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Review article

Impact of nutritional factors on the pharmacokinetics of antipsychotics – a systematic review

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ABSTRACT

Introduction: Nutritional habits and specific dietary components can significantly alter the pharmacokinetics (PK) of antipsychotics, potentially leading in worst cases to therapeutic failure or increased toxicity. Despite its clinical importance, a comprehensive systematic overview of these interactions remains a gap in current psychiatric research. This systematic review aims to evaluate how food intake or specific nutrients influence the PK parameters of antipsychotic medications.

Methods: A systematic search was conducted across Web of Science, PubMed, Cochrane Database, and Scopus. Out of 18,598 identified records, 48 studies were included for data extraction which focused on C_{max}, Area under the curve (AUC), time to maximum concentration (t_{max}), and $t_{1/2}$ under varying nutritional conditions (e.g., fasting vs. fed, caffeine, and vitamin D levels).

Results: The analysis of the included studies reveals highly drug-specific effects. For several second-generation antipsychotics, food intake is critical for bioavailability; for instance, lurasidone and ziprasidone exposure AUC increases 2- to 3-fold when administered with a meal of at least 350–500 kcal. Conversely, amisulpride absorption is significantly reduced by food intake (e.g., ~25% reduction in AUC). Furthermore, clozapine metabolism may be influenced by seasonal vitamin D variations and also caffeine intake, which may be mediated by affecting the metabolism of Cytochrome P450 enzymes.

Conclusions: Nutritional factors are a significant source of PK variability in antipsychotic treatment. The results underscore the necessity of standardized administration guidelines (e.g., "take with food" for ziprasidone or "fasted" for amisulpride) to ensure predictable plasma levels and optimize therapeutic outcomes in clinical practice.

1. Introduction

Antipsychotic treatment is crucial for the pharmacological management of schizophrenia spectrum disorders, bipolar disorder, and other severe psychiatric conditions. Both first-generation (typical) and second-generation (atypical) antipsychotics exhibit complex pharmacokinetic (PK) profiles, characterized by variable oral bioavailability, extensive hepatic metabolism, and substantial interindividual variability (Benkert and Hippius, 2013; Wijesinghe, 2016). Therapeutic response and adverse effect burden are closely linked to systemic drug exposure, commonly quantified using parameters such as maximum plasma concentration (C_{max}), area under the concentration–time curve (AUC), time to maximum concentration (t_{max}), and elimination half-life ($t_{1/2}$) (Grogan and Preuss, 2025).

Oral administration remains the predominant route for most antipsychotics. Consequently, drug absorption is influenced by gastrointestinal physiology, hepatic first-pass metabolism, and transport mechanisms, all of which may be modified by food intake and dietary components (Koziolek and Alcaro, 2019.). Nutritional factors may affect gastric emptying time, intestinal motility, bile acid secretion, splanchnic

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blood flow, and cytochrome P450 (CYP) enzyme activity (Koziolek and Alcaro, 2019). High-fat meals, for example, can increase solubilization of lipophilic compounds, whereas specific dietary constituents such as grapefruit juice may inhibit or induce metabolic pathways (Koziolek and Alcaro, 2019).

Given that many antipsychotics are metabolized via CYP1A2, CYP3A4, and CYP2D6, dietary influences on these enzymes may have meaningful consequences in psychiatric treatment. Inconsistent intake with respect to meals may contribute to fluctuations in plasma levels, potentially leading to subtherapeutic exposure, loss of efficacy, or dose-related adverse events such as sedation, orthostatic hypotension, or QTc prolongation (Muench and Hamer, 2010). Furthermore, patients with severe mental illness frequently display unhealthy dietary patterns, metabolic comorbidities, and high caffeine consumption, which may further complicate pharmacotherapy (Carrà and Bartoli, 2014; Hughes and McHugh, 1998; Leme and Natacci, 2024).

To date, no comprehensive synthesis has systematically evaluated the extent and clinical relevance of nutritional influences on antipsychotic PK. The present systematic review aims to summarize and critically appraise available evidence on the effects of food intake, meal composition, and specific dietary components on PK parameters of orally administered antipsychotics.

2. Methods

2.1. Study design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page and McKenzie, 2021). The review protocol was prospectively registered with the International Prospective Register of Systematic Reviews (CRD420261286007) and was designed to identify, evaluate, and synthesize clinical evidence regarding the impact of nutritional factors on the PK of antipsychotic medications in humans.

2.2. Search strategy and information sources

A systematic literature search was performed on February 2nd, 2026, across four major electronic databases: PubMed (MEDLINE), Web of Science (Core Collection), Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) for clinical studies in humans published between database inception and February 2nd, 2026. The search strategy utilized a combination of Medical Subject Headings (MeSH) and free-text keywords related to (1) psychotropic and antipsychotic drugs, (2) dietary factors, including food, specific nutrients, and beverages, and (3) PK outcomes such as bioavailability, clearance, and plasma concentration. The detailed search strategy for each database is provided in the supplemental materials. To ensure a high level of sensitivity, the initial search was kept broad, encompassing all psychotropic medications. Following preliminary screening, the review scope was narrowed from all psychotropic medications to antipsychotic drugs specifically, due to the unexpectedly large volume and heterogeneity of eligible studies, in order to allow a focused and methodologically consistent synthesis. The reference lists of all included studies and relevant review articles were manually screened to identify potentially eligible studies that were not captured by the electronic search.

2.3. Eligibility criteria

Studies were included in the review if they met the following PICO (Population, Intervention, Comparators, Outcomes)-based criteria:

- **Population:** Human subjects, including both healthy volunteers and patients with psychiatric disorders. Animal models, in vitro studies, and *in silico* simulations were strictly excluded.
- **Intervention/Exposure:** Administration of antipsychotic drugs in conjunction with dietary interventions, such as standardized high-fat or low-fat meals, specific beverages (e.g., grapefruit juice, caffeine, alcohol), or nutritional supplements (e.g., vitamins). Non-nutritional interventions, such as smoking or drug use other than alcohol, were excluded.
- **Comparators:** Fasting conditions, administration with water, or a controlled baseline diet.
- **Outcomes:** Quantitative assessment of PK parameters, e.g., C_{max} , AUC, t_{max} and $t_{1/2}$.
- **Study Design:** Only original clinical trials (e.g., randomized controlled trials, crossover studies, and open-label trials) were eligible. Case reports, conference abstracts or editorials were excluded.

2.4. Study selection and data extraction

Study selection was independently performed by two authors. Following the search, all identified records were exported to a reference management system, and duplicates were removed. The selection process involved two stages. First, titles and abstracts were screened for general relevance. During this stage, the scope was narrowed from general psychotropic drugs to antipsychotic medications specifically as the high number of records ($N > 250$) exceeded the feasibility of a comprehensive systematic review. The original broad search is documented in the Supplementary Materials. Second, the remaining records underwent a full-text assessment to ensure compliance with the predefined inclusion and exclusion criteria.

Data from the final set of included studies were extracted using a standardized form. The extracted information included the first author, year of publication, study design, participant characteristics (sample size and population type), specific drug and dosage, type of nutritional exposure, assessed PK parameters, and the primary PK outcomes.

2.5. Synthesis of results

The results were synthesized qualitatively. The search initially yielded 18,598 records. After the removal of 2266 duplicates, a total of 16,332 records were screened. Based on title and abstract, 283 studies were identified as relevant to psychotropic drugs in general. This pool was then narrowed down to 52 studies focusing specifically on antipsychotics: During the full-text screening, 9 studies were excluded (5 due to ineligible publication types, 3 animal studies, and 1 duplicate). An additional 5 studies were identified through manual reference screening. Consequently, a total of 48 clinical studies were included in the final systematic synthesis (Fig. 1).

2.6. Risk of bias assessment

To assess the methodological quality and potential risk of bias in the included studies, the Cochrane Risk of Bias Tool 2.0 (RoB 2) (Sterne and Savović, 2019) was employed for randomized controlled trials. For non-randomized and observational studies, the Newcastle Ottawa Scale (NOS) (Wells and Shea, 2000) was utilized to evaluate validity and susceptibility to bias. Although some original studies were designed as a randomized crossover bioequivalence trials, the comparison between fed and fasted (or caffeine/non-caffeine, grapefruit/non-grapefruit) conditions represents a non-randomized parallel-group comparison. Therefore, for the purpose of bias assessment in this review, the Newcastle-Ottawa Scale for cohort studies was applied. Minor adaptations were made to account for the PK nature of the outcomes (e.g., adequacy of sampling duration instead of follow-up length). Regarding cross-sectional studies, the Newcastle-Ottawa Scale adapted for cross-sectional studies was applied (Gualdi-Russo and Zaccagni, 2026). The main source of potential bias arises from the lack of randomization between fed and fasted conditions and the absence of statistical

