Adverse Effects of Antipsychotics and Mood Stabilizers

December 31, 2007

Although psychotropic medications have revolutionized the treatment of many psychiatric disorders, the benefits sometimes come at a price. Unwanted adverse effects may limit the use of these agents and may, in some instances, result in serious morbidity and mortality.

In recent years, the adverse effects of second-generation antipsychotics on body weight have become a significant concern for clinicians and their patients; however, other metabolic effects of these drugs, as well as metabolic effects of first-generation antipsychotics and mood stabilizers, also require our attention and awareness. In this article we focus on the phenomenology, evaluation, and management of endocrine and metabolic adverse effects of these commonly used psychotropic agents.

**Lithium and thyroid function**

At therapeutic serum levels, the main action of lithium is to inhibit hormone release from the thyroid gland, which may result in hypothyroidism. Patients with underlying Hashimoto thyroiditis or radiation-induced thyroid injury may be particularly susceptible to this inhibitory effect.\(^1\) In adults, the prevalence of lithium-induced hypothyroidism generally increases with longer duration of therapy--about 20% of women and 5% of men are affected with hypothyroidism after 10 years of continuous treatment.\(^2\) The results of a pediatric study also suggest that patients taking both lithium and valproate may be at particularly high risk of having hypothyroidism develop, since the weak inhibitory action of valproate on the thyroid may synergize with the effects of lithium.\(^3\) Patients should have baseline thyroid function tests (at least for serum thyroid-stimulating hormone [TSH]) performed before beginning lithium treatment; since lithium-induced hypothyroidism may occur at any time during lithium therapy.\(^1-3\) Tests should be repeated 1 to 2 months, 6 months, and 12 months after starting lithium, and yearly thereafter. If hypothyroidism occurs during lithium treatment, replacement thyroid hormone therapy with levothyroxine should be started, and the dosage increased as needed to normalize serum TSH. Since lithium-induced hypothyroidism may occasionally be transient, it may be useful to try to slightly decrease the daily thyroxine dose after several years of treatment; if the serum TSH remains normal on the lower dose, further dose reductions may then be attempted.\(^1\)

**Lithium and parathyroid function**

Mild hypercalcemia may develop in patients receiving lithium, generally in the range of 10.5 to 11.5 mg/dL, with normal or mildly elevated serum levels of parathyroid hormone, usually along with decreased urinary calcium excretion. This constellation of abnormalities appears to be due to a lithium-induced loss of sensitivity of the parathyroid calcium-sensing receptor; the parathyroid gland perceives a higher than normal serum calcium level as normal, and parathyroid hormone secretion is regulated around an elevated set point.\(^4\) About 5% of patients receiving long-term lithium therapy have been found to have hypercalcemia.\(^5,6\) The hypercalcemia is usually not progressive, and kidney stones are uncommon (since the patients are usually hypocalciuric). Although the hypercalcemia is usually reversible if lithium is discontinued, in some instances it has been persistent, and parathyroid adenomas or multigland parathyroid hyperplasia have been found in some patients with lithium-induced hypercalcemia.\(^7\) Because hypercalcemia may occur at any time during lithium therapy,\(^4,7\) serum calcium should be measured 1, 6, and 12 months after starting lithium, and yearly thereafter. If serum calcium levels exceed 11.5 mg/dL or if clinical signs and symptoms of hyperparathyroidism (eg, fatigue, nausea, constipation, worsening osteoporosis) develop, lithium may need to be discontinued.

**Antipsychotics and hyperprolactinemia**

Prolactin secretion is primarily regulated through the suppressive action of dopamine, which is secreted from hypothalamic neurons and delivered to the anterior pituitary through the...
Adverse Effects of Antipsychotics and Mood Stabilizers

Published on Psychiatric Times (http://www.psychiatrictimes.com)

Polycystic ovary syndrome (PCOS) is defined as chronic anovulation and hyperandrogenism, with or without actual polycystic ovaries. Although not all PCOS patients are obese, insulin resistance is the norm, even in patients of normal weight. Recent reports have suggested that women of menstrual age who received valproate were at increased risk for the development of PCOS, characterized by oligomenorrhea, increased serum androgens with resulting hirsutism and acne, and, in some cases, a polycystic ovarian morphology seen on pelvic sonography. Joffe and colleagues recently reported that PCOS developed in about 10% of women with bipolar disorder who were started on valproate without actual polycystic ovaries. Although not all PCOS patients are obese, insulin resistance is the norm, even in patients of normal weight.

If the serum prolactin level is greater than 200 ng/mL or remains elevated despite a change to a different medication, it may be helpful to add a small dose of aripiprazole, which will usually suppress serum prolactin by virtue of its partial dopamine-agonist properties. Women tend to have higher prolactin responses to antipsychotics than men because estrogen stimulates prolactin synthesis and responsiveness. The approximate relative potency of antipsychotics in causing hyperprolactinemia is (in order of decreasing potency) risperidone, haloperidol, olanzapine, ziprasidone, quetiapine, clozapine, and aripiprazole.

Prolactin acts on the hypothalamus to suppress the secretion of gonadotropin-releasing hormone, which results in decreased secretion of luteinizing hormone and follicle-stimulating hormone and, ultimately, hypogonadism. In women, the hypogonadism is manifest most commonly as secondary amenorrhea and infertility; decreased libido and osteoporosis can occur in both women and men as a result of decreased gonadal production of sex steroids. Breast enlargement and breast pain can be seen in both men and women; galactorrhea is more common in women, who have estrogen-primed breasts. Although hyperprolactinemia-induced hypogonadism might be expected to slow pubertal development, normal pubertal progression over a 12-month period was observed in the only study to date that specifically addressed this issue.10 Erectile dysfunction may also occur, perhaps as a direct effect of prolactin on the nervous system11 as well as an effect of hypogonadism.

A recent study based on adverse-event reports submitted to the FDA has suggested that antipsychotic-induced hyperprolactinemia may be associated with an increased incidence of benign, presumably prolactin-secreting pituitary adenomas.12 There were 77 cases of pituitary tumors reported in patients taking antipsychotic agents; 54 of these involved risperidone, the drug with the greatest propensity to cause hyperprolactinemia. Although a causal relationship cannot be excluded, it seems more likely that symptomatic hyperprolactinemia developed in patients receiving antipsychotics, particularly risperidone, who then underwent MRI scanning of the pituitary as part of a diagnostic evaluation. Since incidental pituitary tumors (usually nonfunctioning) are found on MRI scans in about 10% of the general population,13 the tumors found in the patients treated with antipsychotics may bear no relationship to the drug therapy.

During drug therapy, the physician should inquire about menstruation, nipple discharge, breast enlargement, sexual functioning, and (if appropriate) pubertal development. If these are normal, there is no need to measure serum prolactin. However, if problems in these areas are uncovered that are temporally related to antipsychotic therapy, serum prolactin level should be measured. If the level of serum prolactin is elevated but less than 200 ng/mL in a symptomatic patient, other causes of hyperprolactinemia (such as pregnancy, hypothyroidism, and renal failure) should be excluded by measuring serum human chorionic gonadotropin, TSH, and creatinine levels. If these tests are negative, one might try to decrease the dosage of the antipsychotic medication or change treatment to an agent less likely to elevate serum prolactin. If it is not possible to lower the dosage or switch to a different medication, it may be helpful to add a small dose of aripiprazole, which will usually suppress serum prolactin by virtue of its partial dopamine-agonist properties. Dopaminergic drugs, such as bromocriptine or cabergoline, can also be given but may occasionally worsen the underlying psychosis.15

If the serum prolactin level is greater than 200 ng/mL or remains elevated despite a change to a prolactin-sparing agent, an MRI scan of the sella turcica should be performed to exclude a pituitary or parasellar tumor. If the appearance on the MRI scan is normal, one might add aripiprazole or bromocriptine (as above), prescribe sex steroids (eg, oral contraceptives for women of menstrual age, testosterone for men), or give drugs to prevent osteoporosis (eg, bisphosphonates).9

Valproate and polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is defined as chronic anovulation and hyperandrogenism, with or without actual polycystic ovaries. Although not all PCOS patients are obese, insulin resistance is the norm, even in patients of normal weight.15 Recent reports have suggested that women of menstrual age who received valproate were at increased risk for the development of PCOS, characterized by oligomenorrhea, increased serum androgens with resulting hirsutism and acne, and, in some cases, a polycystic ovarian morphology seen on pelvic sonography. Joffe and colleagues17 recently reported that PCOS developed in about 10% of women with bipolar disorder who were started on valproate.
Adverse Effects of Antipsychotics and Mood Stabilizers
Published on Psychiatric Times
(http://www.psychiatrictimes.com)

Antipsychotics and metabolic adverse events
Recently, the focus on the tolerability of antipsychotics has shifted from extrapyramidal syndrome (EPS) toward adverse effects on body weight and related metabolic consequences that seem to be more common with atypical than with typical antipsychotics. The concerns about weight gain are fueled by ample evidence that increased body weight and obesity, particularly increased visceral fat agglomeration, are associated with greatly increased risks for diabetes, dyslipidemia, and hypertension (the metabolic syndrome; see Table 1) and are related to increased coronary heart disease morbidity and mortality. In addition, antipsychotic-induced weight gain has been associated with a lower quality of life and impaired medication adherence. Data suggest that there is an increased prevalence of obesity, diabetes, and dyslipidemia in patients with schizophrenia and bipolar disorder compared with the general population. Increased relative risk estimates range from 2 to 3 times the risk for obesity and diabetes to 4 to 5 times the risk for dyslipidemia. Likewise, prevalence rates for the metabolic syndrome and for calculated 10-year coronary heart disease events have been shown to be about twice as high in patients with schizophrenia and in patients with mixed diagnoses receiving atypical antipsychotics. Rates in patients with bipolar disorder have also been higher than in the general population, although they seem to be less elevated than in patients with schizophrenia.

Antipsychotic effects on body weight and glucose and lipid metabolism
The elevated rate of physical disorders in patients with mental illness is probably the result of a complex interaction of genetic, psychiatric, lifestyle, and treatment factors. Within this multifactorial etiology, medications contribute to weight gain and adverse metabolic outcomes to varying degrees. Clozapine and olanzapine have been shown to have the greatest propensity to lead to weight gain and obesity; quetiapine and risperidone rank intermediate; and, at least in studies of adults with the most extensive antipsychotic treatment histories, aripiprazole and ziprasidone appear to be least associated with adverse effects on body composition. Since weight gain and obesity are associated with increased rates of diabetes and lipid abnormalities in the general population, it is not surprising that atypical antipsychotics have been shown to increase glucose and lipid levels. In general, the adverse effect of the atypical agents on glucose and lipid metabolism follows the order of magnitude of weight gain. However, several recent studies suggest that clozapine and olanzapine, at least, may also have weight-independent, "direct" adverse effects on glucose homeostasis.

Mechanisms of weight gain
Unfortunately, the exact mechanisms of antipsychotic-induced weight gain are unclear. While increased caloric intake is the most favored hypothesis, decreased resting metabolic rate and energy expenditure have also been proposed, although studies have shown mixed results. Proposed mechanisms for these effects include blockade of various neurotransmitter receptor systems, including histamine, serotonin, and a- and b-adrenergic receptors. It is unclear to what degree antipsychotics also interact with any of the multiple hormones and neuropeptides that are relevant for food intake and energy homeostasis.

Monitoring and management
Since the greater recognition of the metabolic risk of atypical antipsychotics, monitoring guidelines have been proposed around the world. In the United States, the American Diabetes Association guidelines and Mt Sinai guidelines are the most prominent. These guidelines recommend baseline assessments of family history of metabolic syndrome components, as well as the assessment in each patient of height and weight, waist circumference, blood pressure, and fasting glucose and lipid.
levels (Table 2). Weight should be checked monthly for the first 3 months and quarterly thereafter. Blood pressure and fasting glucose and lipid levels should be checked at 3 months and then annually (even though earlier recommendations had proposed measurements every 5 years if lipid levels were normal at 3 months). More frequent assessments are recommended for patients with metabolic risk factors, including a family history of diabetes or early cardiovascular death, and/or marked weight gain. Monitoring early weight gain can also be helpful to identify high-risk patients because early weight gain strongly predicts continued weight gain. Furthermore, the presence of abdominal obesity (ie, waist circumference greater than 40 inches in men and greater than 35 inches in women) had a greater than 90% sensitivity for identifying patients receiving atypical antipsychotics who fulfilled criteria for the metabolic syndrome. Measurements to attenuate or reverse medication-induced weight gain and metabolic complications include healthy lifestyle education and behavioral weight loss interventions or pharmacological augmentation with a weight loss agent, such as metformin, sibutramine, orlistat, to-piramate, amantadine, or bupropion. An alternative for the potential reversal of antipsychotic-induced weight gain and metabolic consequences is to switch the patient to an antipsychotic with a lower metabolic burden. However, in the absence of reliable response predictors, the most cost-effective and simple preventive measure is to begin treatment with a lower metabolic risk agent and to use higher metabolic risk antipsychotics only in those patients who do not benefit from this medically driven treatment choice.

**Summary**

Balancing effectiveness of psychotropic medications with their potential for adverse effects is a crucial component of the successful treatment of mental disorders. With few exceptions (eg, diabetic ketoacidosis), endocrine and metabolic side effects are in many ways less acute and overt than other commonly observed adverse effects, such as sedation, EPS, and anticholinergic disorders. However, disruption of normal endocrine function can have serious long-term consequences. Therefore, clinicians need to be familiar with potential adverse effects and be prepared to implement appropriate monitoring and management strategies.

**Drugs mentioned in this article**

Amantadine (Symmetrel)
Aripiprazole (Abilify)
Bromocriptine (Parlodel)
Bupropion (Wellbutrin, Zyban)
Cabergoline (Dostinex, Cabaser)
Clozapine (Clozaril)
Haloperidol (Haldol)
Lamotrigine (Lamictal)
Levothyroxine, Thyroxine (Synthroid, others)
Lithium (Eskalith, Lithane, Lithobid)
Metformin (Glucophage, others)
Olanzapine (Zyprexa)
Orlistat (Xenical)
Quetiapine (Seroquel)
Risperidone (Risperdal)
Sibutramine (Meridia)
Topiramate (Topamax)
Valproate/Valproic acid (Depakote, others)
Ziprasidone (Geodon)

**Drugs Mentioned In This Article**

Amantadine (Symmetrel)
Aripiprazole (Abilify)
Bromocriptine (Parlodel)
Bupropion (Wellbutrin, Zyban)
Cabergoline (Dostinex, Cabaser)
Clozapine (Clozaril)
Haloperidol (Haldol)
Lamotrigine (Lamictal)
Levothyroxine, Thyroxine (Synthroid, others)
Lithium (Eskalith, Lithane, Lithobid)
Metformin (Glucophage, others)
Olanzapine (Zyprexa)
Orlistat (Xenical)
Quetiapine (Seroquel)
Risperidone (Risperdal)
Sibutramine (Meridia)
Topiramate (Topamax)
Valproate/Valproic acid (Depakote, others)
Ziprasidone (Geodon)

References:


Source URL: http://www.psychiatrictimes.com/psychopharmacology/adverse-effects-antipsychotics-and-mood-stabilizers

Links: