Brief Report

Inositol augmentation of lithium or valproate for bipolar depression

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Objective: Despite promising new therapies, bipolar depression remains difficult to treat. Up to half of patients do not respond adequately to currently approved treatments. This study evaluated the efficacy of adjunctive inositol for bipolar depression.

Methods: Seventeen participants with DSM-IV criteria for bipolar depression and a 17-item Hamilton Rating Scale for Depression (HRSD) ≥15 on proven therapeutic levels of lithium or valproate for >2 weeks were randomized to receive double-blind inositol or placebo for 6 weeks. At the end of double-blind treatment, subjects were eligible for an 8-week open-label trial of inositol.

Results: Response was defined *a priori* as >50% reduction in the HRSD and a Clinical Global Impression of 1–2. Four of nine subjects (44%) on inositol and zero of eight subjects on placebo met response criteria ($p = 0.053$). There was no difference between groups in the average change score for the HRSD or Young Mania Rating Scale (YMRS). Response to inositol was highly variable. Of nine subjects randomized to inositol, two had >50% worsening in HRSD scores at the end of treatment, three had no change and four had >50% improvement. Those who had worsening in depressive symptoms on inositol had significantly higher scores at baseline on the YMRS total score and irritability, disruptive/aggressive behavior and unkempt appearance items.

Conclusions: There was a trend for more subjects on inositol to show improvement in bipolar depression symptoms, but, on average, inositol was not more effective than placebo as an adjunct for bipolar depression. Baseline levels of anger or hostility may be predictive of clinical response to inositol.

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Bipolar affective disorder (BPAD) is a chronic mental illness that affects approximately 1% of the adult US population (1, 2) and is associated with a 15% rate of suicide (3). While there are many options for treatment of refractory mania (4–7), bipolar depression that is resistant to treatment with mood stabilizers remains difficult to treat (8). Therapies are available that shorten the duration and reduce the severity of depressive episodes and reduce the risk of recurrence, but up to half of patients do not respond adequately to available treatments for bipolar depression (9). Identification of more effective treatments for the depressed phase of BPAD is a priority.

Myo-inositol (inositol), $C_6H_{12}O_6$, is an isomer of glucose that is a ubiquitous component of mammalian cells and is present in the diet in quantities of approximately 1 g/day. Inositol is a precursor in the phosphatidylinositol second messenger system,

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a signal transduction system involved in the action of neurotransmitters such as the alpha 1 noradrenergic, muscarinic cholinergic, metabotrobic glutamate and serotonin (5HT2) receptors (10). Inositol has been shown to be decreased in the cerebrospinal fluid (CSF), though not the serum, of depressed patients with bipolar and unipolar disorder (11), although others did not replicate this finding (12). Inositol has also been shown to be decreased in the anterior cingulate in adults with unipolar depression (13). Increased levels of the monophosphatase enzyme that breaks down inositol have been reported in patients with depression and schizophrenia (14). Inositol is also decreased in the frontal cortex of postmortem brains of patients with BPAD and suicide victims compared with normal controls (15).

Mood stabilizers appear to share a common mechanism of action that involves stabilization of inositol signaling. In human astrocytoma cells, pharmacologically relevant doses of lithium, valproate or carbamazepine decreased inositol uptake at high inositol concentrations and increased inositol uptake at low inositol concentrations (16). Lithium, valproate and carbamazepine all inhibit the collapse of sensory neuron growth cones and increase the growth cone area, an effect that was reversed by inositol and inhibitors of the enzyme, prolyl oligopeptidase (17). This implicates inositol depletion as a common mechanism that may underlie the therapeutic antimanic action of mood stabilizers. Recent work with valproate acid has revealed that valproate also directly inhibits prolyl oligopeptidase, an action that increases inositol availability (18). Thus, valproic acid can directly increase inositol levels and directly decrease inositol levels. The authors suggest that stable mood may be dependent on stable inositol signaling and propose a model by which valproic acid may limit mood swings to mania by decreasing inositol signaling and may limit mood swings to depression by inhibiting prolyl oligopeptidase and thus increasing inositol signaling.

