Inositol deficiency diet and lithium effects


Objectives: A major hypothesis explaining the therapeutic effect of lithium (Li) in mania is depletion of inositol via inhibition of inositol monophosphatase. However, inositol is also present in the diet. Restriction of dietary inositol could theoretically enhance the effects of Li.

Methods: We used dietary inositol restriction in animal studies and also devised a palatable diet for humans that is 90% free of inositol.

Results: Dietary inositol restriction significantly augmented the inositol-reducing effect of Li in rat frontal cortex. Li reduced inositol levels by 4.7%, inositol-deficient diet by 5.1%, and Li plus inositol-deficient diet by 10.8%. However, feeding with the inositol-deficient diet did not enhance the behavioral effect of Li in the Li-pilocarpine seizure model.

Fifteen patients participated in an open clinical study of the inositol-deficient diet: six rapid cycling bipolar patients responding inadequately to Li or valproate in different phases of illness; two Li-treated bipolar outpatients with residual symptomatology, and seven inpatient Li-treated bipolar patients in non-responding acute mania. The diet had a major effect in reducing the severity of affective disorder in 10 of the patients within the first 7–14 days of treatment.

Conclusion: These results suggest that dietary inositol restriction may be useful in some bipolar patients, but controlled replication is necessary.
depletion of dietary inositol may have few physiologic effects when accomplished alone and inositol is not usually considered an essential nutrient (6), the combination of Li and dietary inositol restriction could have more marked clinical effects. Although inositol provided by diet may not be needed under normal conditions to replenish losses from the PI cycle, Li treatment that inhibits endogenous synthesis should increase the dependence on dietary inositol markedly. Agonist stimulation in the presence of Li can deplete a rat brain of up to 30% of its inositol (7), and thus a manic patient with speculatively hyperactive neurotransmission could require up to 4 gm of inositol per day to replace one third of the total inositol in a 1.2 kg human brain. Restriction of dietary inositol could markedly augment the effects of Li (8). Restriction of dietary inositol could also augment valproate treatment, since valproic acid reduces inositol synthesis in a manner similar to, but distinct from, Li (9–11). It is also possible that inositol depletion could exacerbate the side effects of Li, some of which may be due to the effects of Li on inositol metabolism (12, 13).

We report here on exploratory studies of inositol-deficient diet as an augmenting method for Li treatment of mania and bipolar disorder. First, we replicated our previous preliminary animal study (8) that indicated that dietary inositol restriction may have an effect on inositol level in the brain and enhance the effects of Li. Second, we evaluated possible behavioral effects of feeding with an inositol-deficient diet on the enhancement of pilocarpine seizures in rats treated with Li (14). Such seizures induced by Li and pilocarpine are stereospecifically reversible by intracerebroventricular inositol, and have been considered a behavioral effect of inositol depletion by Li (14). Third, we devised a palatable diet for humans that is 90% free of inositol and tested in a preliminary open study the hypothesis that such a diet would augment the clinical effect of Li and/or valproic acid.

Methods

Animals

Male Sprague–Dawley rats (starting weight 200–250 g) were randomly divided into treatment groups and housed in individual polycarbonate cages. All animals were exposed to a 12-h light/dark cycle and had free access to food and water. The regular food group was fed ordinary rat chow. The Li supplement in food was 0.2% LiCl supplement to ordinary chow. The inositol deficiency food group received only artificial food not containing inositol (sugar 65%, casein 25%, soya oil 5%, minerals 4%, and vitamins 1%).

Serum Li concentration was determined in carotid blood obtained at the time of decapitation. One milliliter of blood from decapitated control and Li-treated rats was centrifuged at 9000 g for 10 min. Serum Li levels were measured using an ion-selective electrode apparatus.

The study was approved by the Ben-Gurion University (Beer-Sheva, Israel) Institutional Review Committee for the Use of Animals, and the procedures were carried out in compliance with the Declaration of the National Institute of Health Guide for Care and Use of Laboratory Animals (15).

