The Relationship of Pharmacology to Side Effects

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Most traditional neuroleptics have a narrow therapeutic-to-toxic index, and thus, the novel antipsychotics are the result of a search to substantially widen the distance between the dose that treats psychosis and the one that produces adverse effects. In vitro binding profiles have been created for the atypical antipsychotics that have been approved by the U.S. Food and Drug Administration (FDA)—clozapine, olanzapine, and risperidone and those that are under FDA review—quetiapine and sertindole. These profiles, which were compared with that of the typical neuroleptic haloperidol, provide guidance for predicting the adverse effects produced by these drugs. Most conventional antipsychotics have central nervous system effects, particularly extrapyramidal symptoms (EPS) and tardive dyskinesia, sedation, and dulling of cognition. Other adverse effects of the typical antipsychotics include the neuroleptic malignant syndrome, orthostatic hypotension, changes in liver function, anticholinergic and antiadrenergic side effects, sexual dysfunction, and weight gain. The newer agents have a lower incidence of EPS and tardive dyskinesia, while weight gain and changes in blood pressure and liver function tests are adverse effects that have been associated with the use of the newer agents. The favorable side effect profile of these new antipsychotics is likely to make patients more willing to continue treatment, and thus these agents represent a step forward in the treatment of patients with severe, chronic mental illness. *(J Clin Psychiatry 1997;58[suppl 10]:55–62)*

When they were developed in the 1950s, neuroleptic drugs revolutionized the treatment of psychosis. They had a nonnarcotic sedative action, and it became possible to calm patients without relying on barbiturates or other agents that produce heavy sedation and physical dependence. These new antipsychotics treated the excitation, aggression, and restlessness as well as the conceptual disorganization and thought disorders of psychosis. These effects on both behavior and thinking represented a leap forward in the pharmacologic treatment of serious mental illness.

The word *neuroleptic* itself was coined to mean "to take control of the neuron," and indeed these agents affected many different physiologic systems.[1] For almost all patients, difficult-to-manage or intolerable side effects came with the beneficial effects. At the time, the side effect profile of the neuroleptics was termed *neurovegetative*, a descriptor for the full range of autonomic nervous system side effects, and extrapyramidal symptoms (EPS) were recognized as a cardinal feature of these drugs. Eventually, the class of neuroleptic drugs came to include several similar chemical entities that had equivalent efficacy and somewhat different side effect profiles.

No matter what the side effect profile of a specific neuroleptic, the entire class produced EPS. In fact, initially the antipsychotic effects and motor effects of neuroleptic drugs were believed to be inextricably linked. Under the neuroleptic threshold concept, the ideal bioassay for defining the therapeutic antipsychotic dose was to find the dose that produced EPS. When the concept was carefully applied, the neuroleptic dose was titrated until the medication induced subtle EPS. In practice, the dosage was often increased until the EPS became intolerable and induction of toxic—as opposed to subtle—side effects became part of the neuroleptic profile.

Today, we understand that the presence of EPS does not mark the therapeutic antipsychotic dose. However, most traditional neuroleptics have a narrow therapeutic-to-toxic index, which means the separation between the dose that produces efficacy and the one that produces EPS and other adverse effects is narrow (Figure 1).[2] Researchers who developed the novel antipsychotic drugs set out to substantially widen the distance between the dose that treats

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Supported in part by funds from the Veterans Affairs Research Program, National Institute of Mental Health grant MH-36657, and core grant RP00163 from the National Institutes of Health.

Presented at the closed symposium "Practical Issues in Using Olanzapine," held August 1–3, 1996, in Boston, Massachusetts, and made possible by an educational grant from Eli Lilly and Company.

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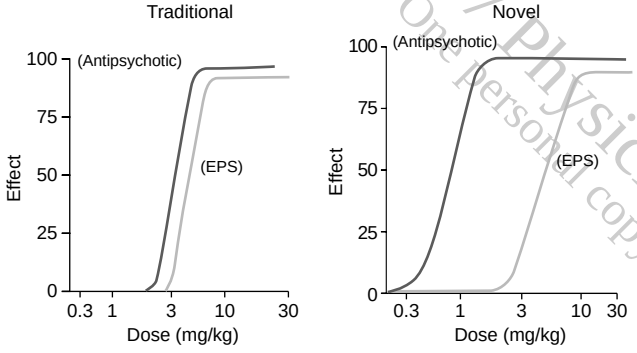
Table 1. Side Effects of Antipsychotic Agents*

