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Effect Size of Lithium, Divalproex Sodium, and Carbamazepine in Children and Adolescents With Bipolar Disorder

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ABSTRACT

Objective: To develop effect sizes for 3 mood stabilizers-lithium, divalproex sodium, and carbamazepine-for the acute-phase treatment of bipolar I or II disorder, mixed or manic episode, in children and adolescents aged 8 to 18 years.

Method: Forty-two outpatients with a mean age of 11.4 years (20 with bipolar I disorder and 22 with bipolar II disorder) were randomly assigned to 6 weeks of open treatment with either lithium, divalproex sodium, or carbamazepine. The primary efficacy measures were the weekly Clinical Global Impression Improvement scores and the Young Mania Rating Scale (Y-MRS).

Results: Using a >=50% change from baseline to exit in the Y-MRS scores to define response, the effect size was 1.63 for divalproex sodium, 1.06 for lithium, and 1.00 for carbamazepine. Using this same response measure with the intent-to-treat sample, the response rates were as follows: sodium divalproex, 53%; lithium, 38%; and carbamazepine, 38% ($[chi]^2_2 = 0.85$, $p = .60$). All 3 mood stabilizers were well tolerated, and no serious adverse effects were seen.

Conclusions: Divalproex sodium, lithium, and carbamazepine all showed a large effect size in the open treatment of children and adolescents with bipolar I or II disorder in a mixed or manic episode.

Bipolar disorders (BPD) are severe and persistent disorders occurring in approximately 1% of adults (Myers et al., 1984). These disorders are now recognized as equally as prevalent in children and adolescents, with an estimated prevalence of 1% (Kashani et al., 1987; Lewinsohn et al., 1995). BPD seriously disrupts the lives of children and adolescents; studies show increased rates of both suicide attempts and completions, poorer academic performance,

disturbed interpersonal relationships, increased rates of substance abuse, legal difficulties, and multiple hospitalizations (Akiskal et al., 1985; Lewinsohn et al., 1995; Strober et al., 1995).

Current clinical practice is to treat manic episodes in children and adolescents with BPD much as one would adults with BPD (i.e., mood stabilizers and antipsychotic agents) (Hirschfeld, 1994; Kafantaris, 1995; McClellan and Werry, 1997). Despite the increasing use of mood-stabilizing agents such as lithium, carbamazepine, and divalproex sodium in bipolar children and adolescents, there are few published, placebo-controlled, double-blind studies of the efficacy of any mood-stabilizing agent in children and adolescents with BPD (Kafantaris, 1995).

Lithium is the oldest and most well-studied mood stabilizer for adults with BPD, and controlled studies have demonstrated its efficacy in the treatment and prevention of manic episodes in adults (Bowden, 1998; Goodwin and Jamison, 1990; Hirschfeld, 1994). There also have been more studies on the use of lithium in bipolar children and adolescents than any other mood stabilizer. However, the majority of these studies were carried out with variable assessment protocols in small samples without placebo control groups (Brumback and Weinberg, 1977; DeLong and Nieman, 1983; McKnew et al., 1981; Varanka et al., 1988) or in larger mixed samples (BPD, attention-deficit/hyperactivity disorder [ADHD], conduct disorder) without adequate controls (DeLong and Aldershof, 1987). The average number of subjects in each of these studies was 18; response rates ranged from 33% to 80%.

In the only well-controlled, prospective study, which used *DSM-IV* criteria for BPD, Geller et al. (1998) administered lithium in a double-blind and placebo-controlled fashion to 25 adolescents with BPD and a secondary substance dependency disorder (most had alcohol and marijuana dependence). In this study the adolescent's diagnosis of BPD preceded the substance abuse by several years. After 6 weeks of treatment, the subjects treated with lithium showed a significant decrease in their substance abuse and a significant improvement in their global assessment of functioning. This study suggested that lithium may be efficacious in the treatment of bipolar adolescents with comorbid substance abuse.

