CNS Drugs (2025) 39:913–935
https://doi.org/10.1007/s40263-025-01206-3

SYSTEMATIC REVIEW

Strategies for Switching between Oral Postsynaptic Antidopaminergic Antipsychotics in Patients with Schizophrenia: A Systematic Review

Christoph U. Correll[1,2,3,4]

Accepted: 26 June 2025 / Published online: 23 July 2025

Abstract

Background Antipsychotic switching is common in the treatment of schizophrenia. Pharmacokinetic and pharmacodynamic properties of antipsychotics can inform switch strategies, as switching from shorter to longer half-life antipsychotics and switching from more antagonistic to less antagonistic or partial agonist agents at dopaminergic, histaminergic, and cholinergic receptors can lead to withdrawal or rebound symptoms, potentially complicating switch results. This systematic literature review of studies investigated switching strategies between oral antipsychotics. Pharmacokinetic and pharmacodynamic characteristics of antipsychotics that can influence switch outcomes were also extracted from publications and prescribing information.

Methods MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and PubMed databases were queried (last search 13 May 2024) for articles published from 1 June 2010 to 1 April 2024, with keywords *(schizophr* OR schizoaff*)* AND (*antipsychotic**) AND (*switch**). Randomized controlled trials, open-label studies, meta-analyses, and reviews of oral antipsychotic switching were included. Records were excluded if they investigated a disease other than schizophrenia or schizoaffective disorder or focused on long-acting injectable or non-approved antipsychotics. Data on switch strategies investigated and study outcomes were manually extracted from randomized controlled trials and open-label switch studies of oral antipsychotics in schizophrenia or schizoaffective disorder. Meta-analyses and review articles were summarized. There was no assessment for risk of bias or specific method to synthesize results.

Results Of the 579 records identified during the systematic review, 80 articles investigated switching of oral antipsychotics in adult patients with schizophrenia, including 58 randomized and non-randomized studies (9 of which investigated ≥ 1 antipsychotic) and 22 review articles or meta-analyses. The antipsychotics investigated during this period were: aripiprazole (studies = 18); paliperidone, ziprasidone, olanzapine, and risperidone (studies = 7 each); brexpiprazole, clozapine and lurasidone (studies = 4 each); amisulpride, (studies = 3); quetiapine and iloperidone (studies = 2 each); and asenapine and lumateperone (1 study each). Most studies that reported a switch method employed cross-titration switching (studies = 39; 69.6%), while abrupt switching (studies = 10; 17.9%) and switching at investigator's discretion (studies = 7; 12.5%) were rare. A total of 24 studies ($N = 3440$ patients) had statistical comparisons between treatment groups, but few studies specifically statistically compared outcomes between different switch strategies (1 trial each for aripiprazole, clozapine, iloperidone, and ziprasidone; $N = 666$ patients), with mixed outcomes. Frequencies of sedative rescue treatments, which could have attenuated potential withdrawal symptoms, were rarely disclosed.

Conclusions Despite the importance and frequency of antipsychotic switching, few studies have specifically investigated outcomes of different switch strategies. General clinical preference appears to utilize gradual switching approaches to avoid potential rebound symptoms. Future research with current and emerging antipsychotics is needed, especially for switching between antipsychotics with different receptor profiles and for switches that are potentially vulnerable to rebound and withdrawal symptoms.

✉ Christoph U. Correll
ccorrell@northwell.edu

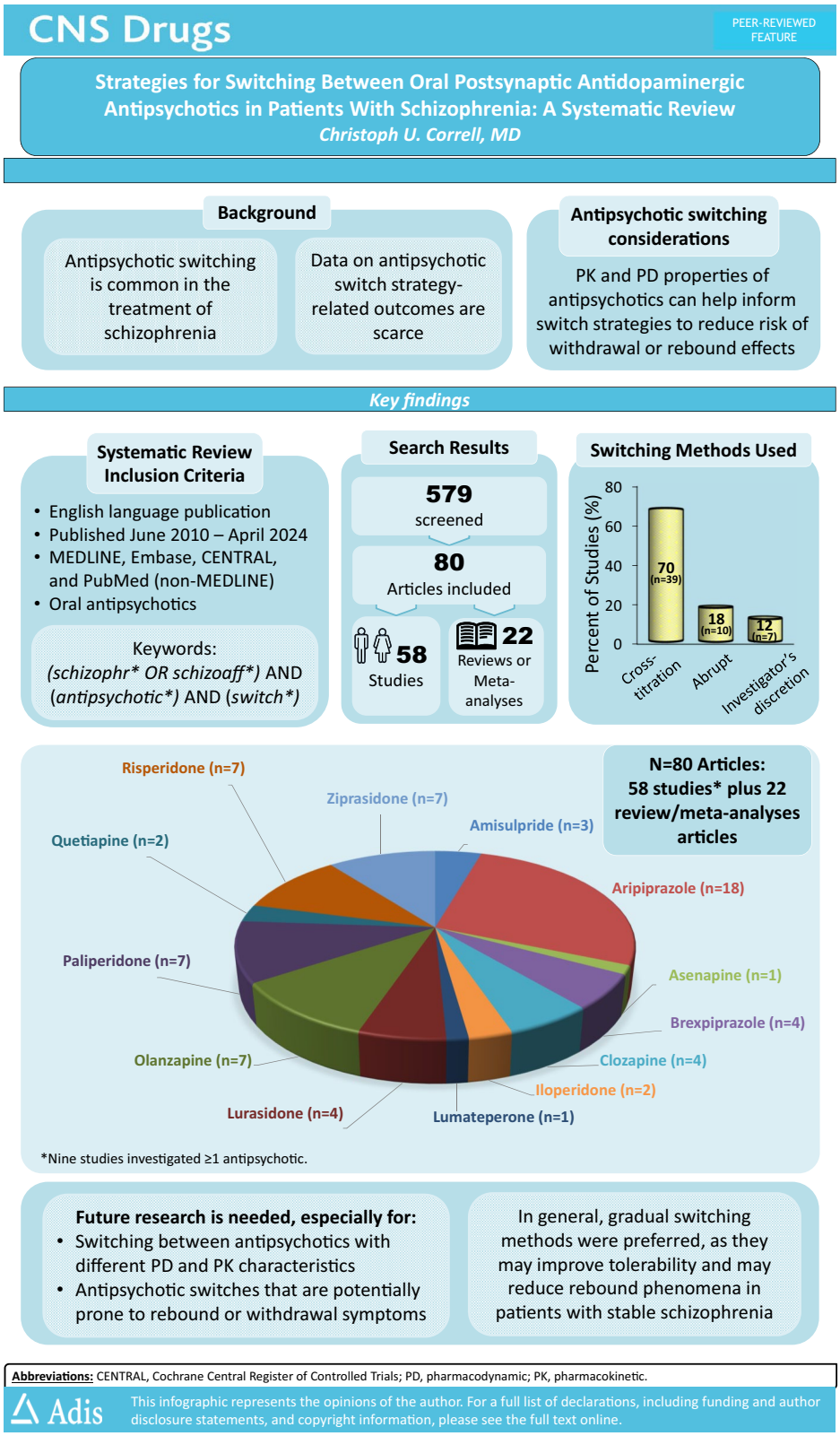
[1] Department of Psychiatry, The Zucker Hillside Hospital, Northwell Health, 75-59 263rd St, Glen Oaks, NY 11004, USA

[2] Department of Psychiatry and Molecular Medicine, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA

[3] Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin Berlin, Berlin, Germany

[4] German Center for Mental Health (DZPG), Partner Site Berlin, Berlin, Germany

Graphical Abstract



Plain Language Summary

People with schizophrenia commonly switch between antipsychotics, but few studies give information about the best way to do this. This paper reviews antipsychotic qualities that can affect a person's experience while switching antipsychotics, such as how antipsychotics pass through the body over time (called pharmacokinetics) and how they work in the body (called pharmacodynamics). Considering these antipsychotic qualities can help clinicians decide how to switch between antipsychotics to reduce the risk of worsening symptoms or side effects. This paper also reviews which switching methods are used most often. Studies published from 2010 to 2024 were found. Of 579 search results, 80 articles involving 13 different antipsychotics were summarized. In most studies ($n = 39$) the current antipsychotic was slowly stopped, and the new antipsychotic was slowly started over the same time period, called cross-titration. Fewer studies ($n = 10$) quickly stopped the current antipsychotic and started the new one, and some studies ($n = 7$) had prescribers decide switch timing. A total of 24 studies, including 3440 participants, reported on comparisons between study groups. However, only four trials (one trial each for aripiprazole, clozapine, iloperidone, and ziprasidone; 666 participants) reported on comparisons of outcomes of different switch strategies. Nevertheless, results of the reviewed studies are mostly in agreement that good practice consists of more gradual antipsychotic switching in people with stable schizophrenia. Unfortunately, comparisons between switching methods and details about medicines used to reduce side effects during the switch were rarely reported. More research is needed to understand the effects of antipsychotic switching methods in people with schizophrenia.

Key Points

While antipsychotic switching is common, relevant, and complex, studies statistically comparing efficacy and safety outcomes between different switch strategies are rare.

This updated review of the pharmacodynamic and pharmacokinetic profiles of oral antipsychotics that can influence antipsychotic switch outcomes may assist clinicians in tailoring switch strategies to individual combinations of pre-switch and post-switch antipsychotics, as well as patient needs.

1 Introduction

Schizophrenia is a chronic, complex disease with a range of positive symptoms (delusions, hallucinations, thought disorder), negative symptoms (anhedonia, amotivation, asociality, affective flattening, alogia), and cognitive dysfunctions [1]. Schizophrenia is a top cause of physical disability [2], resulting in high morbidity and mortality, shortened life expectancy, high suicide rates [3–7], and economic burden [8]. Dopamine receptor antagonist and partial agonist antipsychotics are the pharmacological foundation for the treatment of psychotic episodes that characterize schizophrenia [4, 9], as well as treatment of other severe mental illness [10], including mania in bipolar disorder [11] and depression in major depressive [12, 13] and bipolar disorders [14].

Despite the availability of a variety of first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs), treatment decisions in severe mental illness are complex, and the development of effective treatment plans in clinical practice remains challenging [4, 9, 15, 16]. FGAs and SGAs have similar efficacy profiles for the treatment of schizophrenia and bipolar mania [11, 17, 18]; however, individualized treatment response, remission, and recovery are impacted by a variety of factors that can be difficult to predict [19]. While individualized treatment plans are essential to successful care outcomes, properly designed plans must weigh an individual's likelihood to benefit from treatment while accounting for the risk of adverse effects [10, 20]. Patient preference and additional practical real-world variables such as finances, clinician–patient relationship, daily stresses, and home environment should also be considered when selecting antipsychotic, administration route, and dosage (Fig. 1) [21, 22]. Clinicians should focus on tailoring treatment plans with carefully selected pharmacological treatments alongside non-pharmacological strategies and support systems [4, 22, 23].

Individualized experience while a patient is undergoing antipsychotic treatment is heavily impacted by adverse side effects, such as motor abnormalities, sedation, sexual dysfunction, metabolic dysfunction, and weight gain; these are commonly associated with non-adherence [21, 24]. In particular, acute and chronic adverse motor effects are more common with FGA than SGA therapies [10, 18, 20, 25, 26]. While parkinsonism can be managed through time-limited use of antiparkinsonian agents, FGAs still have higher relapse rates and overall treatment failure rates than SGAs [27]. SGAs are generally better tolerated than

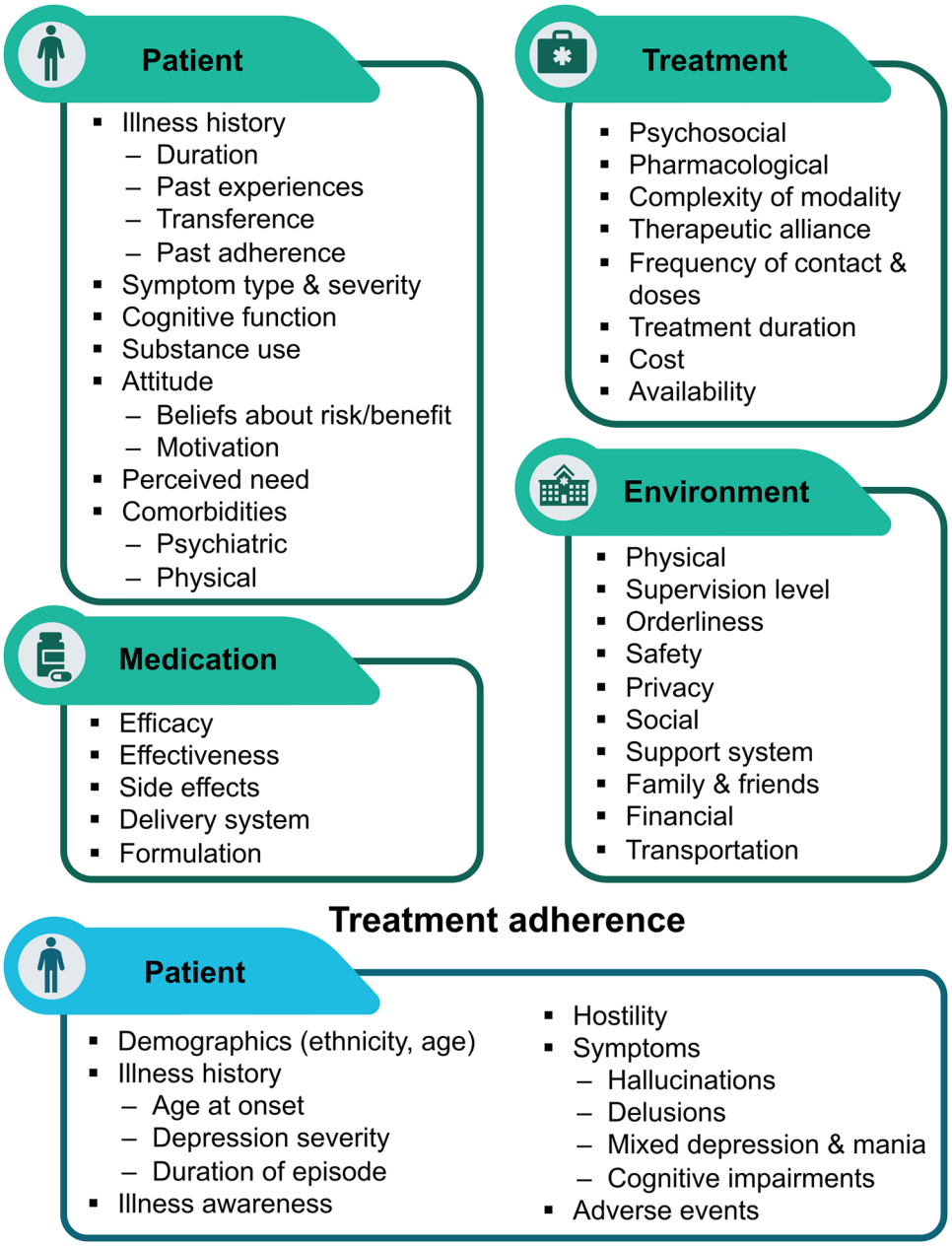


Fig. 1 Variables affecting treatment selection, response, and adherence in severe mental illness. *Source*: Data from Correll et al. and Garcia et al. [21, 22]

FGAs, with relatively predictable side effects [10, 13, 18, 20, 28]. Antipsychotic selection in schizophrenia is further complicated by the burdensome physical health complications inherent to the disease and potentially aggravated by antipsychotic treatment [3, 29–31].