Based on this model, inositol augmentation of mood stabilizer treatment may be a promising therapeutic strategy for bipolar depression.

Orally administered inositol increases CSF inositol levels by 70% in humans (19) and, in doses of 6–20 g/day, has been effective in treatment of unipolar depression, panic disorder, and obsessive compulsive disorder (OCD) (20–22). In a 4-week trial, subjects with unipolar ($n = 22$) or bipolar ($n = 6$) depression randomized to inositol 12 g/day had significantly greater improvements in Hamilton Rating Scale for Depression (HRSD) scores than those randomized to placebo. There was no emergence of mania in this trial and half relapsed after inositol discontinuation (23). In one small, well-designed placebo-controlled trial of inositol augmentation of lithium, valproate or carbamazepine for bipolar depression, Chengappa et al. demonstrated a trend for inositol to improve depressive symptoms. However, there was a substantial placebo effect in this trial (24).

We conducted a 6-week, double-blind, placebo-controlled trial to evaluate whether inositol augmentation of mood stabilizer treatment is effective for bipolar depression. Our hypothesis was that a greater proportion of subjects would respond to inositol augmentation when compared with placebo, that there would be a greater mean reduction in ratings of depression symptoms with inositol augmentation compared with placebo, and that addition of inositol 5–20 g/day in divided doses to mood stabilizer treatment would be safe, well tolerated and not associated with treatment-emergent mania.

Materials and methods

The study was conducted at the Harvard Bipolar Clinical and Research Program at the Massachusetts General Hospital (MGH) and was sponsored by the Stanley Medical Research Institute. Inositol was administered under an Investigational New Drug Application from the US Food and Drug Administration. The protocol was approved by the MGH Human Subjects Committee. After complete description of the study, all subjects signed informed consent prior to participation in study procedures.

Eligible subjects were adults, aged 18–65, who met DSM-IV and Structured Clinical Interview for DSM-IV (SCID) criteria for bipolar I or II disorder, with current episode depressed and a threshold level of symptom severity indicating at least mild depression (a score of 15 or greater on the 17-item HRSD) for two consecutive visits despite more than 2 weeks of proven therapeutic levels of lithium or valproate prior to enrollment. The severity cutoff of 15 on the 17-item HRSD was chosen in order to include subjects who may have had some effect of mood stabilizer treatment on depressed mood but remained symptomatic and still met criteria for current depressive episode. HRSD cutoffs of 13–15 have demonstrated sensitivity of 0.88 and specificity of 0.86 and 0.99, respectively, for major depressive episode (25, 26), and treatment trials in depression have used a clinician-rated score of ≥15 on the 17-item HRSD for inclusion (27, 28). Therapeutic blood levels were defined as follows: lithium serum concentration > 0.80 mEq/L or valproate serum concentration > 50 mg/L. Subjects who were not

eligible included those who had a positive test for any drug of abuse at screening, self-report of active substance abuse in the 2 weeks prior to enrollment or substance dependence in the 2 months prior to enrollment, a diagnosis of schizophrenia, dementia, delirium, seizure disorder, OCD, diabetes mellitus, major medical illness judged to be unstable, mixed affective state or use of any investigational drug in the 30 days prior to enrollment. Women of childbearing potential were eligible if they were using acceptable means of contraception. Screening included a complete medical and psychiatric history, physical examination, and routine laboratory screen that included routine chemistry and hematology panels, urinalysis, thyroid stimulating hormone (TSH), human chorionic gonadotropin (HCG), serum glucose, urine drug and alcohol screen and serum lithium or valproate concentration.

Concomitant antidepressants, antipsychotics, anticonvulsants, benzodiazepines and thyroid supplementation were allowed if the dosage had been stable for at least 2 weeks. Medication dosages were kept constant during both the double-blind and open phases of the study. All subjects who completed the double-blind phase were eligible for the open phase.