Divalproex sodium is another mood-stabilizing agent that has demonstrated efficacy in adults with BPD (Bowden et al., 1994; Pope et al., 1991). A review of adult divalproex sodium studies of the acute treatment of mania showed an average response rate of 56% (Janicak et al., 1993). There are 7 uncontrolled reports of divalproex sodium use in bipolar children and adolescents: 3 case reports (Kastner et al., 1990; Kastner and Friedman, 1992; Whittier et al., 1995) and 4 case series (Papatheodorou and Kutcher, 1993; Papatheodorou et al., 1995; West and McElroy, 1995; West et al., 1994). The average number of subjects was 5. These open studies suggest a wide variability of treatment responses, the frequent use of concomitant antipsychotic agents, and extensive comorbidity. Therefore, while divalproex sodium shows promise as a possible treatment for pediatric BPD based on adult experiences and limited open trials in adolescents with BPD, no one has demonstrated its efficacy in a randomized, controlled trial. Nor has anyone compared divalproex sodium to lithium or carbamazepine in this population.

Carbamazepine has been found to be effective as a second-line treatment of acute mania in adults (Janicak et al., 1993) but has never been studied in a controlled manner with bipolar children and adolescents. The majority of carbamazepine reports in the literature are with children and adolescents with ADHD or conduct disorder, some of whom also had neurological disorders (Cueva et al., 1996; Evans et al., 1987; Kafantaris et al., 1992; Puente, 1975).

This pilot study aimed at developing effect sizes for lithium, divalproex sodium, and carbamazepine in the acute-phase treatment of bipolar I or II children and adolescents during a mixed or manic episode. Typically, effect size is a measure of treatment effect and is calculated as the difference in sample means divided by their common standard deviation (Cohen, 1988). Effect sizes are independent of sample sizes and are important first steps in designing an efficacy trial. Furthermore, this study provided information on tolerability and acceptability of these 3 agents, as well as estimates of when responses occur.

METHOD

Study Population

Subjects included in this report were recruited from the outpatient Pediatric Psychiatry Center at Children's Medical Center of Dallas. This study was approved by the University of Texas Southwestern Medical Center at Dallas Institutional Review Board. Informed consent was obtained from the subjects and their guardians after the nature of the experimental treatment was explained. Subjects had to meet *DSM-IV* (American Psychiatric Association, 1994) inclusion criteria for bipolar I or II disorder during a mixed or manic episode and be 6 to 18 years old. They had to score >=14 on the Young Mania Rating Scale (Y-MRS) (Young et al., 1978). Subjects had to suffer no current general medical illnesses that required medication and have normal intelligence as estimated by their academic performance and placement. Excluded were those with a current or lifetime diagnosis of schizophrenia, obsessive-compulsive disorder, or autistic disorder and those with substance abuse or dependence, a history of organic brain disease, and current use of psychotropic agents within the 2 weeks preceding randomization, including neuroleptics, monoamine oxidase inhibitors, stimulants, and antidepressants. Subjects receiving depot neuroleptics or fluoxetine had to be medication-free for the previous month.

Pre- and Posttreatment Assessments

Patients were seen for a 2-week evaluation period during which they underwent structured interviews and laboratory testing. The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997) was administered to the parent (usually the mother) and child separately by one research assistant who had established reliability and was verified by the principal investigator (R.A.K.), who is board-certified in child and adolescent psychiatry. The Family History Research Diagnostic Criteria (Andreasen et al., 1977) was administered to the parent about the patient's first- and second-degree relatives. Subjects' socioeconomic status was assessed using the Hollingshead Two Factor Index of Social Position (Hollingshead and Redlich, 1958). Subject's level of functioning was rated using the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983), and the subject's family was rated using the Family Global Assessment Scale (D. Mrazek, unpublished, 1992). The patient's parents also completed the Achenbach Child Behavior Checklist (McConaughy et al., 1988) and the Conners Parent Questionnaire (Conners, 1986). Comorbid psychiatric disorders were considered present if subjects met *DSM-IV* criteria using the K-SADS-P (Present Episode) at the time of the structured interview and after they had been medication-free for at least 2 weeks. The primary efficacy measures were the weekly Bipolar Clinical Global Impression (CGI-BP) on the Improvement subscale (Spearing et al., 1997) and the Y-MRS. Response was defined as a change from baseline to endpoint, with a score of 1 or 2 on the CGI-BP or a >=50% improvement in Y-MRS score. The first author (R.A.K.), who had demonstrated excellent interrater reliability and validity using the CGI in a previous childhood depression study (Emslie et al., 1997), completed all efficacy ratings.