Item	Typical Neuroleptics	Clozapine	Risperidone	Olanzapine	Sertindole	Quetiapine
Central nervous system						
EPS	+ to +++	0 to +	+ to +++[a]	0[b]	0[b]	0[b]
Tardive dyskinesia (TD)	+ to +++	0 to +(?)	+ to +++	0 to +(?)	?	?
Seizures	0	+ to +++	0	0	0	0
Sedation	+ to +++	+++	0	+	0	+ to ++
Other						
NMS	+	+	+	?	?	?
Cardiovascular effects[c]	+ to ++	+++	+	0 to +	++	+
Liver transaminase increase	+	+	+	0 to +	0 to +	0 to +
Anticholinergic/antihistaminic	+ to +++	+++	0	0 to +	0	0 to ++
Agranulocytosis	0	+++	0	0	0	0
Prolactin increase	+++	0	+ to +++	0[d]	0[d]	0
Decreased ejaculatory volume	+	0	0	0	++	0
Weight gain	+	+++	++	++	++	++

*Abbreviation: EPS = extrapyramidal symptoms; NMS = neuroleptic malignant syndrome. Symbols: 0 = none or not significantly different from placebo; + = mild; ++ = moderate; +++ = marked; ? = insufficient data available.
[a]Dose-related changes above 6 mg/day.
[b]Not significantly different from placebo-treated group, which may have received typical neuroleptics before entering the study and could have EPS carry forward into the initial weeks of the investigation.
[c]Orthostatic hypotension and prolongation of the QT_c interval.
[d]Dose-related increases within the normal range.

Figure 1. Dose-Response Curve for Traditional and Novel Antipsychotics*



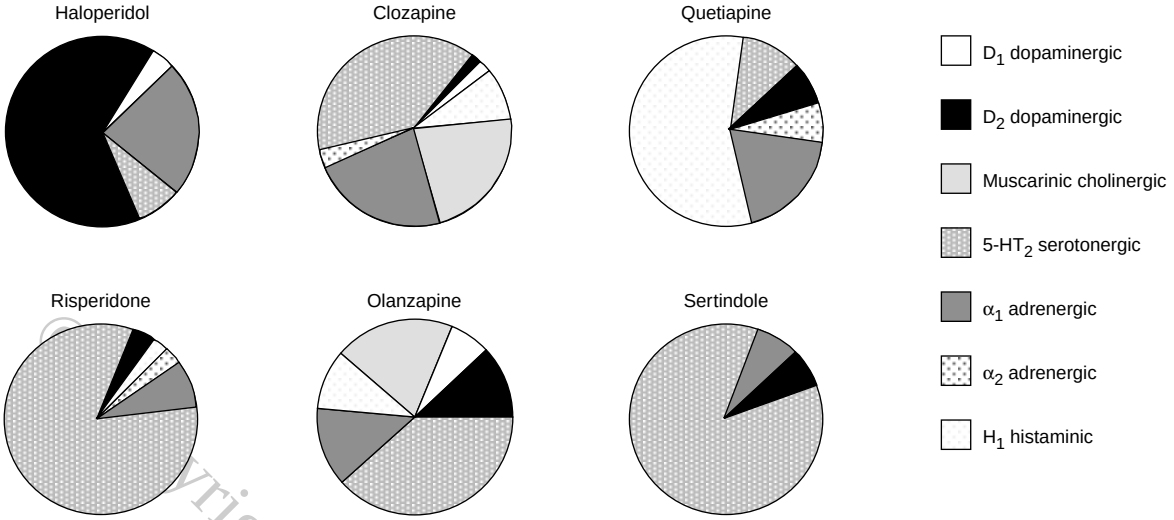
*Data from reference 2, with permission.

psychosis and the one that produces adverse effects. The first of these new agents, released in 1991, was clozapine, which is given in a dose range of 150 to 900 mg/day. Clozapine is efficacious for treatment-refractory psychosis and has a low liability for producing EPS and tardive dyskinesia, but also has troublesome as well as serious side effects.[3] In 1993, risperidone 2 to 16 mg/day was the next novel antipsychotic to be released. At lower doses, it has fewer EPS than traditional antipsychotics and lacks many of the serious side effects of clozapine. Olanzapine 5 to 20 mg/day was recently approved by the Food and Drug Administration (FDA) and released in September 1996. It, as well as the other new antipsychotics that are under FDA review (quetiapine and sertindole), also has a favorable side effect profile. This article will review the side effects of the new antipsychotics by comparing and contrasting them with each other and with the traditional neuroleptics (Table 1).

