Cochrane
Library

Cochrane Database of Systematic Reviews

Inositol for depressive disorders (Review)

Taylor MJ, Wilder H, Bhagwagar Z, Geddes J

Taylor MJ, Wilder H, Bhagwagar Z, Geddes J.
Inositol for depressive disorders.
Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD004049.
DOI: [10.1002/14651858.CD004049.pub2](https://doi.org/10.1002/14651858.CD004049.pub2).

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	1
BACKGROUND	3
OBJECTIVES	3
METHODS	3
RESULTS	4
DISCUSSION	5
AUTHORS' CONCLUSIONS	6
ACKNOWLEDGEMENTS	6
REFERENCES	7
CHARACTERISTICS OF STUDIES	8
DATA AND ANALYSES	11
Analysis 1.1. Comparison 1 inositol versus glucose (placebo), Outcome 1 Hamilton Rating Scale for Depression, trial end point.	11
Analysis 1.2. Comparison 1 inositol versus glucose (placebo), Outcome 2 change in Hamilton depression rating scale (dichotomous).	12
Analysis 1.3. Comparison 1 inositol versus glucose (placebo), Outcome 3 measures of tolerability.	12
WHAT'S NEW	13
HISTORY	13
CONTRIBUTIONS OF AUTHORS	13
DECLARATIONS OF INTEREST	13
SOURCES OF SUPPORT	14
INDEX TERMS	14

[Intervention Review]

Inositol for depressive disorders

Matthew J Taylor¹, Heather Wilder², Zubin Bhagwagar¹, John Geddes¹

¹Department of Psychiatry, University of Oxford, Oxford, UK. ²Centre for Evidence Based Mental Health, Oxford, UK

Contact address: Matthew J Taylor, Department of Psychiatry, University of Oxford, Neurosciences Building, Warneford Hospital, Oxford, Oxfordshire, OX3 7JX, UK. matthew.taylor@psych.ox.ac.uk.

Editorial group: Cochrane Common Mental Disorders Group

Publication status and date: Edited (no change to conclusions), published in Issue 1, 2010.

Citation: Taylor MJ, Wilder H, Bhagwagar Z, Geddes J. Inositol for depressive disorders. *Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No.: CD004049. DOI: [10.1002/14651858.CD004049.pub2](https://doi.org/10.1002/14651858.CD004049.pub2).

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

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.

Objectives

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 methods

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, PSYINDEX 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.

Authors' conclusions

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

PLAIN LANGUAGE SUMMARY

Inositol for depression

Inositol for depressive disorders (Review)

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

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.

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 (CNGC 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.

OBJECTIVES

1. To determine the effectiveness of inositol, whether alone or as an adjunct to other antidepressant medication, in the treatment of depression.

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

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

All patients suffering from a depressive disorder diagnosed according to explicit criteria (e.g. following a specified diagnostic schema such as the American Psychiatric Association's Diagnostic and Statistical Manual), including major depressive disorder, dysthymic disorder, and bipolar affective disorder.

Types of interventions

1. Inositol compared to placebo, 2. Inositol compared to antidepressant medication, or 3. Inositol plus antidepressant compared to antidepressant alone, in the treatment of depressive disorder.

Types of outcome measures

A. Primary outcome measure

Resolution of a depressive episode within defined periods of observation is the primary outcome measure. Resolution is often measured using depressive symptom rating scales, when possible we have analysed these as continuous data. These continuous data, however, are often dichotomised at an arbitrary cut point (e.g. Hamilton Depression Rating Scale score <8, or a >50% reduction on the HDRS) because this facilitates clinical interpretation, accordingly such data are analysed as dichotomous data.

B. Secondary outcome measures

Where possible we have also investigated the following outcomes using continuous and dichotomous data as appropriate:

The overall drop-out rate as a proxy measure of overall acceptability of treatment

The drop-out rate due to side-effects

The number of patients reporting at least one adverse event i.e. troublesome side effects

Quality of life

Global clinical impression rated by the clinician

Global clinical impression rated by the patient

Social functioning

Occupational functioning

Rate of relapse or onset of manic episode

Rates of admission to hospital

Duration of admission to hospital

Mortality due to all causes and specifically suicides and verdicts of undetermined deaths.

Search methods for identification of studies

See Collaborative Review Group search strategy.

