Efficacy and safety of high-dose antipsychotic therapy

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Mr. K, age 21, is admitted to the psychiatry unit with agitation, disorganized behavior, and paranoia. Upon presentation, he has no known medical history or current medications. He is diagnosed with schizophrenia and subsequently tolerates but does not respond to adequate durations of treatment with fluphenazine, 20 mg/d; aripiprazole, 30 mg/d; and risperidone, 6 mg/d. Medication adherence is verified, but Mr. K is reluctant to try a fourth antipsychotic. The treatment team suspects that Mr. K may be a cytochrome P450 (CYP) 2D6 ultra-rapid metabolizer, so they obtain a serum risperidone level. The serum risperidone concentration is subtherapeutic (10 ng/mL). What should be considered next?

Several factors must be considered when a patient with psychosis does not experience significant symptomatic improvement with an adequate antipsychotic trial. This article focuses on high-dose second-generation antipsychotic (SGA) therapy in adults with psychosis. "High-dose" antipsychotic therapy is dosing that exceeds the standard maximum dosage for a given antipsychotic. Existing evidence on the use of high-dose SGAs consists of open-label studies and case reports, as well as a handful of randomized controlled trials (RCTs) with small sample sizes and high dropout rates. In some studies, the use of concomitant interventions (eg, duplicate antipsychotic therapy) limit the interpretation of data. High-dose first-generation antipsychotic therapy is discouraged because of a heightened risk of extrapyramidal symptoms (EPS).

Steps to take before increasing the dose

When considering prescribing high-dose antipsychotic therapy, first confirm that the patient has been adherent to the current medication regimen. Also, screen for factors that might impair drug absorption,

Practice Points

- **Address causative factors for inadequate antipsychotic response before considering high-dose antipsychotic therapy.** Such factors may include treatment nonadherence, noncompliance with administration precautions, or pharmacokinetic drug interactions.
- **Serum drug concentrations may guide antipsychotic dosing when drug interactions or genetic polymorphisms are suspected** of altering drug exposure and response.
- In patients with treatment-resistant schizophrenia who are not candidates for clozapine, **olanzapine may be the best supported high-dose antipsychotic alternative**.
- **Patients who require high-dose antipsychotic therapy should be monitored closely for dose-related adverse effects**, such as extrapyramidal symptoms, QTc prolongation, hyperprolactinemia, sedation, orthostasis, and anticholinergic effects.

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Disclosure

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Clinical Point

When considering high-dose antipsychotic therapy, confirm that the patient has been adherent to their current regimen

