DSM-5 Criteria: Schizophrenia

Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be delusions, hallucinations or disorganized speech:

- Delusions
- Hallucinations
- Disorganized speech (e.g., frequent derailment or incoherence)
- Grossly disorganized or catatonic behavior
- Negative symptoms (i.e., diminished emotional expression or avolition)

Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet the above criteria (i.e., active phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested only by negative symptoms or by two or more symptoms listed above present in an attenuated form.

For a significant portion of time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is a failure to achieve expected level of interpersonal, academic, or occupational functioning).

Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out.

The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).
# Treatment of Schizophrenia

Conduct comprehensive assessment and use measurement-based care. Refer to Principles of Practice on pages 6-10.

Most importantly, assess social support system (housing, family, other caregivers) and evaluate threats to continuity of care (access to medication, adherence, etc.).

*Strongly recommend psychiatric consultation prior to initiation of therapy + psychotherapeutic medication using a multi-disciplinary approach if treated by a non-psychiatrist.*

<table>
<thead>
<tr>
<th>Level 1</th>
<th>Initial Treatment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>✦ Monotherapy with an oral antipsychotic (SGA) other than clozapine*</td>
<td></td>
</tr>
<tr>
<td>✦ If initial trial of antipsychotic monotherapy unsuccessful, try monotherapy with another antipsychotic with low metabolic adverse effects.</td>
<td></td>
</tr>
<tr>
<td>✦ If two failed adequate trials of monotherapy, consider switching to a long-acting injectable antipsychotic medication (LAI) or clozapine.</td>
<td></td>
</tr>
</tbody>
</table>

*Note: Balance efficacy, side-effects, individual vulnerabilities and preferences. Select a medication with lower metabolic risk and lower risk of extrapyramidal symptoms (EPS).*

<table>
<thead>
<tr>
<th>Level 2A</th>
<th>If non-adherence to Level 1:</th>
</tr>
</thead>
<tbody>
<tr>
<td>✦ Consider long-acting injectable antipsychotic medication (LAI)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 2B</th>
<th>If Level 1 is ineffective and/or not well tolerated:</th>
</tr>
</thead>
<tbody>
<tr>
<td>✦ Consider clozapine</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 3</th>
<th>If Levels 1 and 2 are ineffective and/or not well tolerated:</th>
</tr>
</thead>
<tbody>
<tr>
<td>✦ Diagnostic review and/or consultation</td>
<td></td>
</tr>
<tr>
<td>✦ Clozapine if not tried earlier</td>
<td></td>
</tr>
<tr>
<td>✦ Antipsychotic + electroconvulsive therapy (ECT)</td>
<td></td>
</tr>
<tr>
<td>✦ Augmentation of clozapine with lamotrigine if partial or incomplete response to clozapine</td>
<td></td>
</tr>
</tbody>
</table>
### Table 4. Recommended Medications for the Treatment of Schizophrenia: Oral Antipsychotics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Chlorpromazine Equivalents&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Acute Therapy</th>
<th>Maintenance Therapy&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Generation Antipsychotics (FGAs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>100</td>
<td>300-1,000 mg/day</td>
<td>300-800 mg/day</td>
</tr>
<tr>
<td>Fluphenazine HCl</td>
<td>2</td>
<td>5-20 mg/day</td>
<td>5-15 mg/day</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2</td>
<td>5-20 mg/day</td>
<td>6-12 mg/day</td>
</tr>
<tr>
<td>Loxapine</td>
<td>10</td>
<td>30-100 mg/day</td>
<td>30-60 mg/day</td>
</tr>
<tr>
<td>Molindone</td>
<td>10</td>
<td>30-100 mg/day</td>
<td>30-60 mg/day</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>8</td>
<td>16-80 mg/day</td>
<td>16-64 mg/day</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>5</td>
<td>15-50 mg/day</td>
<td>15-30 mg/day</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>5</td>
<td>15-50 mg/day</td>
<td>15-30 mg/day</td>
</tr>
<tr>
<td><strong>Second Generation Antipsychotics (SGAs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>N/A</td>
<td>10-30 mg/day</td>
<td>10-30 mg/day</td>
</tr>
<tr>
<td>Asenapine</td>
<td>N/A</td>
<td>10-20 mg/day</td>
<td>10-20 mg/day</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>N/A</td>
<td>2-4 mg/day</td>
<td>2-4 mg/day</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>N/A</td>
<td>1.5-6 mg/day</td>
<td>3-6 mg/day</td>
</tr>
<tr>
<td>Clozapine</td>
<td>N/A</td>
<td>150-600 mg/day</td>
<td>150-600 mg/day</td>
</tr>
<tr>
<td>Lloperidone</td>
<td>N/A</td>
<td>12-24 mg/day</td>
<td>12-24 mg/day</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>N/A</td>
<td>40-160 mg/day</td>
<td>40-160 mg/day</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>N/A</td>
<td>10-30 mg/day</td>
<td>10-20 mg/day</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>N/A</td>
<td>3-12 mg/day</td>
<td>3-12 mg/day</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>N/A</td>
<td>300-800 mg/day</td>
<td>300-800 mg/day</td>
</tr>
<tr>
<td>Risperidone</td>
<td>N/A</td>
<td>2-8 mg/day</td>
<td>2-8 mg/day</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>N/A</td>
<td>80-240 mg/day</td>
<td>80-160 mg/day</td>
</tr>
</tbody>
</table>

