alerted about potential pregnancy. The increased libido may be related to improvement in negative symptoms and improved fertility. Clozapine (in the standard dose range) and quetiapine do not increase prolactin levels above the upper limits of normal.[9,41] Ejaculatory dysfunction has not been reported for clozapine, risperidone, or olanzapine, and has not been specifically evaluated with quetiapine.[21]

Risperidone is unique among the atypicals in that it produces apparently dose-related increases in prolactin levels equivalent to or perhaps higher than those of the typical neuroleptics. It is still unclear whether this translates into hyperprolactinemic side effects. Only a few patients dis-

continue treatment because of breast tenderness, menstrual irregularities, or galactorrhea.[21] Data presented at the 1997 meeting of the American Psychiatric Association[42] showed that prolactin increase in men and women is dose-related with risperidone and haloperidol. Among women, the risperidone dose was not correlated with adverse events, nor were the adverse events correlated with endpoint prolactin levels. Furthermore, adverse events in men were unrelated to plasma prolactin levels, and the number of adverse events that occurred with 4 to 10 mg/day of risperidone was not significantly higher than with placebo. The olanzapine versus risperidone study[31] showed no increased prevalence of amenorrhea, galactorrhea, or gynecomastia with risperidone, even though the risperidone group had a higher prolactin elevation than the olanzapine group.

Patients are reluctant to spontaneously report sexual problems unless they are asked about function and satisfaction by the clinician. In the past, the sexual side effects of psychotropic drugs have seldom been adequately assessed, but now that physicians routinely question patients about sexual function, sexual dysfunction is emerging as one reason for noncompliance with medication. Studies that have examined noncompliance have suggested that some patients with schizophrenia discontinue their antipsychotic drugs due to sexual side effects either of the antipsychotics themselves or of the anticholinergic medications used to treat EPS caused by the antipsychotics.[3,38,43,44] Clinicians are encouraged to take complete sexual histories from patients at baseline, perhaps even questioning a patient's regular sexual partner about the patient's function if possible. If a patient reports a sexual problem, the dose could be lowered or counseling offered. As the positive and negative symptoms of schizophrenia are resolved, and the initial effects of sedation or weight gain diminish, the patient's sexual functioning should improve.

Hepatic Effects

Serious hepatic effects are unlikely with the atypical antipsychotics. Concern about this side effect dates to the introduction of chlorpromazine, which caused cholestatic jaundice, possibly due to early impurities in the drug.[3] Clozapine causes relatively mild and transient hepatic effects, with 1 case of cholestatic jaundice reported.[3,13,45–47] Mild-to-moderate increases in transaminase enzyme levels are sometimes found in routine laboratory analyses during administration of conventional neuroleptics, clozapine, and olanzapine,[4,48] but cause few patients to discontinue. Alterations in hepatic enzymes have not been reported for risperidone.[49]

Agranulocytosis

With clozapine, agranulocytosis has been a major treatment problem; it can develop quickly (in 1 week). Patients taking this agent must have their blood monitored weekly during the first 6 months of treatment and biweekly thereafter (recently changed from weekly throughout treatment) for a decrease in white blood cells, which raises the cost of treatment. About 0.8% of patients treated with clozapine 4 weeks or longer develop agranulocytosis.[50] Weekly monitoring picks up stepwise decline in many patients who develop agranulocytosis. Granulocyte colony stimulating factors effectively restore stem cells in 2 to 3 weeks. The overall mortality rate due to agranulocytosis is about 1:10,000 because of appropriate monitoring and effective treatment. Agranulocytosis risk may be greater when patients are taking the combination of clozapine and carbamazepine.[51] Patients should not be restarted on clozapine treatment after initial occurrence of symptoms of agranulocytosis, as the symptoms will recur quickly.[51,52] Decreased requirements for monitoring were recently approved by the Food and Drug Administration because most cases of agranulocytosis occur within the first 8 to 24 weeks,[53,54] notwithstanding the occasional outliers in which it has developed after several years of treatment.

No similar hematologic liability exists with risperidone, olanzapine, or quetiapine.[9,49,55] However, recovery from clozapine-induced depression of granulocytes may be prolonged when a patient is switched to olanzapine. Flynn et al.[56] reported that recovery of granulocyte levels above 1500 per mm^3 took a mean of 21.0 days (range, 17–24 days) in 3 patients who were changed from clozapine to olanzapine due to decreased granulocyte levels. The mean time to recovery in 12 patients who were not switched to olanzapine was 3.0 days (range, 1–9 days).

