Prolactin Elevation With Antipsychotic Medications: Mechanisms of Action and Clinical Consequences

Gerald A. Maguire, M.D.

Antipsychotic agents differ in efficacy and side effects such as movement disorders and prolactin elevation because of varying mechanisms of action. A revised nomenclature for antipsychotic agents, which categorizes the drugs according to efficacy, risk of movement disorders, and risk of prolactin elevation, is described. Prolactin elevation, a potential side effect of some antipsychotic medications, is underdiagnosed but can have serious short-term and long-term consequences. Short-term problems include menstrual irregularities, sexual dysfunction, and depression. Long-term problems related to prolactin elevation include decreased bone density and osteoporosis, relapse of psychosis because of poor compliance due to sexual dysfunction or depression, and perhaps cancer, although more research in this area is needed. Despite the serious nature of these effects, prolactin elevation is seldom detected because clinicians often fail to inquire about sexual function or other symptoms that signal that a patient's prolactin may be elevated. These are problems that patients may not bring up with clinicians unless they are asked. Therefore, when patients are taking antipsychotic medications, clinicians should regularly inquire about sexual dysfunction, depression, menstrual disturbances, galactorrhea, and gynecomastia. *(J Clin Psychiatry 2002;63[suppl 4]:56–62)*

Because of varying mechanisms of action, antipsychotic agents differ in efficacy and side effects such as movement disorders and prolactin elevation. Prolactin elevation is a potential side effect of some antipsychotic medications that is underdiagnosed but can have serious short-term and long-term consequences. Despite these serious adverse effects, prolactin elevation is often not detected because of hesitance on the part of the patient to mention the types of problems that elevated prolactin causes, such as sexual dysfunction. However, clinicians can treat patients with agents less likely to lead to elevated prolactin levels. Because the antipsychotic agents' mechanisms of action affect both efficacy and safety profiles, an added advantage of using an antipsychotic that does not raise prolactin is that efficacy may be improved and the risk of movement disorders may be lessened. These 3 factors—efficacy, risk of movement disorders, and risk of elevated prolactin—can be used to categorize the antipsychotic agents.

REVISED NOMENCLATURE OF ANTIPSYCHOTIC AGENTS

Antipsychotic agents have been grouped into older and newer classes of drugs. The terms *typical* and *atypical* are currently used to describe the 2 major classes of antipsychotics. Agents in the newer, atypical antipsychotic class, which were designed to reduce the risk of movement disorders, should be used first-line. These newer antipsychotics were first developed because the older, typical drugs have a limited efficacy profile, a high risk of movement disorders such as extrapyramidal symptoms (EPS) and tardive dyskinesia, and a tendency toward prolactin elevation. All the agents in the atypical class—clozapine, risperidone, olanzapine, quetiapine, and ziprasidone—have been introduced more recently than the other drugs and represent an improvement over the typical agents in some way.

Despite being grouped into the same class, the atypical agents differ in efficacy and safety. Some of the atypical agents are more similar to the typical agents than others. To improve the categorization of these agents, a colleague and I[1] have proposed a revised nomenclature of antipsychotic agents, dividing them into 3 classes rather than 2 (Table 1). In this revised nomenclature, we categorized the agents according to their efficacy, risk of movement disorders, and risk of prolactin elevation, which all result from the varying mechanisms of action of the agents.

Nemec and I[1] have broken down the antipsychotic agents into what we call first-generation, second-generation, and third-generation groups. The category names are not linked to the chronology of when the agents came to market but instead represent advances in antipsychotic technology. For example, clozapine was the first of the so-called atypical agents on the market, but, in our nomenclature, is in the third-generation class because of its efficacy, low potential for EPS and tardive dyskinesia, and lack of prolactin elevation. Clozapine was a revolutionary agent in its time but now is approved only for treatment-refractory schizophrenia due to its potential for agranulocytosis. On the other hand, ziprasidone, which is the latest antipsychotic agent to be approved for use in the United States, is in our second-

From the Department of Psychiatry/Neuro Psychiatry Center, University of California, Irvine.

