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Olanzapine in the treatment of schizophrenia in adolescents – mechanisms of action and therapeutic efficacy

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Summary

The aim of the study is to review mechanisms, efficacy, safety, pharmacokinetics, and guideline positions of olanzapine in youth, with comparison to adults. The authors present a narrative synthesis of randomized trials, open-label studies, meta-analyses, and major guidelines (APA, NICE, Canadian), with focused appraisal of pediatric data. Results show that olanzapine's multi-receptor antagonism (D_2, 5-$HT_2A/2C$, H_1, muscarinic, α_1) underpins robust antipsychotic effects. In adolescents, short-term RCTs show significant improvement in PANSS/BPRS-C and YMRS versus placebo; efficacy is broadly comparable to risperidone and aripiprazole. Pharmacokinetics are similar to adults, though exposure is ~27–34% higher in youth. Adverse effects – especially weight gain, dyslipidemia, hyperprolactinemia, and glycemic abnormalities – are more pronounced in adolescents. Guidelines endorse olanzapine as an option for schizophrenia and as first-line for acute mania; OFC is recommended for bipolar depression by most but not NICE. LAI olanzapine is not approved <18 years. Olanzapine is effective in adolescent psychosis and mania but carries substantial metabolic liability. Given no clear efficacy advantage over other SGAs, it is best positioned as a second-line agent in youth, with preference for monotherapy, cautious dosing, and stringent metabolic monitoring. Evidence for benefits on negative and cognitive symptoms in adolescents remains limited.

Introduction

Olanzapine is one of the most important agents used in the treatment of schizophrenia and bipolar I disorder. Its history dates back to the 1980s, when research in Eli Lilly laboratories led to the discovery of a compound that would transform the management of these serious mental illnesses. In response to the growing need for effective medications with fewer adverse effects compared with earlier neuroleptics

such as chlorpromazine or haloperidol, olanzapine rapidly gained recognition in the medical community. In 1996, following clinical trials, it was approved for use by the U.S. Food and Drug Administration (FDA) [1]. The aim of this paper is to present the mechanisms of action of olanzapine and to evaluate its therapeutic efficacy in treating schizophrenia in adolescents, with particular emphasis on pharmacotherapy safety and potential risks associated with its use.

Indications for the use of olanzapine

Schizophrenia and bipolar I disorder (BD-I) are chronic psychiatric illnesses that substantially affect patients' lives. They are frequently associated with progressive disability and comorbid medical conditions. Moreover, these disorders commonly involve negative symptoms that impair daily functioning and quality of life. In this context, it should be underscored that olanzapine shows high efficacy in reducing positive symptoms of schizophrenia, such as delusions and hallucinations, as demonstrated in numerous meta-analyses [2]. Guidelines identify olanzapine as an effective option for controlling psychotic – particularly positive – symptoms, while cautioning about metabolic risk [3]. At present, there is no conclusive evidence to suggest that olanzapine exerts direct pro-cognitive effects.

Position of olanzapine in the treatment of schizophrenia and bipolar disorder according to APA and NICE Guidelines

1. APA – American Psychiatric Association (USA)

Schizophrenia

The 2020 APA guideline recommends second-generation antipsychotics (SGAs) –including olanzapine – as one therapeutic option. SGAs are not promoted as universally preferred or "first-line above all others"; rather, SGAs and FGAs are considered within the broader antipsychotic class based on individual patient factors [4, 5]. In Canadian guidelines, olanzapine is one of three preferred antipsychotics for first-episode schizophrenia [6]. In other guidelines, although not always named, it is part of the recommended SGA group as an acceptable and commonly used option.

Bipolar disorder

For acute manic episodes, APA primarily recommends lithium or valproate; olanzapine is an adjunctive/combination option (± antipsychotics such as olanzapine) [7]. APA also supports use of olanzapine or other SGAs for mixed and depressive episodes and during maintenance, typically as an alternative rather than the first choice [7].

2. NICE – National Institute for Health and Care Excellence (UK)

Schizophrenia

The 2013 NICE guideline emphasizes shared decision-making considering benefit–risk profiles (including metabolic adverse effects, sedation, QT prolongation, endocrine effects) [3]. SGAs are not categorically preferred; selection is individualized.

Bipolar disorder

Olanzapine is:

- a first-line agent for acute mania alongside aripiprazole, haloperidol, quetiapine, and risperidone.
- a first-line option for acute bipolar depression in combination with fluoxetine (olanzapine–fluoxetine combination, OFC).
- a second-line monotherapy option during maintenance.

