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The use of concurrent long-acting injectable antipsychotic therapy with paliperidone palmitate and aripiprazole monohydrate in a patient with schizophrenia

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Abstract

International schizophrenia guidelines endorse seeking the patient's preference for guiding antipsychotic therapy. There exists a small niche of patients who prefer, or are required to use, long-acting injectable antipsychotic medications due to the adherence benefit. However, they may not be able to achieve adequate symptom reduction prior to experiencing treatment-limiting adverse effects from a single agent. Here, we present a patient case prescribed concurrent long-acting injectable antipsychotic therapy with paliperidone palmitate and aripiprazole monohydrate due to patient preference in the setting of a history of nonadherence to oral medications, treatment-limiting adverse effects to long-acting injectable paliperidone, and failure to achieve adequate symptom reduction with long-acting injectable aripiprazole monotherapy.

Keywords: long-acting injectable antipsychotic, depot antipsychotic, dual, concurrent

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Background

Treatment-resistant schizophrenia (TRS) increases health care system costs and decreases quality of life.[1,2] To manage TRS, the choice of antipsychotic medication should be guided by a careful evaluation of expected symptom reduction, impact of medication adverse effects, and patient preference.[3,4]

International guidelines recommend long-acting injectable (LAI) antipsychotic medications in patients who prefer this treatment modality or have a history of nonadherence.[3,4] Atypical LAI antipsychotics compared with their oral equivalents are more favorable for rate of relapse, adherence to treatment, and preventing hospitalization.[5-8] In Canada, the available LAI antipsychotics are risperidone, paliperidone palmitate, aripiprazole monohydrate, flupentixol decanoate, haloperidol decanoate, and zuclopenthixol decanoate.

The standard of treatment for schizophrenia is pharmacotherapy with a single antipsychotic medication (including the use of clozapine for TRS).[4] In rare and difficult cases in which the patient has exhausted available single-therapy options, including clozapine, the American Psychiatric Association[4] allows for a combined antipsychotic approach for TRS. However, this treatment

approach should not be considered standard nor undertaken without a careful evaluation of the potential risks of additive antipsychotic adverse effects versus the possible individualized benefits of antipsychotic polypharmacy.

Here, we present a challenging patient case in which concurrent LAI therapy with paliperidone and aripiprazole was guided by patient preference due to a history of nonadherence to oral antipsychotics, distressing side effects to LAI paliperidone, and a failure to achieve adequate symptom control with LAI aripiprazole.

Case Report

A 39-year-old female presented to an urban hospital in Canada accompanied by police after she had called with mental health concerns. She endorsed a 1-week history of confusion and feeling overwhelmed with child care responsibilities. Her outpatient psychiatric team reported the patient experienced auditory hallucinations for the past year and paranoid delusions for the prior 6 months, resulting in her isolating at home. They also noted she had a restraining order at her child's school for aggressive behavior.

The patient's psychiatric history was first documented 4 years prior to this admission. During her first admission, oral olanzapine 5 mg daily was initiated for unspecified psychosis, resulting in rapid improvement. After 18 months of olanzapine nonadherence (due to excessive sedation), she was again admitted to psychiatry. Oral risperidone 1 mg daily was initiated and titrated to 2 mg daily after 1 week, resulting in psychotic symptom improvement. The patient then had several emergency room visits and 3 further admissions for medication nonadherence leading to a formal diagnosis of schizophrenia.