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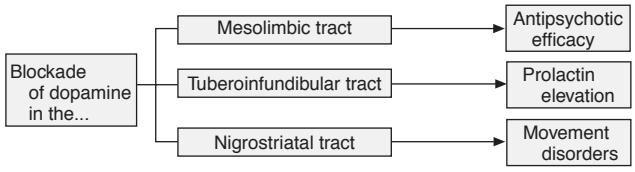
Reprint requests to: Gerald A. Maguire, M.D., Department of Psychiatry/Neuro Psychiatry Center, University of California, Irvine, 101 South City Drive, Building 3, Orange, CA 92868.

Table 1. Revised Nomenclature of Antipsychotic Agents[a]

Antipsychotic	Efficacy	EPS/TD	Prolactin
First generation (eg, haloperidol, chlorpromazine)	Limited to positive symptoms	High	Elevating
Second generation (eg, risperidone, ziprasidone?)	Both positive and negative symptoms	Dose-dependent	Elevating
Third generation (eg, clozapine, olanzapine, quetiapine)	Broad-spectrum (not fully established for quetiapine)	Low	Sparing

[a]Data from Maguire and Nemec.[1] Abbreviations: EPS = extrapyramidal symptoms, TD = tardive dyskinesia, ? = few data available.

Figure 1. Antipsychotic Agent Mechanisms of Action



generation class. Use of ziprasidone is limited to patients without a vulnerability for cardiovascular disease.[2] Under our system, the third-generation agents, which improved efficacy and reduced EPS and tardive dyskinesia while maintaining normal prolactin levels, are the most beneficial.

In the first-generation class are agents currently known as the conventional or typical antipsychotic agents—haloperidol and chlorpromazine, for example. These agents cause patients to have a high risk of EPS (which can predict later development of tardive dyskinesia[3]), they elevate prolactin, and their efficacy in schizophrenia is limited to positive symptoms (delusions and hallucinations).[4] They have little effect on negative symptoms of schizophrenia. In addition, they do not improve—and, in fact, may impair—mood symptoms and cognition.[4]

Our second-generation class of antipsychotics includes atypical agents such as risperidone and ziprasidone, although ziprasidone is so new that studies are few and results are mixed. Risperidone was the second atypical agent in the U.S. market, following clozapine, and it has efficacy against both positive and negative symptoms but a pronounced propensity toward elevating prolactin levels and a dose-dependent risk of EPS.[5] Weiser et al.[6] found that in 76 patients receiving haloperidol, risperidone, or olanzapine, those with more severe EPS were taking haloperidol or risperidone. Risperidone may improve mood symptoms and cognition, although studies are mixed. In terms of mood, Peuskens et al.[7] found in an analysis of double-blind trials of risperidone that in patients with anxiety or depressive symptoms at baseline, these symptoms decreased significantly more and also faster with risperidone than with haloperidol. However, Ashleigh and Larsen[8] reported that in a 10-week trial of risperidone in patients with schizophrenia, an initial good response to the medication was followed in 46% of the patients by intolerable affect, including feelings of agitation and depression and periods of crying and insomnia. The authors noted that at baseline these patients had significantly higher anxiety scores on the Brief Psychiatric Rating Scale. Regarding cognitive function, risperidone has shown some improvement in certain areas. While more effective than haloperidol and the other typical (or first generation) agents against cognitive dysfunction, risperidone and the atypical agents differ in areas of cognition that they improve. For example, risperidone seems to improve working memory better than clozapine and olanzapine, but these third-generation agents improve verbal fluency better than risperidone.[9,10]

In our nomenclature, the third-generation antipsychotics are clozapine, olanzapine, and quetiapine. The agents in the third generation have the lowest risk of movement disorders.[11] These drugs also spare the patient prolactin elevation, and the spectrum of efficacy of these agents includes negative symptoms as well as positive symptoms.[12] Cognition and mood also are improved with these agents over the conventional first-generation drugs[10,13] (although further studies are needed for quetiapine, which is a fairly new drug).