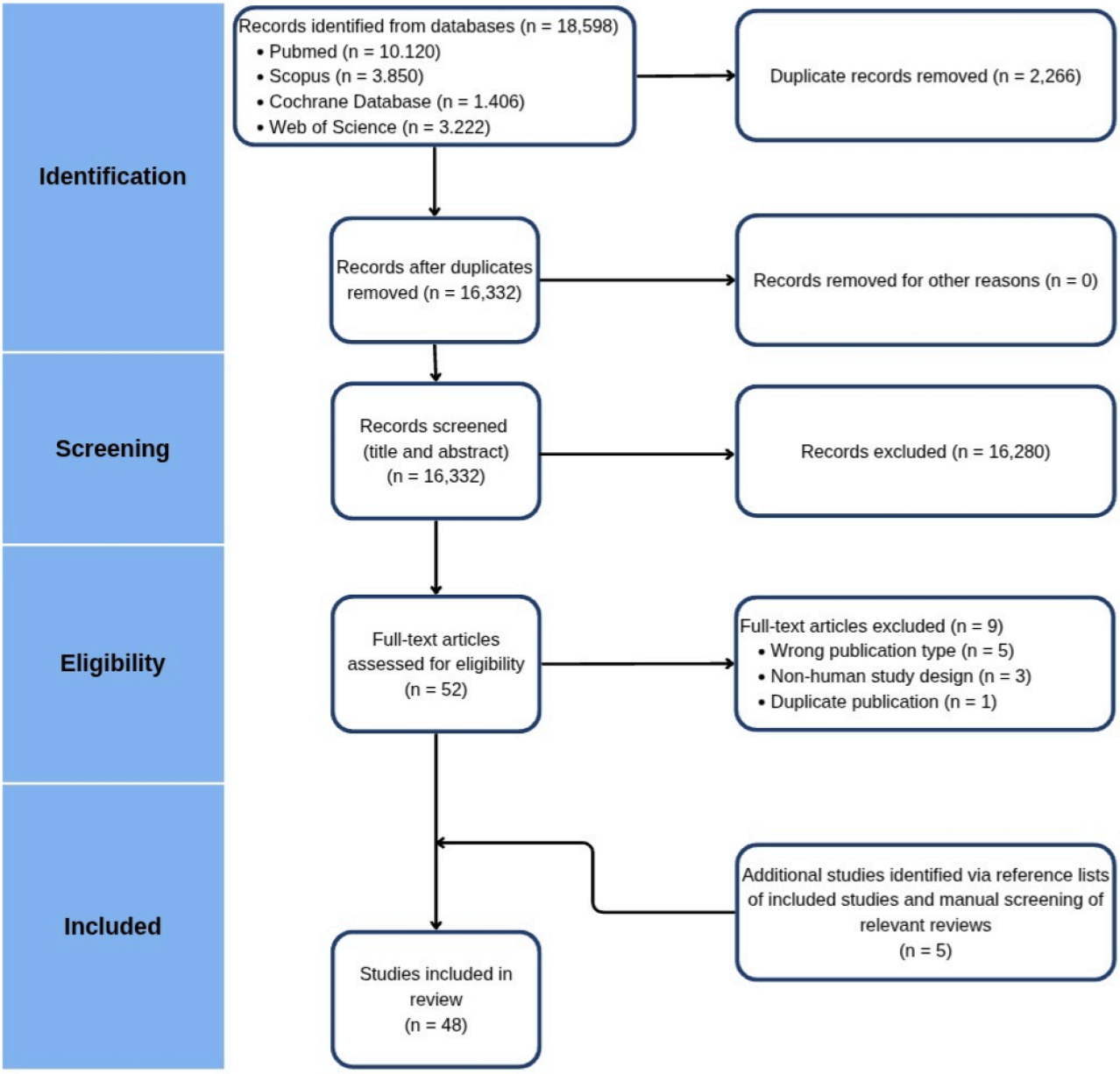

Fig. 1. Flowchart illustrating the process of study identification, screening, eligibility assessment, and inclusion for the systematic review in accordance with PRISMA guidelines.

adjustment for potential PK confounders. Risk-of-bias assessment was independently performed by two human reviewers using the appropriate established assessment tools. All final judgments were reviewed and confirmed by the human reviewers. Any disagreements were resolved through discussion and consensus.

2.7. Certainty of evidence assessment

The certainty of evidence was assessed using the GRADE approach, operationalized in accordance with the methodology previously described for narrative reviews when a meta-analysis has not been performed (Murad and Mustafa, 2017). For each PK interaction, the initial certainty rating was determined by study design. Randomized controlled PK trials started at high certainty, whereas non-randomized studies and observational studies started at low certainty. The certainty of evidence was subsequently evaluated across the five standard GRADE domains: Methodological limitations, indirectness, inconsistency, imprecision, and publication bias. Evidence was downgraded by one or two levels depending on the severity of concerns within each domain (serious or very serious limitations). Methodological limitations were assessed based on issues related to randomization, blinding, confounding, and selective reporting. Indirectness was evaluated by judging the degree of dissimilarity between the available evidence and the clinical research question, particularly with respect to study populations, interventions, and outcomes. Imprecision was assessed based on information size (with values $\leq$400 participants regarded as concerning). Inconsistency was determined by examining the direction and magnitude of effect estimates across studies. Publication bias was considered when selective publication of positive PK findings could not be excluded. In selected cases, certainty was upgraded when large PK effects were observed. The final overall certainty rating (high, moderate, low, or very low) reflected the cumulative assessment across all GRADE domains. Detailed structured evidence profiles and all downgrading decisions are provided in the Supplementary Materials.

3. Results

3.1. Study characteristics

A total of 48 studies met the inclusion criteria. The majority of included studies employed randomized, open-label, crossover designs conducted in healthy volunteers. A smaller proportion of studies involved psychiatric patients receiving maintenance therapy, which were often observational or longitudinal in nature. Sample sizes typically ranged from 8 to 30 participants. Most trials evaluated acute, single-dose PK under fasting (> 8–10 h) versus fed conditions. Nutritional exposures varied but commonly included standardized high-fat breakfasts (approximately 800–1000 kcal, 50% fat), standard breakfasts of defined caloric content, or specific dietary components such as caffeine, grapefruit juice, and alcohol. While the majority of the therapeutics evaluated in the reviewed literature are currently commercially available, several compounds represented non-marketed formulations (specifically JNJ-37,822,681, TAK-063, ACP-103/pimavanserin precursor formulations, and experimental solubilized ziprasidone formulations). Detailed information about the study characteristics of the included trials are provided in the Supplementary Materials.

3.2. Main findings

Food intake alters the PK of multiple antipsychotics with variable effects between compounds (Table 1). Ziprasidone, lurasidone and blonanserin show substantial increases in AUC and C_{max} when administered with food. Amisulpride and sublingual asenapine demonstrate reductions in AUC in the presence of food. For quetiapine extended release high-fat meals increase C_{max} while AUC remains largely unchanged. Several antipsychotics including clozapine, olanzapine, aripiprazole, brexpiprazole and iloperidone exhibit minimal changes in overall bioavailability with food although absorption rates may be delayed.

Additional nutritional components influence PK of specific agents (Table 2). Caffeine increases clozapine plasma concentrations while abrupt withdrawal reduces levels. Grapefruit juice interactions were highly drug specific, producing very large increases in blonanserin exposure while showing negligible effects for clozapine and haloperidol. Acute alcohol intake increases blonanserin systemic exposure. Higher vitamin D levels are associated with reduced aripiprazole and quetiapine concentrations. Gastric pH modifications affect sulpiride absorption with acidic conditions increasing and alkaline conditions reducing bioavailability. Seasonal variations associated with vitamin D levels correspond to fluctuations in clozapine plasma concentrations. These observations describe direct and indirect nutritional influences on absorption metabolism and systemic exposure of antipsychotic medications.

3.3. Risk of bias and certainty of evidence

Risk of bias across randomized controlled trials (RCTs) was predominantly indicated as “some concerns” with several studies raising concerns due to lack of exact methodological description of the randomization process as well as missing study protocols. For non-randomized evidence, Newcastle-Ottawa Scale (NOS) scores for cohort studies were generally moderate, predominantly clustering at 6/9 points. Cross-sectional studies demonstrated moderate methodological quality, with scores between 10 and 11 out of 16.