However, it is necessary to be cautious when comparing drugs by examining studies that have been conducted over many years at many treatment sites by a variety of investigators who used different treatment and assessment schedules. For example, the rate of drug titration markedly influences side effect rates, and these side effects often become the limiting step in determining dose titration. Thus, comparing these various investigations can only produce best-effort estimates. Well-designed, direct head-to-head comparisons of the new agents are needed to fully characterize the differences—and similarities—between specific compounds.

The clinical characteristics of conventional neuroleptics were recognized long before the pharmacologic profiles were identified. The continuum of milligram potency highly correlated with the type of side effects. Compounds such as chlorpromazine and thioridazine, which were high-milligram and low-potency, had less risk of producing EPS but induced more anticholinergic side effects, while low-milligram, high-potency agents such as fluphenazine and haloperidol had a higher incidence of EPS but fewer anticholinergic side effects. In vitro binding profiles that were created later showed that the high-milligram, low-potency drugs had weak activity at dopamine receptors and strong activity at anticholinergic sites.[4] Drugs that were highly anticholinergic also tended to produce more sedation and also usually had antiadrenergic activities that correlated with hypotension. These general characterizations were true for the traditional neuroleptics and the atypical agent clozapine. However, they do not hold true for risperidone, which has little anticholinergic activity and is a relatively potent dopamine receptor antagonist but produces few EPS at doses that are effective in treating psychosis.[5] The antagonistic activity at the $5\text{-}HT_2$ receptors may mediate part of the favorable EPS profile.[6]

Figure 2. In Vitro Profiles of the Relative Ability of Antipsychotics to Bind to Specific Receptors



In vitro binding profiles have been created for the atypical antipsychotics and compared with that of haloperidol (Figure 2). While differences between in vitro and in vivo findings often exist, such profiles reveal the effects of one drug relative to those of another. Haloperidol is primarily a D_2 antagonist, but also has some D_1, α_1-adrenergic, and 5-HT_2 effects. Clozapine affects many receptor subtypes, but has preferential antagonist activity at 5-HT_2 receptors, some activity at α-adrenergic, muscarinic cholinergic, and histaminic receptors, and relatively modest activity at dopamine D_1 and D_2 receptors.[6,7] Risperidone is principally a combined D_2 and 5-HT_2 antagonist, and it has been proposed that this 5-HT_2 antagonism is the reason why risperidone produces fewer EPS at the low end of the dose-response curve.[8] Olanzapine, like clozapine, blocks multiple receptor subtypes. It has similar activity at 5-HT_2, muscarinic cholinergic, histaminic, α-adrenergic, and dopamine D_1 and D_2 receptors.[9] Sertindole is principally a 5-HT_2 antagonist, but also has D_2 and α_1-adrenergic antagonism effects,[10] and quetiapine has preferential activity at histaminic and α_1- and α_2-adrenergic receptors.[11]

These profiles provide guidance for predicting the adverse effects produced by these drugs, which will sometimes be similar and sometimes be different. An evaluation of the side effects of the various agents will provide guidance in selecting the most appropriate antipsychotic for a specific patient. Most conventional antipsychotics have central nervous system effects, particularly EPS and tardive dyskinesia, sedation, and dulling of cognition. Other adverse events include the neuroleptic malignant syndrome (NMS), orthostatic hypotension, and changes in liver function. Some patients also experience anticholinergic and antiadrenergic side effects, sexual dysfunction, and weight gain. Effects of the newer agents include changes in blood pressure and liver function as well as weight gain.

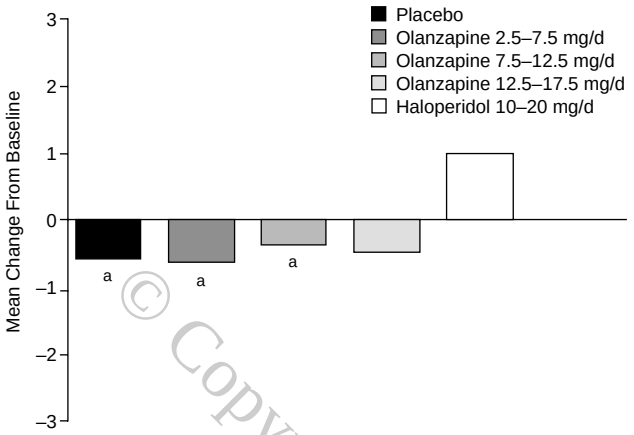
CNS EFFECTS

The incidence of EPS (akathisia, dystonia, and parkinsonism) produced by traditional antipsychotics varies, but most researchers agree that neuroleptic-induced EPS occur in 50% to 75% of patients who take conventional antipsychotics and at even higher rates in the elderly.[12] Tardive dyskinesia occurs in about 20% of patients who receive extended neuroleptic treatment.[12] Other CNS effects include seizures and sedation. Many patients stop taking conventional antipsychotics because of these motor syndromes, and, thus, the newer agents that have a lower incidence of EPS and tardive dyskinesia represent a major clinical advance.

