Baseline Characteristics and Early Response at Week 1 Predict Treatment Outcome in Adolescents With Bipolar Manic or Mixed Episode Treated With Olanzapine:

Results From a 3-Week, Randomized, Placebo-Controlled Trial

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ABSTRACT

Background: Early predictors of response and remission in pediatric mania are lacking, requiring further study.

Methods: This was a post hoc analysis of a 3-week, randomized, placebo-controlled trial of olanzapine conducted between November 2002 and May 2005 in 161 adolescents aged 13–17 years who were diagnosed with a *DSM-IV* acute manic or mixed episode of bipolar I disorder. Data from the olanzapine arm were analyzed to investigate the predictive power of early response or early nonresponse (≥25% or < 25% reduction in Young Mania Rating Scale [YMRS] score, respectively) at week 1 for ultimate response or nonresponse (≥ 50% or < 50% reduction in YMRS score, respectively) and for remission (YMRS total score ≤ 12 [standard definition] or ≤ 8 [stringent definition]) at week 3. Correlates of early response and ultimate response were examined in multivariable regression models.

Results: By week 1, 69.2% of olanzapine-treated adolescents (n = 104, 2.5–20.0 mg/d) achieved early response, and 49.0% reached ultimate response at week 3. Patients with early response and early nonresponse were similar regarding baseline variables except higher scores for sleep and thought content were found with early response ($P < .05$) and higher olanzapine doses with early nonresponse ($P < .01$). At week 3, early response was associated with significantly greater improvements in YMRS, Clinical Global Impressions–Severity of Illness scale (both $P < .001$), and Overt Aggression Scale scores ($P = .024$). Adverse events were similar in patients with early response and early nonresponse, except for higher AIMS scores for patients with early nonresponse ($P = .036$). Early response significantly predicted ultimate response (OR = 5.61, $P < .001$; sensitivity = 86.3, specificity = 47.2, positive predictive value = 61.1, negative predictive value = 78.1). Significantly more early response than early nonresponse patients achieved ultimate response (61.1% vs 21.9%, $P < .001$) and remission defined by YMRS score ≤ 12 (45.8% vs 12.5%, $P < .001$) and YMRS score ≤ 8 (33.3% vs 3.1%, $P < .001$). In multivariable analyses, among other variables, early response remained an independent correlate of ultimate response and remission.

Conclusions: In acute pediatric manic or mixed episodes, early response to olanzapine at week 1 was strongly associated with ultimate response and remission at week 3, while absence of early response predicted the unlikely success of further treatment.

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Early effective treatment is critical in the long-term management of bipolar disorder in adolescents and for achieving response and remission. Although reliable clinical or biological markers for predicting treatment outcomes in acute mania are generally lacking, early treatment response patterns are a good candidate. A number of analyses indicated that early improvement was predictive of eventual remission with pharmacotherapy in adults with bipolar disorder.[1–6] However, all available data supporting the utility of early response or nonresponse for predicting ultimate outcome in acute mania are based on adult samples, and extension to youth with bipolar disorder remains unclear.

Bipolar disorder in youth is a seriously impairing, recurrent, often psychotic illness with a trajectory that continues into adulthood.[7,8] Rapid symptomatic improvement is key, particularly when treating acute manic or mixed episodes. Although treatment guidelines recommend both mood stabilizers and antipsychotics as first-line treatments for acute manic or mixed episodes,[9,10] in pediatric patients, data suggest that symptom improvement and response rates are lower with mood stabilizers than with antipsychotics.[11,12] This greater efficacy pattern may be partly responsible for the dramatic increase in use of second-generation antipsychotics (SGAs) for pediatric bipolar patients.[13,14] However, SGA use is associated with significant weight gain and metabolic effects in youth.[15,16] Predicting antipsychotic response in the adolescent population is crucial, as adolescents with early-onset bipolar disorder have less long-term symptomatic and functional recovery than patients with adulthood-onset bipolar disorder.[17]

Our previous analyses confirmed that early nonresponse robustly predicted

Clinical Points

- Early predictors of response and remission in pediatric mania or mixed episodes are lacking, requiring further study.
- Patients with less than minimal response to olanzapine at week 1 of treatment are unlikely to reach response or remission by week 3, so switching to another agent is a viable consideration.
- Higher baseline depressive symptoms predicted poorer improvement with olanzapine in adolescents with a bipolar manic or mixed episode. Neither early nor ultimate response was associated with olanzapine-related sedative effects or weight gain.

ultimate treatment outcome in adolescents with schizophrenia during monotherapy with aripiprazole[18] or olanzapine.[19] Here, we performed a post hoc analysis of a 3-week randomized placebo-controlled trial conducted in adolescents with a bipolar disorder manic or mixed episode to evaluate whether early response or early nonresponse to olanzapine at week 1 predicts outcome at week 3.

METHODS

This study was a post hoc analysis of data derived from a multisite, 3-week double-blind randomized controlled trial comparing olanzapine and placebo in adolescents with bipolar disorder (ClinicalTrials.gov identifier NCT00050206). A brief description of the parent study follows; additional details have been published.[20] The ethics review boards of the participating institutions approved the study, and written informed consent was obtained from patients and their legal guardians prior to participation in the study.

