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Initiating and Switching Antipsychotic Medications In Schizophrenia

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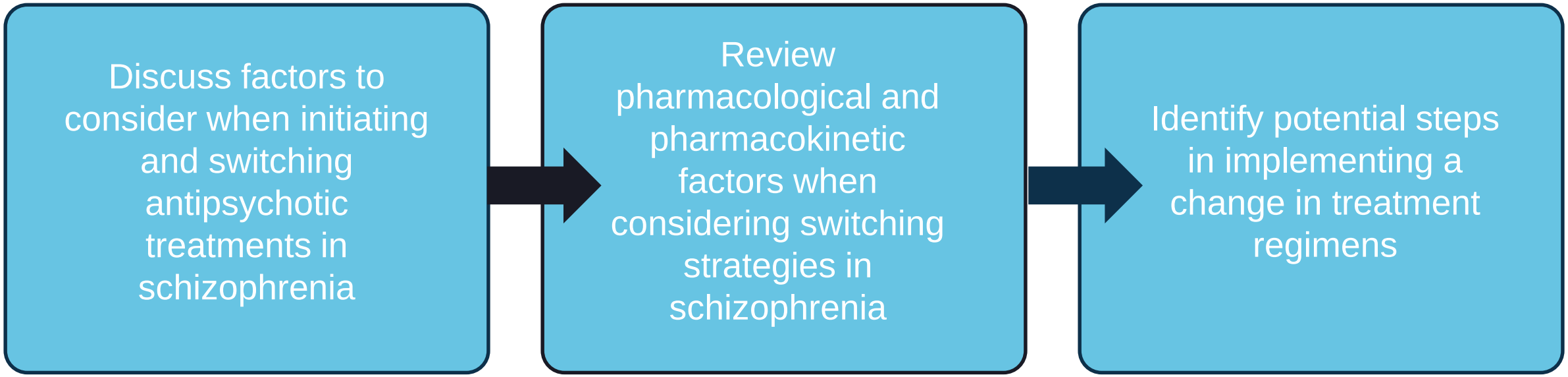
Objectives



Treatment Considerations for Schizophrenia

Schizophrenia is a lifelong condition that often requires ongoing treatment[1,2]

More than 80% of patients relapsed within 5 years following disease onset in one study (N=104)[3]

There are many reasons for relapse (e.g., patients may no longer respond to medication or may relapse despite treatment adherence)[4-6]

Relapse prevention is a major challenge in the care of patients with schizophrenia[3]

Patients with schizophrenia may be prescribed numerous different antipsychotic treatments throughout a lifetime[7]

1. Lieberman JA, et al. Biol Psychiatry. 2001;50(11):884-97;
2. Zhang C, et al. Curr Treat Options Psych. 2001; 3(2):111-8;
3. Robinson D, et al. Arch Gen Psychiatry. 1999;56(3):241-7;
4. Weiden PJ, et al. Schizophr Bull. 1995;21(3):419-29;
5. APA Practice Guideline (2nd ed) 2004:1-114;
6. Leucht S, et al. Am J Psychiatry. 2003;160(7):1209-22;
7. Jonsson, et al. Psychiatry Res. 2011;187(1-2):80–88.

Antipsychotic Switching and Polypharmacy

Switching

- Patients with schizophrenia may undergo cycles of “trial and error” to determine the optimal drug at a dose that is sufficiently efficacious and tolerable[1,2]
- A post hoc analysis of data from a 1-year United States-based study of antipsychotic medications in over 600 patients with schizophrenia showed that almost one-third of patients switched antipsychotic treatment before the end of the study[3]

Antipsychotic Polypharmacy (APP)

- Polypharmacy is often based on perceived potential clinical benefit rather than potential clinical benefit related to receptor profiles[4]
- Polypharmacy is widespread:
  - 19% of new episode schizophrenia cases in a Veteran's Affairs sample (N=1,923)[5]
  - 42.5% of community-based patients with schizophrenia (N = 200)[6]
- Review of studies that enrolled large patient groups revealed that a certain proportion of select patients can benefit from APP without further negative consequences in general.[7]

APP = antipsychotic polypharmacy

1. Arango et al. Schizophr Bull. 2015;41:546–549;
2. Ikeda M, et al. Biol Psychiatry. 2010;67(3):263-9;
3. Nyhuis AW, et al. BMC Psychiatry. 2010;10:75;
4. Langan J, et al. The Psychiatrist. 2010;34:58–62;
5. Gören J, et al. Psychiatr Serv. 2013;64:527–533;
6. Pickar D, et al. PLOS One. 2008;3(9):e3150.
7. Lin et al. International Jn Neuropsychopharm 2020; 23(2): 125–131.