Extrapyramidal Symptoms

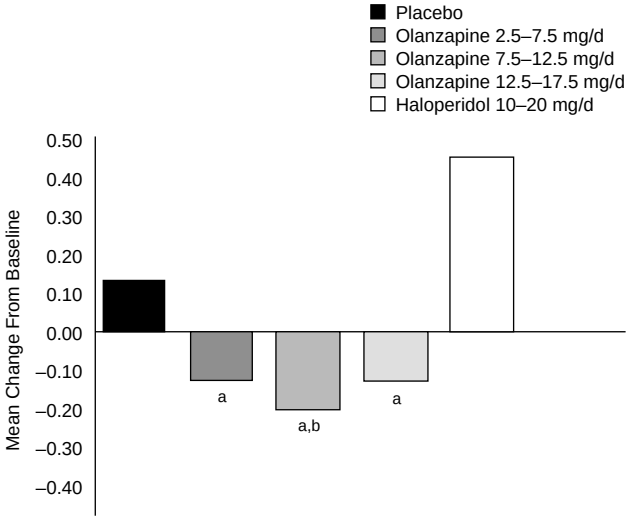
Clozapine was the first novel antipsychotic to demonstrate a truly low EPS profile across the therapeutic dose range. While there is some debate about whether clozapine produces akathisia at a rate that approaches the prevalence rates of traditional neuroleptics, in general the incidence of EPS during clozapine administration is quite low. The incidence of EPS produced by risperidone rises as the dose is increased; it produces few EPS in the dose range of 2 to 6 mg/day, but then shows a dose-related increase in EPS.[5,13] Data show that olanzapine,[14–16] sertindole,[17,18] and quetiapine[19,20] are unlikely to cause EPS. A study that compared three doses of olanzapine (2.5–7.5 mg/day, 7.5–12.5 mg/day, and 12.5–17.5 mg/day), haloperidol, and placebo[15] found that parkinsonism, as measured on the Simpson-Angus Neurologic Rating Scale, decreased in patients treated with olanzapine versus haloperidol (Figure 3). The mean parkinsonism score was about 2.5 for all groups at baseline; scores decreased for the olanzapine-treated patients in all three dose ranges. Findings were

Figure 3. Effects of Three Doses of Olanzapine, Haloperidol, and Placebo on Parkinsonism*



*Data from reference 15, as assessed by the Simpson-Angus Neurologic Rating Scale.
[a]p < .05 vs. haloperidol.

Figure 4. Effects of Three Doses of Olanzapine, Haloperidol, and Placebo on Akathisia*



*Data from reference 15, as assessed by the Barnes Akathisia Scale.
[a]p < .05 vs. placebo.
[b]p < .01 vs. haloperidol.

similar for akathisia as measured on the Barnes Akathisia Scale (Figure 4), and these results were replicated in three other studies,[14,21,22] which showed a lowering of EPS scores during olanzapine treatment and an increase during haloperidol treatment (Figures 5 and 6).

A recent study[16] analyzed the incidence of EPS in a population of 2606 patients from three controlled trials. The authors found that olanzapine was statistically significantly ($p = .014$, $p < .001$) superior to haloperidol in four analyses related to the emergence of EPS and in two analyses related to outcome. In addition, during acute treatment, fewer patients treated with olanzapine (0.3%) than those treated with haloperidol (2.7%) discontinued treatment because of EPS ($p < .001$).

The sertindole database[17,18] also shows a decrease in the amount of EPS. In the quetiapine study,[19] EPS as measured by the Simpson-Angus and akathisia as assessed with the Barnes Akathisia Scale improved or remained the same for most patients and worsened in only 10% to 15% of patients.