Because low rates of antipsychotic treatment adherence are considered a significant clinical challenge, novel delivery methods and formulations have been developed [32, 33]. Additionally, shared decision-making between the patient and clinician may increase treatment adherence and improve patient experience [34, 35]. A systematic review on clinical practice guidelines for the care and management of schizophrenia has recently been published, which may aid in treatment decisions in this population [9].

Historically, much of the knowledge about antipsychotic treatments has been derived from the clinical trial setting, which does not consider real-world data on the use and outcomes of antipsychotics [22]. Clinical trial data cannot be readily generalized to other settings due to restrictive trial eligibility criteria, opportunity for frequent monitoring and adjustments during the trial, and dosing parameters that may not have been based on the real-life target population [22, 36, 37]. In addition, drug labeling may not reflect the optimal dosing range, titration strategies, or switching methods that are often identified after drug approval in real-world

settings. In recent years, several long-term, real-world studies have been published to close this knowledge gap and to investigate the impact of antipsychotic treatments outside of the trial environment [36, 38, 39].

The risk–benefit profile of antipsychotics can be optimized through practical application of the pharmacodynamic (PD) and pharmacokinetic (PK) profiles of available antipsychotics to guide dosing and switching strategies [22]. While a characteristic feature of first- and second-generation antipsychotics is blocking postsynaptic D_2 dopamine receptors to achieve mainly positive symptom efficacy, second-generation dopamine antagonist and partial dopamine agonist antipsychotics also interact with other neuroreceptor targets, possibly enhancing some aspects of efficacy, but also enhancing the complexity of side effect profiles and determination of treatment regimens [10, 20, 40, 41]. Important variations in the binding profile of antipsychotics to different receptor types, including dopaminergic, histaminic, serotoninergic, α-adrenergic, and muscarinic, can be used to predict side effect profiles [40, 42–45]. In addition to binding affinities, considering PK drug properties such as absorption, distribution, and elimination can help anticipate and mitigate adverse effects that may occur when the drug is discontinued or switched [46, 47].

This paper expands on previous information on oral antipsychotics approved before 2010 [22] by adding new PK and PD parameters for oral antipsychotics approved by the US Food and Drug Administration (FDA) since 2010: brexpiprazole, cariprazine, lumateperone, lurasidone, and the combination of olanzapine/samidorphan [48–52] (Sects. 2 and 3). This article focuses on oral antipsychotics, as reviews that focus on the pharmacokinetics and switching between or to long-acting injectables have been previously published [33, 53], and includes an overview of how PK and PD can impact choice of switch strategy (Sect. 4). Additionally, to interrogate the current evidence base of switching strategies as they pertain to second-generation antipsychotics, findings from a systematic literature review are reported in Sect. 5 that investigate antipsychotic switching strategies in schizophrenia, focusing on more contemporary articles published since 2010.

2 Pharmacokinetic Considerations

PK properties (Table 1) relevant to antipsychotic treatment efficacy and safety reported in prescribing information include absorption, distribution, and elimination.

During the process of absorption, drugs are transferred from the administration site to systemic circulation [54]; bioavailability describes the proportion of the dose that is systemically circulated [54]. Absorption heavily impacts the time (t_{max}) to peak concentration (C_{max}) and can inform the time of dosing, as peripheral side effects are closely related to the time of peak levels [54]. Reduction of peak levels can be achieved by slowing drug absorption through tactics such as splitting the dose, dosing with fatty foods, or using extended-release formulations [22]. Distribution of the drug occurs as it circulates systemically throughout the body from the plasma and potentially into other tissues [33]. For antipsychotic efficacy, distribution must include the additional step of unbound drug or metabolites crossing the blood–brain barrier to reach target receptors in the brain [55].

During the elimination process, the drug is metabolized in the body and broken down into smaller metabolites that have different chemical characteristics. If another drug is being taken concomitantly that speeds up, slows down, or occupies metabolism enzymes [56, 57] antipsychotic dose adjustments may be necessary [56, 57]. This is especially important for drugs impacting the cytochrome P450 (CYP) family of enzymes [56, 57]. For example, concomitant use of cariprazine, lumateperone, or combination olanzapine/samidorphan with strong CYP3A4 inducers should be avoided, and dose increases or reductions are required if the antipsychotic is administered concomitantly with other same-type CYP inhibitors or inducers [48–50].

Antipsychotics are removed from the circulation as parent compound or metabolites via excretion, generally through the kidney or liver [58]. The elimination half-life ($t_{1/2}$) describes the time for half of the amount of drug to be removed from the body [33]. The clearance mechanism of an antipsychotic is an important consideration when choosing an antipsychotic and dosage for patients who have known renal or hepatic impairment [58]. In addition, potential biological activity of drug metabolites should be considered, as metabolites may have relatively long $t_{1/2}$ and similar pharmacological activity as their parent compound, as with the major metabolites of cariprazine (desmethyl cariprazine and didesmethyl cariprazine) [49, 59–61].

Together, absorption and elimination $t_{1/2}$ dictate when drug steady state occurs, with approximately five times the elimination $t_{1/2}$ needed to reach steady state. Similarly, if discontinuation occurs at steady state, it takes five times the elimination $t_{1/2}$ for the drug to be removed from plasma. Figure 2 depicts the theoretical elimination time courses that occur after antipsychotic discontinuation. Dose increases during titration are dictated by $t_{1/2}$. While antipsychotics with shorter $t_{1/2}$s may have daily increased doses during initial titration, drugs with longer $t_{1/2}$s may need more gradual weekly dose increases. The dosing schedule should also consider disparities in the blood concentration of the active moiety from the initial dose to steady state. These concentrations can vary widely, as with cariprazine, which has a five- to tenfold increase in C_{max} from day 1 to steady state with even greater changes for active metabolites [62, 63].

Table 1 PD and PK profiles of antipsychotic drugs

Receptor	SGA															FGA		
	AMI	ARI	ASE	BREX	CAR	CLO	ILO	OLA	LUM	LUR	PALI	RIS	QUE	SER	ZIP	HAL	MOL	PER
Pharmacodynamics (K_i Equilibrium Constants)[a]																		
D_2	1.3[c]	0.66[b,c]	8.9[c]	0.30[b]	D_{2L}: 0.49[b] D_{2S}: 0.69[b]	210	3.3	20	32	0.994	2.8	3.77	770	2.7	2.6	2.6	120	1.4[c]
D_3	3.5	0.8	0.42	1.1	0.085	555	7.1	63	–	15.7	7.5	18.0	483	5.76	7.2	4.6	47.7	0.43
5-HT_{1A}	> 10,000[d]	5.5[b,c]	8.6[c]	0.12	2.6	160	33	610	1480	6.38	480	190	300	2200	1.9[b,c]	1800	3797[c]	421
5-HT_{2A}	2000[d]	8.7[c]	0.15[c]	0.47	18.8	2.59	0.2	4	0.54	0.47	1.2	0.15	31	0.14	0.12	61	5000	5[c]
5-HT_{2c}	> 10,000[d]	22[c]	10.46[c]	–	134	4.8	14	11	173[c]	–	48	32	3500	6.0	0.9	4700	> 10,000[c]	132[c]
5-HT_7	11.5	39	0.11	3.7	–	6.3	22	105	–	0.5	6.8	3.5	307	28	6	378	3053	23
α_1	7100[d]	26[c]	8.9[c]	α_{1A}: 3.8 α_{1B}: 0.17 α_{1D}: 2.6	α_{1A}: 155	6.8	0.31	19	< 100	–	10	2.7	8.1	3.9	2.6	17	2500	10
α_2	1600[d]	74[b]	9.5[c]	α_{2C}: 0.59	–	158	3	280	–	α_{2A}: 40.7 α_{2C}: 10.8	80	8	80	190	154	600	625	500
H_1	> 10,000[e]	30[c]	9.0[c]	19	23.2	3.1	12.3	7	> 1000	> 1000	3.4	5.2	19	440	4.6	260	> 10,000[c]	8
M_1	–	6780[c]	5.09[c]	67% inhibition at 10 μM	No affinity	1.4[c]	4898[c]	73	> 1000	> 1000	> 10,000[c]	> 10,000[c]	120[c]	5000	300[c]	> 10,000[c]	> 10,000	1500
M_2	–	3510[c]	4.5[c]	–	No affinity	4.5[c]	204[c]	96	–	–	622[c]	> 10,000[c]	630[c]	N/A	> 3000[c]	> 10,000[c]	N/A	N/A
M_3	–	4680[c]	4.67[c]	–	No affinity	109[c]	> 10,000[c]	132	–	–	> 10,000[c]	> 10,000[c]	1320[c]	2692[c]	> 1300[c]	> 10,000[c]	> 10,000[c]	1848[c]
M_4	–	1520[c]	5.09[c]	–	No affinity	27[c]	8318[c]	32	–	–	> 10,000[c]	> 10,000[c]	660[c]	–	> 1600[c]	> 10,000[c]	–	–
Pharmacokinetics																		
Half-life (h)	12	50-72	First: 6, terminal: 23	91	48–96 (with active metabolite DD-CAR: 168)	12	14–17	30	~18 (IV)	18	21–30	3	IR: 6–7 XR: 24	53–102	7	3–6 (PO) 10–20 (IM)	3	8–12
Peak time (h)	2 Peaks 1,3–4	3–5	1.5	4	3–6	1–4	2–4	6	1–2	1–3	24	1–2	2	10	5	24 po 21 im	1.5	1–3
Metabolism (CYP450 Enzyme)	Mostly renal clearance	2D6 > 3A4	1A2 > 3A4	3A4, 2D6	3A4, 2D6	1A2 (30%) > 2C19 24%) > 3A4 (22%) > 2C9 (12%) > 2D6 (6%)	2D6 > 3A4 > 1A2	1A2, 2D6, 3A4	3A4, 2C8, 1A2	3A4	< 10% hepatic clearance	2D6 > 3A4	3A4	2D6 3A4	Aldehyde oxidase (2/3) > 3A4 (1/3)	3A4	2D6	2D6

Data based on [22, 42, 165–171] and the prescribing information or drug approval packages for each antipsychotic

AMI amisulpride, *ARI* aripiprazole, *ASE* asenapine, *CAR* cariprazine, *CLO* clozapine, *CYP450* cytochrome P450, *DD-CAR* didesmethyl cariprazine, *FGA* first-generation antipsychotic, *HAL* haloperidol, *ILO* iloperidone, *IM* intramuscular, *IR* immediate release, *IV* intravenous, *LUM* lumateperone, *MOL* molindone, *OLA* olanzapine, *PALI* paliperidone, *PD* pharmacodynamics, *PER* perphenazine, *PK* pharmacokinetic, *PO* oral, *QUE* quetiapine, *RIS* risperidone, *SER* sertindole, *SGA* second-generation antipsychotic, *XR* extended release, *ZIP* ziprasidone

[a]Data are presented as the equilibrium constant (K_i) in nM (i.e., concentration of the antipsychotic required to block 50% of the receptors in vitro). Thus, a lower K_i value indicates stronger receptor affinity and binding

[b]Partial agonism

[c]Data from cloned human brain receptors

[d]Data extracted from rat

[e]Data extracted from guinea pig

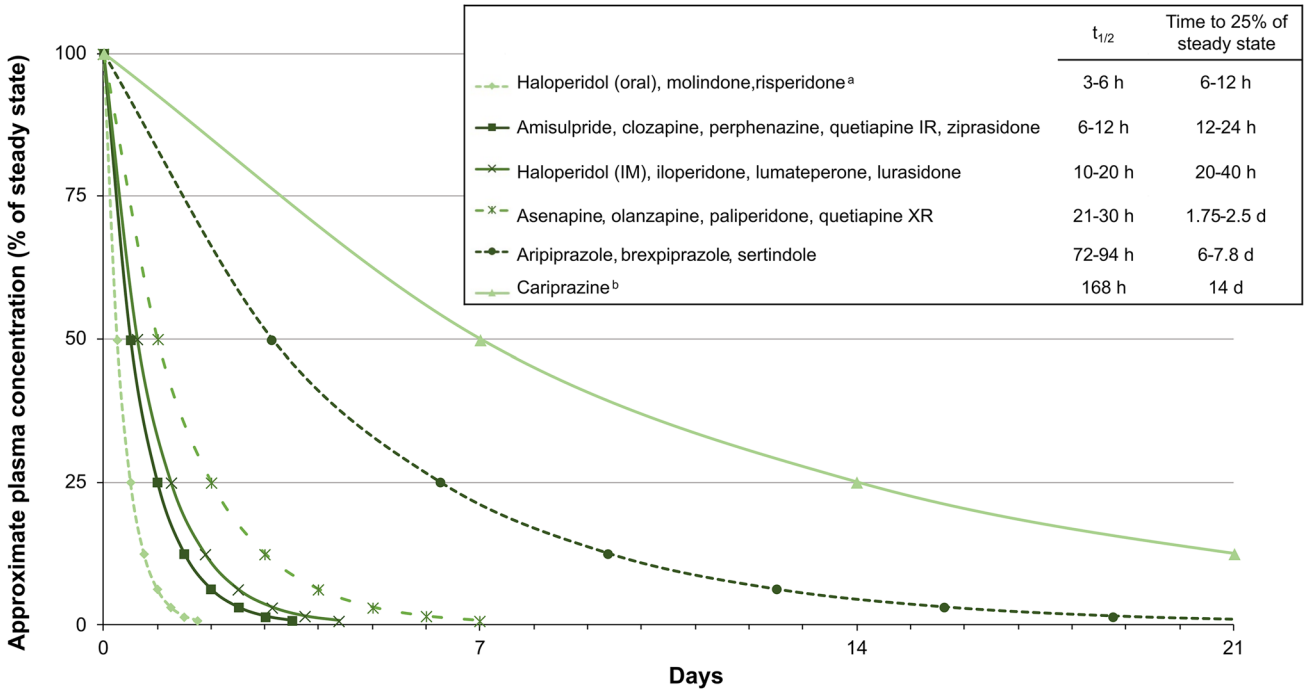


Fig. 2 Approximate reductions in antipsychotic plasma concentrations following abrupt discontinuation. *IM* intramuscular, *IR* immediate release, $t_{1/2}$ half-life, *XR* extended release. [a]The clinical activity of risperidone is achieved by the parent compound as well as its metabolite, 9-OH-risperidone (i.e., paliperidone), which has a 20-h $t_{1/2}$. [b]Effective half-life of total active moieties. Parent half-life of 2–4 days, desmethyl cariprazine 1- to 2-day half-life, and didesmethyl cariprazine 1- to 3-week half-life [62]. *Source*: Modified from Correll et al. 2010 [22]. Elimination half-life values are from Table 1

Together, these PK features can be used to guide the dosage, titration, and switching strategies aimed at optimizing efficacy while minimizing clinically relevant adverse events (AEs). Basic principles of PK and PD for prescribers are described further in Maxwell 2023 [64].

