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The effect of add-on treatment with quetiapine on measures of depression, aggression, irritability and suicidal tendencies in children and adolescents

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Rationale Atypical antipsychotics are frequently prescribed for psychotic and mood disorders in youth, and for symptoms of depression, aggression, irritability and suicidal tendencies, which are associated with subsequent development of borderline personality disorders (BPD).

Objectives This study evaluated the effects of 24-weeks of add-on treatment with quetiapine to selective serotonin reuptake inhibitors (SSRIs) in young people with pronounced symptoms of depression, aggression, irritability and suicidal tendencies.

Methods In an open-label 24-weeks trial, 22 SSRI-treatment resistant patients (age range 9-18 years) with developing BPD were treated with quetiapine (75-600 mg/day) in combination with SSRIs. Symptoms of depression, aggression, irritability and suicidal tendencies were rated with the Overt Aggression Scale Modified (OAS-M), Kutcher Adolescent Depression Scale (KADS-6) and Children Global Assessment Scale (C-GAS) before and after 4-24 weeks of treatment.

Results Quetiapine induced significant ($p<0.001$) improvement after 4-24 weeks, with a modest but significant increase in the C-GAS total scores (i.e. children's general clinical status), and a significant reduction of the total scores in OAS-M, KADS-6 and OAS-M subscales for aggression, irritability and suicidality. There were no discontinuations for adverse effects

Conclusions These preliminary results suggest that quetiapine addition to SSRIs treatment significantly reduced symptoms of depression, aggression, irritability and suicidal tendencies in young people with developing BPD.

Key words**:** quetiapine, borderline personality disorders, add-on treatment, 24-weeks, children and adolescents, aggression, depression, irritability, suicidality

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Conflict of Interest

All authors declared no financial relationship with the Organization that sponsored the research, and have no conflict of interest.

Authors state that they have full control of all primary data and they agree to allow the journal to review their data if requested.

Atypical antipsychotics are prescribed frequently for the treatment of psychotic, disruptive behaviour, personality, mood and pervasive developmental disorders, irritability in autism and learning difficulties in children and adolescents (Adityanjee et al. 2008; De Hert et al. 2011; Zuddas et al. 2011). Besides serotonin reuptake inhibitors (SSRIs), medication used to treat borderline personality disorders (BPD) may include anticonvulsants, but also atypical antipsychotics **(**Abraham and Calabrese 2008**)** such as quetiapine (Adityanjee et al. 2008). In the Republic of Croatia, quetiapine is registered for treatment of psychotic and bipolar disorders in patients over 18. However, in children and adolescents who are refractory to treatment, and who develop various behavioural disorders, primarily with symptoms of BPD, the use of atypical antipsychotics is often regarded as necessary. The aim of this study was to evaluate the effects of 24-weeks of add-on treatment with quetiapine (75-600 mg/day) in patients aged 9-17 years with developing BPD, refractory to previous treatment, who had pronounced symptoms of depression, aggression, irritability and suicidal tendencies.

The open trial included 11 male and 11 female patients 9-17 years old (mean=15.4, SD=1.71), admitted between 2005-2007, with hetero- or auto-aggressive (suicidal tendencies and suicidal thoughts), depressive and irritability symptoms, that correspond to symptoms in adult BPD. Since DSM-IV does not recognize a diagnosis of BPD before the age of 18, diagnosis was categorized as developing BPD, according to DSM-IV criteria, and Revised Diagnostic Interview for Borderline Patients (DIB-R). Refractoriness to treatment was defined when patients had the Children Global Assessment Scale (C-GAS) scores lower than 51 after a few treatment sessions (2 weeks to a few years) with SSRIs (fluvoxamine, sertraline or fluoxetine). After obtaining

patient's assents and parent's consents, patients were treated with quetiapine (average daily dose of 390 mg) as an add-on therapy to various SSRIs. Inclusion criteria: diagnosis of developing BPD, except the age criteria, IQ>90, and no positive therapeutic effect of SSRIs. Exclusion criteria: comorbid depressive, psychotic or eating disorders, and concomitant psychiatric therapy by medication other than SSRIs.

Transient somnolence, dry mouth and fatigue were evident in some patients during the first 2 weeks of the trial but resolved spontaneously; no other clinical side-effects were recorded. None of the patients required anticholinergic medications, no discontinuation due to side effects was recorded, and all patients finished 24 weeks of the trial. Hospital monitoring was undertaken in the period of 6-8 weeks, and outpatient monitoring after discharge from the hospital department. The primary efficacy measure was a change from baseline to end point in the modified version of the Overt Aggression Scale Modified (OAS-M), and secondary efficacy measures were the 6-items Kutcher Adolescent Depression Scale (KADS-6), and the C-GAS. The study was approved by the Ethics Committee of the Psychiatric Hospital for Children and Youth Zagreb. The results, expressed as means ± standard deviations (SD), were evaluated using repeated measures analysis of variance (ANOVA), and Tukey's test. The level of significance was set to p=0.05.

Patients had mean DIB-R scores of 8.91 ± 0.75. Quetiapine (average dose 389.77 ± 153.27 mg/day) treatment for 4-24 weeks significantly increased (p<0.001) the total C-GAS scores, and significantly decreased (p<0.001) total KADS-6, total OAS-M scores, and scores in OAS-M aggression, irritability, and suicidality subscales (Table 1).

To the best of our knowledge, this is the first study to show that the add-on of quetiapine (average dose 390 mg/day) to SSRIs induced a significant reduction of the symptoms of aggression, irritability, affective instability, suicidality, and depression, and significant improvement in the global level of functioning in young people with developing BPD refractory to previous SSRI treatment. The clinical improvement remained stable over 24 weeks of study.

Our results are in line with the reported improvement of the combination of quetiapine and valproate or quetiapine monotherapy in young people with bipolar disorder (DelBello et al. 2006; Zuddas et al. 2011), in youth with co-morbid paediatric bipolar disorder and disruptive behaviour disorder (Barzman et al. 2006), and in aggressive children with conduct disorders (Findling et al. 2007). In contrast to our results, showing that quetiapine improved slightly but significantly depressive symptoms, quetiapine did not affect symptoms of depression in adolescents with bipolar depression (DelBello et al. 2006). Limitations of the study were that adverse effects were not systematically collected and important metabolic indicators such as weight gain, fasting glucose, lipid levels or prolactin increase were not measured (De Hert et al. 2011).

In conclusion, this pilot trial confirmed the clinical impression that 24-weeks of quetiapine treatment, added to standard SSRIs, ameliorated aggressive behaviour, intentional self-injury, chronic anxiety and affective instability, depression, suicidal tendencies and irritability in children and adolescents with developing BPD. However, because of its metabolic adverse effects quetiapine must be used with caution in this patient population and randomised trials with careful safety monitoring are needed.

Authorship

All authors have made a significant contribution to the conception and design or the analysis and interpretation of data, have participated in drafting the article or reviewing and/or revising it for intellectual content, and have approved the final version of the manuscript.

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Table 1. Total scores in the C-GAS, KADS-6, OAS-M, and in the OAS-M subscales for aggression, irritability and suicidality in 22 patients (11 male and 11 female) with developing BPD at baseline and after 4, 8, 12, 16 and 24 weeks of treatment with quetiapine.

	Weeks of treatment:					
	0	4	8	12	16	24
C-GAS scores	32.5±11.9	45.0±11.9*	53.3±11.8*	48.7±8.9*	48.2±9.8*	44.5±14.9*
ANOVA	$F(5, 21)=49.236$; $p<0.001$					
KADS-6 scores	11.9±2.9	8.5±2.8*	7.1±2.7*	8.0±3.3*	7.4±3.4*	7.9±3.4*
ANOVA	$F(5, 21)= 28.685$; $p<0.001$					
OAS-M scores	50.6±25.1	24.7±12.2*	26.4±16.2*	31.1±17.9*	29.6±17.0*	35.7±26.4*
ANOVA	$F(5, 21)=23.551$; $p<0.001$					
OAS-M aggression	39.0±22.5	17.9±9.3*	19.4±13.1*	25.0±15.9*	23.2±14.2*	29.0±23.1**
ANOVA	$F(5, 21)= 17.913$; $p<0.001$					
OAS-M irritability	7.8±1.3*	5.3±1.7*	5.6±1.7*	5.5±1.8*	5.5±2.1*	5.9±2.3*
ANOVA	$F(5, 21)= 20,083$; $p<0.001$					
OAS-M suicidality	3.86±4.16	1.82±2.40*	1.45±2.38*	0.59±0.91*	0.77±1.60*	0.91±2.60*
ANOVA	$F(5, 21)= 14.334$; $p<0.001$					

Data are presented as means ± SD. BPD= borderline personality disorder; C-GAS= Children Global Assessment Scale; KADS-6= Kutcher Adolescent Depression Scale; OAS-M= Overt Aggression Scale - Modified; OAS-M aggression= Overt Aggression Scale - Modified, aggression subscale; OAS-M irritability= Overt Aggression Scale-Modified, irritability subscale; OAS-M suicidality subscale= Overt Aggression Scale – Modified, suicidality subscale; *p=0.001 vs. baseline scores; **p=0.003 vs. baseline scores (Tukey's test).