Even when the incidence of EPS during a clinical study is not significantly different from the incidence in placebo-treated patients, some EPS are likely to be rated as present. When patients enter clinical studies, they have often been previously treated with traditional antipsychotics, and some EPS may carry over into the clinical study period and be assessed as present at baseline, even in the placebo group.[5,13–15,17–21] In recent studies, EPS were assessed as present at least once in 10% to 20% of placebo-treated patients, and thus, if a new drug does produce minor EPS in less than 10% of patients, the incidence may be undetected in early clinical studies. However, to date it appears that the newest antipsychotics have little liability to produce EPS.

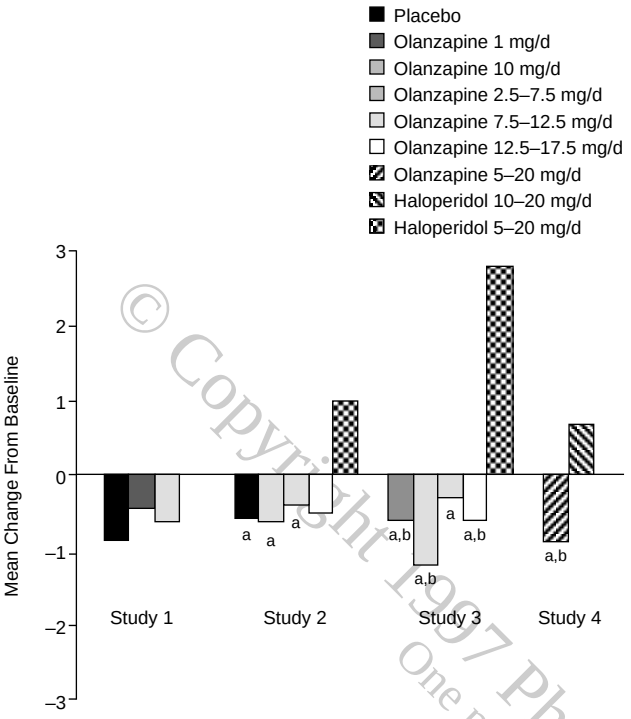
The favorable findings in clinical studies are supported by a number of preclinical studies. Serotonin 5-HT_2 receptor antagonism, which may have a role in mitigating EPS, is common to clozapine, risperidone, olanzapine, sertindole, and quetiapine.[8–10] In addition, clozapine, olanzapine, sertindole, and quetiapine have been shown to have CNS site selectivity for differentially antagonizing limbic (antipsychotic) dopamine receptors, but have little antagonistic effect on the basal ganglia (EPS) dopamine receptors.[23–25]

Tardive Dyskinesia (TD)

The risk of TD increases the longer patients are exposed to conventional neuroleptics; it occurs in about 20% of patients who receive extended treatment with conventional antipsychotics, but in up to 50% of patients in high-risk groups such as the elderly and the medically compromised. TD is a potentially irreversible side effect. However, some evidence supports the theory that drugs that have low liability for EPS will also have a low risk of TD.[26] Experience with clozapine also supports the theory (clozapine has a low liability for both EPS and TD).[27] Risperidone is unlikely to produce TD at lower doses but, like the risk for EPS, the likelihood of TD may increase as the risperidone dose goes up. There is a working hypothesis that neuroleptic doses that are below the threshold for EPS carry a low TD liability, and early studies of olanzapine tentatively suggest that the TD liability during olanzapine treatment is low[28]; data are not yet available for sertindole or quetiapine.

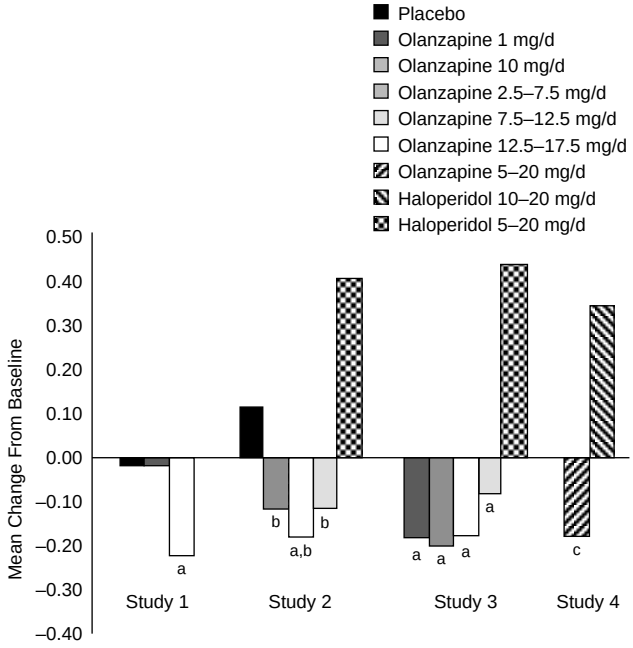
The probability that a patient who is being treated with conventional antipsychotics will develop tardive dys-

Figure 5. Changes in Parkinsonism Across Four Olanzapine Studies*



*Data from references 14 (Study 1), 15 (Study 2), 22 (Study 3), and 21 (Study 4); as assessed by the Simpson-Angus Neurologic Rating Scale.
[a]p < .05 vs. haloperidol.
[b]p < .001 vs. haloperidol.