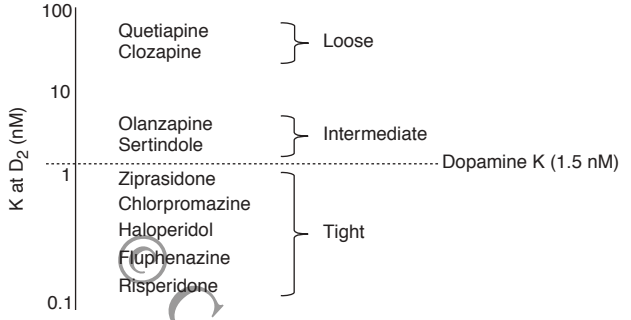
MECHANISMS OF ACTION OF ANTIPSYCHOTICS

The 3 categories—efficacy, movement disorders, and prolactin—that distinguish the antipsychotic generations from one another in our revised nomenclature are effects of dopamine blockade in the brain (Figure 1). The dopamine pathways in the brain that are relevant to efficacy and side effects of antipsychotic agents are the mesolimbic tract, the tuberoinfundibular tract, and the nigrostriatal tract.[14] Blockade of dopamine in the tuberoinfundibular pathway causes prolactin elevation. Blockade of dopamine in the nigrostriatal pathway is the mechanism for extrapyramidal symptoms and also for tardive dyskinesia, which can be attributed to an up-regulation of receptors over time. Dopamine blockade in the mesolimbic pathway causes the antipsychotic effect, and not all atypical antipsychotics are mesolimbic selective. However, the third-generation antipsychotics—olanzapine, clozapine, and quetiapine—are fairly mesolimbic specific in their blockade of dopamine. Because these drugs spare the tuberoinfundibular pathway and the nigrostriatal pathway, they have a lower risk of movement disorders and a lower risk of prolactin elevation.

Efficacy and Risk of Movement Disorders

Seeman and Tallerico[15] studied how tightly the antipsychotic agents bind to the dopamine D_2 receptors, and their work provides understanding of the efficacy of different agents and their relative risk of causing EPS (Figure 2). Their conclusion was that antipsychotic drugs that elicit movement disorders (such as haloperidol, chlorpromazine, fluphenazine, ziprasidone, and risperidone) bind more tightly than dopamine to D_2 receptors, while those that elicit few or no movement disorders (such as

Figure 2. Relative Binding of Antipsychotic Agents to Dopamine D_2 Receptors[a]



[a]Adapted with permission from Seeman and Tallerico.[15]

quetiapine, clozapine, and olanzapine) bind more loosely than dopamine to the D_2 receptors. Seeman and Tallerico concluded that, compared with the tightly bound antipsychotic agents, the more loosely bound agents generally require fewer days for clinical adjustment but require higher clinical doses, and they may dissociate from the D_2 receptor more rapidly, which could lead to relapse earlier than the more tightly bound drugs.

Quetiapine is the agent most loosely bound to the dopamine receptor, which may explain why clinicians often have to administer higher doses of this agent to achieve efficacy. Clozapine is about 3 times more tightly bound to the dopamine receptor than quetiapine. Olanzapine demonstrates moderate binding and is 10-fold more tightly bound to the dopamine D_2 receptor than clozapine. Even more tightly bound agents are the first- and second-generation antipsychotic agents. Ziprasidone, chlorpromazine, haloperidol, fluphenazine, and risperidone are tightly bound to the D_2 receptor, which may explain why these agents may have a greater risk of EPS. Because the second- and third-generation antipsychotic agents have a lower risk of acute EPS than the first-generation agents do, they may also have a lower risk of tardive dyskinesia, because early acute EPS can predict development of tardive dyskinesia over the long term. Few clinical data are available on the EPS potential of quetiapine.

Tollefson et al.[16] compared the third-generation antipsychotic agent olanzapine with the first-generation agent haloperidol in patients with schizophrenia and related disorders (N = 1996). In the 6-week study, the investigators found a lower risk of treatment-emergent extrapyramidal adverse events among patients taking olanzapine than in those taking haloperidol. Dystonic, parkinsonian, akathisia, and residual events were reported significantly less often by those taking olanzapine than haloperidol.

Tran et al.[17] conducted a long-term (28-week) study comparing olanzapine with the second-generation antipsychotic risperidone. The proportions of patients with treatment-emergent spontaneously reported dystonic and parkinsonian events were significantly smaller with olanzapine than with risperidone. When EPS were assessed by rating scales, significantly fewer patients taking olanzapine than taking risperidone were found to have pseudoparkinsonism by the Simpson-Angus scale, akathisia by the Barnes Akathisia Scale, and dyskinesia by the Abnormal Involuntary Movement Scale. The lower rates of EPS with olanzapine than risperidone likely are related to the fact that olanzapine has more mesolimbic-specific action than risperidone.

Table 2. Antipsychotics and Prolactin[a]

Antipsychotic	Prolactin-Sparing	Prolactin-Elevating	First-Line Agent	Second-Line Agent
Olanzapine	✓		✓	
Quetiapine	✓		✓	
Clozapine	✓			✓
Risperidone		✓	✓	
Ziprasidone	?	?		✓[b]

[a]Data from Dickson and Glazer[46] and package inserts. Abbreviation: ? = few data available.
[b]Ziprasidone is indicated for the treatment of schizophrenia, but because of its greater capacity than other antipsychotic agents to prolong the QT interval (which could lead to potentially fatal arrhythmias), other drugs should be tried before ziprasidone in many cases.[2]

Beasley and colleagues[18] assessed the incidence of tardive dyskinesia in patients with schizophrenia who were treated with olanzapine or haloperidol during the 1-year double-blind phase of their study. For olanzapine, the risk of tardive dyskinesia was 0.52%, while the risk of tardive dyskinesia with haloperidol was 7.45%. Although these patients were not naive to antipsychotic treatment, making quantification of the risk of tardive dyskinesia to patients newly treated with olanzapine or haloperidol impossible in this study, these results reflect the incidence of this movement disorder in a clinically relevant population of patients in their mid-thirties with chronic symptomatology and histories of treatment for more than 10 years.

Risk of Prolactin Elevation

The normal range of prolactin levels in nonlactating subjects is between 1 µg/L and 25 µg/L. Kuruvilla et al.[19] found that prolactin levels in patients with schizophrenia are generally within the normal range prior to receiving treatment for psychosis; the schizophrenia itself does not appear to affect prolactin. It is the action of antipsychotic agents that causes the elevation of prolactin. Risperidone and the conventional antipsychotic agents raise prolactin levels, but clozapine, quetiapine, and olanzapine are not associated with significant prolactin increase because they spare dopamine blockade within the tuberoinfundibular tract (Table 2).[20]

In a fixed-dose study[21] comparing quetiapine with haloperidol and placebo in 361 patients with schizophrenia, the prolactin levels remained essentially flat from baseline to endpoint with quetiapine—even at the highest dosage range—while marked elevations were found with haloperidol.

There may be a transient increase of prolactin with olanzapine in the first few weeks of use, but levels tend to remain within the normal range and then return to the baseline levels or even lower. In the Tran et al. study[17] comparing olanzapine with risperidone, a significantly ($p < .001$) lower proportion of patients in the olanzapine treatment group experienced an elevation above standard reference ranges in prolactin concentration

Table 3. Potential Health Disturbances With Prolactin-Elevating Antipsychotic Agents[a]

Women	Men
Short-Term	Short-Term
Menstrual disturbances	Loss of libido
Galactorrhea	Erectile dysfunction
Breast engorgement	Ejaculatory dysfunction
Sexual dysfunction	Reduced spermatogenesis
Infertility	Gynecomastia
Long-Term	Long-Term
Decreased bone density, mediated by relative or absolute deficiency of estrogen	Decreased bone density, mediated by relative or absolute deficiency of testosterone
Cardiovascular disease?	Cardiovascular disease?
Cancer (breast, endometrial)?	Depression?
Depression?	

[a]Abbreviation: ? = few data available.

at any time during the study (51.2% vs. 94.4%). In addition, the increases of prolactin associated with risperidone were more persistent than those associated with olanzapine; at endpoint, the proportion of patients taking risperidone whose prolactin levels were still elevated was significantly ($p < .001$) higher than that of patients taking olanzapine (90.3% vs. 36%).

The prolactin increase with risperidone appears to be unrelated to dosage. A recent analysis[22] of 3 double-blind multicenter trials in patients taking risperidone dosages of 4 to 12 mg/day, haloperidol dosages of 5 to 20 mg/day, or olanzapine dosages of 5 to 20 mg/day did not consistently confirm a dose-response relationship for prolactin elevations with any of the drug treatments. The authors concluded that risperidone strongly increases prolactin (by 45–80 μg/L), haloperidol intermediately increases prolactin (by 17 μg/L), and olanzapine moderately increases prolactin (by 1–4 μg/L). Among patients taking risperidone and haloperidol, the mean change in prolactin levels was greater in women than in men.

CONSEQUENCES OF PROLACTIN ELEVATION

Some clinicians say they do not see effects of prolactin elevation and do not understand its importance. They may think that this side effect does not play a role in their practice. But, in fact, elevated prolactin levels can have many effects on patients, whether male or female, in both the short and long term (Table 3). Clinicians may simply not know about these effects unless they inquire about them because patients can be reluctant to mention them. The effects of hyperprolactinemia usually occur when the patient's prolactin level is between 30 μg/L and 60 μg/L or even higher.[23]

Short-Term Physical Concerns

Prolactin elevation can cause amenorrhea or an irregular menstrual cycle.[20,24] Essentially, typical antipsychotic agents and risperidone can induce early menopause.[20,23,24] Galactorrhea may occur along with menstrual dysfunction.[25] Gynecomastia is another potential effect of elevated prolactin. These are side effects that men and women may be hesitant to mention when seeing their physicians, so it is important to inquire about such possible effects. Patients may not expect this type of side effect to occur with medication, and they should be warned in advance if they begin treatment with a prolactin-increasing agent.

Prolactin elevation may also cause sexual dysfunction in both men and women.[23] Men may experience prolonged erection or priapism. Men and women may also experience loss of libido or fertility and an inability to reach orgasm or ejaculate due to antipsychotic treatment.

When we talk about improving the quality of life in our patients, we must remember that it is important to consider sexual functioning as a measure of quality of life. Also, maintaining patients on their medication is key to their achieving reintegration, and their compliance with the medication will be better if they do not have sexual dysfunction caused by the medication.

Long-Term Physical Concerns

Prolactin levels inversely affect estrogen and testosterone levels in both men and women. If prolactin is increased, testosterone and estrogen are decreased. This in turn is associated with decreased bone density, which may predispose patients to osteoporosis.[20] Patients with schizophrenia are already candidates for osteoporosis because they tend to have other risk factors such as sedentary lifestyle, smoking, poor nutrition, and pathologic water drinking. Therefore, use of an antipsychotic agent that is unlikely to elevate prolactin levels is important for patients' long-term bone health.

Cardiovascular disease is also a risk when estrogen levels are low. Shaarawy et al.[26] found that hyperprolactinemia with estrogen deficiency produced a significant decrease in nitric oxide production, which can predispose patients to certain cardiovascular disorders. Elevated blood pressure was associated with the decrease in nitric oxide.

Strungs and colleagues[27] reported that animal data have suggested that elevated prolactin can lead to breast carcinoma, but studies in humans have been inconclusive. Some human studies have found increased prolactin levels in patients with breast cancer and their daughters, but others have not. Strungs et al. suggested that prolactin may work with stress or estrogen to induce breast cancer. Chen and coworkers[28] described a human prolactin antagonist that inhibited proliferation of breast cancer cells. Prolactin may play a role in endometrial cancer,[29] but much more research into the relationship between cancer and prolactin levels in humans is needed.

Depression

Comorbid depression can affect all the core symptom domains in schizophrenia and can affect all outcome measures. The core symptom domains may be affected in the following ways: positive symptoms may be manifested as mood-congruent delusions or hallucinations; negative symptoms may appear as apathy and social withdrawal; and cognitive symptoms may include impaired concentration and memory. Outcome is affected

by depression in the following ways: compliance with treatment may be compromised; social and vocational functioning and reintegration are lessened; and the risk of suicide is increased. Among patients with schizophrenia, about half will have met criteria for major depressive disorder in their lifetime, which is much greater than in the general population.[30] In the course of schizophrenia, depression can increase the rate of relapse and lead to a longer duration of hospitalization, poorer treatment response, and chronicity of the schizophrenia. Depressive mood in patients with chronic schizophrenia contributes substantially to overall social dysfunction.[31] Management of depression in patients with schizophrenia is a treatment plan priority.

Knowing how to treat depression in schizophrenia means understanding its possible origins. Depression in schizophrenia is brought about by many different causes. One link to postpsychotic depression is difficult to separate from circumstances. When patients are treated for first-break schizophrenia, they are often depressed 3 or 4 months later. It can be rationalized that they are looking ahead at their life and they realize that they are no longer in school or in the home where they were, so they see less potential and see what they have lost.

However, some of this depression—besides reacting to their new diagnosis—may have been induced by the antipsychotic medication. One reason is the extrapyramidal side effects of antipsychotics. Parkinsonian symptoms lead to a greater risk of depression, and massive dopamine blockade could be dysphoric in and of itself. Bradykinesia can look like a depression. Akathisia can lead to anxiety or panic and worsening depression as well. But the drugs that have more risk of EPS also tend to cause prolactin elevation, so there seems to be a relationship between prolactin and depression. Beyond the menstrual irregularities, sexual dysfunction, and potential long-term health concerns that are possible with hyperprolactinemia, a growing body of evidence suggests that prolactin elevation may be associated with depression. Much of this evidence is taken not from the psychiatric literature but from the reproductive literature and literature in endocrinology. For example, in *Gynecological Endocrinology*, Panay and Studd[32] reported that estrogen deficiency, which can occur with increased prolactin, mediates mood, cognition, and psychopathology.

Another theory is that prolactin may have a direct effect on mood, whether it is mediated through estrogen changes or not. Kellner and colleagues[33] reported the results of several studies that they conducted in women with hyperprolactinemia. The authors found increased depression, anxiety, and hostility, as well as decreased libido, in these women. Prolactin elevation in the postpartum stage especially was associated with greater rates of hostility and depression. In these studies, men with hyperprolactinemia did not exhibit more hostility than male controls with normal prolactin levels, and the investigators suggested that hostility in women with hyperprolactinemia may be an evolutionary remnant for protecting the young.

Many patients over the years have required both an antipsychotic and an antidepressant; this fact is further indication of a dysphoric side effect of some antipsychotics. However, the agents that spare prolactin tend to have a better effect on depression. This may or may not be a cause-and-effect situation but at least is an association.

There are data on haloperidol in the treatment of stuttering in which the drug improved fluency, but 2 to 3 months later patients wanted to stop it because they got depressed.[34] They felt dysphoric and slowed down. What clinicians have struggled with is how to treat the psychosis without worsening the mood, and how to treat the mood without worsening the psychosis. Today, data support use of the third-generation agents for a mood disorder and a comorbid psychotic disorder. The third-generation antipsychotics seem to not only avoid the dysphoric side effect of the older agents but also treat the depressive aspects of psychosis.

In the Tollefson et al.[35] blinded study of haloperidol versus olanzapine in patients with schizophrenia (N = 1996), the total scores on the Montgomery-Åsberg Depression Rating Scale (MADRS) were significantly more improved in the olanzapine group than in the haloperidol group ($p = .001$). The authors stated that mood improvement was indirectly related to improved positive, negative, and/or extrapyramidal symptoms, but most of the olanzapine effect on mood was a primary direct effect of the medication. In 300 patients with schizoaffective disorder, Tran et al.[36] found that patients taking olanzapine experienced significantly ($p \leq .01$) more improvement in depressive symptomatology than those taking haloperidol, as measured by the MADRS total scores. Similarly, when Tran et al.[17] compared olanzapine with risperidone in a 6-month trial, olanzapine-treated patients improved more on the depression item of the Positive and Negative Syndrome Scale.

In a study[37] comparing risperidone with haloperidol, there was a trend for risperidone to improve depressive symptoms slightly more than haloperidol, but the difference was not statistically significant. The mild effect of risperidone in improving depressive symptoms was only statistically significantly greater than that of placebo treatment ($p \leq .05$).

In an open-label study[38] of 446 patients taking quetiapine compared with 150 taking risperidone, quetiapine showed significantly ($p = .028$) greater improvement in depressive symptomatology as assessed with the Hamilton Rating Scale for Depression.

In a study[39] comparing ziprasidone with haloperidol in 403 subjects, significant improvement in depressive symptoms on the MADRS was found only against placebo, not between the 2 active drugs ($p < .05$ for haloperidol 15 mg/day, ziprasidone 40 mg/day, and ziprasidone 200 mg/day; $p < .01$ for ziprasidone 120 mg/day).

Using an agent that improves depression decreases the likelihood for suicide in patients with schizophrenia. Suicidal behavior in schizophrenia is impulsive and unpredictable, and depression is closely linked to the risk for suicide.[40] Close to half of patients with schizophrenia attempt suicide, and around 10% unfortunately complete suicide.[41] But olanzapine and clozapine, as compared with conventional antipsychotics, have been shown to provide a suicide prevention benefit.[42] These are the only 2

agents that have shown this effect in schizophrenia. When Tran et al.[17] followed 339 patients for 6 months, 1 olanzapine-treated patient made a suicide attempt, while 7 risperidone-treated subjects did so.

LOWERING ELEVATED PROLACTIN LEVELS

Prolactin levels can be reduced if they become raised during antipsychotic treatment. Drugs that are not associated with prolactin elevation can be used in patients who experience problems related to increased prolactin. David et al.[22] pointed out that when patients were switched from haloperidol to olanzapine, prolactin levels decreased significantly.

Alternatively, other agents that lower prolactin can be used to augment antipsychotic treatment if the patient should not be switched from the antipsychotic medication he or she is taking. Bromocriptine has been an effective treatment for postpartum depression and hostility.[33] Mattox et al.[43] found that the prolactin-lowering agents bromocriptine and pergolide each improved depression in women with tumors that produce prolactin (prolactinomas) who were studied over 20 weeks. In a case report[44] describing a 28-year-old woman who had taken a conventional antipsychotic for 7 years and developed osteoporosis, amenorrhea, and profuse galactorrhea, bromocriptine was beneficial.

It appears that risperidone raises prolactin levels more than any other atypical antipsychotic agent on the market does.[11,20,24] Premenopausal females may have prolactin levels of 100 µg/L or even 200 µg/L when taking risperidone.[24] There is less of an absolute effect in males, but the change in prolactin is of concern, as well as the level it reaches.

Prolactin levels should be measured at baseline in patients who are beginning treatment with agents that increase prolactin levels. Then, if clinical symptoms emerge, prolactin levels can be remeasured to see if there has been a change. For example, a female patient may have a prolactin level of 35 µg/L, which although above the normal range is not that severe. If this patient's baseline prolactin level was 10 µg/L, that would mean quite an increase had taken place. If her normal level was 25 µg/L, that would mean only a slight effect on prolactin had occurred. Only the presence of clinical symptoms, not an elevated prolactin level alone, should dictate changing a patient's treatment strategy. However, if a patient's prolactin level is above 100 µg/L, an MRI scan with fine cuts through the sellae should be considered to check for a pituitary adenoma.

For patients with clinical symptoms of prolactin elevation who are taking an antipsychotic that is known to raise prolactin levels, switching to a prolactin-sparing agent is the logical treatment, without necessarily measuring the patient's prolactin level. However, clinicians should remember that symptoms of menstrual irregularity can be brought about by many different causes and many different medications. If patients are unusually stressed or in a severe depression, their menstrual cycles can get off course. The patient should be asked questions that will elicit information about special circumstances that might be stressful for the patient. If the patient is taking more than one agent, or if it is unclear whether her menstrual irregularity is caused by stress or medication, it is wise to check the prolactin level. Ideally, the prolactin level should be tested a couple of times to get a true reading. The measurement should be done in either a nonfasting or a fasting state and at the same time of day both times, so that the results are similar each time.

Once the patient's prolactin level returns to normal, the associated symptoms should resolve. In women, menses will resume, libido should increase, and fertility may return to normal for the patient's age and health.[24] Estrogen levels should return to age-appropriate levels, thereby reducing the risks of genitourinary symptoms, decreased bone mineral density, and cardiovascular disease. Psychiatric symptoms and cognitive function may also improve as estrogen levels rise. In men, impotence should resolve as prolactin levels decrease.[45] Even bone density will improve as the prolactin level improves.

CONCLUSION

Prolactin elevation is a "Don't Ask, Don't Tell" side effect of certain antipsychotic medications. Patients are unlikely to voluntarily report symptoms they find embarrassing. During antipsychotic treatment check-ups, clinicians need to inquire about galactorrhea and gynecomastia, depressive symptoms, and sexual dysfunction because many patients are reluctant to raise these types of problems without being asked. Prolactin elevation is underdiagnosed but can have serious consequences. When selecting antipsychotic treatment for patients, clinicians must consider the long-term consequences of prolactin elevation with its potential effects on short-term and long-term health problems, poor compliance, and depression.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), pergolide (Permax), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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