Depressão e Inositol

Inositol for depressive disorders

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A substantive amendment to this systematic review was last made on 22 October 2003. Cochrane reviews are regularly checked and updated if necessary.

Synopsis

Inositol is a nutritional supplement that has been suggested as a treatment for depressive disorders. The reviewers found the current evidence is unclear whether or not inositol is of benefit in the treatment of depression. There are ongoing studies that should reduce this uncertainty.

Abstract

Background

There are a number of effective interventions for the treatment of depression. It is possible that the efficacy of these treatments will be improved further by the use of adjunctive therapies such as inositol.

Objective

1. To determine the effectiveness of inositol in the treatment of depression.
2. To determine the adverse effects and acceptability of treatment with inositol.

Search strategy

The Cochrane Controlled Trials Register (CCTR), The Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR) incorporating results of group searches of EMBASE, MEDLINE, LILACS, CINAHL, PSYNDEX and PsycLIT were searched. Reference lists of relevant papers and major textbooks of affective disorder were checked. Experts in the field and pharmaceutical companies were contacted regarding unpublished material.

Selection criteria

All randomised controlled trials that compare treatment with inositol, whether as monotherapy or adjunctive therapy, to an alternative treatment, whether another antidepressant medication or placebo, for patients with a diagnosis of depressive disorder (diagnosed according to explicit criteria).

Data collection and analysis

Data were independently extracted from the original reports by two reviewers. Statistical analysis was conducted using Review Manager version 4.2.1.

Main results

Four trials were identified, with a total of 141 participants. These were short term trials of double-blind design. The trials did not show clear evidence of a therapeutic benefit, nor any evidence of poor acceptability.

Reviewers' conclusions

It is currently unclear whether or not inositol is of benefit in the treatment of depression. Ongoing studies should reduce this uncertainty.

Background

Depression is a major cause of worldwide disability. In the United States the one month prevalence of a major depressive episode has been estimated to be 4.9% (Blazer 1994) and comparable figures have been found in the U.K. (Jenkins 1997). Depressive disorders share central features of low mood, lack of enjoyment, pessimistic thinking, and reduced energy, all of which lead to decreased functioning. The Global Burden of Disease Study found unipolar depression to be the fourth leading cause of worldwide disability even after excluding deaths due to suicide (Murray 1997a). The prevalence of major depressive disorder may be on the increase (CNCG 1992) and the Global Burden of Disease Study predicted that, by 2020, unipolar major depression will be the second leading cause of disability worldwide (Murray 1997b).

There are several effective interventions available for the acute treatment of depression including pharmacotherapy and psychotherapy (Geddes 2001). Since the introduction of antidepressants in the 1950s, the number of available pharmacological treatments has increased, but their efficacy has remained largely unchanged. A recent review reported a response rate of 50% with active drug compared to 32% with placebo (AHCPR 1999). One possible method of improving response to antidepressant medication is by using adjunctive agents such as nutritional supplements.

Inositol, or myo-inositol, is a naturally occurring compound, an isomer of glucose. It is sometimes considered part of the vitamin B complex. Inositol is consumed in a range of foods such as whole-grain cereals, fruits, plants, and meats, and the typical dietary intake of inositol is around 1g per day. It is not a prescription medication, but is widely available as a dietary supplement. Within the body, inositol is used for the production of inositol triphosphate (IP3) and diacylglycerol (DAG), important 'second messengers' allowing cell surface receptors for neurotransmitters, including serotonin, to affect intracellular processes.

Lower than normal levels of inositol are found in the cerebrospinal fluid of people with depression (Barkai 1978). Post mortem studies have shown that levels of inositol in particular areas of the cortex of suicide victims, and people with bipolar disorder are also lowered (Shimon 1997). It has also been reported that the anti-manic effect of lithium treatment is associated with a reduction in inositol levels (Allison 1971; Kofman 1993). These findings raised the possibility that increasing inositol levels in depression might be therapeutic.