3 Pharmacodynamic Considerations

The characteristic feature of postsynaptic dopamine receptor blocking antipsychotics as a class is blocking the dopamine D_2 receptor, which reduces dopaminergic hyperactivity associated with psychosis, aggression, and mania. This target must be carefully tuned, as D_2 blockade also plays a role in regulating motor function, cognition, motivation, and prolactin levels. Additionally, SGAs and low-potency FGAs target α-adrenergic, histaminic, muscarinic, and serotonergic systems.

The effects of antipsychotics can often be anticipated on the basis of which receptors have similar or stronger affinity relative to D_2 receptor binding (Fig. 3). The binding profile of selected approved antipsychotics are reported via constant of inhibition (K_i), which represents the nanomolar concentration of drug needed to occupy 50% of a receptor type (Table 1); thus, a lower K_i indicates a stronger affinity for a receptor system. In addition to receptor occupancy, the intrinsic activity at the receptor as an agonist or partial agonist is also essential to predicting therapeutic and adverse effects. As partial dopamine agonists block the dopamine receptor but provide some agonist activity at the dopamine receptor, they may allow for increased dopamine activity in areas with dopaminergic hypoactivity and reduce the risk of motor adverse effects [22, 65]. To achieve the same level of functional therapeutic blockade, a full antagonist requires 60–75% dopamine occupancy, whereas a higher occupancy of 80–95% is needed for partial agonists to compensate for intrinsic activity [66–68].

The concentration of a drug needed for therapeutic D_2 blockade varies widely between treatments on the basis of affinity and intrinsic activity. At therapeutic dose levels that achieve antipsychotic efficacy, other receptor systems may also be blocked. This results in additional (sometimes adverse) effects (Online Feature Fig. S1). When a drug has a similar or stronger relative affinity for a receptor system (lower K_i) than the dopaminergic target, side effects associated with blocking this pathway are likely to occur. These effects are not always adverse, as blockade of serotonergic (5-HT_{1A}, 5-HT_{2A}, 5-HT_7) and muscarinic (M_1, M_4) receptors is associated with reduced neuromotor adverse effects of antipsychotics [40, 69]. As such, SGAs with a higher

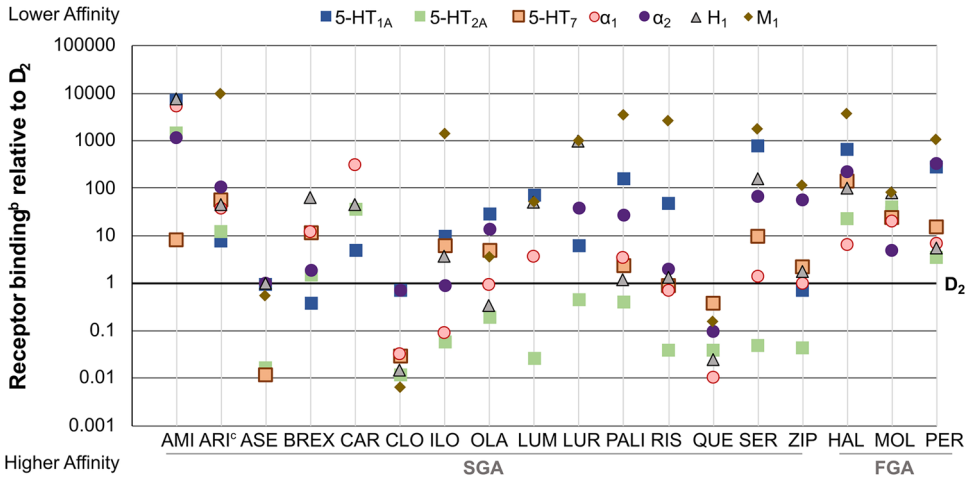


Fig. 3 Receptor binding profiles of antipsychotics relative to dopamine D_2 receptor affinity[a]. *AMI* amisulpride, *ARI* aripiprazole, *ASE* asenapine, *BREX* brexpiprazole, *CAR* cariprazine, *CLO* clozapine, *FGA* first-generation antipsychotic, *HAL* haloperidol, *ILO* iloperidone, *LUM* lumateperone, *LUR* lurasidone, *MOL* molindone, *OLA* olanzapine, *PALI* paliperidone, *PER* perphenazine, *QUE* quetiapine, *RIS* risperidone, *SGA* second-generation antipsychotic, *SER* sertindole, *ZIP* ziprasidone. [a]For each drug, the equilibrium constant for dopamine D_2 receptor affinity was set to 1. Data are presented in nM. [b]Partial agonism. *Source*: Modified from Correll et al. 2010 [22] with references and data from Table 1

affinity for 5-HT_{2A} receptors than D_2 have less frequent motor abnormalities and other adverse effects compared with FGAs, which predominantly block D_2 [22]. Additionally, 5-HT_{1A} antagonism and partial agonism, as well as 5-HT_7 antagonism, can have antianxiety and antidepressant effects [70, 71].

While antipsychotics that have a higher affinity for histaminergic and cholinergic receptors than for dopaminergic receptors (clozapine, olanzapine, quetiapine) have fewer motor disturbances, they are associated with sedation and weight gain. Antipsychotics with "loose" dopaminergic binding, such as clozapine and quetiapine, are prone to quick dissociation from dopamine receptors and allow endogenous dopamine to have frequent access to the receptors, minimizing risk of prolactin or neuromotor abnormalities [72]. Partial dopamine agonism may also minimize the risk of motor abnormalities and hyperprolactinemia [40, 73]. The specific dopamine target has an impact on efficacy; for example, the D_3 receptor targeted by cariprazine seems to be associated with improvement in positive, negative, and cognitive symptoms in schizophrenia [73]. Combination therapy can also be used to modulate risk of adverse effects, such as the FDA-approved combination olanzapine/samidorphan that reduces the risk of weight gain with olanzapine via opioid receptor antagonism by samidorphan [74–76].

4 Pharmacodynamic and Pharmacokinetic Implications of Switching Antipsychotics

Switching between antipsychotics with different PD and PK properties can result in rebound and withdrawal phenomena [77]. There are higher risks for rebound effects if the pre- and post-switch antipsychotics have a large variation in receptor binding affinities (PD rebound when switching from more to less antagonism or partial agonism) or in $t_{1/2}$ (PK rebound when switching from shorter to longer $t_{1/2}$ medications). Conversely, switching from antipsychotics with less antagonism to more antagonism or those with longer $t_{1/2}$ to shorter $t_{1/2}$ protect against rebound phenomena.

During PD rebound, a receptor that was blocked pre-switch and that is no longer targeted may lead to side effects that are the opposite effects of the receptor blockade, due to receptor upregulation and stimulation by the endogenous neurotransmitter. Dopaminergic rebound can also have profound effects with potential worsening or emergent psychosis, mania, agitation, or hyperkinetic motor disturbances (Online Feature Fig. S2) [77]. In the case of histaminergic or cholinergic rebound, the calming, attenuating effects of hypokinetic motor abnormalities are removed and can lead to increased insomnia, agitation, akathisia, Parkinsonism, or dyskinesia (Online Feature Fig. S2). Rebound effects are not observed when switching to a higher affinity antagonist, which will displace a lower affinity antagonist, regardless of the switch strategy between antipsychotics.

A variety of switching strategies may be employed to reduce withdrawal or rebound effects while switching

between antipsychotics (Fig. 4). Abrupt discontinuation of an antipsychotic can help to quickly reduce unwanted side effects of the previous drug but has a higher risk for withdrawal symptoms [78]. Similarly, abrupt initiation of an antipsychotic at the therapeutic dose or quick titration to the therapeutic dose can be associated with quicker resolution of symptoms but has the potential for more side effects than a gradual initiation [78].

A cross-titration schedule or plateau switch strategy involves co-administration of the two antipsychotics. This may be achieved via gradually discontinuing the initial antipsychotic, gradually initiating the new antipsychotic, or both. During delayed gradual cross-titration or plateau cross-titration, the new antipsychotic is initiated while the pre-switch antipsychotic is maintained at the pre-switch dose level to allow slow buildup of the post-switch antipsychotic, especially if the post-switch antipsychotic has a long $t_{1/2}$ or partial agonist activity. Cross-titration strategies may alleviate effects from rapid onset/discontinuation but may also increase the risk of compounding side effects that are shared by both drugs [78]. Therefore, plateau switches should only be performed when the post-switch antipsychotic does not have PD characteristics and side effects similar to the pre-switch antipsychotic. Conversely, when antipsychotics have similar PD, PK, and side effect profiles, then a simple cross-titration can be used, with proportional dose decrease of the pre-switch antipsychotic and concurrent proportional dose increase of the post-switch antipsychotic.

5 Systematic Literature Review

5.1 Methods

A systematic literature review was conducted to investigate the switching methods implemented in clinical trials of antipsychotics in schizophrenia and the clinical outcomes and attitudes toward switching as reflected in review articles since the publication of the 2010 review [22]. The literature search was restricted to studies beginning in 2010 to avoid bias toward older literature or antipsychotics no longer in routine use. The aim of this review was to reflect the modern paradigm for switch strategies that is most relevant for clinicians today, rather than document the historical evolution of switch strategies. The review was not prospectively registered and did not have a formal protocol.

5.1.1 Search Criteria and Strategy

The search included randomized controlled trials (RCTs), open-label switch studies, meta-analyses, and review articles of switching oral antipsychotics in patients with schizophrenia or schizoaffective disorder. Records were excluded if they were abstract only, did not mention switching, did not discuss antipsychotics, enrolled patients with a disease other than schizophrenia or schizoaffective disorder, or were focused on non-FDA-approved treatments, antipsychotic polypharmacy, or long-acting injectable antipsychotics

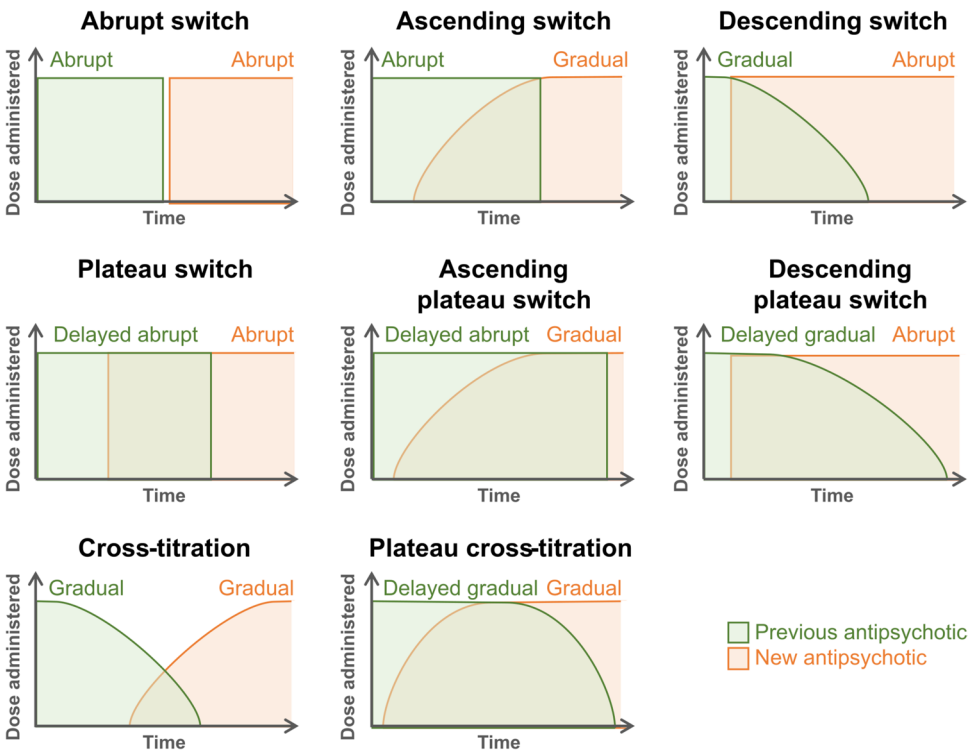


Fig. 4 Different antipsychotic switching strategies

(LAIs, as LAIs have a built-in slow antipsychotic taper that have been reviewed before [53]). Only studies published in English were included. Studies were initially grouped for synthesis as randomized/open-label studies or review/meta-analyses. Trials were further grouped by the antipsychotics investigated.

Keywords for the literature search were (*schizophr* OR schizoaff**) AND (*antipsychotic**) AND (*switch**). MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and PubMed (non-MEDLINE) were searched for English articles published between June 2010 and 1 April 2024. The final searches were conducted 9 April 2024 (Embase and CENTRAL) and 13 May 2024 (MEDLINE and PubMed).

5.1.2 Data Collection

The database searches were conducted together by two researchers (B.G. and S.E. in Acknowledgments). Search outputs were independently screened by title and abstract per the inclusion criteria and manually sorted by the two researchers, followed by collaborative discussion to resolve any discrepancies regarding inclusion. Full-text articles were reviewed independently and no automated tools were used.

Excel spreadsheets were used to collect initial outcomes of interest by B.G., including article/study type, drugs investigated, the switch strategies implemented, and the main conclusion(s) of the article regarding switching. Initial outcomes were verified with the literature by an independent reviewer. Additional outcomes for trial articles were extracted by S.E. including study duration, enrollment, primary efficacy outcome, discontinuation (all cause, inefficacy, adverse event), and rates of commonly reported adverse events. Inferential statistics for efficacy and safety were extracted if reported and accuracy of the second extraction was confirmed by an independent reviewer. There was wide heterogeneity in reported outcomes and missing outcomes were left blank for individual reports. No further assumptions were made about missing data.

5.1.3 Data Synthesis

As this was a qualitative review, risk of bias and causes of heterogeneity between studies were not assessed. Due to the wide variation in available results, data were presented qualitatively with no formal data synthesis and no comparison between studies. No data conversions or statistical calculations were performed, and outputs for all outcomes extracted from individual trial articles are reported in Online Feature Table S1. In text, the switching strategies implemented per antipsychotic (abrupt, cross-titration, etc.) are reported, with an emphasis on trials that compared safety and/or efficacy for multiple switch strategies. For studies without comparisons of switch methods, a brief summary is included to capture the general outcome of the switch strategy implemented in the study. Inferential statistics are reported throughout. Studies that did not report a switch strategy or specified that the strategy was up to the investigator's discretion are included in our discussion for context. There was no formal assessment of study heterogeneity, reporting bias, certainty of the evidence, or sensitivity analyses. Figures were created using Microsoft PowerPoint.

5.2 Search Results

Of the 579 records that were identified ($n = 259$ MEDLINE, $n = 280$ Embase or CENTRAL, and $n = 40$ PubMed non-MEDLINE), 86 duplicates were removed (Fig. 5). During initial screening, 38 citations outside the date range or not in English and 22 that were abstract only were removed. In total, 401 results were excluded on the basis of title and abstract content (Fig. 5), the majority of which were not switching studies or focused on LAI antipsychotics. The resultant full text was reviewed for a total of 92 articles, 12 of which were further excluded from this review on the basis of content. Of 80 articles included, 58 were randomized and non-randomized studies, with 9 of these containing 1 or more antipsychotics of interest; 22 were reviews or meta-analyses. For many of the trials included in this review, data comparing between switching methods were not available; however, the switching strategies used in these studies are reported below as an indicator of the current practices and naturalistic outcomes.