Analysis of brain inositol levels

After 11 days, rats were sacrificed by decapitation, and inositol levels were determined in replicate samples from cerebral cortex after storage at −70°C. Free myo-inositol was analyzed by gas chromatography (GC) using a capillary column as previously described (16) in half of the rat brains and half of the rat brains were sent to another laboratory (WTR) for replication by GC–mass spectrometry. Samples of tissue (approximately 50 mg) were dissected from the cerebral cortex, weighed, added to five volumes of distilled water containing a known amount of (2H)6 myo-inositol (Isotec, Inc., Miamisburg, OH, USA) internal standard, and homogenized. After adding two volumes of ice-cold absolute ethanol to precipitate protein, the solution was centrifuged at 3000 g for 10 min. The supernatant allowed to dry overnight using a Speed Vac Plus SC210A (Savant Instruments, Farmingdale, NY, USA). The dried residuum was then combined with 1 mL of ice-cold, distilled water, and centrifuged at 3000 rpm for 30 min at 4°C to precipitate remaining lipids. The supernatant was again dried overnight, and then combined with 100 μL of acetic anhydride in pyridine (2:1) for 20 min at 70°C to form hexaacetate derivatives. Inositol concentration was measured using the following previously reported gas chromatographic-mass spectrometric (GC-MS) method and an electron impact GC-MS system (Hewlett-Packard 5971B, Fullerton, CA, USA). One microliter of derivatized sample was automatically injected onto a 12 m × 0.20 mm HP-5MS column, with chromatographic conditions as follows: injector temperature 250°C; initial oven temperature 100°C, ramping to 215°C at 25°C/min, then to 270°C at 45°C/min; carrier gas (helium) flow rate 1.0 mL/min; and splitless
injection. Under these conditions, inositol eluted from the column at 9.3 min. The effluent from the GC column was directed into the MS source and subjected to electron impact ionization at 70 keV. Selected ion monitoring was performed at mass values 210 and 214, which were the values for the major peaks of the acetylated fragments of inositol and its deuterated, internal standard isotope, respectively. Endogenous inositol concentration was calculated from the peak area ratio (corrected for natural abundance) and the known amount of internal standard added. Samples were analyzed in duplicate, and the average coefficient of variation within sample runs was 3.7%.

Behavioral study

One group of animals (n = 10) received inositol deficiency food and a second (n = 10) regular food. All of them were treated with Li (0.2% in food for 17 days and 0.25% in food for last 8 days) before pilocarpine injection (10 mg/kg pilocarpine s.c.). After pilocarpine injection, the animals were placed in clear polycarbonate cages, and behavior scored by an observer who was blind to treatment condition.

Behavior was rated for signs of seizure according to a modified version of the scale used by Patel et al. (17): 0 – no response; 1 – gustatory movements and/or fictive scratching; 2 – tremor and/or hind limb extension; 3 – head bobbing; 4 – forelimb clonus; 5 – rearing, clonus, and falling. Each animal was observed for 15 s once every 5–10 min for 100 min. The latency to attain forelimb clonus (a score of 5) was recorded for each rat.

One hundred minutes after pilocarpine injection all animals were sacrificed by decapitation. Blood was collected from the cervical trunk for the determination of Li.

Clinical study

All patients who participated in the study had been treated previously in our bipolar clinic and had well documented histories of illness. Two experienced psychiatrists using an interview based on DSM-IV confirmed diagnosis. Patients participated in the open clinical trial if they met DSM-IV criteria for bipolar or schizoaffective disorder and had no serious physical illness including neurological illness or mental retardation. The study was approved by the Helsinki Committee and all patients gave written informed consent. Inclusion criteria for participating patients were: (i) rapid cycling bipolar patients who had responded inadequately to Li in either phase of illness; (ii) consenting Li-treated bipolar or schizoaffective outpatients with residual affective symptomatology; (iii) inpatient Li-treated bipolar or schizoaffective patients in non-responding acute mania. Patients with any active or serious physical illness were excluded and no patient had drug or alcohol abuse, or clinically significant Axis II disorder. Eleven patients were taking Li only as a mood stabilizer, three were taking Li plus valproate, and one patient on valproate alone was accepted after the results of O’Donnell et al. (9) and Shaltiel et al. (10). Patients were given usual treatment with typical or atypical neuroleptics in addition to the mood stabilizer.

All patients received dietary instruction to achieve inositol depletion (a palatable human diet with over 90% reduction of inositol content; 5, 18). Daily diet diaries were collected every week for the first month. Dietary supervision was available on a daily basis. The nutritional dietary compliance to the low inositol diet was evaluated using a Food Frequency Questionnaire adopted for this purpose. This scale allowed nutritional scoring and analysis of food consumption, a common method in nutritional studies (19).