Treatment with inositol has been effective in so-called 'animal models' of depression (Einat 2001). Inositol taken orally has been shown to increase inositol levels within the central nervous system in humans (Levine 1993). This review aims to assess the available evidence that treatment with inositol, whether alone or as an adjunct to other antidepressant medication, is effective in the treatment of depression.
Description of studies

Four trials met the inclusion criteria for this review, in which a total of 141 participants were randomised. They were all of a parallel group design.

Participants

All participants were aged over 18 years. The trials recruited both male and female participants. One trial (Levine 1995) included people with a diagnosis of unipolar or bipolar depression who had failed to respond to, or had not tolerated, conventional antidepressants. Another trial (Chengappa 2000) included patients with bipolar depression despite adequate doses of a mood stabiliser, almost half (10/22) of whom had already failed to respond to conventional antidepressant. The two remaining trials were both concerned with unipolar depression. In one participants simply had major depression (Levine 1999), in the other they had also failed to improve with conventional antidepressant treatment (Nemets 1999).

Settings

The trials were all performed in outpatient populations. Three trials (Levine 1995; Levine 1999; Nemets 1999) were performed by a group working in Israel. The other trial (Chengappa 2000) was performed in the United States of America.

Interventions

All trials compared the use of oral inositol, at a daily dosage of 12 g, with the use of a glucose placebo. In one trial (Levine 1995) inositol was used as the only antidepressant treatment. In the other studies it was used in addition to conventional antidepressant agents.

Duration

The trials were of short duration with three trials lasting four weeks (Levine 1995; Levine 1999; Nemets 1999), and the remaining trial lasting six weeks (Chengappa 2000).

Primary outcome measures

Three trials used the 24-item Hamilton Depression Rating Scale (HDRS-24), and provided data on scores at trial endpoint. The remaining trial used the 17-item Hamilton Depression Rating Scale (HDRS-17), the Montgomery-Asberg Depression Rating Scale (MADRS), and an additional eight items for the HDRS, and provided data for change in scores over the duration of the trial.

Secondary outcome measures

Ascertainment of side effects of treatment was performed using a modified Treatment Emergent Symptom Scale in one trial (Levine 1995), and using both the UKU Side Effects Rating Scale and spontaneous reports in another (Chengappa 2000). The other studies did not specify the method employed.

Results

Resolution of a depressive episode

Continuous rating scales were used by all four trials allowing comparison of scores between the groups at trial end points. The trial (Levine 1995) comparing treatment with inositol alone to the use of placebo reported a difference in Hamilton Depression Rating Scale (HDRS-24) score of -7.30, favouring inositol, although the 95% confidence intervals (95% CI) are wide (-14.73 to 0.13) and do not exclude an absence of effect. The trials comparing the use of inositol or placebo in addition to an SSRI did not find any statistically significant difference in HDRS-24 score between the groups, and again confidence intervals around the main effect were wide (Levine 1999 WMD 1.80, 95% CI -7.32 to 10.92, Nemets 1999 WMD 1.90, 95% CI -4.55 to 8.35). The remaining trial used a different form of the Hamilton Depression Rating Scale (HDRS-17), and found the change in this score by the trial end point did not differ between inositol and placebo (WMD -0.20, 95% CI -5.90 to 5.50).

Combining these continuous measures using Standardised Weighted Mean Difference (SMD), no statistically significant overall heterogeneity of effect between trials is observed (Chi-square 3.57, df 3, p 0.31). The pooled estimate of effect (SMD -0.08, 95% CI -0.45 to 0.30) is consistent with both a presence or absence of therapeutic benefit. Repetition of these analyses using a random effects model did not qualitatively change the results found. Analysing changes in HDRS score in a dichotomous fashion, e.g. achievement of a 50% reduction in score, also fails to exclude a lack of effect from inositol.

