Endocrine and Metabolic Adverse Effects of Psychotropic Medications in Children and Adolescents

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ABSTRACT

Objective: Despite increasing use of psychotropic medications in children and adolescents, data regarding their efficacy and safety are limited. Endocrine and metabolic adverse effects are among the most concerning adverse effects of commonly used psychotropic medications. **Method:** Selective review of endocrine and metabolic effects of psychotropic medications in pediatric populations, with a focus on monitoring and management strategies. **Results:** Because youth are still developing at the time of psychotropic drug exposure, most reference values need to be adjusted for gender and age. As in adults, youngsters receiving lithium require monitoring for thyroid dysfunction. Psychostimulants appear to cause mild reversible growth retardation in some patients, most likely because of decreased weight or slowing of expected weight gain; some patients may experience clinically significant reductions in adult height. Although still controversial, valproate use has been associated with an increased risk for polycystic ovary syndrome, in addition to causing weight gain. Although more data are required, children and adolescents appear to be at higher risk than adults for antipsychotic-induced hyperprolactinemia, weight gain, and possibly, associated metabolic abnormalities, which is of particular concern. **Conclusions:** Clinicians and caregivers need to be aware of potential endocrine and metabolic adverse effects of psychiatric medications. A careful selection of patients, choice of agents with potentially lesser risk for these adverse events, healthy lifestyle counseling, as well as close health monitoring are warranted to maximize effectiveness and safety. *J. Am. Acad. Child Adolesc. Psychiatry,* 2006;45(7):771–791. **Key Words:** antipsychotics, mood stabilizers, metabolic, endocrine, side effects, children and adolescents.

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During the last decade, psychotropic medications have been prescribed in increasing amounts to children and adolescents, including preschoolers (Olfson et al., 2002; Wong et al., 2004; Zito et al., 2000), in some instances approaching adult utilization rates (Zito et al., 2003). Psychotropic agents are being used for multiple disorders, such as attention-deficit/hyperactivity disorder, mood and anxiety disorders, externalizing disorders, and psychotic disorders (Bhangoo et al., 2003; Guevara et al., 2002; Kelly et al., 2004; Lyons et al., 2004; Staller et al., 2005), even though research evidence for their safety and efficacy in pediatric populations is still sparse (Cheng-Shannon et al., 2004; Findling and McNamara, 2004; Kowatch and DelBello, 2003; Pappadopulos et al., 2004). Recently, the vast gap between the use of psychotropic medications in youths and the available data regarding their efficacy and safety in pediatric populations

has been more fully addressed (Jensen et al., 1999; Vitiello and Jensen, 1997). This has led to a concerted initiative by researchers, policymakers, and the pharmaceutical industry to close this gap (Vitiello et al., 2004). Although the majority of treatment data still is extrapolated from controlled trials in adults, this is likely to change in the next several years. In addition to the traditional focus on efficacy, the authors of these studies need to pay attention to the area of effectiveness, including functional outcome and quality of life, as well as to the standardized assessments of safety and tolerability as these concepts pertain to pediatric populations (Greenhill et al., 2003, 2004; Vitiello et al., 2003).

In this article, we focus on the adverse event potential of psychotropic medications in pediatric populations. In particular, we deal only with their liability to lead to endocrine and metabolic abnormalities. By reviewing common endocrine and metabolic adverse events of psychotropic medications during development, this article aims to increase the awareness of these specific side effects of psychotropic medications and provide recommendations for monitoring and management strategies of such adverse effects in children and adolescents who are in a period of physiologically occurring hormonal, endocrine, and anthropometric changes. It is important to note, however, that the presented monitoring and management recommendations are not treatment guidelines developed as part of an expert consensus panel. In the absence of a more authoritative statement, the strategies suggested in this article are based on a still-limited body of literature on endocrine and metabolic effects of psychotropic drugs in children and adolescents, which were supplemented by extrapolations from data in adult samples.

METHOD

The authors selectively reviewed pertinent literature on endocrine and metabolic side effects of psychotropic medications, focusing on studies and case reports that included children and/or adolescent populations. Relevant articles were obtained by an electronic PubMed literature search, using the following search terms: children or adolescents or pediatric; psychotropic drugs or mood stabilizers or antipsychotics, or psychostimulants; thyroid or parathyroid gland or hypothyroidism; growth or growth retardation; prolactin (Prl) or hyperprolactinemia; weight gain, obesity, dyslipidemia, hyperglycemia, or diabetes; or polycystic ovary syndrome. The identified literature was reviewed for pertinence to the present article and supplemented by a hand search of cited articles and literature known to the authors. Data were included in this review regarding effects of psychotropic drugs on the thyroid and parathyroid gland, antidiuretic hormone release from the posterior pituitary gland, growth, Prl secretion, body composition, glucose and lipid metabolism, and gonadal hormone balance. Furthermore, data were included that provide guidelines regarding monitoring and management strategies for endocrine and metabolic adverse effects of psychotropic medications. Finally, the authors also sought input from several experts in the pediatric endocrine and metabolic area who made further suggestions regarding the presented monitoring and management recommendations.

RESULTS

Psychotropic Drug Effects on Thyroid Function: Lithium, Valproate and Quetiapine

The potential of lithium to adversely affect thyroid function is well known in adults (Kleiner et al., 1999), with fewer data being available in children and adolescents (Gracious et al., 2004; Kafantaris et al., 2003). In addition, antithyroid effects of valproic acid (Eiris-Punal et al., 1999; Vainionpaa et al., 2004) and quetiapine in pediatric populations have been described (Dobbs et al., 2004; McConville et al., 2000). At high concentrations, lithium can inhibit many aspects of thyroid function, but at therapeutic serum levels, the main effect is inhibition of thyroid hormone release from the gland (Kleiner et al., 1999). The fall in circulating thyroid hormone levels causes an increase in serum thyroid-stimulating hormone (TSH), which can stimulate thyroid growth, resulting in goiter and nodularity. These effects of lithium on the thyroid gland are usually reversible when the drug is discontinued or when thyroid hormone replacement therapy is initiated (Bocchetta et al., 1996; Lydiard and Gelenberg, 1982).

Data in adult populations suggest that certain patients may be more susceptible to the inhibitory effects of lithium on the thyroid (Johnston and Eagles, 1999; Kallner and Petterson, 1995; Kleiner et al., 1999; Kusalic and Engelsmann, 1999; Perrild et al., 1990). For example:

1. Patients with thyroid glands damaged by radiation
2. Patients with autoimmune Hashimoto's thyroiditis or circulating antithyroid antibodies
3. Cigarette smokers (who are at increased risk for Hashimoto's thyroiditis)
4. Patients with a family history of thyroid disease
5. Female patients (who are at higher risk of Hashimoto's thyroiditis than males)
6. Patients taking divalproex because valproate may itself have mild inhibitory effects on the thyroid

(Eiris-Punal et al., 1999; Vainionpaa et al., 2004), and lithium may synergize with this

Existing data in adults suggest that lithium administration leads to elevations in serum TSH in 5% to 50% of patients, probably averaging around 10% to 20% (Johnston and Eagles, 1999; Kallner and Petterson, 1995; Kleiner et al., 1999; Kusalic and Engelsmann, 1999; Perrild et al., 1990). In some cases, TSH elevations are transient. However, the percentage of lithium-treated patients with elevated TSH rises with time and does not seem to plateau (Johnston and Eagles, 1999; Kleiner et al., 1999; Kusalic and Engelsmann, 1999; Perrild et al., 1990). There are few data in children and adolescents. In a 4-week study by Kafantaris et al. (2003), lithium produced only minor, transient elevations in serum TSH, which corrected spontaneously. However, in a 20-week study, in which lithium was administered along with divalproex, 24% of patients developed serum TSH >10 μU/mL (Gracious et al., 2004).

