When should you consider combining 2 long-acting injectable antipsychotics?

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Ms. S, age 39, with a 15-year history of schizophrenia and severe paranoid delusions, is admitted after physically assaulting a staff member at a group home. She is receiving paliperidone palmitate, 234 mg every 4 weeks. This has reduced the severity of her symptoms, but she continues to have persistent delusions that affect her ability to accept redirection from staff. Ms. S frequently accuses staff and peers of sexual assault, says that she is pregnant, and does not adhere to treatment recommendations for laboratory monitoring because the "staff uses her blood for experiments."

Ms. S frequently requires administration of oral and IM haloperidol, as needed, when she becomes aggressive with the staff. She has poor insight into her mental illness and does not believe that she needs medication. Ms. S has a long history of stopping her oral antipsychotic after a few days, reporting that it is "harming her baby." Monotherapy has been tried with various long-acting injectable antipsychotics (LAIAs), but she still exhibits persistent delusions. The treatment team decides to add a second LAIA, haloperidol decanoate, 200 mg every 4 weeks, to her regimen.

Treatment-resistant schizophrenia provides a challenge for practicing clinicians. Although clozapine is preferred for treatment-resistant schizophrenia,[1-4] it is not an option for patients who cannot adhere to required laboratory monitoring. Treatment guidelines state that there is limited evidence for combining 2 antipsychotics (aside from augmentation of clozapine treatment) and that such use should be closely monitored and documented.[2-4] Use of a single LAIA is recommended when the patient prefers the formulation or to avoid treatment nonadherence; however, treatment guidelines do not address the simultaneous use of 2 LAIAs.[2,4-6] A few case reports have described successful use of dual LAIAs (***Table 1***,[7-11] ***page 43***). Five of these are summarized here (Yazdi et al[10] was published in German and is only included in ***Table 1***,[7-11] ***page 43***).

Ladds et al.[7] A 49-year-old woman with schizophrenia who was hospitalized for aggressive and bizarre behavior and had been institutionalized for 20 years stopped taking her medication regimen.[7] She started taking 8-hour showers with bleach, talking

Practice Points

- Although **treatment guidelines do not address the use of 2 long-acting injectable antipsychotics** (LAIAs), they recognize the need for 2 oral antipsychotics in cases of treatment resistance; however, evidence is limited.
- **Carefully consider LAIA properties** when choosing a regimen for dual treatment.
- **Use the lowest effective dose of each LAIA** to limit adverse effects and improve patient tolerability of the regimen.

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Table 1

Published case reports of dual LAIA treatment

Case report	Patient	Diagnosis	Dual LAIA regimen
Ladds et al[7]	Female, age 49	Schizophrenia	Risperidone microspheres[a] Fluphenazine decanoate[a]
Wartelsteiner and Hofer[8]	Male	Schizophrenia, paranoid type	Risperidone microspheres, 100 mg every 2 weeks Olanzapine pamoate, 300 mg every 2 weeks
Scangos et al[9]	Vietnamese male, age 26	Schizophrenia	Olanzapine pamoate, 405 mg once a month Haloperidol decanoate[a]
Yazdi et al[10,b]	44 years old	Schizoaffective disorder	Risperidone microspheres, 50 mg every 2 weeks Zuclopenthixol decanoate, 500 mg every 2 weeks
Ross and Fabian[11]	African American male, age 44	Schizophrenia, paranoid type	Paliperidone palmitate, 156 mg once a month Haloperidol decanoate, 400 mg every 2 weeks

[a]Dose not reported

[b]Case report published in German

LAIA: long-acting injectable antipsychotic

Clinical Point

A few case reports have reported successful use of dual LAIAs

incoherently, and believing that someone was poisoning her. She had poor response to oral risperidone monotherapy; however, 2 months after adding oral fluphenazine and benztropine to her regimen, her symptoms substantially improved (doses not reported). Because she had impaired insight into the need for daily medication, she was started on depot fluphenazine decanoate and risperidone microspheres (doses not reported) before discharge. No substantial adverse effects were noted with this regimen.

Wartelsteiner and Hofer.[8] A man who had been diagnosed with paranoid schizophrenia at age 20 presented with thought blocking, incoherence, persecutory delusions, and uncontrolled self-damaging behavior.[8] He had been admitted 27 times over 7 years; during this time he received many antipsychotic monotherapies and combination regimens. A total of 8 oral antipsychotics (including clozapine) and 5 LAIAs had been administered during these trials. He significantly improved with the combination of olanzapine and risperidone. Both medications were switched to LAIA formulations to address medication nonadherence. His symptoms remained stable with risperidone microspheres, 100 mg, and olanzapine pamoate, 300 mg, each administered every 2 weeks. He did not experience any adverse effects with this combination therapy.

