Quetiapine Monotherapy in Adolescents with Bipolar Disorder Comorbid with Conduct Disorder

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Abstract

Bipolar Disorders (BD) are often comorbid with disruptive behaviour disorders (DBDs) (oppositional-defiant disorder or conduct disorder), with negative implications on treatment strategy and outcome. The aim of this study was to assess the efficacy of quetiapine monotherapy in adolescents with BD comorbid with conduct disorder (CD). A consecutive series of 40 adolescents (24 males and 16 females, age range 12–18 years, mean age 14.9 ± 2.0 years), diagnosed with a clinical interview (Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present and Lifetime Version [K-SADS-PL]) according to American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision (DSM-IV-TR) criteria were included. All the patients were treated with quetiapine monotherapy (mean final dose 258 ± 124 mg/day, range 100–600 mg/day). At the end-point (3 months), 22 patients (55.0%) were responders (Clinical Global Impressions-Improvement [CGI-I] score of 1 or 2 and CGI-Severity [CGI-S] ≤ 3 and improvement of at least 30% Children's Global Assessment Scale [C-GAS] during 3 consecutive months). Both CGI-S and C-GAS significantly improved ($p < 0.0001$). Nine out of the 16 patients with suicidality (56.3%) had a reduction in this severe symptom during the follow-up. Nonresponders were more frequently males, and more frequently had an attention-deficit/hyperactivity disorder (ADHD) comorbidity. Eight patients (20.0%) experienced moderate to severe sedation and eight (20.0%) experienced increased appetite and weight gain. In these severely impaired adolescents, quetiapine monotherapy was well tolerated and effective in $> 50\%$ of the patients.

Introduction

COMORBIDITY BETWEEN BIPOLAR DISORDER (BD) and disruptive behavior disorders, including oppositional defiant disorder (ODD) and conduct disorder (CD), has been repeatedly reported in clinical (Biederman et al. 1999, 2003) as well as in epidemiological samples (Lewinshon et al. 1995). According to data from a large, unselected sample of referred children and adolescents, 186 fulfilling criteria for mania and 192 meeting criteria for CD, 76 displayed both the disorders, 40% with CD (76/192) and 41% with BD (76/186) (Biederman et al. 1999). According to our previous data, CD was diagnosed in 23.1% of subjects with BD type I, in 10.3% of subjects with type II, and in 23.8% of subjects with BD-not otherwise specified (NOS) (Masi et al. 2007).

In a previous study, we compared youth with both BD and CD with peers with BD or CD only (Masi et al. 2008). Patients with CD and BD presented higher rates of global aggression at the baseline, namely impulsive aggression, compared with those with either BD or CD alone, more frequent substance abuse, and poorer response to treatments, in terms of both Clinical Global Impressions-Improvement (CGI-I) score and percentage of responders (only

48.9% of BD+CD patients were responders to treatments, compared with 75% of those with BD only). This finding confirms what had been previously reported by our group; that CD comorbidity is the most important negative predictor of treatment nonresponse in BD children and adolescents (Masi et al. 2004). It is of note that a substance abuse (any alcohol and/or drug abuse or dependence) was found in 16.6% of bipolar patients without CD, in 32.1% of patients with CD without BD, and in 46.7% of patients with both the disorders (Masi et al. 2008).

Although there is increasing information about pharmacological treatments in children and adolescents with BD, no studies report experience on medications for BD with comorbid CD. Emerging evidence indicates that atypical antipsychotics are more effective than mood stabilizers in youth with mania (Geller et al. 2012). Among the second generation antipsychotics, efficacy of quetiapine in children and adolescents with BD has been supported by controlled studies (Pathak et al. 2013). Additional studies support the efficacy of quetiapine in aggressive children with CD (Findling et al. 2006). Furthermore, quetiapine was effective in reducing aggression as additional treatment to methylphenidate in youth with attention-deficit/hyperactivity disorder (ADHD) with comorbid ODD/CD

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who did not respond to methylphenidate only (Kronenberger et al. 2007). The aim of this study is to report on our experience with quetiapine monotherapy in a consecutive sample of referred children and adolescents with BD (manic, hypomanic, or mixed episode) and comorbid CD, followed up for 3 months in a third level research hospital.