The majority of articles published during the search period discussed switching to a specific antipsychotic and are summarized in the Individual Antipsychotics section below and in Online Feature Table S1. While these studies provide safety and efficacy outcomes using various switch strategies, few studies provided direct or statistical comparisons between switch strategies. The antipsychotics investigated during this period were: aripiprazole (studies = 18); paliperidone, ziprasidone, olanzapine, and risperidone (studies = 7 each); brexpiprazole, clozapine, and lurasidone (studies = 4 each); amisulpride, (studies = 3 each); iloperidone and quetiapine (studies = 2); and asenapine and lumateperone (1 study each). Of the studies identified in this review reporting switch strategy, the majority used some type of a cross-titration method (studies = 39; 69.6%), while abrupt switching (studies = 10; 17.9%) was rarely used. Comparisons between switch strategies were reported for four independent trials (one trial each for aripiprazole, clozapine, iloperidone, and ziprasidone; 666 patients across the four trials). One iloperidone trial was reported in two separate articles and is included as only one study in this review.

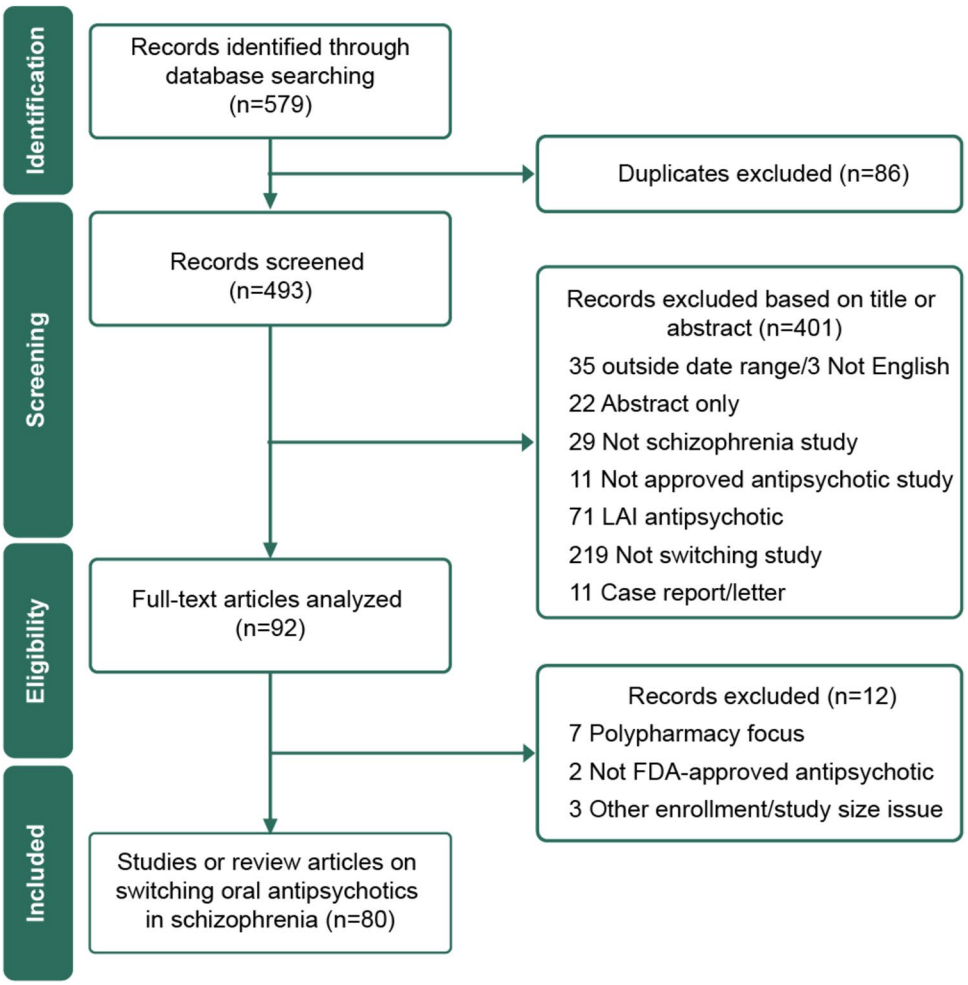


Fig. 5 PRISMA diagram. *FDA* US Food and Drug Administration, *LAI* long-acting injectable

5.3 Impact of Continuing versus Switching Treatment

In a large meta-analysis of 101 RCTs including 13,988 adults with schizophrenia spectrum disorders, continuing treatment with the standard dosage of the current antipsychotic had similar tolerability profiles and similar efficacy as switching antipsychotics [79]. A 2023 meta-analysis investigated the impact of switching antipsychotics in people with schizophrenia and early nonresponse In 2 pooled analyses of 149 patients (3 datasets) who switched antipsychotics or continued treatment and 51 patients (2 datasets) who either switched antipsychotics or augmented treatment; there were no significant standardized mean difference in efficacy between groups [80]. In 2012, an instrument was developed to assess switching between antipsychotics using the Clinical Global Impression (CGI) scale: the CGI-switch scale [81]. However, the CGI-switch scale has not been adopted in subsequent studies.

5.4 Reasons for and Frequency of Switching

In a survey of 190 clinicians, the most commonly indicated reason for switching antipsychotics was poor efficacy (68%) followed by side effects (45%). Unsurprisingly, the most common side effects reported as reasons for switches were weight gain (8.1%), movement disorders (7.7%), and hyperprolactinemia (7.0%) [82]. A post hoc analysis identifying predictors of antipsychotic switching using a multivariate model supports these observations in 191 patients who switched versus 304 people who remained on treatment during a 1-year trial. The only two early treatment variables that predicted switching antipsychotics were worsening of Positive and Negative Syndrome Scale (PANSS) anxiety or depression subscale scores ($P = 0.0320$) or worsening of Barnes Akathisia Rating Scale (BARS) akathisia score ($P = 0.0398$) in the first 2 weeks [83]. A narrative review on strategies for treating acute-phase schizophrenia suggested that switching antipsychotics for lack of efficacy should be considered if the treatment dose has been increased to the upper tolerable limit and there is nonresponse after 2 weeks

of treatment [84], although evidence on next antipsychotic treatment strategies after early nonresponse is slim [80].

A narrative review discussed that a notable motivation for switching antipsychotics is managing antipsychotic-related weight gain, obesity, and metabolic syndrome in patients experiencing cardiometabolic burden by switching to an antipsychotic with lower propensity for weight gain [85]. A meta-analysis including 636 people with schizophrenia or schizoaffective disorder switching medication due to antipsychotic-induced weight or metabolic issues found reductions in weight or body mass index when switching from olanzapine to quetiapine or aripiprazole, but reported no significant difference between utilized switch strategies in weight gain, mental state, or global state [86]. Another meta-analysis of 59 studies including 8554 patients with serious mental illness investigated a variety of cardiometabolic outcomes, concluding that the preliminary evidence supports switching to aripiprazole or ziprasidone to improve cardiometabolic risk [87]. A 2013 literature review to develop evidence-based recommendations to reduce adverse events during antipsychotic switching supported that elective switching to antipsychotics with lower metabolic risk can have tolerability advantages without risking deterioration in efficacy [88]. Switching to address other tolerability issues such as extrapyramidal symptoms or hyperprolactinemia was also supported, with a gradual discontinuation of the initial medication to limit adverse effects early during the switch [88].

In clinical practice, switching antipsychotic therapy in patients with schizophrenia is common [81, 89]. In a Medicaid claims study of 13,007 people with schizophrenia starting oral atypical antipsychotics, 16.3% switched antipsychotics within the first year [90]. Switching rates were similar among the four most commonly prescribed antipsychotics (quetiapine, 525/3335 [15.7%]; risperidone, 501/3222 [15.6%]; olanzapine, 401/2557 [15.7%]; aripiprazole, 277/1779 [15.6%]), and 3.2% of patients added another antipsychotic to their first prescription [90].

5.5 Comparing Switch Methods

When choosing an abrupt or gradual method of switching, clinicians should consider whether a patient is experiencing acute or stable schizophrenia. A meta-analysis compared rapid versus slow initiation of a new antipsychotic in 10 studies of patients switching antipsychotics and in 1 study of 51 patients who were drug free for ≥ 3 weeks. There was no difference between the methods for all-cause study discontinuation in acutely exacerbated patients with schizophrenia (7 studies; rapid initiation $n = 396$, slow initiation $n = 344$; risk ratio [RR], 0.80 [95% CI 0.58–1.13]; test for overall effect $Z = 1.27$, $P = 0.2$) but reported a significant difference in favor of the slow initiation group in patients with stable schizophrenia (three studies; rapid initiation $n = 386$, slow initiation $n = 391$; risk ratio, 1.45 [95% CI, 1.05–2.00]; test for overall effect $Z = 2.26$, $P = 0.02$) [91]. The analysis concluded that rapid antipsychotic initiation may be beneficial in acute schizophrenia due to more rapid effects and better tolerability, while a slower initiation strategy may be safer in patients with stable schizophrenia [91].

Three reviews presented data supporting switching with quicker discontinuation of the previous antipsychotic. A pooled analysis in 600 patients with acute exacerbation of schizophrenia switched to lurasidone via either abrupt antipsychotic discontinuation ($n = 410$) or gradual discontinuation ($n = 190$) indicated that switch strategy did not have a significant impact on efficacy, measured by change in PANSS Total score ($P = 0.839$) or Clinical Global Impressions-Severity (CGI-S) score ($P = 0.941$) [92]. A 2017 meta-analysis of nine RCTs in schizophrenia found no significant differences between immediate ($n = 714$) or gradual discontinuation ($n = 702$) of prior antipsychotic for study discontinuation (RR all cause 1.1; RR inefficacy 1.14; RR intolerability 1.08), efficacy (PANSS/Brief Psychiatric Rating Scale [BPRS] total standardized mean difference [SMD] −0.03; CGI-S SMD −0.02), extrapyramidal symptom scales (Simpson–Angus Scale [SAS] SMD 0.12; BARS SMD 0.16; Abnormal Involuntary Movement Scale [AIMS] SMD 0.27) or treatment emergent adverse events (TEAEs) [93]. A similar meta-analysis investigated five studies with either a wait to discontinue the original antipsychotic strategy ($n = 202$) or a no wait to discontinue the original antipsychotic strategy ($n = 208$) and found no significant differences between groups for study discontinuation (RR all cause 1.27; RR inefficacy 1.19; RR intolerability 1.46), efficacy (PANSS/BPRS total SMD −0.08; CGI-S SMD 0.05), extrapyramidal symptom scales (SAS SMD −0.16; BARS SMD −0.01; AIMS SMD −0.18) or TEAEs [94]. In both these studies, the authors concluded that faster switching may be preferred, as slower switching could lead to increased risk of antipsychotic polypharmacy [93, 94].

However, a meta-analysis including four RCTs found that wait-and-gradual discontinuation of prior antipsychotics ($n = 176$ patients) was preferable to immediate discontinuation ($n = 175$ patients) for all-cause study discontinuation (RR 1.58 [95% CI 1.15–2.17]; test for overall effect $Z = 2.80$, $P = 0.005$) [95].

A narrative review investigated switching to D_2 partial agonists aripiprazole, brexpiprazole, or cariprazine [96]. While the most common strategy was cross-titration, there was a wide variation in switching protocols, and the finding could not generate a strong evidence-based recommendation for a preferable switching strategy to these drugs [96]. One systematic review specifically reviewed the evidence on switching antipsychotics in schizoaffective disorder, summarizing evidence from 14 studies [97]. However, the authors flagged an overall lack of evidence on the topic, concluding

that antipsychotic switching is appropriate for tolerability issues, and that a plateau cross-titration was likely preferable for stabilized patients, with abrupt switching being reserved for specific urgent needs [97].

5.6 Medication Continuation after Switching

In a 2024 retrospective database study of 31,956 people with schizophrenia, switching to a new oral antipsychotic and being discharged from an inpatient facility, the 30-day medication continuation rate was 25.4% (95% CI 24.3–26.5), with a mean time to discontinuation of 62.0 days (95% CI 59.8–64.3) [98]. An electronic health record survey of 577 patients with schizophrenia reported a 53.6% adherence rate (≥ 80% proportion of days covered) to any antipsychotic in the first 180 days; adherence was numerically lower for patients who switched antipsychotics (50.8%) than those who remained on the same antipsychotic (63.9%) [99]. Breakdown by antipsychotic was not reported, and statistical analyses of switching on adherence included patients with other disorders than schizophrenia [99].

5.7 Results for Individual Antipsychotics

For articles investigating switching to specific antipsychotics, the general switch strategy, study enrollment, primary efficacy outcome, discontinuation (all cause, due to inefficacy, due to AEs), and AEs of interest are reported in Online Feature Table S1. Conclusions drawn from these articles about switching are summarized by agent below. In total, 24 of these studies (including a total of 3440 patients) reported statistical comparisons for outcomes between switching groups (e.g., comparing switch strategy/speed, switch versus continuing on current antipsychotic, switch from various prior treatments to 1 new treatment).

5.7.1 Amisulpride

Three studies used a cross-titration method to switch to amisulpride, with a 7-day discontinuation of previous antipsychotic [100–102]. This switch strategy was generally safe, but these studies did not include a detailed discussion on the potential impacts of the switch strategy [100–102].

5.7.2 Aripiprazole

A total of 18 articles focused on switching to aripiprazole. Cross-titration was the most common method when switching to aripiprazole from other antipsychotics [103–114]. The majority of the studies did not compare switch strategies, but rather focused on changes in AE profile upon switching to aripiprazole, such as changes in cardiometabolic profile [103, 104, 111, 113, 115], prolactin levels [106, 114, 116], and cognition [112]. One study left the switching strategy up to the clinical judgment of the investigator [117] and two studies only specified a gradual tapering of previous antipsychotic [115, 116].

In a randomized study in which aripiprazole was newly administered for 2 weeks followed by a fast (1 week, $n = 38$) or slow tapering (4 weeks, $n = 41$) off of the previous antipsychotic, there was no significant difference between efficacy outcomes (PANSS total or subscales, CGI-S, CGI-Global improvement [CGI-I]) between groups. Adverse effects and discontinuations were also comparable between the methods [105].

Three articles reported guidelines and consensus statements for switching to aripiprazole, recommending a three-step plateau-cross-titration strategy, including titrating aripiprazole up to a therapeutic dose, at least a 14-day overlap with the previous antipsychotic, followed by a tapering of the previous antipsychotic [118–120].

5.7.3 Asenapine

One pooled analysis of two randomized double-blind studies assessed switching to asenapine over 4 weeks with abrupt or slow discontinuation based on investigator's discretion [121]. In patients with stable schizophrenia and persistent negative symptoms who were switched to asenapine abruptly (≤ 3-day period), a similar discontinuation rate (81/209 [38.8%]) was found as that in those switched by slow tapering of > 3 days (62/170 [36.5%]). A similar treatment-emergent AE (TEAE) rate was found during the first 28 days (48.8% abrupt versus 52.4% slow taper), but over the course of the full treatment period more patients who switched gradually experienced TEAEs (82.9%) than those treated with abrupt switching (71.8%) [121].

5.7.4 Brexpiprazole

Four studies investigated switching to brexpiprazole. One study investigated switching to brexpiprazole via a plateau cross-titration (2-week titration onto brexpiprazole followed by a gradual 6-week decrease of prior antipsychotics olanzapine, risperidone, or paliperidone) [122]. A long-term study that used a cross-titration strategy over 4 weeks [123] noted that a longer tapering period than the 2 weeks used in this study may be beneficial but did not otherwise present data related to the switch strategy [123]. A retrospective analysis of real-world hospital data investigated factors impacting a successful switch to brexpiprazole, with the switch strategy at the investigator's discretion [124].

