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ORIGINAL RESEARCH

Augmentation of clozapine with amisulpride: an effective therapeutic strategy for violent treatment-resistant schizophrenia patients in a UK high-security hospital

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Objective. Clozapine is used in the management of treatment-resistant schizophrenia and is effective in reducing aggression; however a subgroup of patients is poorly responsive. For violent patients in this group, there is limited literature on the use of strategies to augment clozapine with other agents. Here we present a case series of 6 schizophrenia patients, within a high-security hospital, who have a history of serious violence and who were treated with clozapine augmented with amisulpride.

Methods. We reviewed case notes and health records for evidence of violence/aggression and positive factors such as engagement in activities, and Clinical Global Impression (CGI) scores were formulated. We also examined metabolic parameters before and after augmentation.

Results. All 6 of the patients showed clinical improvement in symptoms and a reduction in their risk of violence to others. Five patients had a reduction in number of violent/aggressive incidents, and all patients showed improvement in engagement in occupational, vocational, and/or psychological work. Metabolic parameters were largely unchanged except for 1 patient whose Body Mass Index (BMI) increased. Five patients reported side effects as unchanged or improved.

Conclusion. These schizophrenia patients with a history of violence showed clinical improvement and reduced aggression and violence with amisulpride augmentation of clozapine. To our knowledge, this is the first report of an antiaggressive benefit of this combination in forensic psychiatric patients. Further studies are warranted to establish the efficacy and anti-aggressive effects of amisulpride augmentation of clozapine.

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Key words: clozapine, amisulpride, augmentation, schizophrenia, violence, forensic.

Introduction

Clozapine is an atypical antipsychotic with actions on multiple neurotransmitter systems.[1] It is one of the few agents that have been shown to improve symptoms in patients with treatment-resistant schizophrenia and is a drug of choice, with response rates between 30% and 60%.[2,3] However, its associated side effects can be severe.[4]

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The potential benefit for patients who are unresponsive to clozapine alone has been sought through augmentation of its effect with other pharmacological agents.[5] This is relatively common clinical practice[6–9]; however the evidence base behind polypharmacy is limited.[10,11] Research to date has augmented clozapine treatment with antipsychotics,[5,12] antidepressants,[13–16] mood stabilizers,[17–20] and glutamatergic agents.[21,22] Antipsychotics used for augmentation of clozapine are often selected based on the theory that they have alternative mechanisms of action to clozapine. A number of promising small studies that have augmented clozapine with amisulpride, a selective D2 antagonist, have shown clinical improvement in patients on combination therapy versus those on clozapine alone.[23–27].

Amisulpride is not approved by the Food and Drug Administration for use in the United States, but it is used in Europe (France, Germany, Italy, Switzerland, Russia, United Kingdom), Israel, India, New Zealand, and Australia to treat psychosis and schizophrenia.

A subgroup of patients with schizophrenia presents with violence.[28] In fact, men with schizophrenia have a significantly increased rate of violent offending compared with men who suffer from non-schizophrenic mental disorders.[29] Given that schizophrenia has a significant relationship with violence, specific treatments to manage this violence may be as important as those to manage the illness.[30] Clozapine has been shown to have a desirable anti-aggressive effect in this population.[31–33] For violent patients within the subgroup who do not respond to clozapine monotherapy, there is no published literature to support the use of clozapine augmentation strategies.

Here we present a case series of patients with schizophrenia who were treated in a high-security hospital and who have a history of serious violence. High-security hospitals look after mentally disordered offenders who pose the highest risk of violence to others. We report the cases of 6 patients from this subgroup who were treated with clozapine augmented with amisulpride.