Drug Interactions

Understanding drug interactions is facilitated by knowing the mechanism of action of the drugs.[13] Clozapine and olanzapine are metabolized by the cytochrome P450 (CYP) 1A2—and possibly the 3A4—isoenzyme, risperidone by the CYP 2D6 isoenzyme, and quetiapine and ziprasidone by the CYP 3A4. Since clozapine and olanzapine are metabolized by the CYP 1A2 isoenzyme, drugs that inhibit CYP 1A2, such as fluvoxamine, can elevate clozapine or olanzapine levels. Inducers of CYP 1A2, such as cigarette smoke hydrocarbons, or carbamazepine, which induces 3A4, potentially decrease blood levels of olanzapine and clozapine. Fluoxetine or paroxetine potentially elevate blood risperidone levels. Blood quetiapine or ziprasidone levels may be elevated by fluvoxamine, nefazodone, and erythromycin.

The effect of fluvoxamine or of valproic acid on plasma clozapine levels is so dramatic that there have been suggestions of lowering the dose of clozapine in patients taking the combination, although this option may be more risky than it is worth in most cases. When a patient taking clozapine exhibits myoclonus, which is a precursor of a major motor seizure, valproic acid can prevent further development of the seizure and at the same time raise plasma clozapine levels about 30% to 35%, with some mood-

stabilizing effect. However, it is best generally to simply adjust the dose of the primary medication, because otherwise the clinician must measure blood levels repeatedly. It is clinically useful for the blood clozapine level to be above 350 ng/mL in patients who have not responded to lower levels, although many patients do respond at much lower levels. Another combination to avoid is clozapine and carbamazepine because of the increased risk for agranulocytosis.[51,57]

CONCLUSION

In the past, adverse effects were sometimes viewed as unimportant considerations in the context of the "greater good"—the reduction of positive symptoms—that the conventional antipsychotic drugs produced. But in this decade, as the atypicals have appeared on the market one by one, efficacy has become more readily taken for granted (i.e., if 1 drug does not help a patient, another most likely will), and patients and their physicians have been allowed to fine-tune their treatment program by selecting drugs that offer an improved quality of life over that of the conventionals. Because patients with schizophrenia often remain on maintenance therapy throughout their lives, it is important that they be able to take drugs that are suited to their own health or personal needs.

In summary, all the atypical antipsychotics cause fewer EPS and may have a lower risk of tardive dyskinesia than the conventional antipsychotics, but have similar efficacy in treating schizophrenia. Besides EPS and tardive dyskinesia, the adverse effects to be aware of with atypical drugs are the following (listed with the drug[s] most likely to cause them):

- seizures—clozapine
- sedation—clozapine, quetiapine, olanzapine
- orthostatic hypotension—clozapine, quetiapine; olanzapine and risperidone (if rapidly titrated)
- anticholinergic effects—clozapine, olanzapine
- weight gain—clozapine, olanzapine
- prolactin increases—risperidone
- hepatic changes—clozapine, risperidone
- agranulocytosis—clozapine

Finally, drug interactions can be dangerous or fatal and should be avoided. Patients' individual concerns and health needs must be taken into account when selecting a drug, and adverse effect profiles of drugs or drug interactions can have much to do with whether the drug is discontinued. Since the atypical agents have fewer adverse effects than the conventional antipsychotics, the atypicals would be better first-line drugs for patients with specific health concerns.

Drug names: carbamazepine (Tegretol, Atretol, and others), chlorpromazine (Thorazine and generic brands), clozapine (Clozaril), erythromycin (E-mycin, Ery-Tab, and others), fluoxetine (Prozac), fluphenazine (Prolixin and generic brands), fluvoxamine (Luvox), haloperidol (Haldol and generic brands), nefazodone (Serzone), olanzapine (Zyprexa), paroxetine (Paxil), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril and generic brands), valproic acid (Depakene and generic brands).