Valproic acid, given alone, had a mild antithyroid effect in some studies, with modest rises in TSH seen in some subjects (Eiris-Punal et al., 1999; Vainionpaa et al., 2004). Quetiapine has been noted to decrease serum total T4 in some studies. Although the mechanism of this effect is unknown, serum free thyroxine and TSH generally remain within the normal range in pediatric (McConville et al., 2000) and adult (Kelly and Conley, 2005) patients receiving quetiapine, suggesting that subjects receiving quetiapine remain euthyroid.

Suggested Management.

1. Obtain baseline thyroid function tests (at least serum TSH) before starting lithium treatment. Patients who are hypothyroid at baseline can be treated with lithium, but be aware that lithium may further impair any residual thyroid function, requiring dose adjustments of the thyroid hormone replacement therapy.
2. Recheck thyroid function tests 1 to 2 months after starting lithium, then at 6 and 12 months after starting lithium, and yearly thereafter.
3. If a patient becomes hypothyroid on lithium, then start thyroxine therapy and titrate the dose until TSH becomes normal. Seek medical consultation if necessary.
4. In some patients, lithium-induced hypothyroidism is transient, and TSH may normalize after 1–2 years of lithium treatment. There are few data on how to check for this in a patient receiving thyroxine replacement therapy; minimally, one could try to slightly reduce the thyroxine dose and see whether TSH remains normal.
5. Patients receiving valproate or quetiapine without lithium should probably have thyroid function tests monitored at 3 months and at 1 year, with additional measurements every 3 months if TSH is elevated; treatment with thyroxine is not needed unless serum TSH rises above the normal range.

Psychotropic Drug Effects on Parathyroid Function: Lithium

Lithium may also adversely affect the parathyroid gland, occasionally causing mild hypercalcemia (Kallner and Petterson, 1995; Kusalic and Engelsmann, 1999), although data in pediatric samples are missing. Patients with lithium-induced hypercalcemia have mild hypercalcemia (typically in the range of 10.5–11.5 mg/dL), normal or mildly elevated serum parathyroid hormone (typical normal reference range 10–65 pg/mL) and decreased urinary calcium. In adults, the hypercalcemia is usually benign and nonprogressive, and is usually reversible when lithium is stopped (Mallette and Eichhorn, 1986). Because the urine calcium excretion is decreased, patients are not at increased risk for kidney stones. The mechanism of this effect appears to involve a resetting of the calcium-sensing mechanism in the parathyroid glands, such that, in the presence of lithium, the parathyroid glands perceive an elevated serum calcium level as normal. Thus, the parathyroid glands have become less sensitive to the parathyroid hormone–suppressing effects of hypercalcemia (i.e., the set point, around which serum calcium is regulated, has been raised; Haden et al., 1997; Shen and Sherrard, 1982). It is important to note that there are virtually no published systematic data on serum calcium concentrations in children treated with lithium. Because many studies of lithium use in children were designed to monitor routine serum chemistries, this may mean no abnormalities were found, but confirmatory evidence is needed.

Suggested Management. Based on the literature for adults, check baseline serum calcium before starting lithium therapy. Recheck serum calcium at 1, 6, and 12 months after starting lithium, and yearly thereafter (Mallette and Eichhorn, 1986). Lithium does not need to be discontinued unless serum calcium is >11.5 mg/dL.

Psychotropic Drug Effects on Antidiuretic Hormone Secretion

In adults, selective serotonin reuptake inhibitors (SSRIs) and the mood stabilizers carbamazepine and oxcarbazepine are known to cause asymptomatic and, occasionally, symptomatic hyponatremia (Fabian et al., 2004; Movig et al., 2002; van Amelsvoort et al., 1994). Although the mechanisms are not entirely clear, these psychotropic agents may directly stimulate the secretion of antidiuretic hormone from the posterior pituitary gland or alter either the sensitivity or set point of the osmoreceptor (Gandelman, 1994).

Both with SSRIs and carbamazepine or oxcarbazepine, older age and concurrent use of diuretic medications are known risk factors, with higher levels of carbamazepine or oxcarbazepine being an additional risk factor (Gandelman, 1994; Lahr, 1985; Madhusoodanan et al., 2002). To date, no cases of SSRI-related hyponatremia have been reported in children or adolescents; however, carbamazepine and, possibly even more so, oxcarbazepine have the potential to cause hyponatremia in children. Based on the limited data, asymptomatic hyponatremia (i.e., $\leq$125 mmol/L) and symptomatic hyponatremia appear to occur in only about 1% to 2% of children and adolescents treated with carbamazepine (Koivikko and Valikangas, 1983) or oxcarbazepine (Holtmann et al., 2002).

Suggested Management. Check serum electrolytes in youngsters receiving SSRIs only if they have otherwise unexplained mental slowing, somnolence, reduced food intake, vomiting, or seizures. If the serum sodium is lower than 130 mmol/L, then water intake should be restricted and in mild cases lowering of the carbamazepine or oxcarbazepine dose can be attempted. In more severe cases, rule out psychogenic polydipsia and consider switching to an alternative psychotropic medication without the potential for hyponatremia.

Psychotropic Drug Effects on Growth: Psychostimulants

Psychostimulants are among the best-documented and well-studied treatments in children and adolescents. It has long been known that some children receiving psychostimulants as treatment for attention-deficit/hyperactivity disorder (ADHD) may experience a slowing of growth, although the frequency and magnitude of this effect is still controversial (for a critical review of published studies, see Poulton, 2005). Typically, height velocity (i.e., yearly gain in height) slows by $\approx$1 cm/year for the first several years of stimulant administration, particularly for the first 6 months, then later resumes at an approximately normal rate (Faraone et al., 2005; MTA Cooperative Group, 2004; Pliszka, 1998; Poulton and Cowell, 2003). Greater slowing of growth may be seen in prepubertal children and in children who are overweight or taller at baseline (Faraone et al., 2005; Spencer et al., 2005). Final adult height is usually normal, although data concerning this point are limited; some individual patients (perhaps 10%) may experience more significant slowing of growth, which may result in permanent deficits in ultimate height (Klein and Mannuzza, 1988; Kramer et al., 2000; Pliszka, 1998). Current trends in prescribing stimulants continuously into adulthood may conceivably result in greater long-term height deficits than were seen in earlier studies involving short-term or intermittent therapy. In addition, the recently introduced sustained-release stimulant preparations appear to result in somewhat greater suppression of growth in height and weight than the immediate-release formulations, at least for amphetamines (Faraone et al., 2005). Growth retardation appears to be found less often in girls than in boys (Biederman et al., 2003). However, as far as this has been investigated, pubertal development does not appear to be slowed in either gender (Biederman et al., 2003; Spencer et al., 1996).

The mechanism of this slowing of linear growth is unclear; it may be caused, in large part, by decreased appetite and food intake while receiving stimulants (Faraone et al., 2005; Pliszka, 1998; Poulton and Cowell, 2003; Spencer et al., 1998), as suggested by concurrent loss of weight or less-than-expected weight gain during development. Growth hormone secretion and action appear to be normal or nearly so (Bereket et al., 2005; Rao et al., 1998; Spencer et al., 1998). Small, transient decreases in serum insulin-like growth factor-1, the mediator of growth hormone action, may occur early in treatment with methylphenidate; mild decreases in serum thyroxine within the normal range were also seen (Bereket et al., 2005). Patients who experience persistent nausea and vomiting as a side effect of stimulants may have the greatest slowing of growth (Kramer et al., 2000). Atomoxetine, a nonstimulant ADHD medication that inhibits norepinephrine reuptake more selectively in the frontal lobe, causes less weight loss than traditional stimulants (Christman et al., 2004); a recent compilation

of data from multicenter clinical trials has reported minimal slowing of growth in height and weight in the majority of subjects receiving atomoxetine for ADHD during a 2-year period (Spencer et al., 2005).