1. Electronic databases were searched:

The Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR), incorporating results of group searches of MEDLINE (1966 -), EMBASE (1980 -), CINAHL (1982 -), PsycLIT (1974 -), PSYINDEX (1977 -) and LILACS (1982 -) using the following terms:

inositol OR myo-inositol OR meso-inositol OR i-inositol OR epi-inositol OR l-chiro-inositol

The Cochrane Library Controlled Trials Register (CTTR), using the following terms:

(inositol* OR myo?inositol* OR myoinositol* OR myo-inositol* OR meso?inositol* OR mesoinositol* OR meso-inositol* OR i-inositol* OR epi?inositol* OR epi-inositol* OR l-chiro?inositol* OR l-chiro-inositol*) AND (depress* OR dysthym* OR (dysthym* NEXT disord*) OR (bipolar disorder))

To supplement the results from the CCDANCTR and the CTTR the databases MEDLINE (1966 - Jan Week 3, 2004), EMBASE (1980 - 2004 Week 3), PsycINFO (1872 - Jan Week 3, 2004), and CINAHL (1982 - Dec Week 2, 2003) were searched using the Cochrane Library RCT filter and the following terms:

(exp inositol OR inositol* OR myo?inositol* OR myoinositol* OR myo-inositol* OR meso?inositol* OR mesoinositol* OR meso-inositol* OR i-inositol* OR i-inositol* OR epi?inositol* OR epi-inositol* OR l-chiro?inositol* OR l-chiro-inositol*) AND (exp depressive disorder OR exp bipolar disorder OR exp major depression OR exp manic depression OR exp manic depressive psychosis OR depress* OR dysthymia OR (dysthym* NEXT disord*))

2. Reference checking

The reference lists of all selected studies were inspected for more published reports and citations of unpublished research. In addition other relevant papers and major textbooks which cover affective disorder were checked.

3. Personal communications

To ensure that as many randomised controlled trials as possible were identified, the authors of significant papers and other experts in the field were contacted.

4. Pharmaceutical Companies

Pharmaceutical companies manufacturing inositol were contacted to find out if they knew of any published or unpublished randomised controlled trials relevant to this review.

Data collection and analysis

1. Selection of trials

Studies generated by the search strategies were checked independently by two reviewers to ensure that they met the previously defined inclusion criteria.

2. Quality assessment

Two reviewers independently assessed the methodological quality of the included studies. The reviewers were not blind to the authorship and source of the papers (Berlin 1997). Quality was assessed according to the Cochrane criteria for quality assessment (Sackett 1997). This pays particular attention to the quality of the randomisation procedure including allocation concealment. On this basis studies were given a quality rating of A (adequate), B (unclear), and C (inadequate). If the raters disagreed, the final rating was made by consensus with the involvement, if necessary, of another of the review group. In addition, aspects of quality such as whether the trial was of a double blind design and reporting of withdrawals and dropouts were described. Where adequate details of randomisation and other characteristics of trials are not provided the authors have been contacted in order to obtain further information.

3. Data extraction

Data were extracted from the included studies about participant characteristics, intervention details, study design, and outcome measures. This included numbers of patients randomised to each treatment group, and the numbers of patients failing to reach the end of the study. For continuous outcome measures, the mean score and standard deviation, and the number of participants evaluated, were extracted for each time point. Any disagreements were resolved by consensus discussions with a third member of the review team.

4. Data analysis

Data were entered into Review Manager 4.1.1 software. For binary efficacy outcomes, a relative risk (with 95% confidence intervals) was calculated using a fixed effects model. Heterogeneity between studies was assessed using the chi-squared test.

Random effects models were used routinely to investigate the sensitivity of results to the choice of statistical method. For continuously distributed outcomes the weighted mean difference (WMD) was calculated when the same scale was used in a similar manner across studies, otherwise, the standardised weighted mean difference (SMD) was used.

We used intention-to-treat data when available, using last observation carried forward where available, and where this was not possible, endpoint data for trial completers was used. Non-quantitative data are presented descriptively. Subgroup analyses were planned to assess the extent to which the results differed between diagnostic groups, e.g. between bipolar affective disorder and major depressive disorder, to explore the possibility of clinical heterogeneity of response. Sensitivity analyses were planned to assess the robustness of the results to the exclusion of studies of lower methodological quality.

