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COMMENT & CRITIQUE

Augmentation of clozapine with paliperidone in treatment-resistant schizophrenia-A case series

There is no doubt that treatment-resistant schizophrenia is one of the most challenging public health issues today; however, previous literature reviews examining the effectiveness of medication or non-pharmacologic augmentation strategies remain inconclusive (1), and clozapine may be the only evidently efficacious antipsychotic medication for treatment-resistant schizophrenia. Nevertheless, clozapine has been associated with side-effects and safety concerns of a potentially life-threatening nature and does not always elicit a complete response (2). According to treatment guidelines, augmentation of clozapine with a second antipsychotic is a reasonable strategy for the treatment of partially responsive patients (3,4), and it has been recognised that switching to or adding another antipsychotic and decreasing the dosage of clozapine may be of clinical benefit in patients with treatment-refractory schizophrenia (5). The augmentation strategy is an alternative approach in the treatment of patients suffering from either psychotic symptoms or side-effects; however, the benefits of the use of this strategy in treatment-resistant schizophrenia remain inconclusive (6).

To date, risperidone is the most extensively documented clozapine augmentation agent (7). Paliperidone, the major metabolite of risperidone, undergoes less hepatic metabolism than risperidone (8,9) and, given once daily, exhibits a fast onset of action and delayed time-to-recurrence. It also appears to be safe and well tolerated (10,11).

Herein, we report our observations of the results of augmentation of clozapine with paliperidone in five patients with treatment-resistant schizophrenia (summarised in Table 1). To the best of our knowledge, there exist no related articles concerning augmentation of clozapine with paliperidone, and this is the first paper to discuss the therapeutic effect and tolerability of this augmentation strategy.

The five patients studied were all in-patients in an acute psychiatric unit, and a summary of all patients in our case series is presented in Table 1. The augmentation strategy was observed to be efficacious in improving the symptoms of these patients, as indicated by the changes in the Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression – Severity Scale (CGI-S) and Personal and Social Performance (PSP) scores from baseline to endpoint. We also observed an improvement in personal and social functioning. In this study, the severity of adverse events during augmentation was found to be generally mild, and the regime was well tolerated.

One patient, Miss C, experienced a relapse of psychosis in the middle of the treatment course, the reasons for which were unclear. In response, we increased the dose of clozapine from 300 to 400 mg daily, and that of paliperidone from 6 mg to 9 mg daily. The patient's BPRS score was 51 on the 28th day, and following the change in treatment, this reduced to 42 in the 8th week; however, we were unable to ascertain whether this change was because of an effect of paliperidone, or clozapine, or both.

Reviews of research into augmentation of clozapine with a second antipsychotic in cases of treatment-resistant schizophrenia have been conducted previously, but no augmentation strategies have been identified as being superior to others (6). Risperidone is one of the most commonly used antipsychotics in augmentation strategies, and one review study found evidence to show that risperidone may have the greatest efficacy and tolerability among other antipsychotics when prescribed to augment clozapine (12). The theory of augmentation is that the addition of a more potent antipsychotic with a higher D2/3 potency increases dopamine receptor blockade (13), and paliperidone, the major metabolite of risperidone, may exhibit a similar or even increased efficacy (9). This is one hypothesis proposed to explain the mechanism of augmentation strategies.

The reasons for which augmentation of clozapine with paliperidone resulted in clinical improvement remain unclear. Paliperidone has some advantages over other antipsychotics, such as a fast onset of action in the early stage of treatment (8), and has been shown to exert effects superior to a placebo, not only in terms of psychopathology but also in personal and social functioning (14). We did indeed observe an improvement in the negative symptoms of our patients. Another point to consider is that the delivery system of paliperidone may provide a stable serum concentration, which improves the safety profile, ensures uniform drug effects and reduces the necessary dosage frequency (15). In our patients, no specific safety issues or side-effects of the augmentation strategy were observed.

In addition, paliperidone has a limited hepatic metabolism, thereby minimising the risk of hepatic drug–drug and drug–disease interactions. As clozapine and paliperidone have different metabolism pathways, the success of this treatment might not be related to drug–drug interaction.