REFERENCES

1. Collaborative Working Group on Clinical Trial Evaluations. Assessment of EPS and tardive dyskinesia in clinical trials. J Clin Psychiatry 1998; (suppl 12):23–27
2. Snyder S, Greenberg D, Yamamura H. Antischizophrenic drugs and brain cholinergic receptors. Arch Gen Psychiatry 1974;31:58–61
3. Hansen TE, Casey DE, Hoffman WF. Neuroleptic intolerance. Schizophr Bull 1997;23:567–582
4. Beasley CM Jr, Tollefson GD, Tran PV. Safety of olanzapine. J Clin Psychiatry 1997;58(suppl 10):13–17
5. Chouinard G. Effects of risperidone in tardive dyskinesia: an analysis of the Canadian multicenter risperidone study. J Clin Psychopharmacol 1995;15 (suppl 1):36S–44S
6. Chouinard G, Jones B, Remington G, et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J Clin Psychopharmacol 1993; 13:25–40
7. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994;151:825–835
8. Peuskens J and the Risperidone Study Group. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. Br J Psychiatry 1995;166:712–726
9. Small JG, Hirsch SR, Arvanitis LA, et al. Quetiapine in patients with schizophrenia: a high- and low-dose double-blind comparison with placebo. Arch Gen Psychiatry 1997;54:549–557
10. Tollefson GD, Beasley CM Jr, Tamura RN, et al. Blind, controlled, long-term study of the comparative incidence of treatment-emergent tardive dyskinesia with olanzapine or haloperidol. Am J Psychiatry 1997;154: 1248–1254
11. Tran PV, Dellva MA, Tollefson GD, et al. Extrapyramidal symptoms and tolerability of olanzapine versus haloperidol in the acute treatment of schizophrenia. J Clin Psychiatry 1997;58:205–211
12. Zimbroff DL, Kane JM, Tamminga CA, et al. Controlled, dose-response study of sertindole and haloperidol in the treatment of schizophrenia. Am J Psychiatry 1997;154:782–791
13. Jibson MD, Tandon R. The newer atypical antipsychotics. J Psychiatr Res. In press
14. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine/benztropine. Arch Gen Psychiatry 1988;45:789–796
15. Meltzer HY, Matsubara S, Lee JC. Classification of typical and atypical antipsychotic drugs on the basis of dopamine $D\text{-}_1$, $D\text{-}_2$ and $serotonin_2$ pKi values. J Pharmacol Exp Ther 1989;251:238–246
16. Van Tol HH, Bunzow JR, Guan HC, et al. Cloning of the gene for a human dopamine D_4 receptor with high affinity for the antipsychotic clozapine. Nature 1991;350:610–614
17. Leysen JE, Janssen PM, Schotte A, et al. Interaction of antipsychotic drugs with neurotransmitter receptor sites in vitro and in vivo in relation to pharmacological and clinical effects: role of $5\text{-}HT_2$ receptors. Psychopharmacology (Berl) 1993;112(suppl 1):S40–S54
18. Moore NA, Calligaro DO, Wong TD, et al. The pharmacology of olanzapine and other new antipsychotic agents. Curr Opin Invest Drugs 1993;2: 281–293
19. Saller CF, Salama AI. Seroquel: biochemical profile of a potential atypical antipsychotic. Psychopharmacology (Berl) 1993;112:285–292
20. 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
21. Casey DE. The relationship of pharmacology to side effects. J Clin Psychiatry 1997;58(suppl 10):55–62
22. Devinsky O, Honigfeld G, Patin J. Clozapine-related seizures. Neurology 1991;41:369–371
23. Meltzer HY, Ranjan R. Valproic acid treatment of clozapine-induced myoclonus [letter]. Am J Psychiatry 1994;151:1246–1247

