ELSEVIER

European Neuropsychopharmacology 7 (1997) 147–155

EUROPEAN NEURO-PSYCHOPHARMACOLOGY

Controlled trials of inositol in psychiatry

Joseph Levine

Ministry of Health Mental Health Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beersheva, Israel

Received 11 July 1996; accepted 28 January 1997

Abstract

Inositol is a simple polyol precursor in a second messenger system important in the brain. Cerebrospinal fluid inositol has been reported as decreased in depression. A double-blind controlled trial of 12 g daily of inositol in 28 depressed patients for four weeks was performed. Significant overall benefit for inositol compared to placebo was found at week 4 on the Hamilton Depression Scale. No changes were noted in hematology, kidney or liver function. Since many antidepressants are effective in panic disorder, twenty-one patients with panic disorder with or without agoraphobia completed a double-blind, placebo-controlled, four week, random-assignment crossover treatment trial of inositol 12 g per day. Frequency and severity of panic attacks and severity of agoraphobia declined significantly with inositol compared to placebo. Side-effects were minimal. Since serotonin re-uptake inhibitors benefit obsessive compulsive disorder (OCD) and inositol is reported to reverse desensitization of serotonin receptors, thirteen patients with OCD completed a double-blind controlled crossover trial of 18 g inositol or placebo for six weeks each. Inositol significantly reduced scores of OCD symptoms compared with placebo. A controlled double-blind crossover trial of 12 g daily of inositol for a month in twelve anergic schizophrenic patients, did not show any beneficial effects. A double-blind controlled crossover trial of 6 g of inositol daily vs. glucose for one month each was carried out in eleven Alzheimer patients, with no clearly significant therapeutic effects. Antidepressant drugs have been reported to improve attention deficit disorder (ADDH) with hyperactivity symptomatology. We studied oral inositol in children with ADDH in a double-blind, crossover, placebo-controlled manner. Eleven children, mean age 8.9±3.6 years were enrolled in an eight week trial of inositol or placebo at a dose of 200 mg/kg body weight. Results show a trend for aggravation of the syndrome with myo-inositol as compared to placebo. Recent studies suggest that serotonin re-uptake inhibitors are helpful in at least some symptoms of autism. However a controlled double-blind crossover trial of inositol 200 mg/kg per day showed no benefit in nine children with autism. Cholinergic agonists have been reported to ameliorate electroconvulsive therapy (ECT)-induced memory impairment. Inositol metabolism is involved in the second messenger system for several muscarinic cholinergic receptors. Inositol 6 g daily was given in a crossover–double-blind manner for five days before the fifth or sixth ECT to a series of twelve patients, without effect. These results suggest that inositol has therapeutic effects in the spectrum of illness responsive to serotonin selective re-uptake inhibitors, including depression, panic and OCD, and is not beneficial in schizophrenia, Alzheimer's, ADDH, autism or ECT-induced cognitive impairment.

1. Introduction

This paper reviews, extends and compares the results of eight controlled studies of inositol treatment in different psychiatric disorders (Levine et al., 1995; Benjamin et al., 1995; Fux et al., 1996; Levine et al., 1994; Barak et al., 1996; Levine et al., 1996a,b; Levine et al., in press). Inositol is a simple isomer of glucose that is a key metabolic precursor in the phosphatidylinositol (PI) cycle. Unlike L-DOPA and tryptophan, which are amino acid precursors of monoamine neurotransmitters and which have been reported to have antidepressant properties, inositol is a precursor of an intracellular second messenger system. The PI cycle is a second messenger system for numerous neurotransmitters (Baraban et al., 1989).

Barkai et al. (1978) reported that depressed patients, both unipolar and bipolar, had markedly reduced levels of inositol in cerebrospinal fluid (CSF). In an open study (Levine et al., 1993a) of eleven depressed patients who had been resistant to previous antidepressant treatment, inositol treatment led to a decline in mean Hamilton Depression Scale (HDS) from 31.7±6 to 16.2±9. Levine et al. (1993b) showed that 12 g daily of inositol raised CSF inositol levels by 70%. We studied 12 g daily inositol in

0924-977X/97/$17.00
PII S0924-977X(97)00409-4

depression in a double-blind controlled trial (Levine et al., 1995).

2. Depression study

Diagnostic entry criteria for the study were Diagnostic statistics manual-III-revised version (DSM-III-R) major depressive disorder or bipolar affective disorder depressed. In fact, patients who were referred to the study and gave informed consent were all antidepressant treatment failures, or side effect dropouts, or in the case of the bipolar depressed patients were lithium prophylaxis patients who had few past problems with mania but intolerable continuation of depression. All medications other than study drugs were stopped at least three days and usually one week before entering the study. No medications other than inositol or placebo were permitted during the trial, except for oxazepam up to 15 mg daily or an equivalent benzodiazepine if the patient had been taking it before the study. The study was approved by the Helsinki Committee (IRB) and the Ministry of Health. Each patient gave written informed consent before participation.

Thirty nine patients entered the trial. Of these, eleven dropped out within one week of starting the trial. Four of these patients were on placebo and reasons for dropout were: one for headache, one developed hypomania, one insomnia, and one because he did not wish to continue in the study. Seven patients dropped out within one week on inositol, two with mild psychotic symptoms, one with weakness and tremor, one with a cutaneous burning sensation, and three because they did not want to continue in the study. These eleven patients are not included in the data analysis. One patient on inositol dropped out after three weeks because of total remission of symptoms and her two-week score was used as a last-value carried forward.