3. Other guidelines and comparative summaries

Across international overviews (APA, NICE, Canadian, Maudsley, Unified Guideline) covering manic, mixed, depressive episodes and maintenance in bipolar disorder:

- Mania: NICE favors SGAs including olanzapine more prominently than APA, which prioritizes lithium/valproate as preferred initial therapy [8].
- Mixed episodes: All guidelines (including NICE) list olanzapine as an option.
- Depressive episodes: OFC (olanzapine + fluoxetine) is recommended by most guidelines, but not by NICE, which more often prefers SSRI/lamotrigine/quetiapine combinations [7, 8].

Table 1. **Position of olanzapine (OLZ) in schizophrenia [7]**

Treatment aspect	Position of olanzapine
Acute phase, first episode	Preferred in Canadian guidelines; accepted across guidelines as an SGA
Maintenance therapy	Recommend continuation if effective
Duration of therapy	May be used long-term (including lifelong)
Integration with psychosocial therapy	Facilitates CBT, family psychoeducation, supported employment, and social skills training by stabilizing positive and negative symptoms

When effective and well tolerated, olanzapine can be used in both acute and long-term management, potentially for many years or lifelong. For patients with difficulty adhering to oral medication, APA suggests considering depot/LAI olanzapine to provide sustained drug delivery and potentially improve adherence. By mitigating positive symptoms (e.g., delusions, hallucinations) and stabilizing functioning, olanzapine can

support engagement in cognitive-behavioral therapy (CBT), family psychoeducation, supported employment, and social/psychosocial skills programs.

Table 2. **Position of olanzapine (OLZ) in bipolar disorder (BD) [7]**

Illness phase	Role of olanzapine (OLZ)
Acute mania	Strong position – first-line across guidelines
Mixed episode	Strong position – preferred; often combined with valproate
Bipolar depression (acute)	Primarily used as OFC (OLZ + fluoxetine)
Maintenance (mania prevention)	Accepted and recommended as mono – or combination therapy
Maintenance (depression prevention)	Limited role – generally not a preferred option

Olanzapine holds a key role in acute mania, recommended both as monotherapy and in combination regimens, and is an established long-term option for relapse prevention of mania. Leading guidelines also classify it as a first-line agent for acute mixed episodes.

Efficacy of olanzapine in youth

The table below summarizes clinical studies assessing the efficacy and safety of olanzapine in children and adolescents with schizophrenia spectrum disorders and mood disorders, including randomized controlled trials (RCTs), open-label studies and reviews.

Table 3. **Clinical studies of olanzapine efficacy and safety in children and adolescents with schizophrenia and mood disorders**

Study/design	*n* (OLZ)	Mean age	Therapeutic efficacy	Adverse events
RCT: Schizophrenia, 6-wk, double-blind randomized, placebo-controlled (2:1 OLZ vs placebo)*	72	≈ 16.1 y	Significantly better BPRS-C, CGI-S, PANSS vs placebo ($p \leq 0.005$); marked improvement in psychotic symptoms	Weight gain: 31.7%; mean +7.4 kg (vs +3.2 kg in adults, $p < 0.001$); 65.1% ≥ 7% weight increase (vs 35.6% adults, $p < 0.001$). Somnolence: 19.8%. Increased appetite: 17.4%. Metabolic changes: ↑ fasting glucose ($p < 0.001$), ↑ total cholesterol ($p = 0.002$), ↑ triglycerides ($p = 0.007$), ↑ ALT ($p < 0.001$). Prolactin: ↑ in 47.4% (mean +11.4 µg/L, $p < 0.001$). Psychiatric AEs: suicide attempts 0.4% (2 pts), suicidal ideation 2.9% (13 pts) [9]

