JCP THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Best Practices for Starting Clozapine in Patients With Schizophrenia:

How to Switch From the Prior Antipsychotic(s)

Georgios Schoretsanitis, MD,[a,b,c] and Jose de Leon, MD[d,e]

Clozapine is a highly efficacious antipsychotic medication and is the standard of care for treatment-resistant schizophrenia (TRS)[1] as well as for reducing the risk of suicidal behaviors[2] and aggression[3] in schizophrenia and schizoaffective disorder. A major obstacle to its use has been tolerability, and efforts have been undertaken to provide advice as to its optimal and safe titration.[4] A prior ASCP Corner column discussed ways of offering clozapine.[5] This article provides advice on how to switch from the prior antipsychotic(s).

To reduce the risk of psychotic relapse, we prefer to add clozapine to a prior antipsychotic or antipsychotics and not to decrease the other antipsychotic dosage until the fourth week or even later, when the clozapine dosage has reached a therapeutic level by providing a plasma concentration of at least 350 ng/mL.

We think that adding clozapine to most individual antipsychotics or antipsychotic combinations is safe, with the exception of the following 4 antipsychotics, which may require slower titrations. These are discussed in turn.

Olanzapine

Olanzapine by itself may not present the risk of myocarditis,[6] but in > 3,000 myocarditis reports worldwide, olanzapine increased the risk of myocarditis seriousness by an odds ratio (OR) of 1.90 (95% confidence interval [CI], 1.35 to 2.68).[7] Olanzapine is mainly metabolized by cytochrome P450 (CYP)1A2, but usually it does not behave as a CYP1A2 inhibitor. In circumstances of saturation of clozapine metabolism, which may occur during myocarditis,[8] olanzapine may behave as a competitive inhibitor of clozapine metabolism. Other adverse drug reactions (ADRs) to consider during the clozapine titration, before olanzapine is discontinued, are sedation and constipation. Both olanzapine and clozapine are antagonists of histaminic (H_1) and muscarinic receptors, and their effects may be additive for, respectively, sedation and constipation. Bowel movements should be monitored, and the need for laxatives should be considered.

Quetiapine

Rarely, quetiapine may be associated with myocarditis during overdose or rapid titration.[6] More importantly, in the large sample of clozapine myocarditis reports,[7] the quetiapine OR was 2.83 (95% CI, 1.82–4.40) for seriousness and 2.12 (95% CI, 1.03–4.35) for lethality. These results suggest that quetiapine may have some pharmacodynamic synergies at the immunologic level that contribute to the risk of myocarditis.[6] Other ADRs to consider during clozapine titration, before quetiapine is discontinued, are sedation and orthostatic hypotension. Both quetiapine and clozapine are antagonists of histaminic (H_1) and α_1 receptors, and their effects may be additive for, respectively, sedation and orthostatic hypotension. The clozapine titration guideline[4] recommends monitoring orthostatic changes in blood pressure and pulse.

Perphenazine

An in vitro study[9] suggests that perphenazine can be an inhibitor of CYP1A2 activity. Thus, it is not surprising that perphenazine can make some clozapine patients behave as poor metabolizers (PMs). Our limited experience in the US[10] and China[11] suggests that perphenazine in therapeutic doses may cause a clinically relevant inhibition of clozapine metabolism in some patients. Clozapine-induced myocarditis was first described in Denmark, and one of the first cases was a patient in whom clozapine was added to perphenazine.[12]

Flupenthixol

Flupenthixol (or "flupentixol") is an antipsychotic used in some European countries and has lesser-known pharmacokinetic properties; according to a case report, it can inhibit clozapine metabolism.[13] Until better studies are

[a]Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zürich, Zürich, Switzerland

[b]The Zucker Hillside Hospital, Psychiatry Research, Northwell Health, Glen Oaks, New York

[c]Department of Psychiatry and Molecular Medicine, Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York

[d]Mental Health Research Center, Eastern State Hospital, Lexington, Kentucky

[e]Biomedical Research Centre in Mental Health Net (CIBERSAM), Santiago Apóstol Hospital, University of the Basque Country, Vitoria, Spain

*Corresponding author: Jose de Leon, MD, Mental Health Research Center at Eastern State Hospital, 1350 Bull Lea Rd, Lexington, KY 40511 (jdeleon@uky.edu).

