Olanzapine approved for the acute treatment of schizophrenia or manic/mixed episodes associated with bipolar I disorder in adolescent patients

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Background: Severe and persistent mental illnesses in children and adolescents, such as early-onset schizophrenia spectrum (EOSS) disorders and pediatric bipolar disorder (pedBP), are increasingly recognized. Few treatments have demonstrated efficacy in rigorous clinical trials. Enduring response to current medications appears limited. Recently, olanzapine was approved for the treatment of adolescents with schizophrenia or acute manic/mixed episodes in pedBP.

Methods: PubMed searches were conducted for olanzapine combined with pharmacology, schizophrenia, or bipolar disorder. Searches related to schizophrenia and bipolar disorder were limited to children and adolescents. The bibliographies of the retrieved articles were hand-checked for additional relevant studies. The epidemiology, phenomenology, and treatment of EOSS and pedBP, and olanzapine's pharmacology are reviewed. Studies of olanzapine treatment in youth with EOSS and pedBP are examined.

Results: Olanzapine is efficacious for EOSS and pedBP. However, olanzapine is not more efficacious than risperidone, molindone, or haloperidol in EOSS and is less efficacious than clozapine in treatment-resistant EOSS. No comparative trials have been done in pedBP. Olanzapine is associated with weight gain, dyslipidemia, and transaminase elevations in youth. Extrapyramidal symptoms, neuroleptic malignant syndrome, and blood dyscrasias have also been reported but appear rare.

Conclusions: The authors conclude that olanzapine should be considered a second-line agent in EOSS and pedBP due to its risks for significant weight gain and lipid dysregulation. Awareness of the consistent weight and metabolic changes observed in olanzapine-treated youth focused attention on the potential long-term risks of atypical antipsychotics in youth.

Keywords: early-onset schizophrenia, pediatric bipolar disorder, antipsychotic

The US Food and Drug Administration (FDA) issued an indication for olanzapine in the treatment of adolescents, 13–17 years old, with schizophrenia or acute manic/mixed episodes in bipolar I disorder (BPI) in December 2009. However, the FDA also formally stated that clinicians may "consider prescribing other drugs first in adolescents" given olanzapine's increased potential for weight gain and hyperlipidemia in adolescents compared with adults. This article reviews the presentation and treatment of early-onset schizophrenia (EOS) and pediatric bipolar disorder (pedBP), the pharmacology and kinetics of olanzapine, the evidence supporting olanzapine's efficacy in these two serious mental illnesses among children and adolescents, the safety and tolerability of olanzapine in pediatric patients, and the probable role of olanzapine within the pediatric population compared with the adult population. The

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information presented in this article was gathered through a systematic PubMed review, with searches conducted for olanzapine combined with pharmacology, schizophrenia, or bipolar disorder. Searches related to schizophrenia and bipolar disorder were limited to children and adolescents. The bibliographies of key-retrieved articles were hand-checked for additional relevant studies. Rigorously, controlled data is limited in this population, so observations from nonblinded trials will also be presented. All conclusions are those of the authors and do not reflect specific recommendations of any national organization or government entity.

Early-onset schizophrenia

The incidence of EOS is not well established with epidemiologic studies. However, a number of geographically limited studies focused on hospital admissions have provided consistent estimates of the incidence in children and adolescents. The illness is very uncommon (~0.3/1000) in children younger than 10 years, then increases to approximately 1.3/1000 between ages 10 and 14 years with an even greater increase between 14 and 18 years with incidence rates varying between 2.0 and 5.5/1000. Indeed, at least 5% of those with schizophrenia become ill prior to 14 years of age and up to 20% appear to become ill prior to 18 years of age.[1–5] The peak age of onset is between 15 and 20 years in males and between 15 and 25 years in females.[6] Modestly more males experience EOS than females (~1.5 males: 1 female).

Diagnostic criteria for EOS are the same as for adult-onset criteria except that psychotic symptoms must be present prior to age 18 years. However, there are some development differences in detailed characteristics of symptoms. Specifically, youth are more likely to have multimodal hallucinations than adults and frequently personalize their hallucinations giving them names that are frequently stereotyped, such as "Satan," "my guardian angel," or the "monster" or derived from visual characteristics, such as the "man with no skin". They seldom have systematized or bizarre delusional symptoms, though vague paranoia is common. Disorganized thinking is frequently observed.[7–10] Younger individuals may have difficulty recognizing their symptoms as abnormal and frequently do not complain spontaneously about hallucinations.[11] Youth who will experience EOS frequently show greater premorbid problems with attention, learning, and socialization than individuals who develop schizophrenia as adults. The onset of symptoms in EOS is most often insidious.[12,13] Youth with EOS who participate in clinical trials often have more severe psychiatric symptoms, greater neurocognitive deficits, and more pronounced gray matter loss than research participants with adult-onset schizophrenia.[14–18] Individuals with EOS are much less likely to have a good outcome than individuals with adult-onset schizophrenia, with the majority having poor or very poor outcomes.[13,19–21]

Treatment of EOS has traditionally been based on the pharmacologic treatments used for adult-onset schizophrenia. There is little systematic use of psychotherapeutic strategies in this population.[22] Efficacy of antipsychotics has been assumed to be generally similar in youth and adults. This view was bolstered by small studies of first-generation antipsychotics (FGAs), including haloperidol, thioridazine, thiothixene, and loxapine that showed relatively high rates of response.[9,23,24] However, considerable sedation was also observed, and there were concerns about extrapyramidal symptoms (EPS), which appear to be somewhat more prevalent in youth than adults.[25] In the 1990s, a pivotal trial was done showing that youth with treatment-resistant schizophrenia had a robust response to clozapine, the prototypic second-generation antipsychotic (SGA) introduced in 1989.[26] However, significant adverse effects were frequent and limited the use of this agent.

As other SGAs have been introduced and approved for use in adults with schizophrenia over the past 20 years (Table 1), including olanzapine in 1996, clinicians embraced them hoping both for greater efficacy and fewer adverse effects than the FGAs or clozapine. There was particularly great enthusiasm for olanzapine because its pharmacologic profile was most similar to clozapine's and it was less prone to EPS than risperidone, which has more potent dopamine D_2 antagonism. Enthusiasm for olanzapine was further increased by a study of olanzapine vs haloperidol in 263 patients with first-episode schizophrenia, who were followed for 2 years.[27] Although there were no difference in symptom reduction between the two agents in a last observation carried forward analysis, a mixed-model analysis demonstrated an acute advantage for olanzapine in Positive and Negative Syndrome Scale (PANSS) total score, PANSS negative and general symptoms, and a depression rating scale. Results of the 2-year data found that patients treated with olanzapine were significantly more likely to enter remission (olanzapine 57%, haloperidol 44%, $P < 0.036$) and continued treatment for a longer period of time (olanzapine 322 days, haloperidol 230 days, $P < 0.0085$) than those treated with haloperidol.[28] Perhaps most importantly, the imaging component of this study found that individuals treated with haloperidol experienced significant decreases