Study Design and Participants

The study included 161 adolescents aged 13–17 years and diagnosed with bipolar I disorder, currently manic or mixed (with/without psychotic features) according to the *Diagnostic and Statistical Manual for Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*) and confirmed with the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version (K-SADS-PL).[21] Inpatients or outpatients with a Young Mania Rating Scale (YMRS)[22] total score ≥ 20 were recruited from 26 sites in the United States (24 sites) and Puerto Rico (2 sites) between November 2002 and May 2005.

Patients were randomly assigned in a 2:1 ratio to olanzapine in flexible doses (2.5–20.0 mg/d) or placebo. Olanzapine was initiated at 2.5 mg/d or 5.0 mg/d, which could be increased by 2.5-mg/d or 5.0-mg/d increments by the investigator's discretion. The present post hoc analyses included only those patients allocated to olanzapine and who had ≥ 2 postbaseline assessments: one to assess early response at week 1 and at least one additional, later assessment to determine ultimate response.

All previous antimanic drugs were tapered during washout to ensure that patients were free of these medications for ≥ 2 days pre-randomization. Antidepressants had to be discontinued ≥ 7 days pre-randomization, with the exception of monoamine oxidase inhibitors (≥ 14 days) and fluoxetine (≥ 5 weeks pre-randomization).

Efficacy and Safety Assessments

The primary efficacy measure was change in YMRS total score. Other efficacy outcome measures included the Children's Depression Rating Scale-Revised (CDRS-R),[23] the Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHRS),[24] the Clinical Global Impressions–Severity of Illness scale (CGI-S) and CGI-Improvement scale (CGI-I),[25] the Overt Aggression Scale (OAS),[26] and the Child Health Questionnaire-Parent Form 50 (CHQ-PF50).[27]

Safety outcomes included severity and frequency of adverse events and changes in body weight, body mass index (BMI), and metabolic measures, including total levels of cholesterol, triglycerides, and fasting glucose. Extrapyramidal side effects were assessed by the Simpson-Angus Scale (SAS),[28] the Barnes Akathisia Rating Scale (BARS),[29] and the Abnormal Involuntary Movement Scale (AIMS).[30] Fasting (≥ 8 hours) glucose and lipid concentrations were measured at baseline and endpoint.

Statistical Analysis

We focused on response prediction of patients randomly assigned to olanzapine only; placebo response patterns are the focus of a separate report.

To be consistent with prior studies of adults with bipolar mania,[2,6] early response and early nonresponse were defined as a ≥ 25% and a < 25% reduction, respectively, in YMRS total score at week 1. Ultimate response was defined as ≥ 50% YMRS total score reduction at study endpoint (last observation carried forward [LOCF]). Remission was defined at endpoint as YMRS total score ≤ 12 (standard definition)[5] or ≤ 8 (stringent definition).[31]

Early response and early nonresponse groups were compared on demographics and baseline characteristics as well as YMRS total, CDRS total, CGI-S, OAS, and CHQ-PF50 scores and all-cause discontinuation using χ^2 test or *t* test for categorical and continuous variables, respectively.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), were calculated to determine the value of early response/early nonresponse for predicting presence or absence of ultimate response and remission at week 3. Furthermore, receiver operating characteristic (ROC) curves were calculated for the reduction in YMRS score at week 1 regarding ultimate response and remission at week 3 (LOCF) to determine, post hoc, the YMRS total score improvement threshold at week 1 with the best predictive power for ultimate response and remission to guide future studies and analyses.

Finally, stepwise-selection logistic regression models for response and remission were performed using baseline

Table 1. Baseline Demographic, Illness, and Treatment Characteristics of Olanzapine-Treated Subjects[a]