J Clin Psychiatry 2022;83(4):22ac14500

To cite: Schoretsanitis G, de Leon J. Best practices for starting clozapine in patients with schizophrenia: how to switch from the prior antipsychotic(s). *J Clin Psychiatry.* 2022;83(4):22ac14500.

To share: https://doi.org/10.4088/JCP.22ac14500

Table 1. Updated International Clozapine Titration Guideline for Adult Inpatients for Coprescription of 4 Antipsychotics (Olanzapine/Quetiapine/Perphenazine/Flupenthixol)[a]

	Asian/Native American		European/Western Asian		Black (US extrapolation)[b]	
	PMs, 4 APs[a], and Other PMs[c]	Non-PMs	PMs, 4 APs[a], and Other PMs[c]	Non-PMs	PMs, 4 APs[a], and Other PMs[c]	Non-PMs
Target D	75–150 mg/d	175–300 mg/d	100–200 mg/d	250–400 mg/d	150–300 mg/d	300–600 mg/d
Week 1						
Day 1	6.25 mg	12.5 mg/d	12.5 mg/d	25 mg/d	12.5 mg/d	25 mg/d
↑D by	6.25 mg	12.5 mg/d	12.5 mg/d	25 mg/d	12.5 mg/d	25 mg/d
Day 7	25 mg/d	50 mg/d	50 mg/d	100 mg/d	50 mg/d	100 mg/d
Alert C[d]	< 118 ng/mL	< 105 ng/mL	< 175 ng/mL	< 140 ng/mL	< 117 ng/mL	< 117 ng/mL
Week 2						
↑D by	12.5 mg	12.5 mg/d	12.5 mg/d	25 mg/d	25 mg/d	50 mg/d
Day 14	50 mg/d	100 mg/d	75 mg/d	200 mg/d	100 mg/d	200 mg/d
Alert C[d]	< 235 ng/mL	< 210 ng/mL	< 263 ng/mL	< 280 ng/mL	< 233 ng/mL	< 234 ng/mL
Week 3						
↑D by	12.5 mg/d	25 mg/d	25 mg/d	25/50 mg/d	25 mg/d	50 mg/d
Day 21	75 mg/d	150 mg/d			150 mg/d	300 mg/d
Non-smoking female			100 mg/d	250 mg/d		
Other sex-smoking groups[e]			125 mg/d	300 mg/d		
Alert C[d]	< 353 ng/mL	< 315 ng/mL	< 350 ng/mL	< 350 ng/mL	< 291 ng/mL	< 351 ng/mL
Week 4						
Non-smoking female	75 mg/d	175 mg/d	100 mg/d	250 mg/d	150 mg/d	300 mg/d
Any APs	Stop[f]	Stop[f]	Stop[f]	Stop[f]	Stop[f]	Stop[f]
Trough C[f]	1 week later	1 week later	1 week later	1 week later	1 week later	1 week later
Other sex-smoking groups[e]	75–150 mg/d	175–300 mg/d	100–200 mg/d	250–400 mg/d	150–300	300 mg/d
↑D by	25 mg/d	25/50 mg/d	25/50 mg/d	25/50 mg/d	25/50 mg/d	25/100 mg/d[g]
Any APs	Stop[f]	Stop[f]	Stop[f]	Stop[f]	Stop[f]	Stop[f]
Trough C[h]	1 week later	1 week later	1 week later	1 week later	1 week later	1 week later

[a]This table provides a 1-page summary of 6 titration schedules proposed by the international clozapine guideline.[4] It includes corrections of errors. More importantly, it adds 4 antipsychotics (olanzapine/quetiapine/perphenazine/flupenthixol) as indications for slower titration in each ancestry group and potential for clozapine PM status. These titrations will require updates as new data are available.

