

Can Augmentation of Clozapine with Paliperidone Improve Negative Symptoms in Schizophrenia Patients with Partial Response to Treatment: A Case Series



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SUMMARY

Clozapine is the only antipsychotic medication that has definitely shown to be effective in treating refractory schizophrenia. Clozapine is typically the medication of choice in schizophrenic patients with a partial response to treatment. When clozapine fails to elicit a full treatment response, augmentation strategies are then explored. It is important to note, however, that in treatment resistant schizophrenic patients, the addition of a second antipsychotic is frequently preferred as an augmentation method. Consistent positive results could not be obtained with previous augmentation strategies.

Paliperidone is a risperidone metabolite that has proven effective in treating schizophrenia. Although most effects of paliperidone on the central nervous system are similar to risperidone, there are some noteworthy differences. In this case series, the treatment of five schizophrenic patients presenting with symptoms, excluding clozapine treatment, were augmented with paliperidone during six months of follow up. This augmentation was tolerated well by the patients, and resulted in a reduction of both positive and negative symptoms. The addition of paliperidone resulted in a remarkable improvement of negative symptoms in our patients. Further evaluation of paliperidone's effects on negative symptoms in schizophrenic patients with a partial response to clozapine treatment may provide another viable treatment choice.

Keywords: schizophrenia, clozapine, paliperidone, negative symptoms

INTRODUCTION

Although positive symptoms in schizophrenia are generally considered to be the most treatment resistant criteria, the importance of negative symptoms has increased in recent years. Clozapine is the only definitely proven treatment to be effective in refractory schizophrenia (Lindström 1988, Meltzer 1994, 1995, Coşar et al 1998, Soyly et al 1999); nevertheless, in a significant portion of patients (40-70%) clozapine treatment yields an inadequate or partial response (Kane et al 1988, Tollefson et al 2001, Anil Yagcioglu et al 2005, Tiihonen et al 2009). In double-blind controlled studies, other new antipsychotics were also shown to treat negative symptoms more effectively than traditional antipsychotics (Kane et al 1988, Marder and Meibach 1994, Zimbroff et al 1997). However, whether these drugs treat true negative symptoms

or secondary negative symptoms due to extrapyramidal system (EPS) symptoms, depression, or psychosis itself is still debated (Meltzer 1994, Carpenter 1995). In either case, patients with persistent negative symptoms can be classified as treatment resistant.

The addition of a second antipsychotic is a commonly applied augmentation strategy for treatment resistant schizophrenia (Anil Yagcioglu et al 2005). Although there are studies reporting both positive and negative results for augmentation with a second antipsychotic, no agent has been shown to be consistently effective in placebo controlled studies (Vayisoglu and Anil Yagcioglu 2014).

Schizophrenia is a chronic illness that significantly impacts the functioning of afflicted patients. Certain changes in neuronal structures can result in worsening of the disease

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and functional loss (Davis et al 1998, Gogtay et al 2003). Nasrallah and Pixley (2006), compared risperidone and paliperidone in a three armed study and found that both risperidone and paliperidone cause significantly more marked neurogenesis in rats than the placebo. Thus, adding paliperidone to treatments of schizophrenic patients with a partial response to clozapine seems reasonable.

Paliperidone is an active metabolite of risperidone. It uses an osmotic controlled oral release delivery system (OROS) that extends release time. Fluctuations in plasma concentration and peak levels are avoided through the use of the aforementioned technology. Paliperidone can be used once daily without need for tapering (Grant and Fitton 1994, Revill et al 2006). Studies in schizophrenic patients demonstrated its superiority to placebos (Kantrowitz and Citrome 2007).

Although most of the effects of paliperidone on the central nervous system are similar to risperidone, they have some noteworthy differences (Richelson and Souder 2000, Dremencov et al. 2007). Paliperidone and risperidone are structurally identical except that risperidone has a hydroxyl group at the 9th position. The presence of a hydroxyl group may be associated with structural and pharmacological effects. For example, the addition of a hydroxyl group at the beta position results in a conversion to noradrenaline which has differences in receptor profile, reuptake mechanism, neuronal pathways, and physiopathology. We can therefore draw the conclusion that paliperidone and risperidone may have some differences in chemical and clinical features (Pani and Marchese 2009).