Interventions

Inositol (Spectrum Chemical Manufacturing Corp./Spectrum Quality Products Inc., Gardena, CA, USA) powder or identical lactose powder were prepared as 950-mg capsules by the MGH Research Pharmacy. The schedule for administration of study medication was as follows: three capsules b.i.d. for 2 days, five capsules b.i.d. for 2 days, and then five capsules t.i.d. Subjects continued to take five capsules t.i.d. or their highest tolerated dose up to five capsules t.i.d. through the end of the third study week. After the third week, the dose was titrated as tolerated in the range of 6–20 capsules per day by the research psychiatrist based on tolerability and response of depressive symptoms. Study medications were distributed weekly.

Assessments

Subjects were monitored weekly during the 6-week double-blind phase of the trial. The Young Mania Rating Scale (YMRS) (29), Brief Psychiatric Rating Scale (30), the 17-item HRSD (31), Clinical Global Impression (CGI), and SAFTEE (32) were administered by semi-structured interview at each visit. Unused medications and self-report of missed doses were collected each week. Weekly pill counts were used along with patient self-report to calculate average weekly inositol doses.

Routine laboratory tests including serum lithium or valproate were performed at baseline and week 6 and repeated at any time during the trial, if needed, to monitor clinical condition.

Analysis

We used an intent-to-treat analysis. Responders were defined *a priori* as those subjects who demonstrated a 50% or greater improvement from baseline at end of treatment in the HRSD score and a CGI of 1 or 2 (not ill at all or borderline mentally ill). Fisher's exact test was performed to compare the proportion of responders in each treatment group. The effect of treatment on the primary outcome measure was considered significant if a one-sided alpha < 0.05. All other comparisons were considered using two-tailed tests of significance. Because of a between-group difference in baseline HRSD scores, continuous outcomes were compared using repeated-measures ANCOVA controlling for baseline HRDS scores and age.

Results

Forty-four subjects were screened. Twenty-two subjects did not meet criteria at screening (of these, two subjects became euthymic after their subtherapeutic lithium levels were increased); two subjects were lost to follow up prior to enrollment; two subjects withdrew consent prior to randomization; and 18 subjects were randomized to receive inositol or placebo. One subject withdrew consent after randomization but prior to receiving study medications. Seventeen subjects entered the study and received study medications. Intent-to-treat analyses were carried out on these 17 subjects. Fifteen subjects completed the double-blind portion of the study. Two subjects, one in the inositol and one in the placebo group, dropped out of the study during the 6-week, double-blind phase due to worsened psychiatric symptoms.

Sixteen subjects had a diagnosis of bipolar I disorder, and one had a diagnosis of bipolar II disorder. There were six women and 11 men with a mean age of 45.76 (12.17) years. Baseline HRSD scores were lower for those randomized to inositol (mean 17.9 $\pm$ 3.1) than for those randomized to placebo (mean 22.1 $\pm$ 3.27) ($t = 2.74$, $p = 0.015$). Table 1 describes further demographic information. Mean maximal inositol dose achieved during the double-blind phase was 13.87 (2.50) grams/day (range 9.5–16.15 g/day). All subjects enrolled in

Table 1. Baseline characteristics

	Inositol (n = 9)	Placebo (n = 8)
Female	5/9	1/8
Age	50.7 (7.9)	40.3 (14.2)
HRSD	17.9 (3.1)	22.1 (3.3)*
YMRS	4.0 (3.6)	6.8 (4.3)
CGI	4.0 (0.8)	4.4 (1.1)
GAF (past month)	60.0 (1.0)	59.0 (8.2)
BPRS	37.78 (7.45)	38.25 (3.77)
Lithium therapy	3	6
Lithium dose	1200 (300)	1075 (240)
Lithium level (mg/dL)	0.98 (0.24)	0.73 (0.30)
Lithium + gabapentin	0	1
Valproate therapy	6	2
Valproate dose	1250 (273.9)	1500 (0)
Valproate level	80.11 (20.36)	86.33 (55.08)
Antipsychotics	6/9	4/8
Antidepressant use	5	4

HRSD = Hamilton Rating Scale for Depression; YMRS = Young Mania Rating Scale; CGI = Clinical Global Impression Scale; GAF = Global Impression of Function; BPRS = Brief Psychiatric Rating Scale.
*$t = 2.7$, $p = 0.015$.

the trial had been on a therapeutic level of lithium or valproate for >4 weeks.

Efficacy results

The primary outcome measure was clinical response. Four of nine (44%) subjects in the inositol group were responders compared with zero of eight subjects receiving placebo ($p = 0.053$; Fisher's exact test) All four responders to inositol were on a concomitant atypical antipsychotic medication, three were on lithium, and two were on an antidepressant medication.

There was no significant difference between the inositol and placebo-treated groups on the mean HRSD score at week 6 (13.8, SD = 8.1 for the inositol group compared to 15.8, SD = 6.8 in the placebo group). From baseline to week 6, there was a mean reduction in the HRSD of 4.11 (8.92) in the inositol group and 6.38 (4.66) in the placebo group. ANCOVA of week 6 HRSD scores by medication status, controlling for baseline score, was not significant, $F(1, 16) = 0.58$, MSE = 3.24, $p > 0.05$, partial $\eta^2 = 0.004$ (see Table 2).

From baseline to week 6, there was a mean increase in the YMRS of 0.80 (5.23) in the inositol group and 0.75 (4.66) in the placebo group. ANCOVA of week 6 YMRS scores by medication status, controlling for baseline score was not significant, $F(1, 16) = 0.12$, MSE = 5.34, $p > 0.05$, partial $\eta^2 = 0.008$ (see Table 2). There were no cases of treatment-emergent mania.

There was a highly variable response to inositol (see Fig. 1). Two subjects had a 50% or greater worsening in HRSD with inositol treatment, three subjects had less than a 25% change, and four subjects had a 50% or greater improvement. Response to placebo was not as variable. Only one of eight subjects receiving placebo had an increase in HRSD score during the trial, and this increase was only 7%. Because of the highly variable response among subjects randomized to

Table 2. Effect of inositol on depression and Clinical Global Impression in patients with treatment-resistant bipolar depression

	Age/sex	Medication	Study medication	Response to double-blind treatment	Weeks on open-extension treatment	Baseline		Week 6		End of open phase	
						HRSD 17	CGI	HRSD 17	CGI	HRSD 17	CGI
1	59/F	Lithium	Inositol	Yes	10	13	5	1	2	2	1
2	47/M	Lithium	Inositol	Yes	8	21	3	8	2	4	1
3	51/F	Valproate	Inositol	Yes	8	22	5	11	2	6	2
4	56/F	Valproate	Inositol	Yes	8	21	4	9	2	14	3
5	50/M	Lithium	Inositol	No	8	18	–	14	3	9	1
6	50/M	Valproate	Inositol	No	8	16	4	27	3	15	3
7	41/F	Valproate	Inositol	No	0	19	3	18	–	NA	NA
8	63/M	Valproate	Inositol	No	0	15	4	12	3	NA	NA
9	39/F	Valproate	Inositol	No	0	16	4	24	–	NA	NA
10	41/M	Lithium	Placebo	No	8	20	5	11	2	15	2
11	28/M	Lithium	Placebo	No	8	23	3	19	3	17	–
12	57/M	Lithium	Placebo	No	8	24	4	16	2	17	2
13	60/M	Lithium	Placebo	No	8	22	5	10	3	16	3
14	52/M	Valproate	Placebo	No	2	17	3	9	3	7	–
15	27/F	Lithium	Placebo	No	0	20	4	18	–	NA	NA
16	30/M	Lithium	Placebo	No	0	23	6	13	–	NA	NA
17	27/M	Valproate	Placebo	No	0	28	5	30	–	NA	NA

HRSD = Hamilton Rating Scale for Depression; CGI = Clinical Global Impression Scale; NA = not applicable.