Characteristic	Total Patients Receiving Olanzapine (n = 104)	Early Responder[b] at Week 1 (n = 72)	Early Nonresponder at Week 1 (n = 32)	*P* Value[c]
Demographic				
Age, median, y	15.0	15.0	14.0	.19
Male	59 (56.7)	41 (56.9)	18 (56.3)	.95
Race				.32
White	69 (66.4)	50 (69.4)	19 (59.4)	
Nonwhite	35 (33.6)	22 (30.6)	13 (40.6)	
Geographic location				.51[d]
Puerto Rico	12 (11.5)	7 (9.7)	5 (15.6)	
United States	92 (88.5)	65 (90.3)	27 (84.4)	
BMI, median, kg/m^2	21.8	22.3	21.5	.40
Illness				
Illness duration, median, y	3.0	3.0	3.0	.40
Age at onset, median, y	12.0	12.0	11.0	.13
Onset before age 13 y	68 (66.0)	45 (62.5)	23 (74.2)	.25
Type of episode				**.01**
Acute manic episode	43(41.3)	24 (33.3)	19 (59.4)	
Acute mixed episode	61(58.7)	48 (66.7)	13 (40.6)	
Schizophrenia in first degree relative, unknown or yes	16 (15.4)	11 (15.3)	5 (15.6)	1.00[d]
Schizophrenia in second degree relative, unknown or yes	29 (27.9)	21 (29.2)	8 (25.0)	.66
Axis I history in first degree relative, unknown or yes	71 (68.3)	52 (72.2)	19 (61.3)	.19
Bipolar disorder in first degree relative, unknown or yes	53 (51.0)	39 (54.2)	14 (43.8)	.33
Bipolar disorder in second degree relative, unknown or yes	54 (51.9)	40 (55.6)	14 (43.8)	.27
YMRS total score, mean (SD)	33.1 (6.6)	33.8 (6.4)	31.4 (6.7)	.08
1. Elevated mood	2.8 (1.0)	2.8 (1.1)	2.9 (0.8)	.46
2. Increased motor activity	3.0 (0.9)	3.0 (0.8)	2.9 (1.0)	.62
3. Sexual interest	1.2 (1.1)	1.1 (1.1)	1.3 (1.0)	.55
4. Sleep	2.4 (1.1)	2.6 (1.0)	2.1 (1.1)	**.02**
5. Irritability	5.5 (1.3)	5.6 (1.3)	5.3 (1.4)	.33
6. Speech (rate and amount)	5.1 (1.5)	5.0 (1.4)	5.3 (1.8)	.52
7. Language thought disorder	2.3 (0.6)	2.3 (0.6)	2.2 (0.6)	.27
8. Thought content	3.4 (2.3)	3.7 (2.3)	2.7 (2.1)	**.04**
9. Disruptive-aggressive behavior	4.8 (1.4)	5.0 (1.4)	4.5 (1.4)	.15
10. Appearance	1.2 (1.1)	1.3 (1.1)	1.0 (1.0)	.22
11. Insight	1.5 (1.4)	1.6 (1.4)	1.4 (1.4)	.54
CHQ-PF50 psychosocial score, mean (SD)	21.1 (11.8)	19.8 (10.9)	24.3 (13.3)	.08
CHQ-PF50 physical score, median	53.6	53.7	52.4	1.00
CGI-S score				.11
4 ("moderate")	37 (35.6)	21 (29.2)	16 (50.0)	
5 ("marked")	49 (47.1)	38 (52.8)	11 (34.4)	
6 ("severe")	18 (17.3)	13 (18.0)	5 (15.6)	
Total score, mean (SD)	4.8 (0.7)	4.9 (0.7)	4.7 (0.7)	.12
OAS total score > 0	95 (91.4)	68 (94.4)	27 (84.4)	.13[d]
Simpson-Angus scale total score > 0	12 (11.5)	11 (15.3)	1 (3.1)	.10[d]
Barnes total score > 0	20 (19.2)	15 (20.8)	5 (15.6)	.60[d]
AIMS total score > 0	6 (5.8)	6 (8.3)	0 (0.0)	.17[d]
CDRS-R total score, median	38.5	41.0	33.5	.09
Treatment				
Olanzapine, mean modal dose, median	10.0	10.0	12.5	**< .01**
Olanzapine, mean maximum dose, median	10.0	10.0	15.0	**< .01**
Benzodiazepine use at week 1	43 (41.3)	12 (16.7)	5 (15.6)	.89

[a]Values shown as n (%) unless otherwise noted.
[b]Early responders showed ≥ 25% reduction from baseline in YMRS total score.
[c]Bolded *P* values significant at < .05.
[d]Fisher exact test.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BMI = body mass index, CDRS-R = Children's Depression Rating Scale-Revised; CHQ-PF50 = Child Health Questionnaire Parent Form 50, CGI-S = Clinical Global Impressions–Severity of Illness scale, OAS = Overt Aggression Scale, YMRS = Young Mania Rating Scale.

variables, early response status at week 1, and sedation and extrapyramidal side effects postbaseline to examine which demographic and illness characteristics—including individual symptoms, manic versus mixed episode, treatment, and adverse effects—predicted ultimate response or remission at endpoint.

RESULTS

Patient Population

Data for 161 patients randomly assigned to olanzapine (n = 107) or placebo (n = 54), and for the 104 patients (93.5%) receiving olanzapine who had at least 2 follow-up visits, were

Table 2. Summary of Efficacy-Related Outcomes Assessed at Week 1 and Week 3 (LOCF) in Olanzapine-Treated Early Responders Versus Early Nonresponders[a]

Outcome	Total Patients Receiving Olanzapine (n = 104)	Early Responder at Week 1 (n = 72)	Early Nonresponder at Week 1 (n = 32)	t/χ^2	OR	*P* Value[b]
Change in individual YMRS item score at week 1						
1. Elevated mood	−0.96 (1.09)	−1.17 (1.15)	−0.50 (0.76)	3.49	…	**.001**
2. Increased motor activity	−1.01 (1.33)	−1.35 (1.33)	−0.25 (0.98)	4.17	…	**<.001**
3. Sexual interest	−0.48 (0.95)	−0.68 (0.96)	−0.03 (0.78)	3.36	…	**.001**
4. Sleep	−1.65 (1.33)	−2.01 (1.19)	−0.84 (1.27)	4.52	…	**<.001**
5. Irritability	−1.61 (1.89)	−2.29 (1.72)	−0.09 (1.28)	6.46	…	**<.001**
6. Speech (rate and amount)	−2.24 (1.76)	−2.69 (1.82)	−1.22 (1.07)	5.16	…	**<.001**
7. Language thought disorder	−0.80 (0.90)	−1.03 (0.86)	−0.28 (0.77)	4.23	…	**<.001**
8. Thought content	−1.28 (2.33)	−1.96 (2.24)	0.25 (1.74)	4.94	…	**<.001**
9. Disruptive-aggressive behavior	−1.72 (1.84)	−2.42 (1.64)	−0.16 (1.22)	6.97	…	**<.001**
10. Appearance	−0.42 (0.90)	−0.56 (0.92)	−0.09 (0.78)	2.48	…	**.015**
11. Insight	−0.44 (1.00)	−0.60 (1.02)	−0.09 (0.86)	2.44	…	**.016**
YMRS total score, % change	−48.24 (27.99)	−56.42 (25.32)	−29.84 (25.09)	4.96	…	**<.001**
Ultimate response, YMRS score reduction ≥ 50%, n (%)	51 (49.0)	44 (61.1)	7 (21.9)	13.65	5.61	**<.001**
Remission, YMRS score ≤ 12, n (%)	37 (35.6)	33 (45.8)	4 (12.5)	…	5.92	**<.001**[c]
Remission, YMRS score ≤ 8, n (%)	25 (24.0)	24 (33.3)	1 (3.1)	…	15.50	**<.001**[c]
CGI-S change in depression score	−0.88 (1.18)	−1.11(1.22)	−0.38(0.94)	3.04	…	**.003**
CGI-S change in mania score	−1.72 (1.27)	−2.07 (1.27)	−0.94 (0.95)	4.51	…	**<.001**
CGI-S change in overall score	−1.62 (1.29)	−2.00 (1.27)	−0.75 (0.88)	5.80	…	**<.001**
OAS total score change	3.22 (3.88)	3.79 (3.62)	1.94 (4.18)	−2.30	…	**.024**
ADHRS score change	−16.96 (85.50)	−18.19 (99.69)	−14.25 (40.04)	0.29	…	.776
CDRS-R score change	−14.33 (25.47)	−16.36 (25.08)	−9.76 (26.13)	1.22	…	.224
CHQ-PF50 point change						
Psychosocial summary	−93.40 (200.50)	−113.40 (233.60)	−53.22 (80.89)	1.91	…	.059
Physical summary	−8.52 (11.26)	−11.26 (86.76)	−2.74 (26.24)	0.75	…	.457
All-cause discontinuation, n (%)	17 (16.35)	12 (16.67)	5 (15.63)	…	1.08	1.000[c]

[a]Values shown as mean (SD) unless otherwise noted.
[b]Bolded *P* values significant at < .05.
[c]Fisher exact test.
Abbreviations: ADHRS = Attention-Deficit/Hyperactivity Disorder Rating Scale, CDRS-R = Children's Depression Rating Scale-Revised, CGI-S = Clinical Global Impressions–Severity of Illness scale, CHQ-PF50 = Child Health Questionnaire Parent Form 50, LOCF = last observation carried forward, OAS = Overt Aggression Scale, YMRS = Young Mania Rating Scale.
Symbol: … = not applicable.

Table 3. Predictive Value of Early Response (reduction in YMRS score ≥ 25% at week 1) for Ultimate Response (reduction in YMRS score > 50%) and Remission to Olanzapine at Study Endpoint (week 3 LOCF)

Variable	Accuracy of ER (25% reduction in YMRS score at week 1) in Predicting UR at Endpoint	Best Predicting UR at Endpoint (35.5% reduction in YMRS score at week 1)	Accuracy of ER (25% reduction in YMRS score at week 1) in Predicting Remission at Endpoint		Best Predicting Remission at Endpoint (39% reduction in YMRS score at week 1)	
			YMRS Score ≤ 12	YMRS Score ≤ 8	YMRS Score ≤ 12	YMRS Score ≤ 8
Sensitivity, %	86.3	70.6	89.2	96.0	70.2	88.0
Specificity, %	47.2	69.8	41.8	39.2	74.6	73.4
PPV, %	61.1	69.2	45.8	33.3	60.4	51.1
NPV, %	78.1	71.1	87.5	96.9	82.0	95.1
Accuracy, %	66.3	70.2	58.7	52.9	73.1	76.9
ER ROC threshold, %	…	35.5	…	…	39.0	39.0
AUC	…	0.75	…	…	0.75	0.84
Lower 95% CL	…	0.66	…	…	0.66	0.76
Upper 95% CL	…	0.84	…	…	0.85	0.92

Calculations

		Outcome (Response/Remission)		
		Positive	Negative	
Predictor (Early Response)	Positive	True Positive (TP)	False Positive (FP)	PPV = TP/(TP + FP)
	Negative	False Negative (FN)	True Negative (TN)	NPV = TN/(FN + TN)
		Sensitivity = TP/TP + FN	Specificity = TN/FP + TN	

Abbreviations: AUC = area under the curve, CL = confidence limit, ER = early response, LOCF = last observation carried forward, NPV = negative predictive value, PPV = positive predictive value, ROC = receiver operating characteristic, UR = ultimate response, YMRS = Young Mania Rating Scale.
Symbol: … = not applicable.