Figure 6. Changes in Akathisia Across Four Olanzapine Studies*



*Data from references 14 (Study 1), 15 (Study 2), 22 (Study 3), and 21 (Study 4); as assessed by the Barnes Akathisia Scale.
[a]p < .01 vs. haloperidol.
[b]p < .05 vs. placebo.
[c]p < .001 vs. haloperidol.

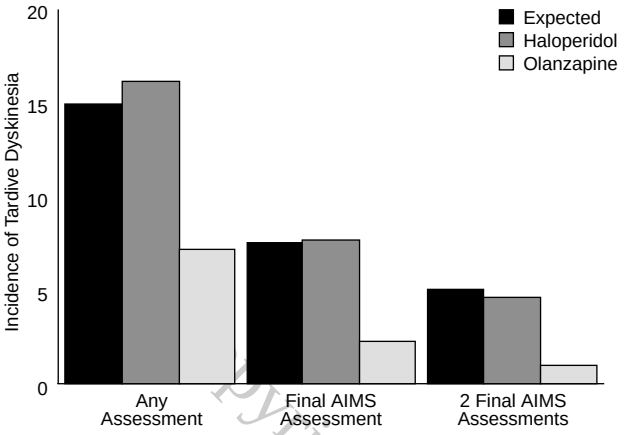
kinesia is about 5% per year or 15% in 3 years. However, only 1% of olanzapine-treated patients were rated as having tardive dyskinesia at the end of one long-term study.[28] Data were integrated from three active-controlled long-term studies of 894 patients who were treated with up to 20 mg/day of olanzapine for a median of 237 days versus 261 patients who were treated with up to 20 mg/day of haloperidol for a median of 203 days. The two groups were similar for duration of disease, age at admission, age at first episode, and previous therapy. The incidence of dyskinetic symptoms in olanzapine-treated patients was statistically significantly less than in haloperidol-treated patients at all three time points measured (Figure 7). This observation coupled with the other findings of low EPS with the new antipsychotics suggests that the new drugs will have a low incidence of TD. However, each agent must be evaluated independently to ensure that there is no existing unknown pathophysiologic mechanism intrinsic to each drug that would negate the predicted low TD profile.

Other CNS Effects

Seizures. In most clinical settings, administration of conventional antipsychotics does not increase the risk of seizure. The common belief that neuroleptics lower the seizure threshold is based primarily on a few studies that were not well controlled. The new atypical antipsychotics show no increase in seizure risk when compared with haloperidol or placebo. Clozapine, however, is the only antipsychotic that has been associated with a dose-related and plasma drug level increase in seizures: doses of clozapine lower than 300 mg/day have a seizure rate of about 1%, doses between 300 and 600 mg/day have a seizure rate of 2.7%, and doses larger than 600 mg/day have a rate of 4.4%.[29]

Sedation. Traditional neuroleptics are sedating, particularly at high doses; this effect can be troubling during extended treatment. While sedation may initially seem beneficial, over the long term, it impairs function. In general high-milligram, low-potency antipsychotics produce more sedation than low-milligram, high-potency agents. This principle carries through to the atypical antipsychotics. The sedative effects of clozapine can be a dose-limiting problem and sometimes cause patients to become noncompliant.[3] Risperidone is sedating only when the dose is titrated rapidly and the sedative effects are transient.[5] Olanzapine[14,15] appears to be more sedating than sertindole[17] in the initial phase of treatment and less se-

Figure 7. Incidence of Tardive Dyskinesia in Patients Receiving Long-Term Treatment With Olanzapine vs. Haloperidol*



*Data from reference 28. Abbreviation: AIMS = Abnormal Involuntary Movement Scale.

dating than quetiapine.[19] Sedation is not a problem with any of these agents during extended treatment for most patients.