**Notes:**
- Consider lower doses for first episode due to better response and higher side effects to medications in pharmaceutically naïve patients. Use atypical antipsychotics and avoid haloperidol completely due to well-documented neuronal cell death caused by haloperidol (and also fluphenazine and perphenazine). Thioridazine is not recommended due to concerns about ventricular arrhythmias (Torsades de Pointes).
- Approximate dose equivalent to 100 mg of chlorpromazine (relative potency); it may not be the same at lower versus higher doses. Chlorpromazine equivalent doses are not relevant to the second generation antipsychotics and therefore are not provided for these agents.
- Drug-drug interactions (DDIs) can impact dosing. Maintenance dose should generally be no less than half of the initial clinically effective dose, as that can result in reduced effectiveness of relapse prevention.
Rajiv Tandon, M.D.
Professor of Psychiatry, University of Florida College of Medicine

INTRODUCTION

The primary objectives in the treatment of schizophrenia are to reduce the frequency and severity of psychotic exacerbation, ameliorate a broad range of symptoms, and improve functional capacity and quality of life. Treatment for schizophrenia includes medication and a range of psychosocial interventions. Antipsychotics are the cornerstone of the pharmacological treatment for schizophrenia. The 21 antipsychotics available in the United States have traditionally been classified into two major groups: 9 first-generation (conventional) agents (FGAs) and 12 second-generation (atypical) agents (SGAs). Whereas the efficacy of these antipsychotic agents in the treatment of schizophrenia is broadly similar (with the exception of clozapine’s greater efficacy in otherwise treatment-refractory patients), there are significant differences in their side-effect profiles. This article summarizes our current understanding of the pharmacotherapy of schizophrenia and is the basis for the 2017-2018 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults. Optimal individualized pharmacological treatment of schizophrenia requires an understanding of:

- The clinical and biological nature of schizophrenia in order to identify targets of treatment and define specific treatment goals;
- How available treatments compare (similarities and differences in terms of efficacy, safety/tolerability, costs, ease of use, and pharmacokinetics and pharmacodynamics); and
- How to use available treatments optimally (targeted, measurement-based, and individualized).

NATURE OF SCHIZOPHRENIA AND DEFINITION OF TREATMENT TARGETS AND TREATMENT GOALS

Schizophrenia is a chronic, remitting and relapsing illness with onset in late adolescence or early adulthood. It is characterized by multiple psychopathological dimensions (positive, negative, cognitive, mood, motor, and disorganization) each of which have distinct neurobiological underpinnings, clinical profiles, and patterns of treatment response. Each of these symptom domains contribute to functional impairment and adversely impact quality of life. Objectives of treatment therefore include maximal reduction in severity of each of these symptom domains and prevention of relapse. Since different patients exhibit varying admixtures of these symptoms, individualized tailoring of treatment is essential.

WHAT DO ANTIPSYCHOTIC MEDICATIONS DO?

Antipsychotic medications are the mainstay in the pharmacological treatment of schizophrenia. They are effective in treating acute psychotic relapses and reducing the likelihood of such relapses. All antipsychotics are effective in reducing positive symptoms (i.e., hallucinations, delusions, and paranoia) and disorganization, but are only minimally effective for negative and cognitive symptoms that significantly contribute to the disability associated with schizophrenia. They can
ameliorate mood and motor symptoms, but can also make them worse (e.g., neuroleptic dysphoria and neuroleptic malignant syndrome). They are associated with a range of adverse effects (e.g., motor, metabolic, and other disturbances) and differ substantially in their side-effect profiles.