Dremencov et al (2007) suggested that risperidone and paliperidone have different effects on serotonergic and dopaminergic neuronal firing after the introduction of a selective serotonin reuptake inhibitor (SSRI). Therefore, unlike risperidone, paliperidone may have positive effects in clinical conditions like depression refractory to SSRI treatment.

In this paper, we present six months of follow up data for five schizophrenia cases whose clozapine treatments were augmented with paliperidone due to an incomplete response. Patient age, education level, age at diagnosis, comorbidity(ies), previous treatment(s), as well as the initial and 6th month results of Positive and Negative Syndrome Scale (PANSS) Turkish Version (Kostakoglu et al 1999), Scale for the Assessment of Negative Symptoms (SANS) Turkish Version (Erkoc et al 1991) and Clinical Global Impression (CGI) (Guy 1976) are summarized in Table 1.

Case 1

A forty seven year old male afflicted with schizophrenia for thirty years was followed for observation. He was unable to work due to his health problems. His prominent symptoms were delusions of infidelity and auditory hallucinations. He

had been hospitalized in different institutions several times and had used multiple combinations of antipsychotics. In 2011, clozapine treatment was started since he met DSM IV criteria for treatment resistant schizophrenia. He was given clozapine 800 mg/day, zuclopenthixol 200mg every 20th day, and biperiden 6 mg/day. In response to the medication, delusions persisted, even increasing at times, and EPS symptoms such as cogwheel rigidity of the extremities, sialorrhea, and difficulty in swallowing persisted. Zuclopenthixol was stopped and paliperidone 6 mg/day was initiated and then increased to 12 mg/day at the 2nd month. At his 8th week follow up visit, EPS symptoms decreased and the CGI score was found to be 3. At the 4th month follow up visit, biperiden was decreased to 4 mg/day because EPS symptoms disappeared. At the 6th month follow up visit, marked improvements were detected both in positive and negative symptoms such as blunted affect and avolition (Table 1).

Case 2

Sixty three year old male patient afflicted with schizophrenia for over forty years. He displayed intermittent auditory hallucinations and prominent negative symptoms such as apathy, social isolation, blunted affect, and poor rapport. He had been using clozapine 400 mg/day and quetiapine 600 mg/day for eight months. He was admitted to the hospital presenting with an increase in social withdrawal, a decrease in motor activities that impairs daily life, and an almost total absence of communication in last two weeks. No pathology could be identified to find a clinical explanation through laboratory or radiological evaluations. Quetiapine was tapered off throughout the course of one month and paliperidone 6 mg/day was added to the clozapine regiment. An increase in motor activity and communication were detected starting at the beginning of the 3rd week. The CGI score also decreased to 3. After the 4th month, we detected a significant decrease in negative symptoms (Table 1).

Case 3

Twenty nine year old female diagnosed with schizophrenia was followed for observation for twelve years. Her initial symptoms were collecting garbage from streets, inappropriate affect, as well as meaningless speeches and behavior. She presented with a history of seven to eight previous hospitalizations. She had been on a medical regiment of clozapine 800 mg/day, zuclopenthixol depot 200 mg every 20th day, and biperiden 4 mg/day for seven years. Three months before arriving at our clinic, recurrent meaningless behaviors, body posturing for short time periods, social withdrawal, and reduction in verbal communication began to manifest. During the last month, she was admitted to our clinic due to her refusal to leave her room, displaying poor personal hygiene, and showing aggression when frustrated. During her first days in our clinic, haloperidol and chlorpromazine injections

Table 1. Summary of 5 schizophrenia patients whose clozapine treatments were augmented with paliperidone due to incomplete response

	First Case	Second Case	Third Case	Fourth Case	Fifth Case
Sex	Male	Male	Female	Male	Male
Education	Primary School	College	Primary School	College	Primary School
Age	47	63	29	37	43
Comorbidity	Absent	Osteoporosis	Absent	Obesity	Absent
Reason of augmentation	Extrapyramidal system symptoms Psychotic symptoms	Negative symptoms	Psychotic symptoms, disorganized behavior	Negative symptoms, anxiety	Psychotic attack
Preclozapine treatments (mg/day)	Olanzapine 30mg, risperidone 8mg, pimozide 12mg, amisulpiride 800mg, quetiapine 900mg, zuclopenthixol depot 200mg (every 20th day)	Haloperidol 40mg, chlorpromazine 300mg, risperidone 4mg, amisulpiride 800mg, quetiapine 800mg, olanzapine 15mg, sulpiride 800mg	Olanzapine 30mg, risperidone 12mg, haloperidol, 60mg, quetiapine 900mg, zuclopenthixol depot 200mg (every 20th day), chlorpromazine 600mg	Risperidone 6mg, olanzapine 20mg, haloperidol 20mg, quetiapine 900mg, amisulpiride 600mg	Haloperidol 50mg, chlorpromazine 400mg, risperidone 6mg, quetiapine 600mg
Latest treatment combination (mg/ay)	Clozapine 800mg, paliperidone 12mg	Clozapine 400mg, paliperidone 6mg	Clozapine 800mg, Quetiapine 600mg, paliperidone 12mg	Clozapine 400mg, paliperidone 9mg	Clozapine 600mg, quetiapine 600mg, paliperidone 9mg
Pretreatment PANSS (P/N/G)					
PANSS-P:	16	11	29	11	17
PANSS-N:	25	31	38	39	27
PANSS-G:	31	34	52	37	35
PANSS-T:	72	76	119	87	69
6th month PANSS (P/N/G)					
PANSS-P:	12	11	21	9	10
PANSS-N:	13	20	20	25	17
PANSS-G:	27	27	31	32	25
PANSS-T:	52	58	72	66	52
Pretreatment SANS					
Affective blunting	14	32	30	32	21
Alogia	11	16	17	22	24
Avolition	10	12	18	18	14
Anhedonia	11	16	14	19	15
Attention	9	10	12	9	8
6th month SANS					
Affective blunting	10	24	24	21	14
Alogia	10	13	14	15	16
Avolition	8	10	13	13	10
Anhedonia	10	11	11	12	10
Attention	9	8	10	9	8
Pretreatment CGI	4	4	6	5	4
6th month CGI	2	2	4	3	2

Abbreviations: PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms; P/N/G, positive/negative/general psychopathology; CGI, Clinical Global Impression.

had to be used to control her violent behavior. Clozapine dosage was maintained while paliperidone 12 mg/day was added. Quetiapine 600 mg/day was also added to sedate the patient. At the end of her first month, there was a significant decrease in her aggression. At her 3rd month follow up visit of treatment, no significant side effects were observed, she displayed increased verbal communication, improved grooming and markedly decreased aggression (Table 1).

Case 4

Thirty seven year old male college student experienced his first psychotic attack at the age of twenty three. His main symptoms at the time of the first attack were suspiciousness, persecutory delusions, social isolation, affective blunting, decreased attention, and anxiety about his body. Although these symptoms decreased with treatment, he had to be hospitalized three times due to psychotic episodes manifesting in increased suspiciousness. In the last five years, the only medication he was using consistently was clozapine 900 mg/day. In addition to clozapine, he used antipsychotics such as quetiapine and antidepressants like venlafaxine, sertraline, and fluoxetine intermittently. His main symptoms upon admission to our clinic were avolition, apathy, and affective blunting although his principle complaint was from high levels of anxiety. During hospitalization no pathological findings were detected through laboratory tests, although it is noteworthy that the patient was obese (body mass index was 40). Clozapine dosage was tapered down to 400 mg/day throughout the course of two months. Diazepam 10 mg/day was added to the regiment to treat anxiety while paliperidone 6 mg/day was added for augmentation. His anxiety level decreased in a week. After one month, avolition, apathy and bodily anxiety were partially relieved. Diazepam was tapered off in a twenty day period after the 1st month follow up visit. Paliperidone was also increased to 9 mg/day. After three months of treatment, the CGI score was 3 and there were no significant drug side effects. His body weight did not experience any significant change while he was using clozapine 400 mg/day and paliperidone 6 mg/day. In his six month follow up visit after treatment, a significant decrease in anxiety level and negative symptoms were observed (Table 1).

Case 5

Forty three year old married male diagnosed with schizophrenia when he was nineteen. He has a history of five previous hospitalizations for psychotic exacerbations. For the last one and a half years, he has been on a regiment of clozapine 600 mg/day and quetiapine 800 mg/day for his diagnosis of treatment resistant schizophrenia. Despite using his medications regularly, he was complaining of hearing voices talking with each other, especially during the night. He was admitted to the hospital and had paliperidone 9 mg/day added to his regiment of clozapine 600 mg/day and quetiapine 600 mg/day.