Inositol content in food was determined based on nutritional information (18). In the Food Frequency Questionnaire that we used the subjects were asked to describe the frequency of eating food containing high levels of inositol. Portion size was specified on the questionnaire. This information was used to calculate daily average inositol intake for that week. In addition, we also used the response to the Food Frequency Questionnaire to score the dietary compliance to the low inositol diet.

Clinical rating scales [Brief Psychiatric Rating Scale, Young Mania Rating Scale (YMRS), Hamilton Depression Rating Scale (HAMD), and Clinical Global Impression] were administered by an experienced psychiatrist (MF) at baseline, weekly during the first month and monthly thereafter. Patients were dropped from the study in case of non-compliance to diet or severe exacerbation of symptoms that required changes in the pharmacological treatment. All patients were evaluated by the clinical treating physician at baseline, weekly during the first month and monthly thereafter for EKG, liver and kidney functions, and blood cell count. At each visit, treatment-emergent symptoms (side effects) were recorded on the Stanley Foundation Bipolar Network Appendix A form, and special attention was paid to common side effects of Li that could conceivably be exacerbated by inositol depletion.
Results

Animal

**Inositol levels in the frontal cortex of rats treated with inositol deficiency diet.** Table 1 shows the effects of inositol deficiency diet on frontal cortex inositol levels in rats treated with 0.2% Li chloride supplement in food for 11 days. One-way parametric ANOVA with planned comparison showed that inositol was significantly depleted by 10.8% only in Li plus inositol-deficient diet-treated group \( (F = 4.1, \text{df}_{1,115}, p < 0.045) \). In the Li-treated group and in the group which received inositol-deficient diet alone there was a trend (4.7% and 5.1%, respectively) toward inositol reduction.

Plasma Li levels in the Li-treated groups were not significantly different, and there was no correlation between Li levels in plasma and inositol levels in the frontal cortex \( (p = 0.4) \).

**Lithium-pilocarpine seizures in rats fed an inositol-deficient diet.** Table 2 illustrates the results. There was no difference in latency to clonus or number of animals attaining forelimb clonus between groups that received inositol deficiency diet or regular food.

Human

Fifteen patients participated in the open clinical study: six rapid cycling bipolar patients responding inadequately to Li or valproate in different phases of illness; two Li-treated bipolar outpatients with residual symptomatology; and seven inpatient Li-treated bipolar patients in non-responding acute mania.

Among the six rapid cycling patients only one was not compliant with diet and dropped out of the study. Another five responded to combination treatment within 2 weeks and maintained this improvement during combination treatment \( (9 \pm 1.4 \text{ point improvement in YMRS for two patients with predominantly manic symptoms and } 11 \pm 5.7 \text{ in HAMD for three patients with predominantly depressive symptoms}) \) (see Table 3). Among the seven Li-treated manic patients, two were not compliant with diet and did not respond. One who was compliant with diet did not improve during 2 weeks of treatment and stopped participation in the study. Another four Li-treated severe manic patients markedly improved within 1 week and became euthymic after 2 weeks \( (34.8 \pm 9.7 \text{ point decrease in YMRS}) \), and were still euthymic during the 4–5 months of continuation treatment. One of them was euthymic for 4 months and relapsed after cessation of diet (see Table 4). Of the two participating outpatients with residual symptoms, one bipolar woman with residual depression had little response over 2 months on the diet, and one 57-year-old woman with chronic hypomania resistant to Li over several years had marked response to the diet \( (6 \text{ point improvement in YMRS}) \) within 1 month that was maintained for 5 months.

The diet had a major effect in reducing the severity of affective disorder in 10 of the 15 patients, including five of six rapid cycling bipolar patients (Table 3), four of seven non-responding acute manic patients (Table 4) and one of the two outpatients with residual symptoms as described above.

### Table 1. Effect of inositol-deficient food (IDF) or regular food (RF) on frontal cortex inositol level

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Plasma lithium level (mmol/L; mean ± SE)</th>
<th>Frontal cortex inositol level (mmol/kg wet weight; mean ± SE)</th>
<th>% depletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDF + Li</td>
<td>31</td>
<td>0.95 ± 0.07</td>
<td>5.27 ± 0.17</td>
<td>10.8</td>
</tr>
<tr>
<td>RF + Li</td>
<td>33</td>
<td>1.05 ± 0.08</td>
<td>5.63 ± 0.26</td>
<td>4.7</td>
</tr>
<tr>
<td>IDF</td>
<td>26</td>
<td>5.61 ± 0.20</td>
<td>5.61 ± 0.20</td>
<td>5.1</td>
</tr>
<tr>
<td>RF</td>
<td>29</td>
<td>5.91 ± 0.24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

One-way ANOVA; planned comparison show statistically significant differences only between RF versus IDF + Li groups \( (F = 4.1, \text{df}_{1,115}, p < 0.05) \).

### Table 2. Effect of inositol-deficient food (IDF) or regular food (RF) on lithium-pilocarpine seizures in rats

<table>
<thead>
<tr>
<th>Food</th>
<th>Protocol</th>
<th>Li plasma level (mmol/L; mean ± SD)</th>
<th>Pilocarpine s.c.</th>
<th>Seizure (%)</th>
<th>Time to seizures (min; mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDF</td>
<td>0.2% LiCl in food for 17 days +</td>
<td>0.56 ± 0.1</td>
<td>10 mg/kg</td>
<td>10</td>
<td>34.6 ± 19.0</td>
</tr>
<tr>
<td>RF</td>
<td>0.25% LiCl in food for last 8 days</td>
<td>0.53 ± 0.04</td>
<td>10 mg/kg</td>
<td>10</td>
<td>34.1 ± 7.9</td>
</tr>
</tbody>
</table>
Table 3. Rapid cycling bipolar patients responding inadequately to lithium

<table>
<thead>
<tr>
<th>ID</th>
<th>Sex/age</th>
<th>BPRS B</th>
<th>YMRS B</th>
<th>HAMD B</th>
<th>CGI severity mania B</th>
<th>CGI severity depression B</th>
<th>Clinical background</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>F/48</td>
<td>29 49</td>
<td>7 46</td>
<td>7 15</td>
<td>4 6</td>
<td>3 3</td>
<td>Rapid cycling, severe mania with 2 year hospitalization</td>
<td>Dropout (non-compliance)</td>
</tr>
<tr>
<td>7</td>
<td>M/52</td>
<td>29 20</td>
<td>0 0</td>
<td>15 6</td>
<td>1 1</td>
<td>4 1</td>
<td>Rapid cycling without euthymic intervals. Entered study after 2 months of treatment-resistant depression</td>
<td>Great improvement in depressive symptoms within 2 weeks. Has been stable and euthymic for 4 months</td>
</tr>
<tr>
<td>9</td>
<td>M/40</td>
<td>35 25</td>
<td>17 7</td>
<td>0 0</td>
<td>4 2</td>
<td>1 1</td>
<td>Rapid cycling without euthymic intervals, predominantly manic with long treatment-resistant hospitalizations. In moderate treatment resistant mania for 1 month on study initiation</td>
<td>Much improvement in manic symptoms within 1 week; maintained for 1 month; then dropped out of study</td>
</tr>
<tr>
<td>10</td>
<td>M/25</td>
<td>23 20</td>
<td>0 0</td>
<td>9 3</td>
<td>1 1</td>
<td>4 2</td>
<td>Rapid cycling without euthymic intervals. Entered study after 2 months of treatment-resistant depression</td>
<td>Great improvement in depressive symptoms within 2 weeks followed by 2 months of euthymia and depressive relapse(^a)</td>
</tr>
<tr>
<td>14</td>
<td>M/59</td>
<td>26 18</td>
<td>8 0</td>
<td>0 0</td>
<td>3 1</td>
<td>1 1</td>
<td>Rapid cycling without euthymic intervals, predominantly manic. Entered study after 1 month of resistant mania</td>
<td>Much improvement in manic symptoms within 1 week. Complete euthymia for 2 months. Dropped from study with new angina pectoris</td>
</tr>
<tr>
<td>15</td>
<td>M/20</td>
<td>34 18</td>
<td>0 0</td>
<td>17 0</td>
<td>1 1</td>
<td>5 1</td>
<td>Rapid cycling without euthymic intervals. Entered study after 2 months of treatment-resistant depression</td>
<td>Much improvement in depressive symptoms within 2 weeks followed by 4 months euthymia</td>
</tr>
</tbody>
</table>

BPRS = Brief Psychiatric Rating Scale; YMRS = Young Mania Rating Scale; HAMD = Hamilton Depression Rating Scale; CGI = Clinical Global Impression; B = baseline. \(^a\)Data before exacerbation and poor compliance with diet.
<table>
<thead>
<tr>
<th>ID</th>
<th>Sex/age</th>
<th>BPRS</th>
<th>YMRS</th>
<th>HAMD</th>
<th>CGI severity mania</th>
<th>CGI severity depression</th>
<th>Clinical background</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/40</td>
<td>54</td>
<td>18</td>
<td>43</td>
<td>0</td>
<td>0</td>
<td>6 1 1 1</td>
<td>Severe manic episodes that never lasted &lt;2 months despite intensive treatment. Entered study 2 weeks after onset of severe mania. Marked improvement after 1 week and euthymic by 2 weeks. Still euthymic after 5 months.</td>
</tr>
<tr>
<td>3</td>
<td>F/42</td>
<td>34</td>
<td>0</td>
<td>23</td>
<td>2</td>
<td>6</td>
<td>1 5 1 1</td>
<td>Severe manic episodes, unstable remissions and long hospitalizations in the past. Entered study after 2 weeks of manic symptoms. Much improvement in manic symptoms within 1–2 weeks followed by 4 months of euthymia and manic exacerbation after cessation of diet. Marked improvement in manic symptoms within 1–2 weeks followed by a month of euthymia. Stopped study to move to another city.</td>
</tr>
<tr>
<td>6</td>
<td>F/43</td>
<td>57</td>
<td>22</td>
<td>48</td>
<td>8</td>
<td>3</td>
<td>1 6 2 1</td>
<td>Severe manic episodes, unstable remissions and long hospitalizations in the past. Entered study after 1 month of manic symptoms. Marked improvement in manic symptoms after 3 months of hospitalization.</td>
</tr>
<tr>
<td>8</td>
<td>M/27</td>
<td>39</td>
<td>41</td>
<td>23</td>
<td>19</td>
<td>0</td>
<td>5 5 1 1</td>
<td>Severe resistant mania after 3 months of hospitalization. No response to treatment, dropped out after 2 weeks.</td>
</tr>
<tr>
<td>11</td>
<td>M/38</td>
<td>52</td>
<td>52</td>
<td>35</td>
<td>34</td>
<td>3</td>
<td>3 6 6 1</td>
<td>Mania severe, 5 month hospitalization, resistant to treatment. Non-compliance.</td>
</tr>
<tr>
<td>12</td>
<td>M/25</td>
<td>45</td>
<td>45</td>
<td>23</td>
<td>23</td>
<td>0</td>
<td>6 6 1 1</td>
<td>Mania severe, 3 month hospitalization, resistant to treatment. Non-compliance.</td>
</tr>
<tr>
<td>13</td>
<td>M/58</td>
<td>28</td>
<td>18</td>
<td>35</td>
<td>0</td>
<td>0</td>
<td>6 1 1 1</td>
<td>Long hospitalizations due to resistant-to-treatment manic episodes in the past, with short unstable remissions and hypomanic residual symptoms. Entered study following 1 month of severe manic symptoms. Much improvement in manic symptoms within 1 week and very much improvement within 2 weeks. Has been stable and euthymic for 4 months.</td>
</tr>
</tbody>
</table>

BPRS = Brief Psychiatric Rating Scale; YMRS = Young Mania Rating Scale; HAMD = Hamilton Depression Rating Scale; CGI = Clinical Global Impression; B = baseline.

Data before exacerbation and poor compliance with diet.
Shaldubina et al.

Three patients dropped out very early from the study because of non-compliance with the diet, and one because of non-response after 2 weeks. One patient was excluded from the study because of exacerbation of manic symptoms after 4 months of stable state. One patient was excluded from the study because of exacerbation of depressive symptoms after 2 months of stable state.

There was a slight elevation of subjective polydipsia in one case. One patient was excluded from the study after 4 months of stable state because of suspicion of a solitary mass in the neck. After workup, nothing pathological was found. One patient was excluded from the study after 2 months of stable state because of the onset of new unstable angina pectoris. There was no exacerbation of Li-induced EKG changes or of Li-induced leukocytosis.

Discussion

Dietary therapy is increasingly in use in the treatment and prevention of atherosclerosis, hypertension, colon cancer, and other diseases (20). In psychiatry dietary approaches became unpopular because of unsupported claims in the past. However, recent studies of omega-3 fatty acid treatment of affective disorder (21) and folic acid supplementation in schizophrenia (J. Levine, Z. Stahl, B.A. Sela, V. Ruderman, R.H. Belmaker, in press) emphasize the fact that metabolic intervention via diet may be important in the management of some psychiatric disorders.

We did not find a significant reduction of inositol levels in the frontal cortex of rats after inositol deficiency diet only or Li only. Because of de novo synthesis of inositol from glucose in the various tissues including the brain, dietary inositol restriction only was not expected to decrease inositol levels in the brain. Li treatment alone often has been reported to decrease inositol in the brain (9, 22), but these findings are not consistent (23) and the magnitude of the effect may vary with the brain area (hypothalamus more than frontal cortex) (24). Dietary inositol depletion together with Li treatment was hypothesized to reduce inositol levels more significantly than Li treatment alone, since only dietary inositol is available if inositol monophosphatase is inhibited by Li. This hypothesis was confirmed by direct inositol measurement in our study.

Lithium-pilocarpine seizures were not enhanced by inositol depletion. Li-pilocarpine seizures were reported to be reversed by myo-inositol and not by its biologically inactive stereoisomer chiro-inositol (25) and this constituted evidence that the model depended on inositol depletion. However, Bersudsky et al. (26) found that inositol depletion via hyponatremia did not result in Li-pilocarpine seizures. Moreover, Evans et al. (27) reported that Li enhances muscarinic excitation by presynaptic facilitation that is not related to inositol depletion (27). Thus the negative results of inositol depletion in this behavioral model do not strongly argue against the possible utility of inositol depletion to enhance the effects of Li in bipolar illness. The Li levels in the behavioral experiment (Table 2) were low because higher Li levels led to such rapid and powerful Li-pilocarpine seizures that a ‘ceiling effect’ could prevent inositol-deficient diet from having an effect. However, these lower levels might have allowed residual inositol synthesis from glucose and thus obviated any effect of the inositol-deficient diet. Either way, this behavioral model may have been inadequate to detect effects of the diet.

The diet had a major effect in reducing the severity of affective disorder in 10 of the patients within the first 7–14 days of treatment. Only two patients who were compliant with the diet did not respond, and another two who responded to treatment experienced exacerbation after cessation of diet.

No exacerbation of peripheral side effects of Li was seen, perhaps because the relatively lower demand of the PI cycle activity in the periphery affords some protection against the inositol-depleted diet aggravating Li-induced peripheral side effects. Such exacerbation could be a concern because inositol supplementation has been reported to ameliorate some side effects of Li such as polyuria (13) or psoriasis (12), and therefore augmented inositol depletion could conceivably bring out such side effects more severely than Li only.

The inositol depletion theory of Li action continues to generate interest and controversy. Williams et al. (28) recently reported a common effect of Li, carbamazepine and valproate on sensory neuron growth cones that was reversible with the addition of inositol. Similarly, Sarkar et al. (29) reported a common effect of Li, carbamazepine and valproate on a pathway regulating the half-life of cellular proteins that could be reversed with the addition of inositol. Silverstone et al. (30) reviewed human imaging findings supporting the inositol depletion hypotheses. However, A. Shaldubina, G. Agam, R.H. Belmaker, G. Berry and Y. Bersudsky (in prep.) studied sodium myo-inositol transporter heterozygous knockout mice. While showing 15% reduction in brain inositol, these animals did not show Li-like behavioral effects in the Porsolt swim.
test. Perhaps a higher degree of inositol depletion is required for these behavioral effects.

Our clinical results are preliminary and need to be viewed with caution. The purpose of such an early study is to rule out the possibility of severe side effects, psychiatric or physical, and to judge acceptability of the intervention. Both objectives were achieved, and dietary inositol depletion can be said to be free of severe or common side effects in Li-treated patients and to be acceptable and practical for a significant number of patients. A controlled study is in order. While some might argue that a study of inositol supplementation to reverse the effects of Li and cause exacerbation of mania would be a more direct test of the inositol hypothesis, an inositol deficiency diet is ethically more acceptable and also raises the possibility of a new practical treatment method.

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References