A RCT investigated tapering a previous antipsychotic and titration of brexpiprazole in 404 patients with schizophrenia,

allowing a 1–4-week switch to brexpiprazole on the basis of investigator judgment [125]. There were lower rates of TEAEs (44%) in the group of patients with longer tapering periods (22–33 days, $n = 291$) compared with the patients who were switched over shorter periods (TEAEs in 62.5–84.2% for groups switched over ≤ 21 days, $n = 113$). Most of the 292 patients who completed 8 weeks of treatment were switched over 22–33 days (80.1%) [125].

5.7.5 Clozapine

Four studies investigated switching to clozapine. Specific switch strategies were not reported for a three-stage switching study (OPTiMiSE) to develop a treatment algorithm for first-episode schizophrenia [126, 127] or a Japanese retrospective analysis of real-world hospital treatment in patients with treatment-resistant schizophrenia or schizoaffective disorder [128].

In a double-blind RCT examining abrupt ($n = 15$) or cross-titration ($n = 18$) switch to clozapine with a 2-week discontinuation of the pre-switch antipsychotic, there were no significant differences between the methods in terms of efficacy (BPRS total and subscores, CGI-S) or tolerability (Calgary Depression Scale for Schizophrenia, AIMS, SAS, BARS, UKU side effect rating scales) [129]. Another small randomized trial investigated switching to clozapine ($n = 15$) or continuing the current antipsychotic ($n = 16$) in patients with schizophrenia and co-occurring cannabis use disorder using a cross-titration method over 4 weeks. While switching to clozapine reduced cannabis use, there were no differences in schizophrenia symptoms (BPRS total and subscales, Scale for the Assessment of Negative Symptoms) or functioning between those switching or continuing prior antipsychotic treatment [130].

5.7.6 Iloperidone

Two articles reported results from an open-label study comparing an abrupt and a gradual discontinuation for switching to iloperidone (titrated up over 4 days) [131, 132]. In the 12-week open-label randomized trial of 500 people with schizophrenia, there were subtle clinical differences during the first 2 weeks for patients switched immediately to iloperidone ($n = 260$) or gradually tapering prior antipsychotic over 2 weeks ($n = 240$) [132]. However, at week 12, Integrated CGI-Change (I-CGI-C) response rates were similar regardless of the switch approach (12–16 mg dose group; immediate 85.0%; gradual 76.2%: 20–24 mg dose group; immediate 83.8%; gradual 86.2%) [132]. Similarly, CGI change from baseline to week 12 was similar between groups (LSMD between switch groups: I-CGI-C, −0.012; Integrated-CGI-S, −0.008) [131]. There was a greater proportion of discontinuations due to AEs over 12 weeks with the abrupt switching method (15.0% in immediate-switch group versus 10.4% in gradual-switch group) that was driven by the AE of dizziness, indicating that a cross-titration method may be beneficial for patients switching from an antipsychotic that blocks α1 receptors [132].

5.7.7 Lumateperone

One open-label study evaluated short-term safety of lumateperone, started abruptly at the target dose, in outpatients with stable schizophrenia who were switched from previous antipsychotics, discontinued according to investigator's discretion [133]. There was maintenance of PANSS-based symptoms and favorable safety, which worsened and trended back toward baseline within 2 weeks of resuming another antipsychotic treatment [133].

5.7.8 Lurasidone

Four studies investigated switching to lurasidone. Two publications reported results of an open-label study switching to lurasidone using a cross-titration approach, with overall improvements in health-related quality of life with lurasidone [134, 135]. An open-label study evaluated switching patients abruptly from risperidone to lurasidone, but the potential impact of switch strategy was not discussed [136]. The final study reported the open-label extension of a switch study, however, no comparisons between the original switching groups were made [137].

5.7.9 Olanzapine

Seven studies investigated switching to olanzapine. Two studies examined switching to olanzapine using a cross-titration method, with switching as safe as remaining on previous treatment in one study [102] and safety not reported in the other trial [112]. Two studies investigated a switch according to investigator's discretion [138, 139], and a retrospective analysis of real-world hospital data and investigation of switching between risperidone and olanzapine did not report the specific switch strategy [128, 140].

A pooled analysis of randomized trials assessed switching to olanzapine or asenapine in patients with stable schizophrenia and persistent negative symptoms who were tapered off the prior antipsychotic at variable rates, up to 28 days. Patients switched abruptly (≤ 3-day period) to olanzapine had a numerically higher discontinuation rate (58/195 [29.7%]) than those switched by slow tapering up to 28 days (33/155 [21.3%]) and a higher proportion of TEAEs during the first 28 days (50.3% abrupt versus 44.5% slow taper) [121]. However, over the course of the full treatment period, more patients who switched to olanzapine experienced a

TEAE with slow taper (80.6%) versus rapid switch (70.3%) [121].

A review article focusing on AEs associated with switching from olanzapine to other antipsychotics asserted that switching from olanzapine to an antipsychotic with a longer $t_{1/2}$ was associated with rebound psychosis and withdrawal-emergent dyskinesia due to reduced antagonism of functional receptors; however, rates of those events were not reported [89]. In this case, a longer switching process would be more suitable when switching to an antipsychotic with a longer $t_{1/2}$, such as aripiprazole, compared with switching to ziprasidone, which has a lower risk of AEs commonly reported with olanzapine [89].

5.7.10 Paliperidone/Paliperidone Extended Release (ER)

Seven studies investigated switching to paliperidone, none of which stratified results by switching method. Four studies switched patients to flexibly dosed paliperidone ER via an abrupt or 2–4-week tapered discontinuation of previous antipsychotic [141–144]. One study did not report the switching method [145]. Two studies examined switching from risperidone to paliperidone in elderly patients, with risperidone discontinued abruptly or tapered within 1 week [146, 147].

5.7.11 Quetiapine/Quetiapine ER

Two studies investigated switching to quetiapine but did not compare between switch strategies. One study evaluated switching to quetiapine ER via a cross-titration method over 4 days [148] and a relapse-prevention long-term trial switched based on symptoms and tolerability [149].

5.7.12 Risperidone

Seven studies investigated switching to risperidone. Studies that did not compare between switch strategies included two with a switch at investigator's discretion [138, 139] and three via cross-titration for patients with unsuccessful aripiprazole treatment [150], agitation-exhibiting patients discontinuing intramuscular haloperidol or adjunctive clonazepam over 3 days [151], and switching from olanzapine over 8 weeks [152]. One study investigating switching between olanzapine and risperidone did not report the specific switch strategy [140].

In another study, hospitalized patients currently receiving high-potency FGAs (haloperidol $n = 60$, fluphenazine $n = 20$) went through a 3-day washout period in a controlled hospital environment before switching to risperidone with dose titration based on clinical state [153]. These patients experienced a worsening clinical state for 14 days after the rapid washout period (numerical increase in mean PANSS total score from 68.4 to 78.0), consistent with a dopamine rebound, but eventually reached a stable state by day 56 with significant improvements from baseline (PANSS total score 66.9; $P < 0.0005$) [153].

5.7.13 Ziprasidone

All seven studies investigating switching to ziprasidone used a cross-titration strategy [103, 115, 154–158], ranging from as little as 4 days overlap [156] to 36 weeks [158]. Five of these studies did not include an emphasis on switch strategy [103, 115, 154–156].

One small randomized double-blind study compared switching to ziprasidone ($n = 22$) versus reducing the dose of a current FGA ($n = 22$) on negative symptoms in hospitalized patients with treatment-resistant schizophrenia, using a prolonged 12- to 36-week switching scheme to reduce the risk of withdrawal psychosis [158]. While ziprasidone had significantly fewer extrapyramidal symptoms ($P < 0.05$), there were numerically higher rates of relapse (45.8% ziprasidone versus 20.8% FGA) and treatment failure (25.0% ziprasidone versus 16.7% FGA) with the ziprasidone group than with the FGA dose-reduction group [158]. The authors hypothesized that the worse results with ziprasidone may be due to twice-daily dosing and the fast kinetics of the drug (dopamine $D_{2/3}$ receptor occupancy $t_{1/2}$ of 8.3 h [159]), which could have led to low receptor occupancy [158].

A small open-label study switching from FGAs to ziprasidone compared an abrupt discontinuation method ($n = 18$) with either a fast-taper (50% dosage of previous antipsychotic for 7 days, $n = 18$) or slow-taper (100% dosage of previous antipsychotic on days 1 and 2 and 50% on days 3–7, $n = 18$) approach [157]. There were potential efficacy advantages to a slow-taper approach early in the study, with significant ($P < 0.05$) improvements with slow taper compared with abrupt discontinuation at weeks 1 and 2 for Brief Psychiatric Rating Scale (BPRS) scores (week 1, −6.775 versus −0.981; week 2, − 6.561 versus −0.624) and CGI-S scores (week 1, −0.197 versus 0.175; week 2, −0.505 versus 0.241); slow taper was also superior to fast taper at week 1 for BPRS scores (− 6.775 versus − 2.258; $P = 0.01$). However, BPRS and CGI-S scores were not significantly different between the three approaches at the end of the 6-week study [157].

5.7.14 Other antipsychotics

No published articles were identified that were specific to switching to cariprazine, haloperidol, molindone, perphenazine, or sertindole in the search period.

6 Discussion

Switching antipsychotics is highly common in the treatment of schizophrenia. However, empirical evidence comparing different switch strategies in detail, with their relative success versus failure rates and underlying reasons, is scarce. Even when studies could have performed such analyses, they were rarely conducted or published. Additionally, as rebound and withdrawal symptoms can be mitigated or masked by the addition of sedating medications, lack of disclosure of the frequency of such strategies needed in each switch strategy arm complicates the interpretability of the results. Finally, studies are often sponsored by the manufacturer of the antipsychotic that the patients were switched to. This may influence the design of the switch studies in a way that reduces the contrast between successful and unsuccessful switch strategies, attempting to show that the new medication can be helpful, no matter how patients receive it.

Nevertheless, results from this systematic review indicate that, except for abrupt antipsychotic switching in patients with acutely exacerbated schizophrenia for whom speed is of the essence, gradual antipsychotic switching in patients with stable schizophrenia has been preferred and represents good clinical practice. Hence, most trials investigating antipsychotic switching in the treatment of schizophrenia in the modern treatment landscape (since 2010) have used a gradual cross-titration approach. Results of this systematic review indicate that while several articles reported similar clinical outcomes with abrupt and gradual switching strategies, more gradual switching strategies are generally considered to be safer to use to reduce rebound phenomena [85, 88, 89, 97]. Abrupt switching may be beneficial in patients with acute schizophrenia in need of quick efficacy improvements, but slower switching strategies are more appropriate in patients with stable schizophrenia who are switching due to adverse effects [91, 95, 97, 119]. In such acute settings, sedating co-medications are used frequently, which may have contributed to the lack of relevant rebound phenomena in these studies. Alternatively, in agitated and acutely psychotic patients, rebound phenomena may not be as readily observable compared with a more stable baseline in outpatient switch studies.

Applying knowledge of the PK and PD properties of antipsychotics can help inform switch strategies between oral antipsychotics. As reviewed, antipsychotics have different PK characteristics related to their $t_{1/2}$. When switching from a shorter $t_{1/2}$ antipsychotic to an antipsychotic with a considerably longer $t_{1/2}$, delayed discontinuation or slow discontinuation of the pre-switch antipsychotic is advisable. This cautionary switch should allow sufficient time for the post-switch antipsychotic to reach therapeutic blood levels before the pre-switch antipsychotic is withdrawn or has already reached subtherapeutic blood levels. Antipsychotics also have different PD characteristics, such as potent D_2-blocking FGAs, SGA "-dones" (with tight 5-HT_{2A} and D_2 binding), SGA "-pines" (with relevant antihistaminergic and anticholinergic effects), SGA "-pips" (with partial D_2 agonism and little/no antihistaminergic and anticholinergic effects), and lumateperone (with tight 5-HT_{2A} and moderate postsynaptic D_2 occupancy and little/no antihistaminergic and anticholinergic effects). Switching within each of these antipsychotic subgroups with comparable PK and PD features can be done relatively easily with a simple cross-titration (i.e., switching "same to same"). However, switching between members of the different antipsychotic subgroups should account for differences in these characteristics when switching from an antipsychotic agent with considerably stronger antagonism at dopamine, histamine, and acetylcholine receptors to an antipsychotic with much weaker antagonism or partial agonism at these receptors. This PD-informed switching approach may avoid potential worsening of symptoms and/or emergence of rebound/withdrawal adverse effects [77]. Of note, the exact same caution will need to be applied when switching to novel antipsychotic agents that do not antagonize post-synaptic dopamine, histamine, or cholinergic receptors, such as muscarinic receptor agonists, positive allosteric modulators, or trace-amine-associated receptor agonists [45, 160–164].

Several limitations of this review need to be taken into consideration when interpreting the results. First, there was wide heterogeneity in study designs. The motivations for conducting the switch trials and corresponding primary endpoints (safety, efficacy, medication satisfaction) were broad, with study types including RCTs, open-label extension studies, post hoc analyses, and real-world data analyses. Sample sizes ranged from small reports of outcomes in 9 patients to a large open-label study of 1693 patients. Despite the importance and frequency of antipsychotic switching and despite ≥ 8 different clinical switching strategies being available, surprisingly few randomized studies have specifically investigated outcomes of different antipsychotic switch strategies, with only four studies during the search period comparing specific antipsychotic switch strategies directly. Additionally, while the search method was developed to maximize the identification of all appropriate articles, it is possible that articles of interest were missed, including those not published in English. Limitations to the interpretation of these studies include that they were often conducted in controlled settings not reflecting real-world conditions, rescue strategies (e.g., benzodiazepine use and use of other AE-mitigating strategies) were almost never detailed, and polarized strategies were not compared (i.e., abrupt switch without rescue medications versus plateau cross-titration). Moreover, in studies when different switch strategies were

employed clinically, surprisingly few studies conducted post hoc analyses to explore potential merits or difficulties associated with different switch techniques. Issues related to differences in patient, illness, and antipsychotic, as well as co-medication characteristics, were also unfortunately not commonly explored. Furthermore, when antipsychotic switch strategy groups were compared, this was done without an attempt to identify patient or treatment characteristics (dose, co-medications) that would influence the outcome related to the switch strategy. The antipsychotic switch studies reviewed here focused on symptomatic efficacy and adverse effect outcomes, but relevant patient-reported outcomes and measures of functioning and quality of life were almost never reported. Finally, data on switching FGAs and older SGAs were uncommon in the literature, and switch studies to a member of the new muscarinic activator class were missing, due to the restricted literature search covering only 2010–2024.

7 Conclusions

Antipsychotic switching is common, clinically relevant, and also complex. This updated review of the PD and PK profiles of available antipsychotics may assist clinicians in tailoring switch strategies to individual combinations of pre-switch and post-switch antipsychotics as well as patient needs. In general, gradual switching is considered preferred in patients with stable schizophrenia and is the most commonly utilized approach in clinical trials to minimize the potential risk of rebound and withdrawal phenomena, due to differences in pharmacodynamic and/or pharmacokinetic characteristics of the pre- and post-switch antipsychotic. However, future research with existing and emerging antipsychotics should focus on comparing different switch strategies and exploring medication, patient, and illness correlates of more successful and less successful antipsychotic switches, and also include patient-reported outcomes and measures of functioning and quality of life.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40263-025-01206-3.