The certainty of evidence across identified food–drug and nutrient–drug interactions ranged from High to Very Low, with most outcomes rated as Low or Very Low certainty due to methodological limitations and substantial imprecision. Downgrading decisions were primarily driven by risk of bias across PK trials and the generally small sample sizes of the included studies. Higher-certainty evidence was observed for clinically relevant positive food effects on highly lipophilic antipsychotics. Blonanserin administered with food demonstrated high-certainty evidence for a marked increase in bioavailability, with AUC increases ranging from +159% to +403%. Moderate-certainty evidence supported substantial food-related increases in systemic exposure for ziprasidone and lurasidone, where AUC increases exceeded twofold in several studies. These ratings were partially upgraded due to the large and consistent magnitude of PK effects observed across trials. In contrast, several antipsychotics demonstrated reduced or clinically negligible food effects.

For beverage-related interactions, the certainty of evidence also varied considerably. Blonanserin combined with alcohol or grapefruit juice demonstrated very large increases in systemic exposure, although the overall certainty remained limited by smaller sample sizes and methodological concerns. Clozapine–caffeine interactions showed inconsistent findings across studies resulting in very low-certainty evidence. Moreover, observational studies examining vitamin D status and antipsychotic PK reported inconsistent or weak associations with drug clearance and plasma concentrations for amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, and risperidone. These findings were substantially downgraded due to non-randomized study designs, risk of bias, and imprecision.

Overall, the certainty assessment highlighted that robust evidence currently exists only for a limited number of clinically important food-related PK interactions, whereas many reported interactions remain supported by sparse and methodologically limited data. Results of the risk of bias and certainty of evidence assessment are presented in the Supplementary materials.

4. Discussion

4.1. Discussion in the context of the literature

With this study, we aimed to evaluate how nutritional factors influence the PK of antipsychotic medications. Although drug–food interactions are well established in clinical pharmacology, they remain inconsistently addressed in psychiatric guidelines. This review therefore focused on two domains: (1) the effect of food intake on gastrointestinal absorption and bioavailability of antipsychotics and (2) the influence of specific dietary components on metabolic pathways, particularly CYP-mediated metabolism.

Understanding these interactions is clinically relevant because antipsychotics are typically administered long-term and often exhibit concentration-dependent efficacy and adverse effects. Even moderate changes in absorption or metabolism may alter systemic drug exposure and therefore could potentially influence treatment response or tolerability. However, direct associations with relapse prevention, efficacy, or toxicity were only rarely assessed in the included studies.

Our findings indicate that nutritional factors are key determinants of antipsychotic PK, mainly via (1) food- and gastrointestinal-mediated changes in absorption and (2) dietary modulation of CYP enzyme activity.

Regarding absorption, a clear distinction emerged between lipophilic compounds with poor aqueous solubility and hydrophilic agents with limited membrane permeability. Antipsychotics classified as Biopharmaceutics Classification System (BCS) class II compounds characterized by poor water solubility and high permeability —such as ziprasidone, lurasidone, and blonanserin (Bocci and Oprea, 2022; Rathi and Patel, 2019; Sözer and Nacak, 2025) —demonstrated pronounced positive food effects. High-fat meals stimulate bile secretion and micelle formation, improving dissolution and intestinal uptake of poorly soluble lipophilic drugs. Delayed gastric emptying and enhanced lymphatic transport may further increase systemic exposure Bocci and Oprea, 2022; Koziolek and Alcaro, 2019; Lentz, 2008; Srinivas, 2011). Clinically relevant increases in total systemic exposure, quantified by AUC, have been reported, including approximately two-fold increases for ziprasidone (Gandelman and Alderman, 2009; Hamelin and Allard,

Table 1
Effects of food intake on the pharmacokinetics of antipsychotics.