Table 1 Current FDA indications for second-generation antipsychotics

Drug	Indication	Approval date
Aripiprazole	Schizophrenia in adults	November 15, 2002
	Maintenance treatment of adult schizophrenia	August 28, 2003
	Acute adult manic/mixed BP1	September 29, 2004
	Maintenance treatment of adult BP1	March 1, 2005
	Schizophrenia in 13–17 year olds	October 29, 2007
	Adjunctive treatment in adult major depression	November 16, 2007
	Acute monotherapy or adjunctive therapy with lithium or valproate in manic/mixed episodes of BP1 in 10–17 year olds	February 27, 2008
	Irritability in autism in 6–17 year olds	November 19, 2009
Asenapine	Schizophrenia in adults BP1 in adults	August 14, 2009
Clozapine	Treatment-resistant schizophrenia	September 26, 1989
	Emergent suicidality in schizophrenia or schizoaffective disorder	December 18, 2002
Olanzapine	Acute psychotic disorders in adults	September 30, 1996
	Manic/mixed in BP1 adults	March 17, 2000
	Maintenance treatment in schizophrenia in adults	November 9, 2000
	Adjunctive use with lithium or valproate in acute mania/mixed BP1	July 10, 2003
	Maintenance treatment in adult BP1	January 14, 2004
	13–17 year olds with schizophrenia may consider other drugs first due to weight gain and dyslipidemia	
	13–17 year olds with mania/mixed BP1 as monotherapy or adjunct to valproate or lithium may consider other drugs first given weight gain/dyslipidemia	December 4, 2009
Quetiapine	Psychotic disorders in adults	September 26, 1997
	Monotherapy or adjunctive therapy in BP1 in adults	January 12, 2004
	Major depression associated with BP1 in adults	October 20, 2006
	Maintenance treatment in adult BP1 as adjunct to lithium or valproate	May 13, 2008
	Treatment of schizoprenia in 13–17 year olds	December 2, 2009
	Acute treatment of mania/mixed BP1 in 10–17 year olds either as monotherapy or adjunctive therapy	
Risperidone	Treatment of schizophrenia in adults	December 29, 1993
	Long-term treatment of schizophrenia in adults	March 3, 2002
	Monotherapy or adjunctive therapy to lithium or valproate in adults with BP1	December 4, 2003
	Irritability in autism in 5–16 year olds	October 6, 2006
	Schizophrenia in 13–17 year olds	August 22, 2007
	BP1 in 10–17 year olds	
Ziprasidone	Schizophrenia in adults	February 5, 2001
	Monotherapy in manic/mixed in BP1 in adults	August 19, 2004
	Maintenance treatment as adjunct to lithium or valproate in BP1 in adults	November 20, 2009

Note: See http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm094303.htm.
Abbreviations: FDA, US Food and Drug Administration; BP1, bipolar 1 disorder.[1]

in brain gray matter volume, whereas neither those treated with olanzapine nor a healthy control group showed any changes.[29] Optimism that olanzapine may have particular advantages for treating youth with psychotic symptoms was also heightened with results published from a small pilot study comparing olanzapine, risperidone, and haloperidol in the treatment of psychotic youth aged 8–20 years.[30] This study in the pediatric population found a modest numeric, but not statistically significant, advantage for olanzapine in the response rate (olanzapine 88%, risperidone 74%, haloperidol 53%), premature drop-out (olanzapine 2/16, risperidone 9/19, haloperidol 7/15, $P = 0.058$), and time to treatment discontinuation (olanzapine 7.4 weeks, risperidone 6.3 weeks, haloperidol 5.7 weeks). However,

the same trial also suggested that adverse events with the SGAs may be more common and more severe in youth than in adults. Proponents of olanzapine also focused on results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study in 1,493 adults with chronic schizophrenia. Although there were few clinically significant differences among SGAs and between SGAs and FGAs in the CATIE study, olanzapine had marginally greater benefits as reflected by greater initial reductions in PANSS, greater initial improvements in the Clinical Global Impression (CGI), lower rate of hospitalization due to psychiatric exacerbation, lower discontinuation rates, and longer time to treatment discontinuation.[29] As discussed in detail later, the Treatment of Early Onset Schizophrenia

Spectrum Disorders (TEOSS) study did not identify any advantage for olanzapine compared with risperidone or molindone in children and adolescents with schizophrenia,[31] suggesting a potential difference in olanzapine's efficacy during different stages of schizophrenia.

Pediatric bipolar disorder

Similar to EOSS, there are few epidemiologic studies that rigorously examine the incidence of pedBP. The primary exception to this is a recent small study done in which 3,021 community subjects (14–24 years of age) in Germany were reassessed 10 years later.[32] This study found that approximately 1.2% of the youth had experienced a manic or hypomanic episode by 12 years of age and approximately 4.5% had experienced a manic or hypomanic episode by 18 years of age. Manic episodes occurred with similar frequency in males and females, whereas hypomanic episodes were about twice as common in females as males and as mania in either gender. Rates dramatically increased during adolescence. Further, 9% of those with a major depressive episode prior to age 17 years subsequently developed bipolar disorder, which was significantly greater than those with later onset of depression. The incidence of manic and hypomanic episodes in this study is greater than the prevalence of bipolar 1 disorder in adults (4.5% lifetime and 2.8 annual),[33] which is typically reported in larger epidemiologic studies, likely due to the expert clinical interviewers used in the German study. In a recent multisite treatment study of 3,658 adults with bipolar disorder, 29% reported onset before age 13 and 67% reported onset by age 18.[34] A study of 119 individuals consecutively admitted to a psychiatric hospital in Norway with bipolar disorder found that 13.5% had onset during childhood and 61.6% had onset prior to age 20 and that those who reported an affective temperament had earlier onset.[35] The period of peak onset appears to be in 12 and 22 years of age.[32] It should be noted that there has been approximately a 40-fold increase in the recognition of bipolar disorder in children and adolescents over the past decade in the US.[36]

Diagnosis of pedBP has been somewhat contentious with many critics arguing that the disorder is misdiagnosed in a large number of youth. The controversy seems related to two major issues.[37] First, in children and many adolescents, the pattern of cycling within a given episode and the duration of episodes appear quite different between youth and adults. Youth frequently have a large number of cycles or mood swings within a single episode of illness. Often, this cycling can occur multiple times a day even though there may be months without an extended euthymic period that

would signal the end of the episode. In contrast, most adults demonstrate a fairly consistent mood state throughout any given episode. In pedBP, a single episode will often last for a very extended period giving the appearance of a chronic condition, whereas in adults, episodes are usually limited to a few weeks.[38,39] Second, children and, to a lesser extent, adolescents frequently experience mixed states of mania and depression, whereas adults less frequently show such states. The sensitivity and specificity of various individual symptoms of mania and their differential manifestations in other childhood diagnoses are eloquently reviewed by Youngstrom et al.[37] Further, there are developmental differences within pedBP, with children frequently showing greater comorbidity with attention deficit hyperactivity disorder. Childhood-onset bipolar disorder is associated with greater mood lability, irritability, and hallucinations than adolescent-onset bipolar disorder. However, many highly concerning symptoms, including psychotic symptoms, suicidality, grandiosity, and decreased need for sleep, increase during adolescence, often to a greater extent in those with childhood-onset bipolar disorder than those with adolescent-onset bipolar disorder.[40] In addition, there is more controversy about the boundaries of the bipolar spectrum in the pediatric population than in the adult population. Criteria for various potential disorders within the spectrum have been most explicitly defined by Leibenluft and colleagues.[41] These criteria subdivide bipolar NOS (Not Otherwise Specified) into categories in which a sufficient number of criteria are not met, symptoms do not appear to have sufficient duration, irritability is primary mood state, and moods are severely dysregulated in the context of many symptoms of hyperarousal but in the absence of psychotic symptoms or elation. The latter category, called severe mood dysregulation, appears most common and is likely to be highly heterogeneous.