Acknowledgements Medical writing support, including conducting the systematic literature review, was provided by Brittany Gifford, PharmD, and Sarah Engelberth, PhD, and Adam Ruth, PhD, of Nucleus Global, an Inizio company, funded by Intra-Cellular Therapies, a Johnson & Johnson company.

Declarations

Funding Open Access funding enabled and organized by Projekt DEAL. The open access fee was funded by the German DEAL agreement. Intra-Cellular Therapies, Inc., a Johnson & Johnson company, funded this study through an unrestricted educational grant. The sponsor had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Conflicts of Interest C.U. Correll has been a consultant and/or advisor to or has received honoraria from AbbVie, Acadia, Adock Ingram, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer-Ingelheim, Bristol-Meyers Squibb, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Delpor, Denovo, Eli Lilly, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Jamjoom Pharma, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedInCell, MedLink, Merck, Mindpax, Mitsubishi Tanabe Pharma, Maplight, Mylan, Neumora Therapeutics, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Sage, Saladax, Sanofi, Seqirus, SK Life Science, Sumitomo Pharma America, Sunovion, Sun Pharma, Supernus, Tabuk, Takeda, Teva, Terran, Tolmar, Vertex, Viatris, and Xenon Pharmaceuticals. He provided expert testimony for Janssen, Lundbeck, and Otsuka. He served on a Data Safety Monitoring Board for Compass Pathways, Denovo, IntraCellular Therapies, Lundbeck, Relmada, Reviva, Rovi, Supernus, and Teva. He has received grant support from Boehringer-Ingelheim, Janssen, and Takeda. He received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, Kuleon Biosciences, LB Pharma, Medlink, Mindpax, Quantic, Terran.

Availability of Data and Material Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Code Availability Not applicable.

Author Contributions Christoph U. Correll was involved in manuscript conception and design; read, critically reviewed, and revised the work; approved the final submitted manuscript, and agrees to be accountable for the work.

References

1. Kahn RS, Sommer IE, Murray RM, et al. Schizophrenia. Nat Rev Dis Primers. 2015;1:15067. https://doi.org/10.1038/nrdp.2015.67.

2. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. 2018;392:1789–858. https://doi.org/10.1016/s0140-6736(18)32279-7.
3. Charlson FJ, Ferrari AJ, Santomauro DF, et al. Global epidemiology and burden of schizophrenia: findings from the global burden of disease study 2016. Schizophr Bull. 2018;44:1195–203. https://doi.org/10.1093/schbul/sby058.
4. American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia. Washington, DC: American Psychiatric Association; 2021.
5. Solmi M, Seitidis G, Mavridis D, et al. Incidence, prevalence, and global burden of schizophrenia-data, with critical appraisal, from the global burden of disease (GBD). Mol Psychiatry. 2019;2023:1–9. https://doi.org/10.1038/s41380-023-02138-4.
6. Correll CU, Solmi M, Croatto G, et al. Mortality in people with schizophrenia: a systematic review and meta-analysis of relative risk and aggravating or attenuating factors. World Psychiatry. 2022;21:248–71. https://doi.org/10.1002/wps.20994.
7. Chan JKN, Correll CU, Wong CSM, et al. Life expectancy and years of potential life lost in people with mental disorders: a systematic review and meta-analysis. EClinicalMedicine. 2023;65. https://doi.org/10.1016/j.eclinm.2023.102294.
8. Chong HY, Teoh SL, Wu DB, et al. Global economic burden of schizophrenia: a systematic review. Neuropsychiatr Dis Treat. 2016;12:357–73. https://doi.org/10.2147/ndt.S96649.
9. Correll CU, Martin A, Patel C, et al. Systematic literature review of schizophrenia clinical practice guidelines on acute and maintenance management with antipsychotics. NPJ Schizophr. 2022;8:5. https://doi.org/10.1038/s41537-021-00192-x.
10. 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. Ther Clin Risk Manag. 2017;13:757–77. https://doi.org/10.2147/TCRM.S117321.
11. 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. Mol Psychiatry. 2022;27:1136–44. https://doi.org/10.1038/s41380-021-01334-4.
12. Wang S-M, Han C, Lee S-J, et al. Second generation antipsychotics in the treatment of major depressive disorder: an update. Chonnam Med J. 2016;52:159–72. https://doi.org/10.4068/cmj.2016.52.3.159.
13. Kishimoto T, Hagi K, Kurokawa S, et al. Efficacy and safety/tolerability of antipsychotics in the treatment of adult patients with major depressive disorder: a systematic review and meta-analysis. Psychol Med. 2023;53:4064–82. https://doi.org/10.1017/S0033291722000745.
14. McIntyre RS, Calabrese JR. Bipolar depression: the clinical characteristics and unmet needs of a complex disorder. Curr Med Res Opin. 2019;35:1993–2005. https://doi.org/10.1080/03007995.2019.1636017.
15. 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 Disord. 2018;20:97–170. https://doi.org/10.1111/bdi.12609.
16. Remington G, Addington D, Honer W, et al. Guidelines for the pharmacotherapy of schizophrenia in adults. Can J Psychiatry. 2017;62:604–16. https://doi.org/10.1177/0706743717720448.
17. Ostuzzi G, Bertolini F, Tedeschi F, et al. Oral and long-acting antipsychotics for relapse prevention in schizophrenia-spectrum disorders: A network meta-analysis of 92 randomized trials including 22,645 participants. World Psychiatry. 2022;21:295–307. https://doi.org/10.1002/wps.20972.
18. 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;394:939–51.
19. Solmi M, Cortese S, Vita G, et al. An umbrella review of candidate predictors of response, remission, recovery, and relapse across mental disorders. Mol Psychiatry. 2023;28:3671–87. https://doi.org/10.1038/s41380-023-02298-3.
20. Pillinger T, Howes OD, Correll CU, et al. Antidepressant and antipsychotic side-effects and personalised prescribing: a systematic review and digital tool development. Lancet Psychiatry. 2023;10:860–76. https://doi.org/10.1016/S2215-0366(23)00262-6.
21. Garcia S, Martinez-Cengotitabengoa M, Lopez-Zurbano S, et al. Adherence to antipsychotic medication in bipolar disorder and schizophrenic patients: a systematic review. J Clin Psychopharmacol. 2016;36:355–71. https://doi.org/10.1097/JCP.0000000000000523.
22. Correll CU. From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics. Eur Psychiatry J Assoc Eur Psychiatr. 2010;25(Suppl 2):S12-21. https://doi.org/10.1016/S0924-9338(10)71701-6.
23. Solmi M, Croatto G, Piva G, et al. Efficacy and acceptability of psychosocial interventions in schizophrenia: systematic overview and quality appraisal of the meta-analytic evidence. Mol Psychiatry. 2023;28:354–68. https://doi.org/10.1038/s41380-022-01727-z.
24. Dibonaventura M, Gabriel S, Dupclay L, et al. A patient perspective of the impact of medication side effects on adherence: results of a cross-sectional nationwide survey of patients with schizophrenia. BMC Psychiatry. 2012;12:20. https://doi.org/10.1186/1471-244X-12-20.
25. Carbon M, Hsieh CH, Kane JM, Correll CU. Tardive dyskinesia prevalence in the period of second-generation antipsychotic use: a meta-analysis. J Clin Psychiatry. 2017;78:e264–78. https://doi.org/10.4088/JCP.16r10832.
26. Carbon M, Kane JM, Leucht S, Correll CU. Tardive dyskinesia risk with first- and second-generation antipsychotics in comparative randomized controlled trials: a meta-analysis. World Psychiatry. 2018;17:330–40. https://doi.org/10.1002/wps.20579.
27. Kishimoto T, Agarwal V, Kishi T, et al. Relapse prevention in schizophrenia: a systematic review and meta-analysis of second-generation antipsychotics versus first-generation antipsychotics. Mol Psychiatry. 2013;18:53–66. https://doi.org/10.1038/mp.2011.143.
28. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet. 2009;373:31–41. https://doi.org/10.1016/S0140-6736(08)61764-X.
29. Vancampfort D, Stubbs B, Mitchell AJ, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World Psychiatry. 2015;14:339–47. https://doi.org/10.1002/wps.20252.
30. Pillinger T, D'Ambrosio E, McCutcheon R, Howes OD. Is psychosis a multisystem disorder? A meta-review of central nervous system, immune, cardiometabolic, and endocrine alterations in first-episode psychosis and perspective on potential models. Mol Psychiatry. 2019;24:776–94. https://doi.org/10.1038/s41380-018-0058-9.

31. Correll CU, Solmi M, Veronese N, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry. 2017;16:163–80. https://doi.org/10.1002/wps.20420.
32. Taub S, Krivoy A, Whiskey E, Shergill SS. New approaches to antipsychotic medication adherence—Safety, tolerability and acceptability. Expert Opin Drug Saf. 2022;21:517–24. https://doi.org/10.1080/14740338.2021.1983540.
33. Correll CU, Kim E, Sliwa JK, et al. Pharmacokinetic characteristics of long-acting injectable antipsychotics for schizophrenia: an overview. CNS Drugs. 2021;35:39–59. https://doi.org/10.1007/s40263-020-00779-5.
34. Kaar SJ, Gobjila C, Butler E, et al. Making decisions about antipsychotics: a qualitative study of patient experience and the development of a decision aid. BMC Psychiatry. 2019;19:309. https://doi.org/10.1186/s12888-019-2304-3.
35. Correll CU. Balancing efficacy and safety in treatment with antipsychotics. CNS Spectr. 2007;12:12–20. https://doi.org/10.1017/S1092852900026298.
36. Katona L, Bitter I, Czobor P. A meta-analysis of effectiveness of real-world studies of antipsychotics in schizophrenia: are the results consistent with the findings of randomized controlled trials? Transl Psychiatry. 2021;11:510. https://doi.org/10.1038/s41398-021-01636-9.
37. Taipale H, Schneider-Thoma J, Pinzón-Espinosa J, et al. Representation and outcomes of individuals with schizophrenia seen in everyday practice who are ineligible for randomized clinical trials. JAMA Psychiat. 2022;79:210–8. https://doi.org/10.1001/jamapsychiatry.2021.3990.
38. Hatta K, Katayama S, Ishizuka T, et al. Real-world effectiveness of antipsychotic treatments in 1011 acutely hospitalized patients with schizophrenia: a one-year follow-up study. Asian J Psychiatr. 2022;67: 102917. https://doi.org/10.1016/j.ajp.2021.102917.
39. Lintunen J, Taipale H, Tanskanen A, et al. Long-term real-world effectiveness of pharmacotherapies for schizoaffective disorder. Schizophr Bull. 2021;47:1099–107. https://doi.org/10.1093/schbul/sbab004.
40. Kondej M, Stepnicki P, Kaczor AA. Multi-target approach for drug discovery against schizophrenia. *Int J Mol Sci*. 2018;19. https://doi.org/10.3390/ijms19103105.
41. Gomes FV, Grace AA. Beyond dopamine receptor antagonism: new targets for schizophrenia treatment and prevention. *Int J Mol Sci*. 2021;22. https://doi.org/10.3390/ijms22094467.
42. Li P, Snyder GL, Vanover KE. Dopamine targeting drugs for the treatment of schizophrenia: past, present and future. Curr Top Med Chem. 2016;16:3385–403. https://doi.org/10.2174/1568026616666160608084834.
43. Lobo MC, Whitehurst TS, Kaar SJ, Howes OD. New and emerging treatments for schizophrenia: a narrative review of their pharmacology, efficacy and side effect profile relative to established antipsychotics. Neurosci Biobehav Rev. 2022;132:324–61. https://doi.org/10.1016/j.neubiorev.2021.11.032.
44. Kaar SJ, Natesan S, McCutcheon R, Howes OD. Antipsychotics: mechanisms underlying clinical response and side-effects and novel treatment approaches based on pathophysiology. Neuropharmacology. 2020;172:107704. https://doi.org/10.1016/j.neuropharm.2019.107704.
45. Correll CU, Solmi M, Cortese S, et al. The future of psychopharmacology: a critical appraisal of ongoing phase 2/3 trials, and of some current trends aiming to de-risk trial programmes of novel agents. World Psychiatry. 2023;22:48–74. https://doi.org/10.1002/wps.21056.
46. Buckley PF, Correll CU. Strategies for dosing and switching antipsychotics for optimal clinical management. J Clin Psychiatry. 2008;69:4–17.
47. Mauri MC, Paletta S, Di Pace C, et al. Clinical pharmacokinetics of atypical antipsychotics: an update. Clin Pharmacokinet. 2018;57:1493–528. https://doi.org/10.1007/s40262-018-0664-3.
48. Caplyta. Prescribing information. Intra-Cellular Therapies Inc.; 2023.
49. Vraylar. Prescribing information. Allergan; 2019.
50. Lybalvi. Prescribing information. Alkermes Inc.; 2021.
51. Latuda. Prescribing information. Sunovion Pharmaceuticals Inc.; 2019.
52. Rexulti. Prescribing information. Otsuka Pharmaceutical Co; 2021.
53. Højlund M, Correll CU. Switching to long-acting injectable antipsychotics: pharmacological considerations and practical approaches. Expert Opin Pharmacother. 2023;24:1463–89. https://doi.org/10.1080/14656566.2023.2228686.
54. Loftsson T. Essential pharmacokinetics: a primer for pharmaceutical scientists. New York: Academic Press; 2015.
55. Luptáková D, Vallianatou T, Nilsson A, et al. Neuropharmacokinetic visualization of regional and subregional unbound antipsychotic drug transport across the blood–brain barrier. Mol Psychiatry. 2021;26:7732–45.
56. Buzea CA, Manu P, Dima L, Correll CU. Drug–drug interactions involving combinations of antipsychotic agents with antidiabetic, lipid-lowering, and weight loss drugs. Expert Opin Drug Metab Toxicol. 2022;18:729–44. https://doi.org/10.1080/17425255.2022.2147425.
57. Buzea CA, Dima L, Correll CU, Manu P. Drug–drug interactions involving antipsychotics and antihypertensives. Expert Opin Drug Metab Toxicol. 2022;18:285–98. https://doi.org/10.1080/17425255.2022.2086121.
58. Sheehan J, Sliwa J, Amatniek J, et al. Atypical antipsychotic metabolism and excretion. Curr Drug Metab. 2010;11:516–25. https://doi.org/10.2174/138920010791636202.
59. Zhang Z, Tang W. Drug metabolism in drug discovery and development. Acta Pharm Sin B. 2018;8:721–32. https://doi.org/10.1016/j.apsb.2018.04.003.
60. Andrade C. Psychotropic drugs with long half-lives: implications for drug discontinuation, occasional missed doses, dosing interval, and pregnancy planning. J Clin Psychiatry. 2022;83:42068. https://doi.org/10.4088/JCP.22f14593.
61. Correll CU, Jain R, Meyer JM, et al. Relationship between the timing of relapse and plasma drug levels following discontinuation of cariprazine treatment in patients with schizophrenia: indirect comparison with other second-generation antipsychotics after treatment discontinuation. *Neuropsychiatr Dis Treat*. 2019;15:2537–50. https://doi.org/10.2147/NDT.S210340.
62. Nakamura T, Kubota T, Iwakaji A, et al. Clinical pharmacology study of cariprazine (MP-214) in patients with schizophrenia (12-week treatment). Drug Des Dev Ther. 2016;10:327–38. https://doi.org/10.2147/dddt.S95100.
63. Periclou A, Willavize S, Jaworowicz D, et al. Relationship between plasma concentrations and clinical effects of cariprazine in patients with schizophrenia or bipolar mania. Clin Transl Sci. 2020;13:362–71.
64. Maxwell SR. Pharmacodynamics and pharmacokinetics for the prescriber. *Medicine*. 2023;52(1):1–10. https://doi.org/10.1016/j.mpmed.2023.10.008.
65. Lieberman JA. Dopamine partial agonists: a new class of antipsychotic. CNS Drugs. 2004;18:251–67. https://doi.org/10.2165/00023210-200418040-00005.
66. McCutcheon RA, Abi-Dargham A, Howes OD. Schizophrenia, dopamine and the striatum: from biology to symptoms. Trens Neurosci. 2019;42:205–20.
67. McCutcheon RA, Krystal JH, Howes OD. Dopamine and glutamate in schizophrenia: biology, symptoms and treatment. World Psychiatry. 2020;19:15–33. https://doi.org/10.1002/wps.20693.

68. Kiss B, Krámos B, Laszlovszky I. Potential mechanisms for why not all antipsychotics are able to occupy dopamine D3 receptors in the brain in vivo. *Front Psychiatry*. 2022;13. https://doi.org/10.3389/fpsyt.2022.785592.
69. Yohn SE, Weiden PJ, Felder CC, Stahl SM. Muscarinic acetylcholine receptors for psychotic disorders: bench-side to clinic. Trends Pharmacol Sci. 2022;43:1098–112. https://doi.org/10.1016/j.tips.2022.09.006.
70. Yatham LN, Goldstein JM, Vieta E, et al. Atypical antipsychotics in bipolar depression: potential mechanisms of action. J Clin Psychiatry. 2005;66:40–8.
71. Stiedl O, Pappa E, Konradsson-Geuken Å, Ögren SO. The role of the serotonin receptor subtypes 5-HT_{1A} and 5-HT_7 and its interaction in emotional learning and memory. Front Pharmacol. 2015;6: 159078. https://doi.org/10.3389/fphar.2015.00162.
72. Seeman P. Targeting the dopamine D2 receptor in schizophrenia. Expert Opin Ther Targets. 2006;10:515–31. https://doi.org/10.1517/14728222.10.4.515.
73. Mohr P, Masopust J, Kopecek M. Dopamine receptor partial agonists: do they differ in their clinical efficacy? Front Psychiatry. 2021;12: 781946. https://doi.org/10.3389/fpsyt.2021.781946.
74. Citrome LL. Olanzapine-samidorphan combination for schizophrenia or bipolar I disorder. Curr Psychiatry. 2022;21:35.
75. Correll CU, Stein E, Graham C, et al. Reduction in multiple cardiometabolic risk factors with combined olanzapine/samidorphan compared with olanzapine: post hoc analyses from a 24-week phase 3 study. Schizophr Bull. 2023;49:454–63. https://doi.org/10.1093/schbul/sbac144.
76. Correll CU, Newcomer JW, Silverman B, et al. Effects of olanzapine combined with samidorphan on weight gain in schizophrenia: a 24-week phase 3 study. Am J Psychiatry. 2020;177:1168–78. https://doi.org/10.1176/appi.ajp.2020.19121279.
77. Cerovecki A, Musil R, Klimke A, et al. Withdrawal symptoms and rebound syndromes associated with switching and discontinuing atypical antipsychotics: theoretical background and practical recommendations. CNS Drugs. 2013;27:545–72. https://doi.org/10.1007/s40263-013-0079-5.
78. Correll CU. Real-life switching strategies with second-generation antipsychotics. J Clin Psychiatry. 2006;67:16953. https://doi.org/10.4088/jcp.v67n0122.
79. Ostuzzi G, Vita G, Bertolini F, et al. Continuing, reducing, switching, or stopping antipsychotics in individuals with schizophrenia-spectrum disorders who are clinically stable: a systematic review and network meta-analysis. Lancet Psychiatry. 2022;9:614–24. https://doi.org/10.1016/S2215-0366(22)00158-4.
80. Rubio JM, Guinart D, Kane JM, Correll CU. Early nonresponse to antipsychotic treatment in schizophrenia: a systematic review and meta-analysis of evidence-based management options. CNS Drugs. 2023;37:499–512. https://doi.org/10.1007/s40263-023-01009-4.
81. Targum SD, Pestreich L, Reksoprodjo P, et al. A global measure to assess switching antipsychotic medications in the treatment of schizophrenia. Hum Psychopharmacol. 2012;27:455–63. https://doi.org/10.1002/hup.2247.
82. Qadir ZS, Kar N, Ball PA, Morrissey H. Antipsychotic use: cross-sectional opinion survey of psychiatrists in India and United Kingdom. Pharmacy. 2023;11:162. https://doi.org/10.3390/pharmacy11050162.
83. Nyhuis AW, Faries DE, Ascher-Svanum H, et al. Predictors of switching antipsychotic medications in the treatment of schizophrenia. BMC Psychiatry. 2010;10:75. https://doi.org/10.1186/1471-244X-10-75.
84. Hatta K, Sugiyama N, Ito H. Switching and augmentation strategies for antipsychotic medications in acute-phase schizophrenia: latest evidence and place in therapy. Ther Adv Psychopharmacol. 2018;8:173–83. https://doi.org/10.1177/2045125318754472.
85. Liao X, Ye H, Si T. A review of switching strategies for patients with schizophrenia comorbid with metabolic syndrome or metabolic abnormalities. Neuropsychiatr Dis Treat. 2021;17:453–69. https://doi.org/10.2147/NDT.S294521.
86. Mukundan A, Faulkner G, Cohn T, Remington G. Antipsychotic switching for people with schizophrenia who have neuroleptic-induced weight or metabolic problems. *Cochrane Database Syst Rev*. 2010;CD006629. https://doi.org/10.1002/14651858.CD006629.pub2.
87. Siskind D, Gallagher E, Winckel K, et al. Does switching antipsychotics ameliorate weight gain in patients with severe mental illness? A systematic review and meta-analysis. Schizophr Bull. 2021;47:948–58. https://doi.org/10.1093/schbul/sbaa191.
88. Newcomer JW, Weiden PJ, Buchanan RW. Switching antipsychotic medications to reduce adverse event burden in schizophrenia: establishing evidence-based practice. J Clin Psychiatry. 2013;74:1108–20. https://doi.org/10.4088/JCP.12028ah1.
89. Xu L, Krishnaswamy S. Switch-associated adverse events: focus on olanzapine. Australas Psychiatry. 2018;26:635–9. https://doi.org/10.1177/1039856218810166.
90. Richards K, Johnsrud M, Zacker C, Sasané R. One-year medication treatment patterns, healthcare resource utilization, and expenditures for Medicaid patients with schizophrenia starting oral atypical antipsychotic medication. Adm Policy Ment Health. 2024;51:207–16. https://doi.org/10.1007/s10488-023-01327-1.
91. Takeuchi H, Thiyanavadivel S, Agid O, Remington G. Rapid vs. slow antipsychotic initiation in schizophrenia: a systematic review and meta-analysis. Schizophr Res. 2018;193:29–36. https://doi.org/10.1016/j.schres.2017.08.012.
92. Takeuchi H, Watabe K. Does short-term antipsychotic discontinuation of up to 3 weeks worsen symptoms in acute schizophrenia? A pooled analysis of placebo washout data. Psychiatry Clin Neurosci. 2023;77:338–44. https://doi.org/10.1111/pcn.13534.
93. Takeuchi H, Kantor N, Uchida H, et al. Immediate vs gradual discontinuation in antipsychotic switching: a systematic review and meta-analysis. Schizophr Bull. 2017;43:862–71. https://doi.org/10.1093/schbul/sbw171.
94. Takeuchi H, Thiyanavadivel S, Agid O, Remington G. Gradual vs. wait-and-gradual discontinuation in antipsychotic switching: a meta-analysis. Schizophr Res. 2017;189:4–8. https://doi.org/10.1016/j.schres.2017.02.011.
95. Takeuchi H, Remington G. Immediate versus wait-and-gradual discontinuation in antipsychotic switching: a meta-analysis. J Psychopharmacol. 2020;34:914–9. https://doi.org/10.1177/0269881120922964.
96. Baumann P, Bauknecht P, Kuzin M, Schoretsanitis G. Switching antipsychotics to partial dopamine D2-agonists in individuals affected by schizophrenia: a narrative review. Int J Psychiatry Clin Pract. 2023;27:367–84. https://doi.org/10.1080/13651501.2023.2231047.
97. Murru A, Hidalgo D, Bernardo M, et al. Antipsychotic switching in schizoaffective disorder: a systematic review. World J Biol Psychiatry. 2016;17:495–513. https://doi.org/10.3109/15622975.2015.1012225.
98. Patel C, Emont S, Cao Z, et al. Post hospitalization clinical quality outcomes among us patients with schizophrenia treated with a long-acting injectable or switched to a new oral antipsychotic: a retrospective cohort study. Drugs-Real World Outcomes. 2024;11:69–79. https://doi.org/10.1007/s40801-023-00408-9.
99. Perkins AJ, Khandker R, Overley A, et al. The impact of antipsychotic adherence on acute care utilization. BMC Psychiatry. 2023;23:64. https://doi.org/10.1186/s12888-023-04558-6.
100. Kim Y, Wang S-M, Kwak K-P, et al. Amisulpride switching in schizophrenic patients who showed suboptimal effect and/or

tolerability to current antipsychotics in a naturalistic setting: an explorative study. Clin Psychopharmacol Neurosci. 2016;14:371. https://doi.org/10.9758/cpn.2016.14.4.371.
101. Liang Y, Yu X. The effectiveness and safety of amisulpride in Chinese patients with schizophrenia who switch from risperidone or olanzapine: a subgroup analysis of the escape study. Neuropsychiatr Dis Treat. 2017;13:1163–73. https://doi.org/10.2147/NDT.S132363.
102. Heres S, Cordes J, Feyerabend S, et al. Changing the antipsychotic in early nonimprovers to amisulpride or olanzapine: randomized, double-blind trial in patients with schizophrenia. Schizophr Bull. 2022;48:1273–83. https://doi.org/10.1093/schbul/sbac068.
103. Chen Y, Bobo WV, Watts K, et al. Comparative effectiveness of switching antipsychotic drug treatment to aripiprazole or ziprasidone for improving metabolic profile and atherogenic dyslipidemia: a 12-month, prospective, open-label study. J Psychopharmacol. 2012;26:1201–10. https://doi.org/10.1177/0269881111430748.
104. Ganguli R, Brar J, Garbut R, et al. Changes in weight and other metabolic indicators in persons with schizophrenia following a switch to aripiprazole. Clin Schizophr Relat Psychoses. 2011;5:75–9. https://doi.org/10.3371/CSRP.5.2.3.
105. Hwang T-J, Lo W-M, Chan H-Y, et al. Fast versus slow strategy of switching patients with schizophrenia to aripiprazole from other antipsychotics. J Clin Psychopharmacol. 2015;35:635–44. https://doi.org/10.1097/JCP.0000000000000426.
106. Jen Y-W, Hwang T-J, Chan H-Y, et al. Abnormally low prolactin levels in schizophrenia patients after switching to aripiprazole in a randomized trial: a biomarker for rebound in psychotic symptoms? BMC Psychiatry. 2020;20:1–10. https://doi.org/10.1186/s12888-020-02957-7.
107. Kanahara N, Takase M, Sasaki T, et al. The effectiveness of very slow switching to aripiprazole in schizophrenia patients with dopamine supersensitivity psychosis: a case series from an open study. Int Clin Psychopharmacol. 2020;35:338–44. https://doi.org/10.1097/YIC.0000000000000322.
108. Lee J-S, Chung S, Lee J-N, et al. Efficacy and tolerability of aripiprazole: a 26-week switching study from oral antipsychotics. Psychiatry Investig. 2010;7:189. https://doi.org/10.4306/pi.2010.7.3.189.
109. Ma CH, Chan HY, Hsieh MH, et al. Identifying dopamine supersensitivity through a randomized controlled study of switching to aripiprazole from other antipsychotic agents in patients with schizophrenia. Ther Adv Psychopharmacol. 2022;12:20451253211064396. https://doi.org/10.1177/20451253211064396.
110. Stroup TS, McEvoy JP, Ring KD, et al. A randomized trial examining the effectiveness of switching from olanzapine, quetiapine, or risperidone to aripiprazole to reduce metabolic risk: comparison of antipsychotics for metabolic problems (CAMP). Am J Psychiatry. 2011;168:947–56. https://doi.org/10.1176/appi.ajp.2011.10111609.
111. Stroup TS, Byerly MJ, Nasrallah HA, et al. Effects of switching from olanzapine, quetiapine, and risperidone to aripiprazole on 10-year coronary heart disease risk and metabolic syndrome status: results from a randomized controlled trial. Schizophr Res. 2013;146:190–5. https://doi.org/10.1016/j.schres.2013.01.013.
112. Suzuki H, Gen K, Inoue Y. An unblinded comparison of the clinical and cognitive effects of switching from first-generation antipsychotics to aripiprazole, perospirone or olanzapine in patients with chronic schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35:161–8. https://doi.org/10.1016/j.pnpbp.2010.10.021.
113. Wani RA, Dar MA, Chandel RK, et al. Effects of switching from olanzapine to aripiprazole on the metabolic profiles of patients with schizophrenia and metabolic syndrome: a double-blind, randomized, open-label study. Neuropsychiatr Dis Treat. 2015;11:685–93. https://doi.org/10.2147/NDT.S80925.
114. Yoon HW, Lee JS, Park SJ, et al. Comparing the effectiveness and safety of the addition of and switching to aripiprazole for resolving antipsychotic-induced hyperprolactinemia: a multicenter, open-label, prospective study. Clin Neuropharmacol. 2016;39:288–94. https://doi.org/10.1097/WNF.0000000000000175.
115. Roffeei SN, Reynolds GP, Zainal NZ, et al. Association of ADRA2A and MTHFR gene polymorphisms with weight loss following antipsychotic switching to aripiprazole or ziprasidone. Hum Psychopharmacol. 2014;29:38–45. https://doi.org/10.1002/hup.2366.
116. Chen CY, Lin TY, Wang CC, Shuai HA. Improvement of serum prolactin and sexual function after switching to aripiprazole from risperidone in schizophrenia: a case series. Psychiatry Clin Neurosci. 2011;65:95–7. https://doi.org/10.1111/j.1440-1819.2010.02156.x.
117. Miura I, Shiga T, Katsumi A, et al. Switching antipsychotics to aripiprazole or blonanserin and plasma monoamine metabolites levels in patients with schizophrenia. Hum Psychopharmacol. 2014;29:199–202. https://doi.org/10.1002/hup.2386.
118. Wisniewski CS, Robert S. Strategies for transitioning therapy to aripiprazole from other antipsychotics in schizophrenia. Ann Pharmacother. 2012;46:1097–104. https://doi.org/10.1345/aph.1Q700.
119. Fagiolini A, Brugnoli R, Di Sciascio G, et al. Switching antipsychotic medication to aripiprazole: position paper by a panel of Italian psychiatrists. Expert Opin Pharmacother. 2015;16:727–37. https://doi.org/10.1517/14656566.2015.1013029.
120. Veznedaroglu B, Dilbaz N, Uzun O, Isik E. TARC: Turkish aripiprazole consensus report-aripiprazole use and switching from other antipsychotics to aripiprazole-consensus recommendations by a Turkish multidisciplinary panel. Ther Adv Psychopharmacol. 2018;8:271–85. https://doi.org/10.1177/2045125318772712.
121. Cazorla P, Mackle M, Zhao J, et al. Safety and tolerability of switching to asenapine from other antipsychotic agents: pooled results from two randomized multicenter trials in stable patients with persistent negative symptoms in schizophrenia. Neuropsychiatr Dis Treat. 2012;8:247–57. https://doi.org/10.2147/NDT.S29891.
122. Nakagome K, Tachimori H, Endo S, et al. A multicenter, single-arm, open-label interventional study of adherence to brexpiprazole during switching from previous antipsychotic drugs in patients with schizophrenia or schizoaffective disorder. Neuropsychopharmacol Rep. 2024;44:187–96. https://doi.org/10.1002/npr2.12416.
123. Ishigooka J, Usami T, Iwashita S, et al. Post-hoc analysis investigating the safety and efficacy of brexpiprazole in Japanese patients with schizophrenia who were switched from other antipsychotics in a long-term study (secondary publication). Neuropsychopharmacol Rep. 2020;40:122–9. https://doi.org/10.1002/npr2.12107.
124. Yamasaki F, Kanahara N, Nakata Y, et al. Can brexpiprazole be switched safely in patients with schizophrenia and dopamine supersensitivity psychosis? A retrospective analysis in a real-world clinical practice. J Psychopharmacol. 2023;37:992–1002. https://doi.org/10.1177/02698811231177268.
125. Correll CU, Shi L, Weiss C, et al. Successful switching of patients with acute schizophrenia from another antipsychotic to brexpiprazole: comparison of clinicians' choice of cross-titration schedules in a post hoc analysis of a randomized, double-blind, maintenance treatment study. CNS Spectr. 2019;24:507–17. https://doi.org/10.1017/S1092852918001086.

