Guide to

LONG-ACTING MEDICATIONS

Antipsychotic Medications and Medication-assisted Treatment Medications for Clinicians and Organizations

NATIONAL COUNCIL
for Mental Wellbeing

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INTRODUCTION: CALL TO ACTION

This guide to long-acting medications (LAMs) is a call to action for psychiatrists, other clinicians and mental health and substance use treatment organizations to increase the use of LAMs, which are also known as long-acting injectables (LAIs). ("Injectables" may arouse a negative reaction.) Drawing upon clinical guidance developed by the American Association of Community Psychiatrists (AACP) and research evidence from the National Institute for Mental Health (NIMH) and others, the National Council for Mental Wellbeing believes that all community mental health and substance use treatment clinicians should provide LAMs as a first-line treatment option to patients and encourages its members to increase and support the safe and effective use of LAMs. Currently, LAMs are most often used as a strategy to address medication nonadherence; however, research supports the use of LAMs as first-tier medications, rather than as a second- or third-tier approach.

This guide is a call to action for using LAMs to treat psychotic disorders, bipolar disorder, opioid use disorder (OUD) and alcohol use disorder (AUD). These disorders share compelling common factors:

1. They are commonly present in patients coming in for evaluation and treatment.
2. Medication is an evidence-based first-line treatment.
3. All four conditions have high rates of suicide.
4. All four conditions have high rates of medication nonadherence for oral/ sublingual (SL)preparations
5. All four conditions have underutilized and effective long-acting injectable formulations that substantially improve treatment outcomes.

The underutilization of LAMs is the result of ineffective strategies to educate and support their use in patient and provider populations. These recommendations are intended for psychiatrists and other clinicians. However, they require organizations to actively establish systems to educate staff, patients and families about the safe and effective use of LAMs and infrastructure, policies and procedures need to deliver this method of treatment. It is further recommended that organizations establish a continuous quality improvement (CQI) process to make necessary improvements that will increase patient understanding of and access to LAMs. Collecting, analyzing and using data is critical to monitoring progress and guiding the change process.

WHAT THE SCIENCE TELLS US

Antipsychotic LAMs

The idea that early treatment leads to better outcomes is standard in medicine, just as early detection offers better prognosis. The longer an illness is left unchecked and unmanaged, the more complex and difficult treatment becomes. Although research is still clarifying the neurodevelopmental aspects of schizophrenia, there is enough science to demonstrate the neurodegenerative effects each psychotic episode has on the brain tissue of a person with psychosis. To avoid further neurodegeneration, some experts have urged psychiatrists to approach treatment of psychosis in much the same way they would treat a heart attack — as something that must be prevented from recurring (Nasrallah & Chen, 2017).

According to Henry A. Nasrallah, MD, there is enough data to show that timely intervention with antipsychotic LAMs (AP-LAMs) reliably prevents relapse in most patients, thereby averting progressive neurodegeneration and subsequent disability in people who develop schizophrenia: "The additional damaging effects of the second episode is what leads to clinical deterioration and can start the process of treatment resistance. But if no psychotic episodes are allowed to recur after the first episode, many patients can return to their baseline functioning, such as school or work" (McKnight, 2017).

To successfully prevent relapse, clinicians should focus on the modifiable or preventable risk factors that lead to poor outcomes, such as longer duration of untreated psychosis, early nonresponse to antipsychotic medications, multiple relapses and nonadherence to medications (Carbon & Correll, 2014). Not surprisingly, research has consistently found a link between poor adherence and relapse (Morken et al., 2008). A major advantage of LAMs over oral medication is the ability to identify nonadherence early; if the patient does not show up for their injection, adherence can be more easily and effectively addressed. Studies have demonstrated significantly increased adherence in patients taking LAMs and significantly fewer psychotic exacerbations or relapses than in patients receiving oral medications (Subotnik et al., 2015). **Using LAMs immediately after discharge from the first hospitalization for psychosis is an effective strategy to prevent the very likely future nonadherence and relapse/deterioration (Llorca et al., 2013; Correll et al., 2016).**

"The prevention of relapse in schizophrenia remains an enormous public health challenge worldwide, and improvements in this area can have tremendous impact on morbidity, mortality and quality of life, as well as direct [hospitalization and outpatient treatment] and indirect [disability] health care costs. ... in our view when all of the data from individual trials and meta-analyses are taken together, the findings are extremely compelling in favor of depot [long-acting injectable] drugs. However, in

many countries throughout the world fewer than 20% of individuals with schizophrenia receive these medications," (Kane et al., 1998). Rather, Kane asserts, clinicians continue to prescribe pills to patients with a brain disorder who are unable or unwilling to take them, resulting in multiple relapses to illness.

Despite the evidence, AP-LAMs are underutilized. Only 15%-28% of eligible patients with schizophrenia in the U.S. receive them (Sajatovic et al., 2018), and predominantly after multiple relapses instead of very early after onset. As a treatment option, AP-LAMs are often reserved for patients who are nonadherent to oral medications, have experienced multiple relapses or have expressed a preference for them.

Evidence from mirror-image studies investigating AP-LAMs in bipolar disorder have shown that AP-LAMs have advantages for people with bipolar disorder. AP-LAM treatment is associated with a significant reduction in days spent in hospital and number of hospitalizations. AP-LAM treatment showed a significant reduction of hypomanic relapses and lower numbers of emergency department visits (Bartoli et al., 2023).

LAMs for Medication-assisted Treatment of Substance Use Disorders

Medication for opioid use disorder (MOUD), previously referred to as medication-assisted treatment or MAT, is the standard-of-care treatment for OUD. The FDA-approved MOUDs are methadone, buprenorphine (BUP) and naltrexone (NTX). They all act at the mu-opioid receptor to attenuate the activity and reinforcing properties of opioids such as fentanyl, heroin or diverted prescription opioid analgesics — methadone as a full opioid agonist, NTX as an opioid antagonist and BUP as a partial opioid agonist. Each has been shown to be effective in the treatment of OUD, with the strongest evidence (including reductions in mortality) for methadone and BUP. However, as with all chronic relapsing/remitting illnesses, poor adherence is a major barrier to optimum outcomes. Dropout with ensuing relapse for daily MOUD is high: 40%-60% at six months in clinical trials (Lee et al., 2018) and as high as 70% (Krawczyk et al., 2021; Williams et al., 2024) in real-world conditions.

LAM extended-release (XR) formulations are an important option and could play a central role in the treatment of OUD and AUD.

Naltrexone and buprenorphine are both available in monthly LAM/XR formulations. XR-NTX, commercially available in the U.S. as Vivitrol, is effective and approved by the U.S. Food and Drug Administration (FDA) for treatment of both OUD and AUD. XR-BUP is commercially available in two formulations, Sublocade and Brixadi.

XR-BUP has demonstrated efficacy, with at least one randomized clinical trial (RCT) demonstrating superiority to daily SL-BUP for treatment retention and opioid abstinence (Marsden et al., 2023);

another trial demonstrated noninferiority in some outcomes and superiority in others (Lofwall et al., 2018). Both trials were conducted in the fentanyl era, and a subgroup analysis has shown effectiveness of XR-BUP among fentanyl users (Nunes et al., 2024). In the largest comparative effectiveness RCT to date, XR-BUP treatment resulted in opioid abstinence in 73% of days over six months versus 62% in the usual care (daily SL-BUP or methadone); 70% of participants in the XR-BUP group received all six intended doses (Marsden et al., 2023).

XR-NTX for OUD has also demonstrated effectiveness (Sullivan et al., 2019; Murphy et al., 2022; Malone et al., 2019), showing superiority over oral NTX. However, XR-NTX use has been much more limited than XR-BUP. One limitation to uptake of XR-NTX has been the hurdle to initiation, which requires a seven- to 10-day period of opioid-free washout that is expanded to 11–15 days if an opioid such as buprenorphine is used to treat withdrawal ("detoxification") beforehand. This has been reduced to four-to-eight days using various buprenorphine-sparing withdrawal management techniques (Shulman et al., 2024), but still occurs largely in specialty settings, especially bed-based care such as inpatient addiction centers. NTX implants with durations of several months are currently being studied.

There is some preliminary support for use of XR-MOUDs in adolescents, including XR-BUP (Schmuhl et al., 2024; Calihan & Bagley, 2024) and XR-NTX (Fishman et al., 2010; Mitchell et al., 2021), but their efficacy has not been adequately studied in this population. However, given the vulnerabilities of adolescents and young adults, including impulsivity, limited executive functioning and risky decision-making, this population is particularly prone to missing doses and dropping out of treatment. Thus, the use of XR-MOUDs should be strongly considered (Fishman et al., 2020; Wenzel et al., 2021; Fishman et al., 2021). Trials of XR-BUP are also underway in additional special populations including people reentering the community from carceral settings and pregnant women.

XR-NTX is also effective and evidence-based for AUD. A meta-analysis of seven trials evaluated a total of 1,500 adults with AUD receiving monthly injections of either placebo or XR-NTX at doses of 150–400 mg for two to six months. It found XR-NTX reduces drinking days and heavy drinking days per month compared with placebo. Reductions are larger with a longer duration of treatment. Early results in an ongoing randomized trial comparing XR-NTX and oral NTX in primary care indicate that XR-NTX is potentially more efficacious, feasible and cost-effective than oral NTX when treating community-dwelling people with alcohol use disorders.

In conclusion, XR-MOUDs, both XR-BUP and XR-NTX, are currently available and confer many advantages for patients over daily MOUDs; most notably, they help vulnerable patients overcome barriers to adherence. They should be strongly considered for all patients with OUD, particularly in cases where challenges with adherence or dropout from treatment have contributed to prior lack of success. Therefore, many practitioners increasingly consider them first-line treatments.

OVERALL ADVANTAGES OF LAMS

LAMs are widely available and have evidence-based clinical benefits over oral medications for people with schizophrenia, schizoaffective disorder, bipolar disorder, OUD and AUD. These include significant prevention, delay or reduction in relapse.

Advantages of LAMs

- Early detection of future nonadherence.
- Prevention of relapse.
- Simplified medication regimen.
- Reduced patient medication-taking burden.
- Improved medication adherence.
- Reduced side effects.
- Allow for more accurate assessment of dosing and regularity of treatment.
- Potential to strengthen the therapeutic alliance.
- Slowing medication clearance.
- Increasing the time for psychosocial interventions.

(Sajatovic et al., 2018)

LAMs simplify the treatment regimen and reduce patient medication-taking burden (i.e., swallowing pills 365 days a year). Patients may also benefit from not having to make daily decisions regarding taking their medication or other circumstances such as having their medication lost, stolen, confiscated, unable to be continued in short-term jail stays, or experiencing pressure to share, sell, divert or misuse their medications (D'Onofrio et al., 2023).

CALL FOR INCREASED USE OF LAMS

The benefits of LAMs go far beyond their use as agents that increase medication adherence. The National Council recommends using LAMs for psychosis and bipolar disorder and indicates LAMs for OUD and AUD are an evidence-based option that is effective, not inferior, possibly even superior, and crucial and lifesaving for some people. For all patients, particularly for those in the early stages of illness, LAMs are a better choice than oral medications, because LAMs have the potential to address a variety of clinical and social challenges and prevent negative outcomes such as frequent relapses and, in the case of AP-LAMs for schizophrenia, brain tissue loss and treatment resistance.

Advantages of LAMs

Clinicians should consider prescribing LAMs for all patients diagnosed with schizophrenia, schizoaffective disorder, bipolar disorder, AUD and OUD. They're particularly beneficial for:

Patients at risk for nonadherence to medications. Patients who experience high utilization of emergency departments, unstable living conditions, co-occurring substance use, cognitive challenges, or anosognosia, ambivalence or limited insight about treatment with medication.

Patients involved in transitions of care. Patients being discharged from psychiatric hospitals, detoxification and drug rehabilitation centers, crisis stabilization units or residential programs, or leaving jail or prison (where they were incarcerated due to nonadherence and recurrence of psychosis, mania or SUD).

Patients demonstrating challenges with adherence. History of nonadherence to oral medications, challenges remembering to take medications as prescribed or misplacing medications.

Patients seeking to relieve the burden of medication-taking. Patients who experience frustration or challenges with regimens associated with taking pills (sometimes two to three times a day) and the associated frequency of visits to the physician and pharmacy.

Patients experiencing first-episode psychosis, OUD or AUD. This is an optimal time to educate patients and families about AP-LAMs, which have the potential to reduce the rate of relapse and mitigate further adverse impact on the brain and functioning.

Patients who indicate using a LAM as their personal preference. This requires education from prescribing clinicians, mental health staff and peer coaches, as well as informational brochures and videos.

Clinicians should have established processes for assessing nonadherence to oral medications, which can be challenging. They should work individually with patients who are identified as non-adherent to determine if LAMs are the right option for them. Additional risk indicators can include absent or limited insight and ambivalence about treatment with medication. The decision whether to take antipsychotic medications may be a daily stressor if the individual believes they do not have a mental illness requiring medication. With LAMs, the decision to take medications needs to be made far less frequently (once every one, two, three or six months, rather than daily).

Examples of Beliefs Related to Limited Insight

- I am not ill and do not need hospitalization or medications.
- I don't know what this medication is for.
- I only take medications when I feel ill.
- I should be strong enough to deal with my problems without medication.
- Medications can't be a good choice because they are not natural.
- I don't want to take a medication that I will become addicted to.

PRESCRIBER BEST PRACTICES

LAMs and Recovery-oriented, Trauma-informed Care

The Substance Abuse and Mental Health Services Administration (SAMHSA) defines recovery as "a process of change through which people improve their health and wellness, live self-directed lives and strive to reach their full potential."

Four major dimensions that support recovery:

Health. Overcoming or managing one's disease(s) or symptoms and making informed, healthy choices that support physical and emotional wellbeing.

Home. Having a stable and safe place to live.

Purpose. Conducting meaningful daily activities and having the independence, income and resources to participate in society.

Community. Having relationships and social networks that provide support, friendship, love and hope.

Recovery is about seeing beyond a person's mental health or substance use problems, helping them recognize their strengths, abilities and interests, and supporting them in achieving their own goals, aspirations and dreams. Resilience and recovery are strongly linked to social inclusion. A key role for mental health and social services is to create opportunities for individuals to take part in social, educational, training, volunteer and employment opportunities (Jacob, 2015).

From a recovery perspective, LAMs should not just be viewed as a tool for preventing relapse, but as a vehicle to help patients work toward their own goals. The process of recovery is highly personal and occurs via many pathways. Hope and healing can only occur within a strong therapeutic relationship; therefore, clinicians should work toward empowering patients to identify the treatment approaches that will lead to achieving their personal goals. This could be as simple as offering education and information on all treatment options, including LAMs and their advantages over oral medication, at the start of treatment.

Recovery Resources

- Wellness Recovery Action Planning (WRAP). An approach to facilitate recovery.
- Recovery Star. A tool that allows people with mental health conditions who are using services to measure their own recovery progress.

It is also important to note that the majority of people living with mental and substance use disorders or homelessness have a history of trauma (Devi et al., 2019; Farrugia et al., 2011). When there is a history of trauma, there is often difficulty establishing trusting relationships.

A strong therapeutic alliance/relationship is a critical component of the treatment process and promoting medication adherence. When a person has a history of trauma, care must be taken to avoid any actual or perceived coercive experience related to intramuscular (IM) injection medication administration to avoid the potential for activating trauma-related symptoms with LAM administration or discussion. This can be addressed by establishing a trusting relationship, avoiding stigmatizing language and highlighting the need for the individual to choose their preferred treatment. Prescribing providers should also be alert to a possible emotional response to an injection if injections have been previously used against the person's will for agitation.

Before administering the first and subsequent injections, provide information, choice and empowerment. This can be achieved by:

- Offering a step-by-step description of what the process entails and what it may feel like.
- Allowing the person to choose the location for the injection (arm, gluteal or subcutaneous) when possible.
- Asking the person if they'd like to have a family member or other person join them in the room for support.
- Asking if there is anything else that can be done to make them feel more comfortable.

For more information on trauma-informed and recovery-oriented care, SAMHSA's Treatment Improvement Protocol: Trauma-informed Care in Behavioral Health Services and Recovery-oriented Systems of Care Resource Guide are helpful resources.

Communicate Effectively and Empower Patients

Talking to patients about LAMs does not have to be uncomfortable for the patient or practitioner. Approaches such as shared decision-making (SDM) and motivational interviewing (MI) can promote effective communication, collaboration, choice and empowerment.

Employ SDM and MI strategies throughout the course of care to help patients make meaningful treatment decisions, feel empowered to make decisions about their care, and experience the clinician as a recovery partner. SDM approaches may include exploring treatment options like oral antipsychotic medications, psychosocial treatment only or LAMs. When sensitively guided by the clinician, this process provides an important foundation for the patient to make self-directed decisions about LAMs. Motivational engagement strategies like MI can be implemented when the clinician identifies clear benefits of LAMs and the person is not ready to try them. Although someone might decline LAMs for months, or even years, assertive MI and SDM are often effective in evoking and increasing the person's motivation over time.

Open the conversation with "Would you be interested in a way to take medication once a month instead of every day and get a lower total dose overall?" Use language that is less frightening and stigmatizing such as long-acting medications rather than "the IM," "long-acting injectables" or "the needle." A person may associate this with previous experiences with short-acting injectable medications administered in coercive situations. Actions that may be perceived as coercive have the potential to activate a person who has a history of trauma, such as physical or sexual abuse.

Use the REAP Model

- **R** **Recognize** life goals.
- **E** **Explain** how an LAM supports their life goals.
- **A** **Acknowledge** patient concerns.
- **P** **Provide** accurate information to patients and their families.

The National Council's Changing the Conversation Tip Sheet provides step-by-step guidance for clinicians on using the REAP model to have conversations about LAMs with patients .

Provide Education

To make informed decisions, patients must be educated about the potential risks and benefits of oral medications as compared to injectable medications. To improve education and involvement of patients in making decisions about treatment:

- Use SDM and MI strategies to promote effective communication, empowerment and collaboration.
- Develop a collaborative treatment plan.
- Provide patient education brochures, videos, infographics and posters that reflect the patient's language and contribute to increased knowledge and decision-making.

Useful resources to share with patients include:

- A discussion guide that helps patients think through potential questions, concerns and options for LAMs.
- Video testimonials of patients who use LAMs.
- Culturally appropriate patient brochures for the medications included in Table A, Selected Long-acting Antipsychotic Medications.

Involve Families and Caregivers

Family members can play an important role in the treatment planning and recovery process. Involving families, other members of the patient's support network or a peer recovery coach in care begins with finding out who, if anyone, is included in their social support network. Always seek patient consent to keep their family and caregivers fully informed about the details of their treatment and what they can do to assist. The patient or staff should then reach out to that person to invite them to join one or more visits with the patient present.

In addition to mental health literacy, the identified support person (or people) will need education about the risks and benefits of LAM and how they can provide support in a way that works for the patient. Culturally appropriate brochures explaining potential risks and benefits of LAMs should be available for family members and the identified support person.

Regardless of whether the patient consents to the clinician sharing treatment information with the family, the clinician may listen to and consider any information that family members share. HIPAA does not require patient consent for a clinician to receive information about them volunteered by others.

Initiating LAMs

Start early.

Initiate discussion about LAMs as the preferred treatment option early in the treatment process and consider a possible long-term LAM transition plan when you begin administering oral medications. Key scenarios or decision points when prescribers should consider introducing LAMs as a treatment option include: new diagnoses, recent relapse, transition from in-patient care or incarceration, and if a patient is at risk for opioid overdose. A study published in the Journal of the American Medical Association (JAMA) about the use of the long-acting injectable risperidone provides more information on the clinical advantages of starting LAMs early (Subotnik et al., 2015). Second generation AP-LAMs are usually preferred due to superior relapse protection, neuroprotection (Nasrallah, 2018) and lower mortality (Taipale et al., 2018).

Convey a clear, optimistic message.

When discussing the recommendation to choose a LAM, use the following approaches:

1. Introduce the option as a "long-acting medication" formulation. Open the conversation with "Would you be interested in a way to take medication once a month instead of everyday and get a lower total dose overall?" Do not start by describing it as an injection. Present the advantages compared to oral medication first:
    - Fewer side effects.
    - More effective in reducing symptoms and preventing return of symptoms. Do not say "control" symptoms.
    - Smoother action — patients don't feel it "kicking in" or fading away.
    - Decreased risk of hospitalization.
    - Addresses the challenge of having to remember to take a pill every day, sometimes multiple times a day.
    - Reduces the total amount of medication taken compared to oral medication.

2. Inform the patient that the frequency of injections is usually once per month or less frequently (every two, three or six months) and compare this to taking a vitamin B-12 shot, a flu vaccine or Depo-Provera injection (for female birth control). Ask for questions.

3. Directly recommend starting a LAM based on your belief that it will be the most effective treatment approach to avoid rehospitalization.

4. Consider letting the patient know that this form of medication, "is more expensive for Medicaid/Medicare/your insurer but we want you to have the best treatment available and we will work hard to get it for you."

Start with a trial of oral medications to check for allergy and tolerability.

For those who are not already taking an oral antipsychotic medication, a trial of oral medications is recommended. The patient should take them for long enough to identify an allergic reaction or severe adverse reactions, response, dosing and/or ability to tolerate the agent. Prescribers can also use this tip sheet on choosing an LAI antipsychotic agent. Start low and go slow.

For XR-BUP and XR-NTX, at least a single dose of the oral is generally recommended beforehand to establish tolerability. The LAM may be started the same day.

The Right Starting Dose is Important.

Start low and go slow with AP-LAMs.

Consider under-dosing the AP-LAMs at the beginning, rather than risk prolonged side effects that may lead the person to refuse further AP-LAM administration. Use this recommended starting dosage tip sheet. Lower dose AP-LAMs can be supplemented with oral doses for easier optimum dose titrations initially.

Start at the full effective dose with XR-BUP and XR-NTX

Under-dosing XR-BUP at the beginning risks breakthrough withdrawal symptoms that may lead the person to refuse further XR-BUP administrations. Use this recommended starting dosage tip sheet. This approach to starting is for when someone has first been stabilized at an equivalent oral dose for BUP and has already completely gone through withdrawal for NTX. If there is concern about whether enough time has passed from last opioid use to start XR-NTX, an oral buprenorphine challenge dose should be given before XR-BUP.

Transition with oral medications.

When starting an AP-LAM, continue prescribing the oral antipsychotic medication the patient is already taking during the initiation period, when recommended or clinically indicated, and allow for flexible dosage adjustment to compensate for initial over- or under-dosing.

For XR-BUP, most patients do not need to continue on SL, but a subgroup may require supplementation with lower doses of the SL (generally 4-8 mg/day) to prevent cravings and/or mild withdrawal-like symptoms for days to weeks (or infrequently, months) while the LAM approaches steady state. For XR-NTX there is no need to continue the oral.

For AP-LAMs, maintain needed oral medications for extrapyramidal symptoms.

Individuals prescribed oral antipsychotic and anti-extrapyramidal symptom (EPS) medications who start on an AP-LAM may be at risk for EPS due to nonadherence of oral anti-EPS medications. Educate patients receiving AP-LAMs about the importance of taking anti-EPS medications when needed, even if they are not taking oral antipsychotic medications. Use of a symptom rating scale is also recommended.

For AP-LAMs, taper EPS medications.

Some patients who require anticholinergic medications to treat EPS on oral medications may no longer need them after switching to a LAM. Others may do well on lower anti-EPS dosing than with oral medication after transitioning to a LAM. Consider discontinuing the anticholinergic in a slow taper of EPS medication after doing well on the LAM for two to four weeks.

Use dosage conversion tables.

See Table A, Selected Long-acting Antipsychotic Medications.

Improve access.

Clinicians can improve access to LAMs by developing the capacity to administer LAMs themselves based on their trusted relationship with the patient, hiring trained nurses to administer LAMs, or training their own nursing staff in the safe and effective administration of LAMs. Access can be greatly increased by providing outreach services — in-home injections.

Organizations may also consider partnering with pharmacy services that can administer LAMs on-site. (This can be accomplished through co-location or cooperative agreements with local pharmacies.) Another option is to consult with the patient's primary care provider to see if the nursing staff can provide LAM injections for your shared patients.

Monitoring LAMs

Anticipate benefits from more consistent plasma levels and lower peaks than occur with oral medications.

People who are at risk of antipsychotic discontinuation syndrome because of abrupt cessation of oral antipsychotics often experience clinical benefits from an AP-LAM. Many patients have fewer side effects because they avoid the higher plasma medication concentration peaks associated with oral absorption. Although XR-BUP pharmacokinetics for target blood levels and full efficacy call for monthly dosing, XR-BUP has a long duration of lingering blood levels — or "tail" — such that it may confer benefits including some overdose protection for several weeks past its intended due date. Many patients describe other benefits over daily SL-BUP, including the absence of the mild-to-moderate withdrawal symptoms that may accompany daily trough blood levels, the absence of acute withdrawal if they run out because of the tail auto-taper effect, as well as less sense of being tethered to a prescriber for fear of running out of medication.

Contraindications for LAMs

Needle phobia is another consideration. This may be addressed with cognitive behavioral therapy (CBT) (University of South Florida, Florida Medicaid Drug Therapy Management Program, 2020).

ORGANIZATIONAL SUPPORTS

Educate Staff

- Educate all staff on the potential benefits of LAMs and how to talk to patients and families about them. Prescribers, therapists, case managers, peer specialists and nurses should all regularly discuss medication adherence and the benefits of LAMs with their patients.
- Strive to include peers on treatment teams. Peer specialists who have lived experience with LAMs can be effective advocates, and support for LAM utilization and education and information they share is particularly valuable.
- Train clinicians and nursing staff proper administration techniques to ensure the safety and efficacy of LAMs and minimize discomfort to patients. Review Z-Track technique, needle stick safety, proper anatomical locations and sterile administration.
- Ensure that all staff are trained in effective communication and engagement strategies, including MI and SDM.

Prevent Missed Appointments

- Offer in-home administration of injections and/or transportation to injection sites.
- Involve family members or other partners in care.
- Involve peer support specialists or recovery coaches in care.
- Provide telephone reminders about appointments for LAMs.
- Provide reminder cards to patients upon administration so they know — and can track — their last LAM date and next LAM date. This minimizes the risk of early or redundant LAM administration by another provider and often increases the patient's participation in the LAM process.

Ensure Safety and Efficacy

- Identify a safe, private space for medication administration.
- Have appropriate supplies on hand such as safety/retracting needles, gauze, alcohol, Band-Aids and gloves.
- Arrange for refrigeration if Risperdal Consta, Vivitrol or Sublocade is to be used.
- Develop a system for sharps and hazardous waste disposal.

Address Potential Barriers

- Take advantage of assistance programs provided by many pharmaceutical companies to support patients and clinicians in navigating coverage and cost of LAMs. The Desk Guide for Obtaining Coverage is a useful resource for staff responsible for supporting patients' access to LAMs.
- Prevent negative patient perceptions of LAMs through education, use of nonstigmatizing language and effective communication and decision-making strategies.
- Overcome stigma associated with injections through patient and family education, brochures, posters and use of destigmatizing language.
- Improve provider knowledge of or experience with LAMs through education and organizational supports, policies and practices.
- Address staff and infrastructure barriers through updates to organizational environments, policies and procedures, including having a nurse or pharmacist handle pharmacy payment assistance needs, providing transportation to injection appointments and involving peer specialists with LAM experience as educators on the treatment team.
- Implement a tracking system or registry to ensure that patients are monitored for signs of medication nonadherence or partial adherence such as hospital admissions, emergency department visits and unexpected symptom recurrence. Ensure that flagged patients receive a recommendation for LAMs.

Institute Policies and Procedures

- Create a formal procedure to communicate LAM orders if a nonprescribing clinician or more than one clinician may be administering LAMs. Update orders through an electronic health record (EHR) when feasible.
- Create or update a bloodborne pathogen exposure policy in case of needlestick.
- Update formulary to include LAMs.
- Create additional policies and procedures that support the safe and effective use of LAMs.

Collect, Analyze and Use Data

- Implement systems to continuously collect, analyze and utilize data on the rate of LAM use by individual clinicians.
- Clinicians, as a group, should periodically review and discuss their individual variations in use of LAMs.
- Collect, analyze and utilize data that demonstrates patient improvements in care, such as progress toward recovery goals or reductions in hospital utilization (such as hospitalizations, emergency department use).

Table A: Selected Long-acting Antipsychotic Medications

Class	Drug *(links to package inserts)*	Dosing Interval	Initiating Dosing / Oral Supplementation Requirements	Medication-Specific Benefits	Medication-Specific Disadvantages	Strategies with Delayed/ Missed Dosing
First Generation	haloperidol decanoate	Every 3 to 4 weeks	Day 1: 50 mg Day 8: (Monthly Dose — 50 mg) Monthly Dose = Total oral Daily Dose x 10 Initiate q4 week interval from Day 8 Optimally, oral supplementation at least 6 weeks (duration recommended based on clinical experience of authors). May taper oral dose earlier and more rapidly if EPS or other side effects.	q4 week dosing, lower cost, lower metabolic risk, clear oral dose conversion. Less metabolic syndrome risk than second-generation antipsychotics. Lower cost than second-generation LAMs.	Risk of: Tardive Dyskinesia (TD), EPS, Neuroleptic Malignant Syndrome (NMS) and prolactinemia. Individuals may associate this medication with haloperidol HCl intramuscular experience, risk of neuroleptic induced negative syndrome. May require anti-EPS treatment.	
	fluphenazine decanoate	Every 2 to 4 weeks	Day 1: Oral dose x 1.25. Alternatively, may initiate 25 mg IM q2 weeks and titrate/ taper based on treatment response and tolerability. Optimally, oral supplementation for 3 to 5 weeks	Can more rapidly titrate or taper due to shorter half-life, and short onset to peak plasma levels (2 to 5 days). Less metabolic syndrome risk than second-generation agents.	q2 weeks, risk of: TD, EPS, NMS and prolactinemia. May require anti-EPS medications.	
Second Generation	Abilify Maintena® (aripiprazole)	Every 4 weeks	400 mg then q4 weeks; 300 mg if slow CYP2D6 metabolizer. Requires 2 weeks of overlap with oral aripiprazole.	Very low risk of prolactinemia. Less metabolic risk than other second-generation antipsychotics, but more than first-generation agents.	Fixed dosing with low dose flexibility. Risks: akathisia, metabolic syndrome, Type 2 Diabetes, dyslipidemia, obesity, hypertension, EPS/ TD. High cost.	For second or third injection: >5 weeks delayed, reload and oral supplement x2 weeks. If fourth dose or thereafter and >6 weeks delayed, reload and oral supplement x2 weeks

Class	Drug *(links to package inserts)*	Dosing Interval	Initiating Dosing / Oral Supplementation Requirements	Medication-Specific Benefits	Medication-Specific Disadvantages	Strategies with Delayed/ Missed Dosing
Second Generation	Abilify Asimtufii® (aripiprazole)	Every 8 weeks	Requires 2 weeks of overlap with oral aripiprazole.	q8 weeks Very low risk of prolactinemia. Less metabolic risk than other second-generation antipsychotics, but more than first-generation agents.	Risk of akathisia, metabolic syndrome, DM2, dyslipidemia, obesity, HTN, EPS/ TD. High cost.	If more than 8 weeks, but less than 14 weeks, have elapsed since the last injection, administer the next dose as soon as possible. The once-every-2-month schedule should be resumed. If more than 14 weeks have elapsed since the last injection, restart concomitant oral aripiprazole for 14 days with the next administered injection.
	Aristada® (aripiprazole lauroxil)	Every 4, 6 or 8 weeks	Dosing and oral dose equivalents: 1064 mg q8 weeks = Abilify Aristada 15 mg PO daily 882 mg q6 weeks = Abilify 15 mg PO daily 882 mg IM q4 weeks > Abilify 20 mg PO daily 662 mg IM q4 weeks = Abilify15 mg PO daily 441 mg q4 weeks = Abilify 10 mg PO daily Requires 3 weeks of overlap with oral aripiprazole or single administration of Astrida Intio.	Low risk of prolactinemia. Less metabolic risk than other second-generation agents, but more than first-generation aripiprazole preparation with dose adjustment options (vs. Maintena). Dosing interval flexibility.	Risk of akathisia, metabolic syndrome, DM2, dyslipidemia, obesity, HTN, EPS/ TD. High cost.	For q8 wk. dosing: Delayed 10-12 weeks from last injection, supplement with oral meds for 7 days. If >12 weeks since last injection, reload dose and oral supplement. For 882 mg or 662 mg dosing: if 8 to 12 weeks since last dose, oral supplement for 7 days. If missed >12 weeks, reload. For 441 mg dosing, see package insert.

Class	Drug *(links to package inserts)*	Dosing Interval	Initiating Dosing / Oral Supplementation Requirements	Medication-Specific Benefits	Medication-Specific Disadvantages	Strategies with Delayed/ Missed Dosing
Second Generation	Aristada Initio® (aripiprazole lauroxil)	Single initial admin-istration	After establishing tolerability with oral aripiprazole, administer 675 mg injection of Aristada Initio (which corresponds to 459 mg of aripiprazole) and one 30 mg dose of oral aripiprazole. The first Aristada injection (441 mg, 662 mg, 882 mg or 1064 mg) may be administered on the same day as Aristada Initio or up to 10 days after.	Low risk of prolactinemia. Less metabolic risk than other second-generation agents, but more than first-generation aripiprazole preparation. Allows prompter use of extended dose intervals.	Risk of akathisia, metabolic syndrome, DM2, dyslipidemia, obesity, HTN, EPS/ TD. High cost.	When a dose of Aristada is missed/ delayed more than 6 to 12 weeks (depending on the dose of Aristada missed) a single dose of Aristada Initio may be used to supplement or re-initiate the standing Aristada dose. See product insert for detailed recommendations.

Class	Drug *(links to package inserts)*	Dosing Interval	Initiating Dosing / Oral Supplementation Requirements	Medication-Specific Benefits	Medication-Specific Disadvantages	Strategies with Delayed/ Missed Dosing
Second Generation	Zyprexa Relprevv® (olanzapine)	Every 2-4 weeks	Target Oral Dose — 10 mg/day first 8 weeks: 210 mg/2 weeks or 405 mg/4 weeks Maintenance Dose: 150 mg/2 weeks or 300 mg/4 weeks Target Oral Dose — 15 mg/day First 8 weeks: 300 mg/2 weeks Maintenance Dose: 210 mg/2 weeks or 405 mg/4 weeks Target Oral Dose — 20 mg/day first 8 weeks: 300 mg/2 weeks Maintenance Dose: 300 mg/2 weeks Oral supplementation generally not necessary	q2-4 weeks LAM option for patients who respond better to olanzapine than other antipsychotics.	Requires monitoring post-injection for 3 hours due to black box warning for post-injection delirium/sedation syndrome. Risk of prolactinemia, metabolic syndrome, DM2, dyslipidemia, obesity, HTN, EPS/TD. High cost.	Typically given by a health care professional in an emergency setting, so patients are unlikely to miss a dose.
	Invega Sustenna® (paliperidone palmitate)	Every 4 weeks	Day 1: 234 mg IM; Day 8: 156 mg IM; then q4 weeks maintenance dose from Day 8. Oral supplementation not necessary.	No oral dose supplementation is needed after loading doses, q4 week interval. Excreted by the kidney, which is advantageous for people with liver disease.	Risk of prolactinemia, metabolic syndrome, DM2, dyslipidemia, obesity, HTN, EPS/TD risk. High cost.	If >6 weeks delay for maintenance dose, administer maintenance dose on day 1 and 8. Exception: if maintenance dose 234 mg follow package insert. If >6 months delay, reload according to package insert.

Class	Drug *(links to package inserts)*	Dosing Interval	Initiating Dosing / Oral Supplementation Requirements	Medication-Specific Benefits	Medication-Specific Disadvantages	Strategies with Delayed/ Missed Dosing
Second Generation	Invega Trinza® (paliperidone palmitate)	Every 12 weeks (3 months)	Transition only from paliperidone palmitate (Invega Sustenna) (stable dose for 4 months). Invega Sustenna to Invega Trinza conversion: 78 mg = 234 mg; 117 mg =410 mg; 156 mg = 546 mg 234 mg = 819 mg Oral supplementation not necessary.	q12 weeks. Excreted by the kidney, which is advantageous for people with liver disease.	Slow to taper or titrate if suboptimal dose or symptom exacerbation. Risk of: prolactinemia, metabolic syndrome, DM2, dyslipidemia, obesity, HTN, EPS/ TD risk. High cost.	If delayed >3.5 to 4 months, administer last dose of Trinza. If miss 4 to 9 months, use re-initiation regimen with Sustenna as per package insert. If > 9 months, reload with Sustenna and follow insert.
	Invega Hafyera™ (paliperidone palmitate)	Every 6 months	Can transition patients after 4 months Invega Sustenna or 3-month cycle of Invega Trinza 2 options for transition: 1. From Invega Sustenna after 5 months stabilization on either 156 mg or 234 mg/month. 2. From Invega Trinza after 1 dose of either 546 mg or 819 mg q3 months. Oral supplementation not necessary.	Longest interval between LAM doses available (every 6 months). May reduce risk of jail or prison due to psychotic relapse when lost to follow-up. Can be given to patients with liver failure or cirrhosis, because it is excreted from the kidney.	Risk of prolactinemia, metabolic syndrome, DM2, dyslipidemia, obesity, HTN, EPS/ TD risk. High cost. Must be given in the gluteal region only — not in the deltoid. Injection site rash or erythema.	Give the usual dose if 1-3 weeks late. Restart Invega Sustenna with next 2 doses at 234 mg initiation dose if 4 weeks late or more.

Class	Drug *(links to package inserts)*	Dosing Interval	Initiating Dosing / Oral Supplementation Requirements	Medication-Specific Benefits	Medication-Specific Disadvantages	Strategies with Delayed/ Missed Dosing
Second Generation	Erzofri® (paliperidone palmitate)	Every 4 weeks	351 mg initial dose, then 39 mg to 234 mg q4 weeks. Recommended monthly dosage for treatment of schizophrenia is 117 mg. Some patients may benefit from lower or higher monthly doses within the additional available strengths (39 mg, 78 mg, 156 mg, 234 mg). Oral supplementation not necessary.	No oral dose supplementation is needed after loading doses, q4 week interval. Excreted by the kidney, which is advantageous for people with liver disease.	Second once-monthly paliperidone palmitate formulation approved July 2024. No advantage in efficacy or safety demonstrated. High cost.	If delayed less than 2 weeks (4-6 weeks since last injection), resume monthly dosing at previously stabilized dose. If more than 6 weeks to 6 months since last injection, resume the same dose (unless stabilized at 234 mg, then administer 156 mg), as soon as possible; then second injection 1 week later; then resume monthly.
	Risperdal Consta® Rykindo (risperidone)	Every 2 weeks	Oral dose conversion oral risperidone to Consta: mg: 3-5 = 37.5 mg: >5=50 >8 mg=N/A Requires at least 3 weeks of overlap with oral risperidone, optimally at least 5 weeks	Less EPS/TD/ NMS/ antipsychotic-induced negative syndrome risk than first-generation agents.	q2 weeks, low therapeutic ceiling vs. Sustenna high risk of prolactinemia, metabolic risk, EPS. Requires refrigeration.** High cost (varies by state formulary).	If missed dose during maintenance for more than 2 weeks, consider oral supplement 6 weeks after restarted injection for duration of missed dose.

Class	Drug *(links to package inserts)*	Dosing Interval	Initiating Dosing / Oral Supplementation Requirements	Medication-Specific Benefits	Medication-Specific Disadvantages	Strategies with Delayed/ Missed Dosing
Second Generation	Perseris® (risperidone SC)	Every 4 weeks	Can administer the low or high dose (90 mg or 120 mg) without any oral supplementation if the patient was previously exposed to either risperidone or paliperidone. Otherwise, give patient 2 mg of risperidone or 3 mg of paliperidone orally for 2 days to rule out any allergic reaction. Oral supplementation not necessary.	No oral supplementation. Rapid onset of action to an early serum peak after a few hours and a later peak after a few days. Subcutaneous instead of IM.	Risk of prolactinemia, metabolic syndrome, DM2, dyslipidemia, obesity, HTN, EPS/ TD risk. Requires lengthy mixing of the medications prior to injection. Injections given SC over abdominal area, requiring lying supine. Patients may feel a nodule under the skin. High cost.	Give SC dose whenever patient returns whether acutely psychotic or stable with no acute psychosis.
	Uzedy® (risperidone SC)	Every 4 or 8 weeks	For q4 week dosing, 50:2 mg Uzedy:oral risperidone. For q8 week dosing, 100:2 mg Uzedy:oral risperidone. Oral supplementation not necessary.	No oral supplementation. Rapid onset of action to an early serum peak after a few hours and a later peak after a few days. Subcutaneous instead of IM. Prefilled syringe.	Risk of prolactinemia, metabolic syndrome, DM2, dyslipidemia, obesity, HTN, EPS/ TD. Patients may feel a nodule under the skin. High cost.	Give SC dose whenever patient returns whether acutely psychotic or stable with no acute psychosis.

Table B: Selected Long-acting Medications for Substance Use Disorders

	Indication		
	Alcohol Use Disorder or Prevent relapse to opioid use disorder after opioid detoxification	**Moderate to severe opioid use disorder**	
Drug *(links to package inserts)*	Vivitrol® (naltrexone)	Sublocade® (buprenorphine)	Brixadi® (buprenorphine)
Dosing Interval	Every 4 weeks	Every 4 weeks	Either weekly or Every 4 weeks (different formulations)
Initiating Dosing / Oral Supplementation Requirements	380 mg every 4 weeks as gluteal IM injection. Oral supplementation not necessary	Requires withdrawal symptoms to be controlled by oral buprenorphine for at least 7 days prior to initiation.	Requires test dose if patient not currently taking oral buprenorphine.
Medication-specific Benefits	q4 weeks vs. daily oral naltrexone	q4 weeks vs daily oral buprenorphine	q4 weeks vs. daily oral buprenorphine
Medication-specific Disadvantages	Must stop using opioids prior to initiation (minimum 7 to 10 days). Requires refrigeration.**	Requires refrigeration.**	

**Refrigeration Requirements:

- Risperdal Consta: The entire dose pack should be stored in the refrigerator (36° to 46°F; 2° to 8°C) and protected from light. If refrigeration is unavailable, Risperdal Consta can be stored at temperatures not exceeding 77°F (25°C) for no more than seven days prior to administration. Do not expose unrefrigerated product to temperatures above 77°F (25°C).
- Vivitrol: The entire dose pack should be stored in the refrigerator (2 °C to 8 °C, 36 °F to 46 °F). Unrefrigerated, Vivitrol can be stored at temperatures not exceeding 77°F (25°C) for no more than seven days prior to administration. Do not expose the product to temperatures above 77°F (25°C). Vivitrol should not be frozen.
- Sublocade: Store refrigerated at 35.6°F to 46.4°F (2°C to 8°C). Once outside the refrigerator this product may be stored in its original packaging at room temperature, 59°F to 86°F (15°C to 30°C), for up to 12 weeks prior to administration. Discard Sublocade if left at room temperature for longer than 12 weeks.

Training Resources: The American Association of Psychiatric Pharmacists offers a complimentary training program on LAMs focused on appropriate patient selection, LAM preparation, administration techniques and engaging patients. The program includes six webinars and tools such as an LAM pocket guide containing information on each available antipsychotic LAM and an LAM administrative toolkit.

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