Summary: Treatment of Schizophrenia with LAIs

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Main Questions:

1. Are LAIs more effective than placebo?

Yes.

All approved LAIs have demonstrated efficacy for people with schizophrenia. In the USA (Correll et al., 2017), these agents include:

- First-generation antipsychotics:
  - Fluphenazine decanoate
  - Haloperidol decanoate
- Second-generation antipsychotics:
  - Aripiprazole monohydrate
  - Aripiprazole lauroxil
  - Olanzapine pamoate
  - Paliperidone palmitate
  - Risperidone microspheres
  - Risperidone extended release subcutaneous injectable

2. Are LAIs more effective than oral antipsychotics?

Yes, in many studies and settings, with some non-differential results, but very rare/virtually no data indicating better efficacy for oral antipsychotics.

Efficacy of LAIs versus oral antipsychotics depends on the study design and included population (Correll et al., 2016). In randomized clinical trials (RCTs) that include patients with better illness insight, less severity/complexity of the disease and better/monitored adherence, LAIs were not more efficacious than placebo (Kishimoto et al., 2014). In mirror image studies (Kishimoto et al., 2013) and cohort/database studies (Kishimoto et al., 2018) that enroll more generalizable patients, LAIs were superior to oral antipsychotics regarding relapse, hospitalization, and all-cause discontinuation risk, despite greater illness severity in patients started on LAIs versus oral antipsychotics in real-world studies. Additionally, LAIs have been associated with a 20–30% reduced all-cause mortality versus oral antipsychotics (Taipale et al., 2018).

3. Are LAIs tolerable?

Yes.

Generally, the adverse effects of LAIs are predictable from knowledge of the adverse effect potential of the oral counterpart and can be tested in an individual patient during lead in treatment with the oral antipsychotic.

Comparing 119 adverse events in patients randomized to an LAI or the same medication given in an oral formulation, 115 (97%) were not different, including discontinuation due to adverse event or mortality. Regarding 3 adverse effects [akinesia, (stiffness) with first generation antipsychotics (FGAs), increase in low density lipoprotein cholesterol, and anxiety], oral antipsychotics had lower events, while prolactin levels and hyperprolactinemia were lower in LAI treated patients (Misawa et al., 2016). Injection pain and injection site reactions are generally mild and infrequent (Correll et al., 2016).

Based on data with FGA-LAIs, there is no current indication that the outcome of neuroleptic malignant syndrome is worse when it occurs during LAI versus oral antipsychotic treatment, as management is symptomatic (Glazer and Kane, 1992).

An exception from the rules above is olanzapine pamoate, which is highly blood soluble and which can, in 1/1,100–1,200 injections, lead to a post-injection somnolence, sedation, and coma syndrome (known as post injection delirium/sedation syndrome, or PDSS). Therefore, at least 3 hours of post-injection observation for the duration of treatment with olanzapine pamoate is required.

4. Are there special populations in whom LAIs should especially be considered or not considered?

While prior guidelines relegated LAI use to a third-tier treatment step, unless patients were non-adherent, had multiple relapses or preferred LAIs, recent evidence and guidance includes offering LAIs to potentially all patients as a treatment option and also considering them for prevention of future non-adherence and relapse/deterioration (Llorca et al., 2013; Malla et al., 2013; Correll et al., 2016; Brugnoli et al., 2016; Galletly et al., 2016; Howes et al., 2017; Sajatovic et al., 2018).

- Populations and clinical scenarios in which first-line use of LAIs should be considered include:
  - Past or current nonadherence leading to deterioration
  - Low illness insight
  - Poor cognition
  - Dangerousness
  - Homelessness
  - Poor support system
  - Suicidality

- Emerging areas of first-line use of LAIs include:
  - High level of insight
  - High functioning (to prevent loss of function)
  - Anticipated nonadherence over time
  - Stabilized first episode and early phase patients (high future non-adherence risk, most to lose from future potential relapse)
  - Treatment-refractory patients who may be "pseudo-resistant" due to covert levels of non-adherence

The only contraindication for deep intramuscular injectable LAIs is significant anticoagulation, presenting a risk for internal bleeding/large hematomas. Needle phobia should be addressed with cognitive behavioral therapy (CBT).

5. How should break-through symptoms during LAI treatment be addressed?

Review and address non-pharmacologic reasons for exacerbation, such as substance use, other comorbid psychiatric or medical illness, psychosocial stressors, etc. Rule out drug-drug interactions and inappropriate injection (insufficient mixing prior to injection, lack of deep intramuscular injection, accumulation of late injection visits, etc.) (Correll et al., 2018).

If the above does not resolve the issue or immediate action is needed, add the same antipsychotic in oral formulation in an attempt to increase the dose. Generally, try to avoid polypharmacy with different antipsychotics, as the evidence for efficacy and safety is lacking (Galling et al., 2017; Correll et al., 2017).

If efficacy is reestablished and the higher dose is tolerated, at the next injection interval, use a higher LAI dose that corresponds to that combined LAI + oral dose. If already at the highest dose, consider changing injection site (deltoid injections lead to higher peak levels but shorter half-life, gluteal injection leads to lower peak levels but longer half-life), change to shortest FDA-approved injection interval (if not already done), or consider off-label strategy of shortening the injection interval (Correll et al., 2016; Correll et al., 2018).

6. How should LAIs best be offered in clinical care?

LAIs need to be destigmatized and presented not as a last resort or in a punitive or mistrustful way, but rather as a highly effective treatment option that offers for many patients a greater likelihood of stability and improved ability to focus on recovery. Data suggest that motivational interviewing and shared decision making, which do not pass the decision simply back to the patient, but that present the evidence and advantages in a respectful and authoritative (yet not authoritarian) way, may yield best results (Correll et al., 2016; Weiden et al., 2017). Inclusion of caregivers/significant others and/or peer counselors should also be considered (Correll et al., 2016). Furthermore, buy-in by and training of all team members can yield very high acceptance of LAIs, with such training, including role play, having been show to result in at least one LAI injection within 3 months of service engagement in >75% of first-episode and early-phase patients with schizophrenia (Kane et al., 2019).

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