**How Do Antipsychotic Medications Compare?**

**Efficacy**

With the exception of clozapine, all antipsychotic medications are about equally effective in treating positive symptoms and disorganization. Clozapine is more effective than other antipsychotics in treating positive symptoms in otherwise treatment-refractory patients and reducing suicidality in schizophrenia. The relatively minor differences in efficacy observed among the other antipsychotic agents principally relate to dosing and different degrees of ease of use. Response over the first 2-4 weeks of antipsychotic therapy is highly predictive of long-term response. The maximum effect, however, may not be achieved for several months, and trajectories of response vary considerably across patients. Responsiveness to antipsychotics also varies as a function of stage of illness, with first-episode patients responding faster and at a higher rate than those at later stages of the illness. Antipsychotics are equally ineffective in treating primary negative and cognitive symptoms while differing in their effects on secondary symptoms [when agents cause extrapyramidal side effects (EPS), they worsen secondary negative and cognitive symptoms].

Antipsychotic medications substantially decrease the likelihood of relapse in schizophrenia, without any consistent differences among agents. Since medication nonadherence is common in schizophrenia, long-acting injectable antipsychotics may have an advantage over oral treatment in reducing relapse rates. Six agents (aripiprazole, fluphenazine, haloperidol, olanzapine, paliperidone, and risperidone) are available in long-acting injectable formulations requiring injections at intervals ranging from 2 weeks to 3 months.

**Safety and Tolerability**

Antipsychotic medications cause a range of side-effects including neurological, metabolic, cardiovascular, gastrointestinal, hematological, genitourinary, musculoskeletal, endocrine, and other side-effects. In contrast to their broadly similar efficacy, antipsychotics differ markedly in their adverse effect profiles. Compared with the FGAs, it is generally believed that the SGAs have a lower risk of EPS but a higher risk of metabolic adverse effects. However, due to differences in pharmacological profiles within the FGA and SGA classes, there is substantial variation within both classes in their propensity to cause EPS and metabolic adverse effects. Increased risk of EPS has been associated with neurotoxicity, however, leading to the panel’s recommendation to preferentially use SGAs rather than FGAs in the initial treatment of schizophrenia. Because of the adverse sequelae of EPS and its treatment (e.g., secondary negative symptoms, secondary depression, secondary cognitive impairment, and tardive dyskinesia), EPS must be avoided. Similarly, because of the increased mortality associated with metabolic side-effects (e.g., hyperlipidemia and diabetes mellitus), these must be minimized.

The 21 antipsychotic medications available in the United States also differ in their propensity to cause other side-effects, such as sedation, hypotension, cardiac arrhythmias, prolactin elevation and
related sexual dysfunction, and anticholinergic effects, with substantial variation within both the FGAs and the SGAs for each of these effects, without any definitive categorical separation between the two classes.

Patients with schizophrenia also vary in their vulnerability to develop various adverse effects with different agents. The likelihood that a patient will develop a particular side effect thus depends on the agent selected, how that agent is used (e.g., dose, titration method, and in combination with what other agents), and the patient’s vulnerability.

**OPTIMIZING INDIVIDUAL OUTCOMES**

Given the significant variability in drug pharmacokinetics and treatment responsivity in individual patients, it should be emphasized that broadly equivalent efficacy across patient groups does not translate into equal efficacy in individual patients. Despite exciting recent developments in pharmacogenetics, it is still not currently possible to predict which antipsychotic may be optimal for a given patient. There is also no best agent or best dose for all patients, although dose ranges for optimal effectiveness do exist. Decisions about antipsychotic therapy, therefore often entail a trial and error process involving careful monitoring of response and adverse effects, an ongoing risk-benefit assessment, and judicious switching if necessary.

Because of the marked inter-individual variability in both efficacy and safety/tolerability, careful measurement of both the beneficial and adverse effects in every patient during the course of antipsychotic treatment is essential. In the DSM-5 (section 3), a simple and reliable 5-point 8-item scale is available to measure response of different symptom dimensions in schizophrenia (and other psychotic disorders). The use of this scale is strongly recommended. It is easy to use and can be administered in a few minutes. Similarly, EPS, metabolic disturbances, and other side-effects should be closely monitored and appropriately addressed.