[b]The titration schedules for Black patients are extrapolated from the US titration schedules.

[c]Other PMs include those for whom the cause of PM status will be maintained during maintenance treatment, including those with obesity or coprescription of valproate or oral contraceptives.

[d]Concentrations (Cs) before week 4 are not at steady state. Measuring them under steady-state conditions will delay titrations. These Cs are alert signs that the titration may be too fast for that patient. These Cs were estimated in each group using clozapine concentration-to-dose ratios.

[e]The rest of the sex-smoking subgroups (smoking female, non-smoking male, and smoking male).

[f]Any coprescribed AP (olanzapine/quetiapine/perphenazine/flupenthixol or any other AP) can be stopped once the target D of week 4 is reached. Another more conservative option for patients whose psychotic relapses can be more dangerous is to wait until the minimum therapeutic D has been reached.

[g]The main goal of the fourth week in these patients is to get a steady-state trough C on 300 mg/d to predict final dose for that specific patient. After getting the steady-state C, D can be increased by 25, 50, or 100 mg depending on tolerance, time to get results from lab on C, urgency to reach a therapeutic D, and need for discharge. If a very high dose is needed (600 mg/d), it may be better to increase not more than 100 mg/d per week, and so wait to week 6 to reach 600 mg/d, but it is always important to balance all aspects using clinical judgment. Moreover, if the patient is a smoker and admitted to a nonsmoking hospital, it may be necessary to consider adding 100 to 200 mg/d after discharge once the patient begins to smoke after discharge.

[h]Trough C refers to the lowest concentration during the day and is usually measured early in the morning before taking any clozapine dose. *Steady state* refers to the equilibrium between absorption and elimination that occurs in plasma concentrations after changing a drug dose. Steady state is usually described as needing at least 5 drug half-lives. In average patients, at least 5 days are required to achieve clozapine steady-state conditions (by assuming clozapine half-life under repeated dosing is approximately 24 hours; thus, 5 × 24 hours is 5 days). The table proposes a week for steady state, which is easier to remember and implement (in many hospitals, Cs cannot be collected during weekends) than 5 days. Some clozapine PMs may have a clozapine half-life of 48 hours and may need 2 weeks to reach steady state; thus, allotting 1 week to reach steady state is a practical compromise. It may be wise in clozapine PMs to get another C 2 weeks after the maintenance dosage has been selected. The trough steady-state C will be used to estimate the minimum therapeutic D needed to reach 350 ng/mL. Supplementary Table S5 of the international clozapine guideline[4] provides help in estimating this minimum therapeutic D based on different Cs.

Abbreviations: AP = antipsychotic, C = concentration, C/D = concentration-to-dose, D = dose, PM = poor metabolizer.

available, it appears safer to consider any patient treated with flupenthixol as a potential clozapine PM.

Update to Titration Guideline

Table 1 presents a summary of the 6 clozapine titrations proposed by the international clozapine guideline[4] and modifies the 3 titrations for clozapine PMs, which should also be used for patients prescribed olanzapine, quetiapine, perphenazine, and flupenthixol. These modifications may help further increase safety during titration and reduce the risk of clozapine-induced myocarditis; they serve to update the clozapine titration guideline.[4] The table recommends stopping any coprescribed antipsychotic, including any long-acting antipsychotic, in week 4, but another option is to wait until the clozapine dosage has provided the minimum therapeutic concentration of 350 ng/mL. The table provides alert numbers for clozapine concentrations during the first 3 weeks, in non-steady conditions, that may indicate

that the patient is a clozapine PM (eg, through inhibitory effects of perphenazine or flupenthixol). In the absence of rapid access to clozapine concentrations, the guideline[4] recommends measuring C-reactive protein (CRP; measured at baseline and weekly at the same time as the white blood cell count) to detect CRP elevations during titration, which could indicate that the titration used may be too rapid for that specific patient.

