Case report

Use of quetiapine for early-onset bipolar disorder

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INTRODUCTION

Early-onset bipolar disorder in children and adolescents (EBD-CA) has raised increasing interest in mental health specialists who provide care to children and adolescents.[1]

Despite such nosological entity having been mentioned since the mid-19th century, its existence has often been questioned and even denied.[2] The difficulty in making a precise diagnosis contributed to such controversy, but in the mid-1970's and 1980's, studies invariably showed that bipolar disorder often has its onset in adolescence and many even before that.[3,4]

The diagnosis of EBD-CA is usually difficult due to the presence of characteristics considered unusual in adult onset, such as fast, ultrafast[5] cycling pattern and presence of mixed states.[6,7] In addition, the common presence of psychotic symptoms, disorganized thoughts, behavioral change and use of psychoactive substances lead to mistaken diagnoses, such as schizophrenia, conduct disorder, oppositional-defiant disorder and attention-deficit/hyperactivity disorder.[2,8-11]

EBD-CA is a severe disease, since it causes major losses in the individual's life, such as social maladaptation, school dropout, difficulty in learning, involvement with illegal practices, contact with psychoactive substances, problems of family relationship, etc.[12]

The pharmacological treatment aims at reestablishing the child's baseline pattern. Many classes of psychotropic drugs are used, among them antidepressants, antipsychotics, mood stabilizers and psychostimulants.[13] There are few studies assessing the efficacy of those drugs in children and adolescents with EBD. Some studies show the efficacy of lithium in bipolar adolescents with comorbid chemical dependence;[14] another study shows an open trial using olanzapine in monotherapy of children and adolescents with EBD;[15] and another study shows the efficacy of valproate in association with quetiapine in the same situation.[16] An open study revealed comparable efficacy between lithium carbonate, carbamazepine and sodium valproate.[17]

However, EBD-CA frequently presents symptoms of mixed mania and fast or ultrafast[5] cycling pattern, which are associated with worse prognosis when present in adults. There is also

evidence of adolescents resistant to those drugs.[18] The presence of a comorbid condition is very common in those situations, attention and hyperactivity disorder being reported in 80-90% of children and 30% of adolescents with EBD.[5,19] Depressive symptoms are usually very intense, with high risk of suicide.[20] All those factors make polypharmacology common and necessary in the treatment of EBD-CA and a great challenge for children's psychiatrists.

The group of psychotropics that present confirmed efficacy in the treatment of EBD-CA includes lithium carbonate and anticonvulsants, such as carbamazepine, valproic acid[21] and, more recently, lamotrigine, topiramate, gabapentin and oxcarbazepine.[22-24]

Atypical antipsychotics have been recently approved by the Food and Drug Administration as antimanic drugs and mood stabilizers for the population of adults[25,26] and children and adolescents.[27] Other studies have also demonstrated the efficacy of risperidone,[28,29] olanzapine,[30] clozapine[31] and, more recently, quetiapine[32-34] in adults or adolescents.

Choosing the stabilizer or drug association to be used is based on the subtype of EBD found after extensive assessment, stage and severity, opting for traditional stabilizers (lithium, carbamazepine and sodium valproate) in types I and II and for atypical antipsychotics in unspecified subtypes, with major irritability and without periodicity, performing new associations and changes in stabilizers in case there is no response, or if the response is partial.[35,36]

We report a case of a patient with EBD-CA having good response to quetiapine after failure of many other therapeutic options. He was receiving care at Affective Disorder Outpatient Clinic, Children and Adolescent Psychiatry Service (SEPIA) at Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo.

CASE REPORT

G., 13 years old, white and adopted. He presented to SEPIA on September 2000, complaining that 6 months ago he started presenting frequent weeping, sadness with no apparent reason, loss of pleasure in the activities he used to like and hopelessness toward the future. He

started eating large amounts of food in a fast and little selective manner, quickly gaining weight, and at night his sleep was agitated, with nightmares or waking in the middle of the night to eat. At school, his main complaint was of hostile behavior, fights with colleagues for any reason, disrespecting and verbally attacking his teachers. He then did not want the company of his friends, moving away from them. G. challenged his parents and had provocative attitudes. His parents had great difficulty in imposing limits, due to the intensity of his explosion. He reported feeling lonely, in many moments of anxiety he said he wanted to die.