table continued on the next page

RCT: Schizophrenia (13–17 y) & manic episodes	–	13–17 y	Improvement in BPRS-C and YMRS; 26-wk open extension	Somnolence, weight gain, ↑ prolactin, ↑ lipids, ↑ liver enzymes; EPS 10% vs 6% [10]
Open-label: schizophrenia/ schizoaffective; 12–19 y	96	12–19 y	Response 62.5% (≥ 30% BPRS reduction); significant BPRS decrease (39.2 → 22.2)	Weight gain in 30.2%; discontinuation for AEs 3.1% [11]
Open-label: bipolar mania; 5–14 y	23	5–14 y	Response 61%; YMRS ↓ by 19 points (p <0.001)	Weight gain 5.0 ± 2.3 kg; EPS not significant [12]
Open-label: schizophrenia, 8–17 y, 10 wk	16	8–17 y	12/16 with significant improvement on BPRS, PANSS, CGI	≈ 6.2 kg weight gain; EPS in 2 pts [13]
Open-label: schizophrenia, 12–17 y, 8 wk	16	13.8 y	Improvement in PANSS, CGI, CGAS; reduction in positive/ negative symptoms	↑ appetite, sedation; EPS in 2 pts [14]
Systematic RCTs (meta-analysis): olanzapine vs risperidone	457 (8 RCTs)	25–80 y (some adolescents)	Overall antipsychotic efficacy comparable across scales	AEs varied by study [15]
Pediatric meta-analysis (mania): olanzapine	161	≈ 15 y	YMRS reduction 18 vs 10 points (placebo); response 48% vs 22%; remission 35% vs 11% (p ≈0.001)	Weight gain +3.7 kg vs +0.3 kg; 42% with ≥ 7% weight increase; ↑ prolactin (girls 25.7% vs 0; boys 62.5% vs 5%) [16]
Retrospective review of RCTs and open-label, mixed diagnoses (6–18 y)	53	6–18 y	Responses: 13/19 (treatment-resistant) and 27/34 (first-episode)	Greater weight gain than risperidone/haloperidol; sedation up to 50%; mild EPS; ↑ glucose, ALT, prolactin [17]

RCT – randomized controlled trial; OLZ – olanzapine; BPRS(-C) – Brief Psychiatric Rating Scale (for Children); CGI-S – Clinical Global Impression–Severity; PANSS – Positive and Negative Syndrome Scale; YMRS – Young Mania Rating Scale; CGAS – Children's Global Assessment Scale; EPS –extrapyramidal symptoms; ALT – alanine aminotransferase.

* Randomization ratio 2:1 indicates two participants receiving OLZ for each participant receiving placebo.

Therapeutic mechanism of olanzapine in adolescents and adults

Olanzapine is a second-generation antipsychotic with broad affinity for multiple neurotransmitter receptors. As an antagonist at dopaminergic (D_2, D_1–D_4), serotonergic (5-HT_2A, 5-HT_2C, 5-HT_3, 5-HT_6), histaminergic (H_1), muscarinic (M_1–M_5), and α_1-adrenergic receptors, it modulates numerous neurochemical processes that underpin its pleiotropic clinical effects.

Dopamine receptor blockade within the mesolimbic and mesocortical pathways reduces positive (e.g., hallucinations, delusions) and, to some extent, negative (e.g., anhedonia, apathy) symptoms in schizophrenia. Antagonism at 5-HT_2A/5-HT_2C receptors contributes to improvement in negative symptoms and mood, relevant for affective presentations. H_1 antagonism underlies sedation, while muscarinic blockade – particularly at M_3 – affects glucose metabolism and contributes to metabolic risk. α_1-adrenergic antagonism may produce adverse effects such as orthostatic hypotension.

Like clozapine, olanzapine exhibits multi-receptor activity; its affinity for 5-HT_2 receptors exceeds that for D_2 receptors, which may influence its therapeutic profile. In treating schizophrenia and bipolar I disorder, olanzapine is effective as monotherapy or as an adjunct to agents such as lithium or valproate [18]. The pharmacologic mechanism is the same in adults and adolescents, as its receptor-binding profile does not vary by age. In 2021, the oral fixed-dose combination of olanzapine with samidorphan (LYBALVI™) received its first U.S. approval for schizophrenia and for bipolar I disorder – including acute manic/mixed episodes and maintenance treatment [19, 20].

Effects on the glutamatergic system and synaptic plasticity

Within the glutamatergic hypothesis of schizophrenia – which emphasizes NMDA receptor dysfunction in cognitive processes and negative symptoms – olanzapine may also influence glutamatergic neurotransmission indirectly at the molecular level. In preclinical models, olanzapine reversed MK-801–induced cognitive deficits and restored GluN1 and phosphorylated GluN2B subunit levels in the prefrontal cortex, potentially reflecting improved synaptic plasticity [21]. Reviews further suggest that antipsychotics may remodel synaptic architecture, including postsynaptic density and neuronal plasticity, by modulating PSD-related factors and expression of genes such as *Homer1a*. Although these findings require further clinical corroboration, they point to mechanisms broader than dopaminergic/serotonergic activity and justify continued research into olanzapine's role in neuronal plasticity [22, 23].

Pharmacokinetics – adolescents vs adults

Adults:

- Absorption: high; $T_{max} \approx 5$–6 h; bioavailability 60–80% [24].
- Distribution: large Vd (~22 L/kg); protein binding ~93%.