126. Leucht S, Winter-van Rossum I, Heres S, et al. The optimization of treatment and management of schizophrenia in Europe (optimise) trial: rationale for its methodology and a review of the effectiveness of switching antipsychotics. Schizophr Bull. 2015;41:549–58. https://doi.org/10.1093/schbul/sbv019.
127. Kahn RS, van Rossum IW, Leucht S, et al. Amisulpride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizophreniform disorder (optimise): a three-phase switching study. Lancet Psychiatry. 2018;5:797–807. https://doi.org/10.1016/S2215-0366(18)30252-9.
128. Watanabe M, Misawa F, Takeuchi H. Real-world effectiveness of high-dose olanzapine and clozapine for treatment-resistant schizophrenia in Japan: a retrospective bidirectional mirror-image study. J Clin Psychopharmacol. 2024;44:151–6. https://doi.org/10.1097/JCP.0000000000001804.
129. Takeuchi H, Lee J, Fervaha G, et al. Switching to clozapine using immediate versus gradual antipsychotic discontinuation: a pilot, double-blind, randomized controlled trial. J Clin Psychiatry. 2017;78:223–8. https://doi.org/10.4088/JCP.15m10286.
130. Brunette MF, Dawson R, O'Keefe CD, et al. A randomized trial of clozapine versus other antipsychotics for cannabis use disorder in patients with schizophrenia. J Dual Diagn. 2011;7:50–63. https://doi.org/10.1080/15504263.2011.57011.
131. Weiden PJ, Citrome L, Alva G, et al. A trial evaluating gradual- or immediate-switch strategies from risperidone, olanzapine, or aripiprazole to iloperidone in patients with schizophrenia. Schizophr Res. 2014;153:160–8. https://doi.org/10.1016/j.schres.2013.11.042.
132. Citrome L, Weiden PJ, Alva G, et al. Switching to iloperidone: an omnibus of clinically relevant observations from a 12-week, open-label, randomized clinical trial in 500 persons with schizophrenia. Clin Schizophr Relat Psychoses. 2015;8:183–95. https://doi.org/10.3371/CSRP.CIWE.103114.
133. Correll CU, Vanover KE, Davis RE, et al. Safety and tolerability of lumateperone 42 mg: an open-label antipsychotic switch study in outpatients with stable schizophrenia. Schizophr Res. 2021;228:198–205. https://doi.org/10.1016/j.schres.2020.12.006.
134. McEvoy JP, Citrome L, Hernandez D, et al. Effectiveness of lurasidone in patients with schizophrenia or schizoaffective disorder switched from other antipsychotics: a randomized, 6-week, open-label study. J Clin Psychiatry. 2013;74:170–9. https://doi.org/10.4088/JCP.12m07992.
135. Awad G, Hassan M, Loebel A, et al. Health-related quality of life among patients treated with lurasidone: results from a switch trial in patients with schizophrenia. BMC Psychiatry. 2014;14:1–10. https://doi.org/10.1186/1471-244X-14-53.
136. Mattingly GW, Haddad PM, Tocco M, et al. Switching to lurasidone following 12 months of treatment with risperidone: results of a 6-month, open-label study. BMC Psychiatry. 2020;5(20):199. https://doi.org/10.1186/s12888-020-02523-1.
137. Citrome L, Weiden PJ, McEvoy JP, et al. Effectiveness of lurasidone in schizophrenia or schizoaffective patients switched from other antipsychotics: a 6-month, open-label, extension study. CNS Spectr. 2014;19:330–9. https://doi.org/10.1017/S109285291300093X.
138. Hatta K, Otachi T, Fujita K, et al. Antipsychotic switching versus augmentation among early non-responders to risperidone or olanzapine in acute-phase schizophrenia. Schizophr Res. 2014;158:213–22. https://doi.org/10.1016/j.schres.2014.07.015.
139. Hong J, Novick D, Brugnoli R, et al. Clinical consequences of switching from olanzapine to risperidone and vice versa in outpatients with schizophrenia: 36-month results from the Worldwide Schizophrenia Outpatients Health Outcomes (W-SOHO) study. BMC Psychiatry. 2012;12:1–9. https://doi.org/10.1186/1471-244X-12-218.
140. Agid O, Schulze L, Arenovich T, et al. Antipsychotic response in first-episode schizophrenia: efficacy of high doses and switching. Eur Neuropsychopharmacol. 2013;23:1017–22. https://doi.org/10.1016/j.euroneuro.2013.04.010.
141. Gattaz WF, de Oliveira Campos JA, Lacerda AL, et al. Switching from oral risperidone to flexibly dosed oral paliperidone extended-release: core symptoms, satisfaction, and quality of life in patients with stable but symptomatic schizophrenia: the RISPALI study. Curr Med Res Opin. 2014;30(4):695–709. https://doi.org/10.1185/03007995.2013.869201.
142. Kim EY, Chang SM, Shim JC, et al. Long-term effectiveness of flexibly dosed paliperidone extended-release: comparison among patients with schizophrenia switching from risperidone and other antipsychotic agents. Curr Med Res Opin. 2013;29:1231–40. https://doi.org/10.1185/03007995.2013.816277.
143. Si TM, Cai SL, Zhuo JM, Zhang LL. Switching to paliperidone extended release in patients with schizophrenia dissatisfied with previous olanzapine treatment: post hoc analysis of an open-label, prospective study. Medicine (Baltim). 2019;98: e13688. https://doi.org/10.1097/MD.0000000000013688.
144. Yang F, Li J, Tan YL, et al. Treatment satisfaction with paliperidone extended-release tablets: open-label study in schizophrenia patients dissatisfied with previous antipsychotic medication. Neuropsychiatr Dis Treat. 2017;13:1089–97. https://doi.org/10.2147/NDT.S130483.
145. Yang DS, Seong SJ, Yoon YR, et al. Changes in plasma concentrations of risperidone and 9-hydroxyrisperidone and the associated clinical effects during the switch from oral risperidone to extended-release paliperidone tablets in patients with schizophrenia. J Psychopharmacol. 2014;28:341–8. https://doi.org/10.1177/0269881113516203.
146. Suzuki H, Gen K, Otomo M, et al. Study of the efficacy and safety of switching from risperidone to paliperidone in elderly patients with schizophrenia. Psychiatry Clin Neurosci. 2013;67:76–82. https://doi.org/10.1111/pcn.12026.
147. Suzuki H, Gen K, Inoue Y, et al. The influence of switching from risperidone to paliperidone on the extrapyramidal symptoms and cognitive function in elderly patients with schizophrenia: a preliminary open-label trial. Int J Psychiatry Clin Pract. 2014;18:58–62. https://doi.org/10.3109/13651501.2013.845218.
148. Chue P, Malla A, Bouchard R-H, et al. The long-term clinical benefit and effectiveness of switching to once-daily quetiapine extended release in patients with schizophrenia. Curr Med Res Opin. 2013;29:227–39. https://doi.org/10.1185/03007995.2012.762903.
149. Smeraldi E, Cavallaro R, Folnegovic-Smalc V, et al. Long-term remission in schizophrenia and schizoaffective disorder: results from the risperidone long-acting injectable versus quetiapine relapse prevention trial (constatre). Ther Adv Psychopharmacol. 2013;3:191–9. https://doi.org/10.1177/2045125313479127.
150. Miura I, Takeuchi S, Katsumi A, et al. Effect of switching to risperidone after unsuccessful treatment with aripiprazole on plasma monoamine metabolites level in the treatment of acute schizophrenia. Hum Psychopharmacol. 2012;27:517–20. https://doi.org/10.1002/hup.2251.
151. Fang M, Chen H, Li L, et al. Comparison of risperidone oral solution and intramuscular haloperidol with the latter shifting to oral therapy for the treatment of acute agitation in patients with schizophrenia. Int Clin Psychopharmacol. 2012;27:107–13. https://doi.org/10.1097/YIC.0b013e32834fc431.
152. Suzuki Y, Sugai T, Ono S, et al. Changes in PR and QTc intervals after switching from olanzapine to risperidone in patients with stable schizophrenia. Psychiatry Clin Neurosci. 2014;68:353–6. https://doi.org/10.1111/pcn.12136.

153. Popovic I, Ravanic D, Popovic V, et al. First generation antipsychotics switch with risperidone in the treatment of chronic schizophrenic patients. Psychiatr Danub. 2011;23:384–8.
154. Karayal ON, Glue P, Bachinsky M, et al. Switching from quetiapine to ziprasidone: a sixteen-week, open-label, multicenter study evaluating the effectiveness and safety of ziprasidone in outpatient subjects with schizophrenia or schizoaffective disorder. J Psychiatr Pract. 2011;17:100–9. https://doi.org/10.1097/01.pra.0000396061.05269.c8.
155. Wang HH, Cai M, Wang HN, et al. An assessor-blinded, randomized comparison of efficacy and tolerability of switching from olanzapine to ziprasidone and the combination of both in schizophrenia spectrum disorders. J Psychiatr Res. 2017;85:59–65. https://doi.org/10.1016/j.jpsychires.2016.11.002.
156. Mencacci C, All I. Efficacy and tolerability of switching to ziprasidone in Italian patients with acute exacerbation of schizophrenia: an open-label trial. Pharmacopsychiatry. 2012;45:236–40. https://doi.org/10.1055/s-0032-1301884.
157. Stip E, Zhornitsky S, Potvin S, Tourjman V. Switching from conventional antipsychotics to ziprasidone: a randomized, open-label comparison of regimen strategies. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34:997–1000. https://doi.org/10.1016/j.pnpbp.2010.05.010.
158. Bogers JP, Schulte PF, Broekman TG, et al. Dose reduction of high-dose first-generation antipsychotics or switch to ziprasidone in long-stay patients with schizophrenia: a 1-year double-blind randomized clinical trial. Eur Neuropsychopharmacol. 2018;28:1024–34. https://doi.org/10.1016/j.euroneuro.2018.06.005.
159. Suzuki T, Graff-Guerrero A, Uchida H, et al. Dopamine $D_{2/3}$ occupancy of ziprasidone across a day: a within-subject pet study. Psychopharmacology. 2013;228:43–51. https://doi.org/10.1007/s00213-013-3012-1.
160. Correll CU, Abi-Dargham A, Howes O. Emerging treatments in schizophrenia. J Clin Psychiatry. 2022;83:39683. https://doi.org/10.4088/JCP.SU21024IP1.
161. Meyer JM, Correll CU. Increased metabolic potential, efficacy, and safety of emerging treatments in schizophrenia. CNS Drugs. 2023;37:545–70. https://doi.org/10.1007/s40263-023-01022-7.
162. Højlund M, Correll CU. Ulotaront: a TAAR1/5-HT1A agonist in clinical development for the treatment of schizophrenia. Expert Opin Investig Drugs. 2022;31:1279–90. https://doi.org/10.1080/13543784.2022.2158811.
163. Correll CU, Citrome L. Pharmacologic treatment of schizophrenia beyond dopamine receptor blockade—Has its time come yet? JAMA Psychiat. 2024;81:118–20. https://doi.org/10.1001/jamapsychiatry.2023.4353.
164. Fabiano N, Wong S, Zhou C, et al. Efficacy, tolerability, and safety of xanomeline-trospium chloride for schizophrenia: a systematic review and meta-analysis. Eur Neuropsychopharmacol. 2025;92:62–73.
165. Psychoactive drug screening program. http://pdsp.Med.Unc.Edu. Accessed 03 Mar 2010.
166. Li P, Zhang Q, Robichaud AJ, et al. Discovery of a tetracyclic quinoxaline derivative as a potent and orally active multifunctional drug candidate for the treatment of neuropsychiatric and neurological disorders. J Med Chem. 2014;57:2670–82. https://doi.org/10.1021/jm401958n.
167. Abbas AI, Hedlund PB, Huang X-P, et al. Amisulpride is a potent 5-HT_7 antagonist: relevance for antidepressant actions in vivo. Psychopharmacology. 2009;205:119–28. https://doi.org/10.1007/s00213-009-1521-8.
168. Richtand NM, Welge JA, Logue AD, et al. Dopamine and serotonin receptor binding and antipsychotic efficacy. Neuropsychopharmacology. 2007;32:1715–26. https://doi.org/10.1038/sj.npp.1301305.
169. Jensen NH, Rodriguiz RM, Caron MG, et al. N-Desalkylquetiapine, a potent norepinephrine reuptake inhibitor and partial 5-HT1A agonist, as a putative mediator of quetiapine's antidepressant activity. Neuropsychopharmacology. 2008;33:2303–12. https://doi.org/10.1038/sj.npp.1301646.
170. Corena-McLeod M. Comparative pharmacology of risperidone and paliperidone. Drugs R&D. 2015;15:163–74. https://doi.org/10.1007/s40268-015-0092-x.
171. Peprah K, Zhu XY, Eyunni SV, et al. Multi-receptor drug design: haloperidol as a scaffold for the design and synthesis of atypical antipsychotic agents. Bioorg Med Chem. 2012;20:1291–7. https://doi.org/10.1016/j.bmc.2011.12.019.