In order to make informed treatment decisions, measurement of the severity of each of the six symptom domains in the course of treatment is necessary. Since antipsychotic agents are primarily effective in the treatment of positive symptoms and disorganization, persistence of these symptoms should prompt consideration of a different antipsychotic regimen including use of clozapine or a long-acting antipsychotic agent. If positive symptoms have improved but depressive symptoms persist, use of an antidepressant should be considered. If positive symptoms improve but negative symptoms worsen, the possibility of EPS should be effectively addressed. In this manner, measurement-based pharmacological treatment enables optimal individualization of treatment in persons with schizophrenia.

To achieve optimal therapy for schizophrenia, clinicians must balance efficacy benefits and side-effect costs of treatment in a way that is customized for the needs and vulnerabilities of the individual patient. The meticulous application of this approach can reduce the significant gap between what we know about best practices and the therapy that is actually provided for patients with schizophrenia.
Clinical Guidance

Schizophrenia is characterized by positive, negative, cognitive, disorganization, and mood symptoms. Antipsychotics are the mainstay of the pharmacological treatment of schizophrenia. Findings concerning efficacy for positive symptoms and disorganization suggest no consistent differences among available antipsychotics, with the exception of clozapine’s superior efficacy for treatment-resistant schizophrenia. Efficacy for negative, depressive, and cognitive symptoms appears to be determined by: 1) The extent to which reduction in positive symptoms brings about improvement in these other domains; and 2) The extent to which extrapyramidal side effects and anticholinergic effects (of the antipsychotic and of agents used to treat EPS) exacerbate them. Thus, the ability of antipsychotics to produce a potent antipsychotic effect without EPS and need for concomitant anticholinergic therapy yield multiple therapeutic benefits. In contrast to their broadly similar efficacy, antipsychotics differ markedly in their propensity to cause various adverse effects. Choice of antipsychotic medication should be based on individual preference, prior treatment response and side-effect experience, medical history and risk factors, and adherence history, with side-effect profile a major determinant of antipsychotic choice. Systematic measurement of efficacy and adverse effects is essential and can guide optimal individualization of antipsychotic treatment.

References

Treatment of Schizophrenia with Long-Acting Injectable Antipsychotics Medications (LAIs)

Conduct a comprehensive assessment and use measurement-based care as found in the Principles of Practice.

Assess social support system (housing, family, other caregivers) and evaluate threats to continuity of care (access to medication, adherence, etc.).

**Strongly recommend psychiatric consultation prior to initiation of therapy + psychotherapeutic medication using a multi-disciplinary approach if treated by a non-psychiatrist.**

**Level 1  Initial Treatment:**

- After stabilization or obtaining a sufficient evidence for efficacy and tolerability, offer any of the following LAIs. Base the selection on past efficacy and tolerability patterns to specific oral or LAI antipsychotics, expected tolerability advantages*, desired injection intervals, and procedural (oral overlap needed - yes versus no)/logistic/access/cost considerations:
  - Aripiprazole monohydrate
  - Aripiprazole lauroxil
  - Paliperidone palmitate
  - Risperidone microspheres
- If initial trial of LAI is unsuccessful, try monotherapy with another LAI from the above group

*Note: Balance efficacy, side-effects, individual vulnerabilities and preferences. Select medication with lower propensity for metabolic and extrapyramidal side-effects.

**Level 2  If Level 1 is ineffective and/or not well tolerated:**

- Consider LAI with greater adverse effect risk [olanzapine: post-injection delirium/sedation syndrome (PDSS); FGA-LAIs: EPS, TD]
  - Olanzapine pamoate
  - Fluphenazine decanoate
  - Haloperidol decanoate