Table 1 presents the demographic and severity data. There were significantly more males in the prepubertal group (73%) and significantly more males with BPD II (77%). The subjects' mean CGAS score was 48.2. The bipolar I subjects had a significantly lower CGAS score (45) than the bipolar II subjects (52). Table 2 shows the *DSM-IV* current, comorbid, nonmood diagnoses. There were high rates of other psychiatric disorders, particularly ADHD (71%), oppositional defiant disorder (38%),

and anxiety disorders (17%).

TABLE 1 Demography, Severity, and Clinical Characteristics

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TABLE 2 Percent (*n*) Current Comorbid *DSM-IV* Nonmood Disorders

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Study Protocol

The design was a 6-week random assignment, open, prospective investigation. After a 2-week assessment period during which all medications were tapered off, if subjects met inclusion/exclusion criteria they were randomly assigned, using the minimization method, to treatment with either lithium, carbamazepine, or divalproex sodium. The minimization method is based on the idea that the next patient to enter the trial is given whichever treatment would minimize the overall imbalance between groups at that stage of the trial (Altman, 1991). Subjects were stratified on the basis of age (< 13 years and > 13 years), gender, and the presence or absence of ADHD. Dose and serum level ranges were monitored with levels after 1, 2, and 4 weeks of treatment. After randomization, subjects returned weekly for 6 consecutive weeks of open treatment.

Recruitment

Through clinical and research referrals, 242 telephone calls were received. Of these, 228 were deemed appropriate for a telephone screen; 140 did not meet study exclusion or inclusion criteria. The remaining 88 were screened in person; 44 did not meet study criteria, and 2 refused randomization. Of the 42 subjects randomized, there were 3 Hispanic Americans and 39 white Americans.

Treatment

Lithium dosage was selected on the basis of the weight algorithms devised by Weller et al. (1986) with a starting dose of approximately 30 mg/kg per day in 3 divided doses. The initial dose of carbamazepine was 15 mg/kg per day in 3 divided doses, whereas the initial dose of divalproex sodium was 20 mg/kg per day, also in 3 divided doses. Serum levels of the different mood stabilizers were measured after 1 week of treatment, and the dosages were then titrated until the following serum levels were reached: lithium, 0.8 to 1.2 mEq/L; carbamazepine, 7 to 10 µg/L; divalproex sodium, 85 to 110 µg/L. Chlorpromazine, 10 to 50 mg/day, was allowed as a "rescue medication" 2 to 3 times per week for sleep or agitation during the first 2 weeks of treatment. Three subjects, one in each treatment group, required low doses of chlorpromazine, typically 10 to 25 mg, for difficulty sleeping for several days during the first 2 weeks of the protocol. Compliance was measured by a pill count at every visit and measurement of serum levels of the different mood stabilizers after 1, 4, and 6 weeks of treatment.

All subjects were medically well as judged by medical history, physical examination, and routine blood tests (e.g., thyroid, liver, and renal function tests; urinalysis; complete blood cell counts; and serum pregnancy tests in females of childbearing age). Laboratory studies were repeated at the end of the acute treatment period, usually week 6. Subjects were seen weekly with their parent(s), and at each visit they were rated on the Y-MRS, the CGI-BP scale, a side effects scale, and the K-SADS Mania and Depression items. No subjects received individual, family, or group therapy. Subjects who missed more than 3 consecutive days of medications were discontinued from the protocol.

