

OLANZAPINE—USE IN CHILDREN AND ADOLESCENTS

SUMMARY

- None of the currently available atypical antipsychotics have regulatory approval for the treatment of schizophrenia or bipolar disorder in the pediatric population. The therapeutic use of olanzapine in children and adolescents has been described in small open-label studies and case reports in children with childhood-onset schizophrenia, bipolar disorder, pervasive development disorders (PDD), attention deficit hyperactivity disorder (ADHD), Tourette's disorder, and anorexia nervosa.
- In childhood-onset schizophrenia, olanzapine had demonstrated clinically significant improvements in children ranging in age from 6 to 18 years with doses from 5 mg up to a mean maximum dose of 16.8 mg.
- In bipolar disorder, olanzapine has demonstrated improvement in manic symptoms as monotherapy and in combination with mood stabilizers in children and adolescents 5 to 17 years old with doses from 2.5 to 5 in combination and up to a mean modal dose of 13 mg/day as monotherapy.
- Olanzapine has shown benefit in treating the target symptoms of pervasive development disorders in children and adolescents with doses ranging from 7.5 up to 30 mg/day. Significant improvements were seen in symptoms including anger/aggression, hyperactivity, and overall symptoms of autism.
- Improvement in symptoms of Tourette's Disorder with olanzapine has been described in several case reports in children and adolescents ranging from 9 to 17 years. One double-blind cross-over study of olanzapine and pimozide found a significant reduction in symptoms for olanzapine 5 mg versus pimozide 4 mg and less reported side effects with olanzapine compared to pimozide.
- Two case series have demonstrated marked reduction in paranoid symptoms and delusional thinking in patients with anorexia nervosa resulting in the patient's ability to gain an appropriate amount of weight. Patients ranged in age from 12 to 17 years old and were treated with 5 to 15 mg/day of olanzapine. In an open-label trial of 20 patients with anorexia nervosa, 10 patients gained an average of 8.75 pounds at the end of the trial. Four patients lost weight.
- The pharmacokinetics of olanzapine in children appears to be similar to that observed for nonsmoking adult patients with schizophrenia.
- In all of the reports mentioned above, the most frequent adverse effects seen with olanzapine therapy were sedation, often transient, and weight gain. There are limited reports on the safety of olanzapine in children taking doses above the

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recommended dosing range. In the cases that have been reported, the effects seen are similar to what has been reported in adults and are primarily an extension of the multireceptor binding profile of olanzapine including anticholinergic effects (ie. tachycardia without arrhythmia), antihistaminic effects (somnolence), and alpha adrenergic antagonist effects (ie. miosis).

INTRODUCTION

Information regarding the therapeutic use of olanzapine in children and adolescents based on controlled clinical trials is limited. Small open-label studies and case reports exist on its use in childhood-onset schizophrenia, PDD, bipolar disorder, ADHD, Tourette's disorder, and anorexia nervosa. Additionally, a small study was done to determine pharmacokinetic parameters of olanzapine in this population and there have been a few case reports of the toxicity profile of olanzapine in overdose in children. This document provides a brief description of the efficacy of olanzapine for the above disease states as well as pharmacokinetic and safety data.

CHILDHOOD ONSET SCHIZOPHRENIA

The therapeutic use of olanzapine in the treatment of childhood onset schizophrenia has been described in three open-label trials, two retrospective chart reviews, and one case series. Kumra and colleagues[1] evaluated 8 children and adolescents (ages 6 to 18) with treatment-refractory schizophrenia in an eight week, prospective, open-label study. Data from 15 patients enrolled in a 6-week open-label clozapine trial were included for comparison. Efficacy was assessed by the Brief Psychiatric Rating Scale (BPRS), Children's Global Assessment Scale (CGAS), Clinical Global Impressions Scale (CGI), Scale for the Assessment of Positive Symptoms (SAPS), and Scale for the Assessment of Negative Symptoms (SANS). The mean dose of olanzapine at the end of the trial was 17.5 mg/day and for the clozapine trial was 317 mg/day. The use of lorazepam (up to 8 mg/day) was allowed as adjunctive therapy with olanzapine as needed. At the end of the trial, compared to baseline, patients treated with olanzapine had a 19% improvement on the BPRS, a 21% improvement on the SANS, and a 6% improvement on the SAPS. However, the magnitude of the effect sizes for each of these scales was greater during the 6-week clozapine trial compared with the 8-week olanzapine trial. Based on the CGI Scale, three patients who took olanzapine were rated much improved, two were rated minimally improved, one no change, one minimally worse, and one much worse. At week 8, three patients (37.5%) in the olanzapine trial met criteria for response with one of the three being a partial responder. Comparatively, eight patients (53%) in the clozapine trial met criteria for response at the end of the 6-week trial. One patient did not complete the olanzapine trial due to increased agitation and worsened psychosis. Adverse events reported statistically significantly greater with olanzapine were headaches, fatigue, and insomnia. There was no statistically significant difference between weight gain seen with olanzapine-treated versus clozapine-treated patients. There was no increase in extrapyramidal side effects as measured by the Abnormal Involuntary Movement Scale (AIMS) or Simpson-Angus Scale (SAS).

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The second open-label trial described 15 children (6 to 13 years old) meeting criteria for schizophrenia before age 12 who were started on open-label olanzapine and observed in the hospital for an average of 11 days. All but one patient was treated with 5 mg. Efficacy was assessed with a 0 to 3 Likert scale of psychotic improvement (0 equals no improvement to 3 equals great improvement). Five patients showed moderate improvement, three showed slight improvement, and two showed no improvement. The most common side effect was sedation. There were no autonomic adverse effects, hemodynamic adverse effects, or weight gain reported[2].

~~The preliminary results of a third open-label trial reported on the use of olanzapine in 164 teenagers with schizophrenia-spectrum disorders. Patients received a mean total daily dose of olanzapine of 11.912.4 mg/day over 8 weeks. Statistically significant decreases were seen from baseline on the Positive and Negative Syndrome Scale (PANSS) total score, positive score, negative score and psychopathology score (p < 0.01 for all). Statistically significant reductions were noted as early as the second week for the PANSS total and positive scores, were seen from a mean baseline of 90.6 to a mean endpoint of 74.2 (p < 0.01). The most common adverse effects seen in these patients were sedation and increased appetite/weight gain. The mean weight gain per week was 1.0 kg with weight gain ranging from 1.1 to 13.4 kg over the duration of the study. No statistically significant differences were seen in EPS rating scale scores from baseline to endpoint[3].~~

The two retrospective chart reviews in childhood-onset schizophrenia include one evaluation of 8 children and adolescents who had a previous response to clozapine and had then subsequently been treated with olanzapine. Olanzapine was reported to be at least as efficacious as clozapine, and in some cases to have fewer side effects than clozapine[4]. The second retrospective review included 24 adolescent (mean age 17.2 years) inpatients with psychosis. Patients were treated with a mean maximum dose of 16.78 mg/day for a mean treatment duration of 60.893.2 days. Symptom ratings based on a scale similar to the CGI-Improvement scale revealed 75% of patients as "very much" or "much improved", 12.5% as "minimally improved", and 4.2% (1 patient) as "worsening of symptoms. Regarding general outcome, 9 patients were assessed as much improved, 10 minimally improved, and 5 with no change. Olanzapine was discontinued early in a total of 2 patients, one for lack of drug effect and one for weight gain. Statistically significant increase in weight was seen during both the pre-treatment period with primarily conventional antipsychotics (2.9 kg/month) and during olanzapine treatment (3.7 kg/month). No other major adverse events were noted[5-7].

The case series describes three patients (14 to 17 years old) with diagnoses of schizophrenia, schizophreniform disorder, or schizoaffective disorder who were treated with olanzapine 10 mg/day. All three patients demonstrated significant clinical improvement. The only adverse effects noted were sedation, which was transient, and weight gain ranging from 15 to 25 kg over a four to five month period[8].

BIPOLAR DISORDER

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The effectiveness of olanzapine in the treatment of bipolar disorder in children/adolescents has been described in, two case series, one small open-label trial, and one case report. Soutullo and co-workers[9] report on the use of olanzapine in seven adolescents (ages 12 to 17) with a primary diagnosis of bipolar disorder, manic or mixed episode. Patients had co-morbid diagnoses including ADHD, Tourette's Disorder, Obsessive Compulsive Disorder (OCD), and drug abuse. Olanzapine response was classified as marked, moderate, minimal, none, or worse based on the CGI scale. Olanzapine was added to therapy in six patients non-responsive to current manic therapy (agents included lithium, divalproex, and carbamazepine). One patient received olanzapine monotherapy. Mean doses were approximately 11 mg/day (0.146 mg/kg/day). Four patients experienced a marked response to olanzapine, one experienced a moderate response, and two a mild response. The most common adverse event was sedation reported by five patients (71%). Chang and Ketter report three cases of pre-pubertal children (9 to 12 years old) experiencing an acute manic episode who each had olanzapine (2.5 to 5 mg/day) added to their existing mood stabilizer therapy (lithium or valproate). Each patient demonstrated dramatic improvement in manic symptoms within five days of starting therapy. The adverse events reported by the patients were mainly sedation and weight gain (10 to 18 pounds over a four to six week time period)[10].

Frazier et al evaluated 23 patients (5 to 14 years old) with bipolar disorder in an open-label trial of olanzapine for up to 8 weeks. Efficacy was assessed using the Young Mania Rating Scale (YMRS), with response defined as $\geq 30\%$ improvement from baseline to endpoint and a Clinical Global Impression -Bipolar Severity (CGI-BP) score of ≤ 3 at endpoint. The mean modal dose of olanzapine received was 9.3 +/- 4.4 mg/day. There was a statistically significant mean change from baseline to endpoint (-19.04, $p < 0.001$) in the YMRS with a response rate of 60.9%. The most common adverse events were increased appetite and somnolence. There was a statistically significant increase in weight (4.98 kg, $p < 0.001$). There were no statistically significant differences from baseline to endpoint in extrapyramidal symptoms[11].

Additionally, Khouzam and colleagues described the resolution of a manic episode in a 17-year old male treated with 5 mg/day of olanzapine[12]. This patient experienced no side effects due to olanzapine treatment.

PERVASIVE DEVELOPMENT DISORDERS (PDD)

One retrospective chart review case series only found benefit for target symptoms in 3 out of 12 patients (age 5 to 17 years) diagnosed with developmental disabilities. However, most of these children had previously been tried unsuccessfully on other medications, and most had other co-morbid conditions including mental retardation, psychotic disorder, and ADHD[13]. There is one case report of a 16-year old boy diagnosed with PDD who presented with an acute manic state approximately 2 to 3 weeks after initiating therapy with 7.5 mg of olanzapine. Olanzapine was discontinued and the manic symptoms gradually subsided[14].

Potenza and associates[15] investigated the use of olanzapine monotherapy in a 12-week open-label pilot study of PDD. A total of eight patients (four children/adolescents and 4 adults) with PDD based on DSM-IV criteria were included. Patients ranged in age from 5 to 42 years (mean 20.9 years). Comorbid diagnoses included posttraumatic stress disorder (1), dysthymia (1), mild or moderate mental retardation (7). The mean dose of olanzapine at the end of the trial was 7.8 mg/day. Several standardized rating scales were used to measure response to olanzapine therapy. They included the Yale-Brown Obsessive Compulsive Scale Compulsion Subscale (Y-BOC-CS), Self-Injurious Behavior Questionnaire (SIB-Q), Vineland Adaptive Behavior Maladaptive Behavior subscales (VMBS), Visual Analog Scale (VAS), CGI global improvement item, and Ritvo-Freeman Real-Life Rating Scale (RF). Seven of the eight patients completed the trial, and six of the completers were deemed clinical responders as measured by rating of much improved or very much improved on the global improvement items of the CGI scale. Significant improvement was seen in the following: overall symptoms of autism, motor restlessness, social relatedness, affectual reactions, sensory responses, language usage, self-injurious behavior, aggression, irritability, anxiety, and depression. A statistically significant change for the olanzapine group in regards to repetitive behaviors was not seen based on the Y-BOC-CS. The most significant adverse effects reported were weight gain and sedation. A significant weight gain was seen in the olanzapine group (from 137.5 ± 55.81 to 155.94 ± 55.13 lbs, $p=0.008$). Three patients reported sedation as an adverse effect.

A second open-label trial evaluated 25 children (6 to 16 years old) with a diagnosis of PDD treated with olanzapine over 3 months. Efficacy was assessed using the Aberrant Behavior Checklist (ABC), the Clinical Global Impression of Severity/Improvement (CGI-S/I), the Matson Evaluation of Social Skills with youngsters (MESSY), the Kiddie-PANSS, and the TARGET. The mean dose of olanzapine used was 10.8 mg/day. Statistically significant improvement was seen on the hyperactivity and excessive speech subscales of the ABC, the CGI, and CGI-S, and sumscores of the TARGET. No effects were found on the MESSY or Kiddie-PANSS. The most significant adverse effects were weight gain (average 4.8 kg) and asthenia[16].

Autism

One report of a 17-year old boy with autism demonstrated an improvement in target symptoms with 30 mg/day of olanzapine[17]. A second case describes the improvement of symptoms in an 8 year old boy diagnosed with autism with hyperactivity who was treated with 7.5 mg/day of olanzapine[18].

