Amisulpride Augmentation of Clozapine in Clozapine-Resistant Schizophrenia: A Case Series

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INTRODUCTION

It has been estimated that 25% to 30% of individuals with a diagnosis of schizophrenia meet the criteria for treatment-resistant schizophrenia.[1,2] This condition is commonly defined as the persistence of positive and negative symptoms despite 2 or more trials, of adequate dose and duration, of antipsychotic medication, with documented adherence.[2] Currently, the only antipsychotic approved for use in treatment-resistant schizophrenia is clozapine. Of patients with this diagnosis, 30% to 60% will respond to an adequate trial of clozapine, defined as 12 weeks or more of treatment with plasma concentration of at least 1070 nmol/L (350 ng/mL).[2] The remaining 40% to 70% of patients are considered to have clozapine resistance, and augmentation with electroconvulsive therapy (ECT) or other medications is often considered.[3,4] Currently, the Canadian and US schizophrenia guidelines do not provide detailed guidance on augmentation strategies.[1,5] However, an international expert working group recently achieved consensus on the use of amisulpride as an augmentation strategy in clozapine resistance for mixed positive and negative symptoms.[6]

Overall, previous prospective controlled studies have shown mixed results for amisulpride augmentation of clozapine, with both positive and negative findings.[7-9] However, in clinical settings globally and in Canada, amisulpride is sometimes considered, given that its mechanism of action and receptor profile may be complementary to those of clozapine.

Amisulpride is a substituted benzamide antipsychotic with a selective affinity for the dopamine D2 and D3 receptors.[10] At lower doses (50–300 mg/day), amisulpride enhances dopamine transmission by selectively antagonizing presynaptic autoreceptors, contributing to the drug's efficacy in addressing primarily negative symptoms, whereas at higher doses (400–800 mg/day), amisulpride antagonizes postsynaptic D2 and D3 receptors in the limbic system, which is predictive of potent antipsychotic activity.[10-12] Furthermore, amisulpride acts as a potent antagonist at the serotonin 5HT7 receptor, which is postulated to contribute to its antidepressant efficacy.[13,14] The limbic selectivity of amisulpride is associated with a low propensity for causing extrapyramidal side effects.[10] Amisulpride has little or no affinity for D1, D4, D5, serotonin, μ-adrenergic, H1 histaminergic, or anticholinergic receptors.[15] Consequently, it is less likely than some other antipsychotics to increase the burden of side effects characteristic of clozapine, such as sedation, weight gain, and anticholinergic effects.[15] Although amisulpride is not currently marketed or approved for use in clinical practice in North America, in Canada it can be obtained through Health Canada's special access program for drugs.[16]

In this retrospective case series, we describe the practice of amisulpride augmentation of clozapine in a Canadian inpatient setting for treatment-resistant schizophrenia.

METHODS

This retrospective case series involved patients admitted to a provincial tertiary inpatient program that provides specialized treatment and services to patients with treatment-resistant schizophrenia in a multidisciplinary setting, with an average length of stay of 25 weeks. At the study institution, patients' symptom severity is measured by applying the Positive and Negative Syndrome Scale (PANSS) on admission and at discharge. The PANSS is a validated psychiatric rating scale and is considered the gold standard for quantifying symptoms related to schizophrenia in clinical trials. It is also used in clinical practice for monitoring treatment outcomes.[17] At both admission and discharge, the PANSS is administered by the most responsible psychiatrist. Most admitted patients who meet the criteria for clozapine resistance are offered ECT; if this therapy is declined, patient-specific pharmacological strategies are typically offered. The criteria for clozapine resistance are 12 weeks of clozapine therapy at a therapeutic level (measured at least once and preferably twice over the course of treatment) with persistence of positive symptoms according to the PANSS, with 1 item rated at 6 or 2 items rated at 4.

Two of the authors (S.P. and M.S.) conducted a chart review, using electronic records, to identify patients with

clozapine-resistant schizophrenia who underwent amisulpride augmentation of clozapine over the period January 1, 2017, to May 31, 2020. The starting date was chosen because our program did not access amisulpride (through the Health Canada special access program for drugs) before 2017. Of the 6 cases identified through this search, S.P. abstracted data for the first 3 cases, and M.S. abstracted data for the last 3 cases. The information collected for each case was reviewed independently by R.R.

This retrospective case series was approved by the Clinical Research Ethics Boards of the University of British Columbia and Vancouver Coastal Health Authority and employed principles highlighted in the Declaration of Helsinki. Given the retrospective nature of this study, patient consent was waived as per the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans and guidance from the local institutional review board.