Table 4. Stepwise Selection Logistic Regression Models for Response and Remission Using Baseline Variables

Ultimate Response: ≥ 50% Reduction in YMRS Total Score at Week 3					Remission: YMRS Score ≤ 12 at Week 3					Remission: YMRS Score ≤ 8 at Week 3				
Significant Predictors	OR	95% CL Lower	95% CL Upper	*P* Value	Significant Predictors	OR	95% CL Lower	95% CL Upper	*P* Value	Significant Predictors	OR	95% CL Lower	95% CL Upper	*P* Value
Early response at week 1	7.816	2.690	22.711	<.001	Early response at week 1	8.639	2.295	32.529	.001	Early response at week 1	14.629	1.815	117.88	.012
Schizophrenia in second-degree relative	4.854	1.345	17.515	.016	Previous psychiatric hospitalization	0.341	0.119	0.976	.046	Male	3.781	1.263	11.321	.017
Baseline CDRS-R score	0.968	0.942	0.995	.020	Baseline CHQ-PF50 Physical summary score	1.046	1.000	1.094	.049	Baseline OAS verbal score	1.621	1.002	2.624	.049
$R^2 = 0.205$					$R^2 = 0.191$					$R^2 = 0.208$				

Abbreviations: CDRS-R = Children's Depression Rating Scale-Revised, CHQ-PF50 = Child Health Questionnaire Parent Form 50, CL = confidence limit, OAS = Overt Aggression Scale, OR = odd ratio, YMRS = Young Mania Rating Scale.

included in the analysis. We analyzed the type of baseline episode as a predictor of ultimate response at week 3. Altogether, 31 of 61 patients with a mixed episode and 20 of 43 patients with a manic episode responded to olanzapine at endpoint, without a significant difference between the two groups ($P = .665$).

Baseline demographic, illness, and treatment characteristics of patients with early response and early nonresponse are shown in Table 1. Most patients were white and from the United States. More patients with mixed episodes (66.7% vs 40.6%, $P = .01$) were in the early response group. Early response patients had higher baseline scores for sleep (2.6 vs 2.1, $P = .02$) and thought content (3.7 vs 2.7, $P = .04$) than patients with early nonresponse. A higher modal dose (12.5 vs 10.0 mg/d, $P < .01$) and a higher maximum dose (15.0 vs 10.0 mg/d, $P < .01$) of olanzapine was received by patients with early nonresponse than by those with early response.

Table 5. Adverse Effects During the 3-Week Trial in Subjects Treated With Olanzapine

Outcome	Early Response (n = 72)	Early Nonresponse (n = 32)	*P* Value[a]
Sedation/somnolence/fatigue/lethargy at week 1, n (%)	34 (47.2)	9 (28.1)	.068
Mean change from baseline, LS mean (SE), mmol/L			
Total cholesterol	0.108 (0.019)	0.114 (0.029)	.664
Triglycerides	0.439 (0.089)	0.207 (0.133)	.152
Fasting glucose	0.016 (0.017)	0.053 (0.024)	.215
Change in body weight, LS mean (SE), %	6.056 (0.437)	5.809 (0.656)	.755
Weight gain ≥ 7%, n (%)	28 (38.9)	12 (37.5)	.893
Change in BMI *z* score, LS mean (SE)	0.256 (0.028)	0.310 (0.042)	.289
Change from baseline, mean (SD)			
SAS total score	−0.04 (1.03)	0.16 (0.68)	.248
BAS total score	0.24 (1.23)	0.13 (1.18)	.668
AIMS total score	−0.06 (0.35)	0.18 (0.81)	**.036**

[a]Bolded *P* values significant at < .05.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, BMI = body mass index, SAS = Simpson-Angus Scale.

Efficacy Outcomes

At week 1, 72 (69.2%) of 104 patients were in the early response group. Significantly more early response than early nonresponse patients achieved ultimate response at week 3 (44 [61.1%] vs 7 [21.9%], $P < .001$). Likewise, significantly more early response than early nonresponse patients remitted per a YMRS total score ≤ 12 at study endpoint (33 [45.8%] vs 4 ([12.5%]), $P < .001$) or a YMRS total score ≤ 8 at endpoint (24 [33.3%] vs 1 [3.1%], $P < .001$). Compared to early nonresponse, early response patients had significantly greater improvements in mean (SD) percent change in YMRS total score at LOCF endpoint (−29.84% [25.09%] vs −56.42% [25.32%], $P < .001$) and greater reduction at week 1 in all individual YMRS items (Table 2). Additionally, early response patients had significantly greater improvement per CGI-S and CGI-I scores ($P < .001$) and OAS score ($P = .024$). The changes in ADHRS score, CDRS-R score, and CHQ-PF50 psychosocial summary and physical summary scores were not significantly different between early response and early nonresponse patients ($P > .05$). Finally, there was no significant difference in all-cause discontinuation between early response and early nonresponse patients ($P = 1.00$) (Table 2).

We compared change in YMRS total scores between olanzapine and placebo at each of the 3 weeks separately in early response and early nonresponse patients (see Supplementary eTable 1). The reduction in YMRS total scores in early response was significantly higher than placebo at weeks 1, 2, and 3 ($P < .001$) but was significantly lower in early nonresponse than placebo patients at week 1 ($P = .01$) and showed no difference between early nonresponse and placebo groups at weeks 2 and 3 ($P > .05$).