Statistical Analysis

Data from the first 41 subjects who were randomized and who completed at least 1 week of treatment were analyzed by a modified intent-to-treat sample analysis, and an adequate treatment sample comprised the 32 subjects who completed at least 5 weeks of treatment. The modified intent-to-treat sample included all subjects who had completed at least 1 week of treatment, whereas the adequate treatment sample included those subjects who had completed at least 5 weeks of treatment. A subject's responder/nonresponder status was determined on the basis of the weekly CGI-Improvement score (response was defined as a score of 1 or 2 on the CGI-BP, "much" or "very much improved" at endpoint) or the weekly Y-MRS scores (response was defined as >=50% improvement from the baseline Y-MRS score at endpoint). Responder status was compared between groups using a $[chi]^2$ test.

A random regression analysis using the intent-to-treat sample (Gibbons et al., 1993) was used to assess differences in change over time in the Y-MRS among the lithium, carbamazepine, and divalproex sodium groups. The effects of several covariates along with interactions were also investigated: the baseline score on the Y-MRS, age, gender, presence of ADHD, and diagnosis (BPD I versus BPD II). The effect size for each treatment using the Y-MRS change from baseline to exit was calculated per Cohen (Cohen, 1988). A *t* test was used to compare the mean serum levels of mood stabilizers between the responders and nonresponders in each treatment group using both the Y-MRS and CGI response criteria.

RESULTS

Of 42 subjects randomized, 6 completed less than 4 weeks of treatment, 10 completed 5 weeks, 13 completed 6 weeks, 10 completed 7 weeks, and 3 completed 8 weeks. Differences in length of treatment were due to some subjects' inability to make scheduled, weekly follow-up visits. A 2-way analysis of variance showed

that time in study did not vary significantly among treatment groups (p = .742), with all groups being in the study about 6 weeks (the carbamazepine group with a mean length of treatment of 5.6 weeks, divalproex sodium group 5.8 weeks, and lithium group 6.0 weeks). Also, the responders did not differ from nonresponders (p = .507) in their length of treatment (mean length of treatment was 5.7 weeks for responders versus 6.0 weeks for nonresponders).

Of the 6 subjects who completed less than 4 weeks of treatment, 2 adolescent subjects stopped lithium after 2 weeks of treatment for unspecified reasons; 1 prepubertal subject developed a rash after 1 week of carbamazepine treatment; 1 subject treated with divalproex sodium was arrested for heroin use at week 3; and 2 adolescent females, 1 on carbamazepine and 1 on divalproex sodium, discontinued their mood stabilizer at week 5 for unspecified reasons.

Effect Sizes

Using the change from baseline to endpoint in the weekly Y-MRS scores in the modified intent-to-treat sample, we found the following effect sizes (Cohen d) for each group: divalproex sodium, 1.63; lithium, 1.06; and carbamazepine, 1.00. The mean change from baseline to exit in the Y-MRS scores was 14.53 in the divalproex sodium group, 9.46 in the lithium group, and 9.00 in the carbamazepine group. The pooled standard deviation was 12.62.

Intent-to-Treat Sample

Data were analyzed by a modified intent-to-treat sample analysis using the 41 subjects who had completed at least 1 week of treatment. Table 3 shows the number of responders in each treatment group at exit with each mood stabilizer. There was no significant difference between the 3 groups when we used as the criterion a CGI-Improvement score of 1 or 2 ($[chi]^2_2$ = 0.66, p = .72) or a 50% improvement in Y-MRS score ($[chi]^2_2$ = 0.85, p = .60). When we used the CGI and Y-MRS criteria, the divalproex sodium group had response rates of 40% and 53% and the lithium group had response rates of 46% and 38%. The carbamazepine group had the fewest responders (31% using the CGI criterion, 38% using the Y-MRS criterion).

TABLE 3 Intent-to-Treat Sample: Percentage of Responders in Each Treatment Group by Response Variable

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Figure 1 illustrates the pattern of response in each treatment group's mean Y-MRS scores in those subjects who were categorized as responders in the intent-to-treat sample based on a >=50% improvement from baseline to end-point in their Y-MRS scores. In the divalproex sodium group, we sometimes observed an increase in bipolar symptoms after 3 weeks of treatment, when parents would report that a subject's manic symptoms appeared "worse." These symptoms would generally resolve by week 4, and the subject would continue to improve if the parents could tolerate this brief period of symptom recrudescence.

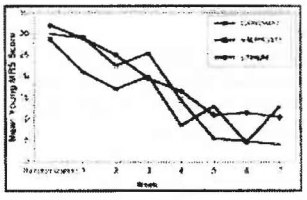

Fig. 1 Responders' mean weekly Young Mania Rating Scale (MRS) scores.

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Cumulative time to response by treatment group and week was calculated using the mean Y-MRS scores in those subjects who were categorized as responders in the intent-to-treat sample based on a >=50% improvement from base-line to that week in their Y-MRS scores. Subjects treated with lithium continued to respond until week 8, whereas no new subjects responded after 5 weeks of treatment in the carbamazepine group and after week 6 in the divalproex sodium group.

Adequate Trial Sample

Data were also analyzed by an adequate trial sample using the 32 subjects who had completed at least 5 weeks of treatment. We found no significant difference between the 3 groups when we used as the criterion a CGI-Improvement score of 1 or 2 ($[chi]^2_2$ = 0.063, p = .97) or a 50% improvement in Y-MRS score ($[chi]^2_2$ = 0.456, p = .79). The carbamazepine group had the fewest responders (44% using the CGI and the Y-MRS criteria). The divalproex sodium group had response rates of 46% and 54% and the lithium group had response rates of 50% and 40% when the CGI and Y-MRS criteria were used.

Random Regression Analysis

In this random regression analysis, only diagnosis made a significant addition to the model. The final model contained terms for treatment group, week, group-by-week interaction, and diagnosis (BPD I versus II). A significant change over time was found (p = .0001). However, the group-by-week interaction was not significant (p = .22), indicating similar changes over time for each mood stabilizer (equal slopes). Those with BPD I had a higher estimated starting Y-MRS score (mean 24.6) than the BPD II (mean 19.7) subjects for all groups (p = .0002), but the change over time was the same for both diagnoses. Although within each diagnosis (bipolar I versus II) the 3 groups had about the same estimated beginning Y-MRS, subjects improved most rapidly in the divalproex sodium group (2.56 points per week) and less rapidly in the other 2 groups (about 1.5 points per week). The differences in slope between the divalproex sodium group and each of the other 2 groups were not significant (p = .16 and p = .12).

Serum Mood Stabilizer Levels

Adequate serum levels were defined as follows: >=0.8 mEq/L for lithium, >=7.0 µg/L for carbamazepine, and >=80 µg/L for sodium divalproex. In the

lithium-treated group, the mean time to reach an adequate serum level was 3.34 ± 2.44 weeks and the mean lithium level at the end of the treatment period was 0.88 + 0.35. In the carbamazepine group, the mean time to reach an adequate serum level was 2.53 ± 1.45 weeks and the mean carbamazepine level at the end of the treatment period was 7.11 ± 1.79.

In the sodium divalproex group, the mean time to reach an adequate serum level was 3.88 ± 1.72 weeks and the mean sodium divalproex level at the end of the treatment period was 82.8 ± 22.92. There were no significant differences in serum levels between the responders and nonresponders in any of treatment groups.

Side Effect Ratings

Mean side effects scores were calculated for each treatment group (Table 4). Nausea was the most common side effect across all 3 treatment groups, with the carbamazepine group showing the highest rate (46%). One subject developed a rash during week 2 of treatment with carbamazepine and elected not to continue in the study. The majority of side effects were mild to moderate and tolerated by most subjects. There were no serious adverse effects necessitating hospitalization.