– Metabolism: primarily hepatic – glucuronidation and oxidation via CYP enzymes (mainly CYP1A2, also CYP2D6). Metabolites are largely inactive; elimination is predominantly renal. No clinically meaningful PK differences between CYP2D6 poor and extensive metabolizers suggest CYP2D6 has limited impact on olanzapine metabolism in adults [25].
– Elimination: t½ ≈ 30–33 h (range 21–54 h); ~60% excreted in urine, ~30% in feces [26].
– Influencing factors: cigarette smoking (strong CYP1A2 induction) lowers exposure and may reduce clinical improvement (e.g., smaller BPRS change) [27]; women and older adults exhibit lower clearance and higher concentration per dose [28]. Genetic variability, diet, and hepatic/renal status may also play important roles.

Adolescents (13–17 years):

– Overall PK is similar to adults, but exposure (AUC; concentration–dose ratio) is ~27–34% higher on average [29].
– Population models: for girls ~70 kg, CL/F ≈ 13.6 L/h; V/F ≈ 899 L; inter-individual variability is moderate.
– Higher exposure likely reflects lower body mass and less smoking (less CYP1A2 induction)
– Clinical implication: despite exposure differences, given wide inter-individual variability, routine dose adjustments solely by body weight or sex are not generally required in adolescents or adults [18].

Adverse effects – adolescents vs adults

Adults:

– Very common: weight gain (≈40% with ≥ 7% increase from baseline), sedation, mild hyperprolactinemia.
– Common (1–10%): metabolic disturbances, dyslipidemia, elevated transaminases, dry mouth, orthostatic dizziness, mild EPS, hyperglycemia, orthostatic hypotension.
– Rare: agranulocytosis, thrombosis, extrapyramidal syndromes, rhabdomyolysis, hypotension, neuroleptic malignant syndrome, sudden death.

Adolescents:

– Weight gain and metabolic abnormalities are more pronounced than in adults (greater changes in weight, LDL cholesterol, triglycerides, prolactin).
– Somnolence, increased appetite, hyperprolactinemia, and metabolic effects are more frequent and marked.
– EPS and other extrapyramidal effects are uncommon – as in adults – but warrant monitoring [24].

Summary:

- Mechanism (antagonism at D_2, 5-HT_2A, H_1, M_1–M_5, α_1) is the same across ages.
- PK: adolescents show ~27–34% higher exposure, yet routine dose adjustments are not mandated due to high inter-individual variability.
- Safety: adolescents typically experience more pronounced metabolic effects (weight, lipids, prolactin) than adults, consistent with the receptor profile.

Dosing in children and adolescents

For schizophrenia in adolescents aged 13–17 years, a recommended starting dose is 2.5–5 mg/day, titrated according to clinical response to a usual target of 10 mg/day. The maximum recommended dose is 20 mg/day in this age group [30]. In adults, the typical starting dose is 10 mg/day, adjustable within 10–20 mg/day. In children and adolescents, initiation at lower doses and more gradual titration are advised due to greater susceptibility to adverse effects—especially weight gain and metabolic disturbances [30].

Challenges in assessing efficacy in youth

Most pediatric studies with olanzapine are short-term. For example, an open-label study in 12 children/adolescents lasted only 6 weeks; similarly, an adolescent anorexia nervosa study spanned 10 weeks. Short follow-up limits assessment of long-term efficacy and safety. Many pediatric studies include small samples, reducing statistical power. Few investigations evaluate long-term outcomes of olanzapine in children and adolescents [18].

Remission as an outcome in schizophrenia

Remission is commonly defined as a sustained 6-month improvement in core psychotic and related symptoms, as per the Remission in Schizophrenia Working Group [31]. The efficacy of olanzapine with respect to remission has been well documented in clinical trials. In one randomized, controlled, blinded study (2011–2016) of 144 adults meeting ICD-10 criteria for schizophrenia, patients received oral olanzapine 2.5–20 mg/day with assessments at six time points. Remission was evaluated by change from baseline to final assessment. The mean baseline PANSS total score was 78.4, indicating marked symptom severity; after one year of olanzapine, the mean score decreased to 23.3, suggesting substantial efficacy in achieving remission. While adult data are encouraging, pediatric evidence remains limited; most youth studies emphasize short-term symptom reduction, safety and tolerability, with remission outcomes infrequently reported in small samples. Thus, extrapolation from adult remission data to adolescents remains tentative.