24. Physicians' Desk Reference. Montvale, NJ: Medical Economics; 1998
25. Beasley CM Jr, Tollefson GD, Tran PV, et al. Olanzapine vs placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology 1996;14:111–123
26. 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
27. Borison RL, Arvanitis LA, Miller BG, et al. ICI 204,636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. J Clin Psychopharmacol 1996;16:158–169
28. Hamner MB, Silber C, Driscoll R, et al. Cardiovascular safety of sertindole. In: New Research Program and Abstracts of the 150th Annual Meeting of the American Psychiatric Association; May 21, 1997; San Diego, Calif. Abstract NR 575:223
29. Sramek JJ, Mack RJ, Awni W, et al. Two rapid-dose titrations of sertindole in patients with schizophrenia. J Clin Psychopharmacol 1997;17:419–422
30. Brecher MB, Lemmens P, van Baelen B. Tolerability and cardiovascular safety of risperidone. In: New Research Program and Abstracts of the 150th Annual Meeting of the American Psychiatric Association; May 21, 1997; San Diego, Calif. Abstract NR 612:233
31. Tran PV, Hamilton SH, Kuntz AJ, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol 1997;17:407–418
32. Tandon R. Cholinergic aspects of schizophrenia. Br J Psychiatry. In press.
33. Parada MA, Hernandez L, Puig de Parada M, et al. Selective action of acute systemic clozapine on acetylcholine release in the rat prefrontal cortex by reference to the nucleus accumbens and striatum. J Pharmacol Exp Ther 1997;281:582–588
34. Kane JM, Casey DE, Daniel DG, et al. Antipsychotic agents: minimizing side effects to maximize compliance. J Clin Psychiatry Intercom; October 1, 1996
35. Schotte A, Janssen PF, Gommeren W, et al. Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. Psychopharmacology (Berl) 1996;124:57–73
36. Daniel DG, Whitcomb SR. Treatment of the refractory schizophrenic patient. J Clin Psychiatry 1998;59(suppl 1):13–19
37. van Kammen DP, McEvoy JP, Targum S, et al. A randomized, controlled, dose-ranging trial of sertindole in patients with schizophrenia. Psychopharmacology (Berl) 1996;124:168–175
38. Milner K, Tomori O, Florence T, et al. Psychotropic medications and sexual dysfunction. In: Buckley PF, ed. Sexuality Among Patients With Serious Mental Illness. Washington, DC: American Psychological Association Press; 1998
39. Friedman S, Harrison G. Sexual histories, attitudes, and behavior of schizophrenic and normal women. Arch Sex Behav 1984;14:555–567
40. Aizenberg D, Zemishlany Z, Dorfman-Etrog P, et al. Sexual dysfunction in male schizophrenic patients. J Clin Psychiatry 1995;56:137–141
41. Goldstein JM. Preclinical profile of Seroquel (quetiapine): an atypical antipsychotic with clozapine-like pharmacology. In: Holliday SG, Ancill RJ, MacEwan GW, eds. Schizophrenia: Breaking Down the Barriers. New York, NY: John Wiley & Sons; 1996:177–208
42. Kleinberg D, Brecher MB, Davis JM. Prolactin levels and adverse events in patients treated with risperidone. In: New Research Program and Abstracts of the 150th Annual Meeting of the American Psychiatric Association; May 21, 1997; San Diego, Calif. Abstract NR 599:229
43. Kopala LC. Clinical experience in developing treatment regimens with the novel antipsychotic risperidone. Int Clin Psychopharmacol 1997;12(suppl 4):S11–S18
44. Kopala LC. Spontaneous and drug-induced movement disorders in schizophrenia. Acta Psychiatr Scand Suppl 1996;389:12–17
45. Kirkegaard A, Jensen A. An investigation of some side effects in 47 psychotic patients during treatment with clozapine and discontinuing of the treatment. Arzneimittelforschung 1979;29:851–858
46. Naber D, Leppig M, Grohmann R, et al. Efficacy and adverse effects of clozapine in the treatment of schizophrenia and tardive dyskinesia: a retrospective study of 387 patients. Psychopharmacology (Berl) 1989;99: S73–S76
47. Dorta G, Siebenmann R, Frohli P, et al. Clozapin-induzierter cholestatischer ikterus: ein fallbericht. Z Gastroenterol 1989;27:388–390
48. Gupta S, Masand PS. Olanzapine: review of its pharmacology and indications in clinical practice. Prim Psychiatry 1997;4:73–82
49. Marder SR. Clinical experience with risperidone. J Clin Psychiatry 1996; 57(suppl 9):57–61
50. Kane JM. Schizophrenia. N Engl J Med 1996;334:34–41
51. Gerson SL, Lieberman JA, Friedenberg WR, et al. Polypharmacy in fatal clozapine-associated agranulocytosis [letter]. Lancet 1991;338:262–263
52. Alphs LD, Meltzer HY, Bastani B, et al. Side effects of clozapine and their management. Pharmacopsychiatry 1991;24:46
53. Malhotra AK, Litman RE, Pickar D. Adverse effects of antipsychotic drugs. Drug Saf 1993;9:429–436
54. Alvir JM, Lieberman JA. Agranulocytosis: incidence and risk factors. J Clin Psychiatry 1994;55(9, suppl B):137–138
55. Beasley CM Jr, Hamilton SH, Crawford AM, et al. Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. Eur Neuropsychopharmacol 1997;7:125–137
56. Flynn SW, Altman S, MacEwan GW, et al. Prolongation of clozapine-induced granulocytopenia associated with olanzapine [letter]. J Clin Psychopharmacol 1997;17:494–495
57. Love RC, Levin GM, Richards AL, et al. Current trends in the use of novel antipsychotics. J Clin Psychiatry Intercom; April 1, 1997

THE COLLABORATIVE WORKING GROUP

The Collaborative Working Group on Clinical Trial Evaluations comprises Chair, Herbert Y. Meltzer, M.D., Director, Division of Psychopharmacology, Vanderbilt University School of Medicine, Nashville, Tenn.; Daniel E. Casey, M.D., Psychiatry Service, Veterans Affairs Medical Center, Portland, Ore.; David L. Garver, M.D., Veterans Affairs North Texas Medical Center, Dallas; Louis Lasagna, M.D., Tufts University, Boston, Mass.; Stephen R. Marder, M.D., Psychiatry Service, West Los Angeles Veterans Affairs Medical Center, Los Angeles, Calif.; Prakash S. Masand, M.D., Department of Psychiatry, State University of New York Health Science Center, Syracuse; Del Miller, Pharm.D., M.D., Department of Psychiatry, University of Iowa Hospitals and Clinics, Iowa City; David Pickar, M.D., Intramural Research Program, National Institute of Mental Health, Bethesda, Md.; Rajiv Tandon, M.D., Department of Psychiatry, University of Michigan Medical Center, Ann Arbor.

DISCLOSURE OF OFF-LABEL USAGE

The authors of this article have determined that, to the best of their clinical estimations, no investigational or off-label information about pharmaceutical agents has been presented that is outside Food and Drug Administration–approved labeling.