Methods

At the time of writing of this case series, 8 patients were receiving augmentation of clozapine with amisulpride in the hospital. Of these, 6 patients were included for this retrospective case series, as they were able to provide informed consent, and the remaining 2 were deemed to lack the capacity to provide consent by their treating psychiatrists. The remaining 6 patients did not have any history of learning disability, brain injury, epilepsy, or concurrent substance abuse. These patients are detained in a high-security hospital under the Mental Health Act 1983 (England and Wales). Patients had a median age of 33.5 years. Five patients were suffering from schizophrenia and 1 from schizo-affective disorder that was treatment-resistant (as per treatment-resistant schizophrenia criteria[2]). These diagnoses were made clinically by the treating consultant. Before amisulpride treatment was initiated, all patients had already received a mean clozapine dosage of 525 mg per day (range 400 mg to 600 mg per day) for at least 4.1 months (range 4.1 months to 13 years and 4 months, median 11.64 months), but were poorly treatment responsive. Clozapine serum levels noted prior to and after augmentation were in the therapeutic range for all patients. Doses of clozapine and amisulpride for each patient were recorded. Any changes in these doses and any concurrent medications, including changes after augmentation, were noted. Combined treatment duration ranged from 1.2 months to 3 years and 9.5 months (median 11.87 months). During the combined treatment period, the mean dosage for amisulpride was 667 mg per day, ranging from 400 mg to 1000 mg per day.

Clinical Global Impression (CGI) scores[34] were formulated retrospectively from clinical information for each patient by examining their illness severity before and after amisulpride augmentation, and also the degree of improvement and side-effects while on this treatment. Patients were also asked for their subjective experience of their illness and side effects while taking clozapine and amisulpride combination therapy. The total duration of illness for each patient was also noted.

Case notes and information from the hospital's information recording system were reviewed for violent/aggressive incidents under the following subcategories: (1) verbal aggression, (2) aggression against property, and (3) aggression against people. The case notes were also reviewed for episodes of seclusion and self-harm, as well as positive factors such as engagement in occupational therapy (OT), vocational therapy, and psychological therapies. Formal risk assessments (HCR-20[35] and the hospital's high-risk assessment) were reviewed to gauge change in risk status, and moves to lower- or higher-dependency wards were noted. Admission reports were examined for patients' index offenses. This information was used to measure levels of aggression prior to augmentation and since augmentation commenced.

We examined metabolic parameters, where these were available, using the latest value prior to and after initiation of augmentation, including BMI (body mass index), total cholesterol:HDL ratio, and blood glucose levels.

Results

Symptom improvement

Of the 6 patients, 3 had a global improvement score of "very much improved," 1 had a score of "much improved,"

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and 2 had a score of "minimally improved." The severity of illness decreased for all patients, although to variable degrees (Table 1).

Clozapine and norclozapine serum levels, PRN medication

Data was available for pre- and post-amisulpride clozapine and norclozapine levels and PRN medication where applicable (Table 1).

Improvement in violence

All patients' risk of violence and aggression to others was reduced following treatment with amisulpride and clozapine, as quantified by percentage reduction in the 90 days pre-amisulpride augmentation and most recent 90 days (where applicable) after augmentation on various parameters (Table 2). This risk reduction was generally associated with clinical improvement in symptoms. However, in 3 cases this reduction in aggression was greater than their overall clinical improvement. This is demonstrated further in individual patient case reports.

Metabolic parameters

One patient's BMI increased from 31.4 to 37.4, but other metabolic parameters appeared to be largely unaffected in all patients (Table 3).

Patient case reports

Patient A was referred for treatment in a high-security setting following multiple assaults driven by delusions in a medium-security unit (MSU). Until 2 months after initiation of augmentation, he remained in long-term segregation (LTS) due to his high risk of assaulting others. During this time, he self-harmed and damaged property, including smashing his TV, and made several threats to assault staff. Following the augmentation strategy, his socialization time on the ward out of LTS has been increased. While he has made threats to assault, he now denies thoughts or intentions of harming others. He is also now engaging in off-ward activities and psychological therapies, and is awaiting a move from high dependency to an assertive rehabilitation ward. Before treatment, patient A was classified as moderately ill, and he is now considered only mildly ill. His side effects of sialorrhea and sedation do not significantly interfere with function.