**Level 3  If Levels 1 and 2 are ineffective and/or not well tolerated:**

- Diagnostic review and/or consultation
- Consider switch to an oral antipsychotic not available as an LAI (if adherence can be assured)
- Clozapine if not tried earlier
- LAI + electroconvulsive therapy (ECT)
- Clozapine + ECT
### Table 5. Recommended Medications for the Treatment of Schizophrenia: Long-Acting Injectable Antipsychotics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose Interval</th>
<th>Dosage Strengths/Forms</th>
<th>Starting Dose</th>
<th>Maintenance Dose</th>
<th>Oral Supplementation</th>
<th>Time to Peak</th>
<th>Steady State</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-Generation Long-Acting Injectable Antipsychotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluphenazine decanoate</td>
<td>Varies</td>
<td>25 and 100 mg/mL ampoules/vials/syringes</td>
<td>Varies, 12.5 mg</td>
<td>Varies, 12.5 to 100 mg</td>
<td>No</td>
<td>2 to 4 days</td>
<td>2 to 3 months</td>
</tr>
<tr>
<td>Haloperidol Decanoate</td>
<td>4 weeks</td>
<td>50 and 100 mg/mL ampoules</td>
<td>Varies, 50 mg</td>
<td>Varies, 300 mg</td>
<td>No</td>
<td>6 to 7 days</td>
<td>2 to 3 months</td>
</tr>
<tr>
<td><strong>Second-Generation Long-Acting Injectable Antipsychotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole monohydrate (Abilify Maintena®)</td>
<td>Monthly</td>
<td>300, 400 mg vial kits and dual-chamber syringe</td>
<td>400 mg</td>
<td>400 mg (300 to 400 mg)</td>
<td>2 weeks</td>
<td>5 to 7 days</td>
<td>400 mg: 4 to 8 months 300 mg: 3 to 4 months</td>
</tr>
<tr>
<td>Aripiprazole lauroxil (Aristada®)</td>
<td>Monthly (every 6 weeks for 882 mg dose)</td>
<td>441, 662, 882 mg prefilled syringes</td>
<td>Varies, 441 to 882 mg</td>
<td>Varies, 441 to 882 mg</td>
<td>3 weeks</td>
<td>4 days</td>
<td>4 to 6 months</td>
</tr>
<tr>
<td>Olanzapine pamoate‡ (Zyprexa Relprevv®)</td>
<td>2 or 4 weeks</td>
<td>210, 300, 405 mg vial kits</td>
<td>Varies, up to 300 mg every 2 weeks</td>
<td>Varies, up to 300 mg every 2 weeks</td>
<td>No</td>
<td>4 days</td>
<td>3 months</td>
</tr>
<tr>
<td>Paliperidone palmitate (Invega Sustenna®)</td>
<td>Monthly</td>
<td>38, 117, 156, 234 mg prefilled syringes</td>
<td>234 mg (day 1) + 156 mg (day 8)</td>
<td>117 mg (38 to 234 mg)</td>
<td>No</td>
<td>13 days</td>
<td>7 to 11 months</td>
</tr>
<tr>
<td>Paliperidone palmitate (Invega Trinza®)</td>
<td>Once every 3 months</td>
<td>273, 410, 546, 819 mg prefilled syringes</td>
<td>Depends on once-monthly dose</td>
<td>Varies, 273 to 819 mg</td>
<td>No</td>
<td>30 to 33 days</td>
<td>Continues steady state at equivalent dose</td>
</tr>
<tr>
<td>Medication</td>
<td>Dose Interval</td>
<td>Dosage Strengths/Forms</td>
<td>Starting Dose</td>
<td>Maintenance Dose</td>
<td>Oral Supplementation</td>
<td>Time to Peak</td>
<td>Steady State</td>
</tr>
<tr>
<td>-------------------------------------------</td>
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</tr>
<tr>
<td>Risperidone Microspheres (Risperdal Consta®)</td>
<td>2 weeks</td>
<td>25, 37.5, 50 mg vial kits</td>
<td>25 mg</td>
<td>25 mg (25 to 50 mg)</td>
<td>3 weeks</td>
<td>4 to 6 weeks</td>
<td>1.5 to 2 months</td>
</tr>
</tbody>
</table>


Notes:
*First-generation long-acting injectable antipsychotic medications (fluphenazine decanoate and haloperidol decanoate) have an oil base. Second-generation long-acting injectable antipsychotic medications (aripiprazole monohydrate, aripiprazole lauroxil, olanzapine pamoate, 1-month and 3-month paliperidone palmitate, and risperidone microspheres) have a water base.

‡Olanzapine pamoate (Zyprexa Relprevv) requires prescriber certification and patient enrollment with the Risk Evaluation and Mitigation Strategy (REMS) program. Administration of olanzapine pamoate requires at least 3-hours of post-injection monitoring for post-injection delirium/sedation syndrome (PDSS). Olanzapine has been found to cause more weight gain and related metabolic side effects than other SGAs.
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

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., 2017) 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.
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; Correll et al., 2016).

- 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.).

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).

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).
REFERENCES:


