Addressing an Underutilized Best Practice for Severe and Persistent Mental Illness: Long-Acting Injectables

TREATMENT CHALLENGES

People with severe and persistent mental illness (SPMI) are at significant risk for relapse and psychiatric hospitalization, primarily related to non-adherence of prescribed oral medications. The resulting periods of destabilization adversely impact emotional, social, legal and financial well-being. Several studies have demonstrated that long-acting injectable antipsychotics (LAI-AP) improve recovery and community tenure.[1][2][3][4][5] As with many behavioral health interventions and developing science, additional research is called for to further substantiate these findings.[6][7]

The individual and societal costs of SPMI conditions are significant. For schizophrenia spectrum disorders, individuals may experience a complex array of issues, including positive, negative and mood symptoms; medical and substance use comorbidities; and cognitive dysfunction that significantly impair social and occupational functioning. Internationally, schizophrenia is a leading cause of years lost to disability, particularly impacting adolescents and young adults.[8] Treatment of schizophrenia conditions aims to improve functioning and recovery across the lifespan, but symptom-reduction and relapse-prevention are important interim goals as well. Evidence-based practices incorporate antipsychotic medications that reduce psychotic symptoms and greatly decrease the risk of relapse. However, medication effectiveness is dramatically decreased by non-adherence.[9] A meta-analysis of studies found that non-adherence is prevalent in an average of 41 percent of participants.[10] Prescribers are often unaware of this issue and generally overestimate medication adherence.[11] Studies also indicate that as little as a 10-day lapse in medication refills can result in a doubling of inpatient admission rates.[12]

BEACON'S POSITION STATEMENT

Long-acting injectable antipsychotic (LAI-AP) medications represent an underutilized treatment intervention for people with severe and persistent mental illness (such as schizophrenia, schizoaffective disorder and bipolar disorder). **As an evidence-based clinical approach, Beacon Health Options (Beacon) strongly recommends that psychiatric prescribers use a shared decision-making process and systematically offer an LAI-AP as a first-line treatment to most individuals who require long-term antipsychotic treatment.** For non-adherent individuals with historically higher levels of risk, additional structural support may be required, such as Medication over Objection (court-ordered medication statutes in 45 states and D.C.)[13] or Assertive Community Treatment (ACT), to ensure continuous medication adherence and community-based tenure.[14][15] This clinical position paper outlines the rationale for appropriate use and expansion of LAI-AP as an evidence-based treatment.

EXPLANATION OF TERMS

- **First-Generation Antipsychotic (FGA):** Initial drugs developed in the 1950s to manage the symptoms of psychosis, delivered orally
- **Second-Generation Antipsychotic (SGA):** Developed in the 1980s to manage the symptoms of psychosis and to address extrapyramidal side effects of FGAs, delivered orally; metabolic syndrome side-effect issues should be closely monitored for SGAs.
- **Long-Acting Injectable (LAI) Antipsychotic Drugs:** First developed in 1966 as an FGA long-acting medication for psychosis, administered intramuscularly (IM) with a one- to four-week effective period. SGA LAI was first introduced in 2001.
  - » **FGA LAI**—Haldol Decanoate (Haloperidol), Prolixin Decanoate (Fluphenazine)
  - » **SGA LAI**—Risperdal Consta (Risperidone), Invega Sustenna/Trinza (Paliperidone), Zyprexa Relprevv (Olanzapine pamoate), Abilify Maintena (Aripiprazole), Aristada (Aripiprazole lauroxil)
- **Severe and Persistent Mental Illness (SPMI):** Impacting 9.8 million American adults (4.1 percent of all adults).[16] The most significant SPMI conditions include schizophrenia, schizoaffective disorder and bipolar disorder. These conditions impair multiple facets of functioning with substantial disease burden on individuals, relatives and friends, the health care system, and society. Often emerging in late adolescence or early adulthood, these conditions contribute to marked impairments in vocational and social activities.

CONSIDERATIONS FOR SELECTING LAI-APS

LAI-APs have demonstrated effectiveness in treating schizophrenia and other severe psychotic disorders. They ensure stable blood levels, leading to reduced risk of relapse. Newer LAI-APs offer additional advantages as they are easier to dose optimally, produce fewer side effects, and fit well with integrated rehabilitation programs. To provide integrated treatment, including medication management, it is important to address psychosocial needs as well as incorporate personal preferences whenever possible within the person-centered care plan.[17] Intensive care coordination helps to address secondary considerations related to LAI-AP adherence, including transportation, scheduling, condition education, access to community support resources, and provider coordination.[18]

LAI-AP ADVANTAGES OVER ORAL ALTERNATIVES	CONSIDERATIONS TO BE ADDRESSED WHEN USING LAI-AP
• Daily administration unnecessary, simplified decision process (members typically prefer once established) • Immediate notification of non-adherence with administration transparency[19 20] and 'natural alerts' if individuals fail to take their medication[21] • Less probability for rebound symptoms and rapidly occurring/abrupt relapses • Overcome partial adherence or overt non-adherence • If a relapse occurs, non-adherence can likely be ruled out[22] • Reduced risk of unintentional or deliberate overdose[23] • Lower relapse rates[24 25 26] • Minimal gastrointestinal absorption problems, circumventing first-pass metabolism[27] • More consistent bio-availability[28] • More predictable correlation between dosage and plasma levels[29] and reduced peak-trough plasma levels[30] • Improved outcomes[31] • Improved individual and physicians' satisfaction[32] • Promotion of regular contact with the mental health care team[33]	• Continuity of LAI treatment started in inpatient setting and continued in outpatient community can be further assisted by Beacon care coordination and medication manufacturer resources[34] • Slow dose titration,[35 36] longer time to achieve steady state levels,[37] and delayed disappearance of distressing and/or severe side effects with less flexibility of dose adjustment[38] requiring advance planning for effective administration • Pain at the injection site can occur, and leakage into the subcutaneous tissue and/or the skin may cause irritation and lesions (especially for 'oily' long-acting injectable) • Transport to outpatient clinics may be necessary or home visits by community nurses for their administration • Risperidone long-acting injectable needs refrigeration • Perception of stigma, requiring education and peer support • Price differentials, possible subsidy needed

To address prescriber concerns regarding continued outpatient management of LAI-APs, prior authorization requirements, and cost issues, Beacon provides care coordination services in conjunction with manufacturer and community-based resources to promote continuous care. To ensure the availability of providers able to administer LAIs, Beacon coordinates psychiatric consultation for primary care physicians serving individuals with stabilized medication protocols. Beacon expects in-network facility providers to offer LAI-AP interventions as a standard evidence-based treatment option for appropriate inpatient cases. In turn, Beacon supports care coordination resources to address continuity of care concerns following LAI-AP initiation and subsequent transition to community-based care.

SUMMARY OF KEY LAI-AP TREATMENT TAKEAWAYS

LAI-APs should be considered for individuals with heightened risk factors, including non-adherence, severe symptoms, comorbid substance use, cognitive impairment, ambivalence or negative attitudes towards medications and poor insight.[39] Research to date has not fully demonstrated an overall effectiveness advantage of newer (SGA) LAIs over older LAIs.[40 41] Therefore, clinicians should consider each person's preferences, prior experience with antipsychotics, health status and the specific side-effect profiles of the medications when selecting an LAI-AP.[42 43] Because LAI-AP dosages are not immediately changeable to adjust for side effects, LAIs may need to follow an initial course of oral medications. This approach is to accommodate dose regulation for those individuals not previously prescribed antipsychotic medications. Because people experiencing recent-onset psychosis are particularly sensitive to side effects, this factor should be considered in the medication selection. The following consensus-based guideline summarizes key LAI-AP practice decisions and adherence tips:[44]

1. LAI-APs are recommended for individuals with schizophrenia, schizoaffective disorder, and bipolar disorder.
   - Based on individual treatment response and medication history, either second-generation antipsychotics (SGA) or first-generation antipsychotics (FGA) LAI-APs may be used after the first episode of schizophrenia.[45]
   - First-generation LAI-APs (depot neuroleptics) must be avoided for bipolar disorder conditions.

2. Although LAI-AP antipsychotics have long been viewed as a treatment for a small subgroup of individuals with non-adherence issues, frequent relapses or who pose a risk to others, LAI-APs should be considered and systematically proposed when maintenance antipsychotic treatment is indicated.

3. According to their efficacy and tolerability, second-line LAI-AP SGAs are recommended as a monotherapy to prevent manic recurrence or in combination with a mood stabilizer to prevent depressive recurrence in the maintenance treatment of bipolar disorder.

4. Shared decision-making improves the acceptance and understanding of the benefits of an LAI-AP, providing individualized information concerning the advantages and inconveniences of the LAI-AP formulation. Intensive care coordination should be incorporated to support adherence as needed.

5. When switching to an LAI antipsychotic, consider two scenarios:
    - Switch from an oral antipsychotic
        - » Prescribe the oral formulation of the antipsychotic to establish tolerability/efficacy
        - » Use an initial dose of the LAI antipsychotic equivalent to the oral form
    - Switch from another LAI antipsychotic
        - » Use several test doses of the oral formulation of the LAI antipsychotic if the individual has never taken this medication previously (to rule out hypersensitivity)
        - » Introduce the new LAI antipsychotic at the scheduled period of the next injection
        - » Use an initial dose of the LAI antipsychotic equivalent to the previous LAI

6. Medication administration
    - Provider reminders to member regarding injection date to improve adherence
        - » First line: phone call and diary
        - » Second line: letter or text message
        - » Coordinate the dates of medical consultations with the scheduled dates of LAI antipsychotic injections
    - Prevent local LAI-AP administration complications
        - » Utilize competent/trained professionals (nurse, psychiatrist, GP)
        - » Check the length of needle and penetrate the deep muscle tissue[46]
        - » Select the injection site according to individual preference
        - » Propose systematically a local anesthetic to reduce pain at the injection site
        - » Permit the change of the injection site for each injection, as needed

As an evidence-based clinical approach, Beacon strongly recommends that psychiatric prescribers use a shared decision-making process and systematically offer an LAI-AP as a first-line treatment to most individuals who require long-term antipsychotic treatment.

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- Lilly https://www.zyprexarelprevvprogram.com/public/Default.aspx

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APPENDIX: PRICING FOR LONG-ACTING INJECTABLE ATYPICAL ANTIPSYCHOTICS

(data gathered on 10/18/17 through First Data Bank Pricing of Wholesale Cost Per Package)

<table>
<tr><th>DRUG</th><th>RECOMMENDED DOSE/DOSE RANGE*</th><th>AVAILABILITY</th><th>PRICING – WHOLESALE PER PACKAGE</th></tr>
<tr><td rowspan="7">Abilify Maintena® (aripiprazole), Aristada® (aripiprazole lauroxil)</td><td rowspan="7">Schizophrenia:
400 mg monthly (Abilify Maintena®)

441 mg to 882 mg monthly or every-six-weeks (Aristada®)</td><td>300 mg Maintena® vial</td><td>$1,478/vial</td></tr>
<tr><td>300 mg Maintena® syringe</td><td>$1,478/syringe</td></tr>
<tr><td>400 mg Maintena® vial</td><td>$1,971/vial</td></tr>
<tr><td>400 mg Maintena® syringe</td><td>$1,971/syringe</td></tr>
<tr><td>441 mg Aristada® syringe</td><td>$1,140/syringe</td></tr>
<tr><td>662 mg Aristada® syringe</td><td>$1,722/syringe</td></tr>
<tr><td>882 mg Aristada® syringe</td><td>$2,281/syringe</td></tr>
<tr><td rowspan="10">Invega® Sustenna®, Invega® Trinza® (paliperidone)</td><td rowspan="10">Schizophrenia/Schizoaffective disorder:
234 mg initial IM dose, 156 mg one week later and 117 mg monthly thereafter with range of 39 to 234 mg based on tolerability and/or efficacy (Invega® Sustenna®)

273 mg to 819 mg IM every three months (Invega® Trinza®) administered after at least four months of stability Invega® Sustenna®

The initial Invega® Trinza® dose should be determined as follows:
<table>
<tr><th>INVEGA SUSTENNA (PALIPERIDONE PALMITATE)® DOSE</th><th>INVEGA TRINZA® (PALIPERIDONE PALMITATE) DOSE</th></tr>
<tr><td>78 mg</td><td>273 mg</td></tr>
<tr><td>117 mg</td><td>410 mg</td></tr>
<tr><td>156 mg</td><td>546 mg</td></tr>
<tr><td>234 mg</td><td>819 mg</td></tr>
</table></td><td>39 mg Sustenna injection</td><td>$397/syringe</td></tr>
<tr><td>78 mg Sustenna injection</td><td>$795/syringe</td></tr>
<tr><td>117 mg Sustenna injection</td><td>$1,192/syringe</td></tr>
<tr><td>156 mg Sustenna injection</td><td>$1,590/syringe</td></tr>
<tr><td>234 mg Sustenna injection</td><td>$2,385/syringe</td></tr>
<tr><td>273 mg Trinza injection</td><td>$2,385/syringe</td></tr>
<tr><td>410 mg Trinza injection</td><td>$3,577/syringe</td></tr>
<tr><td>546 mg Trinza injection</td><td>$4,770/syringe</td></tr>
<tr><td>819 mg Trinza injection</td><td>$7,154/syringe</td></tr>
<tr><td rowspan="4">Risperdal® Consta® (risperidone)</td><td rowspan="4">Schizophrenia:
25 to 50 mg IM every 2 weeks (Risperdal® Consta®)

Bipolar mania:
25 to 50 mg IM every 2 weeks (Risperdal® Consta®)</td><td>12.5 mg Consta injection</td><td>$216/syringe</td></tr>
<tr><td>25 mg Consta injection</td><td>$432/syringe</td></tr>
<tr><td>37.5 mg Consta injection</td><td>$648/syringe</td></tr>
<tr><td>50 mg Consta injection</td><td>$865/syringe</td></tr>
<tr><td rowspan="4">Zyprexa® Relprevv® (olanzapine)</td><td rowspan="4">Recommended dosing of Zyprexa ® Relprevv ® based on corresponding oral olanzapine doses:
<table>
<tr><th>TARGET ORAL OLANZAPINE DOSE</th><th>DOSING OF ZYPREXA RELPREVV DURING THE FIRST 8 WEEKS</th><th>MAINTENANCE DOSE AFTER 8 WEEKS OF ZYPREXA RELPREVV TREATMENT</th></tr>
<tr><td>10 mg/day</td><td>210 mg/2 weeks or 405 mg/4 weeks</td><td>150 mg/2 weeks or 300 mg/4 weeks</td></tr>
<tr><td>15 mg/day</td><td>300 mg/2 weeks</td><td>210 mg/2 weeks or 405 mg/4 weeks</td></tr>
<tr><td>20 mg/day</td><td>300 mg/2 weeks</td><td>300 mg/2 weeks</td></tr>
</table></td><td>210 mg Relprevv injection</td><td>$590/vial</td></tr>
<tr><td>300 mg Relprevv injection</td><td>$842/vial</td></tr>
<tr><td>405 mg Relprevv injection</td><td>$1,137/vial</td></tr>
</table>