Scangos et al.[9] A 26-year-old Vietnamese man with schizophrenia and an extensive history of unprovoked, psychotically driven assaults was given multiple antipsychotics (including clozapine) during hospitalizations, and his medication regimen consistently included 2 antipsychotics. After contracting viral gastroenteritis, he refused oral medications and required short-acting IM administration of both haloperidol, 5 mg, twice a day, and olanzapine, 10 mg, twice a day. Because of concerns about continuing this regimen, he was switched to haloperidol decanoate (dose not reported) and olanzapine pamoate, 405 mg, administered once per month. The injections were scheduled to alternate so that the patient would receive 1 injection

Table 2

Summary of long-acting antipsychotic properties

Drug	Dose range (mg)	Frequency	Injection site(s)	$T_{1/2}$ (days)
First-generation antipsychotics				
Fluphenazine decanoate[12]	12.5 to 100	Every 2 to 4 weeks	Gluteal or deltoid	Approximately 14
Haloperidol decanoate[13]	10 to 15 times oral dose	Every 4 weeks	Gluteal or deltoid	Approximately 21
Second-generation antipsychotics				
Aripiprazole monohydrate[14]	160 to 400	Monthly	Gluteal or deltoid	Approximately 46.5
Aripiprazole lauroxil[15]	441 to 882	Monthly, or every 6 weeks (882 mg only)	Gluteal, deltoid (441 mg only)	29.2 to 34.9
Olanzapine pamoate[16]	150 to 405	Every 2 or 4 weeks	Gluteal	30
Paliperidone palmitate (1 month)[17]	39 to 234	Every 4 weeks	Gluteal or deltoid	25 to 49
Paliperidone palmitate (3 month)[18]	273 to 819	Every 3 months	Gluteal or deltoid	84 to 95 (deltoid) or 118 to 139 (gluteal)
Risperidone microspheres[19]	12.5 to 50	Every 2 weeks	Gluteal or deltoid	3 to 6

[a]For second-generation agents in clinical trials of patients with schizophrenia at rates >5%

Clinical Point

Prior to initiating treatment with 2 LAIAs, previous tolerability of each medication must be confirmed

every 2 weeks. The patient's assaultive behavior was significantly reduced, and no adverse effects were reported.

Ross and Fabian.[11] An African American man, age 44, was receiving haloperidol decanoate, 400 mg every 2 weeks, and oral haloperidol, 20 mg/d.[11] Because of residual symptoms, a history of nonadherence, and concerns about increasing the haloperidol decanoate dose or frequency, oral haloperidol was discontinued and paliperidone palmitate, 156 mg every 4 weeks, was started. The patient was able to transition into a step-down unit, and no adverse effects were reported.

What to consider before initiating dual LAIA treatment

Evaluate the frequency of administration, flexibility of dosing, administration site, adverse effects, and monitoring requirements of each LAIA (*Table 2*[12-19]) to ensure the patient's optimal tolerability of the regimen. Previous tolerability of each medication must be confirmed by evaluating the patient's medication history or oral or IM administration of each agent prior to initiating the LAIA.

When choosing 2 agents that are each administered once every 4 weeks, consider administering the medications together every 4 weeks or alternating administration

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Adverse effects[a]	Monitoring
Extrapyramidal symptoms, hypertension, drowsiness	Hypotension, tardive dyskinesia
Tachycardia, hypotension, hypertension, extrapyramidal symptoms	Hypotension, tardive dyskinesia
Weight gain, akathisia, injection site pain, sedation	Metabolic monitoring, tardive dyskinesia
Akathisia	Metabolic monitoring, tardive dyskinesia
Headache, sedation, weight gain, cough, diarrhea, back pain, nausea, somnolence, dry mouth, nasopharyngitis, increased appetite, vomiting	3-hour post-injection observation at registered health care facility, metabolic monitoring, tardive dyskinesia
Injection site reactions, somnolence/sedation, dizziness, akathisia, extrapyramidal disorder	Metabolic monitoring, tardive dyskinesia
Injection site reaction, weight gain, headache, upper respiratory tract infection, akathisia, parkinsonism	Metabolic monitoring, tardive dyskinesia
Headache, parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight gain, pain in extremity, dry mouth	Metabolic monitoring, tardive dyskinesia

so that the patient receives an injection every 2 weeks. Receiving an injection once every 2 weeks might be beneficial for patients who need close follow-up or are more sensitive to injection site reactions, whereas a regimen of once every 4 weeks might be beneficial for patients who are more resistant to receiving the injections, so there is potentially less time spent agitated or anxious leading up to the date of the injection.

Use the lowest effective dose of each LAIA to limit adverse effects and improve tolerability of the regimen. Monitor patients closely for adverse reactions and discontinue the regimen as soon as possible if a severe adverse reaction occurs.

Related Resource

- Correll CU, Citrome L, Haddad PM, et al. The use of long-acting injectable antipsychotics in schizophrenia: evaluating the evidence. J Clin Psychiatry. 2016;77(suppl 3):1-24.

Drug Brand Names

Aripiprazole monohydrate • Abilify Maintena
Aripiprazole lauroxil • Aristada
Fluphenazine decanoate • Prolixin D
Haloperidol decanoate • Haldol D
Olanzapine pamoate • Zyprexa Relprevv
Paliperidone palmitate (1 month) • Invega Sustenna
Paliperidone palmitate (3 month) • Invega Trinza
Risperidone microspheres • Risperdal Consta

Cost may influence the decision to use 2 LAIAs. The majority of LAIAs in the United States are available only as branded formulations. Insurance companies may require prior authorization for the use of 2 LAIAs.

Although there are no treatment guidelines for combining 2 LAIAs, this practice has been used. A few case reports have described successful use of dual LAIA treatment, but one should consider the risk of the publication's bias. Overall, the decision to use 2 LAIAs is difficult because there is lack of a large evidence base supporting the practice or direction from treatment guidelines. Because of this, dual LAIA treatment should not be used for most patients. In cases of treatment-resistant schizophrenia where clozapine is not an option and adherence is a concern, it is reasonable to consider this strategy on a case-by-case basis.

Clinical Point

Consider whether the patient needs close follow-up or is more resistant to receiving injections when scheduling administrations

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Clinical Point

In patients with treatment-resistant schizophrenia, where clozapine is not an option, consider dual LAIAs on a case-by-case basis

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