American Psychiatric Association Draft *Practice Guideline for the Treatment of Patients with Schizophrenia* – Comments due June 28, 2019

Review of any APA *Practice Guideline* allows us to improve the overall guideline but does not imply endorsement by any given individual or any specialty society who participates in the review process.

First Name, Last Name, and Degrees:	Erica Davis, PharmD, BCPS, BCPP, Lisa W. Goldstone, MS, PharmD, BCPS, BCPP, Stephen R. Saklad, PharmD, BCPP, Carol A. Ott, PharmD, BCPP
Organization (if applicable):	College of Psychiatric & Neurologic Pharmacists
E-mail address:	eadavis@rx.umaryland.edu, lwgoldst@usc.edu,
Phone number (optional):	saklad@uthscsa.edu, caott@iupui.edu
Conflicts of interests (if any):	(Saklad) Employee of The University of Texas at Austin College of Pharmacy. Appointed to the Texas Health and Human Services Commission, San Antonio State Hospital and the UT Health San Antonio Long School of Medicine. Consultant for Alkermes and Otsuka. Speakers bureau for Alkermes and Neurocrine. Speaker for several professional organizations. Treasurer for the College of Psychiatric and Neurologic Pharmacists Foundation. Business Development Council for the College of Psychiatric and Neurologic Pharmacists. Expert witness on both defendant and plaintiff sides. No direct stock ownership in pharmaceutical corporations.

May we list you as a Reviewer in the final Guidelines? ☒ Yes ☐ No

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Are you reviewing this guideline as a representative of an allied organization? ☒ Yes ☐ No

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Organization Name: __College of Psychiatric & Neurologic Pharmacists_____

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Page	Line #	Comment	Rationale	References
41	Footnote 4	Footnote #2 indicates that pimavanserin is not included because it is not FDA-approved for schizophrenia, but Nuplazid is then listed under Footnote #4 as a reference		
42-47	Available preparations column	Recommend indicating that these are the available preparations in the United States	Other countries may have additional formulations that are not listed here	
42	Chlorpromazine row, "preparations"	Recommend deleting "50/2 mL (2 mL)" under short-acting injection and simply listing as "25/mL (1 mL, 2 mL)"	For consistency with the remainder of the table	
37	1091–1117	There are additional reasons that an LAI could be considered. Comprehensively should include: • Provide assured adherence • Continuous antipsychotic coverage • Patient with a history of poor adherence • Fewer medications to take daily • Reduced conflict with caregivers about medication • Fewer opportunities for missing a dose • Fewer Cmax-related adverse effects • Clinicians immediately aware of nonadherence Longer window for intervention in nonadherence	Need guideline to be comprehensive. LAIs remain a greatly underutilized modality in the USA and worldwide.	Correll CU, Sliwa JK, Najarian DM, and Saklad SR. Practical considerations for managing breakthrough psychosis and symptomatic worsening in patients with schizophrenia on long-acting injectable antipsychotics. CNS Spectrums. 2019. doi:10.1017/S1092852918001098
42	Fluphenazine row, "preparations"	List of preparations should include "Elixir: 2.5/5 mL (60 mL)"	Another available preparation in the US	

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42	Loxapine row, "comments"	Recommend including that Adasuve can only be given once per day	Important to include max dosing for reference purposes	Prescribing information, section 2.1: https://www.adasuve.com/PDF/AdasuvePI.pdf
43, 49, 57, 59, 60	Pimozide rows	Recommend removing pimozide from tables, if it is maintained, recommend addition of avoidance of CYP1A2 and CYP3A4 inducers and inhibitors with pimozide.	Pimavanserin was not included as it does not carry the FDA indication for schizophrenia. While pimozide can be used off-label for psychosis, it is also not FDA approved for schizophrenia	Prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/017473s041lbl.pdf
44	Asenapine row, "comments"	Replace "Giving with food or liquid reduces absorption" to "Do not eat/drink for 10 minutes after administration"	To make it clearer how the medication should be administered	Prescribing information, section 2.1: https://www.allergan.com/assets/pdf/saphris_pi
46	Olanzapine row, "preparations"	Recommend indicating that short-acting IM is "10/2 mL"	Consistency and accuracy	
46	Olanzapine row, "comments"	Recommend including why concomitant use of IM olanzapine with benzos is not recommended and also indicate that it is parenteral benzos only	Especially important to note that this is a potentially fatal combination rather than a soft recommendation	Prescribing information, section 5.7: https://pi.lilly.com/us/zyprexa-pi.pdf
46	Paliperidone row, "comments"	Recommend changing "more than 4 days" to "more than 5 days"	To be consistent with the package insert	Prescribing information, section 2.1: http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVEGA-pi.pdf
47	Risperidone row, "comments"	Recommend revising the comment regarding avoiding CYP3A4 inducers or inhibitors, no adjustment is required for this interaction for oral medications. Recommend to retain this information for Table 8 – Perseris LAI dosage form as this dose adjustment is recommended for the injection formulation.	To be consistent with the prescribing information	Prescribing information: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=701e1cd8-2868-4d29-85a9-a2212c88165f
48-56	Bioavailability column	Recommend indicating that this is oral bioavailability		