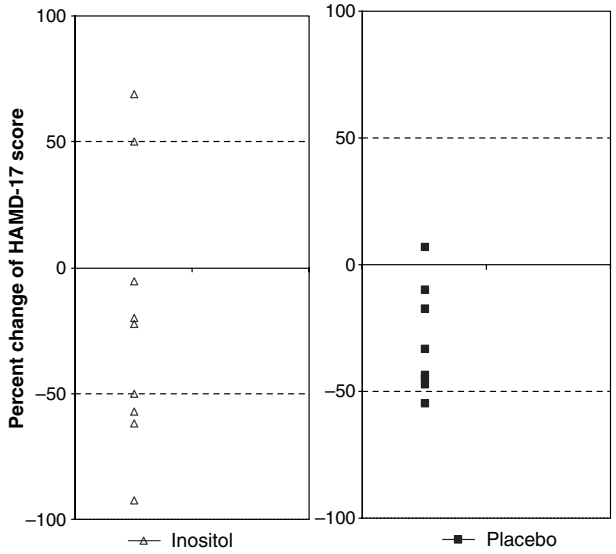

Fig. 1. Hamilton Depression Rating Scale scores during a double-blind, placebo-controlled trial of inositol in patients with treatment-resistant bipolar depression.

inositol, we conducted an exploration of associations between baseline symptoms and change in HRSD scores. The two inositol-treated subjects who had worsening in HRSD scores during the trial had significantly higher baseline mania ratings than those whose depressive symptoms improved or did not change with inositol treatment: YMRS total score, 10.00 (1.41) versus 3.57 (0.92), $t = -3.45$, $p = 0.011$; YMRS irritability item, 3.0 (1.41) versus 0.71 (1.11), $t = -2.46$, $p = 0.044$; speech rate item, 0.50 (0.70) versus 0.00 (0.00), $t = -2.33$, $p = 0.052$; disruptive/aggressive behavior, 2.50 (0.71) versus 0.00 (0.00), $t = -11.67$, $p < 0.0001$; and disheveled appearance items, 1.00 (0.00) versus 0.14 (0.38), $t = -3.06$, $p = 0.018$. The symptoms on the HRSD that worsened with inositol treatment were depressed mood, somatic anxiety, somatic symptoms (GI), and weight loss. Manic symptoms in these two patients did not worsen.

There were no baseline differences in HRSD scores in subjects taking lithium [20.44 (3.3)] versus valproate [19.25 (4.3)] and there was a trend for the lithium-treated group to demonstrate greater improvement in HRSD scores [−8.22 (4.02)] compared to the valproate group [−1.75 (8.48), $t = 2.05$, $p = 0.058$]. Among those randomized to inositol, those who were on lithium ($n = 3$) had a 9.66 (4.9) point reduction in HRSD scores and those on valproate ($n = 6$) had a 1.33 (9.47) point reduction in HRSD scores, $t = 1.73$, $p = 0.13$. Both of the subjects whose HRSD worsened with inositol treatment were treated with valproate.

Follow up and open-extension treatment

Inositol titration in the open phase was identical to the titration for the double-blind phase for those who were initially randomized to placebo. For those who were initially randomized to inositol, their dose of inositol remained stable in the open period.

Six subjects continued treatment with inositol into the open-extension treatment phase, including all four subjects who met the 'responder' criteria at 6 weeks, as previously defined. Four of the six subjects showed improvement on the HRSD 17 scores with continued inositol treatment. Two of these subjects also had improved CGI scores; the other two had stable CGI scores at the end of the open-extension treatment. One subject who had a very low HRSD 17 score at the baseline of the open-extension had an increase of '1' on this measure at the end of the open-extension, but her CGI score decreased. The remaining subject had increased scores on both the HRSD 17 and the CGI at the time of termination. Five subjects who were non-responders to placebo at week 6 chose to participate in the open-extension treatment. Two of these subjects had a slight reduction in HRSD 17 score but no change in GCI, and three had an increase in HRSD with stable CGI scores (Table 2).