Suggested Management. Height and weight should be measured and plotted on a growth chart before beginning stimulants; prior growth records and parental heights should be obtained, if available. Practice parameters published by the American Academy of Child and Adolescent Psychiatry recommend repeat measurements of height and weight at yearly intervals (AACAP Official Action, 2002). If height-for-age decreases by >1 SD while on stimulant treatment, it would be prudent to obtain pediatric endocrine consultation to exclude other disorders that could cause slowing of growth, such as growth hormone deficiency or hypothyroidism, and to assist in deciding if any intervention is needed. Children experiencing clinically significant growth retardation may benefit from reducing the stimulant dose, instituting drug holidays, or changing to an alternative medication not associated with growth delay and/or weight loss.

Psychotropic Drug Effects on Prl Levels: Antipsychotics

Atypical antipsychotics are generally preferred over typical antipsychotics because they cause fewer acute (Kane, 2001) and chronic neuromotor effects (Correll et al., 2004). Moreover, many atypical antipsychotics also cause less hyperprolactinemia than conventional neuroleptics, although this effect varies across agents and is dose dependent.

Secretion of Prl from pituitary lactotroph cells is primarily regulated by tonic inhibition by dopamine; dopamine is secreted from the median eminence of the hypothalamus into the hypothalamic-pituitary portal plexus and transported to the anterior pituitary, where it acts on D2-dopamine receptors on lactotrophs to inhibit Prl secretion. Antipsychotic medications are D2-dopamine receptor antagonists and can therefore raise serum Prl by blocking this tonic inhibitory effect (Haddad and Wieck, 2004; Maguire, 2002).

Typical antipsychotics, such as chlorpromazine or haloperidol, all raise serum Prl acutely. However, in both adults and children, serum Prl levels frequently decrease spontaneously over time during chronic therapy, sometimes to normal values, even though the drug is continued (Brown and Laughren, 1981; Kinon et al., 2003a). Atypical antipsychotics are more variable in their effects on Prl. The atypical antipsychotics vary in their affinity for the D2 dopamine receptor, rate of dissociation from the receptor, and ability to act on the receptor as both a dopamine agonist (which would lower serum Prl) and a dopamine antagonist (which would increase serum Prl; Findling et al., 2003; Grunder et al., 2003; Haddad and Wieck, 2004; Maguire, 2002). Based on adult (David et al., 2000; Haddad and Wieck, 2004; Kane et al., 2002; Kinon et al., 2003b; Maguire, 2002; Potkin et al., 2003; Smith, 2003) and child data (Alfaro et al., 2002; Cheng-Shannon et al., 2004; Pappagallo and Silva, 2004; Saito et al., 2004; Sallee et al., 2000; Shaw et al., 2001; Wudarsky et al., 1999), the relative potency of antipsychotic drugs in inducing hyperprolactinemia is, roughly: Risperidone > Haloperidol > Olanzapine > Ziprasidone > Quetiapine > Clozapine > Aripiprazole.

Both adults and children may develop hyperprolactinemia in response to antipsychotics, but there is some suggestion that this effect may be more pronounced in postpubertal children and adolescents than in adults (Woods et al., 2002; Wudarsky et al., 1999). This may be caused by an age-related decrease in dopamine receptors (Seeman et al., 1987). Additional factors may include the fact that prepubertal samples were often cotreated with psychostimulants to a significant degree, which may counteract some of the dopamine-blocking effects of antipsychotics in the tubero-infundibular pathway, and that Prl-related adverse effects may be more readily measurable or expressed in sexually mature adolescents. Because estrogen stimulates Prl synthesis and enhances Prl responses to all Prl stimulants, women of reproductive age (including adolescents) generally have greater Prl responses to antipsychotics than do prepubertal girls or males of any age (Kinon et al., 2003a, b). This has been reconfirmed in pediatric case reports, as well as in a number of open-label and randomized trials (Alfaro et al., 2002; Cheng-Shannon et al., 2004; Findling et al., 2003; Pappagallo and Silva, 2004; Saito et al., 2004; Sallee et al., 2000).

Hyperprolactinemia may have several effects on the body:

1. Action on the hypothalamus to suppress gonadotropin-releasing hormone secretion and, consequently, secretion of luteinizing hormone and follicle-stimulating hormone from the pituitary, leading to

hypogonadism (amenorrhea, low estrogen in females; low testosterone in males)
2. Action on the breast to stimulate glandular growth and breast milk production, particularly in females
3. Possible direct action on the nervous system to suppress penile erection
4. Possible (controversial) action on the adrenal gland to stimulate secretion of adrenal androgens (dehydroepiandrosterone-sulfate and androstenedione)
5. Possible (controversial) delay in pubertal maturation

The signs and symptoms of hyperprolactinemia are direct consequences of the above actions, and include the following (Halbreich and Kahn, 2003; Maguire, 2002; Miller, 2004; Saito et al., 2004):

1. Amenorrhea or oligomenorrhea in women of reproductive age
2. Breast enlargement/engorgement in males and females
3. Galactorrhea, in females more than in males
4. Libido decreased in both genders
5. Erectile dysfunction in males
6. Osteoporosis caused by hypogonadism in both males and females
7. Failure to enter or progress through puberty in children
8. Possibly hirsutism in females
9. Possible (controversial) relationship to benign pituitary tumors

However, as demonstrated in open-label (Masi et al., 2003; Saito et al., 2004) and randomized studies (Aman et al., 2002) in youths, serum Prl levels are not tightly correlated with these side effects and not all patients with hyperprolactinemia develop these signs and symptoms (Masi et al., 2003). In fact, many adult and pediatric patients continue to have normal gonadal function and no galactorrhea, despite moderately elevated serum Prl (Findling et al., 2003; Haddad and Wieck, 2004; Kinon et al., 2003b; Kleinberg et al., 1999). This may be because of variable individual sensitivities to the effects of hyperprolactinemia, down-regulation of receptor sensitivity, and, in part, to the presence of different molecular forms of Prl with reduced in vivo bioactivity (Smith et al., 2002). Although data are limited, antipsychotic-induced hyperprolactinemia in children often appears to normalize over time (Croonenberghs et al., 2005; Findling et al., 2003). However, this evidence is mostly based on samples predominantly consisting of prepubertal boys who have lower Prl levels to begin with. Nevertheless, most children and adolescents with drug-induced hyperprolactinemia seem to progress normally through puberty (Dunbar et al., 2004). Interestingly, in this pooled database of five studies that included 700 children ages 5 to 15 years with disruptive behavior disorders who received risperidone treatment for 11 or 12 months, growth was accelerated despite Prl elevations. Although growth was not correlated with Prl levels, the more likely reason for this finding is the increase in weight associated with antipsychotic treatment (see following section).

Finally, a recent report has raised the concern that the propensity of a medication to cause hyperprolactinemia may be related to a risk for pituitary tumors. In an unpublished pharmacovigilance study of adverse drug reactions reported to the U.S. Food and Drug Administration since 1968, a higher prevalence of benign tumors of the pituitary gland was found among patients taking risperidone compared with those taking other second-generation antipsychotics or haloperidol (Szarfman et al., 2005). Of 307 reports of pituitary tumors, 64 (20.8%) occurred in patients taking antipsychotic medications (4 in children), and 44 (68.8%) of those involved risperidone. Although this association needs to be clarified further, a potential selection bias and/or cohort effect need to be excluded in controlled studies before one can conclude causality. For example, the higher number of reports of benign pituitary tumors associated with risperidone could be explained by the greater number of patients having been prescribed risperidone, which was the first second-generation antipsychotic to be approved and which has been the number-one prescribed antipsychotic for many years. Another reason for this finding could be that patients taking risperidone are more likely to have hyperprolactinemia or Prl-related side effects than other antipsychotics, which makes it also more likely for them to receive an MRI to rule out the presence of a prolactinoma. In turn, this would also increase the number of reports of benign pituitary tumors, which are present as silent pituitary "incidentalomas" in between 3% and 27% of autopsies and pituitary MRI scans (Chanson and Young, 2003; Oyama et al., 2005).

Suggested Management.

1. In patients receiving antipsychotic medication, inquire about menstruation, nipple discharge, sexual

functioning and pubertal development. If normal, there is no need to measure serum Prl.
2. If problems are found in these areas, which appear to be temporally related to antipsychotic drug therapy, then check serum Prl.
3. If serum Prl is elevated above the normal range, then inquire whether the female patient is taking any form of hormonal contraception and obtain a pregnancy test to rule out pregnancy because both (particularly pregnancy) can elevate Prl levels. In addition, obtain serum TSH and serum creatinine (to rule out hypothyroidism and renal failure, which can also elevate Prl).
4. If serum Prl is <200 ng/mL, then try reducing the dose of the antipsychotic or changing to a more Prl-sparing drug such as aripiprazole, quetiapine, or, in cases with treatment resistance, clozapine (Anghelescu and Wolf, 2004; Keller and Mongini, 2002; Kim et al., 2002; Takahashi et al., 2003).
5. If serum Prl is >200 ng/mL or is persistently elevated despite change to a Prl-sparing drug, then obtain an MRI scan of the sella turcica to look for a pituitary adenoma or parasellar tumor.
6. If the MRI scan is normal, then sex steroids (estrogen or testosterone) could be replaced to treat the hypogonadism, or drugs such as bisphosphonates (e.g., alendronate, risedronate) could be given to treat osteoporosis.
7. A few patients have been treated with dopamine agonists such as cabergoline or amantadine, with partial resolution of the effects of hyperprolactinemia, although psychosis is sometimes worsened (Cavallaro et al., 2004; Cohen and Biederman, 2001; Siever, 1981). The potential for worsening of psychosis can be avoided and Prl levels can be lowered by adding aripiprazole (Wahl and Ostroff, 2005), a drug with partial dopamine agonist properties.
8. Because serum Prl tends to decline and may even normalize with continued antipsychotic drug therapy in both adults (Brown and Laughren, 1981; Kinon et al., 2003a) and children (Croonenberghs et al., 2005; Findling et al., 2003), it may be reasonable in patients who benefit from the treatment and who have only mild Prl-related symptoms to wait 6 to 12 months to determine whether symptoms resolve and hyperprolactinemia diminishes with the passage of time.

Psychotropic Drug Effects on Weight and the Metabolic Syndrome: Antipsychotics and Mood Stabilizers

Psychiatric patients often gain weight, and the mean weight of adult patients with severe mental illness is significantly greater than that of the population without mental illness (Susce et al., 2005). Weight gain, however, is a particular problem when occurring in childhood (Dietz and Robinson, 2005). Many factors contribute to weight gain in psychiatric patients, including sedentary lifestyle, poor diet, and medication effects. Excessive weight gain has several deleterious effects in psychiatric patients, including stigmatization and further social withdrawal, noncompliance with medication, and medical morbidity and mortality, including dyslipidemia, diabetes mellitus, polycystic ovary syndrome, hypertension, sleep apnea, and osteoarthritis (Bray, 2004; Goff et al., 2005). Although an association between weight gain and clinical response to antipsychotic medications has been described in adults (e.g., Ascher-Svanum et al., 2005, Czobor et al., 2002) and children (Masi et al., 2003; Sporn et al., 2005), this association can be explained by the inappropriate use of the last observation carried forward method for both efficacy and weight gain assessments and lack of consideration of nonadherence as a confounder. Patients with less or inadequate response or with treatment nonadherence are more likely to drop out early during the trial and have less time to gain weight compared with patients who are considered responders who stay in the trial longer and/or who adhere to their treatment regimen (Hennen et al., 2004).

The potential for significant weight gain associated with atypical antipsychotics has been a particular concern in the vulnerable pediatric population (Stigler et al., 2004), which may be at even higher risk as compared with adult populations (Ratzoni et al., 2002; Safer, 2004; Sikich et al., 2004; Woods et al., 2002). In addition, other agents, particularly lithium and divalproex, may also induce weight gain in pediatric populations (Egger and Brett, 1981; Henry et al., 2003), and combining these agents with an atypical antipsychotic may lead to more severe problems (Kane et al., 2004).

It is important to note, however, that body weight is expected to rise in growing children, so that merely noting an increase in body weight over time does not in itself signify a problem. Body mass index (BMI) is a

useful way to express body weight adjusted for height because weight is expected to be greater in taller individuals. BMI is calculated as:

$$\text{BMI} = (\text{weight in kg}) / (\text{height in meters})^2$$

or

$$\text{BMI} = (\text{weight in pounds} \times 703) / (\text{height in inches})^2$$

Norms for BMI also change with age and gender; thus, the patient's BMI needs to be compared to a set of values derived from normal children of the same age and gender. Tables and charts of normal values for BMI-for-age are available from the Centers for Disease Control (www.cdc.gov/growthcharts). BMI-for-age can be used continuously from age 2 years through adulthood, and teenage BMI-for-age correlates with BMI, blood pressure, and serum lipids in middle-age adults. To quickly obtain sex- and age-adjusted BMI percentiles and *Z*-scores for a given patient, a Web-based calculator (http://www.kidsnutrition.org/bodycomp/bmiz2.html) is available that calculates results based on data from the third National Health and Nutrition Examination Survey (1988–1994).

Despite the growing concern about abnormal weight gain and obesity in childhood and adolescence (Dietz and Robinson, 2005), a generally accepted definition of clinically significant weight gain during development does not exist. Because it is of importance to determine when the weight gain that can occur with psychotropic medications becomes a health problem, a set of criteria for clinically significant, abnormal weight gain in children and adolescents who are treated with psychotropic medications has recently been proposed (Table 1; Correll et al., 2006a).

The relative weight gain of 5% compared to baseline weight during the first 3 months of treatment was chosen because during this relatively short period normal growth does not contribute to weight change in a relevant way and also because this threshold is consistent with recent recommendations in adults (ADA Consensus Development Conference, 2004). For longer observation periods, however, the weight change needs to be adjusted for sex- and age-adjusted norms. An increase in BMI *Z*-score of ≥0.5 was proposed because Weiss et al. (2004) found that this degree of growth-adjusted weight gain increased the risk for metabolic syndrome by 55%. Finally, youngsters in the "at risk" weight category (i.e., ≥ 85th–94.9th BMI percentile) who already have at least one negative weight-related clinical outcome and youths with BMI or waist circumference percentiles in the overweight/obese category are at high risk for adverse health outcomes and require close monitoring or interventions to reduce the risk, independent of where they started when psychotropic drug treatment began.

All of the atypical antipsychotics share a tendency to promote weight gain, especially in drug-naïve patients (Correll et al., 2005a), but some of these agents appear to be more likely to do so than others. Although larger, long-term studies are clearly needed to better define the relative risks of weight gain in children and adolescents, data from adults (ADA Consensus Development Conference, 2004; Allison et al., 1999; Casey et al., 2004) and from an ongoing, large scale naturalistic study in children and adolescents (Correll et al., 2005a) suggest the following rank order in terms of ability to promote weight gain and development of the metabolic syndrome: Clozapine = Olanzapine >> Risperidone ≥ Quetiapine > Ziprasidone ≥ Aripiprazole.

TABLE 1
Proposed Criteria for the Definition of Significant Weight Gain/Changes in Body Composition in Children and Adolescents

Duration of Treatment	Threshold for Significant Change in Body Composition
First 3 Months	>5% of weight increase compared to baseline
Any Duration	≥0.5 increase in BMI *Z*-score
	Crossing into the "at risk" weight category (i.e., ≥85–94.9 BMI percentile) plus presence of 1 other obesity-related complication, such as hypertension (i.e., ≥90th percentile), dyslipidemia (i.e., fasting cholesterol ≥200 mg/dL, LDL-cholesterol >130 mg/dL, HDL-cholesterol <40 mg/dL, triglycerides ≥150 mg/dL), hyperglycemia (i.e., fasting glucose ≥100 mg/dL), insulin resistance (i.e., fasting insulin >20 μmol/L; Williams et al., 2002), orthopedic disorders, sleep disorders, or gallbladder disease
	Crossing into obesity (i.e., ≥95th BMI percentile) or abdominal obesity (i.e., ≥90th waist circumference percentile)

Note: BMI = body mass index; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

TABLE 2
Criteria for the Metabolic Syndrome in Adults, Children, and Adolescents[a]

Metabolic Syndrome Criteria in Adults (NCEP ATPIII)[b]	Metabolic Syndrome Criteria in Children and Adolescents[c]
Abdominal obesity (i.e., waist circumference ≥102 cm [≥40 in.] in males and ≥88 cm [≥35 in.] in females)	Waist circumference ≥90th percentile, or BMI ≥ 95th percentile (i.e., "overweight")
Fasting serum triglyceride levels ≥150 mg/dL	Fasting serum triglyceride levels ≥110 mg/dL
Fasting HDL-cholesterol <40 mg/dL in males and <50 mg/dL in females	Fasting HDL-cholesterol <40 mg/dL in males and females
Blood pressure ≥130/85 mmHg	Blood pressure ≥90th percentile for sex and age
Fasting glucose ≥110 mg/dL	Fasting glucose ≥110 mg/dL

Note: NCEP = National Cholesterol Education Program.
[a] At least 3 criteria must be met.
[b] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001.
[c] Cook et al., 2003; Weiss et al., 2004.

In addition to and as a potential result of significant weight gain, atypical antipsychotic treatment has been associated with lipid abnormalities, such as elevated triglyceride, total cholesterol and low-density lipoprotein (LDL)-cholesterol levels, and/or decreased high-density lipoprotein (HDL)-cholesterol levels, in adults (Lindenmayer et al., 2003; Meyer, 2001, 2002; Wirshing et al., 2002) and in youths (Correll et al., 2005b). Moreover, weight gain and obesity are also associated with the metabolic syndrome, a constellation of physical and laboratory features that is more common in obese patients and predisposes adults (Bray, 2004; Grundy, 2004) and children (Berenson et al., 1998, Li et al., 2003; McGill et al., 2000; Raitakari et al., 2003) to atherosclerotic cardiovascular disease. The features of the metabolic syndrome are abdominal obesity, dyslipidemia (principally elevated serum triglycerides and low HDL-cholesterol), glucose intolerance, and hypertension. A common cause for all features of the metabolic syndrome appears to be insulin resistance, which can result from weight gain.

Several criteria have been used to define the syndrome in adults, but the most widely accepted is the National Cholesterol Education Program Adult Treatment Panel III definition (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001) that requires the presence of at least three of five criteria (see Table 2). Because in children, normal values for the parameters that are part of the metabolic syndrome change with age, height, and gender, modified criteria have been proposed for use in children and adolescents (see Table 2; Cook et al., 2003; DeFerranti et al., 2004; Weiss et al., 2004). Table 3 lists resources to determine the sex- and age-adjusted values during development.

The metabolic syndrome occurs in about 5% to 10% of all adolescents in the U.S. population and in >30% of those who are overweight (Cook et al., 2003; DeFerranti et al., 2004; Duncan et al., 2004). Importantly, the occurrence of the metabolic syndrome in young individuals predicts early atherosclerosis and vascular disease as adults (Berenson et al., 1998; Li et al., 2003; Raitakari et al., 2003). Moreover, obesity during adolescence predicts later coronary artery disease and colorectal cancer even more strongly than obesity as an adult (Must et al., 1992). The metabolic syndrome has

TABLE 3
Resources to Obtain Sex- and Age-Adjusted BMI, Waist Circumference, and Blood Pressure for Children and Adolescents

Sex- and Age-Adjusted Parameters	Resource for Calculation
BMI percentile	Growth charts: www.cdc.gov/growthcharts
BMI percentile and *Z*-scores	Web-based calculator: http://www.kidsnutrition.org/bodycomp/bmiz2.html
Waist circumference percentile	Tables: Fernandez et al., 2004
Blood pressure percentiles	Tables: National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004

Note: BMI = body mass index.

also been found to be more prevalent in adults treated with atypical antipsychotics compared to the healthy population (Almeras et al., 2004; Basu et al., 2004; Cohn et al., 2004; Correll et al., 2006b; Heiskanen et al., 2003; McEvoy et al., 2005; Straker et al., 2005). Data on the prevalence of metabolic syndrome are missing for children and adolescents treated with antipsychotics. In antipsychotic-treated adults (Cohn et al., 2004; McEvoy et al., 2005) and particularly in those with the metabolic syndrome (Correll et al., 2006b), the 10-year risk for coronary heart disease events is elevated. However, the relationship between atypical antipsychotics and the metabolic syndrome has also been disputed because illness and genetic and unhealthy lifestyle factors may also be responsible (Mackin et al., 2005; Toalson et al., 2004). Nevertheless, because weight gain is a leading pathway to the metabolic syndrome, this risk needs to be considered in youngsters receiving psychotropic medications that can increase weight.

Diabetes mellitus is another much-feared consequence of significant weight gain and obesity. Although there may be differences among atypical antipsychotics, the U.S. Food and Drug Administration has issued a "black box" warning about the development of diabetes mellitus in patients receiving any atypical antipsychotic. In case reports, diabetes has been described in children and adolescents receiving these agents (Courvoisie et al., 2004; Koller et al., 2004; Saito and Kafantaris, 2002; Selva and Scott, 2001). Some of these patients developed diabetic ketoacidosis or nonketotic hyperosmolar states associated with extreme hyperglycemia, and there have been several deaths in adults because of uncontrolled diabetes. Although weight gain undoubtedly plays a role in the development of diabetes and insulin resistance in patients receiving atypical antipsychotics, there may also be direct effects on insulin secretion (Ader et al., 2005; Bergman and Ader, 2005; Henderson et al., 2005). Based on adult data, patients at high risk for diabetes or dyslipidemia include those with obesity; those who rapidly gain weight on the antipsychotic drug; those with a family history of diabetes, hyperlipidemia, or early coronary heart disease; nonwhite ethnic groups; and patients receiving either olanzapine or clozapine (Henderson, 2001). Furthermore, treatment with divalproex, alone or in conjunction with antipsychotics, may increase the risk for insulin resistance and diabetes, which has been described in adult (Luef et al., 2002; Pylvanen et al., 2003; Roste et al., 2005) and pediatric populations (Correll et al., 2005c; Saito and Kafantaris, 2002).

Suggested Management — Preventive and Ameliorative Interventions. General strategies and principles of weight control described for youths include controlling the environment, monitoring behavior, setting goals, rewarding successful behaviors, identifying and solving problems, and adapting parental skills (Dietz and Robinson, 2005). Specific preventive and interventional strategies aimed at minimizing weight gain and related health problems associated with psychotropic medications are summarized in Table 4. These strategies include educating and monitoring as well as reinforcing healthy

TABLE 4

Strategies for the Prevention and Management of Weight Gain and Metabolic Abnormalities in Patients Receiving Psychotropic Medications

Healthy lifestyle behaviors
1. Replace all drinks containing sugar (soda, punch, juice), "diet" drinks, and whole milk with at least 2 L of water and moderate amounts of unsweetened tea or low-fat milk
2. Eat every 3–4 hours, with no more than 2 meals in the evening or at night
3. Eat small portions at meals
4. Eat breakfast every morning
5. Eat slowly, drink an ample amount of water between bites, and take second helpings only after a delay
6. Eat no more than one fast food meal per week
7. Replace refined white flour and processed sugar products with whole-grain and other food items that have a low glycemic index (i.e., ≤55; http://www.glycemicindex.com)
8. Do not snack when full and replace high-fat, high-calorie snacks with ample amounts of fruits or vegetables
9. Limit saturated fat intake, but avoid extensive consumption of processed fat-free food items
10. Eat at least 25–30 g/day of soluble fiber from fruits, vegetables, and/or whole grains
11. Limit watching television or playing computer/video games to <2 hours/day
12. Perform moderate to vigorous physical activity for at least 30–60 minutes/day
Medication choice
Avoid starting treatment with medications that are associated with marked or extreme weight gain
Consider switching to an agent that is associated with less weight gain potential
Additional weight loss treatment (if weight gain/obesity remain problematic despite the first and second strategies)
Initiate/refer to formalized, nonpharmacological weight loss program
Initiate adjunctive pharmacological weight loss treatment

lifestyle behaviors; choosing an agent with a lower likelihood of adverse effects on body composition and metabolic status, ideally, at the beginning of treatment or when marked initial weight gain becomes apparent; and initiating a formalized, nonpharmacological weight loss treatment (e.g., special diet, Weight Watchers, behavioral weight management program) or a pharmacological intervention if the first and second steps insufficiently addressed weight gain and metabolic complications. Therapies that have had some success in producing weight loss in pediatric patients receiving antipsychotics include metformin (Morrison et al., 2002), topiramate (Pavuluri et al., 2002), amantadine (Gracious et al., 2002), and orlistat (Chanoine et al., 2005). Dyslipidemia should be treated initially with dietary measures; if this is not sufficient, drug therapy may be given with a fibric acid derivative (gemfibrozil or fenofibrate), a statin, fish oil, or niacin, if appropriate. Diabetes may be treated with diet, oral hypoglycemic agents, or insulin, as needed, but it should also be remembered that diabetes induced by atypical antipsychotic agents may sometimes disappear when the drug is stopped or changed (Cheng-Shannon et al., 2004; Domon and Webber, 2001).

For the prevention of weight gain and related metabolic complications, the initial choice of a psychotropic agent with the least negative impact, as well as healthy lifestyle counseling that promotes a healthy diet and regular exercise, should be an integral part of any treatment with a mood stabilizer or antipsychotic medication. Although therapeutic lifestyle changes have shown modest efficacy in reducing weight gain that has already occurred in adults (Ball et al., 2003; Menza et al., 2004; Vreeland et al., 2003), these measures may be even more effective in the prevention or attenuation of weight gain caused by psychotropic medications, particularly in normal-weight individuals that have not yet failed multiple attempts at implementing therapeutic lifestyle changes.

Strategies for the prevention of weight gain and obesity in children and adolescents are presented in Table 4. For these strategies to be successful, interventions must be simple, realistic, and measurable. Moreover, the entire family system should be involved (Hopper et al., 2005). Not surprisingly, studies have shown strong associations between parental BMI, food intake, and attitudes toward activity and those observed in their children (Davison and Birch, 2001; Francis et al., 2003). Furthermore, the entire spectrum of unhealthy lifestyle behaviors should be targeted in youngsters and their parents because focusing on the remediation of just one aspect of weight gain–promoting behavior, such as a high-fat diet, for example, is easily counterbalanced by other behaviors, such as deriving up to one third of daily calories from fast foods, snacks, and desserts (Van Horn et al., 2005). Summarized below are the data from studies in children and adolescents that guided the selection of the proposed management options. In general, to limit weight gain associated with psychotropic medications, parents and children should pay attention to the amount, frequency, and type of foods and drinks consumed. At the same time, families should decrease the amount of sedentary behaviors and increase exercise.

1. Sugar-containing drinks should be replaced with at least 2 L of water per day and moderate amounts of unsweetened tea or fat-reduced milk because sugar-containing beverages (Berkey et al., 2004; Giammattei et al., 2003; Harnack et al., 1999; Ludwig et al., 2001) and large amounts of milk (Berkey et al., 2005) have been found to promote weight gain. In general, liquid forms of energy appear to be less satiating than solid food (DiMeglio and Mattes, 2000; Himaya and Louis-Sylvestre, 1998). More important, although still a matter of debate (American Dietetic Association., 2004), so-called diet drinks that contain artificial sweeteners may increase food intake more than ingestion of water alone (Blum et al., 2005), possibly because of adaptation to a disassociation between sweetness (ordinarily calorie rich and appetite suppressing) and energy content (Appleton et al., 2004; King et al., 1999; Lavin et al., 1997).
2. The average number of meals should be approximately four to less than six meals per day because lower or higher numbers seem to be associated with higher BMI and rates of obesity (i.e., a lower number of meals leads to a reduction in metabolic rate to retain calories during a supposed shortage, whereas a higher number of meals is associated with greater caloric intake; Thompson et al., 2006). In addition, the average number of meals in the evening or at night, when fewer calories are used, should be less than two (Thompson et al., 2006).
3. The serving size of meal portions, which has increased in fast food restaurants over the past decade, should be reduced because larger portions

have been shown to increase food intake both in normal weight and overweight individuals (Rolls et al., 2002). This can be accomplished by serving food directly onto plates or by the use of smaller plates.