Predictive Value of Early Response and Nonresponse

Regarding the predictive values of early response at week 1 for ultimate response at endpoint, the sensitivity (78.1%) and NPV (86.3%) were high, while the PPV (61.1%) was moderate and specificity (47.2%) was low. Predictive values of early response for remission (YMRS total score ≤ 12) were high regarding sensitivity (89.2%) and NPV (87.5%), but specificity (41.8%) and PPV (45.8%) were low, and similar results were also obtained when the stricter definition of remission (YMRS total score ≤ 8)

was applied. The accuracy of early response in predicting ultimate response and remission was moderate (52.9%–66.3%) (Table 3).

ROC Curves to Determine the Best Cutoff for Early Response and Nonresponse

ROC curves were generated to find the optimal cutoff threshold for improvement at week 1 to predict ultimate response or remission/nonremission at week 3. A cutoff threshold of 35.5% reduction in YMRS total score at week 1 to predict ultimate response showed the highest accuracy (70.2%) and the greatest area under the curve (0.75). ROC curves showed an optimal cutoff point of 39% reduction in YMRS total score at week 1 to best predict remission with both the liberal and the stringent definition (Table 3).

Predictors of Ultimate Response and Remission

The stepwise-selection logistic regression analysis showed that predictors of ultimate response included early response ($P < .001$), schizophrenia in second-degree relatives ($P = .016$), and a lower baseline CDRS-R total score ($P = .020$). Predictors of less stringently defined remission (YMRS total score ≤ 12) included early response ($P = .001$), less previous psychiatric hospitalization ($P = .046$), and a higher baseline CHQ-PF50 physical summary score ($P = .049$). Predictors of more stringently defined remission (YMRS total score ≤ 8) included early response ($P = .012$), male sex ($P = .017$), and a higher baseline OAS verbal score ($P = .049$) (Table 4).

Multiple ordinal logistic regression analyses were performed to identify predictors for 4 categories of reduction in YMRS scores at study endpoint (1%–25%, 25%–49%, 50%–74%, and ≥ 75%) (see Supplementary eTable 2). Results indicated that later illness onset predicted an improved response across all categories ($P = .030$ to .010), longer days to maximum dose predicted improvement ≥ 25% ($P = .020$ to 0.005), higher baseline YMRS scores predicted improvement in 3 of 4 categories (all except 50%–74%; $P = .032$ to .014), and higher baseline CDRS-R scores predicted improvement in the < 25% improvement category only ($P = .010$).

Adverse Effect Outcomes

More early response patients reported sedation-related adverse effects at week 1 than early nonresponse patients (47.2% vs 28.1%) without significance ($P = .068$); however, we tested this variable for inclusion in the logistic regression models, which resulted in its dropping out as nonsignificant. There were no differences in metabolic outcomes between early response and early nonresponse patients. Both early response and early nonresponse patients gained body weight over the 3-week treatment, with 38.9% of early response patients and 37.5% of early nonresponse patients gaining ≥ 7% of baseline body weight. Moreover, mean levels of blood cholesterol, triglycerides, and fasting glucose increased from baseline to endpoint in both groups. Early nonresponse patients had an increase in AIMS scores compared to early response patients ($P = .036$) (Table 5).

DISCUSSION

The main findings from this post hoc analysis of the olanzapine group from a 3-week placebo-controlled trial in adolescents with mania include the following: (1) most of the symptomatic improvement with olanzapine was achieved by week 1; (2) early response at week 1 significantly predicted ultimate response and remission; (3) a threshold for early response of ≥ 35% reduction in YMRS score was identified as having the best predictive validity for ultimate response and remission at endpoint; (4) early response patients had better efficacy than early nonresponse patients on most efficacy outcomes; (5) adverse effects did not differ significantly between early response and early nonresponse patients except for dyskinesia (ie, higher AIMS scores) in early nonresponse; and (6) early response was the first significant predictor of ultimate response and remission in stepwise selection logistic regression analyses that identified only 2 or 3 additional clinical predictors, and early response was the only predictor that was present in all 3 models, while the other clinical predictors were unique to either ultimate response or either of the 2 definitions of remission.

Per the threshold of a 25% improvement in YMRS total score at week 1 to define early response, 69% of the olanzapine-treated adolescents with bipolar disorder were categorized as having early response. Thus, our finding demonstrates that a substantial number of adolescents with a manic or mixed episode of bipolar disorder can be expected to have early symptom improvement within the first week during treatment with olanzapine. This observed proportion of early response was considerably higher than in a study of adult patients randomized to olanzapine,[6] in which early response at week 1 was achieved by 47% using the same YMRS threshold. Conversely, the early response rate in our study was considerably lower than in another study of adults treated with olanzapine or risperidone,[2] in which early response rates were 86% and 84%, respectively, again with ≥ 25% YMRS total score reduction at week 1 as the early response definition. Reasons for this difference in the proportion of early response are unclear, but could possibly relate to differences in the age of the population, prebaseline exposure to antipsychotics, and degree of required washout, each of which will affect prebaseline response status and baseline severity of psychopathology. These findings and potential determinants of early response and ultimate response or remission should be followed up in future studies.

A high percentage of patients who eventually responded or remitted had already started their early improvement, indicated by high sensitivity values. However, only a subset of early improvers will continue to gain clinical benefit to the level of response or remission, as indicated by limited values for specificity and PPV. Notably, patients not achieving sufficient improvement were less likely to reach response or remission by week 3 as indicated by high NPV values. The absence of an early improvement with treatment means that an individual patient has only a small

chance of still reaching response or remission if treatment remains unchanged.[6] From a clinical viewpoint, NPV and specificity for prediction of ultimate nonresponse may be the most important variables, since an accurate and early identification of nonresponders provides an opportunity of changing treatment to more effective options without exposure of patients to ultimately ineffective or suboptimal treatments.[32] Therefore, our results suggest that in cases of early nonresponse to adequately dosed olanzapine at week 1, a change of antipsychotic treatment is probably a better choice than continuing treatment if a quick resolution of the symptoms is paramount. Just waiting is unlikely to provide substantial benefit for the patient, provided that effective doses have been reached within the first week. Therefore, measurement-based approaches to identifying early nonresponse patients as soon as week 1 have relevant implications for informing clinical care decisions. To what degree these results generalize to other antipsychotics in the treatment of bipolar disorder mania in youth needs further investigation.

Consistent with studies in adults with bipolar disorder,[1–6] we confirmed that early response at week 1 had significantly better outcomes across a variety of efficacy measures, including improvements in YMRS, CGI-S, and CGI-I scores. Exceptions were the lack of a difference in ADHRS, CDRS-R, and CHQ-PF50 scores between early response and early nonresponse patients at week 3.

Contrary to the threshold of ≥25% reduction in YMRS score used for early response in prior studies of adults with mania, we found that thresholds of around 35%–40% (35.5%–39.0%) reduction in YMRS total score at week 1 were the optimal cutoff point for early response to predict ultimate response and remission. Whether these higher early response/early nonresponse thresholds at week 1 can be replicated and should be used in future studies alongside or instead of the traditional ≥25% YMRS score reduction threshold also requires further study. However, since clinicians do not generally use the YMRS in usual care settings, either training with and implementation of the YMRS are needed or YMRS changes need to be linked statistically to CGI-I scores, as has been done in schizophrenia,[33] which indicated that a 20%–30% reduction in the total score of psychosis-related scales was equivalent to "minimally improved" on the CGI-I, a 1-item, 7-point scale that can be scored quickly and implemented easily in clinical care.[34]

Multiple ordinal logistic regression analyses showed that later illness onset had a positive impact on response, consistent with other pediatric studies[17,35–37] showing that older age was associated with greater improvement of mania or mixed states. Similarly, in adults, early-onset bipolar disorder also predicted poorer outcome.[38] Moreover, higher baseline depressive symptoms predicted poorer improvement (<25% YMRS reduction), suggesting that mixed states are more difficult to treat.[39–41] Conversely, longer time to maximum dose indicated better improvement (≥25% YMRS reduction), which is very likely due to less need to increase the dose in patients with better response in this flexible-dose study.

Finally, when entering baseline variables as potential moderators of the change in symptom severity in stepwise-selection logistic regression analyses, we confirmed that early response at week 1 remained a robust and significant independent predictor of response and remission while other variables only singularly predicted one or the other outcome.

Besides that early nonresponse patients were less likely to respond in the future, we also found that olanzapine was not even superior to placebo in early nonresponse patients at week 1 and similar to placebo at following visits. Conversely, the improvement of symptoms in early response patients was consistently superior to placebo at all 3 visits. These findings strengthened our hypothesis that patients not responding early to olanzapine at week 1 will benefit as little from it as from placebo in the continuing treatment.

Given prior evidence from adult studies that BMI may be a negative predictor of outcome for bipolar disorder,[42,43] we assessed the impact of BMI as a predictor to treatment response, but found that baseline BMI, BMI change, and weight gain at endpoint were not associated with early response. However, present findings converge with findings from the Treatment of Selective Serotonin Reuptake Inhibitor Resistant Depression in Adolescents study[44] to indicate that BMI does not predict or moderate response to pharmacologic treatment of refractory depression in adolescents. The absence of an association between BMI and treatment outcome in our study may be explained by the fact that we allowed for dose increase after insufficient response to treatment, which may partly offset potential lower drug concentration caused by higher BMI. Moreover, sedation is a common effect of olanzapine, and the sedative effect can be considered to be adverse or positive.[45] It is hard to distinguish the antimanic and sedation effects of antipsychotics in clinical practice. We found that sedation was not associated with early response, meaning that sedation is not a prerequisite for an antimanic effect of olanzapine.

The parent study from which the data for this post hoc analysis were derived was the basis for the US Food and Drug Administration (FDA) approval of olanzapine for the treatment of bipolar manic or mixed episode associated with bipolar I disorder in pediatric patients aged 13–17 years. Therefore, the dose titration (initiation at 2.5 mg or 5 mg and dose increases by 5 mg up to a maximum of 20 mg/d) are entirely consistent with the FDA label.[20] However, despite the proven efficacy of olanzapine for the treatment of pediatric mania, it is generally considered second line for this indication due to its significantly greater cardiometabolic adverse effects than observed with other antipsychotics used for pediatric patients.[11,15,16,46]

Limitations

Results from this study must be interpreted within its limitations. First, the study was a post hoc analysis derived from a randomized controlled trial; its generalizability to real-world samples and clinical practice may be reduced.