All patients were given inositol or glucose in identical containers according to a pre-arranged random code. The drug was in powder form and patients were instructed to take two teaspoons morning and evening in juice. A modified Treatment Emergent Symptom Scale was used to monitor side effects. Hematology, blood chemistry, liver function and kidney function were assessed at baseline and after four weeks of inositol treatment.

HDS declined from 32.9±5 at baseline to 28.7±7 at two weeks and 28.9±10 at four weeks in the placebo group, and from 33.4±6 at baseline to 27.3±8 at two weeks and 21.7±10 at four weeks in the inositol group. Analysis of variance of the final improvement scores (baseline minus week 4) for all subjects showed that inositol reduced the HDS significantly more than placebo ($F_{1,26}=4.48$, $p=0.04$). After two weeks of treatment, there was no difference in the improvement scores between placebo and inositol groups. (see Table 1).

Table 1
The effect of inositol or placebo treatment on mean±S.D. HDS

Placebo			Inositol		
Baseline	2 W	4 W	Baseline	2 W	4 W
32.87±5.4	29.27±7.2	28.93±10.4	33.38±6.1	27.31±8.0	21.61±9.7

Data from Levine et al. (1995)

Side effects in placebo group were agitation and tension in one patient, headache in one, and insomnia in one. In the inositol group one patient complained of nausea and one of flatus. There were no abnormalities in urea, sodium, potassium, calcium, phosphate, creatinine, alkaline phosphatase, alaninaminotransferase, aspartic aminotransferase, creatimine phosphokinase, lactic dehydrogenase, urinalysis, CBC or differential. Two patients showed a mild increase after four weeks of inositol in fasting blood sugar that disappeared in one upon repeat, although the patient remained (at her request) on open inositol treatment. The other patient showed the same mild increase several weeks after discontinuation of inositol.

This study was the first use of the precursor strategy for a second messenger rather than a neurotransmitter in treating depression. As with other precursors such as L-DOPA for dopamine or tryptophan for serotonin, doses of several grams per day seem necessary for central nervous system effects of inositol.

An important observation in the present study was the absence of manic episodes in the bipolar depressed patients treated with inositol. Considerable evidence suggests that Li acts by reducing inositol levels at some intracellular brain site (Berridge et al., 1989; Kofman and Belmaker, 1993). This would reduce the functional activity of hypothetical overactive receptors in mania. The present results suggest that when these hypothesized signaling systems are *not* overactive, additional inositol does not increase their activity.

3. Panic study

Since some antidepressants are also effective against panic disorder we decided on a trial of inositol treatment for panic disorder. Patients had a DSM-III-R diagnosis of panic disorder or panic disorder with agoraphobia (Benjamin et al., 1995). Patients previously on medications withdrew from them at least one week before commencing a formal washout period; only two patients actually withdrew from medications this close to the study. Patients were prepared to go off conventional treatments in the hope of finding a new treatment without troubling side-effects. The only medication allowed apart from inositol and placebo was oral lorazepam 1 mg as needed for anxiety.

Placebo was mannitol ($n=10$) or glucose ($n=11$). The treatments were supplied in an identical-appearing white powder form with similar taste and solubility. Patients took

6 g of medication twice a day, dissolved in juice. All subjects began with a one-week "run-in" period on open placebo ($n=10$) or no medication ($n=11$). Thereafter each patient was randomly assigned to double-blind placebo or inositol for four weeks; he or she then crossed over to the alternate substance for another four weeks.

Patients completed daily panic diaries 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, HDS and Hamilton Rating Scale for Anxiety (HAS). A panic score was calculated by taking the mean of severity of attacks (range=0 to 10) and the number of symptoms per attack, and multiplying this average by the number of attacks per week. Baseline measures are 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 performed comparisons of placebo and inositol results using the means for the end of the third and fourth weeks of the two treatments.

Twenty-five patients were enrolled; 21 patients completed the study. Two withdrew before commencing treatment. One patient, who began on inositol, completed four weeks of inositol and one week of placebo, and then withdrew without a clear explanation. He improved on inositol. One patient, who began on placebo, withdrew after three weeks because of hypomania. There were nine males and twelve females. Mean (standard deviation, S.D.) age was 35.8 (S.D. 7). Five patients had panic disorder and sixteen had panic disorder with agoraphobia. Mean duration of illness was 3.9 (S.D. 3) years.

Every outcome measure improved more on inositol than on placebo. For number of panic attacks, panic scores and phobia scores this difference was significant (Table 2); for HAS and HDS scores it was not (not shown). When we analysed the data from weeks 3 and 4 of the first month alone, as if this were a parallel groups study, co-varying for baseline measures, phobia scores did not differ in the first month, but number of panic attacks was significantly lower on inositol: on placebo 10.1 (S.D. 10), on inositol 2.4 (S.D. 1); ANCOVA (baseline as covariate) $F_{(1,18)}=5.7$, $p=0.03$. Panic scores tended to be lower in the first month: on placebo 41.7 (S.D. 41), on inositol 9.4 (S.D. 9); ANCOVA (baseline as covariate) $F_{(1,18)}=3.5$, $p=0.08$.

Eleven patients used lorazepam for anxiety. Lorazepam use did not differ between the placebo and inositol phases (mean±S.D. in mg/week=3.8±6 on placebo, 3.0±5 on inositol, paired t-test, $t_{df20}=1.6$, $p=0.12$), nor did lorazepam use interact with inositol's effects on panic attacks. For phobia, lorazepam users had less response to inositol than did abstainers (phobia scores by treatment× lorazepam use, $F_{(1,14)}=8.9$, $p=0.01$). The effect of inositol appears clinically meaningful; number of attacks per week fell from about ten to about six on placebo, and to about three and a half on inositol. Ten out of twenty-one subjects were classified as "true" inositol responders and three were placebo responders.

4. Obsessive–compulsive disorder study

The role of serotonin in obsessive compulsive disorder (OCD) is supported by the specific effectiveness of serotonin re-uptake inhibition in this illness and the ability of serotonin agonists to exacerbate the syndrome. Rahman and Neuman (1993) reported that desensitization of serotonin receptors is reversed by addition of exogenous inositol. We therefore planned a trial of inositol in OCD. Since anti-OCD doses of serotonin selective re-uptake inhibitors (SSRI) are usually higher than antidepressant doses, we chose to give 18 g/day of inositol in OCD (Fux et al., 1996).

Fifteen patients entered the trial and thirteen completed and were included in data analysis. All met DSM-III-R criteria for OCD; all were physically healthy with no

Table 2
Mean (S.D.) number of panic attacks, panic scores and phobia scores of patients at baseline, with placebo treatment and with inositol treatment

Week	Baseline	Placebo				Inositol			
		1	2	3	4	1	2	3	4
No. attacks per week									
Mean	9.7	8.3	7.0	6.1	6.3	5.0	4.2	3.0	3.7[a]
(S.D.)	(15)	(17)	(10)	(9)	(9)	(8)	(6)	(5)	(4)
Panic scores									
Mean	72	63	33	24	31	27	18	10	11[b]
(S.D.)	(140)	(160)	(50)	(31)	(50)	(49)	(19)	(11)	(11)
Phobia scores									
Mean	5.5	3.1	3.2	3.4	3.4	3.3	3.0	2.2	2.2[c]
(S.D.)	(2)	(3)	(3)	(3)	(3)	(3)	(3)	(2)	(2)

[a] Repeated measures ANOVA (weeks 3 and 4 placebo vs inositol) $F(1,19)=4.9$, $p=0.04$, interaction with order of treatment NS
[b] Repeated measures ANOVA (weeks 3 and 4 placebo vs inositol) $F(1,19)=9.0$, $p=0.007$, treatment×order of treatment $F=7.2$, $p=0.01$
[c] Repeated measures ANOVA (weeks 3 and 4 placebo vs. inositol) $F(1,19)=6.1$, $p=0.02$, interaction with order of treatment NS
Modified from Benjamin et al. (1995)

evidence of diabetes or gastrointestinal disorder. The trial was of crossover design, six weeks in each phase. Six patients started the trial on placebo and seven patients on inositol. Patients were drug free for at least one week before beginning the trial. There was no washout between the phases of the crossover. Patients were free of drug or alcohol abuse. The protocol was approved by the IRB and all patients gave written informed consent. The dose of inositol (18 g/day) was given as two teaspoons in juice three times daily; placebo was glucose, in texture appearance and taste extremely similar to inositol. OCD was assessed using the Yale–Brown Obsessive–Compulsive Scale (Y–BOCS). Depression and anxiety were rated using the HDS and HAS. Ratings were performed by psychiatrists experienced in anxiety disorder at baseline, 3, 6, 9 and 12 weeks. Two clinics participated, one (MF) where patients were recruited in a non-selective manner and one (AA) where resistant patients were referred. Data were analyzed both separately and together. Mean age was 33.7 (23–56); 8 F, 5 M. Mean duration of illness was 8.1±5 years (1–17 range). Five patients had responded well in the past to SSRI; five had partial response; three poor responses. None met criteria for major depression. Only lorazepam up to 2 mg daily was allowed in addition to the study drug.

Table 3 summarizes the data. Mean improvement from baseline to six weeks in the Y–BOCS on inositol was 5.9±5.0 and on placebo 3.5±2.8 ($p=0.04$, paired t-test). For subscale obsession, mean improvement on inositol was 3.0±2.8 vs. placebo, 2.0±1.6 ($p=0.12$, NS). For subscale compulsion mean improvement on inositol was 3.0±2.8 and for placebo 1.5±1.4. ($p=0.03$). HAS improved on inositol 2.5±4.4 and on placebo 1.3±4.5, ($p=0.2$, NS). HDS improved 3.8±5.4 on inositol and 1.4±5.3 on placebo ($p=0.03$, paired t-test). Analysing patients in the non-selective clinic only (MF, patients No. 1–No. 9), improvement on inositol was 8.33±4 and on placebo 4.6±2.6 ($p=0.02$). Patients referred as resistant (AA, patients No. 10–No. 13) had high baseline Y–BOCS and did not respond to inositol for OCD.

5. Schizophrenia study

Levine et al. (1993a) found no benefit of inositol treatment in unselected schizophrenic patients using 6 g inositol daily. Since many antidepressant compounds are useful in negative signs schizophrenia, we decided to repeat a study of inositol in schizophrenia using only patients with severe negative signs. Moreover, Levine et al. (1993a) studied inositol effects in schizophrenic patients taking high doses of neuroleptics, which could mask possible benefit of inositol on negative signs of schizophrenia. We therefore decided to study inositol effects only in patients on low doses of neuroleptic treatment (Levine et al., 1994).

Fourteen chronic schizophrenic patients from the inpatient service of Abarbanel Hospital were accepted for study if they met the following criteria: (1) DSM-III-R diagnosis of chronic schizophrenia; (2) predominantly negative symptoms; (3) treatment with less than 300 mg of chlorpromazine neuroleptic equivalents; (4) physically healthy, age 20–65; (5) never previously participated in a trial of inositol treatment; (6) willing and able to sign consent form.

The protocol was approved by the Helsinki Committee and the Ministry of Health. Two patients dropped out of the study at their own request after two weeks and data

Table 3
The effect of inositol or placebo treatment on Y–BOCS scores

No	Order	Baseline	Placebo 3 wks	6 wks	Inositol 3 wks	6 wks
1	PL/IN	22	21	17	14	11
2	IN/PL	17	13	15	15	12
3	IN/PL	27	17	24	25	20
4	PL/IN	30	28	27	23	22
5	PL/IN	14	12	13	12	3
6	IN/PL	28	22	20	8	13
7	IN/PL	16	0	8	5	5
8	PL/IN	21	24	17	12	18
9	IN/PL	18	14	11	16	14
Mean±S D, MF Clinic		21.44±5 7	16 78±8.3	16 89±6 1	14 44±6 4	13 11±6 4
10	IN/PL	24	21	23	24	25
11	PL/IN	24	22	23	25	23
12	IN/PL	34	34	35	33	34
13	PL/IN	26	24	23	25	24
Mean±S.D., both clinics		23 15±5 9	19 38±8.4	19 69±7 3	18 23±8 2	17.23±8 65
HAS Mean±S.D.		15 00±9 7	12 83±8.5	13 50±9 5	12.83±9 0	12 33±10 3
HDS Mean±S D		14 83±8.6	13 25±9 0	13 75±9 6	12 42±9 6	11 00±9 1

Modified from Fux et al (1996)

Table 4
The effect of one month inositol or placebo treatment on total PANSS scores

Name	Sex	Age	Years of illness	Dose[a]	Total PANSS		
					Baseline	Inositol 28 days	Placebo 28 days
GD	M	43	7	50	50	38	52
KN	M	40	8	50	79	68	76
RA	M	37	12	50	114	87	96
MY	M	25	6	50	90	80	79
CTz	F	49	23	50	117	118	86
HB	F	56	23	300	85	92	89
SD	F	36	7	200	81	73	74
RY	F	63	42	100	68	67	67
MZ	F	59	26	100	142	114	104
ZM	F	50	34	150	124	131	125
ZE	F	38	22	300	95	91	87
KM	F	40	10	200	95	96	96
$x \pm$S.D		45±11	19±12	138±93	95±26	87±27	85±18

[a] in CPZ equivalents.
Modified from Levine et al. (1994).

presented relate only to the twelve patients who completed the trial. Four were males, eight females, mean age of 44.7 years (range 26–63), mean years ill 18.9 (range 6–42) and mean neuroleptic drug dose in chlorpromazine equivalents was 138±93 mg (range 50–300). Patients were assessed with the Positive and Negative Symptom Scale (PANSS) at baseline and after two and four weeks of inositol or placebo. Inositol 12 g daily or placebo (dextrose of equivalent texture) was given in 3 g doses, four times daily dissolved in juice. Order was randomized, seven patients receiving inositol first and five placebo first. There was no 'washout' between legs of the crossover. Blood samples for hematology, kidney and liver function were taken at baseline and after four weeks of inositol and placebo. Neuroleptic doses were not changed throughout the study.

Table 4 illustrates the results of one month of inositol treatment or placebo. There was no significant effect of inositol treatment compared with placebo on the total PANSS scores (Table 4). The positive symptom subscale of the PANSS was slightly increased after 4 weeks of inositol compared with 4 weeks of placebo, consistent with inositol's antidepressant effect (Levine et al., 1994).

6. Alzheimer's disease study

Since antidepressant drugs may have beneficial effects in the demented elderly we considered a trial of inositol in Alzheimer's Disease. A dose of 6 g was chosen despite the safety of 12 g in younger patients, for geriatric pharmacokinetic considerations. Twelve female patients mean age of 81.6 years participated in the study (Barak et al., 1996). All patients were hospitalized at the Abarbanel Mental Health Center, psychogeriatric ward. All agreed to participate and informed consent was co-signed by patients and their guardians. The study was approved by the Helsinki Committee (IRB) and the Ministry of Health. Inclusion criteria in the study were:

1. dementia of the Alzheimer type according to DSM-III-R;
2. score of 80, or less, on the cognitive subscale of CAMDEX (CAMCOG) examination (Roth et al., 1986);
3. estimate of severity of depressive symptoms not higher than minimal;
4. age 65 years or over

All patients were given inositol 6 g daily or placebo (dextrose) in a double-blind crossover design. Each drug, inositol or dextrose, was given in powder form in random order. One teaspoon in the morning and one in the evening was administered in juice. No medications other than placebo were permitted during the trial's eight weeks, except for oxazepam up to 15 mg daily, or an equivalent benzodiazepine if the patients had been taking it before the study. The Cambridge mental disorder of the elderly examination (CAMDEX) (Roth et al., 1986) was used as the basic measurement. Section A (the patients present physical and mental state), Section B (CAMCOG; the cognitive examination), Section C (interviewer's observations) and Section D (physical examination) were administered at the beginning of the study. Section B, the CAMCOG was then repeated at two weeks, four weeks, six weeks and eight weeks.

Table 5 summarizes the results of the repeated CAMCOG measurements on inositol or placebo treatment. Analysis of the improvement scores, (week 4 minus baseline) for all patients showed that inositol increased the total CAMCOG score from an average of 31.36±20.90 to 40.09±24.54 while the placebo group went from a

Table 5
CAMCOG subscales ($x \pm S.D.$)

Subscale	Placebo		Inositol	
	Baseline	4 wks	Baseline	4 wks
Orientation	4.64±3.26	4.09±3.33	4.09±2.77	5.36±2.94
Language	10.64±7.67	10.55±7.06	9.0±6.57	11.0±6.60
Attention	1.09±1.81	1.54±1.92	1.09±1.30	1.55±2.11
Praxis	5.64±4.52	6.0±3.67	4.91±3.45	6.45±3.96
Perception	1.64±0.67	1.91±0.30	1.64±0.50	2.0±0.0
Calculation	0.64±1.12	0.82±0.98	0.73±0.90	0.82±1.08
Abstraction	1.0±2.05	0.55±1.21	0.45±1.21	0.91±2.07
Memory	8.0±5.64	9.27±6.33	7.54±5.12	8.36±5.92
Total	35.90±25.96	39.27±25.10	31.36±20.90	40.09±24.54

Modified from Barak et al. (1996)

baseline score of 35.90±25.96 to a score after four weeks of 39.27±25.10. The trend shown for increased improvement on inositol was not significant.

7. ADDH

Antidepressants (Biederman et al., 1989) have been reported as having beneficial effects on ADDH children. Therefore, we examined the effect of 200 mg/kg inositol in ADDH (Levine et al., 1996a). Patients were offered inositol therapy in the out-patient children and adolescent clinic. Inclusion criteria for this study were:

1. Age older than 4 years, no known physical illnesses.
2. DSM-III-R diagnosis of ADDH by two senior psychiatrists.
3. No history of mental retardation and IQ above 85.
4. Written informed consent by both parents.

All patients were given inositol (200 mg/kg body weight), or glucose in identical containers according to a pre-arranged random code. The drug was in powder form and patients were instructed to take it dissolved in juice in two divided doses, morning and evening. The Conners Parent Teacher Rating Scale (CPTRS, Conners, 1973) Hebrew version was used to monitor the effects. This is a simple scale of eleven items abstracted from the Parents and Teachers Rating Scale, as used previously by our group (Weizman et al., 1984). The scale was administered at baseline, two weeks, four weeks, six weeks and eight weeks and was completed by the children's parents.

The study was of a double-blind crossover, placebo-controlled design. After four weeks containers were returned to the control investigator (JL) and identical containers containing alternate medication given out. All medications other than study drugs were stopped at least three days and usually one week before entering the study. No medications other than inositol or placebo were permitted during the trial. All the study patients (except one, No. 10) had responded to previous medications or had never been treated (No. 6, No. 8). Table 6 shows the total CPTRS from the nine patients that completed the study. Analysis of the final improvement scores (baseline minus week 4) for the nine patients who finished the study showed a tendency for placebo to reduce the CPTRS more than inositol ($t=1.699$, $n=9$, $p=0.13$ paired t-test). The dose of inositol or placebo used in the present study is a full order of magnitude lower than the dose of other sugars claimed to worsen ADDH (Wender and Solanto, 1991) and thus the mechanism of this effect is unlikely to be related.

8. Autism study

Recent studies of SSRI with positive benefit in autism have given renewed impetus to the search for effective treatments of autism. Rahman and Neuman (1993) showed that exogenous inositol enhances serotonin function in a rat brain electrophysiological model. We therefore performed a study of inositol in autism (Levine et al., in press).

The study was approved by the Helsinki Committee and informed consent signed by all the participants' legal guardians. Ten children entered the study after DSM-III-R diagnosis of infantile autism. There were nine males and one female. Mean age was 5.6±3.2 years. Mean age at diagnosis was 19.5±5.2 months. The rating instruments

Table 6
Total parent teacher Conners scores

No	First Drug	Placebo		Inositol	
		Baseline	4 wks	Baseline	4 wks
1	In	24	17	24	24
2	Pl	29	27	27	27
3	In	21	9	18	21
4	Pl	9	5	5	24
5	In	14	19	18	14
6	Pl	26	19	19	15
7	In	13	9	18	13
8	Pl	28	16	16	27
9	In	21	23	21	21
$x \pm S.D.$		20.5±7.1	16.0±7.1	18.4±6.1	20.7±5.5

In, Inositol; Pl, Placebo
Modified from Levine et al. (1996a)

Table 7
CARS scores during inositol or placebo treatment

No	Placebo		Inositol	
	Baseline	4 wks	Baseline	4 wks
1	41 5	48 5	40 5	41 5
2	32 5	38 5	38 5	35
3	42 5	40	40 5	42.5
4	38 5	33 5	–	–
5	36 5	30 5	33 5	36 5
6	47	42	42	36 5
7	45 5	45 5	45 5	45 5
8	36 5	40 5	40 5	33
9	50	50	50	50
10	55	51	51	56
MEAN	42 5	42 0	42 4	41 0
(S D)	(6 9)	(6 8)	(5 5)	(7 6)

Modified from Levine et al. (in press)

used for evaluation of inositol's effects and side-effects was the Childhood Autism Rating Scale (CARS) (Schopler et al., 1980). All subjects were evaluated at baseline, two weeks, four weeks, six weeks and eight weeks. The study's duration was eight weeks. Containers of inositol were pre-coded by one of the investigators (JL) and distributed by the blinded investigators to the subjects. Dextrose, of similar texture and taste, served as placebo. Myo-inositol or placebo (dextrose) 200 mg/kg body weight was dissolved in juice in two equal daily doses. Table 7 summarizes the CARS during this study. No significant statistical differences were found.

9. ECT-induced cognitive impairment study

ECT-induced memory impairment may be pharmacologically reversible. We studied naloxone in ECT-induced memory impairment with negative results (Levine et al., 1990) and physostigmine with positive results (Levine et al., 1987). Some theories of ECT-induced memory deficits postulate a cholinergic deficit reversible with physostigmine (Levine et al., 1987), and several muscarinic cholinergic receptors are linked to PI as a second messenger. Therefore we hypothesized that exogenous inositol might enhance cholinergic function and reverse ECT-induced memory impairment. Since there are no previous studies of possible interaction of ECT and inositol, a lower dose of inositol was chosen for study with ECT for safety reasons. We studied the effect of 6 g inositol daily on cognitive effects of ECT in humans (Levine et al., 1996b)

The protocol was approved by the Human Subjects Committee and the Ministry of Health. All patients gave written informed consent. There were fifteen subjects including ten females and five males, mean age 49 years (range 27–72). Patients were treated with ECT for a variety of indications including DSM-III-R major depressive disorder (eight patients) schizoaffective disorder depressed (two patients) and neuroleptic non-responsive schizophrenia (five patients). Patients were free of psychotropic medication for at least seven days before beginning ECT treatment.

Cognitive function tests were as in Levine et al. (1987), (1990), and included orientation (place, date, date of birth, country of birth and the name of the hospital and of the treating physician), digit repetition, pictures recall test (a set of twelve pictures of daily occurrences presented to the subjects simultaneously, after which they were withdrawn and the subjects were requested to describe them), story repetition (recall of a story consisting of twenty sentences) and categorization (to list as many objects as they could belonging to each of three categories within 60 s). For story repetition and picture recall tests, three different versions were used, each for a different time point. The different versions were the same used in previous studies (Levine et al., 1987, 1990).

The fifth and sixth ECT were each given six days after the previous ECT treatment. Myo-inositol or dextrose placebo was given for five days before the fifth or sixth ECT. The study design was controlled, crossover double-blind. Myo-inositol was given in powder, dissolved in juice, 3 g a.m. and 3 g p.m.; placebo was dextrose powder dissolved in juice. Seven patients received inositol first and then placebo, and eight patients vice versa. Cognitive function tests were administered after the fifth ECT and after the sixth ECT. Each time cognitive function tests were administered at 20, 60 and 90 min following ECT.

Mean length of seizure was 40.3±13 s for the inositol phase and 40.5±12 s for the placebo phase. HDS for depressed patients and Brief Psychiatric Rating Scale (BPRS) for schizoaffective and schizophrenic patients were administered 24 h following the fifth and sixth ECTs. No differences were found for the inositol versus placebo phases of the study. Table 8 shows the clinical results at 60 min and 90 min after ECT. There were no significant effects of inositol treatment on any of the measures.

10. Discussion

Inositol is a precursor in the PI second messenger cycle linked to norepinephrine α-1, 5-Hydroxytriptamine-2 (5-HT-2) (serotonin) and other receptors thought to be involved in affective and anxiety disorders. This review demonstrates superiority over placebo of a second messenger precursor strategy in the treatment of depression as well as in the treatment of panic disorder and OCD. However, one should remember these are relatively small studies of a pilot nature.

Various catecholamine and 5-HT precursors were previously reported in the treatment of depression, including tryptophan, 5-HTP, tyrosine and L-DOPA, all serving as substrates or products for the rate limiting enzymes within the biosynthetic pathways. Van Praag (1987) summarized the experience with these precursors until the mid 1980s

Table 8
Lack of effect of inositol on ECT-induced cognitive dysfunction

	60 min		90 min	
	Placebo	Inositol	Placebo	Inositol
Orientation	10 60±1 8	11.27±1 7	10 67±2 0	11 33±1 3
Digital repetition	97 60±28 3	99 07±29.2	95 60±26 8	97 87±26 7
Story repetition	9 00±6.3	9.33±6 8	11 66±6.8	12.13±7 1
Visual test	15 33±3 1	14 07±4 1	17 07±3 5	16 93±3 3
Categorization	7 67±3 1	5.73±2 7	8 47±2 4	7 67±2 1

Modified from Levine et al (1996b)

pointing to the scanty information for catecholamine precursors (only four controlled studies with tyrosine and three studies with L-DOPA), the former showing some promise as compared to placebo. Van Praag pointed to the fact that tyrosine hydroxylase, the rate limiting enzyme of the catecholamine pathway is practically saturated physiologically, thus hypothesizing no benefit from tyrosine administration. This concept held up clinical trials with tyrosine until the 1980s. However, Van Praag (1987) stresses, under certain conditions tyrosine loading might increase catecholamine synthesis. Van Praag (1987) also summarized serotonin precursors' use in depression, stating that only a few small studies were done with 5-HTP and tryptophan, showing some promise for 5-HTP, while the results for tryptophan were less clear. Since tryptophan hydroxylase is the rate limiting step of serotonin production, the superiority found by this author (Van Praag, 1987) for 5-HTP as compared to tryptophan is understandable. All these precursor strategies were not supported by drug companies and were practically abandoned. The case of these precursors may be relevant to several issues for developing PI cycle precursor treatment strategy.

First, inositol presents a similar case to tyrosine, as phosphatidylinositol synthetase, the rate limiting enzyme of the PI cycle, is considered to be saturated (brain inositol level is about 10 mM and K_m for the enzyme is 1 mM, Haussinger et al., 1994) Thus one would not expect that exogenous administration of inositol, preceding the rate limiting step, will have any effect on the PI cycle activity, excluding certain conditions with a shortage of brain inositol. Recently, Shimon et al. (1996) found in post mortem study that certain brain areas of bipolar and suicidal patients do demonstrate low inositol levels.

Second, much like the above precursors, inositol is an orphan drug. Being a natural substance, inositol is difficult to patent. Drug companies do not support drug trials with this drug and thus large scale trials are practically not feasible One cannot avoid asking whether inositol will have the same fate as previous precursor strategies, raising curiosity at first, next, being used as a strategy for non-responding patients and then forgotten.

We hope that this will not be the case. Inositol is a precursor in the second messenger cycle. The above mentioned precursors are but early steps in the synthesis of neurotransmitters, and why would one give them if one can raise, in more robust ways, the synaptic level of the neurotransmitter itself? Inositol presents a down-stream step in the first-second-third messenger transduction pathway and thus presents more than just another step in the biosynthesis of the first transmitter.

Inositol shows medium to high "size of the effect" (SE) and "mean difference effect size" (MDES) for depression and OCD. SE and MDES are descriptions of magnitude of change in units of standard deviations (the first uses standard deviation of the pretreatment baseline and the second uses standard deviation of the change) (Goldenberg, 1987). These parameters are independent of sample size and thus may be used to compare clinical trials in a non-inferential way. The MDES values obtained for inositol studies in depression, OCD and panic studies are 0.83, 0.97, 0.31 respectively. Cohen (1988) regards MDES of 0.25 as being detectable but small, 0.5 as medium and 0.8–1.0 or more as large. The findings of inositol efficacy in depression are in line with other tricyclics. The finding of inositol in OCD demonstrating MDES of 0.97 compared to 1.48 for clomipramine and 0.69–0.35 for SSRIs (Griest et al., 1995), suggest inositol might be at least as effective as SSRIs in OCD. The MDES in panic is relatively small and future studies will tell its place in the treatment of this disorder. The SE obtained for inositol in depression, OCD and panic studies are 1.36, 0.73, 0.15 respectively. Since Cohen (see Goldenberg (1987)) suggested that values of 0.3 and above indicate large size of the effect, it seems both inositol studies of depression and OCD demonstrate large SE, while this is not the case for the inositol study of panic disorder.

What is the mechanism behind inositol effects in depression and/or the two anxiety disorders? One can suggest a shortage of inositol in certain brain areas in one or more of these disorders and its supplementation by exogenous inositol (see above). However, at least two other possibilities exist. First, Batty and Downes (1995) reported that exogenous inositol regulates phospholipase C, the enzyme that breaks down PI, in a complex manner. Second, there is now data demonstrating inositol attenuation of 5-HT-2 receptor desensitization, (Rahman and Neuman, 1993). The latter finding of a role for inositol in attenuation of 5-HT-2 receptor desensitization, together

with the evolving therapeutic profile for inositol resembling that of the SSRIs, suggest a study of inositol addition to SSRIs in depression, OCD and panic disorders.

Acknowledgments

The author would like to thank all his clinical collaborators in inositol studies: Yoram Barak, Mirtha Gonzalves, Henry Szor, Avner Elizur, Jonathan Benjamin, Alex Aviv, Mendel Fux, Daniel Levy, Aliza Ring, Ada Aviram, Agnes Holan, A. Glasman, T. Pomerantz and S. Stier. The author is especially grateful to Professor R.H. Belmaker, who conceived the possible utility of inositol as a therapeutic strategy in psychiatry

References

Baraban, J M , Worley, P F and Snyder. S.H (1989) Second messenger systems and psychoactive drug action focus on the phosphoinositide system and lithium Am J Psychiatry 146, 1251–1260

Barak. Y , Levine, J , Glasman, A , Elizur, A and Belmaker, R H. (1996) Inositol treatment of Alzheimer's disease Prog Neuropsychopharmacol Biol. Psychiatry 20, 729–735

Barkai. A , Dunner. D L , Gross, H A , Mayo, P. and Fieve, R R (1978) Reduced *myo*-inositol levels in cerebrospinal fluid from patients with affective disorder Biol Psychiatry 13. 65–72

Batty. I.H and Downes, C.P. (1995) The mechanism of muscarinic receptor-stimulated phosphatidylinositol re-synthesis in 1321N1 astrocytoma cells and its inhibition by Li^+ ions. J Neurochem 65. 2279–89

Benjamin, J . Levine, J . Fux. M , Aviv, A , Levy, D and Belmaker, R H (1995) Double blind controlled trial of inositol treatment of panic disorder Am J Psychiatry 52. 1084–1086

Berridge, M D Downes, C P and Hanley, M R (1989) Neural and developmental action of lithium· a unifying hypothesis. Cell 59 411–419

Biederman. J , Baldessarini, R , Wright, V, Knee, D and Harmatz, J (1989) A double-blind placebo controlled study of desipramine in the treatment of attention deficit disorder J Am Acad Child Adolesc Psychiatry 28, 777–784

Cohen. J (1988) Statistical power analysis for the behavioral sciences 2nd ed , Erlbaum, Hillsdale, NJ

Conners, C.K (1973) Rating scale for use in drug studies with children Psychopharmacol Bull (special issue) 9, 24–29

Fux, M . Levine, J.. Aviv, A and Belmaker. R.H (1996) Inositol treatment of obsessive–compulsive disorder Am J Psychiatry 153. 1219–1221

Goldenberg. S C (1987) Persistent flaws in the design and analysis of psychopharmacology research in Meltzer, H Y (Editor) Psychopharmacology. The Third Generation of Progress. Raven Press. New York. pp 1005–1012

Griest, J H , Jefferson, J.W , Kobak, K A , Katzelnick. D J. and Serlin, R C (1995) Efficacy and tolerability of serotonin transport inhibitors in obsessive compulsive disorder. Arch Gen Psychiatry 52, 53–59

Haussinger. D . Laubenberger. J , Dahl. V, Ernst, T . Bayer, S . Langer, M . Gerok. W. and Hennig. J (1994) Proton magnetic resonance spectroscopy studies on human brain myo-inositol in hypo-osmolarity and hepatic encephalopathy Gastroenterology 107. 1475–1480

Kofman. O and Belmaker R H (1993) Biochemical. behavioral and clinical studies of the role of inositol in lithium treatment and depression Biol. Psychiatry 34, 839–852

Levine. Y , Elizur. A and Korczyn. A D (1987) Physostigmine improves ECT-induced memory disturbances Neurology 37 871–875

Levine Y., Salgenik, I , Etzion. T., Levy, A . Neumann, M and Korczyn, A (1990) Naloxone fails to improve post ECT memory and cognitive disturbances Brain Dysfunction 3, 193–196

Levine, J . Gonzalves. M , Barbam. I , Stier, S , Elizur, A., Kofman, O and Belmaker, R H (1993a) Inositol 6 gm daily may be effective in depression but not in schizophrenia Hum Psychopharmacol. 8, 49–53

Levine. J . Rapaport, A . Lev. L , Bersudsky, Y , Kofman. O , Belmaker, R H . Shapiro, J and Agam, A (1993b) Inositol treatment raises CSF inositol levels. Brain Res 627, 168–170

Levine. J , Goldberger. I Rapaport, A , Schwartz, M . Schields, C . Elizur. A , Belmaker, R H , Shapiro, J and Agam, G (1994) CSF inositol levels in schizophrenia are unchanged and inositol is not therapeutic in anergic schizophrenia Eur Neuropsychopharmacol 4, 487–490

Levine, J . Barak. Y Gonsalves M , Elizur. A., Schor, H , Kofman, O and Belmaker, R H (1995) Double blind study of inositol versus placebo in depression Am J Psychiatry 152. 792–794

Levine. J., Ring, A . Barak, Y , Elizur, A and Belmaker, R.H (1996a) Inositol may worsen attention deficit disorder with hyperactivity Hum Psychopharmacol 10, 481–84.

Levine. J.. Pomerantz, T . Stier. S. and Belmaker, R H (1996b) Lack of effect of 6 gm inositol treatment on post-ECT cognitive function in humans J Psychiatr Res. 29, 487–89.

Levine J . Aviram A , Holan A , Ring A . Barak Y and Belmaker. R H Myo-inositol treatment of infantile autism. a double-blind placebo controlled trial J Neural Transm (in press)

Rahman. S and Neuman. R.S (1993) Myo-inositol reduces serotonin ($5\text{-}HT_2$) receptor induced homologous and heterologous desensitization Brain Res 631, 349–351

Roth M , Tym. E , Mountjoy, C Q , Huppert. F A.. Hendrie, H , Verma, S and Goddard, R (1986) CAMDEX, a standardized instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia Br J Psychiatry 149, 698–709

Schopler, E.. Reichler, R J.. Devellis R F and Kenneth. D (1980) Toward objective classification of childhood autism: childhood autism rating scale J Autism Dev Disord. 10, 91–103

Shimon, H , Agam. G , Belmaker, R.H , Hyde. T and Kleinman, J E (1996) Reduced inositol levels in frontal cortex of post-mortem brain from bipolar patients and suicides, Am J Psychiatry (under revision).

Van Praag, H M (1987) Monoamine precursors in depression· present states and prospects. In: Zohar, J and Belmaker, R H. Treating resistant depression PMA Publishing, New York, pp 297–306

Wender, F H and Solanto. M V (1991) Effects of sugar on aggressive and inattentive behavior in children with attention deficit disorder with hyperactivity and normal children Pediatrics 88. 960–969

Weizman. A , Weitz, R , Szekely, G A , Tyano, S. and Belmaker, R.H (1984) Combination of neuroleptic and stimulant treatment in attention deficit disorder with hyperactivity J Am Child Psychiatry 23, 295–298