OTHER ADVERSE EFFECTS

Neuroleptic Malignant Syndrome

The prevalence of the neuroleptic malignant syndrome (NMS), which was identified shortly after the first antipsychotics were developed, ranges between 0.01% and 1%. NMS is a syndrome of hyperthermia and is usually associated with other symptoms of severe motor rigidity, autonomic nervous system instability, and elevated creatine phosphokinase (CPK). Although the new antipsychotics are expected to have less liability for NMS than the traditional neuroleptics, clinicians should continue their vigilance about this serious adverse effect until more data are available. A few scattered cases of NMS have been reported with clozapine and risperidone.[30–32] While none have been reported for olanzapine, sertindole, or quetiapine, only a few thousand patients have been treated with these new agents, which may not be a sufficient number to assess the risk for NMS.

Agranulocytosis

Except for clozapine, antipsychotics have little consistent pathophysiologic impact on the hematologic profile. However, agranulocytosis occurs in 0.5% to 2% of patients who take clozapine.[3] Because of this risk, patients who take clozapine need to have their blood monitored weekly for a decrease in white blood cells. Fortunately, olanzapine, risperidone, sertindole, and quetiapine have no known hematologic liability.

Cardiovascular Effects

The two main types of cardiovascular effects of antipsychotic treatment are changes in blood pressure and myocardial conduction. Orthostatic hypotension—the most common cardiovascular adverse effect—is correlated with the antagonistic effects of antipsychotics at α-adrenergic receptors and is more likely with the high-milligram, low-potency agents such as clozapine, chlorpromazine, thioridazine and the rapid titration of risperidone. Orthostatis is a rare problem with olanzapine, unlike what is expected from the pharmacologic profile. It has also been reported for quetiapine[19] and sertindole. However, orthostatic hypotension, which is of special concern in the elderly, can occur during treatment with any conventional or atypical antipsychotic. This side effect can usually be managed with careful dose adjustment, and patients often become partially or fully tolerant to it.

Changes in electrical conduction of the myocardium, which are identified through changes in the electrocardiogram, are also an effect of treatment with some antipsychotics. Prolongation of the QT interval, which is sometimes presented as QT_c (correction of the QT in relation to heart rate), is the conduction effect that is discussed most frequently. Although there have been no reported untoward clinical consequences, sertindole administration has been associated with a dose-related prolongation of the QT interval.[18] While the practical meaning of this prolongation is unclear, it may be a factor in the use of sertindole. The risperidone package insert mentions QT_c, but it is generally not a clinical concern with this agent. Because the QT_c probably occurs because of alternations in ion channels in the myocardium, it is unlikely to be noted in a receptor binding profile of a drug. However, the data to date indicate that QT_c is unlikely to be a problem with olanzapine or quetiapine.

Hepatic Effects

Liver function abnormalities have been noted with the antipsychotics since they were first developed. Mild-to-moderate increase in transaminase enzyme levels are sometimes discovered in routine laboratory analyses during administration of conventional neuroleptics, clozapine, and risperidone but are seldom the reason for drug discontinuation. However, the risk of changes in liver function tests is generally increased in the chronically mentally ill because this population has a higher incidence of hepatitis B and C than the general population. Recent studies with olanzapine, sertindole, and quetiapine show that if transaminase enzyme levels increase, they are within the range that is seen during treatment with haloperidol and other conventional neuroleptics and usually return to normal.[14,15,17–19] In fact, the normal clinical course is an increase in transaminase enzyme levels during the first few weeks of treatment and then a gradual return to normal levels.

Sexual Dysfunction

Few studies have investigated the incidence of sexual dysfunction in patients being treated with antipsychotics, and patients are often reluctant to report these effects spontaneously. Thus, the true incidence and negative impact of antipsychotics on sexual function are unknown. However, some problems have been linked to increased prolactin levels, which can lead to breast swelling, tenderness, and discharge as well as irregularities in the menstrual cycle and sexual function. Standard antipsychotic doses of conventional neuroleptics and risperidone can increase prolactin levels above normal in a dose-related fashion, but only a few patients discontinue treatment because of breast tenderness and galactorrhea or menstrual irregularities. Clozapine (in the normal dose range), olanzapine, sertindole, and quetiapine do not routinely increase prolactin levels above normal, although doses of olanzapine, and sertindole at higher doses may cause increases in prolactin toward the upper end of normal.[15,17,25]

While there are few data, ejaculatory dysfunction has long been noted during treatment with some antipsychotics, putatively because of α-adrenergic blockade. For example, thioridazine has been associated with retrograde ejaculation in a minority of men. The volume of ejaculate is decreased, often to none, in about 20% of men who are taking sertindole.[17,18] The problem resolves itself in 5% of the men during extended treatment, and the volume of ejaculate returns to normal upon drug discontinuation. These problems have not been reported for clozapine, risperidone, olanzapine, or quetiapine.