Adverse events and safety data

Two subjects were withdrawn from the study because of worsening psychiatric symptoms. One subject who was randomized to inositol was withdrawn from the study after the week 5 visit just prior to being hospitalized for increasing agitation and passive suicidal ideation. This subject had discontinued inositol 1 week prior to hospitalization. One subject who was receiving placebo dropped out of the study 3 days after initiation of study medications because of new onset psychosis and suicidal ideation. This subject was subsequently hospitalized and study medication was discontinued.

Adherence

Based on the return of empty bottles of inositol, all subjects except the two who dropped out were adherent to the study medication and procedures. All participants had a therapeutic dose of lithium or valproate throughout the study.

Discussion

In this study, there was a trend suggesting that inositol augmentation of mood stabilizer treatment may be superior to placebo for refractory bipolar

depression on the primary outcome measure, a responder analysis. However, on average, inositol was not superior to placebo on the secondary outcome measure, change from baseline in the 17-item HRSD. These results are consistent with those of Chengappa et al. (24) who found a trend toward improvement in depressive symptoms with inositol in subjects with adequately treated bipolar depression despite a large placebo response. In the present study we attempted to reduce the placebo response rate with a rigorous definition of response and by requiring severe symptoms of depression on two consecutive visits despite at least 4 weeks of proven therapeutic levels of lithium or valproate. Despite these efforts to reduce the placebo effect, five of eight placebo-treated patients had more than a 7-point reduction in the HRSD.

The response to inositol was highly variable, and depression scores in two subjects worsened considerably. We conducted an exploratory secondary analysis to evaluate whether baseline clinical factors were associated with variability in response to inositol. The two subjects who worsened with inositol treatment had significantly higher mean scores at baseline on YMRS total scores and irritability, increased speech, disruptive/aggressive behavior and disheveled appearance items than the other seven subjects. This exploratory secondary analysis suggests that depressed subjects with symptoms of agitation may respond less well to inositol treatment. Cheng et al. proposed an intriguing model in which mood stabilizers exert antimanic action by decreasing inositol signaling and exert antidepressant activity by increasing inositol signaling. However, we are unable to provide a simple explanation for the effect of baseline symptoms on observed variability in clinical response to inositol in terms of this model (18). In the model, manic symptoms at baseline would be associated with higher baseline inositol tone and addition of inositol, at least in the absence of mood stabilizer treatment, would be associated with further increase in inositol tone and increased manic symptoms. In this study, mania ratings did not worsen with inositol treatment in patients with higher baseline manic symptoms. Rather, higher baseline ratings of mania were associated with worsening of depressive symptoms with inositol treatment. This discussion is speculative as it is based on an exploratory analysis in nine participants. However, further investigation into baseline predictors of the effect of inositol on mood may be warranted.

Low inositol levels have been previously shown to be associated with bipolar depression (11). The effect of inositol on depressive symptoms has been variable (33), and it is possible that inositol may be effective as an antidepressant in a subset of patients with lower baseline inositol. A limitation of this trial is that we did not have measures of baseline CSF inositol levels. The conclusions of this trial are limited by the small sample size and the unequal distribution of gender across treatment groups. The small sample size did not permit use of a multivariable analysis to control for effects of age and gender. Because the baseline HSRD scores were different across groups, we compared change scores (week 6 score or LOCF − baseline score) in addition to end of treatment scores. Finally, this study was designed to evaluate whether inositol would be effective as an adjunctive treatment to lithium or valproate. It is not known whether inositol may be effective as monotherapy.

In conclusion, there was a trend for more subjects with bipolar depression to improve on inositol than placebo as an adjunct to lithium or valproate. Response to inositol was variable and may be related to baseline symptoms of agitation or mania. The results suggest that further study to determine whether inositol may be effective in a subpopulation without agitation or aggressive behavior and whether inositol may be more effective in treatment-resistant lithium-treated patients than valproate-treated patients may be warranted. Additionally, further study into the relationship between measures of phosphoinositol signaling and clinical mood symptoms and into whether inositol may be effective in a subset of patients with low inositol levels may also be warranted.

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