Antipsychotics	Effect on AUC	Further significant PK observations	Certainty of evidence	Clinical recommendation	References
Ziprasidone	↑↑ (up to 101%)	Cmax increased by 67–101%; t1/2 decreased by 19–40%; tmax prolonged by 37–45%.	Moderate	Take with a meal of at least 500 kcal to ensure adequate absorption and therapeutic plasma levels.	(Gandelman and Alderman, 2009; Hamelin and Allard, 1998; Miceli et al., 2007; Thombre and Herbig, 2011)
Lurasidone	↑↑ (109–156%)	Cmax increased by 102–190%; tmax delayed by approximately 33%.	Moderate	Must be taken with food (at least 350 kcal) to maximize bioavailability.	(Preskorn and Ereshefsky, 2013; Yu and Fang, 2025)
Blonanserin	↑↑ (100–400%)	Cmax increased 2- to 5-fold; tmax delayed (80–140%); t1/2 prolonged (32–81%); Cl/F decreased significantly (61–82%).	High	Mandatory administration with meals due to a massive food effect on bioavailability.	(Chen and Wang, 2014; Lei and Yan, 2024; Nemoto and Takagaki, 2025; Saruwatari and Yasui-Furukori, 2010;Shang and Wang, 2018; Sun and Song, 2025; Wen and Shang, 2013)
Zuclopentixol	↑ (26%)	No other significant non-AUC parameters reaching statistical significance were reported.	Low	Maintain consistent intake (either always with or always without food) to ensure stable plasma levels.	(Aaes-Jørgensen and Liedholm, 1987)
Dixyrazine	↑ (79%)	Cmax increased by 75%.	Low	Take with food to improve bioavailability.	(Liedholm et al., 1985)
Flupentixol	↑ (26%)	tmax delayed by 50%; Cl/F decreased by 22%.	Low	Maintain consistent intake; however, the food effect is likely of little clinical relevance.	(Wu and Xu, 2019)
TAK-063	↑ (78%)	Cmax increased by 86%; tmax delayed (median 6 h vs 3–4 h in fasting).	Very low	Take with food to increase peak concentration and total exposure.	(Tsai and Chrones, 2016)
Amisulpride	↓ (25–38%)	Cmax decreased by 43–54%; tmax shortened by 27%; t1/2 increased by 55%.	Very low	Take in a fasted state or maintain consistent conditions relative to meals.	(Cao and Su, 2024; Jang and Jeong, 2014; Wang and Peng, 2025)
Asenapine (sublingual)	↓ (21–22%)	Specific Cmax changes for sublingual application not highlighted; eating immediately after administration reduces bioavailability.	Low	Avoid eating or drinking immediately after sublingual administration.	(Dogterom and de Greef, 2015)
Sertindole	→	tmax significantly delayed (from 8.7 to 12.9 hours).	Low	Can be taken regardless of meals.	(Wong and Linnen, 1997)
Aripiprazole	→	For ODT and oral films: tmax delayed by 67–150%.	Low	Can be taken regardless of meals.	(Li and Yang, 2025; Xiang and Xu, 2021)
Brexiprazole	→	Cmax slightly decreased (~23%); tmax significantly delayed by ~170%.	Low	Can be taken regardless of meals.	(Wang and Shang, 2025)
Iloperidone	→	tmax delayed by 95%.	Low	Take with food to delay absorption, which significantly reduces side effects like dizziness.	(Sainati and Hubbard, 1995)
Quetiapine (immediate release)	→	tmax significantly delayed by 113%.	Low	Can be taken regardless of meals.	(Luo and Zhao, 2023)
Quetiapine (extended release)	↑ (16–19%)	Cmax increased by 93%; tmax decreased by 20%; t1/2 decreased by 27%.	Low	Avoid high-fat meals; take without food or with a light meal to prevent rapid drug release.	(Huang and Zhang, 2019)
Sulpiride (AEA)	→	Bioavailability highly variable; low gastric acidity leads to positive food effect, high acidity to negative effect.	Very low	Maintain consistent intake conditions; effect is highly dependent on individual gastric acidity.	(Shinkuma et al., 1991)
JNJ-37,822,681	↓ (11%)	Ka was 55% lower in the fed condition.	Low	Maintain consistent intake conditions.	(Hoeben and Neyens, 2013)
Clozapine	→	Cmax decreased by ~20% in suspension/ODT formulations; tmax slightly delayed.	Low	Generally can be taken regardless of meals.	(Choc and Hsuan, 1990; Disanto and Golden, 2009; Glue and Gale, 2012)
Olanzapine	→	No clinically relevant effects on non-AUC PK parameters observed.	Low	Can be taken regardless of meals.	(Du and Li, 2020; Sun and McDonnell, 2019)
Olanzapine (ODT)	↓ (~20%)	Cmax reduced by approximately 20–21%.	Low	Prefer fasting state or maintain consistent conditions as exposure is slightly reduced with food.	(Fan and Zhang, 2020)
Pimavanserin	→	No clinically relevant effects on non-AUC PK parameters observed.	Low	Can be taken regardless of meals.	(Vanover and Robbins-Weilert, 2007Gandelman and Alderman, 2009)

AUC: Area Under the Concentration–Time Curve.
AEA: Polyvinylacetal diethylaminoacetate.
CL/F: Apparent Total Body Clearance After Extravascular Administration.
Cmax: Maximum Observed Plasma Concentration.
Ka: Absorption Rate Constant.
ODT: Orally Disintegrating Formulation.
t1/2: Elimination Half-Life.
tmax: Time to Reach Maximum Plasma Concentration.
PK: Pharmacokinetic(s).
Two arrows indicate an increase of 100% or more percent.

Table 2
Effects of other nutritional components on the pharmacokinetics of antipsychotics.

Antipsychotics	Effect on AUC	Further significant PK observations	Certainty of evidence	Clinical recommendation	References
Blonanserin + grapefruit juice	↑↑ (482%)	Cmax increased by 344%; t1/2 increased by 209%; Cl/F decreased by 83%; more adverse events reported.	Moderate	Avoid grapefruit juice due to a massive increase in systemic exposure and toxicity risk.	(Shang and Wang, 2018)
Blonanserin + alcohol	↑↑ (144%)	Cmax increased by 135%; t1/2 prolonged by 75%; tmax delayed by 100%.	Moderate	Avoid alcohol as it significantly increases drug exposure and potential side effects.	(Deng and Ni, 2018)
Clozapine + caffeine	↑ (20%)	N-desmethylclozapine increased by 7%; smoking remains a more dominant factor in metabolism.	Very low	Monitor clozapine levels when caffeine intake changes significantly.	(Flanagan and Obee, 2024; Raaska and Raitasuo, 2004)
Clozapine + caffeine withdrawal	↓ (26%)	Metabolite norclozapine concentration decreased by 12% after 5 days of withdrawal.	Very low	Dose adjustments may be needed if caffeine is discontinued to avoid subtherapeutic levels.	(Carrillo and Herraiz, 1998)
Clozapine + grapefruit juice	→	Multiple studies confirm no significant effect on parent drug or metabolites.	Low	Can be taken regardless of grapefruit juice consumption.	(Lane and Chiu, 2001; Lane and Jann, 2001; Vandel and Netillard, 2000)
Haloperidol + grapefruit juice	→	No significant impact on plasma concentrations observed.	Very low	Can be taken regardless of grapefruit juice consumption.	(Yasui and Kondo, 1999)
Sulpiride (AEA) + orange juice	↑ (Potential increase)	Increased gastric acidity tends to lead to higher bioavailability (not statistically significant).	Very low	Maintain consistent beverage choices to avoid fluctuations in gastric acidity and absorption.	(Shinkuma and Hamaguchi, 1989)
Sulpiride (AEA) + sodium bicarbonate	↑ (Potential increase)	Low gastric acidity leads to a positive food effect for the AEA-coated formulation.	Very low	Avoid antacids at the time of dosing to prevent unintended changes in absorption.	(Shinkuma and Hamaguchi, 1989; Shinkuma et al., 1991)
Clozapine + vitamin D	↑ (Positive correlation)	Complex relationship; toxic levels (>1000 ng/mL) more frequent in winter; seasonal fluctuations observed.	Very low	Consider seasonal monitoring of clozapine levels, especially in patients with vitamin D deficiency.	(Manca and Mula, 2023)
Quetiapine + vitamin D	↓ (Negative correlation)	Strong negative correlation (Kendall's tau = −0.64), possibly due to CYP3A4 induction by Vitamin D.	Very low	Be aware that high Vitamin D levels might lead to lower quetiapine concentrations.	(Gaebler and Finner-Prével, 2022)
Aripiprazole + vitamin D	↓ (Negative correlation)	Significant negative correlation (Kendall's tau = −0.48).	Very low	Monitor for reduced efficacy if Vitamin D levels are high or supplemented.	(Gaebler and Finner-Prével, 2022)
Amisulpride + vitamin D	→	No significant relationship found between Vitamin D levels and drug concentrations.	Very low	No clinical action required regarding Vitamin D status.	(Gaebler and Finner-Prével, 2022)
Olanzapine + vitamin D	→	No significant correlation observed.	Very low	No clinical action required regarding Vitamin D status.	(Gaebler and Finner-Prével, 2022)
Risperidone + vitamin D	→	No significant relationship found.	Very low	No clinical action required regarding Vitamin D status.	(Gaebler and Finner-Prével, 2022)

AUC: Area Under the Concentration–Time Curve.
AEA: Polyvinylacetal diethylaminoacetate.
CL/F: Apparent Total Body Clearance After Extravascular Administration
Cmax: Maximum Observed Plasma Concentration.
t1/2: Elimination Half-Life.
tmax: Time to Reach Maximum Plasma Concentration.
PK: Pharmacokinetic(s).
Two arrows indicate an increase of 100% or more percent.

1998; Miceli et al., 2007), lurasidone (Preskorn and Ereshefsky, 2013; Yu and Fang, 2025) and up to five-fold for blonanserin when administered with food (Sun and Song, 2025). However, the most clinically actionable evidence concerns ziprasidone and lurasidone, both of which require administration with adequate caloric intake to achieve reliable systemic exposure and fasting administration may lead to subtherapeutic plasma concentrations. For example, insufficient D2 receptor occupancy has been reported when ziprasidone is taken with meals below 500 kcal, suggesting that inadequate caloric intake may mimic a missed dose (Gandelman and Alderman, 2009).

Furthermore, AUC and C_{max} increased for blonanserin when administered with ethanol (Deng and Ni, 2018). Ethanol can act as a co-solvent in the gastrointestinal tract, enhancing the solubility of lipophilic drugs and facilitating increased mucosal uptake (Koziolek and Alcaro, 2019). This mechanism suggests that alcohol consumption may lead to unexpectedly elevated plasma levels and an increased risk of adverse effects beyond additive sedation.

In contrast, hydrophilic agents with low membrane permeability such as amisulpride appear susceptible to negative food effects (Skrobecki and Chmielińska, 2017; Wang and Peng, 2025; Dos Santos Pereira et al., 2026). Food intake may reduce absorption through slower diffusion to the epithelial surface, and potential competition for intestinal transporters (Koziolek and Alcaro, 2019; Wang and Peng, 2025; Dos Santos Pereira et al., 2026; Dos Santos Pereira and Tadjerpisheh, 2014). Additionally, weakly basic drugs such as amisulpride may dissolve less efficiently when gastric pH increases after food intake, further decreasing absorption (Abuhelwa and Williams, 2026; Younes et al., 2026). Moreover, formulation-specific effects were observed. Sublingual formulations of asenapine require a food-free interval after administration because food intake can interfere with mucosal absorption (Dogterom and de Greef, 2015). For most other antipsychotics, food mainly delays gastric emptying and prolongs time to maximum plasma concentration without substantially altering total exposure. An exception is quetiapine extended-release, where high-fat meals may accelerate drug release and modestly decreased tmax which may alter the intended modified-release characteristics of the product (Huang and Zhang, 2019).

Dietary components may also influence antipsychotic metabolism through modulation of CYP enzymes. Fig. 2 provides an overview of antipsychotics metabolized via CYP enzymes or predominantly eliminated renally, adapted from (Benkert and Hippius, 2013; Deeks and Keating, 2010). One of the most clinically relevant metabolic

