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Case Report

Mood Stabilizer Augmentation with Olanzapine in Acutely Manic Children

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ABSTRACT

We report on three cases of acutely manic prepubertal children diagnosed with bipolar disorder who were treated with olanzapine in addition to their existing mood stabilizer regimens. All three had marked improvement of their manic symptoms within 3–5 days of beginning olanzapine therapy as measured by clinician-rated instruments. Adverse effects included sedation and weight gain. These results suggest that olanzapine may have an antimanic or mood stabilizing effect in acutely manic children with bipolar disorder.

INTRODUCTION

Antipsychotics have been routinely used in the acute and chronic treatment of bipolar disorder (Tohen and Zarate 1998). Due to their low incidence of tardive dyskinesia, atypical antipsychotics may be attractive alternatives to typical antipsychotics. The advent of atypical antipsychotics has also raised the possibility of these agents having antimanic, ant.i.d.epressant, or mood stabilizing properties. Olanzapine is an atypical antipsychotic similar in structure and receptor affinity to clozapine, but without the side effects of agranulocytosis, seizures, or hypotension. In open studies and case reports, researchers have found olanzapine useful as augmentation to traditional mood stabilizers in acutely manic adults (Ketter et al. 1998; McElroy et al. 1998). Olanzapine has been suggested to be effective monotherapy in some adults with mania (Ravindran et al. 1997) and has been reported to work rapidly to alleviate mixed mania (Ketter et al. 1998). A double blind placebo controlled study recently found olanzapine monotherapy superior to placebo in manic adults (Tohen et al. 1999). However, there have also been reports of manic symptoms, including aggression and agitation, induced by treatment with olanzapine (John et al. 1998; Lindenmayer and Klebanov 1998; London 1998), possibly due to agitation secondary to discontinuation of traditional antipsychotics. Thus, the efficacy olanzapine in treating mania has not yet been fully established.

There have been fewer reports of olanzapine use in children and adolescents. Olanzapine was found to be moderately effective in eight children with schizophrenia in an open label study (Kumra et al. 1998). However, a recent study reported discontinuation of open olanzapine treatment in five children with various psychiatric disorders due to persistent side effects (sedation, weight gain, and akathesia) and lack of significant improvement of symptoms (Krishnamoorthy and King 1998). Bipolar disorder was among the

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differential diagnoses for three of these children, but it was not clear that any of them were experiencing a manic state due to bipolar disorder. In another open case series, five out of seven adolescents with manic episodes were reported to have responded well to either addition of olanzapine to their medication regimens or, in one case, olanzapine monotherapy (Soutullo et al. 1999). There have been no reports of mood stabilizer augmentation with olanzapine in acutely manic prepubertal children. Here, we report on three cases of acutely manic prepubertal children with bipolar disorder who responded to olanzapine's being added to their existing mood stabilizer regimen.

CASE REPORTS

Case 1

R.C., a 12-year-old boy, was first diagnosed with attention-deficit hyperactivity disorder (ADHD) at age 6. His family history was significant for his mother's having bipolar disorder and numerous maternal relatives with depression. After 3 years of therapy with sustained release methylphenidate 20 mg QD, he began to experience increasingly labile mood, with frequent bouts of depressed mood alternating with extreme irritability and tantrums; however, no other medications were tried.