It was reported in a review article that paliperidone treatment results in no clinically meaningful changes in body weight or glucose, insulin or lipid profiles, although controversial results have been obtained regarding drug-related changes in prolactin level (16). However, some studies have shown that paliperidone and risperidone have similar side-effects such as movement disorders, weight gain, tachycardia, increases in serum prolactin and increased potency of sexual

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Table 1. Summary of the five patients included in this study

	Case 1: Miss A	Case 2: Mr. B	Case 3: Miss C	Case 4: Mr. D	Case 5: Mr. E
Sex	Female	Male	Female	Male	Male
Source	In-patient	In-patient	In-patient	In-patient	In-patient
Education	Senior high school	Junior high school	Senior high school	Senior high school	Senior high school
Age	36	38	33	40	27
Onset age	25	18	20	36	18
Diagnosis	Schizophrenia paranoid type	Schizophrenia paranoid type	Schizophrenia paranoid type	Schizophrenia paranoid type (Note 1)	Schizophrenia disorganised type
Comorbidity	Clozapine-related seizure	Type 2 DM	None	Seizure, brain concussion	None
Previous antipsychotic treatment	Fluanxol Etumine Haloperidol OlanzapineRisperidone	Amisulpride Risperidone	Haloperidol Risperidone Quetiapine Olanzapine Aripiprazole	Amisulpride	Risperidone
Augmentation indication	Prominent psychosis, seizure	Metabolic syndrome (Note 2)	Metabolic syndrome (Note 3), prominent negative symptoms	Prominent negative symptoms, seizure	Prominent positive symptoms
Treatment course	8 weeks	8 weeks	8 weeks	8 weeks	4 weeks
Clozapine dose before augmentation	800 mg/day	400 mg/day	300 mg/day	200 mg/day	500 mg/day
Endpoint regimen	Paliperidone 12 mg/day, clozapine 300 mg/day	Paliperidone 9 mg/day, clozapine 400 mg/day	Paliperidone 9 mg/day, clozapine 400 mg/day	Paliperidone 9 mg/day, clozapine 200 mg/day	Paliperidone 6 mg/day, clozapine 500 mg/day
Baseline	PANSS 93 (P/N/G = 26/24/43) PSP 47	CGI-S 5	CGI-S 4	CGI-S 4	CGI-S 5
Endpoint	PANSS 75 (P/N/G = 24/17/34) PSP 57	CGI-S 3 CGI-I 2 BPRS: 41 (51 on the 28th day)	CGI-S 3 CGI-I 3	CGI-S 3 CGI-I 3	CGI-S 4 CGI-I 3
Side-effects after augmentation	None	None	None	None	None

Notes:

1.Schizophrenia diagnosed before seizure and brain concussion. Before augmentation, brain computed tomography revealed senile brain parenchyma atrophic change. Neurological examination showed no focal signs.

2.Short-term reports of metabolic effects. Waist circumference was 117 cm before augmentation, and 103 cm in the eighth week of treatment in case 2.

3.Short-term reports of metabolic effects. Waist circumference was 86 cm before augmentation, and 84 cm in the eighth week of treatment. Body weight was 53–54 kg without significant change in case 3.

dysfunction (17). We have not yet obtained long-term metabolic profile data, and further studies are required in order to investigate these important issues.

There are several limitations in our observational study. First, the patient's sample was small. Second, our patients were all in-patients of an acute psychiatric unit and as such their psychotic symptoms and signs may have been relatively severe. In addition, details of previous psychiatric treatment were lacking. Third, we did not measure the psychotic condition of all patients using the BPRS and PANSS; PSP and PANSS were only applied in case 1 and BPRS only in case 3, the latter for which a baseline score was not obtained. Application of these rating scales may be of assistance in better clarifying patients' symptoms and signs. Fourth, the duration of observation was only 4–8 weeks, which may not be sufficient to observe effects in a refractory illness. Fifth, the drug metabolic profiles require long-term evaluation using follow-up studies, as do the safety profiles.

This report describes the onlycase series to date in which an augmentation strategy involving clozapine with paliperidone was used. The reasoning behind the addition of a second antipsychotic to clozapine was to address the prominent positive and negative dimensions of symptoms that occurred despite adequate dosage and a suitable treatment course, and to investigate the metabolic syndrome and safety concerns associated with this strategy. Paliperidone is the choice for a second antipsychotic owing to its early onset of efficacy, stable serum concentration, limited hepatic metabolism and negative symptom improvement. Although a good efficacy and tolerability in the course of augmentation was observed in this study, well-designed randomised controlled trials with larger samples are needed in future in order to verify our results.

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