Table 1

Metabolic pathways and prescribing considerations for SGAs

Antipsychotic	Notable metabolic pathway(s)	SGA dosing recommendations based on pharmacokinetic drug interactions and genetic polymorphisms
Asenapine	CYP1A2	Dosage reduction may be necessary when prescribed with a strong CYP1A2 inhibitor
Aripiprazole	CYP2D6, CYP3A4	50% of the usual dosage should be administered in CYP2D6 poor metabolizers or when a strong CYP2D6 or 3A4 inhibitor is prescribed concomitantly
		25% of the usual dosage is recommended in CYP2D6 poor metabolizers who are prescribed a strong CYP3A4 inhibitor
		25% of the usual dosage is recommended in patients who are prescribed a strong CYP2D6 and CYP3A4 inhibitor
		The usual dosage should be doubled over 1 to 2 weeks when strong CYP3A4 induction is present
Brexpiprazole	CYP2D6, CYP3A4	50% of the usual dosage is recommended when given with a strong CYP2D6 or CYP3A4 inhibitor
		25% of the usual dosage is recommended for CYP2D6 poor metabolizers who are prescribed a moderate to strong CYP3A4 inhibitor
		25% of the usual dosage is advised in patients who are prescribed a moderate to strong CYP2D6 and CYP3A4 inhibitor
		The usual dosage should be doubled and adjusted based on response in patients who are taking a strong CYP3A4 inducer
Cariprazine	CYP3A4	50% of the usual dosage is recommended when given with a strong CYP3A4 inhibitor
		Concomitant treatment with a CYP3A4 inducer is not advised
Clozapine	CYP1A2, CYP2D6, CYP3A4	One-third of the usual dosage is recommended when given with a strong CYP1A2 inhibitor
		Treatment with a strong CYP3A4 inducer is not advised
		Dosage reduction should be considered when a strong CYP3A4 or CYP1A2 inducer is discontinued
		Dosage reduction may be necessary in CYP2D6 poor metabolizers
Iloperidone	CYP2D6, CYP3A4	Dosage reduction is recommended when given with a strong CYP2D6 or CYP3A4 inhibitor
		50% of the usual dosage is recommended in CYP2D6 poor metabolizers
Lumateperone	CYP3A4, UGT enzymes	Lumateperone should not be prescribed with a CYP3A4 inducer or moderate to strong CYP3A4 inhibitor
		Concomitant treatment with UGT inhibitors should be avoided
Lurasidone	CYP3A4	Do not prescribe with a strong CYP3A4 inhibitor or inducer
		50% of the usual dosage is recommended when given with a moderate CYP3A4 inhibitor
		Higher dosages may be necessary when given with a moderate CYP3A4 inducer
Olanzapine	UGT1A4, CYP1A2	Dosage reduction may be necessary when prescribed with a CYP1A2 inhibitor

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Table 1 continued

Antipsychotic	Notable metabolic pathway(s)	SGA dosing recommendations based on pharmacokinetic drug interactions and genetic polymorphisms
Paliperidone	P-gp and CYP3A4 (in vitro); limited role of CYP3A4 in elimination in vivo; 60% excreted unmetabolized	Higher doses may be necessary when given with a strong CYP3A4 and P-gp inducer
		Dosage reduction may be necessary if concomitant treatment with a strong CYP3A4 and P-gp inducer is stopped
		Dosage reduction may be necessary when given with divalproex sodium
Quetiapine	CYP3A4	1/6 of the usual dosage is recommended when prescribed with a strong CYP3A4 inhibitor
		Up to 5 times the usual dosage may be necessary when given with a strong CYP3A4 inducer
		A 5-fold dosage reduction is advised within 7 to 14 days of stopping concomitant treatment with a strong CYP3A4 inducer
Risperidone	CYP2D6	Patients who are prescribed a CYP2D6 inhibitor should receive a lower starting dosage, with titration to no more than 8 mg/d[a]
		Slow titration to up to double the usual dosage is recommended when carbamazepine or another enzyme inducer is prescribed concomitantly
Ziprasidone	N/A	Package insert does not provide formal dosage adjustment recommendations in this context

[a]Although this recommendation is contained within the drug label, risperidone is not routinely dosed above 6 to 8 mg/d, regardless of potential drug interactions, due to a dose-related risk of extrapyramidal symptoms. Further caution is advised when potential drug interactions are present

CYP: cytochrome P450; P-gp: P-glycoprotein; UGT: UDP-glucuronosyltransferase; SGA: second-generation antipsychotic

Source: References 2-17

Clinical Point

Causes of inadequate efficacy should be addressed before considering the use of high-dose antipsychotic therapy

such as bariatric surgery or noncompliance with administration precautions.[1] For example, administration of lurasidone with less than 350 calories may considerably decrease absorption.[2] Dosage requirements may vary based on ethnicity, gender, CYP polymorphisms, and pharmacokinetic drug interactions (***Table 1***[2-17]).[1,18,19] Causes of inadequate efficacy should be addressed before considering the use of high-dose antipsychotic therapy.[1] Under certain circumstances, serum drug concentrations may be used to guide antipsychotic dosing (***Table 2***,[2-17] ***page 42***). Inadequate response despite a therapeutic serum concentration may indicate pharmacodynamic failure.[1] Inadequate response in the context of subtherapeutic serum concentrations, good medication adherence, and compliance to administration precautions may be indicative of a genetic polymorphism or drug interaction.[1] Changes in antipsychotic dosing or selection may be warranted, depending on associated risks and benefits.

