Pharmacogenomics and Personalized Medicine

Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

Olanzapine Pharmacokinetics: A Clinical Review of Current Insights and Remaining Questions

Priyanka Kolli[1], Grace Kelley[1], Marianela Rosales[2], Justin Faden[1], Ryan Serdenes[3]

[1]Department of Psychiatry, Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA; [2]Department of Psychiatry and Human Behavior, Thomas Jefferson University Hospital, Philadelphia, PA, USA; [3]Department of Psychiatry, Johns Hopkins School of Medicine, Baltimore, MD, USA

Correspondence: Ryan Serdenes, Email rserdenes@gmail.com

Abstract: Olanzapine is one of the most widely used antipsychotics since its initial approval by the US Food and Drug Administration in 1996 and has undergone extensive pharmacokinetic study. Despite being utilized in clinical psychiatry for decades, there remain questions regarding the variety of available formulations, the utility of therapeutic drug monitoring, altered kinetic properties in special populations/medical illnesses, the use of high-dose olanzapine, and drug interactions, among many others. We performed a narrative literature review of olanzapine pharmacokinetics in June 2023 using the US National Library of Medicine's PubMed.gov resource (https://www.ncbi.nlm.nih.gov/pubmed) and Google Scholar. Herein, we review clinically relevant aspects of olanzapine pharmacokinetic data while highlighting knowledge gaps and potential areas of future study.

Keywords: olanzapine, pharmacokinetics, drug-drug interactions, pharmacodynamics, clinical psychopharmacology

Introduction

The field of pharmacokinetics examines how exogenous substances are absorbed, distributed, metabolized, and excreted by the body.[1] Conversely, pharmacodynamics is the study of how a drug impacts the body's physiological processes.[2] Multiple intrinsic and extrinsic factors influence pharmacokinetics including age, sex, genetic variants, concomitant medications, drug-drug/drug-food interactions, renal and hepatic function, and medical comorbidities.[2,3] Judicious medication and dosing regimens are informed by pharmacokinetic principles to balance drug efficacy, tolerability, and limit toxicity. The method of drug administration and absorption also plays a central role in pharmacokinetics, and medications with various formulations, such as olanzapine, can have differing pharmacokinetic properties.[4]

Olanzapine is a highly efficacious second-generation antipsychotic (SGA) utilized for the management of schizophrenia, bipolar disorder, major depressive disorder (MDD) as adjunctive treatment, and agitation associated with schizophrenia or bipolar disorder.[5] Despite its initial approval in 1996, there has been a resurgence of interest in olanzapine due to the development and approval of new formulations by the US Food and Drug Administration (FDA) and other formulations currently under investigation in clinical trials.[6,7] Meta-analyses, efficacy trials, and comparison trials have consistently ranked olanzapine as one of the most efficacious antipsychotic medications for the treatment of schizophrenia and bipolar disorder.[8–13] However, utilization and enthusiasm for olanzapine are tempered by tolerability concerns, and amongst antipsychotic medications, olanzapine consistently ranks as one of the leading contributors of metabolic syndrome, weight gain, and dyslipidemia.[11,14] Accordingly, many guidelines have relegated olanzapine to being a second-line treatment option.[15–18] Although, olanzapine-samidorphan was recently approved for the treatment of schizophrenia and bipolar disorder and has shown efficacy in partially ameliorating olanzapine-induced weight gain.[19]

Olanzapine is one of the most studied antipsychotic medications and despite metabolic concerns, it remains widely used due to its superior efficacy profile. However, despite robust data being available, unknowns related to olanzapine pharmacokinetics remain – especially regarding the variety of available formulations, the utility of therapeutic drug

Received: 1 August 2023
Accepted: 30 November 2023
Published: 21 December 2023

monitoring (TDM), altered kinetic properties in special populations/medical illness, the use of high dose olanzapine, and drug interactions, among many others. The focus of this review will be to provide an overview of olanzapine and its pharmacologic profile while emphasizing clinically relevant pharmacokinetics along with current insights, knowledge gaps, and potential areas of future study.

Methods

We performed a literature review of olanzapine pharmacokinetics through June 2023 using the US National Library of Medicine's PubMed.gov resource (https://www.ncbi.nlm.nih.gov/pubmed) and Google Scholar. The following keywords in various combinations were searched: "Olanzapine", "Pharmacokinetics", "Absorption", "Distribution", "Metabolism", and "Elimination". We identified additional literature by examining the reference lists of the results from our initial keyword search. Accordingly, we described major findings as opposed to formally evaluating literature quality to maintain a clinical focus. The resulting article content was reviewed by the authors for information regarding the pharmacokinetic profile of olanzapine, relevant drug interactions, and considerations in medical illness/special populations.

General Pharmacology

Pharmacokinetic and Pharmacodynamic Profile

Olanzapine is a thienobenzodiazepine derivative, discovered during efforts to synthesize an alternative to clozapine without hematologic side effects requiring frequent laboratory monitoring.[20] The pharmacokinetics of olanzapine have been extensively studied over the past three decades in healthy patients, patients with psychopathology, and special populations.[3,21–23] Olanzapine has a high affinity (Ki≤100 nM) at the dopamine (D1-4), adrenergic (alpha 1), histamine (H1), muscarinic (M1-2 and M4-5, only moderate affinity at M3), and serotonin receptors (5-HT2A/C, and 5-HT3/6 receptors).[5] Daily doses of ≥12 mg have been shown to antagonize at least 65% of striatal D2 receptors while doses >20 mg can attain more than 80% receptor occupancy.[24,25] Olanzapine demonstrates less D2 occupancy compared to 5HT2A occupancy within therapeutic dose ranges.[26] The mesolimbic and mesocortical brain regions seem most implicated in olanzapine's pharmacodynamics.[27,28]

Olanzapine demonstrates dose-dependent linear pharmacokinetics comparable to other atypical antipsychotics.[22,28] Orally administered olanzapine is almost completely absorbed but only has about 60% oral bioavailability given contributions from first-pass metabolism.[28] Olanzapine undergoes extensive biotransformation and less than 10% is estimated to be renally excreted without being metabolized.[5] Olanzapine is converted to clinically inactive metabolites via UDP-glucuronosyltransferase (10'/4'-N-glucuronides, major metabolites), CYP1A2 (4'-N-desmethylolanzapine), flavin mono-oxygenase 3 (olanzapine N-oxide), and to a lesser extent by CYP2D6 (2-hydroxymethyl olanzapine).[5,22,29,30] Given its lipophilicity, olanzapine has a large volume of distribution ranging from 16.4 ± 5.1 L/Kg and is highly protein bound by albumin and alpha-1-acid glycoprotein.[28] The time to maximum concentration and the half-life of olanzapine is approximately 6 hours and 33 hours, respectively.[28] Examination of radiolabeled olanzapine suggests that approximately 60% is renally eliminated with the remainder being mostly fecally excreted.[31]

Pharmacogenomic Considerations

Several polymorphisms influencing olanzapine pharmacokinetics have been identified, specifically UDP-glucuronosyltransferase, CYP1A2, and P-glycoprotein. Both the UGT1A4 and 2B10 alleles are associated with increased and decreased formation of glucuronidated olanzapine products, respectively.[29] At least five CYP1A2 alleles have been identified across several studies—although only two, the *1D and *1F alleles are associated with significant changes in olanzapine plasma levels, resulting in increased and typically decreased levels respectively.[32–34] However, clinical recommendations on CYP1A2-dependent olanzapine dosing are yet to be established given conflicting data from other studies.[34–37]

Olanzapine functions as both a substrate and an inhibitor of P-glycoprotein.[38] The impact of P-glycoprotein on olanzapine pharmacokinetics is uncertain, likely due to the variability of P-glycoprotein local tissue expression and

function. However, the T allele of the P-glycoprotein gene ABCB1 has recently been associated with increased olanzapine plasma levels.[38] Additionally, olanzapine, via inhibition of P-glycoprotein, can potentiate its own CNS penetration.[38] These pharmacogenomic influences on olanzapine pharmacokinetics have clinical consequences such as the development of metabolic syndrome.[39] The clinical relevance of these observations to clinicians whose patients are not completing genetic profiling remains poorly understood. Further study into creating guidelines for when it is appropriate or clinically relevant to perform genetic testing could be valuable.

Available Formulations and Pharmacokinetic Differences

Olanzapine is currently available in the following forms: oral tablet, oral disintegrating tablet (ODT), short-acting intramuscular (IM) injection, depot long-acting intramuscular injection (LAI), and intravenous injection (IV).[5,40–43] Table 1 provides an overview of the FDA-approved olanzapine formulations.[41,44,45] There are no statistically significant pharmacokinetic differences between the ODT and the standard oral formulation.[40] IM olanzapine reaches its maximum plasma concentration about 8–12 times faster compared to oral dosing and attains a peak plasma concentration possibly up to five times the oral dose. Despite this, the half-lives of short-acting intramuscular olanzapine and oral olanzapine remain similar.[5,41,44] The LAI formulation, olanzapine pamoate, has a half-life of approximately 30 days which is rate limited by the speed of intramuscular absorption, and plasma concentrations increase gradually over the first 3 months of administration until a steady state is reached.[42] While an intranasal olanzapine preparation was developed and studied for the treatment of agitation in schizophrenia and bipolar disorder, it is not FDA approved for clinical use at this time.[46] The safety of IV olanzapine has been established in emergency settings for agitation, although no studies have been dedicated to investigating the pharmacokinetics of this route to our knowledge.[43,47] Of note, for both olanzapine combination preparations with fluoxetine (Symbyax) and samidorphan (Lybalvi) there are no clinically significant pharmacokinetic differences when compared to olanzapine monotherapy.[19,48,49]

Table 1 Overview of FDA Approved Olanzapine Formulations

Formulations	Brand Name	Available Dose Strengths	Recommended Dose in Healthy Adults	Time to Maximum Concentration	Half Life
Oral tablet	Zyprexa	2.5 mg 5 mg 7.5 mg 10 mg 15 mg 20 mg	10 mg - 20 mg/day	6 hours	30 hours
Orally Disintegrating Tablet	Zyprexa Zydis	5 mg 10 mg 15 mg 20 mg	10 mg - 20 mg/day	6 hours	30 hours
Short-acting injectable	Zyprexa intramuscular	10 mg/vial	-Dose may range from 2.5 mg to 10mg -Exceeding 3 doses (10 mg 2–4 hours apart) in 24 hours is not recommended	15–45 minutes (Maximum concentration is ~5 times greater than oral formulation)	30 hours
Extended-release intramuscular injectable	Zyprexa Relprevv	210 mg/vial 300 mg/vial	-Dose may range from 150 mg to 300 mg every 2 weeks -Exceeding 405 mg every 4 weeks is not recommended	Within first week of injection	30 days

Dosing Considerations

Initiation, Titration, and Tapering

Olanzapine is usually initiated at a total daily dose of 5 mg for schizophrenia or bipolar disorder and titrated as clinically indicated, although lower (2.5 mg) or higher (10 mg) starting doses can be warranted based on a patient's psychiatric history, medical comorbidities, and pharmacokinetics.[50] While clinical trials suggest the optimum total daily dose of olanzapine for schizophrenia ranges from 10mg to 20mg, higher doses have been demonstrated to be efficacious in treatment-resistant schizophrenia.[51–53] Abrupt discontinuation of olanzapine can precipitate cholinergic rebound and increase the risk of psychiatric decompensation, therefore, gradually tapering olanzapine can attenuate these adverse consequences.[54]

High Dose Olanzapine

Olanzapine has been tolerated at doses as high as 50 mg/day in case reports of patients with treatment-resistant schizophrenia; however, expert panels have suggested 40 mg/day as the maximum daily dose.[55,56] In some situations, olanzapine dosed at 40 mg/day is more efficacious in treating psychotic disorders than doses of 20 mg/day or less.[56] Clinicians should weigh the risks and benefits of higher doses, up to 40mg, which come with increased risk for side effects. Olanzapine's pharmacokinetic properties appear to be consistent in doses up to 40 mg, although there are reports of increased rates of akathisia and weight gain at doses beyond 20 mg.[57] Olanzapine overdoses up to 2 g have been reported with the most common side effects being CNS depression, delirium, extrapyramidal symptoms, and anticholinergic symptoms, whereas cardiac arrhythmias and/or death are either rare or underreported.[5,58] There is limited data on olanzapine pharmacokinetics in overdose and no relationship has been found between the dose ingested and the rate of CNS depression, delirium, Intensive Care Unit admission, or hospital length of stay.[58]

Therapeutic Drug Monitoring

The metabolism of olanzapine can be influenced by various factors such as age, gender, body weight, smoking status, and drug interactions–all of which can affect therapeutic efficacy and tolerability.[59] TDM evaluates medication plasma concentration levels which can help ensure adequate dosing for efficacy and reduce the risk of toxicity.[60] TDM can be particularly useful in special populations such as the elderly, patients with hepatic or renal impairment, in the setting of suspected non-adherence, and patients with comorbid medical conditions that may affect the metabolism of olanzapine.[61] TDM allows for an optimized dose of olanzapine for each patient, thus keeping with an "n=1" approach to personalized medicine, and helps to account for variability in individual pharmacokinetics, pharmacodynamics, and concurrent medications/medical conditions. Olanzapine serum levels between 20 to 40 ng/mL are suggested to be optimal, while levels beyond 80–100 ng/mL increase the likelihood of adverse events and toxicity.[59,62] However, it's important to be mindful that TDM may not always reflect cerebral drug exposure, especially in the context of a disturbed blood-brain barrier associated with certain medical illness. As olanzapine plasma levels are not commonly obtained, additional study on their clinical utility is needed.

Medical Illness Impacts on Olanzapine Pharmacokinetics

Absorption & Distribution

There is limited pharmacokinetic data on olanzapine absorption and distribution in the context of medical illness. Olanzapine is a lipophilic weak base that is readily absorbed and reaches peak concentrations approximately 4–6 hours following an oral dose.[5,41,44] The process of drug absorption is multifactorial with several contributors including gastrointestinal motility, intestinal blood flow, gastric emptying time, gastric and intestinal pH, gut wall permeability, bile secretions, and gut flora, among others.[63] Despite olanzapine being a weak base, there have been no notable changes in the oral bioavailability of olanzapine after the administration of single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids.[5] Additionally, concomitant consumption of food or liquid does not affect the rate or extent of absorption.[5] In a Roux-en-Y gastric bypass (RYGB) experimental model, olanzapine had less dissolution compared with the in vitro control condition representing the pre-operative patient.[64] We were unable to identify other

pharmacokinetic studies of olanzapine in the context of relevant medical illnesses impacting absorption such as inflammatory bowel disease, gastroparesis, or Zollinger-Ellison syndrome among others. Olanzapine has a large volume of distribution and is extensively bound by plasma proteins, albumin, and α1-acid glycoprotein.[5,28] Known factors that may affect the distribution of drugs in the body include pregnancy, obesity, renal disease, hepatic disease, heart failure, and extracorporeal therapies among others.[5,65,66]

Metabolism & Elimination

Olanzapine is mostly metabolized hepatically via second-phase glucuronidation, which is typically maintained in liver disease; therefore, the pharmacokinetics of olanzapine may be maintained in individuals with hepatic impairment.[66] However, in the context of cirrhosis, decreased alpha-1-acid-glycoprotein and albumin can result in an increased concentration of unbound olanzapine.[67] Moderate hepatic impairment can reduce olanzapine clearance by about 45%, increasing systemic exposure and prolonging elimination half-life.[68] Studies have shown that urinary concentrations of olanzapine 10-N-glucuronide increase in patients with cirrhosis, suggesting increased compensatory glucuronidation which may explain the lack of significant pharmacokinetic differences compared with healthy patients.[22] Of note, some rat models suggest a relationship between glucuronidation of olanzapine and the gut microbiome; however, this has yet to be replicated in human models.[69] A dosage adjustment is not recommended for patients with severe renal impairment, as studies show no statistically significant difference in various pharmacokinetic parameters between patients with renal impairment versus those with normal renal function.[22] However, there is possible evidence showing a risk for adverse effects such as hypothermia in patients with renal dysfunction.[70] Of note, olanzapine is not removed during dialysis; however, due to its lipophilicity would be expected to be sequestered by extracorporeal membrane oxygenation.[5,22]

Drug-Drug Interactions

Olanzapine and Benzodiazepines

A 2009 post-marketing study found concomitant use of IM olanzapine and parenteral benzodiazepines has been associated with an increased risk of respiratory depression, after which a warning against co-administration was issued by the Food and Drug Administration.[5,71,72] Parenteral administration of benzodiazepines is recommended to be avoided within the first hour after IM olanzapine administration.[73] Despite the reported risk, pharmacokinetic explanations for this interaction remain elusive. In an analysis of 539,000 cases where IM olanzapine was used, there were 29 fatalities documented, of which 15 reported concomitant benzodiazepine use. Among elderly patients, benzodiazepines were co-administered in seven out of the nine fatal cases.[71] An analysis of concurrent IM olanzapine and lorazepam administration was conducted at a county psychiatric hospital. The study identified 91 instances of administering both medications within a 24-hour period, with 41 of these occurrences taking place within a 60-minute timeframe. Notably, none of the 91 cases resulted in serious adverse events including bradycardia, bradypnea, hypotension, or oxygen desaturation.[72] Additional research into the mechanism and higher-quality studies are necessary to determine the safety of combining parenteral benzodiazepines with olanzapine.

Olanzapine and Alcohol

Alcohol metabolism primarily occurs via CYP2E1, and there is no substantial evidence of metabolic interactions between olanzapine and alcohol.[22] In a retrospective study conducted in an Emergency Department setting, administration of IM olanzapine in combination with benzodiazepines did not lead to any vital sign changes in non-alcohol-intoxicated patients. However, the administration of IM olanzapine monotherapy or with benzodiazepines was linked to a decline in oxygen saturation in alcohol-exposed patients. Oral olanzapine regardless of benzodiazepine coadministration, in alcohol intoxicated patients did not have a significant impact on oxygen saturation, suggesting oral olanzapine may be a preferable choice in this population.[74]

Olanzapine and Smoking

Smoking tobacco or marijuana induces the CYP1A2 enzyme, leading to a decrease in the serum levels of olanzapine.[22,75] Active smokers had a lower average maximum plasma concentration of olanzapine and a 23% higher clearance compared to nonsmokers.[22] These findings suggest that smoking affects the pharmacokinetics of olanzapine and should be taken into consideration when prescribing this medication.

Olanzapine and Other Psychotropics

Fluvoxamine, carbamazepine, and fluoxetine have the most data regarding psychotropic drug interactions with olanzapine. Coadministration of fluvoxamine, a strong CYP1A2 inhibitor, with olanzapine, has been shown to significantly increase the half-life and peak plasma concentration of olanzapine.[22,76] Administration of olanzapine and carbamazepine, a CYP1A2 inducer, increases the clearance of olanzapine. According to a study conducted on ten healthy volunteers pretreated with 2 weeks of carbamazepine, a single 10mg dose of olanzapine had a substantial reduction in the maximum plasma concentration and elimination half-life and an increase in the plasma clearance.[77] When fluoxetine, a CYP2D6 inhibitor, was administered with olanzapine, olanzapine showed statistically significant changes in clearance and maximum plasma drug concentration. However, these changes were considered to be clinically insignificant.[49] Given these pharmacokinetic changes, patients prescribed concomitant olanzapine and fluvoxamine, carbamazepine, or fluoxetine, respectively, should be carefully monitored. There are no metabolic interactions between valproic acid or lithium with olanzapine and no dose adjustment appears necessary when using olanzapine with either of the mood stabilizers.[5,22]

Tolerability and Safety

General Considerations

Tolerability issues from olanzapine have been long established, and a 1998 study identified side effects such as orthostatic hypotension, constipation, weight gain, dizziness, akathisia, and prolactinemia.[78] A 2017 clinical review found similar tolerability issues and expanded the list of adverse effects to include: sedation, weight gain/metabolic syndrome, hypotension, cardiovascular events, GI adverse events (nausea, vomiting, diarrhea, and constipation), dry mouth and dental caries, liver dysfunction, binge eating, sexual dysfunction, and endocrine adverse effects (DKA, hypothyroidism, and hyponatremia).[79] Often noted as a consideration before treatment initiation, olanzapine is amongst the highest-risk antipsychotics for associated metabolic syndrome.[12,79] Conversely, olanzapine is found to have milder extrapyramidal symptoms (EPS) than many other first-generation antipsychotics (FGAs) and SGAs.[79] When compared to other SGAs, olanzapine is found to minimally increase prolactin at levels comparable to clozapine, quetiapine, and ziprasidone, and at much lower levels than risperidone and paliperidone.[12] This is thought to be secondary, in part, to olanzapine's relatively low D2 receptor affinity within the tuberoinfundibular pathway.[80] SGAs, including olanzapine, are also less associated with hyposalivation and dental caries compared to FGAs.[81] In a year-long randomized, double-blinded study of 400 patients comparing olanzapine, risperidone, and quetiapine there was only 10% discontinuation of olanzapine due to side effect intolerance.[82] Two large meta-analyses of antipsychotics have also found olanzapine to have among the lowest discontinuation rates.[11,12]

Post-Injection Delirium

The long-acting injectable formulation of olanzapine has a specific tolerability concern known as post-injection delirium/sedation syndrome (PDSS), which carries an FDA black-box warning.[5] In the olanzapine LAI clinical trials program, they assessed 45,000 injections administered to 2054 patients and found that 0.07% of injections resulted in PDSS in 1.4% of patients.[83] Common PDSS symptoms include drowsiness, confusion, slurred speech, agitation, and ataxia, consistent with olanzapine overdose and suggestive of anticholinergic syndrome.[83,84] Between 2009 and 2015, there were no reported cases of PDSS symptoms beginning beyond three hours of injection, with approximately 91% of cases occurring within the first hour.[85] It was found that low Body Mass Index (BMI) and increased age were mild risk factors for PDSS.[83,86] Nevertheless, according to a 2017 observational study involving 3538 patients, it was found that PDSS was associated with higher dosage and male gender, rather than BMI and age.[87]

An investigation into the mechanism of PDSS studied the plasma concentrations of olanzapine in patients with reported PDSS events (n=12).[88] In all cases examined the olanzapine concentration became supratherapeutic within hours, returned to the therapeutic range within days to weeks, and did not seem to be related to depot injection dose. Mechanistically, iatrogenic intravascular injection followed by fast dissolution of the pamoate salt within the bloodstream may explain PDSS.[88]

Cardiac Considerations

When compared to other antipsychotics, olanzapine exerts a moderate QTc prolonging effect.[79] A 2006 study examining the cardiac effects of olanzapine, found olanzapine caused IKr blockade resulting in prolongation of cardiac repolarization. Therapeutic doses (5–20mg) of olanzapine result in peak plasma concentrations of 0.016–0.16uM, much less than the olanzapine concentration found to have a significant effect on cardiac repolarization, 5.7uM. This makes it unlikely that patients treated with therapeutic levels of olanzapine will have lengthening of cardiac repolarization.[89] However, changes to the metabolism of olanzapine could increase plasma concentration, as with inhibition of CYP1A2 or CYP2D6 activity.[5,86] Even with toxic plasma concentrations of olanzapine prolonging QTc, it rarely led to torsades de pointes, and atrioventricular blocks or bundle branch blocks were not typically observed.[90] In a 10-week, prospective, open-label, observational study, other cardiac markers such as PR interval, QRS complex, and RR interval were not demonstrated to be significantly different from baseline after the initiation of olanzapine.[91] The QTc prolonging effects associated with olanzapine have been predominantly noted in patients who exhibit multiple other risk factors for QTc prolongation.[89]

Respiratory Considerations

There are reports where olanzapine was suspected to contribute to a severe decline in respiratory status.[92,93] The use of any antipsychotic in patients with chronic obstructive pulmonary disease increases the risk of acute respiratory failure by 1.5 times.[79] Both FGA and SGAs are associated with an increased risk of pneumonia, but research suggests an increased mortality rate from pneumonia in patients on FGAs compared to patients on SGAs.[79] When compared to quetiapine, olanzapine was associated with an increased risk of pneumonia in patients older than 65.[94] There are several potential mechanisms thought to contribute to the increased risk of pneumonia seen with SGA use, including sialorrhea, cough and swallowing reflex dysfunction, and increased sedation.[95]

In a prospective observational study, Cole et al observed 3.7% of patients administered IV olanzapine and 2.0% of those administered IM olanzapine had subsequent respiratory depression, some of which required intubation.[47] In a retrospective analysis by Martel et al, hypoxia was observed in 10.4% of patients following IV olanzapine administration. However significant respiratory intervention, such as intubation, was used in only 2.1% of patients. Based on the infrequency of severe airway complications, they concluded that IV olanzapine is safe for use in Emergency Departments.[96] When examining the safety of IV olanzapine in 46 acutely agitated patients with neurological injuries, olanzapine was found to be low risk for respiratory depression with only four patients requiring additional oxygen support, and no patients requiring intubation.[97]

Specific Populations

Women's Health

Several studies have investigated the differences in olanzapine pharmacokinetics between males and females. Females have significantly higher olanzapine plasma concentrations than males likely due to slower CYP1A2 metabolism along with sex differences in volume of distribution.[98] Although, there is a lack of empirical evidence indicating a difference in efficacy or occurrence of adverse reactions between male and female populations. Consequently, there are no recommendations suggesting dosage adjustments specifically for women.[5]

In one double-blind study, olanzapine was found to cause dose-dependent elevations in prolactin levels but chronic use of olanzapine did not result in persistent prolactin elevations.[22] Olanzapine use seems to cause a dose-dependent increase in prolactin levels, although there is conflicting research regarding the persistence of hyperprolactinemia. Elevated prolactin has been known to lead to gynecomastia, galactorrhea, and sometimes breast cancer. Although no

direct link between olanzapine and breast cancer has been identified.[5] A prudent prescriber should weigh the risk of olanzapine administration in patients with a personal history or family history of known prolactin-dependent breast cancer.

The decision to use olanzapine in pregnancy should be carefully considered in light of the potential impact on fetal development. Olanzapine plasma concentrations in pregnant patients are slightly lower compared to non-pregnant patients which can possibly be attributed to the physiologic changes noted in pregnancy, such as increased clearance and volume of distribution.[65,99] In a large cohort of pregnant patients on antipsychotic therapy, maintenance of olanzapine during the first trimester was associated with increased risk of gestational diabetes compared with risperidone, aripiprazole, or ziprasidone.[100] Despite pregnancy-induced changes to olanzapine pharmacokinetics, no specific dosage guidelines have been recommended.[65]

Olanzapine has a higher placental passage compared to haloperidol, risperidone, and quetiapine.[101] Olanzapine treatment during pregnancy is associated with low birth weight and increased neonatal intensive care unit admissions[101] In a recent population-based birth cohort study, olanzapine was associated with double the risk of major congenital malformations and a nearly four times increased risk of musculoskeletal malformations compared to infants unexposed to antipsychotics during pregnancy.[102] Careful consideration is needed when prescribing olanzapine to pregnant patients and the risks and benefits of pharmacotherapy should be discussed with the patient.

Antipsychotic medications with low excretion into human breast milk and minimal adverse effects in breastfed infants are ideal choices. Olanzapine is preferred during breastfeeding because it is found to be at low levels in breast milk and undetectable in the serum of breastfed infants. A systematic review of SGAs concluded that olanzapine is safe during breastfeeding, suggesting that it is a reasonable treatment option for mothers with psychotic disorders who are breastfeeding their infants.[103,104]

Pediatrics

Olanzapine is approved by the FDA for the treatment of schizophrenia and bipolar disorder in those 13 years and above.[5] It is also used off-label for a variety of indications in the pediatric patient population, including autism spectrum disorder, tic disorders, and delirium among others.[105] The association between olanzapine half-life and pediatric age appears to be parabolic and hepatically mediated with children between 6 months and 6 years old experiencing shorter olanzapine half-lives.[105] Body weight also seems to be a significant contributor to olanzapine clearance in pediatric populations.[105] Maharaj et al described weight and age-based pediatric olanzapine dosing recommendations to attain similar plasma concentrations compared to adults.[105] Future research would help further elucidate optimal pediatric dosing strategies, which is especially important given children seem more likely to experience the olanzapine side effects, such as weight gain and sedation compared to adults.[5,106] It is unclear if the availability of olanzapine/samidorphan will appreciably alter this dynamic, however, it should be noted that olanzapine/samidorphan is not FDA-approved for individuals < 18 years at this time.

Geriatrics

Elderly patients may exhibit altered pharmacokinetics of olanzapine, although published results are inconsistent. While Gex-Fabry et al reported a 27% increase in olanzapine plasma concentrations of olanzapine in patients over the age of 60 years, Skogh et al found no relationship between concentration-to-dose ratios and age.[59,107] However Callaghan, found that the weight-corrected concentration/dose ratios of olanzapine increased by an average of 9.4% per decade of life.[22] Elimination half-life and time to maximum drug plasma concentration for olanzapine in the elderly were found to be 53% and 34% longer respectively.[22] Further study into the changes in the pharmacokinetics of olanzapine in the elderly is warranted, but based on current evidence clinicians may consider lower dosing and slower titrations when utilizing olanzapine in older patients.

Conclusion

This narrative review examines the current literature on olanzapine pharmacokinetics with an emphasis on clinical practice. A question that needs to be answered is: Why review the pharmacokinetics of olanzapine now? Despite

olanzapine demonstrating favorable efficacy when compared to other antipsychotic medications, its utilization has waned due to tolerability concerns. However, its efficacy still makes it a medication of high interest as evidenced by the newly approved olanzapine/samidorphan combination tablet and alternative formulations under investigation. How best to maximize efficacy and tolerability remains a clinical question. Understanding the pharmacokinetic properties of olanzapine can help to optimize its usage, especially as each distinct formulation of olanzapine has unique pharmacokinetic data. Despite many unknowns, the existing olanzapine pharmacokinetic data can assist practitioners in navigating medical decision-making. We hope our narrative review serves as a reference for evidence-based olanzapine dosing as well as intellectual scaffolding for the development of clinically relevant pharmacokinetic research questions.

Disclosure

Dr. Justin Faden reports grants from BioXcel Therapeutics, non-financial support from Noven Pharmaceuticals, outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. Fan J, de Lannoy IAM. Pharmacokinetics. *Biochem Pharmacol*. 2014;87(1):93–120. doi:10.1016/j.bcp.2013.09.007
2. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol*. 2004;57(1):6–14. doi:10.1046/j.1365-2125.2003.02007.x
3. Jovanović M, Vučićević K, Miljković B. Understanding variability in the pharmacokinetics of atypical antipsychotics–focus on clozapine, olanzapine and aripiprazole population models. *Drug Metab Rev*. 2020;52(1):1–8. doi:10.1080/03602532.2020.1717517
4. Correll CU, Kim E, Sliwa JK, et al. Pharmacokinetic characteristics of long-acting injectable antipsychotics for schizophrenia: an overview. *CNS Drugs*. 2021;35(1):39–59. doi:10.1007/s40263-020-00779-5
5. Olanzapine [package insert]. Indianapolis (IN): Eli Lilly and Company; 2009.
6. Lybalvi [package insert]. Waltham (MA): Alkermes Inc; 2021.
7. Ward K, Citrome L. The treatment of acute agitation associated with schizophrenia or bipolar disorder: investigational drugs in early stages of their clinical development, and their clinical context and potential place in therapy. *Expert Opin Investi Drug*. 2020;29(3):245–257. doi:10.1080/13543784.2020.1727884
8. Bahji A, Ermacora D, Stephenson C, Hawken ER, Vazquez G. Comparative efficacy and tolerability of pharmacological treatments for the treatment of acute bipolar depression: a systematic review and network meta-analysis. *J Affect Disorder*. 2020;269:154–184. doi:10.1016/j.jad.2020.03.030
9. Kishi T, Ikuta T, Matsuda Y, et al. Pharmacological treatment for bipolar mania: a systematic review and network meta-analysis of double-blind randomized controlled trials. *Molecul psychiatr*. 2022;27(2):1136–1144. doi:10.1038/s41380-021-01334-4
10. Nestsiarovich A, Gaudiot CE, Baldessarini RJ, Vieta E, Zhu Y, Tohen M. Preventing new episodes of bipolar disorder in adults: systematic review and meta-analysis of randomized controlled trials. *Eur. Neuropsychopharmacol*. 2022;54:75–89. doi:10.1016/j.euroneuro.2021.08.264
11. Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet*. 2019;394(10202):939–951. doi:10.1016/S0140-6736(19)31135-3
12. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;382(9896):951–962. doi:10.1016/S0140-6736(13)60733-3
13. Schneider-Thoma J, Chalkou K, Dörries C, et al. Comparative efficacy and tolerability of 32 oral and long-acting injectable antipsychotics for the maintenance treatment of adults with schizophrenia: a systematic review and network meta-analysis. *Lancet*. 2022;399(10327):824–836. doi:10.1016/S0140-6736(21)01997-8
14. Pillinger T, McCutcheon RA, Vano L, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *Lancet Psychiatr*. 2020;7(1):64–77. doi:10.1016/S2215-0366(19)30416-X
15. Buchanan RW, Kreyenbuhl J, Kelly DL, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull*. 2010;36(1):71–93. doi:10.1093/schbul/sbp116
16. Galletly C, Castle D, Dark F, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. *Austra N Z J Psychiatr*. 2016;50(5):410–472. doi:10.1177/0004867416641195
17. Keating D, McWilliams S, Schneider I, et al. Pharmacological guidelines for schizophrenia: a systematic review and comparison of recommendations for the first episode. *BMJ open*. 2017;7(1):e013881. doi:10.1136/bmjopen-2016-013881
18. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disorder*. 2018;20(2):97–170. doi:10.1111/bdi.12609
19. Faden J, Serdenes R, Citrome L. Olanzapine-samidorphan combination tablets for the treatment of schizophrenia and bipolar I disorder-what is it, and will it be used? *Expert Rev Neurother*. 2022;22(5):365–376. doi:10.1080/14737175.2022.2060742
20. Citrome L, McEvoy JP, Todtenkopf MS, McDonnell D, Weiden PJ. A commentary on the efficacy of olanzapine for the treatment of schizophrenia: the past, present, and future. *Neuropsychiatr Dis Treat*. 2019;5:2559–2569. doi:10.2147/NDT.S209284
21. Cong L, Wan Z, Li P, et al. Metabolic, genetic, and pharmacokinetic parameters for the prediction of olanzapine efficacy. *Eur J Pharm Sci*. 2022;177:106277. doi:10.1016/j.ejps.2022.106277

22. Callaghan JT, Bergstrom RF, Ptak LR, Beasley CM. Olanzapine: pharmacokinetic and pharmacodynamic profile. *Clin Pharmacokinet*. 1999;37(3):177–193. doi:10.2165/00003088-199937030-00001
23. Mao JH, Han L, Liu XQ, Jiao Z. Significant predictors for olanzapine pharmacokinetics: a systematic review of population pharmacokinetic studies. *Expert Rev Clin Pharmacol*. 2023;16(6):575–588. doi:10.1080/17512433.2023.2219055
24. Bishara D, Olofinjana O, Sparshatt A, Kapur S, Taylor D, Patel MX. Olanzapine: a systematic review and meta-regression of the relationships between dose, plasma concentration, receptor occupancy, and response. *J Clin Psychopharmacol*. 2013;33(3):329–335. doi:10.1097/JCP.0b013e31828b28d5
25. Kapur S, Zipursky RB, Remington G, et al. 5-HT2 and D2 receptor occupancy of olanzapine in schizophrenia: a PET investigation. *Am J Psychiatry*. 1998;155(7):921–928. doi:10.1176/ajp.155.7.921
26. Bymaster FP, Rasmussen K, Calligaro DO, et al. In vitro and in vivo biochemistry of olanzapine: a novel, atypical antipsychotic drug. *J Clin Psychiatr*. 1997;58(10):28–36.
27. Vinish M, Elnabawi A, Milstein JA, et al. Olanzapine treatment of adolescent rats alters adult reward behaviour and nucleus accumbens function. *Int J Neuropsychopharmacol*. 2013;16(7):1599–1609. doi:10.1017/S1461145712001642
28. Mauri MC, Paletta S, Maffini M, et al. Clinical pharmacology of atypical antipsychotics: an update. *EXCLI J*. 2014;13:1163.
29. Erickson KK, Zhu J, Lazarus P. Olanzapine metabolism and the significance of the UGT1A448V and UGT2B1067Y variants. *Pharmacogene Geno*. 2011;21(9):539. doi:10.1097/FPC.0b013e328348c76b
30. Calligaro DO, Fairhurst J, Hotten TM, Moore NA, Tupper DE. The synthesis and biological activity of some known and putative metabolites of the atypical antipsychotic agent olanzapine (LY170053). *Bioorg Med Chem Lett*. 1997;7(1):25–30. doi:10.1016/S0960-894X(96)00567-7
31. Kassahun K, Mattiuz E, Nyhart E, et al. Disposition and biotransformation of the antipsychotic agent olanzapine in humans. *Drug Metab Dispos*. 1997;25(1):81–93.
32. Czerwensky F, Leucht S, Steimer W. CYP1A2* 1D and* 1F polymorphisms have a significant impact on olanzapine serum concentrations. *Ther Drug Monit*. 2015;37(2):152–160. doi:10.1097/FTD.0000000000000119
33. Söderberg MM, Dahl ML. Pharmacogenetics of olanzapine metabolism. *Pharmacogenomics*. 2013;14(11):1319–1336. doi:10.2217/pgs.13.120
34. Soria-Chacartegui P, Villapalos-García G, Zubiaur P, Abad-Santos F, Koller D. Genetic polymorphisms associated with the pharmacokinetics, pharmacodynamics and adverse effects of olanzapine, aripiprazole and risperidone. *Front Pharmacol*. 2021;12:711940. doi:10.3389/fphar.2021.711940
35. Hägg S, Spigset O, Lakso H, Dahlqvist R. Olanzapine disposition in humans is unrelated to CYP1A2 and CYP2D6 phenotypes. *Eur J Clin pharmacol*. 2001;57(6–7):493–497. doi:10.1007/s002280100343
36. Cabaleiro T, López-Rodríguez R, Ochoa D, Román M, Novalbos J, Abad-Santos F. Polymorphisms influencing olanzapine metabolism and adverse effects in healthy subjects. *Human Psychopharmacol*. 2013;28(3):205–214. doi:10.1002/hup.2308
37. Zubiaur P, Soria-Chacartegui P, Villapalos-García G, Gordillo-Perdomo JJ, Abad-Santos F. The pharmacogenetics of treatment with olanzapine. *Pharmacogenomics*. 2021;22(14):939–958. doi:10.2217/pgs-2021-0051
38. Schmitt U, Kirschbaum KM, Poller B, et al. In vitro P-glycoprotein efflux inhibition by atypical antipsychotics is in vivo nicely reflected by pharmacodynamic but less by pharmacokinetic changes. *Pharmacol Biochem Behav*. 2012;102(2):312–320. doi:10.1016/j.pbb.2012.04.002
39. Koller D, Almenara S, Mejía G, et al. Metabolic effects of aripiprazole and olanzapine multiple-dose treatment in a randomised crossover clinical trial in healthy volunteers: association with pharmacogenetics. *Adv Ther*. 2021;38(2):1035–1054. doi:10.1007/s12325-020-01566-w
40. Markowitz JS, DeVane CL, Malcolm RJ, et al. Pharmacokinetics of olanzapine after single-dose oral administration of standard tablet versus normal and sublingual administration of an orally disintegrating tablet in normal volunteers. *J Clin Pharmacol*. 2006;46(2):164–171. doi:10.1177/0091270005283839
41. Battaglia J. Intramuscular olanzapine: treating acute agitation in psychosis and bipolar mania. *Curr Psychiatry*. 2004;3:76–78.
42. Heres S, Kraemer S, Bergstrom RF, Detke HC. Pharmacokinetics of olanzapine long-acting injection: the clinical perspective. *Int Clin Psychopharmacol*. 2014;29(6):299. doi:10.1097/YIC.0000000000000040
43. Lorenzo MP, Burgess J, Darko W. Intravenous olanzapine in a critically ill patient: an evolving route of administration. *Hospital Pharm*. 2020;55(2):108. doi:10.1177/0018578718823484
44. fda.gov, A. ZYPREXA (olanzapine) Label; 2015. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/020592s042s043,021086s022s023,021253s026lbl.pdf. Accessed December 1 2023.
45. fda.gov, A. ZYPREXA RELPREVV (olanzapine) For Extended Release; 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022173s027lbl.pdf. Accessed December 1 2023.
46. Kooij KL, Luijendijk MC, Drost L, Platenburg G, van Elburg A, Adan RA. Intranasal administration of olanzapine has beneficial outcome in a rat activity-based anorexia model. *Eur Neuropsychopharmacol*. 2023;71:65–74. doi:10.1016/j.euroneuro.2023.03.008
47. Cole JB, Moore JC, Dolan BJ, et al. A prospective observational study of patients receiving intravenous and intramuscular olanzapine in the emergency department. *Ann Emergency Med*. 2017;69(3):327–336. doi:10.1016/j.annemergmed.2016.08.008
48. Symbyax [package insert]. Indianapolis (IN): Eli Lilly and Company; 2003.
49. Gossen D, De Suray JM, Vandenhende F, Onkelinx C, Gangji D. Influence of fluoxetine on olanzapine pharmacokinetics. *Aaps Pharmsci*. 2002;4(2):56–61. doi:10.1208/ps040209
50. Nemeroff CB. Dosing the antipsychotic medication olanzapine. *J Clin Psychiatr*. 1997;58(10):45–49.
51. Takeuchi H, Fervaha G, Lee J, Agid O, Remington G. Effectiveness of different dosing regimens of risperidone and olanzapine in schizophrenia. *Eur Neuropsychopharmacol*. 2015;25(3):295–302. doi:10.1016/j.euroneuro.2014.12.008
52. Citrome L, Kantrowitz J. Olanzapine dosing above the licensed range is more efficacious than lower doses: fact or fiction? *Expert Rev Neurother*. 2009;9(7):1045–1058. doi:10.1586/ern.09.54
53. Beasley CM, Tollefson G, Tran P, et al. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology*. 1996;14(2):111–123. doi:10.1016/0893-133X(95)00069-P
54. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge university press; 2021.
55. Reich J. Use of high-dose olanzapine in refractory psychosis. *Am J Psychiatry*. 1999;156(4):661. doi:10.1176/ajp.156.4.661
56. Kinon BJ, Volavka J, Stauffer V, et al. Standard and higher dose of olanzapine in patients with schizophrenia or schizoaffective disorder: a randomized, double-blind, fixed-dose study. *J Clin Psychopharmacol*. 2008;28(4):392–400. doi:10.1097/JCP.0b013e31817e63a5

57. Mitchell M, Riesenberg R, Bari MA, et al. A double-blind, randomized trial to evaluate the pharmacokinetics and tolerability of 30 or 40 mg/d oral olanzapine relative to 20 mg/d oral olanzapine in stable psychiatric subjects. *Clin Ther*. 2006;28(6):881–892. doi:10.1016/j.clinthera.2006.06.008
58. Morgan M, Hackett LP, Isbister GK. Olanzapine overdose: a series of analytically confirmed cases. *Int Clin Psychopharmacol*. 2007;22 (3):183–186. doi:10.1097/YIC.0b013e32805aedf5
59. Gex-Fabry M, Balant-Gorgia AE, Balant LP. Therapeutic drug monitoring of olanzapine: the combined effect of age, gender, smoking, and comedication. *Ther Drug Monit*. 2003;25(1):46–53. doi:10.1097/00007691-200302000-00007
60. Hiemke C, Baumann P, Bergemann N, et al. AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. *Pharmacopsychiatry*. 2011;21(06):195–235.
61. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. *Pharmacopsychiatry*. 2018;51(01/02):9–62. doi:10.1055/s-0043-116492
62. der AGNP Federführend TA, Rao ML, Hiemke C, Grasmäder K, Baumann P. Olanzapin: pharmakologie, pharmakokinetik und therapeutisches drug monitoring. *Fortsch Der Neurol Psychiatr*. 2001;69(11):510–517. doi:10.1055/s-2001-18381
63. Stillhart C, Vučićević K, Augustijns P, et al. Impact of gastrointestinal physiology on drug absorption in special populations—An UNGAP review. *Eur J Pharm Sci*. 2020;147:105280. doi:10.1016/j.ejps.2020.105280
64. Seaman JS, Bowers SP, Dixon P, Schindler L. Dissolution of common psychiatric medications in a Roux-en-Y gastric bypass model. *Psychosomatics*. 2005;46(3):250–253. doi:10.1176/appi.psy.46.3.250
65. Zheng L, Yang H, Dallmann A, Jiang X, Wang L, Hu W. Physiologically based pharmacokinetic modeling in pregnant women suggests minor decrease in maternal exposure to olanzapine. *Front Pharmacol*. 2022;12:793346. doi:10.3389/fphar.2021.793346
66. Withers N. The Liver Impaired Patient. In: *Handbook of Consultation Liaison Psychiatry*. New York: Springer; 2008:248–269.
67. Telles-Correia D, Barbosa A, Cortez-Pinto H, Campos C, Rocha NB, Machado S. Psychotropic drugs and liver disease: a critical review of pharmacokinetics and liver toxicity. *World J Gastroint Pharmacol Ther*. 2017;8(1):26. doi:10.4292/wjgpt.v8.i1.26
68. Sun L, Yagoda S, Du Y, von Moltke L. Effect of hepatic and renal impairment on the pharmacokinetics of olanzapine and samidorphan given in combination as a bilayer tablet. *Drug Design Devel Ther*. 2019;22:2941–2955. doi:10.2147/DDDT.S205000
69. Cussotto S, Walsh J, Golubeva AV, et al. The gut microbiome influences the bioavailability of olanzapine in rats. *EBioMedicine*. 2021;2021:66.
70. Kansagra A, Patel S, Wilcox SR. Prolonged hypothermia due to olanzapine in the setting of renal failure: a case report and review of the literature. *Ther Adv Psychopharmacol*. 2013;3(6):335–339. doi:10.1177/2045125313490304
71. Marder SR, Sorsaburu S, Dunayevich E, et al. Case reports of postmarketing adverse event experiences with olanzapine intramuscular treatment in patients with agitation. *J Clin Psychiatr*. 2010;71(4):2392. doi:10.4088/JCP.08m04411gry
72. Williams AM. Coadministration of intramuscular olanzapine and benzodiazepines in agitated patients with mental illness. *Mental Health Clinician*. 2018;8(5):208–213. doi:10.9740/mhc.2018.09.208
73. Olanzapine [Package Insert]. Utrecht, The Netherlands: Lilly, SA; 2006.
74. Wilson MP, Chen N, Vilke GM, Castillo EM, MacDonald KS, Minassian A. Olanzapine in ED patients: differential effects on oxygenation in patients with alcohol intoxication. *Am J Emergency Med*. 2012;30(7):1196–1201. doi:10.1016/j.ajem.2012.03.013
75. Anderson GD, Chan LN. Pharmacokinetic drug interactions with tobacco, cannabinoids and smoking cessation products. *Clin Pharmacokinet*. 2016;55(11):1353–1368. doi:10.1007/s40262-016-0400-9
76. Chiu CC, Lane HY, Huang MC, et al. Dose-dependent alternations in the pharmacokinetics of olanzapine during coadministration of fluvoxamine in patients with schizophrenia. *J Clin Pharmacol*. 2004;44(12):1385–1390. doi:10.1177/0091270004270291
77. Lucas RA, Gilfillan DJ, Bergstrom RF. A pharmacokinetic interaction between carbamazepine and olanzapine: observations on possible mechanism. *Eur J Clin pharmacol*. 1998;54(8):639–643. doi:10.1007/s002280050527
78. Kasper S. Risperidone and olanzapine: optimal dosing for efficacy and tolerability in patients with schizophrenia. *Int Clin Psychopharmacol*. 1998;13(6):253–262. doi:10.1097/00004850-199811000-00003
79. Solmi M, Murru A, Pacchiarotti I, et al. Safety, tolerability, and risks associated with first-and second-generation antipsychotics: a state-of-the-art clinical review. *Thera Clin Risk Manage*. 2017;29:757–777. doi:10.2147/TCRM.S117321
80. Compton MT, Miller AH. Antipsychotic-induced hyperprolactinemia and sexual dysfunction. *Psychopharmacol Bull*. 2002;36(1):143–164.
81. Hu KF, Chou YH, Wen YH, et al. Antipsychotic medications and dental caries in newly diagnosed schizophrenia: a nationwide cohort study. *Psychiatr Res*. 2016;245:45–50. doi:10.1016/j.psychres.2016.07.047
82. McEvoy JP, Lieberman JA, Perkins DO, et al. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. *Am J Psychiatry*. 2007;164(7):1050–1060. doi:10.1176/ajp.2007.164.7.1050
83. Detke HC, McDonnell DP, Brunner E, et al. Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection, I: analysis of cases. *BMC psychiatr*. 2010;10(1):1. doi:10.1186/1471-244X-10-43
84. Seebaluck J, Downes MA, Brown J, Harris K, Isoardi KZ, Chan BS. Case series profile of olanzapine post-injection delirium/sedation syndrome. *Br J Clin Pharmacol*. 2023;89(2):903–907. doi:10.1111/bcp.15588
85. Bushe CJ, Falk D, Anand E, et al. Olanzapine long-acting injection: a review of first experiences of post-injection delirium/sedation syndrome in routine clinical practice. *BMC psychiatr*. 2015;15(1):1–8. doi:10.1186/s12888-015-0450-9
86. Łukasik-głębocka M, Sommerfeld K, Teżyk A, Panieński P, Żaba C, Zielińska-Psuja B. Post-injection delirium/sedation syndrome after olanzapine long-acting intramuscular injection–who is at risk? *Basic Clin Physiol Pharmacol*. 2015;117(3):213–214. doi:10.1111/bcpt.12394
87. Meyers KJ, Upadhyaya HP, Landry JL, et al. Postinjection delirium/sedation syndrome in patients with schizophrenia receiving olanzapine long-acting injection: results from a large observational study. *BJPsych Open*. 2017;3(4):186–192. doi:10.1192/bjpo.bp.116.004382
88. McDonnell DP, Detke HC, Bergstrom RF, et al. Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection, II: investigations of mechanism. *BMC psychiatr*. 2010;10(1):1. doi:10.1186/1471-244X-10-45
89. Morissette P, Hreiche R, Mallet L, Vo D, Knaus EE, Turgeon J. Olanzapine prolongs cardiac repolarization by blocking the rapid component of the delayed rectifier potassium current. *J Psychopharmacol*. 2007;21(7):735–741. doi:10.1177/0269881106072669
90. Ciszowski K, Sein Anand J. Zaburzenia elektrokardiograficzne w ostrych zatruciach olanzapiną. *Przeglad Lekarski*. 2011;68:8.
91. Choure BK, Gosavi D, Nanotkar S. Comparative cardiovascular safety of risperidone and olanzapine, based on electrocardiographic parameters and blood pressure: a prospective open label observational study. *Indian J Pharmacol*. 2014;46(5):493. doi:10.4103/0253-7613.140579