CASE DESCRIPTIONS

The 6 cases in which patients with clozapine resistance received amisulpride augmentation of their clozapine therapy are summarized in Table 1. All 6 patients were Caucasian. ECT was offered to all of the patients before initiation of amisulpride, and all declined. The mean clozapine dose at the time of admission was 383.3 mg/day, and the mean serum level of clozapine/norclozapine concentration was 1726/1088 nmol/L before initiation of amisulpride. Although the PANSS rating was obtained at the time of admission, rather than the time when amisulpride was started, the psychiatrists' progress notes indicated no marked improvement in clinical presentation from the time of admission to the initiation of amisulpride.

Four of the 5 patients who tolerated amisulpride had a greater than 20% reduction in total PANSS score at the time of discharge (Table 1). In terms of the negative symptoms subscale, 3 of the 5 patients who tolerated amisulpride had a greater than 20% reduction in this symptom domain, despite a higher dosage range of amisulpride. In case 6, amisulpride was discontinued because of symptomatic hyperprolactinemia (amenorrhea); cases 1 to 5 displayed asymptomatic hyperprolactinemia at the time of discharge. Prolactin increases were noted as early as 1 to 2 weeks after starting the amisulpride treatment.

In case 4, the patient's clozapine therapy was discontinued 7 days before discharge as a precautionary measure, because of abnormal ventricular septal motion detected by echocardiography. The patient was maintained on amisulpride monotherapy until discharge.

In case 2, the patient's clozapine dose was decreased because of initiation of fluvoxamine 25 mg/day. Fluvoxamine is a potent inhibitor of cytochrome P450 1A2 (CYP1A2), which is the main enzyme involved in clozapine metabolism.[19] Addition of fluvoxamine to clozapine will result in phenoconversion to poor metabolizer status at CYP1A2.[19] In this patient, fluvoxamine was initiated after assessment of the clozapine–norclozapine ratio by the treating psychiatrist, which indicated extensive metabolizer status at CYP1A2. The serum levels from admission to discharge depicted a change in this ratio from 0.99 to 2.7.

Extrapyramidal symptoms (EPS) associated with the augmentation strategy were recorded if there was any use of anti-EPS medication after initiation of amisulpride or verified symptoms were clearly documented in the patient's chart (or both). No significant changes in EPS were noted in any of the cases, nor was there a significant weight increase for any patient. There was a clinically insignificant increase in QTc interval after initiation of amisulpride in cases 1 and 3 (16 ms and 25 ms from baseline, respectively). Similarly, there was a decrease in QTc interval after initiation of amisulpride in cases 2 and 5 (15 ms and 7 ms from baseline, respectively). The remaining 2 patients did not undergo electrocardiography at a time close to discharge.

DISCUSSION

This case series supports the notion that augmentation of clozapine with amisulpride in patients with clozapine resistance may result in measurable improvements in both positive and negative symptom domains. Multiple confounding factors can influence a reduction in PANSS score in a specialized inpatient setting; consequently, we cannot attribute observed improvements exclusively to amisulpride augmentation. These variables include (but are not limited to) increased contact time with the health care team in a controlled environment and increased availability of cognitive behavioural therapy. Consequently, our data might not be generalizable to outpatient settings. Furthermore, in case 2, augmentation with fluvoxamine occurred concomitantly with amisulpride, which might have contributed to the measurable improvements at the time of discharge.

Although for each patient both admission and discharge PANSS scores were determined by the same psychiatrist, not a masked rater, we could not ensure retrospectively whether the scoring and calculations had been conducted without error or whether observer bias had been avoided. In addition, because the initial PANSS scores were obtained at the time of admission, not at the time of amisulpride initiation, we had to use progress notes to determine if there were marked improvements in the clinical presentation. Consequently, we do not know whether the PANSS scores had already declined, before initiation of amisulpride. Furthermore, given the retrospective nature of this study, data collection was limited to information that was available in the chart.

We strengthened the chart review process by utilizing data abstractors who were clinical pharmacists with specialization in mental health and strong familiarity with the organization of the electronic chart system. Abstracted data

TABLE 1. Summary of Cases[a]

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (years)[b]	63	31	26	25	59	45
Sex	Male	Male	Female	Male	Male	Female
Length of stay (days)	210	145	123	91	133	139
Clozapine dosage on admission (mg/day)	575	425	250	300	450	300
Clozapine/norclozapine plasma concentration on admission (nmol/L)	2132/1136	1303/1319	1350/639	1443/977	2649/1698	1479/759
Other psychotropic medications on admission	Aripiprazole 400 mg IM q4weeks	Paliperidone LAI 525 mg IM q90days	None	Lithium 600 mg PO qHS	None	None
Clozapine augmentation[c] attempted before admission	Olanzapine, loxapine, aripiprazole	Paliperidone, olanzapine	None	None	Aripiprazole	None
Duration of clozapine use before amisulpride (days)	6804	188	264	352	10 573	2369
Clozapine dose at discharge (mg/day)	500	125	225	Discontinued	400	300
Clozapine/norclozapine plasma concentration at discharge (nmol/L)	1244/663	2284/848	1891/827	NA	2177/1342	1640/817
Amisulpride dose at discharge	200 mg BID	400 mg BID	400 mg BID	400 mg BID	400 mg BID	None
Other psychotropics at discharge	None	Fluvoxamine 25 mg daily	None	Quetiapine 50 mg PO hs	None	Brexpiprazole 2 mg PO daily
Amisulpride duration (days)	61	53	90	84	60	60
PANSS total score						
On admission	102	118	84	79	94	78
At discharge	80	90	67	47	83	78
Change[d]	–30.6%	–31.8%	–31.5%	–34.7%	–17.2%	0%
PANSS positive subscale score						
On admission	23	35	20	26	25	19
At discharge	17	25	18	12	20	21
Change[d]	–37.5%	–35.7%	–15.4%	–73.7%	–27.8%	+16.7%
PANSS negative subscale score						
On admission	25	21	18	19	23	23
At discharge	21	19	18	10	18	18
Change[d]	–22.2%	–14.3%	0%	–75%	–31.3%	–31.3%
QTc (ms)						
On admission	458	439	416	422	469	460
At discharge	474	424	441	NA	462	NA
Prolactin (µg/L)						
On admission	NA	20.7	8.9	11.4	21.7	NA
After starting amisulpride (no. of days)	106 (7 days)	39.9 (10 days) 45.7 (24 days)	133.4 (12 days)	91.1 (38 days)	65.5 (14 days)	215.6 (18 days) 197 (55 days) 16.0 (26 days post stop)
BMI						
On admission	23.7	37.0	36.1	21.3	23.1	22.3
At discharge	21.1	32.8	34.9	21.4	23.1	21.3
Tobacco smoking status	Smoker	Smoker	Smoker	Smoker	Smoker	Nonsmoker

LAI = long-acting injection, NA = not available, PANSS = positive and negative syndrome scale.
[a]All patients had a diagnosis of treatment-resistant schizophrenia.
[b]Age is presented in years at the time of admission.
[c]Clozapine augmentation before admission represents antipsychotics tried in the past to augment clozapine therapy.
[d]Obermeier and others[18] have provided information about calculation and interpretation of PANSS scores.

for each case were also reviewed independently by another clinical pharmacist.

Hyperprolactinemia was a consistent finding across all 6 patients. In a 2-week study of patients with schizophrenia, prolactin elevation was markedly greater with amisulpride than with other atypical agents.[20] Elevated prolactin levels have been associated with oligomenorrhea, amenorrhea, galactorrhea, decreased libido, infertility, breast cancer in women,[21] and decreased bone mass; these outcomes should be taken into account when augmentation is being considered.[22] Although amisulpride has been associated with dose-dependent QT prolongation,[23] the patients described in our case series did not experience clinically relevant increases in QT at therapeutic doses of amisulpride.

As mentioned above, amisulpride is not readily available in Canada and requires approval from Health Canada. Such approval generally takes about 24 hours, and shipping to the practitioner's office or pharmacy takes another 6 to 8 weeks. Consequently, advance planning is important. Amisulpride also poses cost concerns, as it is available from only 1 manufacturer, and a single amisulpride 400-mg tablet costs twice as much as a clozapine 200-mg tablet. A cost–utility analysis would be of benefit to evaluate the overall cost effectiveness of this intervention.

CONCLUSION

To our knowledge, this is the first study examining the practice of augmentation of clozapine therapy with amisulpride in Canada, based on obtaining the medication through Health Canada's special access program for drugs. Given the extended duration of stay in our tertiary facility, we have been able to provide details about the tolerability and efficacy of this augmentation strategy for the cases reported here. In light of mixed evidence of benefit, elevated costs, and barriers to access, the decision to prescribe amisulpride in Canada should be taken with caution and proactive planning. Further studies are needed to better understand the long-term efficacy and tolerability of this augmentation strategy. Future studies should focus on better characterization of subgroups of patients with treatment-resistant schizophrenia, to allow for greater precision in the selection of patients most likely to benefit from such an augmentation strategy.

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