SGAs and high-dose administration

The SGA with the greatest evidence for high-dose administration is olanzapine, which is similar in structure and receptor pharmacology to clozapine.[20,21] The use of high-dose olanzapine is controversial. High-dose olanzapine has been compared to clozapine in patients with treatment-resistant schizophrenia (TRS) and schizoaffective disorder. Meltzer et al[22] reported similar efficacy with clozapine, 300 to 900 mg/d, and olanzapine, 25 to 45 mg/d. In this study, high-dose olanzapine caused more weight gain when compared to clozapine. Olanzapine dosages of up to 100 mg/d have been prescribed for TRS; however, this is not common practice.[23] A study comparing 10, 20, and 40 mg/d in patients with non-TRS or schizoaffective disorder showed no advantage with higher dosages.[24]

There is limited data on high-dose treatment with other SGAs.[17] Orthostasis may limit iloperidone's safety at high doses,

Table 2

Maximum daily dosages and estimated therapeutic ranges for SGAs

Antipsychotic	FDA-approved maximum dosage in adults with schizophrenia (mg/d)	Estimated therapeutic serum concentration range (ng/mL)[b]
Aripiprazole	30	150 to 350
Asenapine	20	1 to 5
Brexpiprazole	4	40 to 140
Cariprazine	6	10 to 20
Clozapine	900	350 to 600
Iloperidone	24	5 to 10
Lumateperone	42	Not well established
Lurasidone	160	15 to 40
Olanzapine	20	20 to 80
Paliperidone	12	20 to 60
Quetiapine	800	100 to 500
Risperidone	16[a]	20 to 60
Ziprasidone	200	50 to 200

[a]Not routinely dosed above 6 to 8 mg/d due to a dose-related risk of extrapyramidal symptoms
[b]Serum antipsychotic concentrations should be obtained as a trough at steady state. Therapeutic ranges are an estimation and vary by source

SGAs: second-generation antipsychotics

Source: References 2-17

Clinical Point

Olanzapine may be the best-supported high-dose antipsychotic alternative to clozapine

and single doses of asenapine should not exceed 10 mg.[25] Limited sublingual surface area and saliva saturation result in decreased bioavailability with higher asenapine doses.[25,26] In a small RCT of patients with stable schizophrenia or schizoaffective disorder, aripiprazole was relatively well-tolerated up to 75 mg/d, whereas akathisia and tachycardia occurred with 90 mg/d.[27] Case reports have documented successful treatment with aripiprazole, 60 to 75 mg/d; however, dizziness and worsening psychosis, agitation, and confusion have been observed.[28-31]

There is a paucity of data on high-dose risperidone and paliperidone, possibly due to their potent dopamine-2 (D2) receptor antagonism and dose-related risk of EPS.[1] At risperidone dosages >6 mg/d, the balance between D2 and serotonin-2A (5-HT2A) receptor potency is lost, which increases the potential for EPS.[32] In one RCT, long-acting injectable (LAI) risperidone, up to 100 mg biweekly, was well-tolerated but no more effective for TRS than 50 mg biweekly.[33] A case report suggested improvement of TRS in a patient administered risperidone LAI, 75 mg vs 37.5 mg biweekly, but it is unclear if a 50-mg dosage was tried.[34] Another case report documented improvement in schizophrenia symptoms with risperidone LAI, 125 mg biweekly; however, anticholinergic therapy was required for EPS.[35]