Most of the current longitudinal studies of pedBP involve limited follow-up and focus primarily on rates of remission and relapse.[42–46] However, adults with childhood-onset bipolar disorder appear to experience significantly worse outcomes, including more rapid relapse, less euthymia, and poorer functioning and quality of life than those with adult-onset bipolar disorder.[34] In addition, rates of suicidality and suicide attempts are particularly high in adolescents with bipolar disorder (72%–76% and 31%–44%, respectively).[47,48] Suicidality in bipolar youth appears to be increased in those with psychotic symptoms.[49]

Treatment for pedBP has evolved from treatment of adults with bipolar disorder with specific treatment studies for pedBP limited until the past decade. Until 2007, lithium

was the only mood-stabilizing agent specifically approved by the FDA for the treatment of acute mania in adolescents. However, this indication does not reflect specific evaluation of the efficacy and safety of lithium in adolescents. Despite this, valproate was probably the most widely used mood stabilizer in the pediatric population until the SGAs were introduced in the 1990s because of its availability in a sprinkle formulation, more favorable therapeutic index (ratio of toxic dose to therapeutic dose), and less onerous side-effect profile compared to lithium. Carbamazepine was also used to some extent. As other antiepileptic drugs, including oxcarbamazepine, gabapentin, topiramate, and lamotrigine, began to be used in adults, they were embraced for use in the pediatric population because they frequently did not require monitoring of blood levels. Lithium was among the first agents specifically studied in youth. Lithium led to greater reductions in the substance use and improvements in the Clinical Global Impressions Scale than placebo in a sample of 25 adolescents with both bipolar disorder and substance abuse.[50] A subsequent open trial found that lithium, in conjunction with an antipsychotic in nearly 50% of the cases, led to reduction in acute manic symptoms in approximately two-thirds of adolescents with acute mania and remission in about one-quarter of the participants.[51] Further, although no placebo-controlled trials of lithium for mania have been completed in pedBP, one study evaluated the rapid discontinuation of lithium by replacement with placebo or continuation of lithium over 2 weeks in youth who had responded to therapeutic doses of lithium for at least 4 weeks.[52] Surprisingly, more than 50% of the participants in both the lithium and the placebo groups experienced significant symptom exacerbation. In addition, among adolescents with both psychotic and manic symptoms, long-term treatment with antipsychotics in addition to lithium was generally required to maintain the initial response to treatment.[53]

Other open-label studies in pedBP have described significant responses to valproate and carbamazepine, as well as lithium.[54,55] However, in many of these trials, the majority of youth were concurrently taking antipsychotics or other mood stabilizers. In the only randomized but open monotherapy trial of mood stabilizers published to date, more than 50% of the participants did not respond to the initially randomized mood stabilizer though 80% of these responded to combined treatment with two mood stabilizers.[56] Studies exploring discontinuation of one mood stabilizer after stabilization on combination treatment support are consistent with the requirement of combination therapy for many youth with bipolar disorder.[57] Significantly, recent

placebo-controlled trials of mood stabilizers published to date have failed to demonstrate efficacy of either oxcarbamazepine or valproate.[58,59]

Antipsychotics were initially used adjunctively in treatment-resistant bipolar disorder in adults. Clozapine appeared particularly effective. Subsequently, other second-generation agents were studied as a treatment of all phases of bipolar disorder, particularly risperidone and olanzapine. Initially, antipsychotics were used as adjunctive treatment to mood stabilizers and appeared to have increased benefit with no major tolerability issues.[60] A blinded, placebo-controlled trial of quetiapine adjunctive therapy demonstrated significantly greater reduction in mania scores and greater response rate than valproate monotherapy.[61] An open-label trial of olanzapine monotherapy was also very promising.[62] Subsequently, a double-blind trial comparing quetiapine with valproate demonstrated superior response and remission rates with quetiapine even though reductions in mean mania scores did not differ.[63] Since that time, placebo-controlled trials of each of the atypical antipsychotics other than clozapine – olanzapine,[64] aripiprazole,[65] risperidone,[66] and quetiapine[67] – have found that each active agent reduced the Young Mania Rating Scale (YMRS)[68] score to a significantly greater extent than placebo over 3 weeks among youth experiencing acute manic/mixed episodes. Based on these results, risperidone and aripiprazole were approved for the acute treatment of mixed and manic episodes of bipolar disorder in youth of 10–17 years old, and olanzapine and quetiapine were approved in adolescents. There has also been one small, double-blind pilot study that failed to show any advantage for quetiapine over placebo in the treatment of depression within pedBP.[69] Notably, a large National Institute of Mental Health (NIMH)-sponsored comparative trial of risperidone, valproate, and lithium has been recently completed and should be reported soon. In summary, there is evidence for significant benefit from antipsychotics in the treatment of mixed and manic states in youth and a lack of efficacy of valproate and oxcarbamazepine. There is no empiric evidence yet of an effective treatment for depression or relapse prevention in youth with bipolar disorder.

Olanzapine pharmacology and pharmacokinetics

Olanzapine is a thienobenzodiazepine analog that binds to a large number of neurotransmitter receptors, including the dopamine D_1, D_2, and D_4 receptors, serotonin $5-HT_{2A}$, $5-HT_{2C}$, $5-HT_6$, and $5-HT_3$ receptors, histamine H_1 receptor, muscarinic receptors, α- and β-adrenergic receptors, γ-amino butyrate $(GABA)_{a1}$ receptor, and the benzodiazepine binding sites.[70] Its binding profile is more similar to clozapine's

than any other atypical antipsychotic. Olanzapine's antipsychotic and mood-stabilizing effects are likely the result of potent antagonism at dopamine and serotonin receptors, with affinity constants ranging from 4 nM to 31 nM. It also binds with high affinity to H_1 and M_1 receptors. The drug binds with moderate affinity to 5-HT_3 and M_{2-5} receptors and binds weakly to GABA, benzodiazepine binding sites, and β-adrenergic receptors. It is also likely that olanzapine regulates various signaling pathways within the brain, including the extracellular signal-related kinases (ERK1/2), particularly with long-term treatment.[71] Developmental differences in the binding profile of olanzapine have not been examined to our knowledge. Olanzapine's metabolic adverse effects have been hypothesized to relate to its histaminergic binding profile.[72,73] In addition, olanzapine-associated weight gain has been linked to genetic variations in the 5-HT_{2A}, 5-HT_{2C}, and $β_3$-adrenergic receptor, leptin, and the G-protein $β_3$ subunit genes.[74–76] The anticholinergic side effects are likely related to the muscarinic antagonism and the orthostatic hypotension related to antagonism at α-adrenergic receptors.