Acceptability of treatment

None of the trials found any statistically significant difference in drop out rates between the groups receiving inositol and those receiving placebo. A pooled estimate for the four trials taken together was calculated, since it was judged that tolerability of treatment with inositol would not be substantially affected by the differences between the study designs. This analysis also found no significant difference (RR 1.49, 95% CI 0.77 to 2.90). Similarly no significant difference was found in numbers of dropouts attributed to side effects (RR 0.81, 95% CI 0.32 to 2.09), nor in the numbers of subjects experiencing at least one adverse event (RR 0.89, 95% CI 0.48 to 1.64).

Other outcomes

Levine 1995 reports one person receiving placebo dropping out from the study because of hypomania, and Chengappa 2000 reports one person from the placebo arm developing mania after switching to inositol in an open-label period of follow-up. No trial reported any admissions to hospital during double-blind treatment, but Chengappa 2000 reports one person from each arm being admitted during open-label follow-up, and Levine 1999 reports one person from the inositol arm being admitted shortly after the end of the trial. No deaths were reported during the trials.

Chengappa 2000 assessed Clinical Global Impression rated by the clinician, but does not report the results separately. None of the trials described assessing quality of life, clinical global impression rated by the patient, social functioning or occupational functioning.

Subgroup analysis

The planned subgroup analysis by type of depressive disorder was not performed because of the small amount of data available and use of differing outcome measures between trials.

Sensitivity analysis

The planned sensitivity analysis excluding trials of low methodological quality was not performed given the small number of trials identified and their similar methodological quality.

Discussion

It is unclear on the basis of the current evidence whether or not inositol is effective in the treatment of depression. The limited evidence limits the precision of the results, and also means that a single unidentified trial could have a substantial effect on the results. As there are few studies, indirect methods of identifying publication bias such as funnel plots are of very limited value. The included trials did not find evidence that inositol was any less well tolerated than a glucose placebo. However, the small number of people randomised means that infrequent but serious adverse events cannot be excluded.

Reviewers' conclusions

Implications for practice

The currently available evidence does not indicate a clear benefit from the use of inositol in depression. People with depression and their clinicians may wish to await further evidence before using inositol in a widespread fashion.
Implications for research

Further randomised evidence is required to reduce the uncertainty surrounding the estimates of effect of inositol. There are at least two ongoing randomised trials (Sachs; STEP-BD) using inositol in bipolar disorder that should reduce this uncertainty when completed.

Acknowledgements

We would like to thank the CCDAN Editorial Team for their support, information and advice.

Potential conflict of interest

JG has received research funding and support from Sanofi-Aventis and GlaxoSmithKline and is currently in discussion with several other companies that manufacture SSRIs about collaboration on planned independent trials and systematic reviews.

Notes

This review is in the process of being updated. We hope to publish the updated version in Issue 1, 2008.