There has been one published open-label pilot study comparing olanzapine and haloperidol in children with autistic disorder. Twelve children with a diagnosis of DSM-IV autistic disorder (mean age 7.8 years) were randomized to receive 6 weeks of open-label treatment with haloperidol or olanzapine. The primary outcome measure was the Clinical Global Impression (CGI) Scale and secondary outcome measures included the

Children's Psychiatric Rating Scale (CPRS) and four of its factors (ie. Autism Factor, Anger/Uncooperativeness Factor, Hyperactivity Factor, and Speech Deviance Factor).

For the olanzapine treatment group one patient was rated as very much improved, four were rated as much improved, and one as minimally improved based on CGI Improvement scores. For the haloperidol treatment group, one patient was rated as very much improved, two were rated as much improved, and three were rated as minimally improved. There was no statistically significant difference between the olanzapine and haloperidol treatment groups. The olanzapine treatment group showed a statistically significant decrease in the Anger/Uncooperativeness and Hyperactivity Factors compared to the haloperidol treatment group. The mean doses received at the end of the study were 7.9 mg/day for olanzapine and 1.4 mg/day for haloperidol. The most common adverse effects experienced by both treatment groups were weight gain and sedation. Weight gain was significantly higher in the olanzapine group (mean 9 pounds vs 3.2 pounds, $p = 0.040$). There were no other statistically significant differences between treatment groups in adverse effects[19].

Mental Retardation

A report of two cases describes a 9 year old boy with mild mental retardation, mixed receptive/expressive language disorder, and a bipolar disorder, and a 10 year old boy with severe mental retardation, an autistic disorder, and a bipolar disorder whose target symptoms markedly decreased on 10 mg/day and 20 mg/day, respectively[20].

A retrospective chart review of all patients less than 25 years of age (mean age 19 years) with mental retardation found almost 30% had been or were currently receiving atypical antipsychotics for at least 6 weeks (risperidone $n=22$, olanzapine $n=14$). Approximately 57% of patients receiving risperidone and 57% of patients receiving olanzapine were defined as much improved or very much improved based on the Clinical Global Impression Improvement Scale (CGI-I) score. The mean doses of risperidone were significantly higher for patients with co-existing psychotic symptoms (3.5 mg/day) compared to those without psychotic symptoms (1.69 mg/day). For olanzapine, the mean dose for patients with psychotic symptoms was 12.9 mg/day and 7.7 mg/day for those without psychotic symptoms. Seventeen percent of risperidone-treated and 21% of olanzapine-treated patients experienced some type of movement disorder adverse effect. Sedation and weight gain were the most common non-movement related adverse effects with both risperidone and olanzapine therapy[21].

TOURETTE'S DISORDER

The control of symptoms of Tourette's Disorder through treatment with olanzapine has been described in several case reports. In these reports children ranged in age from 9 years to 17 years. All cases reported an improvement in symptoms with minimal adverse effects[22-25].

There has been one double blind trial reported on the use of olanzapine in this disorder. Paci and colleagues evaluated 4 patients with severe Gilles de la Tourette Syndrome (GTS) in a 52-week double blind crossover study of olanzapine (5 and 10 mg) versus low dose pimozide (2 and 4 mg). They found a significant reduction in GTS rating scale scores with olanzapine compared to baseline and pimozide 2 mg and a significant reduction for olanzapine 5 mg vs pimozide 4 mg. Patients were also reported to have experienced less adverse effects during olanzapine vs pimozide treatment[26].

ANOREXIA NERVOSA

The benefits of olanzapine in the treatment of adolescents with anorexia nervosa has been described in two-three case series and an open label study. La-Vie and colleagues described less anxiety, agitation, and paranoid symptoms in a 15-year old female who was treated with 15 mg/day of olanzapine for 6 months. The patient reported mild sedation which decreased on continued use[27]. Boachie et al also reported decreased anxiety and agitation in hospitalized children with anorexia nervosa. Additionally, weight gain and improvement in sleep, general functioning and overall compliance were reported with olanzapine use [28]. While Mehler et al, found a marked reduction in anorexic symptoms including delusional thinking and a general overall improvement in psychopathological symptoms in five adolescent females (12 to 17 years of age) treated with 5 to 12.5 mg/day of olanzapine. A reduction in delusional thinking occurred within one week in all five of these patients. Weekly average weight gain in these patients continued during olanzapine therapy at the same rate as prior to olanzapine therapy. Only one patient noted any adverse effects of olanzapine therapy (increased appetite)[29].

To date, there has been one published trial using olanzapine in anorexia nervosa, which has included pediatric patients[30]. Powers and colleagues enrolled twenty patients with anorexia nervosa to an open label trial of olanzapine 10mg for 10 weeks. Of these twenty patients, six were between 14 and 18.5 years of age. For the eighteen patients that received medication, a mean weight gain of 5.0 lbs was seen from Day 1 to last weight measurement obtained. Of the fourteen patients that completed the study, ten of the patients gained weight (mean weight gain of 8.75 lb) while four patients lost weight (mean weight loss of 2.25 lb). The authors reported sedation as the most common adverse event, which resolved by the end of 10 days in all cases.

ADDITIONAL CASE REPORTS

Several single case reports have also been published on the use of olanzapine to treat a variety of disorders including Bipolar disorder, psychosis not otherwise specified, schizophrenia, and attention deficit disorder[31-29], catatonia[32], and stuttering[33], acute agitation[34], cancer pain[35], and visual hallucinations in craniometaphyseal dysplasia[36].

PHARMACOKINETICS

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Grothe and co-workers[3742] completed a study to characterize the pharmacokinetics of olanzapine in 8 children and adolescents (ages 6¹⁰ to 18 years) with a diagnosis of schizophrenia. Patients received olanzapine (2.5 to 20 mg/day) over 8 weeks. At the end of week 8 extensive plasma sampling was done for 36 hours following a 20 mg dose (n=7) and a 15 mg dose (n=1). The average steady state plasma concentration was determined to be 92.6 ng/ml, mean elimination half-life was 37.2 hours and the average clearance was determined to be 9.6 L/hr. Overall, the pharmacokinetic profile in these children was similar to that observed for nonsmoking adult patients with schizophrenia treated with olanzapine.

SAFETY

The most common adverse effects reported in children/adolescents from the above literature are weight gain and somnolence[1,2,3,5-11, 15, 16, 19, 21]. Limited reports have suggested that weight gain with antipsychotic use may be greater in adolescents compared to adults[385-4138]. There have been two case reports describing weight gain associated with hypertriglyceridemia in pediatric patients[42, 43].

Elevations in prolactin have also been reported to be higher in children than adults and olanzapine plasma levels were found to correlate with prolactin serum levels[44, 45].

There have been a limited number of case reports in a pediatric population describing the safety of olanzapine taken in doses above the recommended dosing range. There has been one report of high-dose olanzapine in an adolescent. Olanzapine 40 mg daily was added in combination with lorazepam and sertraline in a 14-year-old male with autism due to persistent hallucinations and delusions. A dispensing error resulted in an actual dose of 80 mg daily for 2-weeks. Mild tremors were the only side effects reported which disappeared upon a dose taper to 40 mg daily[4633].

There have also been a few reports on the safety of olanzapine taken in overdose in a pediatric population. A summary of the reported cases is provided in the table below.

TABLE 1: CASE REPORTS OF PEDIATRIC OVERDOSE CASE REPORTS

Reference	Age	Approximate Amount Ingested	Co-ingestants	Maximum serum level	Symptoms
<u>3447</u>	30 months	7.5-15 mg	None	11 ng/ml	Stupor, agitation, hypersalivation, tachycardia, miosis
<u>3548</u>	18 months	30-40 mg	None	213 ng/ml	Somnolent, combative, decreased response rate, hypoactive bowel sounds, tachycardia
<u>3649</u>	12 months	Unknown	None	0.34 mcg/ml	Lethargic, irritable, agitated, tachycardia, miosis, myoclonus
<u>3750</u>	9 yrs	100 mg	Acetaminophen		Combative, unable to follow commands, tachycardia, hypotension, decreased GI motility, jitteriness, tremors of extremities, cogwheel rigidity, stiff jaw, severe dystonia of neck
<u>5138</u>	6 yrs	10 mg	None	Not reported	Slurred speech, staggering gait, extreme drowsiness, agitation, mild tremor
<u>3952</u>	15 yrs	115 mg	None	Not reported	Unresponsive, Glasgow Coma Score 8, anticholinergic symptoms
<u>5340</u>	3 yrs	Unknown	None	Not reported	Lethargy
<u>4154</u>	16 years	Unknown	Bupropion Venflaxine	334 ng/ml	Comatose, unresponsive, tachycardia, miosis, generalized tonic-clonic seizure, prolonged QTc (450msec)

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SUMMARY/CONCLUSIONS

Large, double-blind, well-controlled clinical trials of olanzapine have not been conducted in children and adolescents with any of the atypical antipsychotics currently available. Limited data from small studies and case reports indicate that olanzapine may offer some potential benefit for pediatric patients with schizophrenia, bipolar disorder, PDD, mental retardation, Tourette's disorder, and anorexia nervosa.

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