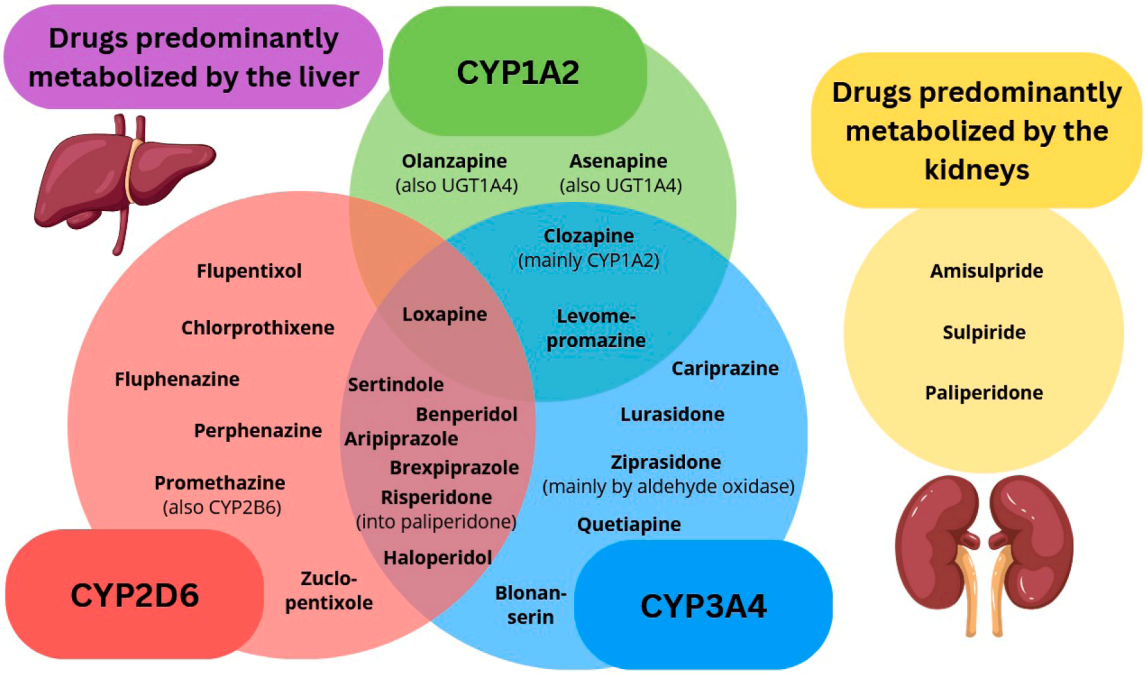

Fig. 2. Schematic overview of the principal metabolic and excretory routes of antipsychotic medications.

interactions involves abrupt changes in caffeine intake during clozapine therapy. Caffeine acts as a competitive inhibitor of CYP1A2, the primary enzyme responsible for clozapine metabolism (Doude van Troostwijk and Koopmans, 2003; Evans and Richards, 2025), and may increase clozapine plasma concentrations by approximately 20% (Raaska and Raitasuo, 2004), particularly when caffeine intake changes abruptly (Carrillo and Herraiz, 1998). Because smoking strongly induces CYP1A2 activity, caffeine intake must be interpreted within the context of smoking status as a strong confounding factor (Flanagan and Obee, 2024). Another clinically relevant but strongly drug-specific interaction involves grapefruit juice–mediated intestinal CYP3A4 inhibition (Bailey and Malcolm, 1998). For blonanserin, grapefruit juice markedly increases systemic exposure, suggesting extensive presystemic metabolism via intestinal CYP3A4 (Shang and Wang, 2018), while no significant interaction has been demonstrated for clozapine or haloperidol (Lane and Chiu, 2001; Lane and Jann, 2001; Vandel and Netillard, 2000; Yasui and Kondo, 1999). The marked contrast between blonanserin and clozapine illustrates that grapefruit juice interactions should not be generalized across antipsychotics as a pharmacological class. Furthermore, observational studies report an inverse association between serum vitamin D levels and plasma concentrations of aripiprazole, quetiapine, and clozapine (Gaebler and Finner-Prével, 2022; Manca and Mula, 2023), possibly mediated by vitamin D receptor–induced CYP3A4 expression (Qin and Wang, 2019).

Our findings are consistent with established PK principles and prior pharmacological research. The pronounced positive food effects observed for lipophilic antipsychotics reflect the well-known role of bile-mediated solubilization in improving the absorption of poorly soluble drugs. Similarly, the negative food effects observed with hydrophilic agents such as amisulpride align with previously described diffusion barriers in the gastrointestinal tract, where increased viscosity and luminal dilution reduce drug transport to the intestinal epithelium (Koziolek and Alcaro, 2019).

The metabolic interactions identified in this review are consistent with prior literature on CYP-mediated drug metabolism. The interaction between caffeine and clozapine illustrates how environmental factors can influence CYP1A2 activity and variability in drug exposure. Notably, abrupt changes in caffeine intake—such as during hospitalization—may be more clinically relevant than stable consumption (Flanagan and Obee, 2024). Furthermore, the drug-specific effects of grapefruit juice highlight the role of presystemic metabolism, as the magnitude of interaction depends on the extent of intestinal first-pass metabolism (Bailey and Malcolm, 1998). Accordingly, a strong interaction was observed for blonanserin, whereas no clinically relevant effects were reported for clozapine or haloperidol, suggesting differing contributions of intestinal CYP3A4 to their clearance. Vitamin D-related effects on CYP3A4 activity represent a biologically plausible but currently unconfirmed hypothesis for altered plasma concentrations of antipsychotics metabolized via this pathway. Importantly, the available evidence is based predominantly on observational cross-sectional data and remains highly susceptible to confounding factors including smoking behavior, physical activity, dietary patterns, sun-avoidance behaviors, seasonality, and comorbidities (Vasileiou and Nena, 2026). Accordingly, the identified associations should be interpreted as hypothesis-generating observations rather than evidence of established causal PK mechanisms.