RESULTS

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 who 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).

Setting

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.

Risk of bias in included studies

Allocation

The trials gave few details of the randomisation procedures followed. The methods used to maintain concealment of allocation were unclear, therefore all the trials received a 'B' rating according to Cochrane criteria ([Sackett 1997](#)).

Blinding

All the trials described the use of 'double-blind' methods, with blinding of subjects achieved using a glucose placebo in the same powdered form as the inositol. One trial ([Nemets 1999](#)) explicitly states that the outcome assessor was blind to treatment allocation, but it is unclear in the other trials whether the blinding was of clinician and/or outcome assessor.

Reporting of withdrawals and dropouts

All the trials reported numbers of withdrawals and dropouts, but none included all of these participants in analyses. [Chengappa 2000](#) reports data from all those who had at least one post-randomisation assessment; the other studies analysed those who had completed at least one week ([Levine 1995](#)), three weeks ([Nemets 1999](#)) or four weeks ([Levine 1999](#)) of treatment.

Effects of interventions

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.

AUTHORS' 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.

REFERENCES

References to studies included in this review

Chengappa 2000 {published data only}

* Chengappa KN, Levine J, Gershon S, Mallinger AG, Hardan A, Vagnucci A, et al. Inositol as an add-on treatment for bipolar depression. *Bipolar Disorders* 2000;**2**(1):47-55. [MEDLINE: 11254020; 31]

Levine 1995 {published data only}

Belmaker RH. Controlled trials of inositol in psychiatry. XX1st Collegium Internationale Neuro-psychopharmacologicum, Glasgow, Scotland, 12th-16th July. 1998. [60]

Belmaker RH, Levine JA, Kofman O. Inositol - a novel augmentation for mood disorders. 151st Annual Meeting of the American Psychiatric Association, Toronto, Ontario, Canada. 30th May-4th June. 1998. [59]

Benjamin J, Agam G, Levine J, Bersudsky Y, Kofman O, Belmaker RH. Inositol treatment in psychiatry.. *Psychopharmacology Bulletin* 1995;**31**(1):167-75. [MEDLINE: 7675981; 41]

Einat H, Shaldubina A, Belmaker RH. Epi-inositol: A potential antidepressant. *Drug Development Research* 2000;**50**(3-4):309-15. [MEDLINE: 2000356172; 10]

Levine J. Controlled trials of inositol in psychiatry. *European Neuropsychopharmacology* 1997;**7**(2):147-55. [MEDLINE: 9169302; 37]

* Levine J, Barak Y, Gonzalves M, Szor H, Elizur A, Kofman O, et al. Double-blind, controlled trial of inositol treatment of depression. *American Journal of Psychiatry* 1995;**152**(5):792-4. [MEDLINE: 7726322; 44]

Levine J, Barak Y, Kofman O, Belmaker RH. Follow-up and relapse analysis of an inositol study of depression. *Israel Journal of Psychiatry and Related Sciences* 1995;**32**(1):14-21. [MEDLINE: 7622343; 42]

Levine 1999 {published data only}

* Levine J, Mishori A, Susnosky M, Martin M, Belmaker RH. Combination of inositol and serotonin reuptake inhibitors in the treatment of depression. *Biological Psychiatry* 1999;**45**(3):270-3. [MEDLINE: 10023500; 35]

Nemets B, Fux M, Levine J, Belmaker RH. Combination of antidepressant drugs: The case of inositol. *Human Psychopharmacology* 2001;**16**(1):37-43. [MEDLINE: 2001103564; 6]

Nemets B, Levine J, Mishori A, Belmaker RH. Combination of inositol and serotonin reuptake inhibitors in the treatment of depression. XX1st Collegium Internationale Neuro-psychopharmacologicum, Glasgow, Scotland, 12th-16th July. 1998. [57]

Nemets 1999 {published data only}

* Nemets B, Mishory A, Levine J, Belmaker RH. Inositol addition does not improve depression in SSRI treatment failures.

