Original Research

A Consecutive Series of Treated Affected Offspring of Parents With Bipolar Disorder: Is Response Associated With the Clinical Profile?

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Objective: In adults with established bipolar disorder (BD), differential response to mood stabilizers has been associated with the clinical profile. Long-term treatment studies of youth with BD are lacking. This paper provides longitudinal observations of response to mood stabilizers early in the course of illness in youth with BD.

Method: We report on 15 research patients who, as adolescents, met DSM-IV lifetime criteria for a bipolar spectrum disorder and required long-term treatment. These youths derived from families with one parent having BD whose course and long-term treatment response were determined in accordance with research criteria. The patients were offered lithium, and if they failed to respond or refused it, they were treated with either an anticonvulsant or an atypical antipsychotic. Using a validated scale, an independent rater retrospectively blindly scored the response to long-term treatment.

Results: Those patients who stabilized on lithium derived from lithium-responsive families, whereas those who stabilized on an antipsychotic derived from lithium-nonresponsive families. The clinical course in the youths stabilized by lithium differed from that in the youths stabilized by an atypical antipsychotic.

Conclusions: Our findings suggest that the clinical profile may help in selecting effective stabilizing treatment and that a proportion of youth can be stabilized on monotherapy. This is a small case series with nonrandom treatment assignment, and the findings should be considered tentative.

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Clinical Implications

- The clinical profile of the affected offspring may help to predict response to a given mood stabilizer.
- Offspring response to a mood stabilizer is associated with that of the parent with BD.
- A subset of youth with BD can be stabilized with selected monotherapy.

Limitations

- Although carefully studied prospectively, the observations were based on a small series of affected offspring who were not randomly assigned to treatment.
- The youths with BD included in this series came from well-characterized families to identify factors associated with long-term treatment response and were not selected for generalizability.
- Although the response was scored blindly and retrospectively by an independent rater using a validated scale, the actual long-term treatment was monitored in an open fashion.

Key Words: *bipolar illness, early onset, high risk, mood stabilizers, family history, treatment response, heterogeneity*

Evidence from community,[1,2] clinical,[3–5] and high-risk[6–10] studies has shown that early-onset BD continues to recur through adolescence and into adulthood. Further, studies have demonstrated that an elevated risk for completed suicide continues throughout the course of untreated illness[11,12] and may be increased in the early stages of illness.[13,14] In addition, there is evidence of a burden-of-illness effect with respect to cognitive deficits and, possibly, structural changes in the brain.[15–19] It is therefore imperative to find early treatments that can prevent recurrences and decrease the associated morbidity and mortality.

Although there are accruing data on the efficacy of acute antimanic treatments,[20–24] virtually no data exist on the efficacy of long-term mood-stabilizing treatments in youth with BD. Early case reports supported the effectiveness of extended lithium treatment in children and adolescents.[25–28] Some of these reports included offspring manifesting varied psychopathology but deriving from lithium-responding parents with BD, whereas others included youth suffering from syndromes consistent with BD. The first published placebo-controlled trial of short-term lithium treatment in a heterogeneous group of youth with BD and secondary substance use reported that lithium had benefits in terms of Global Assessment of Functioning scores and a decrease in substance use.[29] In a naturalistic follow-up study of adolescent patients with mania, Strober and colleagues[30] found a significantly increased relapse rate in nonadherent patients and in those discontinuing lithium over the 18-month observation period, compared with those complying with lithium therapy. A more recent naturalistic, prospective, follow-up study of adolescent patients with mania concluded that lithium prophylaxis delayed the mean time to relapse and reduced the overall number of recurrences.[31]

However, there is a widely held assumption that lithium will not be an effective prophylactic agent for many patients, given that BD in youth is often described as atypical, with a high rate of negative predictors for lithium response, including comorbidity, mixed manic episodes, and a nonremitting course.[32,33] It is also commonly speculated that combinations of mood stabilizers will be needed in youth with BD, owing to the severity and complexity of the disorder.[34] These assumptions are yet to be tested.

Abbreviations used in this article

BD	bipolar disorder
CGI	Clinical Global Impression
SADS	Schedule for Affective Disorders and Schizophrenia
SADS-L	SADS-Lifetime Version

When treating adolescents with mood disorders, clinicians are encountering not only a lack of systematic studies but also a dilemma in that clinical trials of antidepressants that proved to be markedly efficacious in adults with depression have led mostly to negative outcomes in youth with depression.[35–39] In addition, a recent randomized, double-blind, controlled study of oxcarbazepine in the treatment of mania in children and adolescents proved negative.[40] Therefore, actual studies must be done in the early-onset population and the findings not simply generalized from studies of adults with established illness.

The efficacy of stabilizing treatments can only be definitively proven in a prospective, well-designed, properly conducted randomized clinical trial. However, such designs are challenging, given that recent studies indicate that BD is markedly heterogeneous in clinical manifestations and in treatment response[41–44] and that the earliest manifestations in youth usually meet criteria for various diagnoses. Thus effective treatments for afflicted adolescents will not be found by further clinical trials in heterogeneous populations, and it would be ethically unacceptable to perform investigations in diagnostically mixed groups with varied psychopathology.

To design appropriate treatment studies well, one requires a good knowledge and appreciation of the important variables that affect outcome. In the history of medicine, careful longitudinal study of individual patients has often provided the required insights necessary to properly formulate hypotheses and to inform study design. Thus it may be essential to precede randomized controlled clinical trials with careful longitudinal study of individual patients. For example, evidence from adult studies shows that long-term response to mood stabilizers clusters in families[45] and is related to the clinical profile of the patients, including their family history and clinical course.[42,46] Such clinical factors may need to be considered in treatment studies involving adolescent patients with BD.

As an initial step in this direction, we present a case series of patients from an ongoing, prospective, high-risk study.[7,47] The purpose of the high-risk study was to compare outcomes in clinically homogeneous subgroups of offspring identified on the basis of their parent's unequivocal response to a long-term monotherapy, not to observe a representative sample of youth with BD. The children entered the high-risk study because they had a unilineal family history of BD (that is, one affected parent and one well parent). The offspring included in this case series met DSM-IV criteria for early-onset bipolar spectrum disorder and were identified as requiring treatment. They were offered standard treatment with lithium, and if they failed or refused, they were switched to a stabilizer that was effective for their parent and (or) that fit their clinical profile.

The open treatment was carefully and systematically documented. Subsequently, an independent expert used a standardized rating scale to blindly analyze the outcome.

Method

Youth With BD

As part of an ongoing prospective high-risk study,[7] the principal investigator clinically assessed consenting adolescent offspring of identified families (described below), using the Kiddie-SADS-Present and Lifetime Version interviews[48] and blinded to family affiliation and treatment response. Offspring were then reassessed annually and at any time that symptoms developed. From this high-risk cohort, we report on 15 offspring who met lifetime DSM-IV criteria for a bipolar spectrum disorder. A consensus team of 2 or more independent research psychiatrists (at least one of whom was a child and adolescent subspecialist) determined final diagnosis and clinical characteristics, including the nature of the clinical course. The team was given all relevant clinical information but remained blind to any information about the family of origin and treatment response of the parent or offspring. We included 2 offspring with chronic depressive disorder because of the high likelihood of latent BD, given their family history,[49,50] and because of previously failed trials of antidepressant treatment.

Family History

For participation in the high-risk study, the proband parent had to have met DSM-IV criteria for BD I on the basis of SADS-L interviews.[51] The diagnosis was confirmed by blinded team consensus review that included 2 or more research psychiatrists and used all relevant clinical information.[7,47] Unequivocal response to long-term lithium treatment was determined in accordance with research protocols described in detail in earlier publications.[47,52,53] In essence, these parents were excellent lithium responders: they remained free of recurrences during the whole period of adequate lithium treatment. However, if the parent was identified as a lithium nonresponder, he or she was treated sequentially with monotherapies until an effective stabilizing treatment was found. In all cases, the other (nonproband) parent was unaffected for a lifetime major psychiatric disorder on the basis of SADS-L interviews.