4. Patients should be encouraged to consume the greater amount of their daily calories earlier in the day, when there is still ample time to burn them. Eating breakfast regularly was associated with lower BMIs in children and adolescents (Affenito et al., 2005; Barton et al., 2005).
5. Food should be eaten slowly and second helpings obtained only after a sufficient time delay because it takes time for the local satiety signals to reach the brain and abort food intake (Woods, 2005), thereby reducing the risk of overeating as a result of increased appetite and fast consumption of large amounts of food.
6. Fast food intake should be limited to no more than once per week because the number of fast food meals has been associated with negative body composition outcomes in children and adolescents (Thompson et al., 2004).
7. Food consumed should preferentially have a low glycemic index (GI). Although data are conflicting (Liese et al., 2005; Nielsen et al., 2005; Raben, 2002), consumption of a low GI meal has shown to prolong satiety (Ball et al., 2003), reduce caloric intake (Warren et al., 2003), and improve insulin resistance status (Ebbeling et al., 2003). The GI of food signifies its ability to raise blood sugar. A GI of ≤55 is considered low, a GI of 56 to 69 is considered medium, and a GI of ≥70 is considered high. (The GI for any food type can be found at http://www.glycemicindex.com.)
8. Snacking in a sated state, often occurring during television watching (Matheson et al., 2004a,b), should be avoided because snacks consumed by adults in a sated state 215 minutes after lunch did not decrease overall energy intake at dinner as compared with eating no snacks (Marmonier et al., 2002). At the same time, high-fat, high-calorie snacks should be replaced with fruits and vegetables.
9. Families should also reduce saturated fat intake, but avoid extensive consumption of processed fat-free food items (German and Dillard, 2004). Saturated fat intake has been associated with blood lipid abnormalities in youth (Nicklas et al., 2002). Many processed reduced-fat and fat-free food items have an added carbohydrate load that increases energy intake without causing as much satiety as a balanced food that contains some fat. More important, dairy products, an excellent source of calcium, do not have to be reduced drastically because they have not been associated by themselves with higher BMI in children (Berkey et al., 2005; Phillips et al., 2003).
10. Youngsters and their families should consume at least 25 to 30 g/day of soluble fiber from fruits, vegetables, and whole grains because higher fiber intake increases postmeal satiety, which decreases subsequent feeding as well as cholesterol levels (Holmes and Kwiterovich, 2005; Liese et al., 2005).
11. Families should limit the time spent watching television to no more than 2 hours/day (Committee on Nutrition, 2003). This pertains to video and computer games as well because time spent watching television or playing video/computer games has been associated with higher BMI in children (Berkey et al., 2000). Therefore, it is advisable to budget screen time and to remove television sets and computers from the bedrooms of obese or overweight children and those who spend more than the recommended 2 hours sitting in front of a screen.
12. Youngsters should perform moderate to vigorous physical activity for at least 30–60 minutes/day (Fulton et al., 2004) because aerobic exercise has been shown to improve insulin resistance and HDL-cholesterol status in adults and youths, even independent of weight loss (Boule et al., 2005; Katzel et al., 1995; Kimm et al., 2005; Patrick et al., 2004; Raitakari et al., 1996). In addition, adult studies have shown that exercise also improves compensatory regulation of food intake after high caloric intake (i.e., significantly fewer calories are consumed after exercise to make up for high caloric intake before exercise), whereas this compensatory decrease is not as efficient in nonexercising individuals (Blundell et al., 2003). A recent study of 878 adolescents ages 11 to 15 years, 42% of whom were from minority backgrounds, found that failing to meet the 60 minutes/day moderate-to-vigorous physical activity guideline was associated with overweight status for

both girls and boys (Patrick et al., 2004). To achieve this goal, parents should also try linking unhealthy behaviors with desired physical activity, for example, making a rule that a child can watch his or her favorite show on television only if the child uses the treadmill or similar devices for the first 30 minutes of the show.

Despite having good face validity, it must be noted that the strategies detailed above and proposed in Table 4 are based on data from nonpsychiatric pediatric samples. Therefore, their effectiveness in pediatric populations treated with psychotropic medications that can increase weight still need to be established. Nevertheless, at this stage of knowledge, clinicians may want to instruct families to post Table 4 in an easily accessible place in the kitchen (e.g., the refrigerator) so that every family member is encouraged to adopt healthy lifestyle behaviors that can help to minimize weight gain and metabolic complications.

Monitoring Strategies. Monitoring patients on atypical antipsychotic agents should include measurements of body height and weight at each visit and the BMI percentile should be calculated. Blood pressure also should be routinely assessed. In view of data indicating that abdominal obesity is most closely related to the metabolic syndrome in adults treated with antipsychotics (Straker et al., 2005), quarterly measurements of waist circumference may also be helpful. Children and adolescents are still growing, so these data are only useful for them in conjunction with the use of age- and sex-adjusted waist circumference percentiles (Fernandez et al., 2004). Monitoring for diabetes should include a baseline fasting blood glucose measurement before a drug is instituted, if possible; follow-up blood glucose determinations should be performed at 3 months after starting the drug and every 6 months thereafter. High-risk patients (as above) should have fasting blood glucose measurements performed at least quarterly. Patients should be asked at each visit about unintended weight loss, polyuria, and polydipsia, which, if present, could indicate the onset of hyperglycemia. In conjunction with fasting blood sugar measurements, a fasting serum lipid panel should be obtained at baseline before drug therapy is begun, at 3 months after starting the drug, and every 6 to 12 months thereafter if results are within normal limits and BMI percentile values are stable. Although diabetes mellitus is a temporally more distant but serious potential side effect of psychotropic medications associated with weight gain, an earlier indicator of increased risk for diabetes consists of increasing insulin resistance. Insulin resistance denotes a compensatory increase in insulin secretion in response to increasing body fat mass, particularly abdominal fat, to keep fasting blood glucose stable (Rosenbloom et al., 1999). Although insulin resistance can be measured, calculating the product of fasting insulin (μmol) × fasting blood glucose (mmol/L)/22.5 (Matthews et al., 1985) to obtain insulin measurements, which are not subject to standardized assays in the United States, is expensive and impractical. Recently, the ratio of fasting triglycerides to HDL-cholesterol was proposed as a widely applicable and sensitive measure of insulin resistance (McLaughlin et al., 2005). The same authors (McLaughlin et al., 2005) proposed a triglyceride/HDL-cholesterol ratio of 3.5 mg/dL as the threshold to predict insulin resistance and LDL phenotype in adults with a sensitivity and specificity that is comparable to the metabolic syndrome criteria proposed by the Adult Treatment Panel III (i.e., sensitivity, 52%, and specificity, 85%; Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). Based on these data, it appears that calculating the triglyceride/HDL-cholesterol ratio from the results of the lipid panel may provide clinicians with an easy tool to track the effect of psychotropic medications on insulin resistance in their adult patients and to identify patients who need to expend greater effort in targeting weight loss and exercising or who require a change in medication treatment or referral to a medical specialist. This use of the triglyceride/HDL-cholesterol ratio has yet to be replicated in other adult populations and to be validated in children and adolescents, however.

It is important to note that although it may be sometimes difficult and infeasible to obtain fasting baseline blood work for glucose and lipids in severely ill and/or uncooperative youngsters, every attempt should be made to obtain such fasting blood work as close as possible to the initiation of an antipsychotic or valproic acid. This is important because only baseline values will allow a proper risk–benefit evaluation. The clinical relevance of a strongly abnormal or borderline abnormal metabolic value vis-à-vis an observed pharmacological treatment efficacy will depend greatly on whether these abnormalities are just a little different from premorbidly abnormal levels or represent a substantial increase from baseline.