92. Hofmann MS, Overman MJ, Nates JL. Acute benzodiazepine toxicity exacerbated by concomitant oral olanzapine. *J Community Support Oncol*. 2016;14(4):178–179. doi:10.12788/jcso.0187
93. Mouallem M, Wolf I. Olanzapine-induced respiratory failure. *Am J Ger Psychiatr*. 2001;9(3):304–305. doi:10.1097/00019442-200108000-00016
94. Mehta S, Pulungan Z, Jones BT, Teigland C. Comparative safety of atypical antipsychotics and the risk of pneumonia in the elderly. *Pharmacoepidemiol Drug Saf*. 2015;24(12):1271–1280. doi:10.1002/pds.3882
95. Dzahini O, Singh N, Taylor D, Haddad PM. Antipsychotic drug use and pneumonia: systematic review and meta-analysis. *J Psychopharmacol*. 2018;32(11):1167–1181. doi:10.1177/0269881118795333
96. Martel ML, Klein LR, Rivard RL, Cole JB, Heard K. A large retrospective cohort of patients receiving intravenous olanzapine in the emergency department. *Aca Emer Med*. 2016;23(1):29–35. doi:10.1111/acem.12842
97. Tsai YV, Fawzy JH, Durkin JB, Then JE, McGinnis CB. Off-label use of intravenous olanzapine for agitation after neurologic injury. *Hospital Pharm*. 2021;56(6):697–701. doi:10.1177/0018578720946767
98. Weiss U, Marksteiner J, Kemmler G, Saria A, Aichhorn W. Effects of age and sex on olanzapine plasma concentrations. *J Clin Psychopharmacol*. 2005;25(6):570–574. doi:10.1097/01.jcp.0000185427.08268.db
99. de Lima Moreira F, de Lima Benzi JR, Pinto L, de Lucca Thomaz M, Duarte G, Lanchote VL. Optimizing therapeutic drug monitoring in pregnant women: a critical literature review. *Ther Drug Monit*. 2023;45(2):159–172. doi:10.1097/FTD.0000000000001039
100. Park Y, Hernandez-Diaz S, Bateman BT, et al. Continuation of atypical antipsychotic medication during early pregnancy and the risk of gestational diabetes. *Am J Psychiatry*. 2018;175(6):564–574. doi:10.1176/appi.ajp.2018.17040393
101. Newport DJ, Calamaras MR, DeVane CL, et al. Atypical antipsychotic administration during late pregnancy: placental passage and obstetrical outcomes. *Am J Psychiatry*. 2007;164(8):1214–1220. doi:10.1176/appi.ajp.2007.06111886
102. Ellfolk M, Leinonen MK, Gissler M, Kiuru-Kuhlefelt S, Saastamoinen L, Malm H. Second-generation antipsychotic use during pregnancy and risk of congenital malformations. *Eur J Clin Pharmacol*. 2021;77(11):1737–1745. doi:10.1007/s00228-021-03169-y
103. Fortinguerra F, Clavenna A, Bonati M. Psychotropic drug use during breastfeeding: a review of the evidence. *Pediatrics*. 2009;124(4):e547–56. doi:10.1542/peds.2009-0326
104. Uguz F. Second-generation antipsychotics during the lactation period: a comparative systematic review on infant safety. *J Clin Psychopharmacol*. 2016;36(3):244–252. doi:10.1097/JCP.0000000000000491
105. Maharaj AR, Wu H, Zimmerman KO, et al. Population pharmacokinetics of olanzapine in children. *Br J Clin Pharmacol*. 2021;87(2):542–554. doi:10.1111/bcp.14414
106. Liu XI, Schuette P, Burckart GJ, et al. A comparison of pediatric and adult safety studies for antipsychotic and antidepressant drugs submitted to the United States Food and Drug Administration. *J Pediatr*. 2019;208:236–242. doi:10.1016/j.jpeds.2018.12.033
107. Skogh E, Reis M, Dahl ML, Lundmark J, Bengtsson F. Therapeutic drug monitoring data on olanzapine and its N-demethyl metabolite in the naturalistic clinical setting. *Ther Drug Monit*. 2002;24(4):518–526. doi:10.1097/00007691-200208000-00010