Dose-dependent adverse effects, including EPS, sedation, anticholinergic effects, orthostasis, hyperprolactinemia, and QTc prolongation, may limit the safety of high-dose antipsychotic therapy.[1,20,36] Two studies showed no correlation between QTc prolongation and ziprasidone dosages of up to 320 mg/d for psychosis.[37,38] QTc prolongation was more likely at higher ziprasidone concentrations.[37] Higher concentrations, but not higher dosages, also trended toward improvement in positive symptoms, and concentrations >100 ng/mL were associated with more negative symptoms.[37] A case report described improvement in positive symptoms of schizoaffective disorder with ziprasidone, 320 mg/d, but activation, hostility, and depression worsened.[39]

Compared with other antipsychotics, high-dose clozapine and quetiapine may be less likely to cause EPS due to lower D2 receptor occupancies.[40] Nevertheless, increased activity at other postsynaptic receptors may lead to constipation, metabolic effects, and sedation.[1,41,42] Case reports suggest efficacy with quetiapine, 1,200 to 2,400 mg/d, vs lower dosages for patients with TRS.[43,44] However, RCTs of quetiapine, 600 and 800 mg/d vs 1,200 mg/d, have not demonstrated an efficacy advantage with high-dose treatment in patients with schizophrenia or schizoaffective disorder.[41,45] High-dose quetiapine has also resulted in photopsia, cardiotoxicity, orthostasis, dysphagia, and sedation.[43,46,47]

Proceed with caution

In light of safety concerns and a lack of high-quality evidence for high-dose antipsychotic therapy, alternative solutions for inadequate response to treatment should be considered. Underlying causes of poor response should be addressed, and alternative antipsychotics should be utilized, when appropriate. A clozapine trial remains first-line for TRS. Olanzapine may be the best-supported high-dose antipsychotic alternative when clozapine is not an option. High antipsychotic dosages are not well-studied in patients with genetic polymorphisms or unavoidable drug interactions. Serum antipsychotic concentrations may facilitate dosing in these patients.

If high-dose antipsychotic therapy is deemed necessary, its ongoing appropriateness should be continually re-evaluated. Higher antipsychotic dosages and D2 receptor occupancies may be required to manage acute psychosis, but efficacy may be maintained and adverse effects limited with the use of lower dosages during maintenance treatment.[48,49] Long-term treatment with high-dose antipsychotic therapy should be avoided, when possible. If high-dose antipsychotic therapy is prescribed, the rationale should be well-documented. Dosage adjustments should not be made until steady state is reached on a given dosage. Electrocardiograms should be obtained at baseline, steady state, and routinely thereafter.[3,20] Tolerability should be assessed regularly, and screening for drug interactions should be conducted when new medications are initiated.

Related Resource

- Barnes TRE, Drake R, Paton C, et al. Evidence-based guidelines for the pharmacological treatment of schizophrenia: updated recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2020;34(1):3-78.

Drug Brand Names

Aripiprazole • Abilify
Asenapine • Saphris
Brexpiprazole • Rexulti
Cariprazine • Vraylar
Clozapine • Clozaril
Iloperidone • Fanapt
Lumateperone • Caplyta
Lurasidone • Latuda
Olanzapine • Zyprexa
Paliperidone • Invega
Quetiapine • Seroquel
Risperidone • Risperdal
Risperidone long-acting injection • Risperdal Consta
Ziprasidone • Geodon

CASE CONTINUED

Because Mr. K's serum risperidone level is subtherapeutic (10 ng/mL), his risperidone dosage is cautiously titrated to 10 mg/d, divided (serum concentration: 22 ng/mL). Mr. K develops mild orthostasis but denies other adverse effects. His psychotic symptoms resolve, and he is discharged with education on nonpharmacologic management of orthostasis. The rationale for high-dose risperidone is relayed to his outpatient psychiatrist, as well as a recommendation to monitor Mr. K closely for continued efficacy and tolerability.

Clinical Point

If high-dose antipsychotic therapy is prescribed, the rationale should be well-documented

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continued

Clinical Point

Dosage adjustments should not be made until steady state is reached on a given dosage

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