In his first appointment at SEPIA, he was psychiatrically assessed and the structured interview Diagnostic Interview for Children and Adolescents was applied, besides the Children Depression Rating Scale to measure the intensity of depressive symptoms. After assessment, he was diagnosed with depression associated with dysthymic disorder since he was 11 years of age (double depression), and a treatment with fluoxetine 10 mg was initiated, gradually increasing the dose until 50 mg/day. For 3 months, the patient presented fluctuations between moments of improvement in sadness and irritation, with persistent insomnia, anhedonia and increased appetite, and moments of improvement in dysphoric symptoms, but the internal feeling of sadness and hopelessness worsened. The patient was gradually moving away from his academic activities, friends and extracurricular events.

After 3 months taking fluoxetine with no significant improvement in symptoms, the antidepressant drug was replaced by paroxetine. Fifty days after starting paroxetine 30 mg/day, the patient seemed happier, dyed part of his hair blonde, and was more talkative. According to his mother’s report, there was a period of 4 days, between two appointments, in which G. thought everything was wonderful, that he could do anything he wanted and was absolutely sure that everything would be better from then on. He used to hug his colleagues and people in the street. Although his mother was surprised and satisfied with the improvement in her son’s depressive symptoms during that short period, she was worried about the worsening in explosiveness that

occurred over the same period. In one occasion, explosiveness and aggressiveness reached such a proportion that G. pulled the kitchen's door off, due to a minor frustration.

Due to the change in symptom pattern, we chose to cancel the antidepressants and observe the patient with no medication for 2 weeks, to determine whether he was presenting symptoms of behavioral activation secondary to the use of antidepressants or whether he was progressing to an EBD condition, independent of taking antidepressants.

During the observation period, G. presented significant worsening of irritation, sadness, lack of perspective and also of anger attacks with physical aggressiveness.

In that occasion, due to the presence of clearly manic symptoms (elevated mood, social disinhibition and grandiosity) of 4 days, his diagnosis was replaced by EBD. Although the patient presented clearly manic symptoms, he did not meet the criteria of symptom duration proposed by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and International Classification of Diseases (ICD-10) for the diagnosis of manic episode. For that reason, we proposed a diagnosis of unspecified very early onset bipolar disorder (< 13 years).

Valproic acid was introduced, with slight improvement in irritation and aggressiveness symptoms, but not lasting for more than 3 consecutive weeks. Drug doses were gradually adjusted to 1,750 mg of valproic acid. In spite of the improvement in aggressiveness and explosiveness symptoms, there was worsening of depressive symptoms. Paroxetine was then associated with valproic acid, aiming at improvement in depressive symptoms. Even taking a mood stabilizer, by increasing paroxetine to 30 mg/day, the patient started presenting elevated mood, frequent risks, he thought everything was going fine and that he could do anything he wanted. Paroxetine dose was gradually reduced and, when reaching the dose of 10 mg/day, the patient presented sadness once again, besides worsening in irritability and despondency.

The antidepressant drug was then replaced by sertraline, with little response to improvement in depressive symptoms, although there were fewer explosions and irritability, comparing with the period using paroxetine. Sertraline was used for 1 month, with worsening in mood fluctuations after

the dose was increased from 25 to 50 mg/day. We tried to associate topiramate up to 100 mg/day, with significant worsening in explosive behavior. For that reason, sertraline and topiramate were cancelled 15 days after using the second medication. In that occasion, the patient developed enuresis, and imipramine 50 mg/day was prescribed. That medication was cancelled 1 month later for having worsened his behavior.