Second, we were able to evaluate early response and its predictive validity only within the first 3 weeks of treatment, whereas prediction of longer-term outcome is also very important. Third, the definition of response or remission in this study using YMRS score did not take into account the severity of any depressive symptoms that may have been present. Fourth, the study allowed for flexible dosing, which could have introduced heterogeneity, but also resulted in greater generalizability. Fifth, although differences in time since study enrollment between early response and early nonresponse subjects could have played a role regarding the respective response patterns, we did not have data available to compute this variable. Finally, it is unknown whether the predictive power of early improvement would differ if medications other than olanzapine were used to treat acute mania or mixed states. Future studies of early response and early nonresponse in pediatric bipolar disorder are needed that investigate other antipsychotics and traditional mood stabilizers and that follow patients for longer periods to assess the relationship between early response/early nonresponse and sustained remission over a longer duration. Furthermore, different thresholds for early response may need to be tested a priori that take into account our ROC curve finding of a higher threshold than ≥ 25%.

CONCLUSIONS

Adolescents with manic- or mixed-episode bipolar disorder receiving olanzapine achieved the majority of symptomatic improvement during the first week of treatment. Early response at week 1 predicted ultimate response and remission at week 3. Early response patients had high predictive power for ultimate response, and early nonresponse patients were more likely to remain nonresponders at the study endpoint. A 25% improvement threshold for defining early response may be too low, and a 35% threshold may be more accurate and will need to be explored in future studies. Taken together, our findings strengthen the case for the implementation of an early improvement measure as a tool for a measurement-based prediction of treatment outcomes that can inform early treatment decision-making in clinical practice.

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Supplementary material: See accompanying pages.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.

Supplementary material follows this article.

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Supplementary Material

Article Title: Baseline Characteristics and Early Response at Week 1 Predict Treatment Outcome in Adolescents With Bipolar Manic or Mixed Episode Treated With Olanzapine: Results From a 3-Week, Randomized, Placebo-Controlled Trial

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List of Supplementary Material for the article

1. **eTable 1** Change in YMRS Total Score from Baseline to Each of the Follow-up Visits in ER, ENR of Olanzapine and Placebo

2. **eTable 2** Predictors for 4 Category Reductions of YMRS Randomized to Olanzapine at Study Endpoint (Week 3 LOCF)

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Supplementary eTable 1. Change in YMRS Total Score from Baseline to Each of the Follow-up Visits in ER, ENR of Olanzapine and Placebo

	ER (**n = 72**)		ENR (**n = 32**)		PBO (**n = 54**)		ER vs PBO	ENR vs PBO
Week	Mean	SD	Mean	SD	Mean	SD	*p*-value	*p*-value
1	-16.75	7.39	-3.31	3.92	-8.06	7.38	**<.001**	**0.011**
2	-18.24	8.76	-9.28	8.03	-7.49	10.56	**<.001**	0.336
3	-20.25	8.95	-10.22	7.61	-11.11	9.05	**<.001**	0.674

Bolded p-value: $p<0.05$.

Patients with ER showed a ≥25% reduction from baseline in YMRS Total score.

Abbreviations: ER = early response, ENR = early non-response; PBO = placebo; SD = standard deviation, YMRS = Young's Mania Rating Scale

Supplementary eTable 2. Predictors for 4 Category Reductions of YMRS Randomized to Olanzapine at Study Endpoint (Week 3 LOCF)

Percent Improvement over No Improvement Category	Predictor	OR	95% LCL	95% UCL	*p*-value
1 to 24%	Age at onset	1.491	1.064	2.089	**0.020**
	Days to maximum dose	1.520	1.053	2.195	0.206
	Baseline YMRS score	1.279	1.051	1.556	**0.014**
	Baseline CDRS-R score	1.112	1.025	1.205	**0.010**
25 to 49%	Age at onset	1.378	1.031	1.841	**0.030**
	Days to maximum dose	1.632	1.143	2.330	**0.007**
	Baseline YMRS score	1.223	1.017	1.472	**0.032**
	Baseline CDRS-R score	1.073	0.993	1.158	0.074
50 to 74%	Age at onset	1.480	1.096	1.999	**0.010**
	Days to maximum dose	1.679	1.174	2.400	**0.005**
	Baseline YMRS score	1.151	0.956	1.387	0.137
	Baseline CDRS-R score	1.065	0.986	1.152	0.110
75%+	Age at onset	1.455	1.072	1.975	**0.016**
	Days to maximum dose	1.530	1.070	2.186	**0.020**
	Baseline YMRS score	1.234	1.023	1.488	**0.028**
	Baseline CDRS-R score	1.069	0.989	1.156	0.091

Bolded p-value: $p<0.05$.

Multiple Ordinal Logistic Regression Analyses,

(1) Later age at illness onset has a positive impact on an improved response across all categories.

(2) Longer days to maximum dose indicate improvement ≥25%.

(3) Improvement in 3 of the 4 categories is associated with higher baseline YMRS scores (exception is 50 - 74%).

(4) Higher baseline CDRS-R scores predict improvement in the < 25% improvement category only.

Abbreviations: CDRS-R = Children's Depression Rating Scale-Revised, LCL = Lower Confidence Limit, LOCF = Last Observation Carried Forward, OR = Odd Ratio, UCL = Upper Confidence Limit, YMRS = Young's Mania Rating Scale