Olanzapine is well absorbed after oral administration and reaches maximal levels in about 5 hours in adults. Eating does not appear to affect olanzapine's bioavailability. It is excreted in the urine (65%) and feces (35%) over the course of approximately 7 days.[77] It is metabolized extensively within the liver undergoing glucuronidation (to yield the primary metabolic products), allylic hydroxylation, oxidation, and dealkylation. Oxidation occurs primarily via the CYP1A2 cytochrome P450 enzyme (Figure 1).[78]

Levels are affected by smoking (leading to ~30% reduction in plasma level), gender (women have ~85% increased plasma levels), carbamazepine (decreased plasma levels), and fluvoxamine and other selective serotonin reuptake inhibitors (SSRIs) (increased plasma levels).[79–84] The elimination half-life ranges from about 27 hours in smokers to 37 hours in nonsmokers. Plasma levels of olanzapine appear to increase slowly over a period of months with a slightly slower time course in women compared with men.[81,85] There are no significant differences that appear in bioavailability or half-life of oral tablet and the orally disintegrating form of olanzapine.[86]

In general, the pharmacokinetics of olanzapine are similar in youth and adults.[87,88] Adolescents experience considerable intra-individual variability across time despite stable dosing, which appears somewhat greater in adolescents than adults.[85,89] The concentration-to-dose ratio of olanzapine appears generally linear.[78] However, adolescents appear to have a higher (~34%) concentration-to-dose ratio than adults even after adjustment for weight.[90]

Olanzapine efficacy in EOS

The first report of olanzapine treatment in youth with schizophrenia was an open trial done in eight youth with childhood-onset, who had not responded to prior trials with antipsychotics other than clozapine.[91] In this study, there was modest improvement in overall symptoms and negative symptoms but no significant change in positive symptoms. A comparison group of 15 treatment-resistant youth exposed to clozapine demonstrated greater benefits only after 6 weeks of treatment. In a trial of 15 children younger than 13 years of age, 10 showed moderate or marked improvements in psychotic symptoms.[92] However, all patients who had been previously exposed to antipsychotics did not improve. In contrast, an open-label study of 9 other treatment-resistant children found significant improvements at 12 weeks from baseline in all symptom domains and found that eight of the children sustained improvements over the course of 1 year.[93] However, two double-blind studies comparing clozapine and olanzapine in youth with treatment-resistant schizophrenia had similar findings to the initial report.[94,95] In each of these trials, clozapine resulted in greater reductions in negative symptoms and, in the most recent trial, greater response rates.

Olanzapine has also been tested in youth with schizophrenia, who are not treatment resistant. The initial open trials for these youth were done in 2003, and included 20 youth (6–15 years old) and 16 adolescents (12–17 years old) respectively.[96,97] Both trials showed significant improvements in symptoms, illness severity, and function within 6–8 weeks of initiating treatment. However, improvements in negative symptoms were reported to occur later in the trial that included children and adolescents.[97] In the Ross trial, 74% of the youth were considered responders and retained that response status after 1 year of treatment. A similar response rate has been achieved in other open-label trials including a large 6-week trial with an additional 18-week follow-up in 96 adolescents.[98,99]

Subsequently, olanzapine was openly compared with risperidone and haloperidol in physicians' choice (nonrandomized) treatment of 43 adolescents with schizophrenia.[100] There were no apparent differences in antipsychotic efficacy between the three treatments with significant benefit within 4 weeks of starting treatment. However, haloperidol was associated with greater emergence of depressive symptoms. A more recent trial that involved 16 adolescents with psychotic symptoms treated with olanzapine, 50 treated with risperidone, and 18 treated with quetiapine also failed to detect differences between the antipsychotic efficacy of the agents
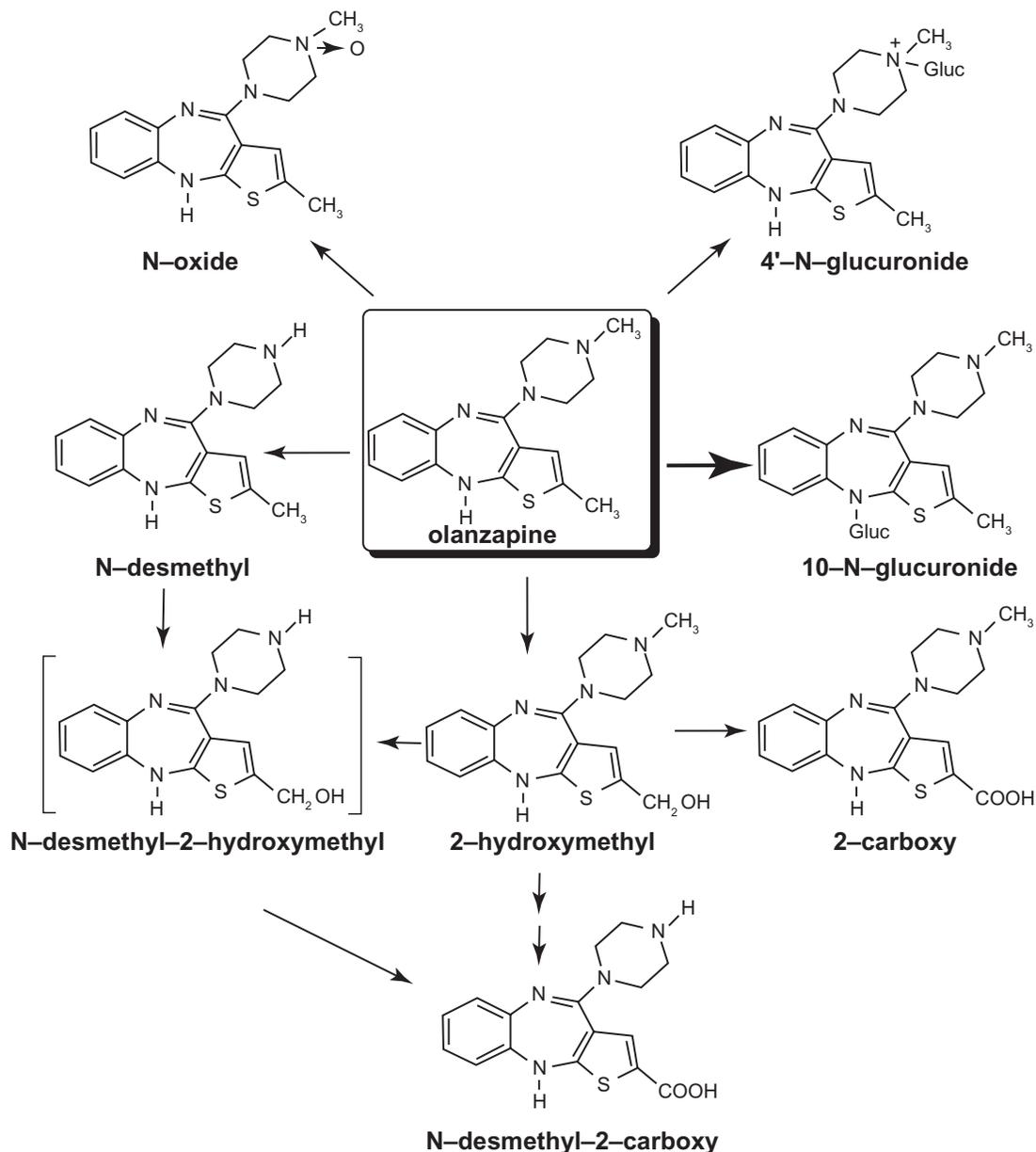
Figure 1 Metabolism of olanzapine. The chemical structure and metabolism of olanzapine are shown. Copyright © 1997. Modified with permission from Kassahun K, Mattiuz E, Nyhart E Jr, et al. Disposition and biotransformation of the antipsychotic agent olanzapine in humans. *Drug Metab Dispos*. 1997;25(1):81–93.[77]

at 6 months when baseline psychopathology scores were included as a covariate in the analysis.[101] However, olanzapine consistently showed the greatest number of reductions in all types of psychotic symptoms. A double-blind, randomized trial of acute psychotic symptoms in 50 youth with either affective or schizophrenic psychoses also failed to show statistically significant differences between treatments.[30] In this study, the olanzapine group showed the greatest response rate (88% compared with 74% for risperidone and 53% for haloperidol) and longest duration of treatment. However, the numeric superiority of olanzapine may have partially reflected the preponderance of youth with affective psychoses (69%)

in the olanzapine group in contrast with the other two groups where schizophrenic diagnoses were more common. A larger (n = 116), placebo-controlled, randomized trial comparing olanzapine (n = 34) with risperidone (n = 41) and molindone (n = 40) exclusively in youth with EOS, known as the TEOSS trial, again found no statistically significant or numeric differences in symptom reduction between the agents.[31,102] However, in contrast to the earlier study, olanzapine treatment was sustained for a numerically shorter period, and numerically fewer participants treated with olanzapine responded than those treated with the other two agents (olanzapine: 34%; risperidone: 46%, molindone: 50%).