Materials and Methods

Among the patients referred to our tertiary care hospital (Service for Mood and Anxiety Disorders) in the period from January 2009 through December 2012, a consecutive series of 40 adolescents (24 males and 16 females, age range 12–18 years, mean age 14.9 ± 2.0 years, 20 inpatients and 20 outpatients) received a diagnosis of BD (manic, hypomanic, or mixed episode), comorbid with CD, based on historical information, symptoms ratings according to American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV), and a structured clinical interview, the Schedule for Affective Disorders and Schizophrenia for School-Age Children- Present and Lifetime Version (K-SADS-PL) (American Psychiatric Association 1994; Kaufman et al. 1997), administered individually to the parents and to the patients by four child psychiatrists trained in the use of this interview. Additional criteria for the inclusion in the study were a CGI-Severity (CGI-S) score ≥ 4 (Guy 1976) and a Children Global Assessment Scale (C-GAS) (Shaffer et al. 1983) score ≤ 50 . Exclusion criteria were a diagnosis of intellectual disability and/or pervasive developmental disorder and/or schizophrenia. These patients were also not included in previous studies from our group.

The severity of the illness at baseline and end-point was assessed by means of the CGI-S and CGI-I scores. Functional impairment was assessed with the C-GAS. In this study, patients with a CGI-I score of 1 ("Very Much Improved") or 2 ("Much Improved"), a

CGI-S score of ≤ 3 , and an improvement of at least 30% of C-GAS were considered responders.

Twenty-three (57.5%) were also receiving individual psychotherapy before the onset of quetiapine, and the treatment remained unchanged during the follow-up.

All subjects and parents received detailed information on the characteristics of the assessment instruments and different treatment options, all parents gave a written informed consent, and all the patients gave their consent as well (written in the case of inpatients).

Chi-square analyses were performed on categorical variables and a paired *t* test was performed on continuous variables. Considering the large number of comparisons performed and the number of subjects in each group, our results were prone to both type I and type II errors. Considering the large number of comparisons, *p* values were based on two tailed tests with $\alpha = 0.005$, using a *post-hoc* Bonferroni correction.

Results

This was a sample of severely impaired patients in terms of clinical severity (CGI-S = 5.7 ± 0.7) and functional impairment (C-GAS = 37.5 ± 3.8). Furthermore, 16 (40.0%) patients presented with substance abuse, and 40 (40.0%) suicidality (persistent ideation and/or suicide attempts).

The patients presented a complex pattern of comorbidity. Twenty-one (52.5%) presented at least one comorbid anxiety disorder: 13 with generalized anxiety disorder, 9 with social phobia, 5 with separation anxiety disorder, 4 with panic disorder, and 4 with simple phobias. Six patients (15.0%) had an obsessive-compulsive disorder. Fifteen patients (37.5%) had co-occurring ADHD, and 10 (25.0%) filled diagnostic criteria for borderline personality disorder.

TABLE 1. COMPARISONS BETWEEN RESPONDERS ($N=22$) AND NONRESPONDERS ($N=18$)

	Responders $n=22$	Nonresponders $n=18$	<i>t</i> or χ^2	<i>p</i>
Males, <i>n</i> (%)	9 (40.9)	15 (83.3)	5.8 (1)	0.016*
Inpatients, <i>n</i> (%)	14 (63.6)	6 (33.3)	2.5 (1)	0.112
Age, mean (SD)	14.7 (2.0)	15.2 (2.1)	-0.8 (38)	0.447
CGI-S baseline, mean (SD)	5.8 (0.7)	5.6 (0.8)	0.8 (38)	0.404
CGI-S end, mean (SD)	3.5 (0.6)	4.4 (0.7)	-4.4 (38)	0.000*
C-GAS baseline, mean (SD)	36.6 (3.1)	38.6 (4.4)	-1.7 (38)	0.100
C-GAS endpoint, mean (SD)	52.6 (4.6)	43.5 (4.4)	6.1 (38)	0.000*
CGI-I, mean (SD)	1.8 (0.5)	3.1 (0.9)	-6.3 (38)	0.000*
Quetiapine dosage	257 (130)	258 (119)	-0.0 (35)	0.980
Comorbidity, <i>n</i> (%)				
Any anxiety disorder	13 (59.1)	8 (44.4)	0.4 (1)	0.545
Generalized anxiety disorder	8 (36.4)	5 (27.8)	0.1 (1)	0.812
Social phobia	6 (27.3)	3 (16.7)	0.2 (1)	0.676
Separation anxiety disorder	3 (13.6)	2 (11.1)	0.1 (1)	0.810
Panic disorder	4 (18.2)	0 (0)	1.9 (1)	0.168
Simple phobia	2 (9.1)	2 (11.1)	0.1 (1)	0.751
Obsessive-compulsive disorder	3 (13.6)	3 (16.7)	0.0 (1)	0.859
Borderline personality disorder	8 (36.4)	2 (11.1)	2.2 (1)	0.142
ADHD	4 (18.2)	11 (61.1)	6.1 (1)	0.014*
Substance abuse	9 (40.9)	7 (38.9)	0.0 (1)	0.846
Suicidality	10 (45.5)	7 (38.9)	0.0 (1)	0.923
Psychotherapy	15 (68.2)	8 (44.4)	1.4 (1)	0.234

*Statistically significant ($p < 0.005$).