Patient B was admitted to the high-security hospital following incidents of setting fires, absconding, and multiple assaults on staff, all driven by psychotic symptoms. This included 1 serious assault, wherein the victim required hospitalization. In the months leading up to augmentation, he exhibited multiple episodes of violence, verbal aggression, and self-harm. The self-harm was

TABLE 1. Illness characteristics and medication details

Patient	Age	Duration of illness (years)	Length of current admission in HSH (months)	Duration of pre-augmentation clozapine treatment (months)	Duration of augmentation so far	Original clozapine dose	Current clozapine dose	Concurrent medication	PRN medication	Amisulpride dose	Clozapine, norclozapine level (mg/l)		Severity of illness pre-augmentation	Severity of illness present
											Pre	Post		
A	40–44	18	23.8	8.55	7.46	550	600**	–		800	0.37, 0.19	0.72, 0.28	4	3
B	30–34	11	30.5	13.71	1.22	500	500	Sertraline	Promethazine 50 mg/day	800	1.14, 0.37	0.81, 0.32	6	4
C	25–29	4	24.1	4.11	18.58	575	575	Valproate, zopiclone	Chlorpromazine 200 mg/day	600	0.37, 0.18	0.45, 0.23	5	4
D	35–39	15	44.2	27.81	16.27	400	300	–		400	0.74, 0.39	0.67, 0.37	5	2
E	40–44	17	45.5	159.75	42.90	600	750	Valproate, sertraline		1000	0.87, 0.26	0.88, 0.24	7	5
F	20–24	7	8.7	9.57	6.90	525	400	–		400	0.46, 0.33	0.46, 0.48	5	3

Notes: HSH = High Security Hospital. CGI = Clinical Global Improvement. CGI Severity of illness: 1 = Normal, not at all ill; 2 = Borderline mentally ill; 3 = Mildly ill; 4 = Moderately ill; 5 = Markedly ill; 6 = Severely ill; 7 = Among the most extremely ill patients; 0 = Not assessed.

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TABLE 2. Change in measures of aggression after augmentation with amisulpride

		Violence					
Patient	Age	Verbal aggression[a]	Aggression against property[a]	Aggression against others[a]	Self-harm[a]	Risk of violence to others[b]	Dependency
A	40–44	70	100	50	100	↓	=
B	30–34	50	100	50	100	↓	=
C	25–29	20	100	80	n/a	↓	=
D	35–39	=	=	=	n/a	↓	↓
E	40–44	50	=	100	n/a	↓	↓
F	20–24	=	=	100	n/a	↓	↓*

Notes: ↓ – Reduction; = – No change; n/a – not applicable; ↓* – Awaiting move to lower dependency ward.
[a] Percentage reduction.
[b] As assessed by HCR-20.

TABLE 3. Metabolic parameters before and after augmentation with amisulpride

	Pre-Augmentation				Present			
Patient	BMI	Glucose	Total cholesterol:HDL ratio	Side effect profile	BMI	Glucose	Total cholesterol:HDL ratio	Side effect profile
A	33	5.0	4.8	Sedation, hypersalivation.	33	5.2	4.6	nc
B	35	6.0	10	Occasional hypersalivation	35	4.9	10.9	nc
C	39	5.2	3.8	Sedation	37	4.7	-	Sedation, weight gain, joint stiffness
D	31	–	5	Weight gain, sedation, hypersalivation, constipation	37	-	5.4	Weight gain, sedation, hypersalivation, constipation, raised prolactin
E	32	–	–	None	33	7.6	4.6	None
F	26	–	–	Hypersalivation	27	4.1	5.4	nc

Notes: BMI = Body Mass Index; HDL = high density lipoprotein; nc = no change.

severe, including a suicide attempt that required medical attention for broken bones. He also made a serious assault on a member of staff and was being nursed continuously in LTS. Once augmentation was initiated, he was able to engage in ward activities; his aggression was generally improved, and self-harm ceased. He made 1 assault on another patient, requiring LTS to be resumed. Before augmentation, patient B was severely ill and is now considered only moderately ill; he is still psychotic, and his side effects of sedation and sialorrhea have not worsened.

Patient C was admitted to high-security facilities following his index offence of robbery and assault and his consistently aggressive behavior toward staff while in prison, which was linked to paranoid delusions. He also has a history of extensive property damage and arson, and has a high risk of harm to others. Since initiation of augmentation therapy, he has had his escort requirements reduced, been taken off the high-risk register, and been given more grounds privileges. He has had only 1 incident of verbal aggression, 1 incident of aggression against property, and 1 episode of seclusion. His engagement with OT is generally improving. After treatment, his mental state is minimally improved, and he is now considered moderately ill. His side effects of sialorrhea and sedation are no worse and do not significantly interfere with function.

Patient D was admitted to the high-security hospital following an index offence of homicide, which was driven by delusional symptoms. He has a long history of violence prior to this offense. Since admission, he has not been violent and his behavior has remained nonviolent throughout the addition of amisulpride to his treatment regimen. The reduction in his risk of violence has facilitated a move from a high-dependency ward to a low-dependency one. He has recently been engaging well with OT and vocational activities; his improvement has allowed his dose of clozapine to be reduced. Patient D was classified as markedly ill before beginning amisulpride, and now he is considered borderline mentally ill, with his main symptom being lack of insight. His side effects do not significantly interfere with function.

Patient E has an index offence of homicide, which was driven by delusional symptoms, and a long history of violence, with 7 reports of assault prior to his index

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offense, despite being prescribed clozapine in the community. He also has a history of weapon use, and he posed grave and immediate risk to others in MSU. Since augmentation, he has been attending off-ward activities, including education, asking for a ward job, and attending all scheduled therapy sessions. He is being assessed for group cognitive behavioral therapy (CBT). He has made 1 threat, but there have been no violent events and he has moved to a lower-dependency unit. Patient E was one of the most severely ill patients in the hospital when he was first admitted. Since starting amisulpride, he has been much improved without side effects. He is still markedly ill, but is happy with his current medication and does not report any side effects.

Patient F has a history of violence prior to admission to the high-security hospital. At his previous MSU, he committed a series of assaults, including his index offense of wounding with intent. He was placed on the high-risk register due to his risk of harm to others. His behavior and mental state have been exemplary since admission; he has been able to be removed from the high-risk register, and has transferred to medium security. His illness is very much improved; he has gone from being markedly ill to only mildly ill while following augmentation therapy and has had no side effects.

Discussion

We report a case series of 6 forensic patients who suffer from treatment-resistant schizophrenia or schizoaffective disorder, with a history of extreme violence, who are being treated in a high-security hospital. These patients were treated with clozapine that was subsequently augmented with amisulpride because of a lack of clinical efficacy of clozapine alone.

All 6 of the patients showed clinical improvement in symptoms with the amisulpride augmentation regimen and also a reduction in their risk of violence to others. Five of the 6 patients had a reduction in number of violent/aggressive incidents. Three of the 6 patients were eligible to move to lower-dependency wards. Two of the patients who had a presentation of self-harming behavior showed a reduction in this. The dose of clozapine prescribed was reduced for 2 patients and increased for 2 patients. All patients showed an improvement in engagement in occupational, vocational, and/or psychological work. Metabolic parameters (where available) were largely unchanged, except for one patient who had an increase in BMI. Side effects were reported as unchanged or improved in 5 of the 6 patients. To our knowledge, this is the first report of this combination treatment having a positive effect on reducing aggressive behavior and risk of violence in schizophrenia patients.

Strategies for augmentation of clozapine

Our findings are largely in keeping with previous studies that have investigated augmentation of clozapine with amisulpride or sulpiride. Sulpiride is an atypical antipsychotic that is closely related to amisulpride. Small, randomized, controlled trials (RCTs), open studies, and retrospective studies have demonstrated this effect, but there have been no large RCTs in this area to date. These trials all demonstrated a reduction in positive and negative symptoms.[23–25] In a single-blinded RCT, amisulpride was found to be a superior augmenting agent to quetiapine,[36] and in other studies, augmentation with amisulpride allowed the prescribed clozapine dose to be reduced.[26,27,37] Our findings were in keeping with studies that found that this treatment combination did not increase side effects.[27,37]

There have also been promising results in studies using other pharmacological agents to augment the actions of clozapine. Ziprasidone, risperidone, and aripiprazole have some evidence base to suggest that they may be effective augmenters of clozapine.[38,39,41] A meta-analysis[40] of clozapine augmentation with a 2nd antipsychotic from 14 randomized, placebo-controlled, double-blind studies that showed augmentation conferred a small benefit over placebo. Some of our patients were taking valproate concurrently with amisulpride and clozapine (initiated before amisulpride augmentation). Mood stabilizers have also been investigated as augmenting agents with clozapine, but the evidence is both limited and mixed.[5,42]

Rationale for augmentation of clozapine with amisulpride

Clozapine has a low D2 affinity and is possibly more selective of the mesolimbic system, resulting in fewer extra-pyramidal side effects (EPS). As well as having a low affinity, it also appears to have a faster dissociation time at D2 receptors, which may allow endogenous D2 to bind to the receptors more easily despite the antagonism.[43] This may contribute to the reduced side effect profile. Clozapine also acts at many other receptors, such as serotonin 5HT-2A receptors. Unfortunately, up to 70% of treatment-resistant patients are also poorly responsive to clozapine.[2]

Amisulpride is a selective D2 and D3 antagonist,[44,45] which appears to have little activity in the striatum and is instead selective for the mesolimbic system, thus causing fewer EPS.[46] It also seems to have effects on 5HT-7 receptors,[47] as well as presynaptic autoreceptors, which may be important in modulating endogenous dopamine production.[48] Amisulpride does not affect the pharmacodynamics of clozapine metabolism.[42] Similarly, clozapine does not alter serum levels of amisulpride.[49] The most popular theory explaining the efficacy of amisulpride as an augmenting agent with clozapine is that the receptor profiles of the 2 drugs

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are complementary. It is possible that in clozapine nonresponders, the levels of the D2 receptor blockade cannot be met by clozapine alone.[43] Studies have shown that the levels of the D2 blockade need to be high, around 80%, for significant response.[50,51] In these patients who do not respond to clozapine monotherapy, the selective action of amisulpride in the mesolimbic system may allow the D2 blockade to reach these therapeutic levels. The D3-blocking effect of amisulpride may also be important.

Treating violent and aggressive behavior

Violent behavior is uncommon among schizophrenia sufferers in the community.[52] However, it remains a significant problem among patients in a forensic setting who tend to have severe illnesses that are poorly responsive to standard pharmacological therapy. Our 6 patients from this subgroup were all considered an extremely high risk of harm to others, such that they were admitted to conditions of high security. Studies which have included randomized controlled trials have demonstrated that aggressive treatment-resistant patients initiate fewer aggressive and violent incidents when treated with clozapine.[31,32,53]. This is thought to be due to clozapine's wide receptor profile which includes dopamine and 5-HT receptors, which are implicated in the neurochemistry of aggression.[54,55]

Our patients were all taking clozapine for at least 17 weeks (median: 11.64 months) prior to the addition of amisulpride with minimal change in their risk of aggression and violence toward others. Following addition of amisulpride to their treatment regimens, all patients were assessed as having a greatly reduced risk of violent and aggressive behavior. It is unlikely that the risk reduction in these patients is due to a late effect of clozapine, as several studies have proposed that 3–6 months of clozapine treatment is sufficient to assess response to this medication.[56–59]

There are various possible reasons for the reduced risk of violence in these patients. First, it is possible that their aggressive behavior was reduced secondary to an overall clinical improvement in their illness on both amisulpride and clozapine. In one study, 40% of violent patients retrospectively reported that at least 1 violent incident had been motivated by a concurrent delusion.[60] However, the authors concluded that overall, violent incidents were probably not motivated by concurrent delusions. Two of our cases both committed a homicide based on their delusional beliefs, and so a reduction in their positive symptoms would reduce their risk of similar violent incidents in the future. It has been reported that the lower levels of aggression seen with clozapine monotherapy are associated with a reduction in positive symptoms.[61] However, for 3 of our subjects, risk of violence to others has reduced disproportionately to their clinical improvement. Other studies have suggested that aggressive behavior is not tightly coupled to severity of illness.[52,62] It is also considered that violence is often a separate dimension of the schizophrenia illness, and executive functioning can predict treatment response. However, clozapine retains its anti-aggressive benefits in those with lower cognitive functioning.[63]

This area warrants further research to establish firmly whether clozapine and also clozapine augmentation with amisulpride have a specific anti-aggressive effect in excess of their antipsychotic efficacy. Our results show a reduction in aggressive behaviors for most patients and improvement in engagement for all patients following augmentation with amisulpride compared with their clozapine monotherapy.

Important considerations

However, there are limitations in extrapolating from our data to a wider setting. The retrospective nature of this case series, lack of objective rating scales, and the small sample size limit our ability to draw firm conclusions from our data. Research exploring pharmacotherapy with forensic psychiatric patients is a difficult area to conduct, as subjects who are enrolled in RCTs are not representative of the most difficult-to-manage patients found in secure units.[64] Retrospective analysis has allowed us to take a naturalistic approach, demonstrating more clearly how this augmentation strategy may be advantageous on an individual patient basis in a high-security hospital setting. It is also very difficult to quantify the beneficial effects of patient engagement with occupational therapy and psychological therapy sessions, which all these patients attended to some degree over the course of treatment post-augmentation, and this may well have contributed to their improvement.

However, there are also advantages to our approach: We were able to access large volumes of historical data for all patients. Also, due to these subjects being inpatients in a high-security setting, there are no issues with concurrent substance misuse and lack of compliance with medications. All patients were fully compliant with the amisulpride/clozapine combination therapy, and only 2 patients reported a worsening of their side effects. No new concurrent medication was prescribed to any patients after initiation of amisulpride.

Patients who are treatment-resistant are often also highly symptomatic, requiring long periods of hospital care.[65] This care often requires a disproportionately high amount of the total cost of schizophrenia treatment.[66] Patients with a history of schizophrenia and violence in the forensic setting are associated with higher treatment costs. Strategies to bring about improvement in this subgroup of patients in their

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symptoms and violence would be of immense cost benefit to health services.

Conclusion

Clozapine is an antipsychotic of choice for treating patients with treatment-resistant schizophrenia. However a significant proportion of patients do not respond to clozapine alone, and other agents have been added to augment the response of clozapine. We report our experience of augmentation of clozapine with amisulpride in violent treatment-resistant patients in a high-security hospital.

We have found that in all of these patients with clozapine-unresponsive schizophrenia, amisulpride augmentation of clozapine treatment had a clinical benefit and reduced episodes of violence and risk of violence. This is the first time that the combination of clozapine and amisulpride has been reported to have an anti-aggressive effect in patients who had previously been very violent. Further research would better determine the beneficial effects of this augmentation strategy on violent patients with treatment-resistant schizophrenia.

Disclosures

The authors do not have anything to disclose.

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