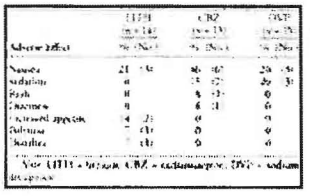

TABLE 4 Adverse Effects by Treatment Group

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DISCUSSION

These data revealed that in children and adolescents with bipolar I and II disorder, mixed or manic episode, there were large effect sizes for all 3 of the mood stabilizers studied. Cohen has suggested that in the behavioral sciences an effect size of 0.2 indicates a small effect, 0.5 a medium effect, and >0.8 a large effect (Cohen, 1988). A medium effect size is one that a trained observer will recognize in a clinical situation. The response rates for each mood stabilizer varied depending on the outcome measure. The CGI change scale used was designed to force a choice between either "very much improved" or "much" (a positive response) versus the next CGI response category of minimally improved (a nonresponder). This CGI change score is similar to what clinicians use to determine whether to continue a medication; if the patient is much or very much improved, then it is reasonable to continue the medication; if not, then many times a change is made after 4 to 6 weeks of treatment. The other response variable we chose (>=50% improvement from baseline to endpoint on the Y-MRS score) is based on a continuous measure which, some would argue, is more sensitive to change.

Perhaps the most balanced way of looking at these response rates is by examining the mean of both response variables in both the intent-to-treat and the adequate trial samples, which yield response rates of 46% to 50% for divalproex sodium, 42% to 45% for lithium, and 34% to 44% for carbamazepine. Bowden et al. (1994) reported that marked improvement occurred at day 21 in 49% of their lithium-treated group and 48% of their divalproex sodium-treated group. Geller et al. (1998) reported a 46% response rate to lithium at week 6 using a categorical cutoff score on the CGAS of >=65 for response. Thus, our response rates for both lithium and divalproex sodium are in the same range as other reports in adults and adolescents. But it is important to recognize that more than half of these patients did not respond to monotherapy with any of these 3 mood stabilizers. Our clinical experience with these patients is that they frequently respond to a combination of mood stabilizers, atypical antipsychotic agents, and/or stimulants. We are exploring these combinations in a 6-month continuation treatment protocol with these patients.

With a larger sample size these differences may turn out to be statistically significant. But with response rates that we found for each mood stabilizer (42% for lithium and 46% for sodium divalproex), it would take a sample size of approximately 1,200 subjects to detect a significant difference between the divalproex sodium and lithium groups at a .05 level of significance using a response criterion of a > 50% improvement from the baseline Y-MRS score. Such a study is not feasible because of the cost and large number of bipolar subjects needed. Compliance was a major problem in our bipolar adolescents, with a significant proportion (31%) failing to comply with any mood stabilizers after several weeks of treatment despite their initial assent to do so.

In some patients treated with divalproex sodium, we sometimes observed an increase of bipolar symptoms after 3 weeks of treatment that would typically resolve the following week. A similar phenomenon has not been observed among adult bipolar patients treated with divalproex, and it suggests a transitory difference between adults and children in their neurochemical response to divalproex sodium. This also suggests that clinicians should not discontinue treatment with divalproex sodium if a worsening in bipolar symptoms is seen after after 2 to 3 weeks of treatment, but rather continue for another several weeks before deciding to discontinue treatment with divalproex sodium.

Finally, our cumulative time to response data suggests that for lithium carbonate a treatment period of at least 8 weeks is adequate, whereas for sodium divalproex and carbamazepine 6 weeks appears adequate.

Limitations

The small sample size and the lack of a placebo control group limit this study. Also, the child and adolescent psychiatrists completing the outcome ratings were not blind to the subject's medication status. However, this study is the first to compare these 3 mood stabilizers in children and adolescents with BPD. Larger placebo-controlled trials are needed in these seriously ill and difficult-to-treat patients.

Clinical Implications

Divalproex sodium, lithium, and carbamazepine all showed a large effect size, as defined by Cohen (1988), in the treatment of children and adolescents with bipolar I or II disorder in a mixed or manic episode. These mood stabilizers were for most part well tolerated, and response rates were similar to those of adult mania studies.

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