Long-Term Treatment

Although polypharmacy is common in many clinical settings, we used one mood stabilizer to treat offspring with BD to assess whether they could be maintained on monotherapy and to evaluate the response to individual medications. We advised the adolescents that lithium was the standard, evidence-based, long-term treatment for adults with bipolar illness but that there were no applicable data on long-term treatments for adolescents. Their decision whether to accept lithium or another treatment reflected this advice as well as the information they obtained about the alternatives. In all cases, the individual patients made the final decision. Although they were aware of the agent that helped their affected parent, our observations suggested that this information did not appreciably influence their choice (see Discussion). Lithium was titrated into the therapeutic range (at or above 0.7 mmol/L) and monitored in accordance with clinical guidelines.

If the offspring failed on a trial of adequate lithium treatment (determined by a major recurrence with sufficient blood levels), they were offered an anticonvulsant or atypical neuroleptic. The choice between the latter 2 alternative agents was based on the parent's treatment response, the offspring's clinical profile, and the acceptability to the patient (Table 1).

Quetiapine was started and titrated against clinical state and tolerability and dosed within the therapeutic range; the median daily dosage over the observation period was 200, 150, 800, and 900 mg, respectively, for the 4 individual patients. Lamotrigine was titrated against clinical state in accordance with recommended guidelines, and the median daily dosage over the observation period was 150 mg. Divalproex sodium was titrated against clinical state and blood levels, the median daily dosage was 1000 mg, and the median blood level was 557 μmol/L (local therapeutic reference range 350 to 700).

At the time of writing, all offspring had been treated for 1 or more uninterrupted years after acute stabilization. The patients were seen monthly, on average; detailed clinical progress notes were kept, and CGI ratings were made at each visit. The beginning of the treatment period assessed was defined when the patient was no longer acutely ill, with a CGI-Severity score of 2 or less for 2 consecutive weeks. An independent research psychiatrist, who did not know the offspring and was blind to the response status of the proband parent, used a validated long-term treatment-response rating scale[45] and retrospectively rated treatment response in extracts from records in which information about treatment was blinded.

The rating scale provides a composite score summarizing the completeness of response, modified to reflect the probability that the improvement was due to the treatment rather than to a spontaneously fluctuating or remitting course. First, the completeness of response is scored on a scale of 0 to 10, with the frequency and severity of any residual symptoms taken into account. Next, the score is modified, with points being taken away for systematic use of concomitant medication, nonadherence, and mild severity or low frequency of recurrences prior to treatment. Thus the final score represents the degree of response that is attributable to the treatment rather

Table 1 Description of treated offspring

Patient offspring number	Offspring DSM-IV diagnosis	Clinical course	Mood disorder onset (age in years)	Index episode	Major lifetime episodes	Start of treatment (age in years)	Start of adequate treatment (age in years)	Parent treatment response	Offspring treatment response	Response scores
01	BD I	Episodic	19	Major depression	4	25	32	LiR	Li	7
02	BD I	Episodic	18	Major depression	3	20	21	LiR	Li	10
03	BD II	Episodic	16	Major depression	3	18	19	LiR	Li	8
04	BD II	Episodic	16	Major depression	5	19	19	LiR	Li	10
05	BD NOS	Episodic	15	Major depression	7	22	27	LiR	Li	7
06	BD II	Episodic	13	Major depression	5	23	25	LiR	Li	8
07	BD NOS	Episodic	25	Major depression	2	25	27	LiR	LTL	9
08	BD NOS	Episodic	11	Major depression	6	17	19	LiR	Li	9
09	BD II	Episodic	16	Major depression	4	17	19	LiR	Li	8
10	BD I	Episodic	16	Minor depression	3	24	24	LiR	Li	10
11	BD II	Chronic	15	Major depression	Chronic	22	24	LiNR	Li NR	2
									QTP	—
12	MDD	Chronic	13	Major depression	Chronic	14	19	LiNR	QTP	7
13	MDD	Chronic	18	Major depression	Chronic	21	21	LiNR	QTP	8
14	BD NOS	Chronic	18	Major depression	Chronic	20	20	LiNR	Li NR	0
									QTP	9
15	BD II	Chronic	18	Major depression	Chronic	19	24	LiNR	DVP	8

NOS = not otherwise specified; LiR = lithium responsive; LiNR = lithium nonresponsive;
Li = lithium; LTL = lamotrigine; MDD = major depressive disorder; QTP = quetiapine; DVP = divalproex sodium; — = no data

than to the spontaneous course of the illness. Response for this study was defined as a total score of at least 7 out of 10. Nonresponse was a score below 7, and in this series, the 2 nonresponders to lithium scored 0 and 2, respectively. In the previous studies, a score of 7 or more was associated with very good long-term stabilization.[45,46]

This study was approved by the local research ethics board, and written consent was obtained from all subjects.

Results

Course Prior to the Medication Trial

The median age of onset of the bipolar spectrum disorder was 16 years, as defined by the onset of the first diagnosable mood episode. In this series, the first mood episode was depressive for all offspring. Eight offspring had a history of an antecedent anxiety or sleep disorder in childhood. Six offspring, 5 of whom were from lithium-nonresponsive families, had a history of mood instability and (or) substance abuse in the year preceding the onset of the mood disorder. Interestingly, 9 of the 10 offspring from lithium-responsive families were completely well in the year before the onset of the mood disorder, as determined by a prospective clinical assessment made as part of the high-risk study protocol.

Treatment Prior to the Medication Trial

The mood-stabilizing treatment assessed in this case series was the first trial of long-term mood-stabilizing treatment for all offspring. Ten offspring had received a previous acute treatment with an antidepressant, one had experienced a previous trial of individual psychotherapy, and one had participated in family therapy because the individual's depressive disorder was interpreted as a reaction to family stress. No offspring were on antidepressants within 2 months of the onset of the evaluated mood-stabilizing treatment.

Long-Term Treatment Response

The median duration of the completed long-term treatment trials was 14 months (range 12 to 19 months). All the responders to lithium came from lithium-responsive families. The bipolar spectrum disorder in the offspring who did well on lithium was characterized by an episodic illness course with a good quality of spontaneous remission as determined on prospective, repeated clinical research assessments, psychological testing, and blind consensus review prior to the treatment.[7,47,54]

Of the 3 offspring who responded to atypical antipsychotic monotherapy (patient 11 had not completed 1 full uninterrupted year at the time of writing), each had a parent who failed to stabilize on long-term lithium monotherapy and subsequently remitted on long-term treatment with an atypical antipsychotic.

Table 2a Parental and offspring response to mood stabilizers

	Parental response	
Offspring response	Lithium	Other
Lithium	9	0
Other	1	5

$\chi^2 = 11.25$, $P = 0.001$

Table 2b Offspring response to mood stabilizer and course of illness

	Offspring mood stabilizer response	
Clinical course	Lithium	Other
Episodic	9	1
Chronic	0	5

$\chi^2 = 11.25$, $P = 0.001$

A chi-square analysis demonstrated that the response to mood stabilizers in the offspring was significantly associated with the response in the parent (Table 2a; $\chi^2 = 11.25$, $P = 0.001$). Further, response to lithium in the offspring was significantly associated with an episodic course of illness; response to other mood stabilizers was associated with a chronic illness course (Table 2b; $\chi^2 = 11.25$, $P = 0.001$).

None of the offspring with depression switched into hypomania or mania during the observation period on monotherapy. Those who failed on lithium treatment did so because of relapses of major depressive episodes with marked comorbid anxiety. Interestingly, in this study, no patient discontinued treatment because of adverse effects or poorly tolerated treatment.

Discussion

In this paper, we have presented observations from a series of systematically treated affected offspring of well-characterized parents with BD. The parents had an established, clear-cut response to long-term treatment with either lithium or alternatives. The first key finding from this series is that, at least in a subset of youth with BD, monotherapy appears effective.

Second, our observations suggest that treatment response in the affected offspring is associated with the treatment response in the affected parent. This is convergent with

previous findings that lithium response clusters in affected adult family members.[45]

Third, the clinical profile of the patient with early-onset BD may help in selecting effective mood-stabilizing treatment. Specifically, a subgroup of adolescents with BD who stabilized on lithium monotherapy shared distinct clinical features, including an episodic remitting clinical course and a family history of remitting mood disorders responsive to long-term lithium monotherapy. Further, a subgroup of adolescents with BD who did not respond to lithium but responded to an atypical antipsychotic were characterized by a chronic nonepisodic clinical course and a family history of chronic psychiatric disorders, including psychotic spectrum disorders responsive to antipsychotics.

As indicated in Table 1, latency from illness onset to adequate prophylactic treatment in this population was surprisingly high. Had these individuals not been in a prospective high-risk study, it is likely that prophylactic treatment would have been delayed even further. Latency was related to both caregiver and patient variables. Recent high-risk studies have indicated that the brain dysregulation that later presents as BD often starts with nonspecific manifestations.[7,10,55] A substantial number of offspring in this series had early childhood presentations of sleep and anxiety disorders. In addition, there was a more recent antecedent history of mood instability and substance use, especially among the offspring of lithium nonresponders. Further, the BD in this series began with depressive episodes construed as reactions to life events by the health professionals consulted. In summary, it appears that the variable and nonspecific early presentations of psychopathology in this case series posed a significant diagnostic challenge, despite the loaded family history.

Moreover, we encountered significant ambivalence in the patients themselves about the BD diagnosis and the need for long-term treatment. Our findings support those of other researchers[56,57] suggesting that patient factors related to the acceptability of and adherence to long-term treatment are paramount to a successful outcome. In other words, accurate diagnosis and efficacious treatments are necessary but not sufficient steps to achieve successful early stabilization of BDs in youth.

The major limitation of this study was that findings were based on a small number of patients. As well, the treatment assignment was nonrandomized. Therefore, any conclusions must be interpreted in this light and considered tentative. In addition, the success of treatment in the parent could have biased the decision of the patient as to which mood stabilizer to try initially. The effect of this bias on selection and response to the mood stabilizer was likely minimal for 2 reasons. First, although the adolescent patients were aware of the agent that helped their affected parent, they typically conceptualized their illness as being different from that of their parent.[58] Second, treatment failure was defined as a recurrence of a full-blown mood episode.

It should be noted that, since none of the offspring in this high-risk study met lifetime criteria for bipolar spectrum disorder prior to adolescence, we do not have experience with mood stabilizers in young children. In this case series, we included offspring with chronic major depression, given that they derived from families with BD and previously failed antidepressant treatment. Although this is not standard practice in treatment, the likelihood that the depressive illnesses were related to the BD segregating in the family was high, and we felt justified because of the failure to respond to standard treatment.

Conclusions

Drawing inferences from careful clinical observation of individual cases has been an important and time-tested first step in generating new hypotheses in medicine. The observations presented here, if replicated, may ethically justify designing and performing randomized clinical trials that would test the importance of the individual clinical profile and parental treatment response in selecting effective stabilizing treatments for adolescents suffering from BD.

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Résumé : Une série consécutive d'enfants de parents souffrant de trouble bipolaire affectés et traités : la réponse est-elle dans le profil clinique?

Objectif : Chez les adultes souffrant d'un trouble bipolaire (TB) établi, la réponse différentielle aux régulateurs de l'humeur est associée au profil clinique. Il manque des études sur le traitement à long terme des jeunes souffrant de TB. Cet article offre des observations longitudinales de la réponse aux régulateurs de l'humeur tôt dans le cours de la maladie des jeunes souffrant de TB.

Méthode : Nous rendons compte de 15 patients de recherche qui, adolescents, satisfaisaient aux critères de durée de vie du DSM-IV pour un trouble du spectre bipolaire et nécessitaient un traitement à long terme. Ces jeunes étaient issus de familles où un parent souffrait de TB dont l'évolution et la réponse au traitement à long terme étaient déterminées conformément aux critères de recherche. On a offert du lithium aux patients, et s'ils n'y répondaient pas ou qu'ils le refusaient, ils étaient traités avec un anticonvulsivant ou un antipsychotique atypique. À l'aide d'une échelle validée, un juge indépendant a noté rétrospectivement à l'insu la réponse au traitement à long terme.

Résultats : Les patients qui se sont stabilisés par le lithium venaient de familles répondant au lithium, alors que ceux qui se sont stabilisés par un antipsychotique venaient de familles ne répondant pas au lithium. L'évolution clinique des jeunes stabilisés par le lithium différait de celle des jeunes stabilisés par un antipsychotique atypique.

Conclusions : Nos résultats suggèrent que le profil clinique peut aider à sélectionner un traitement stabilisateur efficace, et qu'une proportion de jeunes peuvent être stabilisés par une monothérapie. Il s'agit d'une petite série de cas affectés à un traitement de façon non aléatoire, et les résultats doivent être considérés provisoires.