During her fourth psychiatric admission, oral risperidone was restarted and transitioned to LAI paliperidone (per standard loading dose regimen), followed by a maintenance dose of paliperidone 100 mg (ie, paliperidone palmitate 156 mg) IM every 28 days. After being stabilized on LAI paliperidone 100 mg for 6 months in the community, the patient presented to the emergency department for antipsychotic-associated extrapyramidal symptoms (EPS). On physical exam, bilateral cogwheeling and tremors were present. Consequently, as an outpatient, LAI paliperidone was directly switched to LAI aripiprazole 300 mg IM every 28 days on the date of the next scheduled paliperidone injection. Aripiprazole was chosen due to having a different pharmacological profile compared with paliperidone, the remaining LAI antipsychotics available are typical antipsychotics (thus, carrying a higher risk of EPS), and she consented to only the LAI modality. The patient preferred aripiprazole rather than a dose reduction of LAI paliperidone due to the distressing nature of her EPS and declined oral anticholinergic therapy. She was not given oral aripiprazole prior to initiation of LAI aripiprazole due to the risk of nonadherence and possible psychiatric destabilization. During her sixth month of LAI aripiprazole treatment, the patient was admitted for acute psychosis, and aripiprazole was increased to 400 mg IM every 28 days.

The patient continued on LAI aripiprazole 400 mg for 3 months prior to the present admission (last administered dose was 1 week before admission). In addition to LAI aripiprazole, her outpatient psychiatrist prescribed oral aripiprazole 10 mg daily for residual psychosis. Her family physician had also started zopiclone 7.5 mg at bedtime for insomnia symptoms. Her oral medications were not ordered on admission due to questionable nonadherence.

Admission laboratory investigations were unremarkable and included a complete blood count, a lipid and electrolyte panel, hepatic and renal function tests, and hemoglobin A1c. Her prolactin level was 42 mcg/L. The electrocardiogram was normal with a QTc of 457 ms. Her body mass index was 22 kg/m^2. The patient had no known drug allergies and no nonpsychiatric medical conditions. She denied alcohol or recreational drug use and reported smoking 5 to 6 cigarettes daily.

Shortly after admission, oral paliperidone 3 mg daily was initiated for inadequately controlled psychotic symptoms in addition to her ongoing LAI aripiprazole therapy. Paliperidone was chosen because of historical efficacy with the LAI formulation. Oral paliperidone was increased in 3 mg increments weekly due to persistent paranoid delusions to a dose of 9 mg daily. The patient tolerated the addition of oral paliperidone to her LAI aripiprazole therapy, and no EPS or other adverse effects were observed or reported. After 3 weeks of antipsychotic combination therapy, she reported fewer hallucinations and delusions.

On the third week of admission, the patient was presented the option of receiving dual LAI therapy with paliperidone and aripiprazole as she preferred the LAI route of administration, was tolerating the combination, and was reluctant to receive LAI paliperidone as a single medication due to her traumatic presentation for paliperidone-associated EPS. Clozapine was considered, but the patient refused the mandatory weekly blood work, and her inconsistency in oral adherence to aripiprazole may have been a contributing factor to the present admission. Typical antipsychotic medications carry an elevated risk of drug-induced EPS; thus, this class was not considered. Due to the less convenient biweekly admin-

istration of LAI risperidone, paliperidone was again preferred.

The risks of combined antipsychotic therapy were thoroughly explained to the patient, and she consented to receive both LAI agents. The patient was administered IM aripiprazole 400 mg and IM paliperidone 100 mg in opposite deltoid muscles on the date of the next scheduled aripiprazole injection, and oral paliperidone was discontinued. Paliperidone 100 mg was prescribed (equivalent to oral paliperidone 9 mg daily) as the patient had been stabilized without any reported or observed EPS. The patient was discharged 3 days after receiving the dual LAI medications. Follow-up was arranged with an outpatient psychiatric team for subsequent dual LAI administration and ongoing surveillance.

At the 1-year mark postdischarge, the patient continues to receive dual LAI therapy at unchanged doses. There have not been any psychiatric presentations since initiating therapy, and it has allowed her to remain out of the hospital for the longest period of time since her psychosis symptoms began. On monthly assessments, the patient denies psychotic symptoms and has not experienced EPS, akathisia, or symptomatic hyperprolactinemia.

Follow-up lab work and monitoring parameters are unremarkable and include a complete blood count, metabolic monitoring, and an electrocardiogram. Repeat prolactin remained unchanged with dual LAI therapy. The patient maintains insight that the dual LAI regimen controls her paranoia and has been preventing hospitalization.

Due to psychosocial stressors, including being the primary caregiver for her 6 children, her outpatient psychiatrist diagnosed her with generalized anxiety disorder and is treating with escitalopram 20 mg daily. With the addition of escitalopram to LAI therapy, the increased risk of QTc prolongation is being monitored by a yearly electrocardiogram. Insomnia continues to be a concern, but sleep hygiene strategies are being optimized. Informed consent was obtained from the patient for publication.

Discussion

Guidelines by the American Psychiatric Association[4] allow for antipsychotic polypharmacy to be considered for rare cases of TRS in which a single medication does not achieve adequate symptom reduction. In patients with a preference for LAI medications, documented oral nonadherence, and for whom a single agent does not satisfactorily reduce symptoms without the patient experiencing adverse effects, utilizing a concurrent LAI approach is an intriguing concept.

A systematic review of the literature was performed to identify other cases of dual LAI therapy with aripiprazole and paliperidone or risperidone. PubMed, EMBASE, and Google Scholar were indexed using the following search terms: *long-acting injectable antipsychotic* or *depot antipsychotic* and the results were filtered to include only case reports detailing *concurrent*, *alternating*, *dual*, *combined*, or *combination*. Reference lists of obtained case reports were searched for any additional cases.

There was a total of 9 dual LAI case reports[9-14] as shown in the Table. Although there were no cases with the combination of aripiprazole and risperidone/paliperidone, there were 2 cases[13,14] of concurrent atypical LAI antipsychotics. Both cases described clinical improvement after the second atypical antipsychotic was added orally. However, oral nonadherence led to decompensation, resulting in the initiation of dual LAI treatment.[13,14] Similarly, our patient improved when the second atypical antipsychotic, paliperidone, was added orally to LAI aripiprazole. The remaining 7 cases involved a typical and an atypical antipsychotic, of which 6 describe the patient as not achieving adequate psychotic symptom reduction with the use of a single LAI agent (Table). Comparable to our patient, all 9 cases report nonadherence to oral antipsychotic medications. Several themes arose across the cases reported in the literature. First, dual LAI therapy is only utilized in challenging cases[9-14] in which the use of oral antipsychotic medications has not been successful. Second, a majority of the authors[9,10,12,13] recommend close monitoring given the rarity of this treatment plan. Last, clinicians should consider concurrent LAI medications with varied receptor activity.[10,11,13]

Augmenting risperidone/paliperidone with aripiprazole is previously described in the literature but has been largely isolated to treatment of antipsychotic-associated hyperprolactinemia.[15-18] Although our patient had no recorded episodes of galactorrhea, she did have unchanged, persistently elevated prolactin from baseline and throughout treatment with varying LAI antipsychotic regimens, including combination LAI treatment.

Positive symptoms of schizophrenia are correlated with excess dopamine in the mesolimbic pathway, and negative symptoms and cognitive impairment are linked to insufficient dopamine in the mesocortical pathway.[19] Dopamine receptor blockade is associated with EPS in the nigrostriatal pathway and hyperprolactinemia in the tuberoinfundibular pathway.[19] Compared to a traditional dopamine antagonist, aripiprazole also acts as an antagonist in the mesolimbic pathway to treat positive symptoms, an agonist in the mesocortical pathway to mitigate negative symptoms, and prevents full blockade in the nigrostriatal and tuberoinfundibular pathway to

TABLE: Published cases using dual long-acting injectable antipsychotic medications for the treatment of schizophrenia