Tables

Characteristics of included studies

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<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
<th>Allocation concealment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chengappa 2000</td>
<td>parallel group double blind design, randomised allocation</td>
<td>24 adults, bipolar affective disorder, current episode depressed (DSM-IV criteria), Hamilton Depression Rating Scale (17 item) &gt;14 at entry, taking lithium valproate or carbamazepine in therapeutic dosage</td>
<td>(1) 2g of inositol in water three times daily increased to 4g three times daily after one week in addition to usual medication OR (2) 2g of grape sugar (glucose) in water three times daily increased to 4g three times daily after one week in addition to usual medication</td>
<td>Hamilton Depression Rating Scale (17 and 25 item), Montgomery Asberg Depression Rating Scale, Clinical Global Impression, Young Mania Rating Scale, UKU Side Effects Scale</td>
<td>Six week duration</td>
<td>B – Unclear</td>
</tr>
<tr>
<td>Levine 1995</td>
<td>parallel group double blind design, randomised allocation</td>
<td>39 adults (12 male, 16 female; ages 20-80) with major depressive episode or bipolar disorder, current episode depressed (DSM-III-R criteria), not responded to or not tolerated antidepressant treatment or intolerable continuation of depression despite use of lithium</td>
<td>3-7 day washout period (medications except benzodiazepines stopped) then (1) 6g inositol (in juice) twice daily OR (2) 6g glucose (in juice) twice daily</td>
<td>Hamilton Depression Rating Scale (24 item), modified Treatment Emergent Symptom Scale</td>
<td>Four week duration</td>
<td>B – Unclear</td>
</tr>
<tr>
<td>Levine 1999</td>
<td>parallel group double blind design, randomised allocation</td>
<td>36 adults (8 male, 19 female completed), major depression (DSM-IV criteria)</td>
<td>3-7 day drug free period then (1) 3g inositol in juice or tea four times daily plus SSRI OR (2) 3g grape sugar (glucose) in juice or tea four times daily plus SSRI</td>
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</tbody>
</table>
Outcomes Hamilton Depression Rating Scale (24 item)

Notes

Allocation concealment B – Unclear

Study Nemets 1999

Methods parallel group double blind design, randomised allocation

Participants 42 adults (14 male, 22 female completed), major depression without psychotic features (DSM-IV criteria), no more than mild improvement in symptoms after at least 3 weeks treatment with SSRI, Hamilton Depression Rating Scale (24 item) score >17

Interventions (1) 3g inositol in juice or tea four times daily in addition to SSRI OR (2) 3g grape sugar (glucose) in juice or tea four times daily in addition to SSRI

Outcomes Hamilton Depression Rating Scale (24 item)

Notes

Allocation concealment B – Unclear

Characteristics of excluded studies

Study Reason for exclusion
Levine 1995b not a trial of treatment for depression, not explicitly randomised
Levine 1997 not a trial of treatment for depression

Characteristics of ongoing studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial name or title</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Starting date</th>
<th>Contact information</th>
<th>Notes</th>
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<tr>
<td>STEP-BD</td>
<td>(Systematic treatment enhancement program for bipolar disorder)</td>
<td>5000 patients with bipolar disorder or cyclothymic disorder (DSM-IV criteria) in 20 centers</td>
<td>Lithium, valproate, bupropion, paroxetine, lamotrigine, risperidone, inositol, tranylcypromine, Cognitive Behaviour Therapy, Family-Focused Therapy, Interpersonal and Social Rhythms Therapy</td>
<td>For more information, call toll-free: 1-866-240-3250 <a href="mailto:stepbd@mailcity.com">stepbd@mailcity.com</a> <a href="http://www.stepbd.org">www.stepbd.org</a></td>
<td>enrolling</td>
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<tr>
<td>Sachs 98-325A</td>
<td>treatment refractory bipolar depression (n=20)</td>
<td>inositol or placebo added to stable mood stabiliser</td>
<td>enrolling</td>
<td>Gary Sachs, MD, Massachusetts General Hospital Boston, Massachusetts</td>
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</tr>
</tbody>
</table>

References

References to studies included in this review
Chengappa 2000 (published data only)
Levine 1995 (published data only)
Belmaker RH. Controlled trials of inositol in psychiatry. XX1st Collegium Internationale Neuro-psychopharmacologicum, Glasgow, Scotland, 12th-16th July. 1998.

Levine 1999 {published data only}


Nemets 1999 {published data only}

* indicates the major publication for the study

References to studies excluded from this review
Levine 1995b

Levine 1997

Ongoing studies
Sachs
Sachs G. Inositol. 1998:-.

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Additional references
AHCPR 1999

Allison 1971

Barkai 1978

Berlin 1997

Blazer 1994

CNCG 1992

Einat 2001

Geddes 2001

Jenkins 1997

Kofman 1993

Levine 1993

Murray 1997a

Murray 1997b

Sackett 1997

Shimon 1997