Anticholinergic Effects

Anticholinergic/antihistaminic side effects, which include dry mouth, blurred vision, urinary difficulties, constipation, possible cognitive impairment, and confusion, occur most frequently in patients who take high-milligram, low-potency antipsychotics. The new antipsychotic compounds are correlated with a range of anticholinergic side effects, and, in some cases, the side effects are difficult to explain on the basis of the receptor binding profile.

For example, the receptor-binding profile of clozapine is highly anticholinergic, which does produce constipation in some patients.[6] However, patients who take clozapine often also experience increased salivation, which is usually attributed to cholinergic agonism rather than antagonism. Risperidone lacks these anticholinergic side effects. The receptor-binding profile of olanzapine makes it surprising that it has so few anticholinergic effects, and this lack might be a clue that olanzapine has more complex activity at muscarinic receptors than is currently understood.

Weight Gain

Weight gain is likely to be a problem with this new group of drugs as it has been with the traditional antipsychotics. When chlorpromazine was introduced, the large majority of patients gained considerable amounts of weight, and similar problems have occurred to varying degrees with all antipsychotics. Weight gain is often a factor in noncompliance with treatment and has long-term consequences of medical morbidity. Weight gain is a clinically significant problem in clozapine-treated patients and is also likely to occur in patients taking risperidone,[5,13] olanzapine,[14,15] sertindole,[17,18] and quetiapine.[19] Patients in clinical studies of olanzapine, sertindole, and quetiapine gained, on average, approximately 2 to 8 pounds (1 to 4 kg) over the first 6 to 8 weeks of treatment, and some patients continued to gain several pounds before their weight stabilized. Similar percentages of patients being treated with these three different agents gain ≥ 7% of body weight. Since weight gain is likely to be a concern for patients taking any antipsychotic drug, it is important to develop some behavioral and educational strategies to help manage the weight issues.

Other Adverse Effects

Some side effects occur rarely or seem to be associated with a specific drug. For example, patients taking phenothiazines such as chlorpromazine have an increased risk of sunburn because of a photosensitivity reaction. This has not been reported with any of the new agents. Patients taking more than 800 mg/day of thioridazine occasionally experience irreversible pigmentary retinopathy. This retinopathic effect has also not been reported for any of the new agents. Nasal congestion occurs in about 20% of patients being treated with sertindole, but usually is not a reason for drug discontinuation.[17,18] The proposed mechanism for this nasal congestion is α-adrenergic blockade, though other physiologic components may be factors.

SUMMARY

The receptor-binding profiles—and the adverse effects—differ among the newest antipsychotics, olanzapine, sertindole, and quetiapine. Patients who are treated with olanzapine may observe mild anticholinergic effects, a small transient increase in transaminase enzyme levels, and some weight gain. Those who take sertindole might experience nasal congestion (20% of patients), decreased ejaculatory volume, prolongation of the QT_c, and weight gain. The adverse effects of quetiapine include sedation, orthostatic hypotension, mild transient abnormalities on liver function tests, and weight gain.

Overall, the adverse effects profiles of the newest antipsychotics represent a major improvement over those of the older neuroleptics. Olanzapine, sertindole, and quetiapine produce minimal or no EPS across the effective dose range and probably will have low rates of TD as well as minimal elevation in prolactin levels, and liver dysfunction. For sertindole, the prolongation in the QT_c, decreased ejaculatory volume, and nasal congestion may be

clinical concerns that can be addressed by careful medical management and counseling. Weight gain, on the other hand, is likely to be a serious clinical problem for selected patients taking these drugs, just as it has been for those taking conventional neuroleptics. The long-term difficulties related to excessive weight are a potential major public health problem and are likely to contribute to medical morbidity in psychotic patients just as is seen in nonpsychotic overweight people. Persistent efforts aimed at education and behavioral management of weight gain will be important to enhance compliance.

The traditional neuroleptics, when they were developed, were a major advance for psychotic patients but, because they affected many neurotransmitters, had treatment-limiting side effects. The favorable side effect profile of these new antipsychotics is likely to make patients more willing to continue treatment, and thus these agents represent another step forward for patients with serious acute and chronic mental illness.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril), fluphenazine (Prolixin and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal), thioridazine (Mellaril and others).

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