At the third week of his hospital stay, he reported that he was hearing voices less frequently. The voices totally disappeared after four months of treatment. The CGI score decreased to 2. No significant side effects related with treatment were observed. The patient also experienced a significant decrease in affective blunting (Table 1).

DISCUSSION

There are many studies in literature about the augmentation of clozapine in treatment resistant schizophrenic patients (Vayisoglu and Anil Yagcioglu 2014). The addition of risperidone to clozapine is among the most commonly used approaches and both positive and negative results have been reported with this strategy (Anil Yagcioglu et al 2005, Josiassen et al 2005, Honer et al 2006).

In our review of literature, we were unable to find a randomized, placebo controlled study about the augmentation of clozapine with paliperidone. We were, however, able to find two case series. Esslinger et al (2010), after the cessation of accompanying agents due to metabolic and other side effects, added paliperidone to clozapine in four cases. Two of these cases responded well to this augmentation and two cases did not. In this paper, the authors especially noted the opportunity to decrease clozapine dosage, and therefore metabolic side effects, in two patients who responded to augmentation with paliperidone. Chang et al (2011) observed improvements in PANSS, Brief Psychiatric Rating Scale (BPRS), CGI, and Personal and Social Performance (PSP) scales after eight weeks of follow up in five cases whose clozapine treatments were augmented with paliperidone. In both case series, the combination of treatments were tolerated well and no significant side effects were observed. The observations in our study concurred with Chang et al (2011).

In our first case, the PANSS score decreased from 72 to 52 (a 27.7% decrease) mainly due to decreases in negative symptoms as shown in Table 1. It is debated whether atypical antipsychotics actually treat true negative symptoms or just negative symptoms secondary to depression, EPS, or psychosis (Meltzer 1994, Carpenter et al 1995). On the other hand, a decrease in the negative symptom score, resulting from recent clozapine use, of a patient who has been afflicted with schizophrenia for several years and who has been using clozapine in recent years due to incomplete treatment response is nothing short of remarkable.

In our second case; we excluded major depression because negative symptoms of schizophrenia were continually present since the onset of the disease. Beginning from the third week of treatment, an increase in motor activity and communication was detected. The CGI score decreased to 3. After four months of treatment, a significant decrease in negative symptoms was detected. In the follow up visit at the end of 6th

month, the PANSS score decreased from 76 to 58 (a 23% decrease) and there was more prominent improvement of negative symptoms (Table 1).

In the third case, the addition of quetiapine to the clozapine-paliperidone combination may be regarded as a confounding factor. Low potency antipsychotics (like quetiapine) are included in a group of antipsychotics that are characterized by low antipsychotic activity while having high sedating activity (Fleischhacker and Widschwendter 2006). Her previous treatments included a high dosage of quetiapine that was discontinued due to lack of effectiveness. Thus, we concluded that the positive response following the addition of paliperidone and quetiapine was due to paliperidone, rather than quetiapine. At the end of 6th month, the PANSS score decreased from 119 to 73 (a 31.1% decrease). Likewise, negative symptoms also showed improved (Table 1).

Our fourth case was obese and experienced a partial recovery in bodily anxiety, avolition, and apathy allowing for a decrease in clozapine dosage after addition of paliperidone. However, the decrease in clozapine dosage did not result in any significant decrease in the patient's weight. The paliperidone dose was gradually increased. At the end of 6th month, the PANSS score decreased from 87 to 66 (a 24.1% decrease) and negative symptoms also regressed (Table 1).

Our fifth case stated that the voices decreased after the 3rd week and almost totally disappeared after the 4th month of paliperidone augmentation. After the 6th month, the PANSS score decreased from 69 to 52 (a 24.6% decrease). The decrease in affective blunting was quite remarkable in this patient (Table 1). Although quetiapine was included in this patient's treatment, he had been using quetiapine for one and half years with no additional relief in psychotic symptoms. Based upon the previous statement, we concluded that the beneficial effect was primarily due to paliperidone.

In conclusion, the combination of paliperidone and clozapine is tolerated well by the patient, doesn't result in significant side effects, and provides relief in positive and especially negative side effects. This beneficial effect may be attributed to the combination's different effects on the firing of serotonergic and noradrenergic neurons. Confirmation of these results with placebo controlled, double blind, and randomized studies may yield a definitive viable treatment option in schizophrenic patients with an incomplete response to treatment.

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