At age 11 years, R.C. presented to our outpatient clinic with extreme irritability, racing thoughts, initial insomnia, hypersexuality, and hyperactivity. He was tapered off of the methylphenidate over 2 weeks, but these symptoms continued and worsened over the next month. He was diagnosed with bipolar disorder, rapid cycling, and begun on divalproex, eventually titrated to 500 mg qhs (serum level 98 μg/mL). RC responded partially with less irritability, insomnia, and racing thoughts. However he still experienced mood lability, hyperactivity, inattention, and significant depressed mood. Sustain release methylphenidate 20 mg QD was added back to his regimen along with lithium carbonate 300 mg b.i.d. Over the next 3 weeks, R.C.'s condition improved, with an euthymic mood, decreased mood lability, and decreased hyperactivity. Lithium was discontinued after 1 month of treatment, however, due to an elevated serum thyroid stimulating hormone (TSH) level of 7.9 μIU/mL. Levothyroxine 0.1 mg was started, resulting in a TSH level of 2.1 μIU/L in 1 month, and was maintained at this dose. R.C. continued in a euthymic condition for 2 months, until, during a trip to Europe, he experienced severe initial insomnia and began sleeping only 3 hours per night. After 1 week, he was floridly manic, with increased speech, euphoric mood, hyperactivity, grandiosity, eccentric behavior, and poor judgment, including yelling at strangers in museums and having paranoid delusions. Upon his return to the United States, he was evaluated at our clinic, and he had a Young Mania Rating Scale (YMRS) score of 25 and Global Assessment of Function (GAF) score of 55. Olanzapine 2.5 mg qhs was added to his current medications. After 2 days, in which he slept a total of 24 hours, his condition improved dramatically, with a resolution to his baseline condition. He began to sleep normally, achieving 9 hours of sleep per night. His YMRS after 4 days was 4. His Clinical Global Impression (CGI) was rated as Markedly Improved. Thyroid studies were performed to rule out iatrogenic hyperthyroidism: serum TSH level was 3.5 μIU/mL and free thyroxine level was 1.1 ng/dL, both within the normal reference range.

Over the next month, RC continued to do well, but gained 18 lb. This weight gain was a 22% increase from his initial weight of 81 lb, but placed him at his ideal body weight (perhaps due to prior low weight secondary to appetite suppression with methylphenidate treatment). Olanzapine was then discontinued to prevent further weight gain, and R.C. continued to do well at a 1-month follow-up.

Case 2

M.L. was a 10-year-old boy diagnosed with ADHD and bipolar disorder, being treated with divalproex (serum level 102 μg/mL) and lithium carbonate (0.7 mEq/L). Psychiatric family history revealed his mother's having bipolar disorder. He was receiving home schooling due to a past protracted hospitalization and was doing well for the prior 3 months. However, during his parents' divorce proceedings, he began to experience bursts of giddiness, irritability, racing thoughts, and unusual behavior. He became extremely dysphoric and began having intermittent paranoid delusions that unspecified people were planning to hurt him.

Upon presentation in our clinic, his YMRS score was 22, GAF was 55, and he was diagnosed as acutely

manic. Olanzapine 2.5 mg qhs was added to his regimen, which was increased to 5 mg qhs the next day. M.L. experienced mild sedation and increased sleep over the next 3 days. By the fifth day, he was noticeably improved, with decreased rate of speech and decreased racing thoughts, and he remained only mildly irritable. There were no further episodes of psychotic behavior. YMRS score was 5, and M.L. was considered Markedly Improved on the CGI. M.L. was continued on olanzapine 5 mg qhs for 1 week and then eventually tapered to 2.5 mg qhs. He had no further manic episodes for 2 months subsequently on the same medication regimen. During treatment with olanzapine, he reported initial sedation for the first 3 days and no other adverse effects.

Case 3

D.T. was a 9-year-old boy who presented to our clinic with a prior diagnosis of depression and ADHD. His prior psychiatrist had prescribed sertraline 150 mg QD and sustained release methylphenidate 20 mg b.i.d. for the past 2 years and, for unclear reasons, gabapentin 300 mg t.i.d. for the past month. However, D.T. was experiencing racing thoughts, hyperactivity, irritability, and severe initial insomnia. All medications were tapered over 2 weeks and eventually discontinued. However, he continued to display manic symptoms for 2 weeks and was diagnosed with bipolar disorder NOS, as it was unclear whether or not these agents had precipitated the mania. Divalproex was started and titrated up to 250 mg QAM and 375 mg qhs, with a serum level of 78 μg/mL over the next 4 weeks. There was mild improvement in initial insomnia and irritability, but D.T. continued to have episodic bursts of extreme irritability as well as racing thoughts and hyperactivity. His YMRS score at this time was 19.