One double-blind, placebo-controlled trial of olanzapine has been done in adolescents 13–17 years old with schizophrenia.[103] In this international multisite trial, 72 youth were treated with olanzapine and 35 with placebo. Olanzapine treatment led to much greater and highly statistically significant improvements in the CGI Severity score ($P = 0.004$), the Brief Psychiatric Rating Scale for Children (BPRS-C)[104,105] ($P = 0.003$), the PANSS total score ($P = 0.005$), and positive symptom scale ($P = 0.002$), but not negative symptoms. However, a reviewer at the FDA raised concerns about the study because the positive results of the study were primarily driven by the Russian sites not the US sites.[106] Although the BPRS-C symptom reduction seen with olanzapine was similar in both sites (US: −21, Russia: −17), there were dramatic differences in the magnitude of reduction with placebo (US: −15; Russia: −3), resulting in markedly different changes in the P value (US: $P = 0.258$; Russia: $P = 0.003$). Importantly, an FDA audit of two Russian sites found no concerns about the conduct of the study. The FDA Director of the Division of Psychiatry Products, Dr. Thomas Laughren, believed that these differences between sites probably reflected differences in the availability of care for youth with schizophrenia between the two countries and greater heterogeneity of the study population at US sites and also believed that olanzapine should be approved in adolescent schizophrenia.

Olanzapine efficacy in pedBP

Olanzapine was initially reported to be useful for treating mania and mixed states in an 8-week, open-label prospective study of 23 youth aged 5–14 years old.[62] There was a highly significant improvement in the YMRS[107] (−19.0, $P < 0.001$) and overall response rate (defined as ≥30% reduction in YMRS and CGI-Severity score of mild or less severe) was 61%. Subsequently, DelBello and colleagues[108] examined the effects of olanzapine treatment on brain neurochemistry using proton spectroscopy in 19 adolescents with mania, who were scanned prior to beginning treatment and on days 7 and 28 of treatment. Ten healthy control adolescents were scanned to assess normal variability in brain metabolites over 4 weeks. Ten (58%) of the participants had remission of symptoms. All participants showed increases in ventral prefrontal choline. However, those with remission showed significant increases in medial ventral prefrontal N-acetyl aspartate within 7 days of treatment ($P = 0.05$) and had increased baseline levels of ventral prefrontal choline compared with nonremitters ($P < 0.001$). Because N-acetyl aspartate is believed to reflect neuronal vitality, this finding suggests

potential beneficial changes in brain structure among some adolescents whose mania is treated with olanzapine. The only randomized, placebo-controlled trial of olanzapine for the treatment of manic and mixed states in adolescents (13–17 years old) was conducted by Eli Lilly.[64] In that study, 107 youth were treated with olanzapine and 54 with placebo for 3 weeks. The olanzapine group showed significantly greater reduction in the YMRS than the placebo group (olanzapine: −17.7, placebo: −10.0, $P < 0.001$). Olanzapine also led to dramatically higher response and remission rates than placebo (olanzapine: 48.6% and 35.2%, placebo: 22.2% and 11.1%, $P = 0.002$ and $P = 0.001$, respectively). We are unaware of any trials that have compared the efficacy of olanzapine and other mood-stabilizing agents in the pediatric population.

Olanzapine safety and tolerability in youth

Despite the evidence supporting the efficacy of olanzapine in EOS and pedBP, concerns about excessive weight gain with olanzapine emerged early. As olanzapine was used more frequently in youth, additional concerns about metabolic abnormalities, liver function abnormalities, sedation, and prolactin elevations emerged. Subsequently, the safety and tolerability of olanzapine in the pediatric population have been examined in comparison to adults treated with olanzapine. An early postmarketing surveillance study examined the database for olanzapine through March 31, 2000, linked it with patient exposure estimates during the same period provided by Eli Lilly, and divided the analysis into children (birth to 9 years), adolescents (10–19 years), and adults (20 years and older).[109] The study found that extrapyramidal syndrome complaint risks were similar across development, and tardive dyskinesia complaint risks were comparable in adolescents and adults. Overrepresented complaints in children included weight gain, liver function abnormalities, sedation and tardive dyskinesia. Overrepresented complaints in adolescents included weight gain, liver function abnormalities, sedation, and prolactin increases. A more recent analysis done by Eli Lilly compared the weight and metabolic data from 454 adolescents aged 13–17 years old exposed to olanzapine (primarily under open conditions) for as long as 32 weeks to the pooled weight data from 7,847 adults treated with olanzapine for up to 32 weeks and pooled metabolic data from adults from four trials.[107] The adolescents experienced more frequent and severe weight gain than the adults (>7% weight gain in 65.1% of adolescents and 35.6% of adults, $P < 0.001$; mean weight gain 7.4 kg in adolescents and 3.2 kg in adults,

$P < 0.001$). Adolescents were also much more likely to develop hyperprolactinemia (adolescents: 55.5%, adults: 29.0%, $P < 0.001$). However, in contrast, adults had more adverse metabolic changes than the adolescents with 11.8% of adults and 3% of adolescents moving from normal or impaired glucose to high glucose ($P < 0.001$), and 31%–38% of adults compared with 17%–21% of adolescents developed borderline dyslipidemias ($P < 0.001$ for all). This likely reflects other lifestyle and metabolic problems including lower insulin reserves in the adults.

The largest and most definitive data review of olanzapine's safety and tolerability in adolescents, pools all six Eli Lilly-sponsored trials of olanzapine in a total of 179 youth studied under placebo-controlled conditions for up to 6 weeks and 454 youth exposed to olanzapine (primarily under open conditions) for as long as 32 weeks.[110] There have also been some trials that compared adverse effects observed in youth treated with olanzapine or other antipsychotics, including data between 45 and 52 weeks of exposure.[30,31,93,101,102,111–115] We will examine each of the main adverse effects observed with olanzapine separately.

Weight gain
In the Eli Lilly placebo-controlled adolescent database, youth gained 3.9 kg when treated with olanzapine compared with 0.2 kg when treated with placebo ($P < 0.001$). In the adolescent-exposure database, the overall weight gain was 7.4 kg, with nearly two-thirds gaining more than 7% of their baseline weight and a 13.3 percentile increase in body mass index (BMI), which is a more appropriate measure of increased size in youth. Overall, 4% of adolescents withdrew from treatment because of weight gain. In examining the time course of weight gain, there appears a marked reduction in the slope of weight gain after 4 weeks of treatment.[110] Similar findings of rapid weight gain followed by slower weight gain have been observed in other trials.[96,102,111,114]

In the comparative studies, olanzapine consistently demonstrated the greatest weight gain both acutely and with more extended use as summarized in Table 2. In almost all cases, it has led to significantly more weight gain than other antipsychotics with a very high level of significance. Further, in contrast with the adult literature, studies that directly compare clozapine and olanzapine treatment in youth have found that clozapine increases weight to a lesser or equivalent extent than olanzapine does.[95,113,114] One study examining 65 youth treated with olanzapine, clozapine, or risperidone found elevations in parents' and patients' pretreatment BMIs. Female gender and younger age when treated were associated

with the magnitude of antipsychotic-associated weight gain independent of medication. Further, individuals with low pretreatment BMIs initially show more rapid weight gain than their heavier peers even though total weight gain with treatment is less.[116]

Glucose metabolism
In the Eli Lilly placebo-controlled database, olanzapine-treated youth showed a 3.6 mg/dL (0.2 mmol/L) increase in fasting glucose, whereas placebo-treated youth showed a similarly sized decrease. Although not clinically significant, this finding was highly statistically significant ($P < 0.001$). Further, 3% of adolescents in the exposure database moved from normal or borderline glucose levels into the diabetic range.[110] Increases in fasting glucose with olanzapine treatment ranging from 0.6 to 10 mg/dL have been reported in several other pediatric trials (Table 2).[30,31,95] A study of 45 antipsychotic-naïve youth treated with olanzapine found significant increases in glucose, insulin, and insulin resistance (measured with homeostasis model assessment–insulin resistance [HOMA-IR]) with P values between 0.02 and 0.03.[115] There have also been multiple case reports of youth developing diabetes during olanzapine treatment.[117–120] It is clear that youth are less likely to rapidly develop diabetes as a consequence of olanzapine treatment than adults because most teens have large insulin reserves. It is not yet clear to what extent these increases in glucose persist with sustained treatment.

Lipid metabolism
In the Eli Lilly database, youth treated with olanzapine showed increases in total cholesterol and triglycerides relative to their peers treated with placebo [cholesterol 11.7 mg/dL (0.03 mmol/L) compared to no change and triglycerides 26.7 mg/dL (0.03 mmol/L) compared to a decrease of 8.9 mg/dL (−0.1 mmol/L); $P = 0.002$ and $P = 0.007$, respectively]. Those in the exposure database showed identical changes. Approximately one-fifth of the patients developed borderline elevations in total cholesterol (>200 and <240 mg/dL), low-density lipoproteins (LDL cholesterol >130 and <160 mg/dL), and triglycerides (>150 and <200 mg/dL), and 17.8% developed hypertriglyceridemia.[110] Interestingly, changes in lipid levels were slightly less in the study of antipsychotic-naïve youth ranging from 11.5 mg/dL for LDL cholesterol to 24.3 mg/dL for triglycerides with all P values less than 0.004.[115] Similar changes have been reported in other small

Table 2 Reported weight and metabolic changes with pediatric olanzapine treatment

Parameter study	Treatment duration	Olanzapine N	Observed changes		P value between drugs
			Olanzapine	Other agents	
Weight gain					
Lilly placebo database[110]	3–6 wk	179	3.9 kg	Placebo 0.2 kg	P < 0.001
Lilly total exposure database[110]	up to 32 wk	450	7.4 kg		
Kumra et al[91]	8 wk	8	3.4 kg		
Frazier et al[62]	8 wk	23	5 kg		
Ratzoni et al[111]	12 wk	21	7.2 kg	Risperidone 3.9 kg Haloperidol 1.1 kg	P = 0.02
Ross et al[97]	6 wk	19	3.8 kg 12.8 kg/12 mo		
Findling et al[96]	8 wk	16	6.5 kg		
Mozes et al[93]	12 wk	9	6.1 kg		
Sikich et al[30]	8 wk	16	7.2 kg	Risperidone 4.9 kg Haloperidol 3.6 kg	P = 0.0009
Shaw et al[94]	8 wk	12	3.6 kg	Clozapine 3.8 kg	
Mozes et al[112]	12 wk	12	5.8 kg	Risperidone 4.5 kg	
Fleischhaker et al[113]	6 wk	15	4.6 kg	Risperidone 2.8 kg Clozapine 2.5 kg	P = 0.03
Quintana et al[98]	10 wk	16	6.2 kg		
Sikich et al[31]	8 wk	35	6.1 kg	Risperidone 3.6 kg Molindone 0.3 kg	P = 0.0001
Kumra et al[95]	12 wk	21	BMI 0.7 kg/m²	Clozapine 0.7 kg/m²	
Castro-fornieles et al[101]	24 wk	16	11.7 kg	Risperidone 6.1 kg Quetiapine 6.0 kg	P = 0.02
Dittmann et al[99]	6 wk 24 wk	96 32	5.1 kg 11.7 kg		
Fleischhaker et al[114]	45 wk	8	16.2 kg	Risperidone 7.2 kg Clozapine 9.5 kg	
Correll et al[115]	12 wk	45	8.5 kg	Risperidone 5.3 kg Quetiapine 6.1 kg Aripiprazole 4.4 kg	
Fasting glucose					
Lilly placebo database[110]	3–6 wk	179	3.6 mg/dL	Placebo −3.6 mg/dL	P < 0.001
Lilly total exposure database[110]	up to 32 wk	450	1.8 mg/dL		
Sikich et al[30]	8 wk	16	10.0 mg/dL	Risperidone −7.9 mg/dL Haloperidol −0.3 mg/dL	
Sikich et al[31]	8 wk	35	0.6 mg/dL	Risperidone 1.2 mg/dL Molindone 0.9 mg/dL	
Kumra et al[95]	12 wk	21	3.6 mg/dL	Clozapine 4.5 mg/dL	
Correll et al[115]	12 wk	45	3.1 mg/dL	Risperidone 1.1 mg/dL Quetiapine 2.6 mg/dL Aripiprazole 0.5 mg/dL	
HOMA-IR					
Sikich et al[31]	8 wk	35	1.2	Risperidone 0 Molindone 0.5	
Correll et al[115]	12 wk	45	0.62	Risperidone 0.2 Quetiapine 0.35 Aripiprazole 0.55	
Total cholesterol					
Lilly placebo database[110]	3–6 wk	179	11.7 mg/dL	Placebo 0.0	P = 0.002
Lilly total exposure database[110]	up to 32 wk	450	7.8 mg/dL		
Sikich et al[31]	8 wk	35	19.9 mg/dL	Risperidone 10.2 mg/dL Molindone 0 mg/dL	P < 0.002

(*Continued*)

Table 2 (*Continued*)

Parameter study	Treatment duration	Olanzapine N	Observed changes		P value between drugs
			Olanzapine	Other agents	
Kumra et al[95]	12 wk	21	17.2 mg/dL		
Correll et al[115]	12 wk	45	15.6 mg/dL	Risperidone 3.5 mg/dL	
				Quetiapine 9.1 mg/dL	
				Aripiprazole 2.8 mg/dL	
LDL cholesterol					
Lilly placebo database[110]	3–6 wk	179	7.8 mg/dL	Placebo 0 mg/dL	P = 0.002
Lilly total exposure database[110]	up to 32 wk	450	7.8 mg/dL		
Sikich et al[30]	8 wk	16	7.6 mg/dL	Risperidone 2.9 mg/dL	
				Haloperidol 0.1 mg/dL	
Sikich et al[31]	8 wk	35	14.7 mg/dL	Risperidone −9.6 mg/dL	P = 0.003
				Molindone 0.5 mg/dL	
Correll et al[115]	12 wk	45	11.5 mg/dL	Risperidone 0.2 mg/dL	
				Quetiapine 3.9 mg/dL	
				Aripiprazole 7.4 mg/dL	
Triglycerides					
Lilly placebo database[110]	3–6 wk	179	26.7 mg/dL	Placebo −8.9 mg/dL	P = 0.007
Lilly total exposure database[110]	up to 32 wk	450	26.7 mg/dL		
Sikich et al[30]	8 wk	16	26 mg/dL	Risperidone −2 mg/dL	
				Haloperidol 22 mg/dL	
Sikich et al[31]	8 wk	35	21.6 mg/dL	Risperidone 7.1 mg/dL	
				Molindone −5.8 mg/dL	
Kumra et al[95]	12 wk	21	11.4 mg/dL	Clozapine 16.8 mg/dL	
Correll et al[115]	12 wk	45	24.3 mg/dL	Risperidone 9.7 mg/dL	
				Quetiapine 37.0 mg/dL	
				Aripiprazole −2.4 mg/dL	

studies that included individuals previously exposed to antipsychotics (Table 2).[30,31,95] Again there is limited information about the long-term course of these lipid changes.

Liver dysfunction

The Eli Lilly databases also report significant elevations in liver enzymes associated with olanzapine treatment. Alanine aminotransferase (ALT) increased by 20.0 and 21.4 U/L, aspartate aminotransferase (AST) increased by 6.4 U/L and 8.2 U/L, and γ-glutamyltransferase (GGT) increased by 7.5 and 9.0 U/L in the placebo-controlled and exposure databases, respectively ($P \leq 0.002$ for each comparison). In contrast, total bilirubin decreased significantly (-1.7 and -1.1 μmol/L) in the two databases. Similar increases in ALT and AST have been reported in other pediatric studies of olanzapine.[30,31] In the TEOSS trial, such elevations were more common in youth treated with olanzapine than those treated with either risperidone or molindone. In this study, there also appeared to be a tendency for these increases to diminish somewhat with continuing treatment.[102] Eight (1.8%) of the 454 participants in the Lilly adolescent exposure database discontinued treatment due to liver function problems. These elevations may reflect nonalcoholic steatohepatitis (nonalcoholic fatty liver disease), although imaging studies and long-term follow-up is not yet available. In a retrospective chart review of youth treated with olanzapine alone, divalproex alone, or the combination of olanzapine and divalproex, 59% of those treated with olanzapine alone had at least 1 elevated hepatic enzyme over an average of 8 months of treatment while only 26% of those treated with divalproex alone did. However, all of those treated with the combination experienced at least 1 elevation and 42% of these had persistent elevations throughout the treatment period. One of the youth treated with both agents developed clinically significant steatohepatitis that resolved when the olanzapine was stopped.[121]

Hyperprolactinemia

In adults, olanzapine has not been associated with significant increases in prolactin. However, children and adolescents appear very sensitive to the prolactin-increasing effects of all antipsychotics, including olanzapine.[122] The Eli Lilly placebo databases report acute prolactin increases of 11.4 μg/L with olanzapine compared with a slight decrease with placebo ($P < 0.001$). In the longer-term exposure database, the increase is much more significant at 23.0 μg/L compared with a decrease of -4.2 μg/L in the pooled adult

data ($P = 0.004$). Interestingly, fewer female adolescents experienced prolactin elevations than male adolescents. Similar changes have been described in other clinical trials.[30,31] Further, Wudarsky reported that 7 of 10 youth treated with olanzapine had elevations above the upper limits of normal for their age and gender. However, prolactin elevations with risperidone have consistently been found to be more extreme than with olanzapine in pediatric patients.[30,31] It appears that olanzapine plasma concentration is significantly correlated with serum prolactin levels.[123] However, most clinical trials do not report high rates of prolactin-related adverse events, such as menstrual irregularities, gynecomastia, or galactorrhea. The large Eli Lilly exposure database identified such problems in only 0.6%–4.2% of participants. The long-term consequences of moderate elevations in prolactin during adolescence are unknown.

Sedation

Most pediatric trials of olanzapine report high rates of sedation ranging from about 40% to 91%.[30,31,95,96,100] In the Eli Lilly databases, the incidence appears somewhat lower (17.4%–19.0%). However, if the reported rates of somnolence are generally additive to those of sedation, the rates move into the 40% range reported in other studies. Unfortunately, sedation often does not resolve in individuals who continue long-term treatment.[100,102] Sedation can have significant impact upon a youth's ability to participate in school and other age-appropriate activities. Less than 1% of youth in Eli Lilly's databases discontinued participation due to sedation.

Extrapyramidal symptoms

Almost all types of extrapyramidal adverse effects, including parkinsonian symptoms, dystonia, dyskinesia, tardive dyskinesia, akathisia, and neuroleptic malignant syndrome (NMS), have been reported in youth treated with olanzapine. However, these adverse events appear to occur much less often with olanzapine than with other antipsychotics including aripiprazole in youth. The incidence in the Lilly exposure database was 2.3% for parkinsonian symptoms, 5.5% for akathisia, and 1.4% for dyskinetic movements. Generally, those symptoms that do occur are minimal to mild. In comparative studies, olanzapine is consistently associated with fewer and less-severe extrapyramidal adverse events than risperidone, haloperidol, or molindone.[30,31,100] There is 1 case report of persistent dystonic movements emerging during olanzapine treatment and persisting up to 6 weeks after switching to clozapine treatment.[124] However, very few children and adolescents have been maintained for an extended period on a single antipsychotic or followed for sufficiently long periods to rigorously assess the medication-specific incidence of this late appearing and persistent adverse effect.

Neuroleptic malignant syndrome

NMS is a rare, potentially fatal, and idiosyncratic drug reaction that often occurs early in the course of antipsychotic treatment. NMS previously has been associated with the use of classical high-potency neuroleptics.[125,126] Case reports suggest that NMS resulting from treatment with olanzapine and other SGAs has a more insidious course than NMS precipitated by first-generation high-potency agents. In addition, temperature elevations may emerge late in the course. Cognitive symptoms including agitation and delirium may be more prominent. However, there have been two case reports of classic NMS occurring during olanzapine monotherapy,[127,128] one with olanzapine overdose,[129] and several in the context of polypharmacy with other psychotropics (as described in two recent reviews).[126,130]

Hematologic effects

Although clozapine is best known for its risk of hematologic abnormalities, there are many case reports of neutropenia being caused by other antipsychotics as well. Olanzapine and ziprasidone seem to be more likely than the other newer antipsychotics to cause such abnormalities.[131] There are some case reports where olanzapine was the only medication being taken.[132] Consequently, the FDA required a label change noting the risk of neutropenia and leukopenia with olanzapine treatment in August 2009. The label notes that this risk appears to be heightened in individuals with a history of blood dyscrasias or low white blood cell counts, particularly those induced by other drugs or those on drugs that have similar effects. In such cases, the patient's blood count should be monitored frequently when treatment is initiated and treatment should be interrupted if the absolute neutrophil count drops below 1000 cells/cm^3. It is unknown whether the risk for neutropenia is greater in the pediatric population than in the adult population.

Overdose

In adult studies, Lily data of over 3,100 subjects showed that the largest ingestion was 300 mg and that person did well with supportive care. However, there are multiple other reports of fatalities that some believe are related to olanzapine.[133–135] There have been at least two fatalities in children who have overdosed on olanzapine.[136] Often, individuals
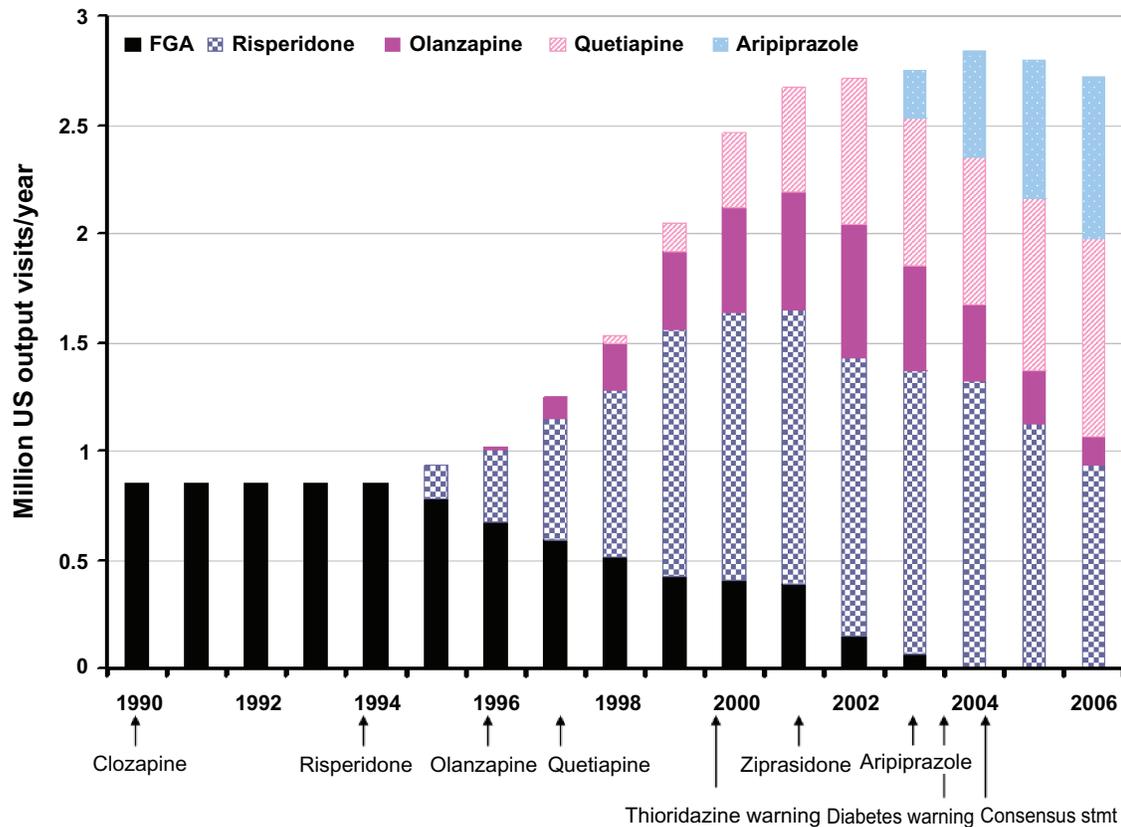
Figure 2 Patterns of antipsychotic use in the pediatric population of the United States. Following the introduction of each second-generation antipsychotic except clozapine, there has been rapid use within the pediatric population. However, risperidone, the first agent introduced after clozapine, has consistently been used more widely than the other agents. Further, safety considerations appear to have limited use of clozapine, ziprasidone, and earlier in 2003, olanzapine. This figure is a synthesis of data from multiple sources.[135–140,142] Number of prescriptions and proportion related to each agent are approximate.

with olanzapine overdoses develop EPS or NMS, respiratory symptoms, and mental status changes.[129,137–139] Overdoses in pediatric patients are reviewed by Theisen.[140] Management is primarily supportive and symptoms may take several days to a few weeks to fully resolve.

Olanzapine use in the pediatric population

The pattern of olanzapine's use over time in the US pediatric population relative to other antipsychotics is shown in Figure 2. When olanzapine was approved by the FDA in 1996, it almost immediately began being used in the pediatric population.[140–149] However, its use never became as prevalent as risperidone's. Quetiapine's use was of similar magnitude by 2001. However, as data about olanzapine-associated weight gain emerged, the FDA issued requirements that SGA labels warn about the weight and metabolic risks; the American Diabetes Association and the American Psychiatric Association released a consensus statement indicating that olanzapine and clozapine had the greatest risk for such side effects and olanzapine use in the pediatric population

quickly diminished to 5% or less of the total antipsychotics prescribed.[146,148]

Evidence from the CATIE trial that showed a slight advantage of olanzapine over other first-line antipsychotics in total duration of treatment and symptom response and from a first-episode study showing neuroimaging benefits compared with haloperidol, as well as the similarities between the binding profiles of olanzapine and clozapine, led some clinicians to use olanzapine in a few youth with very severe or persistent psychotic symptoms.[27,29,150] Youth with bipolar disorder are even less likely to be treated with olanzapine. In a recent study of pediatric bipolar treatment, it was used less often than any other antipsychotic (including FGAs).[151]

Olanzapine appears to be used more frequently in some parts of Europe but still to a lesser extent than either risperidone or quetiapine. In the CAFEPS longitudinal naturalistic study of youth with positive psychotic symptoms about 15% were treated with olanzapine.[101] In Canada, use is also somewhat greater than in the United States with about 6000 children (~22% of those who are treated with antipsychotics) receiving prescriptions for olanzapine annually between

2003 and 2006.[147] In countries outside the United States, aripiprazole appears to be less frequently used, so olanzapine and quetiapine are likely to be viewed as the antipsychotics with the least risk for EPS.

Conclusions

Olanzapine has clear efficacy for pedBP and EOSS. However, it also appears to have very great potential for promoting weight gain, increased insulin secretion, and dyslipidemia in children and adolescents. These adverse risks appear to be remarkably increased relative to other antipsychotics with the possible exception of clozapine. In the light of this extreme risk and because there is no compelling evidence that olanzapine has greater antipsychotic efficacy than other agents in either unselected youth with EOSS and other psychotic illnesses or in treatment-resistant EOSS, we argue that olanzapine should not be considered a first-line treatment for EOSS. Because there is clear evidence that clozapine has superior efficacy to olanzapine in treatment-resistant EOSS, we feel clinicians and families should seriously consider a trial of clozapine rather than olanzapine in such youth. There are no comparative studies examining the mood-stabilizing or antimanic properties of olanzapine relative to other SGAs. In the absence of any empiric data regarding comparative efficacy, olanzapine's heightened risks for weight gain and metabolic dysregulation suggest to the authors that it should not be considered a first-line treatment for pedBP either. However, because there is no treatment of choice for youth with pedBP, who have failed to respond to multiple first-line treatments, olanzapine might have a role in treating such children and adolescents.

Although olanzapine is unlikely to be used frequently in the pediatric population, it remains an alternative for some individuals. Such individuals might include those who are underweight, have no family history of diabetes or dyslipidemia, or are particularly sensitive to the extrapyramidal side effects of antipsychotics with more potent dopamine D_2 receptor binding. These conclusions are supported by the FDA's recent decision to approve olanzapine for the treatment of adolescents with schizophrenia or manic/mixed states in bipolar disorder, provided clinicians and families carefully consider prescribing other agents first due to olanzapine's marked risks for significant weight gain and lipid dysregulation in adolescents.

Olanzapine has played a critical role in alerting scientists and the public to the metabolic consequences of most antipsychotics, particularly within children and adolescents. The consistent weight and metabolic changes observed in olanzapine-treated youth spurred investigations of such effects among youth treated with other antipsychotics and provided a strong impetus for long-term studies of antipsychotic tolerability in youth.

Disclosures

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