The patient maintained mood fluctuations and oppositional attitude toward his mother, who could not control him, due to his impulsive and potentially aggressive behavior. This generated apprehension between his relatives, because, at the age of 14 years, the patient already had a well developed body (approximately 1.80 m and 110 kg).

For approximately 14 months, with assessments every 15 days, the patient was more controlled in some occasions, but the stabilization did not last for more than 2 weeks; the patient soon presented significant mood fluctuation, with irritability, aggressiveness, depressive symptoms, anhedonia, and difficulty in social and family relationships. Over that period, oxcarbazepine (maximum dose of 1,500 mg for 8 months), levomepromazine (maximum dose of 100 mg for 2 months) and carbamazepine (maximum dose of 1,000 mg for approximately 3 months, being cancelled due to change in liver enzymes) were introduced.

On September 2003, escitalopram 10 mg/day was introduced, and 1 month later quetiapine fumarate 100 mg. As the patient still presented new moments of irritation and sadness, topiramate was reintroduced, but cancelled 2 months later due to the occurrence of enuresis. Escitalopram was maintained at 10 mg/day.

Due to the maintenance of aggressiveness (he threatened to hit his father with a baseball bat), provocative attitude, excessive ingestion of food, constant irritation and childish attitude, quetiapine fumarate was increased to 200 mg, and then to 250 mg.

From that moment on, the patient became stable and did not present behavioral changes, complaints of irritation, sadness or despondency; he also made plans to get back to school and to his

extracurricular activities, such as gymnastics. The patient remained stable for more than 8 months, which had not been previously achieved.

CONCLUSION

The psychopharmacological treatment of EBD-CA is very complex. Besides the difficulty in clinical diagnosis, many cases do not satisfactorily respond to conventional mood stabilizers. In addition, the existence of poorly defined stages and presence of fast or ultrafast cycles make the choice of the most appropriate drug difficult, since the use of some drugs, such as antidepressants, may worsen the disorder, especially when used in mixed stages of the disease, which, in most children, are hard to identify. Regarding G,'s case, such difficulty might have contributed, at least in the beginning, for choosing the most indicated drug for each disorder stage, since the prevalence, from the start, of depressive symptoms induced the authors to use increasing doses of antidepressants at some moments of the treatment. It is important to stress that great part of the current knowledge on EBD in children and adolescents, with regard to diagnosis and treatment of the disorder, was not available when the patient started his treatment. For that reason, symptoms of explosiveness and aggressiveness, which were already indicating a possible progress to EBD, were interpreted, at that time, as part of the depressive condition and, therefore, were treated using antidepressants.

The use of different antidepressants at increasing doses may have contributed to the initial worsening in the patient’s condition and further difficulty in responding to other therapeutic options. Those data reflect the complexity of diagnosing and proving treatment for EBD in children and adolescents.

In the case described herein, quetiapine showed safety and efficacy in symptom remission and stabilization, without presenting significant side effects, especially extrapyramidal. This profile of safety and tolerability had already been described in previous case reports.[37, 38] Although there

are case reports in the literature on induced mania in patients with schizoaffective disorder,[39,40] this effect was not observed in our case.

Further studies involving higher populations are needed to confirm whether the results observed in this case may be extrapolated to other children and adolescents with EBD.

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ABSTRACT

Bipolar disorder in children and adolescents has become a great challenge for professionals who work with this type of patients, as well as for researchers interested in studying it in depth. Firstly, diagnostic assessment is difficult; secondly, to establish a safe, long-term and effective treatment is challenging. Different cycling patterns, predominance of mixed episodes, severity of symptoms and need of polypharmacy makes the treatment of child and adolescent bipolar disorder very complex and requiring a wider range of therapeutic resources. The present case reports a successful use of quetiapine for a bipolar adolescent diagnosed at the age of 12 years who had been unsuccessfully treated using many therapeutic options. Quetiapine showed efficacy in both acute and prophylactic treatment of early-onset bipolar disorder.

Keywords: *Bipolar disorder, quetiapine, adolescent, treatment.*

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