Published online: July 4, 2022.

Relevant financial relationships: In the last 3 years, **Dr Schoretsanitis** has served as a consultant for HLS Therapeutics. **Dr de Leon** reports no conflicts of interest.

Funding/support: This article received no support from any funding agency, commercial business, or not-for-profit institution.

Acknowledgment: The authors thank Lorraine Maw, MA (Mental Health Research Center at Eastern State Hospital), for editorial assistance. Ms Maw declares no competing interest during the last 36 months.

ORCID: Georgios Schoretsanitis: https://orcid.org/0000-0002-3851-4117; **Jose de Leon:** https://orcid.org/0000-0002-7756-2314

REFERENCES

1. Siskind D, McCartney L, Goldschlager R, et al. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. *Br J Psychiatry*. 2016;209(5):385–392.
2. Taipale H, Lähteenvuo M, Tanskanen A, et al. Comparative effectiveness of antipsychotics for risk of attempted or completed suicide among persons with schizophrenia. *Schizophr Bull*. 2021;47(1):23–30.
3. Citrome L, Volavka J. Specific anti-hostility effects of atypical antipsychotics in persons with schizophrenia: from clozapine to cariprazine. *Harv Rev Psychiatry*. 2021;29(1):20–34.
4. de Leon J, Schoretsanitis G, Smith RL, et al. An international adult guideline for making clozapine titration safer by using six ancestry-based personalized dosing titrations, CRP, and clozapine levels. *Pharmacopsychiatry*. 2022;55(2):73–86.
5. Rubio JM, Kane JM. How to make an effective offer of clozapine. *J Clin Psychiatry*. 2021;83(1):21ac14000.
6. De Las Cuevas C, Sanz EJ, Rohde C, et al. Association between myocarditis and antipsychotics other than clozapine: a systematic literature review and a pharmacovigilance study using VigiBase. *Expert Rev Clin Pharmacol*. 2022;15(1):65–78.
7. De Las Cuevas C, Sanz EJ, Ruan CJ, et al. Clozapine-associated myocarditis in the World Health Organization's pharmacovigilance database: focus on reports from various countries [published online July 21, 2021]. *Rev Psiquiatr Salud Ment (Engl Ed)*. 2021;21:S1888-9891(21)00070-7.
8. Koenig M, McCollum B, Spivey JK, et al. Four cases of myocarditis in US hospitals possibly associated with clozapine poor metabolism and a comparison with prior published cases. *Neuropsychopharmacol Hung*. 2022;24:29–41.
9. Shin JG, Soukhova N, Flockhart DA. Effect of antipsychotic drugs on human liver cytochrome P-450 (CYP) isoforms in vitro: preferential inhibition of CYP2D6. *Drug Metab Dispos*. 1999;27(9):1078–1084.
10. Cooke C, de Leon J. Adding other antipsychotics to clozapine. *J Clin Psychiatry*. 1999;60(10):710.
11. Ruan CJ, Zang YN, Cheng YH, et al. Around 3% of 1,300 levels were elevated during infections in a retrospective review of 131 Beijing Hospital in-patients with more than 24,000 days of clozapine treatment. *Psychother Psychosom*. 2020;89(4):255–257.
12. Jensen VE, Gøtzsche O. Allergisk myocarditis ved klozapinbehandling [Allergic myocarditis in clozapine treatment]. *Ugeskr Laeger*. 1994;156(28):4151–4152.
13. Wagner X, Kluge M. Abrupt decrease of clozapine plasma concentration after discontinuation of flupentixol comedication. *J Clin Psychopharmacol*. 2019;39(2):168–169.