Study (year)	Sex	Age, y	First LAI Antipsychotic	Additional LAI Antipsychotic	Were Both LAI Antipsychotics Administered on the Same Day?	History of Oral Nonadherence	Was There Improvement or Resolution of Symptoms?
McInnis and Kasinathan[9] (2019) Case A	M	17	Olanzapine pamoate 405 mg IM every 14 d	Zuclopenthixol decanoate 600 mg IM every 14 d	Yes	Yes	Yes
McInnis and Kasinathan[9] (2019) Case B	M	17	Zuclopenthixol decanoate 400 mg IM every 14 d	Paliperidone palmitate 150 mg IM monthly	Yes (when injection dates overlapped)	Yes	Yes (paliperidone was discontinued upon start of zuclopenthixol; however, psychosis symptoms worsened, leading to paliperidone restart)
McInnis and Kasinathan[9] (2019) Case C	M	16	Paliperidone palmitate 150 mg IM monthly	Zuclopenthixol decanoate 600 mg IM every 14 d	Yes (when injection dates overlapped)	Yes	Yes
Li et al[10] (2019) Case A	F	35	Flupentixol decanoate 40 mg IM every 2 wk; changed to flupentixol decanoate 20 mg IM every 4 wk after aripiprazole initiation	Aripiprazole 400 mg IM monthly	No, each LAI alternates every 2 wk	Yes	Yes (psychotic symptoms returned when flupentixol was discontinued; thus, both LAIs were maintained)
Li et al[10] (2019) Case B	M	46	Flupentixol decanoate 40 mg IM every 2 wk; changed to flupentixol decanoate 40 mg IM monthly after paliperidone started	Paliperidone palmitate 150 mg IM monthly	No, each LAI alternates every 2 wk	Yes	Yes
Ladds et al[11] (2009)	F	49	Risperidone IM[a]	Fluphenazine IM[a]	Not reported	Yes	Not reported
Scangos et al[12] (2016)	M	26	Olanzapine pamoate 405 mg IM monthly	Haloperidol decanoate IM monthly[a]	No, each LAI alternates every 2 weeks.	Yes (dual LAI therapy was prescribed to reduce daily short-acting IM injections due to oral nonadherence)	Yes
Lenardon et al[13] (2017)	M	52	Olanzapine pamoate 405 mg IM every 10 d	Aripiprazole 400 mg IM monthly	Yes (when injection dates overlapped)	Yes	Yes
Wartelsteiner and Hofer[14] (2015)	M	20	Olanzapine pamoate 300 mg IM every 2 wk	Risperidone 100 mg IM every 2 wk	Yes	Yes	Yes

LAI = long-acting injectable.

[a]No dose was specified.

minimize EPS and hyperprolactinemia, respectively.[19] Our patient was reluctant to resume paliperidone monotherapy due to her EPS history. She consented to receive LAI paliperidone after she had tolerated the addition of oral paliperidone to LAI aripiprazole and continues to receive the combination without any EPS. Theoretically, this may have been due to aripiprazole acting as a partial agonist to prevent full dopamine blockade in the nigrostriatal

pathway. However, the literature on this treatment approach is limited.

Initiating dual LAI therapy is not without risks. Depot antipsychotic medications have a limited opportunity to reverse potential complications after a large, sustained dose of the medication has been administered. These risks can include EPS, akathisia, metabolic syndrome, cardiac abnormalities, and neuroleptic malignant syndrome.[20] However, many of these complications, apart from injection-related reactions, are also present with oral equivalents. Preceding dual LAI therapy, clinicians should complete a careful evaluation of the risks and benefits, obtain informed consent from the patient or agent, and create a treatment plan to reevaluate the need for antipsychotic polypharmacy. For transparency, we cannot exclude the possibility of aripiprazole-associated insomnia (diagnosed approximately 2 months after LAI aripiprazole initiation) or antipsychotic-associated anxiety (diagnosed approximately 6 months after dual LAI initiation).

Conclusion

To summarize, we report a patient case with schizophrenia who, after weighing the risks and benefits of a nonstandard treatment plan, consented to receive dual LAI therapy with aripiprazole and paliperidone to improve medication adherence resulting in the stabilization of her symptoms. This patient case demonstrates a dual LAI regimen with 2 atypical antipsychotic medications that is unique from the current literature in that aripiprazole, a partial dopamine type 2 receptor agonist, is used in combination with paliperidone, a dopamine type 2 receptor antagonist.

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