Antipsychotic polypharmacy and risk of complications in schizophrenia

Polytherapy is more frequently associated with weight gain, elevations in cholesterol and triglycerides, and insulin resistance [32]. In a study across 34 community clinics, first-episode schizophrenia (FES) was significantly associated with high cardiometabolic risk. Longer illness duration correlated with higher fat mass and BMI, and longer antipsychotic exposure correlated with increased dyslipidemia and other metabolic abnormalities, consistent with clinical observations. Olanzapine was associated with higher triglycerides, insulin and insulin resistance; quetiapine with increased triglyceride/HDL-C ratios. Early psychiatric intervention, preference for lower-metabolic-risk agents, close adverse-effect monitoring, and preventive measures (e.g., smoking cessation) were important to improve health in FES [33].

In children and adolescents, olanzapine adverse effects occur more frequently than in adults. Younger children often experience rapid weight gain, sedation and hepatic dysfunction; adolescents more commonly exhibit hyperprolactinemia and metabolic abnormalities. Long-term studies report average weight gains of 9–12 kg within a year, with >15% baseline weight increase in ~40% of patients. Females more often report subjective adverse effects (dry mouth, constipation, menstrual irregularities), whereas males more often show greater weight gain and neurological symptoms. Pediatric patients also have higher exposure per dose than adults, increasing adverse-effect risk [34, 35].

Polypharmacy is strongly discouraged in youth. Polish recommendations emphasize greater vulnerability to adverse effects and limited safety data for combinations in this population. Monotherapy at the lowest effective dose with regular metabolic monitoring is advised; antipsychotic combinations should be reserved for exceptional cases [36]. Despite this, polypharmacy remains common in practice. Developmental populations show 30–40% rates of concurrent antipsychotic use, especially in inpatient settings, highlighting a gap between guidelines and practice and the need for particular caution in youth [37].

Olanzapine treatment in adolescents – despite effective reduction of psychotic and manic symptoms – has complex effects on quality of life and academic/social functioning. Symptom control can improve family functioning and educational continuity; however, adverse effects – especially weight gain, sedation and psychomotor slowing – may lower self-esteem, impair cognition and motivation, and contribute to stigma and peer isolation. Consequently, long-term gains in quality of life and social integration may be constrained, and current guidance (e.g., AACAP, NICE) recommends particular caution and generally short-term use in this age group [38].

Comparison of olanzapine with other SGAs in youth

Randomized trials and network meta-analyses in adolescents (8–19 years) with schizophrenia-spectrum diagnoses show broadly comparable antipsychotic efficacy among aripiprazole, risperidone and olanzapine (improvement in PANSS total and positive symptoms vs placebo), with important safety differences. Olanzapine consist-

ently produces the greatest weight gain and most unfavorable metabolic changes; risperidone (and paliperidone) more often increases prolactin; akathisia/EPS are reported more frequently with aripiprazole or molindone. Given no clear efficacy advantage of olanzapine over other SGAs in antipsychotic-naïve youth, its clinical role as a second-line option is justified by its adverse metabolic profile – particularly in patients with obesity/metabolic-syndrome risk factors [39].

In antipsychotic-naïve pediatric cohorts, observational data show especially rapid and substantial weight gain after SGA initiation, with olanzapine yielding the largest mean weight increases and unfavorable lipid changes even in the short term. Aripiprazole and risperidone also cause weight gain but typically less than olanzapine. These findings reinforce the need for careful first-line selection and intensive metabolic monitoring in adolescents [40].

Long-acting injectable (LAI) olanzapine

Oral olanzapine may produce plasma concentration fluctuations dependent on adherence and dosing patterns. LAI formulations provide more stable release and more consistent exposure, potentially reducing therapeutic fluctuations that can lead to clinical deterioration and increased metabolic risk. However, depot/LAI olanzapine is not approved for patients under 18 years of age, limiting its pediatric use to oral formulations under close medical supervision. Therefore, any consideration of long-acting therapy in adolescents must be based on individualized risk–benefit assessment and available alternatives [41].

Conclusions

In adults, olanzapine improves both positive and negative symptoms. In the pediatric literature, evidence for efficacy against negative symptoms in adolescents is limited. Most child and adolescent trials focus on positive symptoms (psychosis, mania) and behavioral disturbances rather than isolated negative symptoms. Nonetheless, olanzapine is associated with substantial adverse-effect risks, including weight gain and metabolic disturbances such as insulin resistance. Youth appear more susceptible to these adverse effects, necessitating regular monitoring of glucose and lipid parameters.

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