Psychotropic Drug Effects on Weight and the Polycystic Ovary Syndrome: Valproic Acid

Polycystic ovary syndrome (PCOS) is defined as chronic anovulation and hyperandrogenism, with or without actual polycystic ovaries. Clinical features include oligomenorrhea, hirsutism, and acne. PCOS is linked with insulin resistance and dyslipidemia, and many (but not all) patients with PCOS are obese. Growth in stature is normal, as is the timing of puberty. Risk factors for PCOS include family history of PCOS, Caribbean Hispanic and African American ancestry, history of premature pubarche, and/or obesity (Driscoll, 2003). Although subject to considerable debate, a consensus appears to be emerging that administration of divalproex is associated with an increased risk of PCOS (El-Khayat et al., 2004; Isojarvi et al., 2001; McIntyre et al., 2003; Mikkonen et al., 2004; Morrell et al., 2003; O'Donovanet al., 2002; Stephen et al., 2001; Vainionpaa et al., 1999). In a recent study of 230 adult females, oligoamenorrhea with hyperandrogenism developed in 9 (10.5%) of 86 women on valproate compared to only in 2 (1.4%) of 144 women on a nonvalproate anticonvulsant or lithium (relative risk 7.5, $p = .002$; Joffe et al., 2006). Nevertheless, the mechanisms and risk factors for this effect are still unclear. Recent laboratory studies have reported that valproate increases the expression of androgen biosynthetic enzymes in cultured ovarian

TABLE 5

Endocrine and Metabolic Monitoring in Children and Adolescents Treated with Second-Generation Antipsychotics and Mood Stabilizers

Assessments Before Choosing SGA or Mood Stabilizer	Assessments Before Starting SGA or Mood Stabilizer	Follow-up Assessments	Frequency of Follow-up Assessments[a]
Personal and family medical history	Height, weight	Height, weight	At each visit
Dietary habits	Blood pressure, pulse	Blood pressure, pulse	3-monthly
Exercise habits	Fasting blood work[b]	Dietary habits	Monthly for 3 mo and 3-monthly
Daytime sedation	Prolactin[c]	Exercise habits	Monthly for 3 mo and 3-monthly
Appetite level		Daytime sedation	Monthly for 3 mo and 3-monthly
Sexual symptoms/signs		Appetite level	Monthly for 3 mo and 3-monthly
Height, weight[d]		Sexual symptoms/signs	Monthly for 3 mo and 3-monthly
Blood pressure, pulse[d]		Fasting blood work[b]	At 3 months and 6-monthly
Fasting blood work[b,d]		Prolactin[c]	Only when symptomatic
Prolactin[c,d]		Thyroid-stimulating hormone[e,f]	At 1,[e] 3,[f] 6 mo[e] and annually
Thyroid-stimulating hormone[d,e,f]		Serum calcium[e]	At 1 mo, 6 mo, and annually[e]
Serum calcium[d,e]			

Note: SGA = second-generation antipsychotics.

[a] Earlier and/or more frequent assessments are indicated if patients develop significant weight gain or metabolic abnormalities.

[b] Full blood count with differential, serum electrolytes, liver and kidney function, thyroid-stimulating hormone, glucose, and lipid profile.

[c] In case of abnormal sexual symptoms or signs; draw fasting in the morning and approximately 12 hours after the last antipsychotic dose.

[d] Optional assessments to inform choice of an SGA will depend on patient condition and appropriateness of waiting for test results.

[e] If started on lithium.

[f] If started on valproic acid or quetiapine.

cells (Nelson-DeGrave et al., 2004). Large prospective studies are needed to clarify the nature of this apparent association, which may involve more than just the effects of weight gain because atypical antipsychotics may also cause substantial weight gain but do not appear to be associated with an increased risk of PCOS. Therefore, at each visit, patients taking valproic acid derivatives should be asked about menstrual dysfunction (irregular or missed menses), as well as hirsutism and acne.

Suggested Management. Patients taking valproic acid drugs should be counseled regarding diet and exercise in an attempt to avoid weight gain. If the patient is manifesting oligomenorrhea or hirsutism, then pediatric/medical/endocrinologic/gynecologic referral may be appropriate for institution of treatment with either a combination oral contraceptive or progestin. Additional treatment options include insulin-sensitizing agents (e.g., metformin), antiandrogens, topical treatments for acne, and various treatments for hirsutism. Other mood stabilizers (e.g., lithium, lamotrigine) do not appear to be associated with PCOS and may be substituted for divalproex if needed (Isojarvi et al., 2001; Joffe et al., 2006; McIntyre et al., 2003; Morrell et al., 2003; O'Donovan et al., 2002; Stephen et al., 2001).

Summary and Clinical Implications

The endocrine and metabolic adverse effects of psychotropic medications can limit their use in children and adolescents. More important, in youths such medication effects occur in the context of physiological changes in hormonal and endocrine levels and body composition. This means that normal adult values must be adjusted to account for age- and sex-appropriate developmental changes. These changes include use of the BMI percentiles or *Z*-scores instead of weight or BMI to assess the young person's body composition. In addition, lipid thresholds need to be adjusted and percentile cutoffs are to be used for waist circumference and blood pressure measurement. Clinicians should be vigilant about the potential for thyroid dysfunction and weight gain with lithium; PCOS, weight gain and insulin resistance with valproate; and hyperprolactinemia, weight gain, and all components of the metabolic syndrome with atypical antipsychotics. Young people treated with these agents should have assessments of the respective clinical and laboratory parameters at baseline and regularly thereafter (see Table 5).

As always, primary prevention is preferable over secondary prevention. This means that in the absence of available predictors for efficacy in a given individual, those treatments should be selected first that are most acceptable to patients and that have the least potential for individually relevant adverse effects. Furthermore, healthy lifestyle counseling at the time of treatment initiation, rather than after adverse metabolic effects have occurred, is the preferred strategy, even though its effectiveness for the prevention of weight gain in populations treated with antipsychotics or mood stabilizers still must be demonstrated. In cases of significant adverse changes, clinical symptoms, or abnormal laboratory values, patients should either be switched to an agent with a decreased risk for these adverse events or receive additional treatments. Taking into account the different endocrine and metabolic effects of psychotropic medications and the special considerations that apply to pediatric populations will enable clinicians to more comprehensively treat youngsters who are in need of often long-term psychotropic medication treatment.

It is important to re-emphasize that the monitoring and management recommendations made in this article are based on the existing and still-limited database in children and adolescents reviewed by the authors. Even though many of the suggested strategies may have face value, they should not be mistaken as treatment guidelines based on ample and definitive evidence. In the absence of such data, however, the presented recommendations are a preliminary attempt at providing guidance to clinicians who are faced with the management of psychiatrically ill patients who are in need of psychotropic drug treatment. Clearly, more research is needed to study the most appropriate monitoring strategies and intervals and to compare different management options to help select the most effective treatments for the prevention and amelioration of endocrine and metabolic adverse effects of psychotropic medications that are frequently used in pediatric populations.

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Widening Social Inequalities in Risk for Sudden Infant Death Syndrome Kate E. Pickett, PhD, Ye Luo, PhD, Diane S. Lauderdale, PhD

Objectives: In 1994, the US Public Health Service launched the "Back to Sleep" campaign, promoting the supine sleep position to prevent sudden infant death syndrome (SIDS). Studies of SIDS in the United States have generally found socioeconomic and race disparities. Our objective was to see whether the "Back to Sleep" campaign, which involves an effective, easy, and free intervention, has reduced social class inequalities in SIDS. *Methods:* We conducted a population-based case-cohort study during 2 periods, 1989 to 1991 and 1996 to 1998, using the US Linked Birth/Infant Death Data Sets. Case group was infants who died of SIDS in infancy (N = 21,126); control group was a 10% random sample of infants who lived through the first year and all infants who died of other causes (N = 2,241,218). Social class was measured by mother's education level. *Results:* There was no evidence that inequalities in SIDS were reduced after the Back to Sleep campaign. In fact, odds ratios for SIDS associated with lower social class increased between 1989–1991 and 1996–1998. The race disparity in SIDS increased after the Back to Sleep campaign. *Conclusions:* The introduction of an inexpensive, easy, public health intervention has not reduced social inequalities in SIDS; in fact, the gap has widened. Although the risk of SIDS has been reduced for all social class groups, women who are more educated have experienced the greatest decline. **American Journal of Public Health** 2005;95:1976–1981.