Evidence beyond the studies included in this review suggests that herbal and dietary factors may influence CYP enzyme activity. For example, Hypericum perforatum (St. John's Wort) has been shown to reduce plasma concentrations of several CYP3A4 substrates (Roby and Anderson, 2000). Case reports further indicate that botanicals such as ginseng, Ginkgo biloba, and milk thistle may contribute to clinically relevant PK interactions affecting psychotropic medications (Woroń and Siwek, 2018). Additionally, cruciferous vegetables have been reported to increase CYP1A2 activity by 20–40% (Eagles and Gross, 2020), while polycyclic aromatic hydrocarbons in smoked foods can induce several CYP isoenzymes (Elsherbiny and Brocks, 2011). Although these mechanisms are well documented in other pharmacological contexts, their relevance for antipsychotic therapy remains insufficiently studied.

4.2. *Clinical implications*

The findings support the development of more granular, "lifestyle-aware" prescribing guidelines.

- **Administration Instructions:** For ziprasidone (≥500 kcal) and lurasidone (≥350 kcal), 'take with food' should be regarded as a core prescribing instruction necessary for therapeutic drug exposure rather than a tolerability recommendation. Inconsistent caloric intake may lead to clinically meaningful reductions in bioavailability and potentially subtherapeutic exposure. Conversely, amisulpride may benefit from fasting administration to maximize uptake, while asenapine sublingual tablets require a strictly food-free interval after administration.
- **Blonanserin Management:** Patients require careful counselling regarding consistent food intake to avoid fluctuations and should avoid grapefruit juice and alcohol due to the risk of substantial exposure increases.
- **Dietary Transitions**: During clozapine therapy, clinicians should assess caffeine consumption and anticipate changes during hospitalization or smoking cessation. Therapeutic drug monitoring may be useful during such transitions.
- **Formulation Matters:** Patients receiving extended-release quetiapine should avoid extremely high-fat meals that may disrupt the intended release profile and produce transient peaks in plasma concentration.

4.3. Limitations

Several limitations should be considered when interpreting the findings of this review. First, many included studies were conducted in small cohorts of healthy volunteers under controlled single-dose conditions, limiting generalizability to real-world psychiatric populations with chronic illness, metabolic comorbidities, or polypharmacy. Single-dose PK studies may furthermore not adequately reflect steady-state conditions or long-term dietary habits encountered in clinical practice. Second, substantial heterogeneity existed regarding the definition of the fed state. While recent studies generally used standardized high-fat meals according to regulatory guidance, older studies often applied meals with insufficiently characterized caloric and macronutrient composition, thereby complicating direct comparisons across studies. Third, several findings regarding caffeine intake, vitamin D status, or seasonal effects were derived from observational trials and are therefore susceptible to residual confounding, such as smoking behavior. Mechanistic attribution to CYP modulation remains speculative and should be investigated in prospective controlled studies. Forth, although the magnitude of the food effect observed with blonanserin was among the largest identified in this review, the direct global clinical relevance of this interaction is partly limited by the regional availability of blonanserin, which is currently prescribed predominantly in East Asian countries. Fifth, the clinical interpretation of food effects additionally depends on the formulation studied. Several observed interactions were formulation-specific and cannot necessarily be generalized to all commercially available dosage forms of the same active substance. Finally, most included studies assessed surrogate PK endpoints such as AUC, C_{max}, or plasma drug concentrations rather than direct clinical outcomes. Consequently, although altered systemic exposure may plausibly influence efficacy or tolerability, direct evidence linking nutritional PK interactions to relapse prevention, symptom improvement, or toxicity remains limited for most antipsychotics.

4.4. Future directions

Future studies should prioritize clinical investigations in psychiatric populations to better reflect real-world treatment conditions. In addition to controlled PK trials, observational analyses of therapeutic drug monitoring databases could help clarify how long-term dietary habits influence antipsychotic serum concentrations. Further research on drug–herb interactions is also warranted, given the increasing use of dietary supplements and herbal preparations that may modulate CYP enzyme activity. Finally, most available data focus on acute food effects, whereas the impact of long-term dietary patterns remains largely unexplored. Longitudinal studies are therefore needed to determine how chronic dietary modifications influence the PK and safety of antipsychotic medications.

4.5. Conclusion

Nutritional factors significantly influence the PK of several antipsychotic medications, with effects ranging from modest delays in absorption to clinically relevant increases in AUC. Food-dependent bioavailability is a prerequisite for the efficacy of ziprasidone, lurasidone, and blonanserin, whereas evidence regarding amisulpride suggests a potentially clinically relevant negative food effect, although findings remain heterogeneous across studies. Metabolic interactions—particularly caffeine-mediated CYP1A2 inhibition—may be a safety concern for clozapine. To optimize therapeutic outcomes and minimize variability in response rates, psychiatric care should include comprehensive, drug-specific dietary counselling as a standard component of psychopharmacology.

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Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the author(s) used Google Gemini (Google LLC; access date: 02/23/2026) for linguistic refinement and stylistic editing. After using this tool, the author(s) carefully reviewed and edited the content as needed and take full responsibility for the content of the published article.

CRediT authorship contribution statement

Michael Schepp: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Melanie Engel:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Anna Hirschbeck:** Writing – review & editing, Supervision, Methodology. **Annabel Müller-Stierlin:** Writing – review & editing, Supervision, Methodology. **Alkomiet Hasan:** Writing – review & editing, Supervision, Methodology. **Astrid Röh:** Writing – review & editing, Supervision, Methodology.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Alkomiet Hasan reports a relationship with Janssen, Otsuka, Recordati, and Lundbeck that includes: speaking and lecture fees. Alkomiet Hasan reports a relationship with Rovi, Recordati, Otsuka, Lundbeck, and Janssen that includes: consulting or advisory. Co-author Alkomiet Hasan is the editor of the German AWMF S3 and the WFSBP schizophrenia guidelines. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2026.117332.

Data availability

The data that support the findings of this study are available within the article and its supplementary materials. Additional information is available from the corresponding author upon reasonable request.

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