After D.T.'s parents declined institution of a second mood stabilizer (lithium or carbamazepine), olanzapine 2.5 mg was added at bedtime. The parents reported dramatic improvement in D.T.'s condition after 3 days. Upon reevaluation after 7 days, D.T. was noticeably less irritable, appearing euthymic, and reported cessation of racing thoughts. He was not hyperactive and was compliant with the psychiatric evaluation for the first time. His YMRS score was 1, and his CGI was rated as Markedly Improved. D.T. continued on olanzapine and divalproex and was doing well 6 weeks after institution of olanzapine. He gained 10 lb, from an initial weight of 79 lbs., and continued to experience mild daytime sedation.

DISCUSSION

We report on three prepubertal children with bipolar disorder and acute mania who all responded dramatically within 5 days to augmentation of their mood stabilizers with olanzapine. They were all managed as outpatients, and all were maintained on lithium and/or valproate during the olanzapine trial. This rapidity of response to olanzapine in acute mania is similar to two adult case reports by Ketter et al. (1998). All three patients also experienced considerable sedation in the first few days after beginning olanzapine treatment and slept more than their normal amount (over 10 hours per night). Disruption of sleep-wake cycles has been purported to be involved in triggering mania or exacerbating rapid cycling in bipolar patients (Kasper and Wehr 1992; Wehr et al. 1982), and restoration of normal sleep patterns may resolve mania fairly rapidly (Nowlin-Finch et al. 1994; Robertson and Tanguay 1997). Thus, resolution of their manic symptoms may have also been facilitated by a return of a normal sleep cycle. This may have been especially pertinent in case 1, in which R.C. suffered jet lag and subsequent disruption of his sleep cycle while in Europe.

Furthermore, all three children were maintained on their previous mood stabilizers during the olanzapine trial. In case 3, it is possible that D.T. may have continued to have increasing benefit from divalproex during treatment with olanzapine, as he had only begun on divalproex 4 weeks prior. However, the rapid time course of improvement with olanzapine addition suggests this agent was important in achieving remission. The two other patients had been maintained on a constant dose of lithium and divalproex for at least 2 months prior to their manic episode, again suggesting the role of olanzapine in their rapid remission.

The adverse effects experienced by our patients after olanzapine addition were predominantly sedation and weight gain. This is consistent with case reports of olanzapine use in prepubertal children, in

which 50% gained at least 16 lb (Krishnamoorthy and King 1998). In a larger trial of olanzapine in bipolar adults, the mean weight gain over 4 weeks was 4.6 lbs (2.1 kg; Tohen et al. 1999), substantially less than the 10 or 18 lb reported here. However, the children in our report were also being treated with either lithium or divalproex, both of which may have contributed to the weight gain. It remains to be seen if younger children are in some way more susceptible to this particular adverse effect of olanzapine.

Other agents have historically been used temporarily in conjunction with standard mood stabilizers (i.e., lithium or valproate) to treat acute manic states. Typical antipsychotics, such as haloperidol or chlorpromazine, have a long history of use in both acute and chronic treatment of mania (Tohen and Zarate 1998). Benzodiazepines, such as lorazepam or clonazepam, have also been used adjunctively. The efficacy of these medications supports the possibility of sedation or restoration of sleep as a major contributor to resolution of acute mania. However, typical antipsychotics have a significant adverse effect profile, including potential for extrapyramidal symptoms and tardive dyskinesia. Benzodiazepines do not share these adverse effects, but in children may cause behavioral disinhibition (Graae et al. 1994; Reiter and Kutcher 1991). Olanzapine, as of yet, does not appear to have significant potential for these particular adverse effects, suggesting that it may be an attractive alternative to typical antipsychotics or benzodiazepines for acute, or possibly chronic, treatment of childhood mania.

The rapid response of all three acutely manic children in this report to olanzapine addition supports the possibility of olanzapine's having antimanic or mood stabilizing properties. Further research needs to be conducted to determine if olanzapine is effective in children with acute mania, whether in monotherapy or adjunctive therapy to conventional mood stabilizers.

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