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Clozapine Combined with Paliperidone Observations in Schizophrenic Patients with Insufficient Responses to Clozapine Monotherapy

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Abstract

Treatment resistance to clozapine often leads to antipsychotic combinations. Well-designed trials evaluated the add-on of several atypical antipsychotics, but the augmentation with paliperidone, the active metabolite of risperidone, has never been evaluated. Treatment of four cases resulted in a decrease of the PANSS-positive subscale, the mean initial clozapine dose could be lowered, mean prolactin increased, but the observed general tolerance was good. In conclusion, combined antipsychotic treatment with CLZ and PAL might be a successful strategy in individual patients, but efficacy and tolerance should be further evaluated in controlled clinical trials (German J Psychiatry 2010; 13: 37-).

Keywords: Antipsychotic, augmentation, clozapine, combination, paliperidone, treatment resistance

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Introduction

Treatment resistance (Jaeger et al., 2008) challenges antipsychotic pharmacotherapy and causes individual burden and socio-economic costs. When even clozapine (CLZ), the first choice antipsychotic in treatment resistance (Kane et al., 1988), fails to achieve remission, combinations with other second generation antipsychotics, mood stabilizers and other psychoactive substances are commonly used (Zink et al., 2010). The frequent constellation of partial response to clozapine (30 to 40% of CLZ-treated patients) has been evaluated by case studies and open trials (Zink & Dressing 2005). Several placebo-controlled clinical trials have investigated the add-on of risperidone (RISP) (Yagcioglu et al. 2005; Freudenreich et al. 2007; Honer et al. 2006; Josiassen et al. 2005) without allowing final conclusions as detailed in a set of recent meta-analyses (Barbui et al. 2009; Correll et al., 2009; Paton et al., 2007; Taylor & Smith, 2009). Recently, one head-to-head trial compared CLZ combined with RISP or with ZIP (ziprasidone) and suggested similar efficacy while the respective profile of side effects diverged (Zink et al., 2009). Paliperidone (PAL), the active metabolite of RISP, proved to have antipsychotic efficacy in several clinical trials, and has been characterized regarding pharmacological parameters, therapeutic and side effects (Meltzer et al. 2008; Nussbaum & Stroup 2008). Until now, the combined application of PAL and CLZ in cases of CLZ-resistant psychotic symptoms has never been evaluated. Therefore, we summarized our therapeutic experiences obtained in four cases (see Table1 for pharmacological and psychometric details).

Case Reports

Case 1

This 25 years old male patient (92 kg, BMI 27.5 kg/m^2) suffered from paranoid schizophrenia according to DSM IV criteria and was found treatment resistant to QTP (quetiapine) and RISP (sufficient doses and treatment periods), but responded to some degree to CLZ-monotherapy. However, he complained about CLZ-associated side effects such as weight gain, sedation and sialorrhea as well as persisting

Table 1: Medication dosages, serum levels and PANSS ratings for the 4 reported cases. The last line gives the means before and after combination of CLZ with PAL. Abbreviations: CLZ: clozapine, DCLZ: desmethyl-clozapine, f: female, GP: global psychopathology, m: male, PAL: paliperidone, PANSS: positive and negative syndrome scale, pos: positive symptoms, neg: negative symptoms. The tiny improvement of PANSS positive score (-15 %, Student's t-test: p=0.04, Mann-Whitney-U-test p=0.102) is marked by *****.

	Prior to combination				Combined treatment: CLZ and PAL					
Case Number (sex, age)	CLZ doses (mg /day)	CLZ serum levels (DCLZ) (mg/L)	Prolactin (µg/L)	PANSS (pos/ neg/GP)	CLZ doses (mg/ day)	PAL Doses (mg/ day)	CLZ serum levels (DCLZ) (mg/L)	PAL doses (mg/ day)	Prolactin (µg/L)	PANSS (pos/neg/ GP)
1 (m, 25)	700	0.30 (0.32)	5.5	17/29/31	550	12	0.32 (0.25)	12	39	16/29/33
2 (f, 28)	700	0.22 (0.19)	3.5	16/10/26	450	9	0.15 (0.10)	9	141	12/12/26
3 (f, 38)	350	0.35 (0.22)	130	18/21/50	250	12	0.19 (0.16)	12	112	13/19/29
4 (m, 27)	550	0.29 (0.28)	3.5	17/26/39	625	6	0.31 (0.37)	6	4	17/20/37
Mean	575	0.29 (0.25)	36	17/22/37	469	10	0.24 (0.22)	10	74	14.5*/20/31

anxiety, paranoid ideas, and auditory hallucinations. Moreover, he showed a marked negative syndrome. After 3.5 months of CLZ-monotherapy (see table 1), we therefore added PAL (12 mg/day) which allowed a reduction of CLZ-dose. This treatment strategy appeared well-tolerated, but no major improvement of the psychotic syndrome was observed after 8 weeks. Hence, the patient was finally switched to an antipsychotic combination of CLZ with APZ (aripiprazole) and discharged.

Case 2

This 28 years old female patient (92.3 kg, BMI 30.7 kg/m^2) was diagnosed with secondary progressive multiple sclerosis (MS) at the age of 19 and presented first psychotic symptoms 9 years later. There was no evidence for an active inflammatory process of MS as revealed by magnetic resonance tomography and sampling of cerebrospinal fluid. Therefore, we attributed her paranoid ideas accompanied by disturbed formal thinking and auditory hallucinations, to paranoid schizophrenia, but discussed the diagnosis of an organic delusional, schizophrenia-like disorder. The psychotic syndrome was found resistant to RISP, olanzapine (OLZ) and amisulpride (AMS) (sufficient doses and treatment periods), it partially responded to antipsychotic CLZ-monotherapy over a period of 9 weeks (see table 1). The patient complained of sedation and gain of body weight. We added PAL (9 mg/day) and observed after further 7 weeks some improvement of the positive symptoms allowing a CLZ dose reduction and the discharge into outpatient treatment.

Case 3

This 38 years old female patient (74.8 kg, BMI 32.5 kg/m2) was first diagnosed with paranoid schizophrenia (DSM IV) at the age of 25. After several treatment attempts with typical and atypical antipsychotics (sufficient doses and treatment periods), she turned out to be partially resistant to CLZ-monotherapy and therefore received RISP and afterwards AMS in combination with CLZ. Because of disabling auditory hallucinations prompting to commit suicide despite combined treatment with CLZ and AMS (AMS: 800 mg/day, serum level 76 µg/L), she was referred to the hospital. In addition to the psychotic syndrome, she suffered from CLZ-induced weight gain and elevation of serum prolactin (130 µg/L). We stopped AMS, continued CLZ (see table 1) and combined with PAL (12 mg/day), and during 7 weeks of CLZ/PAL-treatment, we were able to reduce the CLZ dose and serum prolactin levels decreased. Positive symptoms responded to the treatment; however, weight gain proceeded to 77.4 kg (BMI 33.8 kg/m2). The patient was released into her sheltered workshop and outpatient treatment.

Case 4

This 27 years old patient (105.4 kg, BMI 32.8 kg/m2) first presented with a schizoaffective psychosis at the age of 22. A current psychotic exacerbation due to treatment incompliance did not respond to APZ, AMS, and QTP (sufficient doses and treatment periods). Finally, CLZ lead to an incomplete response. After two months of treatment (see table 1), we augmented the antipsychotic CLZ-monotherapy with PAL (6 mg/day), however, we only observed minor changes of PANSS. Over a period of 9 weeks, the treatment was well tolerated, but body weight increased to 108 kg (BMI 33.7 kg/m2) and serum creatine kinase rose to 508 U/l without any evidence for malignant neuroleptic syndrome. We therefore switched to CLZ/APZ, leading to a more pronounced response, stop of weight gain and reduction of CK (291 U/L).

In summary, the presented patients exhibited psychotic symptoms resistant to CLZ-monotherapy. After addition of PAL (10 ± 3 mg/day) for a mean period of 8 weeks, the PANSS-positive subscale improved in two patients by more than 20% and over the whole sample by 15 %. While the clinical importance of statistical testing is highly limited by low case numbers, this improvement turned out to be significant (table 1). The mean initial CLZ dose could be lowered. During combined treatment, mean prolactin increased, while one patient previously had experienced a prolactin elevation during treatment with CLZ and AMS. Despite the reduction of CLZ doses, we observed a continued gain of body weight from a mean of 91.1kg (BMI: 30.9 kg/m2) before to 94.25 kg (BMI: 32.0 kg/m2) after PAL add-on. Other metabolic parameters such as fasting glucose, total triglycerides, total cholesterol, blood pressure, heart rate and ECG parameters including QT_C interval did not show sig-

nificant changes. Subjective and observed tolerance was good.

Discussion

The presented cases allow preliminary clinical estimations of combined CLZ/PAL-treatment in patients with partial response to CLZ. While selective reporting of positive courses often limits the value of case reports and case series, our small sample has not been censored and summarizes favourable (cases 2 and 3) and insufficient outcomes (cases 1 and 4). The described overall improvements of psychotic positive symptoms correspond with similar observations in open trials involving CLZ and RISP (Zink & Dressing 2005). In the light of ambiguous results of RCTs involving RISP and meta-analyses (see introduction) cautious interpretation appears advisable. We consider sufficiently powered, long-term RCTs necessary to evaluate the strategy of combining CLZ with PAL.

The proposed add-on approach might be able to reduce the daily CLZ-dose, some directly dose-related side effects, and long-term disadvantages of CLZ. However, the reductions of CLZ dose and serum-levels in our patients were not significant and weight gain continued despite of CLZ reduction. In parallel to observations with risperidone (Zink et al. 2009), an elevation of serum prolactin levels seems possible under PAL co-treatment and might increase the burden of side effects.

In conclusion, combined antipsychotic treatment with CLZ and PAL might be a successful strategy in individual patients, but efficacy and tolerance has to be further evaluated in controlled clinical trials.

Declaration of interests

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