Indications for Antipsychotic Treatment Switching

- Poor treatment response*:
  - Persisting and impairing positive or negative symptoms[1,2]
  - Persisting and impairing mood symptoms or cognitive impairment[1,2]
  - Little-to-no improvement in psychosocial functioning[1,2]
  - Relapse or clinical instability due to poor adherence in an otherwise treatment-responsive patient[2,3]
  - Ongoing high suicide risk despite otherwise adequate antipsychotic therapy[4]
- Intolerable adverse effects:
  - Severe adverse effects[2]
  - Metabolic adverse events[5]
  - Adverse effects leading to threatened or actual nonadherence[6]
  - Aggravation of general medical condition by an antipsychotic drug[7]
  - Adverse-effect burden clearly increased as a result of specific drug-drug interaction(s)[7]
- Request of patients and/or caregivers[7]
- Other reasons:[2]
  - Reduce the cost of treatment
  - Simplify the dosing schedule

*Assuming the pre-switch antipsychotic agent was of adequate dose and duration and that other factors associated with poor antipsychotic treatment response have been ruled out.

1. Masand PS, et al. Ann Pharmacother. 2000;34(2):200-7;
2. Masand PS. Prim Care Companion J Clin Psychiatry. 2005;7(3):121-9;
3. Kane JM. J Clin Psychiatry. 2003;64(suppl 16):34-40;
4. APA Practice Guideline (2nd edition) 2004:1-114;
5. Stroup TS, et al. Am J Psychiatry. 2011;168:947–956;
6. Ganguli R. Am J Health-Syst Pharm. 2002;59(suppl 8):S22-S26;
7. Burns T, et al. Curr Med Res Opin. 2002;18(4):201-8.

Switching an Antipsychotic Medication: Individualized Considerations

Patient-related[1-4]

- Age
- Medical history
- Life stressors/family surroundings
- Substance use
- Previous experience with switching medications
- Ability to follow instructions, level of supervision
- Time commitment/demands on treatment team

Medication-related[1,5]

- Type and dose of antipsychotic discontinued
- Previous duration of treatment
- Concomitant medication
- Pharmacoeconomic issues
- Pharmacokinetic considerations
- Pharmacologic considerations

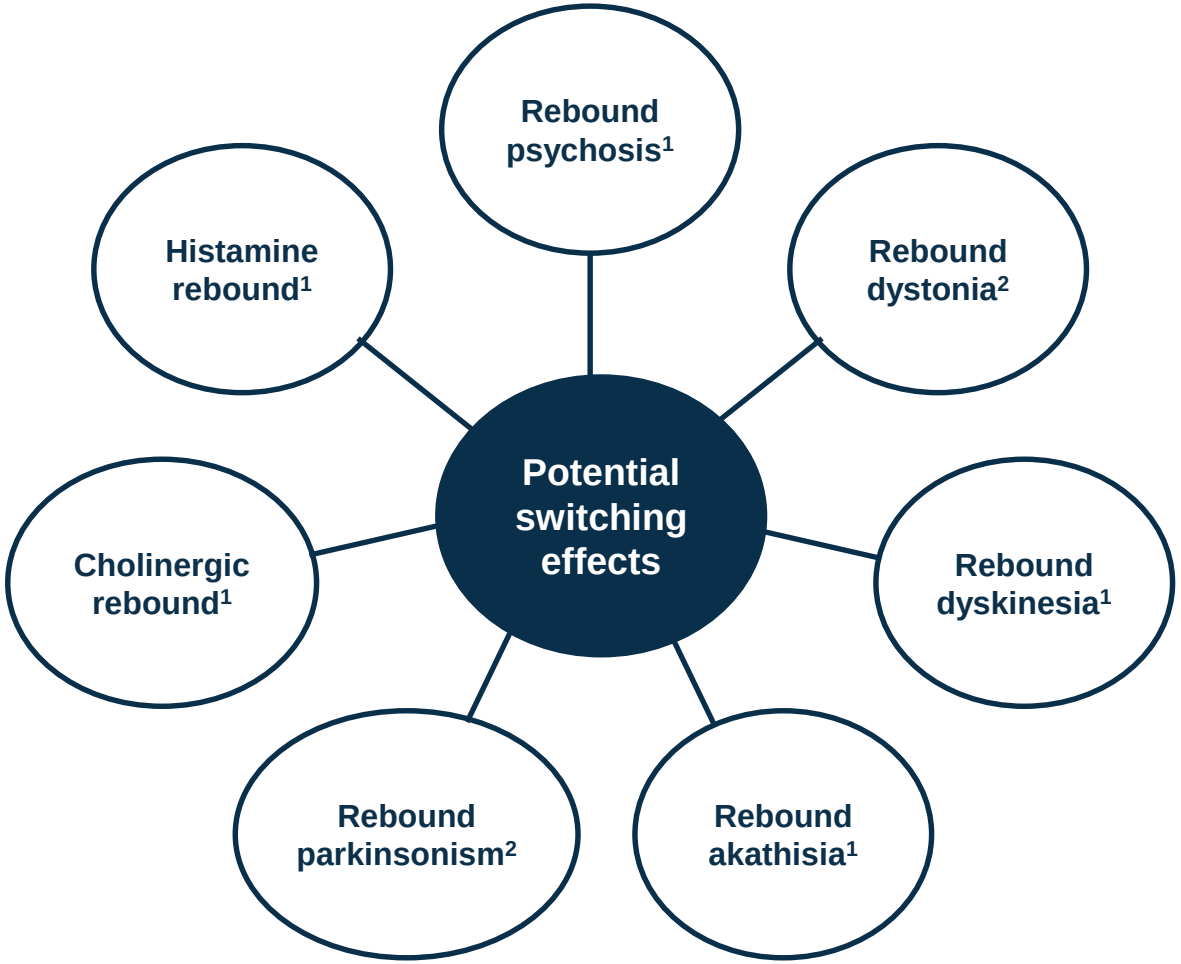
Illness-related[1]

- Psychiatric diagnosis
- Inpatient or outpatient
- Acute/chronic phase
- Severity of illness

1. Burns T, et al. Curr Med Res Opin. 2002;18:201–208;
2. Masand PS, et al. Ann Pharmacother. 2000;34(2):200-7;
3. Weiden PJ, et al. J Clin Psychiatry. 1998;59(suppl 19):36-49.
4. Law MR, et al. Psychiatr Serv. 2008;59(5):540-6;
5. Correll CU. Eur Psychiatry. 2010;25:S12–S21.

Pharmacologic and Pharmacokinetic Considerations

Potential Withdrawal Effects When Switching Antipsychotic Treatments



1. Correll CU. Eur Psychiatry. 2010;25:S12–S21.
2. Burns T, et al. Curr Med Res Opin. 2002;18:201–208.

Receptor-based Causes of Withdrawal and Rebound Effects1

- Differences in binding affinities between compounds
- Exposure of previously blocked (ie, upregulated) receptors to endogenous ligand
- Variations in proportionality of receptor types targeted by new drug

Receptor Type	Potential Rebound/Withdrawal Effects
Dopamine (D_2)	Psychosis, mania, agitation, akathisia, withdrawal dyskinesia
Adrenergic (α_1)	Tachycardia, hypertension
Adrenergic (α_2)	Hypotension
Histamine (H_1)	Anxiety, agitation, insomnia, restlessness, EPS/akathisia
Muscarinic (central; M_1)	Agitation, confusion, psychosis, anxiety, insomnia, sialorrhea, EPS/akathisia
Muscarinic (peripheral; M_{2-4})	Diarrhea, sweating, nausea, vomiting, bradycardia, hypotension, syncope
5-HT_{1A} (partial agonism)	Anxiety, EPS/akathisia
5-HT_{2A}	EPS/akathisia, possible psychosis
5-HT_{2C}	Possible decreased appetite

5-HT, serotonin; EPS, extrapyramidal symptoms.

1. 1. Correll CU. *Eur Psychiatry.* 2010;25:S12–S21.

Pharmacokinetic Properties

Pharmacokinetic (PK) properties, which refer to the absorption, distribution, metabolism and elimination (ADME) of a drug, are an important consideration when switching medications[1,2]

- A change in formulation can alter the PK parameters of a drug (i.e., oral versus injectable)[3]

The potential for altered PK parameters or additional adverse effects can be considered when two or more antipsychotic drugs are used concomitantly, even for a short period[4]

- Cytochrome P450 isoenzymes are involved in many elimination pathways, and induction or inhibition can change concentration levels[4]
- Caution is warranted when cross-tapering antipsychotic treatments eliminated via the same cytochrome P450 subsystem[4]

An individual's enzyme metabolic status (i.e., poor metabolizer, extensive [fast] metabolizer) can also be considered[5]

1. Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 4th Edition. New York, NY: Cambridge University Press; 2013.
2. Correll CU. Eur Psychiatry. 2010;25:S12–S21;
3. Mallikaarjun S, et al. Schizophr Res. 2013;150(1):281-8.
4. Edlinger M, et al. CNS Drugs. 2005;19:27–42;
5. Arranz MJ, et al. Mol Psychiatry. 2007;12:707–747.

Practice Guidelines and Antipsychotic Switching Strategies in Schizophrenia

Practice Guidelines

2020 APA 3rd Ed. (American Psychiatric Association)[1]	Patients whose symptoms have improved with an antipsychotic medication should continue to be treated with an antipsychotic medication.
	Patients receive treatment with a long-acting injectable antipsychotic medication (LAI) if they prefer such treatment or if they have a history of poor or uncertain adherence.
	Antipsychotics should be implemented in the context of a person-centered treatment plan that includes evidence-based nonpharmacological and pharmacological treatments for schizophrenia.
Florida Medicaid[2]	*Level 1:* Monotherapy with an SGA is recommended – either oral, or oral SGA followed by the same SGA-LAI. If the initial trial is unsuccessful, try monotherapy with another SGA (either oral or LAI) with low metabolic adverse effects
	Level 2A: If non-adherent or refractory to Level 1, try LAI. Additional recommendations provided if Level 1 is ineffective in at least two trials.
	Level 3: If Levels 1 and 2 are ineffective or not well tolerated, conduct diagnostic review, try clozapine if not tried earlier, or try antipsychotic + ECT. Additional recommendations provided for partial or incomplete response.
German Assoc. for Psychiatry, Psychotherapy, and Psychosomatics[3]	Recommend the oral route of administration in cooperative patients, unless the patient requests a different route.
	Because of their guaranteed administration and good bioavailability, depot antipsychotics are an effective alternative to oral medication. Suggest offering depot antipsychotics as an alternative treatment for relapse prevention.

ECT, Electroconvulsive Therapy; SGA: Second Generation Antipsychotic; LAI: Long Acting Injectable

1. https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines. Accessed May 12, 2021.
2. http://floridabhcenter.org/documents/2019%20Psychotherapeutic%20Medication%20Guidelines%20for%20Adults%20with%20References_06-04-20. Accessed June 7, 2021.
3. https://www.awmf.org/fileadmin/user_upload/Leitlinien/038_D_G_f_Psychiatrie__Psychotherapie_und_Nervenheilkunde/038-009e_S3_Schizophrenie_2020-01. Accessed June 8, 2021.

APA Practice Guideline: SMI Adviser Commentary

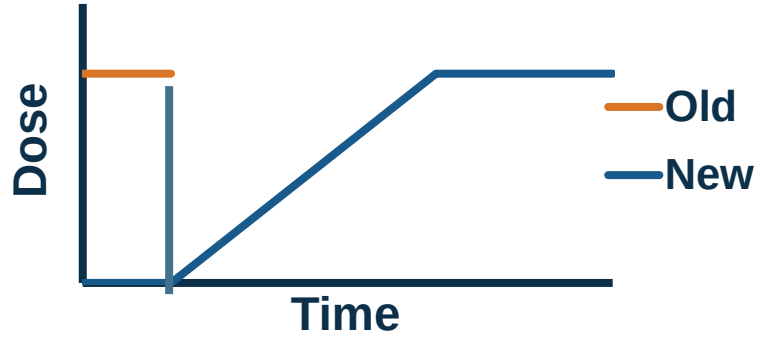
- Patient can only express a preference if LAIs are offered by the clinician as a good alternative to oral antipsychotics
- LAIs are a possible choice for any stage of illness, including first-episode psychosis
- LAIs are specifically suggested if non-adherence is known or a clinical possibility
- Consideration of non-adherence is important to avoid mistakenly labeling a patient as treatment-resistant; A time-limited LAI trial can resolve this uncertainty around adherence
- APA adds that all pharmacological treatments "should be implemented in the context of a person-centered treatment plan that includes evidence-based nonpharmacological and pharmacological treatments for schizophrenia."
  - Emphasis: Simply prescribing an LAI does not constitute good psychiatric care
- APA Guideline is consistent with a recent, extensively revised German Schizophrenia Guideline
  - German Guideline emphasizes that LAIs are an evidence-based and effective choice for patients who require antipsychotic maintenance treatment in order to prevent a relapse.
  - German Guideline adds that choosing an LAI is guided by side effects and injection interval, not efficacy differences.

LAI, long-acting injectable antipsychotic; APA, American Psychiatric Association

1. https://smiadviser.org/knowledge_post/what-do-apas-schizophrenia-treatment-guidelines-say-about-long-acting-injectable-antipsychotics

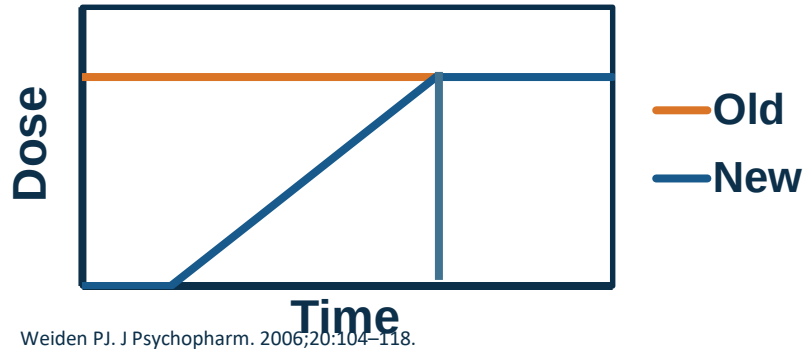
Switching Options in Oral Therapy: Abrupt Antipsychotic Discontinuation and Replacement

A) Before Initiation of New Drug Therapy[1]



Clinical Considerations	
May minimize potential administration and dosing errors[1]	Patient is exposed to suboptimal therapeutic dosage[1] May be associated with withdrawal syndromes[1,2] Possible increase in symptom exacerbation[1]

B) Once Reaching Therapeutic Dose of New Medication[1,2]

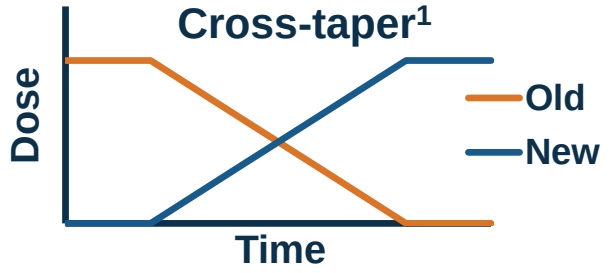


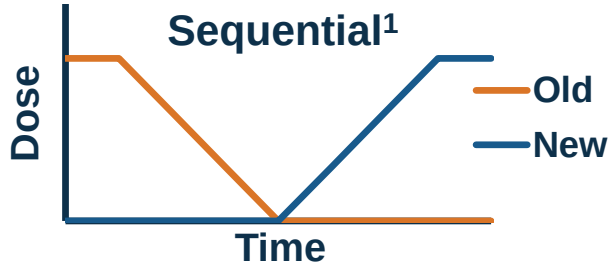
Clinical Considerations
Patient is exposed to side effects of 2 medications[1]
Possibility for adverse drug–drug interactions[2]
Potential for medication administration/dosing errors[3]

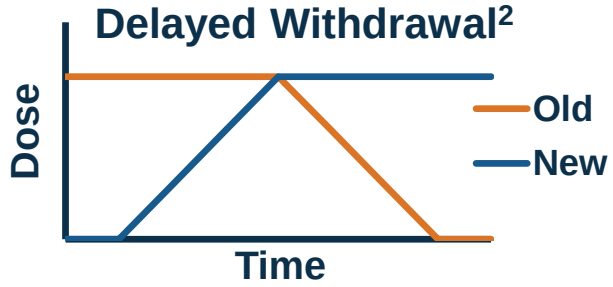
Note: Based on patients with schizophrenia.

1. Weiden PJ. J Psychopharm. 2006;20:104–118.
2. Edlinger M, et al. CNS Drugs. 2005;19:27–42.
3. Burns T, et al. Curr Med Res Opin. 2002;18(4):201-8.

Switching Options in Oral Therapy: Gradual Antipsychotic Discontinuation and Replacement1,2







Clinical Considerations	
• Potential risk of breakthrough psychosis/relapse[2]	• Patient may be exposed to subtherapeutic doses of both medications[2] • Potential risk for drug interactions[1]
• Lower risk of withdrawal symptoms[1] • Lower risk of drug interactions[1]	• Patient may be exposed to subtherapeutic doses[1] • Potential risk of symptom exacerbation[1]
• Avoids exposure to subtherapeutic doses[2]	• Potential risk for side effects of 2 medications[2]

Note: Based on patients with schizophrenia.

1. Edlinger M, et al. CNS Drugs. 2005;19:27–42.
2. Weiden PJ. J Psychopharm. 2006;20:104–118.

Additional Considerations

	Abrupt discontinuation	Cross-tapering	Overlap and discontinuation
When to consider	Severe adverse effects from pre-switch antipsychotic treatment[1]; patient taking a low dose of pre-switch antipsychotic treatment[1]; absent history of acute adverse outcomes following antipsychotic treatment withdrawal[1]; patient taking long-acting injectable antipsychotic agent[2]	Appropriate for most routine clinical situations[1]; pre-switch antipsychotic treatment has clinically significant anticholinergic properties[1]; pre-switch antipsychotic treatment has clinically significant antihistaminergic properties; for elderly patients (very slowly)[1]	Appropriate for patients who were recently stabilized but require antipsychotic treatment switch[2]; perhaps safest for patients with high potential for relapse[2]
When to avoid	Switching from atypical antipsychotic (dibenzodiazepine derivative) (unless discontinuing due to severe adverse effect)[2]; switching from other antipsychotic treatments with potent anticholinergic properties[1]	Urgent switch is required (usually because of severe adverse effects)[1]	Urgent switch is required (usually because of severe adverse effects)[1]
Setting	Inpatient[1]	Inpatient (rapid); outpatient (slower)[1]	Outpatient[3]

1. Burns T, et al. Curr Med Res Opin. 2002;18(4):201-8.
2. Ganguli R, et al. Am J Health-Syst Pharm. 2002;59(suppl 8):S22-S26.
3. Weiden PJ. J Psychopharm. 2006;20:104–118.

Switching To and From LAI Antipsychotic Medication1

LAI → LAI

- Substitute the new LAI for the previous one at a planned injection appointment
- Equivalent of a cross-taper oral switch

LAI → Oral

- Stop the LAI, and the natural plasma level decay provides antipsychotic agent coverage while the new oral agent builds to steady state
- May take weeks or months for the LAI medication to wash out, with the oral agent achieving steady state within 5 to 10 days

Oral → LAI

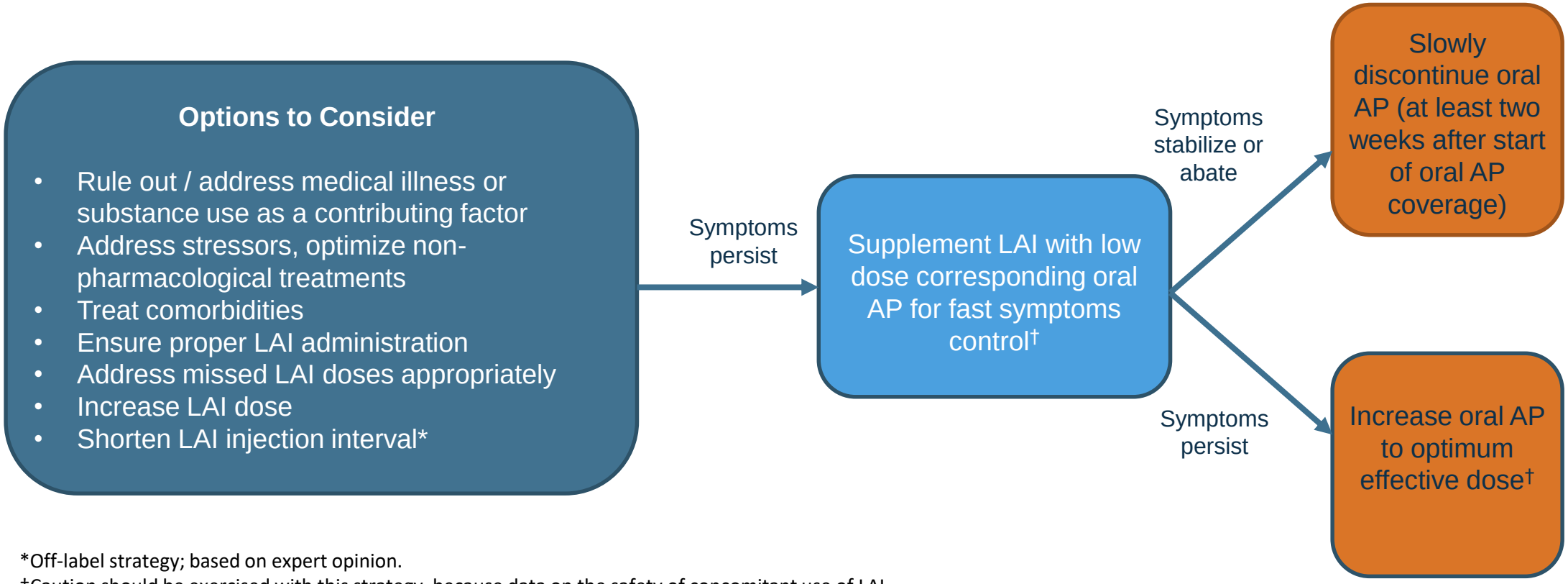
- What are the equivalent doses?
- What is the expected time to steady state of the LAI medication?
- Should a loading strategy be planned?
- What are the potential interactions between the 2 agents?

For all these scenarios, be careful to avoid cholinergic rebound, sedative-withdrawal rebound, and any switching/withdrawal motor syndromes

LAI, long-acting injectable antipsychotic

1. 1. Haddad P, et al. Antipsychotic long-acting injections. Oxford University Press; 2011.

Florida Medicaid Guidelines: Management of Breakthrough Psychosis with LAIs



*Off-label strategy; based on expert opinion.
†Caution should be exercised with this strategy, because data on the safety of concomitant use of LAI and oral APs are limited, especially over extended periods of time.

1. LAI, long-acting injectable antipsychotic; AP, antipsychotic
2. http://floridabhcenter.org/documents/2019%20Psychotherapeutic%20Medication%20Guidelines%20for%20Adults%20with%20References_06-04-20. Accessed June 7, 2021

Implementing a Change in Treatment Regimen

Steps in Deciding on an Elective Antipsychotic Switch

- Recommendations from the literature
- Identify target symptoms and side effects
- Translate those therapeutic targets into outcomes that can be tracked
- Determine if the therapeutic target is amenable to a pharmacologic intervention
- Optimize current treatment regimens, if possible
- Evaluate the appropriateness of adjunctive interventions
- Conduct risk/benefit assessment with the patients

1. Newcomer JW, et al. J Clin Psychiatry. 2013;74:1108–1120.

Steps in Implementing a Switch

- Recommendations from the literature
- Educate the patient about the benefits/risks of the new medication
- Select the next medication in conjunction with the patient
- Make a plan for switching antipsychotic treatments with attention to the potential sleep-wake effects of both treatments
- Monitor the patient more closely during the switch
- Be alert for rebound and new-onset side effects
- Provide short-term medication to manage sleep disturbances, agitation, and anxiety
- Evaluate efficacy and safety/tolerability outcomes

1. Newcomer JW, et al. J Clin Psychiatry. 2013;74:1108–1120.

Summary

- Indicators for switching antipsychotic treatments include poor treatment response and intolerable adverse effects[1]
- Many clinical considerations can be considered before deciding on a switch strategy (cross-taper, sequential, delayed withdrawal)[2,3]
- Potential withdrawal effects associated with switching antipsychotic treatments include rebound of psychosis, dystonia, dyskinesia, akathisia, parkinsonism, histamine, and cholinergic[4,5]
- Recommendations suggest patients be actively involved during the implementation of a switch, including being educated about the benefits/risks of the potential new medication and being involved in the selection of the new medication[6]

1. 1. Ganguli R. Am J Health-Syst Pharm. 2002;59 (Suppl 8):S22-6;
2. Edlinger M, et al. CNS Drugs. 2005;19:27–42;
3. Weiden PJ. J Psychopharm. 2006;20:104–118;
4. Correll CU. Eur Psychiatry. 2010;25:S12–S21;
5. Burns T, et al. Curr Med Res Opin. 2002;18:201–208;
6. Newcomer JW, et al. J Clin Psychiatry. 2013;74:1108–1120.

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