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48-56	Elimination half-life column	Recommend indicating that this is half-life in adults	Half-life can change depending on the patient's age	
53	Lurasidone row, "comments"	Creatinine clearance should be "mL/min" (not mg/min)		
61	Clozapine row, "comments"	Recommend changing "agranulocytosis" to "severe neutropenia"	To reflect new language used by the clozapine REMS	REMS, Section 2: https://www.clozapinerems.com/CpmgClozapineUI/rems/pdf/resources/Clozapine_REMS_A_Guide_for_Healthcare_Providers.pdf
62	Ziprasidone row, "QT prolongation"	Ziprasidone should have at least 2, maybe 3 +'s	A lot of literature to support ziprasidone's ability to prolong the QTc	Harrigan EP, Miceli JJ, Anziano R, et al. J Clin Psychopharmacol. 2004;24:62-69.
63	Haloperidol row, "available strengths"	Recommend including that haloperidol decanoate comes in both 1 mL and 5 mL vials		
64	Risperidone row, "available strengths"	Recommend including volume: "90/0.6 mL, 120/0.8 mL"	To be consistent within the table (see paliperidone palmitate and aripiprazole lauroxil)	
65	Fluphenazine row, "dose conversions"	IM to PO ratio should be 10:12.5 or 1:1.25 (not 1:2.5, which would give 10:25)		
67	Paliperidone palmitate (Sustenna) row, "dose conversions"	Recommend indicating that these doses are monthly	For consistency and clarification	
67	Paliperidone palmitate (Trinza) row,	Missing "mg" after 819		

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	"dose conversions"			
74	1353	"(ANC <500)" needs units		
74	1355-6	"In patients who have stopped or interrupted treatment with clozapine for 30 days or more, the monitoring frequency for treatment initiation will be needed." Recommend adding a statement that a restart of the dose titration will also be needed.	Restarting the dose titration is required for patients who have had even a brief lapse in treatment to avoid dose-related side effects, including orthostatic hypotension, seizures, and neutropenia.	Prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019758s062lbl.pdf
77	1451-52	Recommend including "or dose increase"	NMS is more likely to occur when antipsychotics are initiated as well as when doses are increased	DSM-5: "Parenteral administration routes, rapid titration rates, and *higher total drug dosages* have been associated with increased risk"
77	1477-82	Dermatological reactions can also occur with risperidone, clozapine, olanzapine, quetiapine, and haloperidol, including hyperpigmentation and cutaneous reactions. Recommend to add these medications to the guideline statement.	Dermatological reactions have been associated with other antipsychotic medications in addition to thioridazine and chlorpromazine.	Bliss SA, Warnock JK. Psychiatric medications: adverse cutaneous drug reactions. Clinics in Dermatology 2013;31:101-9. PMID 23245981 doi:10.1016/j.clindermatol.2011.11.014.
80	1566-7	Recommend to add iloperidone and paliperidone to the list of medications in this statement with a risk of QTc prolongation.	Iloperidone and paliperidone both have warnings in the prescribing information related to QTc prolongation.	Prescribing information: (iloperidone) https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=eeb0fcfd-e4e8-4fb1-9635-901dc9446235 (paliperidone) https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=74702340-19bf-467e-80cd-68dca9d374d2
83	1707	Change "agranulocytosis" to "severe neutropenia"	As above to reflect new language in clozapine REMS	

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86	1808	Recommend indicating that NMS is self-limited with "resolution within a week of medication discontinuation"	To avoid confusion that it will go away even if medications are not stopped	
87	1843	Insert "for" before "delineating"	Sentence flow	
87	1862-1865	Recommend indicating that another risk factor for TD is long-term treatment with antipsychotics	DSM-5 indicates TD diagnosis can only be made after use of a neuroleptic for "at least a few months", making this an important risk factor for clinicians to be aware of	
90	1948-1950	Recommend rewording sentence starting with "Its etiology…"	This sentence is confusing as written	
92	2033	Missing comma between "akathisia" and "parkinsonism"		
95	2160	The requirement for two trials appears to be unjustified in light of more recent findings and should be reduced to a single adequate trial.	Excessive duration of inadequate or partially effective treatment is associated with poorer function and overall outcome.	Hahn RS, 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. http://dx.doi.org/10/1016/S2215-0366(18)30252-9.
96	2184	The education about the need for use of clozapine after one or two failed adequate trials with good adherence and tolerability is greatly lacking and should be emphasized much more strongly in this guideline. Withholding a potentially effective agent like clozapine is unethical.		
96	2200	Recommend indicating that a gap of 48 hours or more requires retitration	Many clinicians are unaware of the specific time frame; therefore, it	Package insert, section 2.5: http://clozaril.com/wp-

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			would be prudent to include this for completeness	content/themes/eyesite/pi/Clozaril_PI.pdf
97	2221	Should "about" be "above"?		
97	2225	Suggest discussing the clozapine to norclozapine ratio in a little more detail, including the typically "desired" ratio of 2		Legaré N et al. Medical hypotheses 2013;80(6):689-691.
97	2249	"(ANC <500)" needs units		
97	2249	Disagree that the highest risk of severe neutropenia is only in the "initial month". Would argue that the highest risk is within the first 4-5 months	Package insert states that the "Risk of neutropenia appears greatest during the first 18 weeks on treatment and then declines."	Package insert, section 5.1: http://clozaril.com/wp-content/themes/eyesite/pi/Clozaril_PI.pdf
99	2295	Would caution against recommending bulk forming laxatives like psyllium	Due to increased risk for obstruction	Many references including Bailey et al. Ther Adv Psychopharmacol. 2015;5(5):256-562.
105	2502	Please include this meta-analysis reference in support of ECT in clozapine refractory patients. This meta-analysis reported that ECT was effective: SMD = 1.5 [1.06, 1.94] P = 0.000		Ahmed S, et al. Combined use of electroconvulsive therapy and antipsychotics (both clozapine and non-clozapine) in treatment resistant schizophrenia: a comparative meta-analysis. Heliyon 2017;3:e00429. doi: 10.1016/j.heliyon.2017.e00429.
111	2750-1	This section notes the possibility of clinical destabilization; recommend to consider adding a statement that takes into account the risk of withdrawal symptoms and rebound psychosis relative to the differing pharmacology of the antipsychotic medications	Longer cross-titration schedules may be needed to avoid these risks.	Cerovecki A, et al. Withdrawal symptoms and rebound syndromes associated with switch and discontinuing atypical antipsychotics: theoretical background and practical recommendations. CNS Drugs 2013;27:545-72. PMID 23821039. doi:10.1007/s40263-013-0079-5.

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120	Benztropine column, "time to peak"	Indicate that this is for oral formulation only. Recommend including that IM formulation onset is within minutes		
121	Amantadine column, "comments"	There should be some discussion about the potential for diminished therapeutic effect of antipsychotics with amantadine	Due to its dopamine agonist properties	
125	3147	Recommend including that beta-blockers can lower both blood pressure and heart rate		
128	Valbenazine column, "hepatic impairment"	Maximum dose should be "40 mg" not 80 mg		Package insert, section 2.2: https://www.ingrezza.com/PI
234-9		Consider adding a statement regarding a lack of comparative evidence for newer SGAs (brexpiprazole and cariprazine)		
250		There is a recommendation for the use of anticholinergic medication based upon low evidence. Recommend adding a statement regarding the risk versus benefit of the long-term use of anticholinergic medications.		
250		Benzodiazepines or beta-adrenergic blocking agents are recommended for use in the treatment of akathisia. Recommend that more specific information be provided relative to specific benzodiazepines (e.g. lorazepam) and beta blockers (e.g. propranolol) rather than generally stating the drug classes.		
252-5		The reason for Table C-2 is unclear. Is this table simply a review of available published systematic review or should these be taken as a recommendation for the use of VMAT2		

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		inhibitors? VMAT2 inhibitors are expensive and not available to all patients. Amantadine is not included in the table and there is a statement regarding insufficient evidence. Does this suggest that APA considers everything in the table as a possible option for treatment? Recommend to consider clarification.		
–	–	General comment about comparisons between oral and LAI antipsychotics study methodology. While significant differences are observed in a metal analysis of RTCs, cohort studies do show the clinician-expected advantage of LAIs over oral (hospitalization rate and all cause discontinuation). RTCs are confounded by both an increased attention to the patients' medication taking-behavior by the study design and an adherence selection bias in recruiting patients into an RTC.	Guideline appears to limit use of LAIs excessively.	Kishimoto T, Robenzadeh A, Leucht C, Leucht S, Watanabe K, Mimura M, Borenstein M, Kane JM, and Correll CU. Long-Acting Injectable vs Oral Antipsychotics for Relapse Prevention in Schizophrenia: A Meta-Analysis of Randomized Trials. Schizophrenia Bulletin 2014;40(1):192–213. doi:10.1093/schbul/sbs150 Kishimoto T, Hagi K, Nitta M, Leucht S, Olfson M, Kane JM, and Correll CU. Effectiveness of Long-Acting Injectable vs Oral Antipsychotics in Patients With Schizophrenia: A Meta-analysis of Prospective and Retrospective Cohort Studies. Schizophrenia Bulletin 2018;44(3):603–619. doi:10.1093/schbul/sbx090