CGI-S, Clinical Global Impressions-Severity; CGI-I, Clinical Global Impressions-Improvement; C-GAS, Children Global Assessment Scale; ADHD, attention-deficit/hyperactivity disorder.

The mean quetiapine dosage was 258 ± 124 mg/day (range 100–600 mg/day).

CGI-S score improved from 5.7 ± 0.7 at the baseline (severely to extremely severely ill), to 3.9 ± 0.8 (mild to moderately ill) at the end-point ($t = 12.1$, $df = 39$, $p < 0.0001$, 95% CI 1.52–2.13, mean difference 1.82 ± 0.96), whereas C-GAS improved from 37.5 ± 3.8 to 48.5 ± 6.4 ($t = -10.2$, $df = 39$, $p < 0.0001$, 95% CI -13.15 to -8.79 , mean difference -10.98 ± -6.91).

According to our measures of clinical response (CGI-I 1 or 2 and CGI-S ≤ 3 and improvement of at least 30% C-GAS during 3 consecutive months), 22 patients (55.0%) were responders. When responders and nonresponders were compared according to selected variables, only male/female ratio (40.9% males in responders vs. 83.3% in nonresponders, $p = 0.016$) and ADHD comorbidity (18.2% in responders, 61.1% in nonresponders, $p = 0.014$) were higher in nonresponders, whereas age, severity and functional impairment at the baseline, anxiety comorbidity, co-occurring substance abuse, and suicidality did not differ between groups (Table 1). Nine out of the 16 patients with suicidality (56.3%) saw this severe symptom reduce during the follow-up.

Quetiapine was well tolerated. Eight patients (20.0%) experienced moderate to severe sedation and eight (20.0%) experienced increased appetite and weight gain.

Discussion

Some definite clinical features can significantly distinguish patients diagnosed as having CD and BD from those with both the disorders, including a greater severity and a more frequent resistance to treatments (Biederman 1999, 2003; Masi et al. 2008). There is poor available information on pharmacological treatment in BD comorbid with CD. Our sample is the largest series of patients with BD and comorbid CD referred to a third level hospital for a pharmacological treatment. All the patients were treated with quetiapine monotherapy. In the whole group, 52.5% of the patients were responders according to our criteria, combining both CGI-I, and an improvement of both CGI-S (clinical severity) and C-GAS (functional impairment). Furthermore, both CGI-S and C-GAS significantly improved in the whole group. It is of note that during the follow-up period, a significant reduction in suicidality was observed in 9 out of the 16 patients with suicidality (56.3%). Nonresponders were more frequently males and presented a higher rate of ADHD comorbidity, whereas age, severity, anxiety comorbidity, substance abuse, and suicidality did not differentiated responders from nonresponders.

Quetiapine was well tolerated, as side effects were not severe (sedation, increased appetite), and did not require drug discontinuation.

A limitation of our study is that it was neither randomized nor controlled, only subjects referred to a single treatment site were included, and the referral to our third level hospital was usually aimed at starting a pharmacotherapy. This selection bias may limit the generalization of the conclusions, because our sample may represent a subgroup of more severely impaired subjects. Furthermore, we have used as outcome measure CGI-S and C-GAS, which are not specific measures of depressive symptoms' severity and improvement. However, there is evidence that global ratings can be more sensitive to change during acute treatment than scores on itemized symptom rating scales. The CGI and CGAS scores (severity and improvement) are the most widely used measure in psychopharmacological studies in children and adolescents as global measures of severity of illness and improvement.

Further research is needed to support these data with large, randomized, placebo-controlled studies. However, clinical studies, albeit not controlled, might represent a helpful source of information regarding the effectiveness of a treatment under more ordinary clinical conditions, that is, which include longer follow-ups.

Disclosures

Dr. Masi was on the advisory boards for Eli Lilly, Shire, and Novartis; has received research grants from Eli Lilly and Shire; and has been a speaker for Eli Lilly, Shire, Sanofi-Aventis, Novartis, and Lundbeck. Dr. Pfanner has received research grants from Eli Lilly and has been speaker for Eli Lilly. Drs. Pisano, Milone, and Manfredi do not have conflicts of interest to declare.

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