Double-Blind, Placebo-Controlled, Crossover Trial of Inositol Treatment for Panic Disorder

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Objective: *Because they found in an earlier study that inositol, an important intracellular second-messenger precursor, was effective against depression in open and double-blind trials, the authors studied its effectiveness against panic disorder.* *Method:* *Twenty-one patients with panic disorder with or without agoraphobia completed a double-blind, placebo-controlled, 4-week, random-assignment crossover treatment trial of 12 g/day of inositol.* *Results:* *The frequency and severity of panic attacks and the severity of agoraphobia declined significantly more after inositol than after placebo administration. Side effects were minimal.* *Conclusions:* *The authors conclude that inositol's efficacy, the absence of significant side effects, and the fact that inositol is a natural component of the human diet make it a potentially attractive therapeutic for panic disorder.*

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Inositol is an isomer of glucose and a natural constituent of the normal human diet (1). Interest in inositol accelerated with the discovery of the phosphatidyl-inositol cycle. The phosphatidyl-inositol cycle is a second-messenger system used by some noradrenergic α_1 and serotonin$_2$ receptors, among others. Kofman and Belmaker (2) showed that pharmacological doses of inositol have behavioral effects in animals. Twelve g/day of inositol penetrates the blood-brain barrier in man (3). Acting on a report that inositol CSF levels are low in depressed patients (4), we found that inositol in doses of 6 g/day and 12 g/day is a potential treatment for depression in both open and double-blind, placebo-controlled trials (5). Because some antidepressants are also effective against panic disorder, we decided to conduct a trial of inositol treatment for panic disorder.

METHOD

The subjects for the study were 25 patients who had a DSM-III-R diagnosis of panic disorder or panic disorder with agoraphobia. They were screened with a routine psychiatric and medical evaluation. Exclusion criteria were other psychiatric disorders, physical disorders, and pregnancy. All patients gave written informed consent to their participation in the study, and the design was approved by the institutional review boards of the centers where the study was conducted. Patients who were taking medications withdrew from them at least 1 week before beginning a formal washout period; only two patients actually withdrew from medications this close to the study. Patients were prepared to curtail conventional treatments for panic disorder in the hope of finding a new treatment without troubling side effects. The only medication allowed apart from inositol and placebo was 1 mg of oral lorazepam as needed for anxiety.

Placebo was mannitol (N=10) or glucose (N=11) (21 patients completed the study). The treatments were supplied in identical-appearing white powders with similar tastes and solubilities. Patients took 6 g of medication dissolved in juice twice a day. All patients began with a 1-week "run-in" period during which they received open placebo (N=10) or no medication (N=11). Thereafter each patient was randomly assigned to double-blind placebo or inositol for 4 weeks; each patient then crossed over to the alternate substance for another 4 weeks.

Patients completed daily panic diaries (6) in which they recorded the occurrence of panic attacks, the number of symptoms (from a DSM-III-R list) in each attack, and the subjective severity of each attack. They also recorded their daily use, if any, of lorazepam. Investigators reviewed the diaries at each weekly assessment and completed the Marks-Matthews Phobia Scale (7), the Hamilton Anxiety Rating Scale (8), and the Hamilton Depression Rating Scale (9).

A panic score was calculated by taking the mean rating of severity of attacks (range=0–10; 0=nonexistent, 10=worst ever) and the number of symptoms per attack and multiplying this mean by the number of attacks per week.

Baseline measures were the results at the end of the run-in week. Since the run-in phase of the trial was brief, and there was no washout phase between the placebo and the inositol phases, we used the means for the end of the third and fourth weeks of the two treatments to compare placebo and inositol results.

RESULTS

Of the 25 patients enrolled in the study, 21 completed it. Two withdrew before beginning treatment. One pa-

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TABLE 1. Number of Panic Attacks at Baseline, During Placebo Administration, and During Inositol Treatment for 21 Patients With Panic Disorder

Patient	Panic Attacks per Week								
	Baseline (Week 0)	Placebo Administration				Inositol Treatment			
		Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4
1	6	1	1	0	3	1	4	0	—[a]
2	6	1	0	2	0	2	1	1	1
3	6	1	4	0	0	3	4	3	4
4	6	4	5	1	4	4	3	2	4
5	0	0	0	0	2	0	0	0	0
6	6	6	7	10	10	10	8	5	8
7	1	2	5	2	4	0	2	0	1
8	10	6	8	6	4	4	5	4	2
9	0	1	0	1	0	0	0	1	2
10	0	0	0	1	1	0	0	0	1
11	0	0	0	1	0	0	5	3	3
12	3	0	1	0	0	0	1	2	0
13	3	2	3	3	4	3	2	1	1
14	2	1	2	3	4	3	2	1	1
15	3	3	4	3	2	3	3	4	4
16	5	6	5	4	5	8	3	2	2
17	7	2	4	6	7	8	6	4	3
18	56	67	32	15	32	35	24	21	12
19	14	17	23	28	14	10	13	8	14
20	49	48	32	30	26	7	0	0	0
21	21	6	10	13	10	4	3	0	8

[a]For this patient, the mean number of attacks while receiving inositol was computed from weeks 2 and 3.

TABLE 2. Mean Number of Panic Attacks, Panic Scores, and Phobia Scores at Baseline, During Placebo Administration, and During Inositol Treatment for 21 Patients With Panic Disorder

Measure	Baseline (Week 0)		Placebo Administration								Inositol Treatment							
			Week 1		Week 2		Week 3		Week 4		Week 1		Week 2		Week 3		Week 4	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Number of attacks/ week[a]	9.7	15	8.3	17	7.0	10	6.1	9	6.3	9	5.0	8	4.2	6	3.0	5	3.7	4
Panic score[b]	72	140	63	160	33	50	24	31	31	50	27	49	18	19	10	11	11	11
Phobia score[c]	4.3	3	3.1	3	3.2	3	3.4	3	3.4	3	3.3	3	3.0	3	2.2	2	2.2	2

[a]Significant difference between placebo and inositol at weeks 3 and 4 ($F=4.9$, $df=1, 19$, $p=0.04$; repeated measures ANOVA).
[b]Significant difference between placebo and inositol at weeks 3 and 4 ($F=9.0$, $df=1, 19$, $p=0.007$; repeated measures ANOVA). Significant interaction between treatment and order of treatments ($F=7.2$, $df=1, 19$, $p=0.01$).
[c]Significant difference between placebo and inositol at weeks 3 and 4 ($F=6.1$, $df=1, 19$, $p=0.02$; repeated measures ANOVA).

tient completed 4 weeks of inositol and 1 week of placebo and then withdrew without a clear explanation; he improved while taking inositol. Another patient completed the initial 3 weeks of placebo but dropped out because of hypomania before the crossover to inositol.

Nine of the patients were men and 12 were women. Their mean age was 35.8 years (SD=7). Five patients had panic disorder and 16 had panic disorder with agoraphobia. The mean duration of illness was 3.9 years (SD=3). Response to previous treatments did not affect response in this study (data not shown). Ten patients were randomly assigned to placebo first, and 11 were assigned to inositol first.

Patients improved more on every outcome measure while receiving inositol than they did while receiving placebo. The difference in number of panic attacks, panic scores, and phobia scores was significant (tables 1 and 2); the difference in Hamilton anxiety and depression scores was not (not shown). When we conducted an analysis of covariance (ANCOVA) with baseline data as the covariate on the data from weeks 3 and 4 of the first month alone, as if this were a parallel groups study, we found that the phobia scores did not differ in the first month. This ANCOVA found that the number of panic attacks was significantly lower during inositol treatment, however: the mean number of panic attacks was 10.1 (SD=10) during placebo administration and 2.4 (SD=1) during inositol treatment ($F=5.7$, $df=1, 18$, $p=0.03$). The ANCOVA also found that panic scores tended to be lower in the first month: the mean panic score was 41.7 (SD=41) during placebo administration and 9.4 (SD=9) during inositol treatment ($F=3.5$, $df=1, 18$, $p=0.08$).

Eleven patients used lorazepam for anxiety. Lorazepam use did not differ between the placebo and inositol phases (mean=3.8 mg/week, SD=6, during placebo ad-

ministration and mean=3.0 mg/week, SD=5, during inositol treatment) (t=1.6, df=20, p=0.12, paired t test). Lorazepam use did not interact with inositol's effects on panic attacks. The patients who were taking lorazepam had less response to inositol for phobia than did those who were not taking lorazepam (F=8.9, df=1, 14, p=0.01, for phobia scores by treatment by lorazepam use).

Two patients complained of sleepiness while taking inositol. One patient complained of stomachache while taking placebo.

DISCUSSION

The effect of inositol appears to be clinically meaningful: the number of attacks per week fell from about 10 to about six while patients were taking placebo, and to about three and a half while they were taking inositol. Ten of the 21 patients were classified as "true" inositol responders and three were placebo responders (analysis available on request from Dr. Benjamin).

We have previously shown that inositol has antidepressant efficacy (5). Many antidepressants are also antipanic agents. Most biochemical theories of anxiety and depression implicate the same protagonists—namely, noradrenergic and serotonergic pathways. Important subtypes of these receptors use the phosphatidyl-inositol cycle as their intracellular second messenger (10).

The absence of substantial side effects and the fact that inositol is a natural component of the human diet make it a potentially attractive therapeutic. Inositol has been given to patients with diabetes in a dose of 20 g/day without ill effects (11). Future attempts to replicate or augment the effect reported here should consider using the higher dose. The second-messenger strategy, as opposed to the transmitter-receptor strategy, is a novel one for psychopharmacology and deserves further investigation.

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