Journal of Neural Transmission 1999;**106**(7-8):795-8. [MEDLINE: 10907738; 33]

References to studies excluded from this review

Levine 1995b {published data only}

Levine J, Pomerantz T, Stier S, Belmaker RH. Lack of effect of 6 g inositol treatment of post-ECT cognitive function in humans. *Journal of Psychiatric Research* 1995;**29**(6):487-9. [MEDLINE: 8642546; 40]

Levine 1997 {published data only}

Levine J, Shectman T, Lefkifker E, Horesh N, Shapiro J, Agam G, et al. Inositol may reverse lithium-induced polydipsia but not polyuria. *Human Psychopharmacology* 1997;**12**:459-65. [48]

References to ongoing studies

Sachs {published data only}

Sachs G. Inositol. Stanley Medical Research Institute (<http://www.stanleyresearch.org/> accessed November 2002) 1998.

STEP-BD {published data only}

Anon. Systematic treatment enhancement program for bipolar disorder. ClinicalTrials.gov (<http://clinicaltrials.gov/> accessed November 2002) 2002.

Additional references

AHCPR 1999

Agency for Health Care Policy and Research. Treatment of depression - newer pharmacotherapies. Summary, Evidence Report/Technology Assessment. <http://www.ahcpr.gov/clinic/deprsumm.htm> 1999.

Allison 1971

Allison JH, Stewart MA. Reduced brain inositol in lithium-treated rats. *Nature - New Biology* 1971;**233**(43):267-8. [MEDLINE: 72051635]

Barkai 1978

Barkai AI, Dunner DL, Gross HA, Mayo P, Fieve RR. Reduced myo-inositol levels in cerebrospinal fluid from patients with affective disorder. *Biological Psychiatry* 1978;**13**(1):65-72. [MEDLINE: 78104254]

Berlin 1997

Berlin JA. Does blinding of readers affect the results of meta-analyses? University of Pennsylvania Meta-analysis Blinding Study Group. *Lancet* 1997;**350**(9072):185-6. [MEDLINE: 97393756]

Blazer 1994

Blazer DG, Kessler RC, McGonagle KA, Swartz MS. The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. *American Journal of Psychiatry* 1994;**151**(7):979-86. [MEDLINE: 8010383]

CNCG 1992

Cross-National Collaborative Group. The changing rate of major depression: cross-national comparisons.. *JAMA* 1992;**268**(21):3098-105. [MEDLINE: 93059971]

Einat 2001

Einat H, Belmaker RH. The effects of inositol treatment in animal models of psychiatric disorders. *Journal of Affective Disorders* 2001;**62**(1-2):113-21. [MEDLINE: 21101533]

Geddes 2001

Geddes JR, Butler R, Warner J. Depressive disorders in adults. Clinical Evidence. London: BMJ Publishing Group, 2001.

Jenkins 1997

Jenkins R, Lewis G, Bebbington P, Brugha P, Farrell M, Gill B, et al. The national psychiatric morbidity surveys of Great Britain - initial findings from the household survey. *Psychological Medicine* 1997;**27**(4):775-89.

Kofman 1993

Kofman O, Belmaker RH. Ziskind-Somerfeld Research Award 1993. Biochemical, behavioral, and clinical studies of the role of inositol in lithium treatment and depression. *Biol Psychiatry* 1993;**34**(12):839-52. [MEDLINE: 94154087]

Levine 1993

Levine J, Rapaport A, Lev L, Bersudsky Y, Kofman O, Belmaker RH, et al. Inositol treatment raises CSF inositol levels. *Brain Research* 1993;**627**(1):168-70. [MEDLINE: 94123095]

Murray 1997a

Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet* 1997;**349**(9063):1436-42. [MEDLINE: 97307104]

Murray 1997b

Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* 1997;**349**(9064):1498-504. [MEDLINE: 97310291]

Sackett 1997

Sackett D. The Cochrane Collaboration Handbook. Oxford: Update Software, 1997.

Shimon 1997

Shimon H, Agam G, Belmaker RH, Hyde TM, Kleinman JE. Reduced frontal cortex inositol levels in postmortem brain of suicide victims and patients with bipolar disorder. *American Journal of Psychiatry* 1997;**154**(8):1148-50. [MEDLINE: 97390548]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Chengappa 2000

Methods	parallel group double blind design, randomised allocation
Participants	24 adults, bipolar affective disorder, current episode depressed (DSM-IV criteria), Hamilton Depression Rating Scale (17 item) >14 at entry, taking lithium valproate or carbamazepine in therapeutic dosage
Interventions	(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
Outcomes	Hamilton Depression Rating Scale (17 and 25 item), Montgomery Asberg Depression Rating Scale, Clinical Global Impression, Young Mania Rating Scale, UKU Side Effects Scale
Notes	Six week duration

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Levine 1995

Methods	parallel group double blind design, randomised allocation

Inositol for depressive disorders (Review)

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Levine 1995 (Continued)

Participants	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
Interventions	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
Outcomes	Hamilton Depression Rating Scale (24 item), modified Treatment Emergent Symptom Scale
Notes	Four week duration

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Levine 1999

Methods	parallel group double blind design, randomised allocation
Participants	36 adults (8 male, 19 female completed), major depression (DSM-IV criteria)
Interventions	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
Outcomes	Hamilton Depression Rating Scale (24 item)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

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	

Risk of bias

Inositol for depressive disorders (Review)

Nemets 1999 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

DSM-IV - Diagnostic and Statistical Manual 4th edition; DSM-III-R - Diagnostic and Statistical Manual, 3rd edition, revised; SSRI - Selective serotonin reuptake inhibitor.

Characteristics of excluded studies [ordered by study ID]

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 [ordered by study ID]

Sachs

Trial name or title	98-325A
Methods	
Participants	treatment refractory bipolar depression (n=20)
Interventions	inositol or placebo added to stable mood stabiliser
Outcomes	
Starting date	enrolling
Contact information	Gary Sachs, MD, Massachusetts General Hospital Boston, Massachusetts
Notes	

STEP-BD

Trial name or title	STEP-BD (Systematic treatment enhancement program for bipolar disorder)
Methods	
Participants	5000 patients with bipolar disorder or cyclothymic disorder (DSM-IV criteria) in 20 centers
Interventions	Lithium, valproate, bupropion, paroxetine, lamotrigine, risperidone, inositol, tranylcypamine, Cognitive Behaviour Therapy. Family-Focused Therapy, Interpersonal and Social Rhythms Therapy
Outcomes	
Starting date	enrolling

Inositol for depressive disorders (Review)

STEP-BD (Continued)

Contact information

For more information, call toll-free: 1-866-240-3250 stepbd@mailcity.com
www.stepbd.org

Notes

DATA AND ANALYSES
Comparison 1. inositol versus glucose (placebo)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hamilton Rating Scale for Depression, trial end point	4	113	Std. Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.45, 0.30]
1.1 inositol monotherapy	1	28	Std. Mean Difference (IV, Fixed, 95% CI)	-0.71 [-1.48, 0.06]
1.2 inositol augmentation of other treatments	3	85	Std. Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.31, 0.55]
2 change in Hamilton depression rating scale (dichotomous)	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 failure to decrease HDRS score by 15 points	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 failure to decrease HDRS score by 15 points and by at least 50%	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 failure to reduce HDRS(17) by 50% and have CGI of 2 or less (completers)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 measures of tolerability	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 overall drop-outs	4	142	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.77, 2.90]
3.2 drop-outs attributed to side effects	4	142	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.32, 2.09]
3.3 subjects with at least one adverse event	4	142	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.48, 1.64]

Analysis 1.1. Comparison 1 inositol versus glucose (placebo), Outcome 1 Hamilton Rating Scale for Depression, trial end point.

Study or subgroup	inositol		glucose		Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
1.1.1 inositol monotherapy							
Favours inositol -4 -2 0 2 4 Favours placebo							

Analysis 1.2. Comparison 1 inositol versus glucose (placebo), Outcome 2 change in Hamilton depression rating scale (dichotomous).

Analysis 1.3. Comparison 1 inositol versus glucose (placebo), Outcome 3 measures of tolerability.

WHAT'S NEW

Date	Event	Description
1 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 2, 2004

Date	Event	Description
22 October 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

MT, HW, and JG conceived the review. MT, HW, ZB, and JG designed the review. MT and HW selected trials. ZB and JG assessed methodological quality. MT and HW extracted data. MT performed data analysis. MT, HW, ZB, and JG contributed to data interpretation and the writing of the review. MT coordinated the review and will act as guarantor.

DECLARATIONS 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.

SOURCES OF SUPPORT

Internal sources

- Department of Psychiatry, University of Oxford, UK.
- Oxfordshire Mental Healthcare NHS Trust, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Antidepressive Agents [*therapeutic use]; Depressive Disorder [*drug therapy]; Inositol [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans