Tryptophan and 5-Hydroxytryptophan for depression (Review)

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[Intervention Review]

Tryptophan and 5-Hydroxytryptophan for depression

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ABSTRACT

Background

5 Hydroxytryptophan (5-HTP) and tryptophan are so-called natural alternatives to traditional antidepressants, used to treat unipolar depression and dysthymia.

Objectives

To determine whether 5-HTP and tryptophan are more effective than placebo, and whether they are safe to use to treat depressive disorders in adults.

Search strategy

CCDANCTR-Studies and CCDANCTR-References were searched on 12/2/2008). Reference lists, book chapters and conference proceedings were checked. Experts and trialists were contacted for unpublished studies.

Selection criteria

Trials were included if they were randomized, included patients with unipolar depression or dysthymia, compared preparations of 5-HTP or tryptophan with placebo, and included clinical outcomes assessed by scales assessing depressive symptoms.

Data collection and analysis

Data was extracted independently by the three reviewers, onto data collection forms. Inclusion criteria were applied to all potential studies independently and a coefficient of agreement (Kappa) was calculated for them. Disagreement was resolved by reaching consensus. Trial quality was scored according to risk of bias. Analysis for 5-HTP and tryptophan were combined due to the small number of included trials.

Main results

108 trials were located using the specified search strategy in 2001. An additional three trials were located when the search strategy was repeated in 2004. Of the total number of trials located in both searches, only two trials, involving a total of 64 patients, were of sufficient quality to meet inclusion criteria. The available evidence suggests these substances were better than placebo at alleviating depression (Peto Odds Ratio 4.10; 95% confidence interval 1.28-13.15; RD 0.36; NNT 2.78). However, the evidence was of insufficient quality to be conclusive.

Authors' conclusions

A large number of studies appear to address the research questions, but few are of sufficient quality to be reliable. Available evidence does suggest these substances are better than placebo at alleviating depression. Further studies are needed to evaluate the efficacy and safety of 5-HTP and tryptophan before their widespread use can be recommended. The possible association between these substances and the potentially fatal Eosinophilia-Myalgia Syndrome has not been elucidated. Because alternative antidepressants exist which have been proven to be effective and safe the clinical usefulness of 5-HTP and tryptophan is limited at present.

PLAIN LANGUAGE SUMMARY

Tryptophan and 5-Hydroxytryptophan for depression

5-HTP (Hydroxytryptophan) and tryptophan have been examined to see whether these treatments are effective, safe and acceptable in treating unipolar depression in adults. The researchers reported that the symptoms of depression decreased when 5-HTP and tryptophan were compared to a placebo (non-drug). However, side effects had occurred (dizziness, nausea and diarrhoea). They also reported that tryptophan has been associated with the development of a fatal condition. More evidence is needed to assess efficacy and safety, before any strong and meaningful conclusions can be made. Until then, the reviewers propose that the use of antidepressants which have no known life threatening side effects remain more attractive. The review sets out the required methodology for effectively studying these substances in proper controlled studies.

BACKGROUND

Depression is the most commonly diagnosed psychiatric condition (Edgell 1972). There are many theories regarding aetiology of depression. However, its precise aetiology is still largely unknown (Rousseau 1987). For many years cerebral serotonin deficiency has been recognised as a possible cause of depression. This hypothesis has been supported by demonstrating improvement in depression in patients receiving medications known to increase cerebral serotonin precursor levels (Pare 1959; Coppen 1963), and by post-mortem analysis of cerebral and CSF tissue demonstrating serotonin deficiency in affected individuals (Shaw 1967; Bourne 1968; Pare 1969).

Antidepressants remain the mainstay of therapy for patients with depression, with psychotherapy playing a very important adjunctive role (Edgell 1972). There is an increasing trend towards the use of so-called natural alternatives to traditional antidepressants. These alternatives include substances such as St Johns Wort, Kava-Kava, tyrosine, tryptophan and 5-Hydroxy-L-tryptophan (5-HTP) (Jorm 1997). Tryptophan and 5-HTP are the focus of this review.

5-HTP is synthesised from the amino acid tryptophan. The body absorbs tryptophan, converts it to 5-HTP then forms it into serotonin, both centrally and peripherally (Lader 1981). Both tryptophan and 5-HTP are able to penetrate the blood-brain barrier. A normal Western diet contains about 0.5g of tryptophan daily, of which only 2-3% is used in central serotonin production (Beckmann 1983). Tryptophan is transported across the blood-brain barrier by a carrier mechanism which also transports tyrosine, pheylalanine, leucine, isoleucine, and valine.

Increase in dietary tryptophan increases the amount transported across the blood-brain barrier. Increase in the other amino acids transported by the same carrier reduces the transport of tryptophan (Wurtman 1976; Wurtman 1981).

5-HTP penetrates the brain and is converted to serotonin within serotonergic neurons, and neurotransmitter within dopaminergic and noradrenergic neurons (Lader 1981). Therefore, depressed patients administered 5-HTP or tryptophan should experience improvement. However clinical trials in which patients have been administered tryptophan or 5-HTP have given conflicting results and reached differing conclusions. Some reviewers have found both substances to have an antidepressant effect (Gelenberg 1982; Praag 1981). Other reviewers have found the evidence supporting use of tryptophan and 5-HTP for depression to be weak (Murphy 1978; D'Elia 1978; Beckmann 1983).

5-HTP and tryptophan are both known to have side effects. Nausea and gastrointestinal distress are the most notable, making it very difficult to blind participants to treatment in randomized controlled trials. Of greater concern is the possible association of tryptophan with Eosinophilia-Myalgia Syndrome (EMS). This syndrome affected nearly 1 500 tryptophan users in 1989 and led to over 30 deaths. It is still uncertain whether the tryptophan, which contained an impurity identified by analytical chromatography, was the cause (Toyo'oka 1991). Tryptophan was subsequently

withdrawn from the market in the USA (Blackburn 1997). The nature of the tryptophan-EMS association has not yet been fully elucidated. It is also possible it is a chance association only, it is due to excess tryptophan itself, or it is due to a combination of the impurity and excess tryptophan (Horowitz 1996). A similar impurity has recently been identified in 5-HTP. The significance of this is also unknown (Michelson 1994).

OBJECTIVES

1. To evaluate the efficacy and acceptability of 5-HTP in unipolar depression.

2. To evaluate the efficacy and acceptability of tryptophan in unipolar depression.

The following hypotheses were tested:

1. 5-HTP is more effective than placebo in the treatment of unipolar depression.

2. Tryptophan is more effective than placebo in the treatment of unipolar depression.

METHODS

Criteria for considering studies for this review

Types of studies

Studies compared 5-HTP or tryptophan to inert placebo.
Studies included a design which involved double blind randomized allocation to treatment groups.
Quasi-randomized trials were considered for inclusion and analysis separately.
Trials included some measurement of depression as an outcome variable.

Types of participants

Trials contained a comparison group receiving inert placebo.
Trials of adults with unipolar depression diagnosed according to any recognised criteria, irrespective of age, gender, race or nationality were eligible for inclusion.
Ambulatory settings and hospital settings were included.
Patients with a concurrent diagnosis of another psychiatric or medical disorder were included.

Types of interventions

Trials compared either 5-HTP or tryptophan to placebo.
Comparison groups were allocated to active treatment or inert placebo.
Placebos excluded any currently used antidepressant drug.

Types of outcome measures

Primary outcomes of interest were:
1 - change in depression by the end of the trial as determined by symptom scale. Clinical improvement or exacerbation or no change was determined by symptom scale measurement.
2 - acceptability of the treatment as measured by drop-out during the trial and post randomisation exclusions, numbers reporting at least one side-effect during the trial, specific side-effects, and deaths.
3 - relapse of depression.

Search methods for identification of studies

See: Collaborative Review Group Strategy
1. Electronic Searching
The CCDAN registers were searched as follows
CCDANCTR-Studies (searched on 12/2/2008)
Diagnosis = Depress* or Dysthymi* or "Adjustment Disorder*" or "Mood Disorder*" or "Affective Disorder" or "Affective Symptoms")
and
Intervention = tryptophan or 5-htp or 5-hydroxtryptophan or Hydroxytryptophan
and
Intervention = Placebo
CCDANCTR-References (searched on 12/2/2008)
Keyword = Depress* or Dysthymi* or "Adjustment Disorder*" or "Mood Disorder*" or "Affective Disorder" or "Affective Symptoms")
and
Free-text = tryptophan or 5-htp or 5-hydroxtryptophan or Hydroxytryptophan

2. Hand Searching
The reference lists of included studies were scanned for published reports and citations of unpublished research.
Book chapters on treatment of depression were scanned for description of trials.
Conference abstracts were searched for references.
3. Personal Communication
Unpublished data was to be sought from relevant authors and experts in the field

Data collection and analysis

LOCATING AND SELECTING STUDIES
Three reviewers (KS, JT and CDM) carried out the inclusion criteria application.

The inclusion criteria were applied to all potential studies independently and a coefficient of agreement (Kappa) calculated. Disagreement was resolved by reaching consensus.

CRITICAL APPRAISAL

The methodological quality of the included studies was independently evaluated by the three reviewers.

Details of method of randomisation, blinding, whether intention-to-treat analysis was done, and number of patients lost to follow up was recorded.

The trials were scored according to concealment of allocation (A=low risk, B=moderate risk, C=high risk) (Cochrane Handbook 1994).

COLLECTING DATA

The results of each trial were summarised on an intention-to-treat basis in 2x2 tables for each outcome, for tryptophan and 5-HTP separately. Only trials with a score of A and B were used.

ANALYSING AND PRESENTING RESULTS

The studies were grouped for meta-analysis according to the appraisal above. 5-HTP and tryptophan were analysed together due to the small number of trials which met inclusion criteria. Meta-analysis was performed (Review Manager 4.01) using various techniques. The Peto odds ratio, odds ratio, relative risk, risk difference were all calculated. When overall results were significant both the relative risk reduction (RRR) and number needed to treat (NNT) were calculated. Additionally, the number needed to harm (NNH) and the confidence interval around these measures were calculated. Graphical presentations were assessed also.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

See: Tables of characteristics of included and excluded studies

In 2001, a total of 108 clinical controlled or possibly trials that investigated 5-HTP and tryptophan in depression were located using the above search strategy. Forty-nine studies were excluded on the basis of the abstract as they were not limited to 5-HTP or tryptophan as a treatment for depression. Fifty-nine trials were quality scored using the original article as the abstract was not sufficiently detailed to draw conclusions about the study. Of these, 23 were excluded as they were not placebo controlled, four were excluded as they did not evaluate the efficacy of 5-HTP or tryptophan as a monotherapy, six were excluded as they did not pertain primarily to depression, two were excluded as they were double publications of the same trial, and 11 were excluded as they were not adequately randomized or double blind. The 11 remaining trials, including two non-English language trials, were evaluated. Three were subsequently excluded on the basis of methodologic weaknesses and inability to extract necessary parameters from the results. Six were excluded as they were crossover trials. The remaining two trials, including a total of 64 patients met inclusion criteria (Thomson 1982, Van Praag 1972).

The search strategy was repeated in 2004. An additional 27 abstracts were located. Twenty-four abstracts were excluded as they were not limited to 5-HTP or tryptophan as a treatment for depression. Three trials were quality scored using the original article. Of these, one was excluded as it did not evaluate the efficacy of 5-HTP or tryptophan as a monotherapy (Levitan 2000), one was a case-control study (Russ 1990), and one did not have a placebo group for comparison (Kline 1973).

Participants had depression varying in severity from mild to severe. The duration of the studies was short - up to 10 weeks. One study assessed 5-HTP, the other, tryptophan. The Hamilton Depression Rating Scale was used as the primary measure of response to treatment. The Global Rating Scale, Venables scale, Zung scale and Visual Analogue Scale were also used.

Out of the total of 64 patients in the trials, seven patients on active treatment withdrew from the study prematurely, compared with 11 patients on inactive placebo.

Risk of bias in included studies

See: Table of characteristics of included studies

The description of concealment of allocation was rated as A in both studies (Thomson 1982, Van Praag 1972).

Effects of interventions

The small number of patients included overall increases the risk of publication bias and makes generalization about efficacy of 5-HTP and tryptophan difficult, however, the results indicated that 5-HTP and tryptophan were better than placebo at alleviating symptoms of depression (Peto odds ratio 4.10; 95% confidence interval 1.28 - 13.15). The risk difference was 0.36 and the number needed to treat 2.78. The number of patients on active treatment reporting side-effects was four. Dizziness, nausea and diarrhoea were the side-effects cited. The number needed to harm was not calculated due to small numbers. No deaths related to the use of 5-HTP or tryptophan were reported in the studies. There were no side-effects in the placebo groups.

DISCUSSION

A large number of studies are available which appear to address the research questions, however few are of sufficient quality to be reliable. Available evidence from randomized trials is insufficient

to evaluate conclusively whether or not 5-HTP and/or tryptophan have any superior effect over placebo in the treatment of mild to severe unipolar depression. Available evidence does, however, suggest these substances are better than placebo at alleviating depression.There are insufficient data to evaluate the side-effect profile of each treatment, and their relative safety.

Randomized controlled trials that have evaluated clinical effects of 5-HTP and tryptophan treatment for depressive disorders are limited in their reliability by poor methodological quality (see table - Excluded Studies). Trials varied significantly regarding severity of depression, doses of 5-HTP and tryptophan studied, settings, and comparative interventions. In several trials comparing 5-HTP and tryptophan to other antidepressants, the 5-HTP and tryptophan were used instead of placebo because it was assumed that they were no better than placebo in managing depression, and because ethics committees in several instances felt it was unethical to use an 'inactive' placebo in depressed inpatients (Seppala 1978; Linnoila 1980). A comparison of 5-HTP and tryptophan with other available antidepressants was not performed in this review.

Tolerability of 5-HTP and tryptophan was acceptable in the included studies. Few adverse effects were noted. Side-effects resulting in withdrawal were dizziness and epigastric pain. Diarrhoea was also reported but did not result in patient withdrawal. No patient in the placebo group withdrew due to side-effects. No deaths were reported. Published case reports, however, have questioned the link between tryptophan and the development of eosinophilia-myalgia syndrome, which has been fatal in an number of cases (Toyo'oka 1991). The link has, to date, remained unproven. The same impurity identified in tryptophan has also been found in 5-HTP (Horowitz 1996; Michelson 1994). Systematic studies evaluating long-term side effects of 5-HTP and tryptophan do not exist.

AUTHORS' CONCLUSIONS

Implications for practice

Results of this meta-analysis are inconclusive due to the small number of sufficiently rigorous studies available on which to base conclusions. It is therefore difficult to recommend or discourage the use of 5-HTP and tryptophan in treatment of unipolar depression. More evidence is clearly needed to assess efficacy. Although the order of magnitude of effectiveness of 5-HTP and tryptophan was found in this study to be similar to Selective Serotonin Reuptake Inhibitors (SSRIs) and Tricyclic Antidepressants (TCAs), the body of evidence evaluating the efficacy and safety of SSRIs and TCAs is more rigorous and comprehensive (Trindade 1997). Also, the relative potency of SSRIs and TCAs is possibly much greater, even though order of effectiveness is comparable. In settings where depression is mild, and the use of traditional antidepressants is unacceptable to the patient, tryptophan and 5-HTP may be considered as treatment alternatives.

The possible link between tryptophan and 5-HTP and a potentially fatal side-effect makes their clinical use less appealing until this issue is resolved, particularly due to the availability of other antidepressants with proven efficacy and safety.

A further issue complicating use of 5-HTP and tryptophan is the type of preparation and dose. Trials evaluated used widely varying doses and dosage schedules. No consensus about appropriate dosage and frequency of administration exists to guide the clinician's prescribing.

Implications for research

Large, well designed, placebo-controlled, randomized controlled trials are needed to assess clinical utility of 5-HTP and tryptophan in the treatment of depression. Future studies should focus on the following issues:

- evaluation of efficacy in well-defined subgroups of patients with unipolar depression of varying severity

- evaluation of side-effects, particularly potentially life-threatening side-effects.

- comparisons of different dosage, frequency of administration, and preparations of 5-HTP and tryptophan

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Thomson 1982

Methods	Randomized, double blind placebo-controlled trial
Participants	28 patients with mild depression of at least 2 weeks duration, aged 18-65 years, and 26 controls. 7 patients dropped out of the treatment group and 13 dropped out of the placebo group.
Interventions	Placebo for 1 week followed by 12 weeks of L-Tryptophan 1 gram tds, placebo group received identical placebo capsules for 13 weeks
Outcomes	Hamilton Depression Rating Scale, Global Rating Scale, and Visual Analogue Scale
Notes	Over 15% dropout rate, 7 withdrawals in active treatment group, 1 due to epigastric pain and 2 due to dizziness

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Van Praag 1972

Methods	Randomized, double blind placebo-controlled trial
Participants	10 severely depressed inpatients for whom ECT therapy was being contemplated
Interventions	3 weeks of 5-Hydroxytryptophan given as 200 mg capsules at a dosage increasing to 3 grams daily and to a total of 50 grams per 3 weeks (total duration 3 weeks) followed by 2 weeks of placebo. Identical placebo was given to the control group for a total duration of 5 weeks.
Outcomes	Hamilton Depression Rating Scale, Venables Scale and Zung Rating Scale
Notes	Patients also received barbiturates as needed

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

Alino 1976	No group treated with 5-hydroxytryptophan alone
Angst 1977	No placebo
Asheychik 1989	Alcoholic patients No intention to treat analysis performed
Ayuso 1971 a	No placebo, no group treated with tryptophan alone
Barker 1987	No placebo, no group treated with tryptophan alone
Barr 1994	Patients had obsessive-compulsive disorder and not depression
Brewerton 1992	Patients had bulimia, no clinically useful measurement of change in depressive symptoms made
Carroll 1970	Not randomized, no placebo
Chouinard 1978	No placebo
Cooper 1980	Unable to extract data for unipolar patients alone, patients had major medical comorbidities
Coppen 1970	No placebo
Coppen 1976 c	No placebo
D'Elia 1977 b	Republication of previous study
Dunner 1972	No placebo
Dunner 1975	No placebo
Farkas 1976	Crossover study
Glassman 1969	No randomisation performed
Harris 1980 a	Patients had maternity blues and not depression
Herrington 1976	No placebo
Hoes 1981	No randomisation, not double blind, no intention to treat analysis
Honore 1982	No placebo, no patients treated with tryptophan alone

(*Continued*)

Jacobsen 1987 a	Patients had seasonal affective disorder and not depression
Jensen 1975	No placebo
Kirkegaard 1978	No placebo
Kline 1964	No randomisation, no intention to treat, no standardised assessment, no placebo
Kline 1973	No placebo group
Levitan 2000	Tryptophan given in combination with fluoxetine
Lindberg 1979 a	No placebo
Linnoila 1980	Tryptophan was the placebo
Lopez Ibor 1973	No placebo
Lucca 1995	No placebo
MacSweeney 1975	Not randomized controlled trial
Matussek 1974	Open study - no randomisation, no blinding and no placebo
McCance-Katz 1992	Not about primary outcome of our study, not randomized, IV tryptophan as single dose
McGrath 1990	Patients had seasonal affective disorder and not depression
Meltzer 1984	Not randomized, no placebo
Mendels 1975 b	Unable to extract data for unipolar patients alone
Mendlewicz 1980 b	Unable to extract data for unipolar patients alone
Murphy 1974	Crossover study
Nolen 1985	No blinding
Nolen 1988 a	No placebo
Nolen 1988 b	No Placebo
Poldinger 1991	No placebo

(*Continued*)

Prange 1974 a	Patients had mania and not depression
Price 1998	Tryptophan depletion was the subject of study, not tryptophan administration to treat depression
Quadbeck 1984	No randomisation, no placebo
Rao 1976	No placebo
Raotma 1978	No measurement of depressive symptoms
Rousseau 1987	No treatment group administered tryptophan alone
Russ 1990	Case-control study
Salomon 1994	Not randomized, no placebo
Seppala 1978	No placebo
Shaw 1970	No placebo
Shaw 1972	No placebo
Smith 1984	Crossover study
Steinberg 1999	Patients had premenstrual dysphoria and not depression
Walinder 1975	No treatment group administered tryptophan alone
Worrall 1979 b	No placebo
Zarcone 1977	Not randomized
Zhao 1989	Crossover study

DATA AND ANALYSES

Comparison 1. L-Tryptophan and 5-HTP versus placebo for the treatment of depression

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Numbers of responders	2	46	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.10 [1.28, 13.15]

Comparison 2. Side-effects of L-Tryptophan and 5-HTP versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Numbers with side-effects	2	64	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.41 [1.01, 54.19]

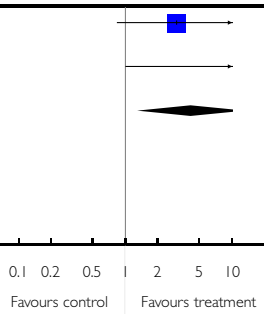
Analysis 1.1. Comparison 1 L-Tryptophan and 5-HTP versus placebo for the treatment of depression, Outcome 1 Numbers of responders.

Review: Tryptophan and 5-Hydroxytryptophan for depression

Comparison: 1 L-Tryptophan and 5-HTP versus placebo for the treatment of depression

Outcome: 1 Numbers of responders

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Thomson 1982	13/21	5/15		79.4 %	3.04 [0.82, 11.22]
Van Praag 1972	3/5	0/5		20.6 %	13.08 [1.01, 170.31]
Total (95% CI)	**26**	**20**		**100.0 %**	**4.10 [1.28, 13.15]**
Total events: 16 (Treatment), 5 (Control)					
Heterogeneity: Chi^2 = 0.99, df = 1 (P = 0.32); I^2 =0.0%					
Test for overall effect: Z = 2.38 (P = 0.017)					



Analysis 2.1. Comparison 2 Side-effects of L-Tryptophan and 5-HTP versus placebo, Outcome 1 Numbers with side-effects.

Review: Tryptophan and 5-Hydroxytryptophan for depression

Comparison: 2 Side-effects of L-Tryptophan and 5-HTP versus placebo

Outcome: 1 Numbers with side-effects

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Thomson 1982	3/28	0/26		74.2 %	7.42 [0.74, 74.66]
Van Praag 1972	1/5	0/5		25.8 %	7.39 [0.15, 372.38]
Total (95% CI)	**33**	**31**		**100.0 %**	**7.41 [1.01, 54.19]**

Total events: 4 (Treatment), 0 (Control)

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 1.97 (P = 0.048)

F E E D B A C K

Did review contain a Coppen paper?

Summary

I cannot find the studies reviewed for the Tryptophan review. Do they include a fascinating study in about 1975, by Dr A Coppin, in London, that showed L-tryptophan, combined with vitamins B6 and C, in a proprietary blend called Optimax, to be as good as Imipramine in depression? This study is cited in Dr Anthony Hordern's big 1970s book Tranquillity Denied. It may be hard to find in the literature, although I believe it did appear in the British Journal of Psychiatry.

Reply

I have reviewed the comment from Doctor Peers. The study he refers to is listed in the excluded studies of our review and was considered in the meta-analyses. Actually, there are four studies in the excluded studies of our review with Dr Coppen as an investigator. They did not meet inclusion criteria for the review as they were not placebo controlled.

Contributors

Dr Robert Peers
GP and nutrition researcher

WHAT'S NEW

Last assessed as up-to-date: 11 February 2008.

6 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2000

Review first published: Issue 3, 2001

28 November 2001	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

KELLY SHAW: Protocol development, literature search, assessment of trials and data extraction. Principal reviewer performing the analysis and interpretation of data, as well as the development of the final review.

JANE TURNER: Assessment of trials, data extraction and development of the final review.

CHRISTOPHER DEL MAR: Assessment of trials and data extraction, interpretation of the data and development of the final review.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Royal Australian College of General Practitioners, Australia.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

5-Hydroxytryptophan [therapeutic use]; Antidepressive Agents, Second-Generation [*therapeutic use]; Depression [*drug therapy]; Randomized Controlled Trials as Topic; Tryptophan [*therapeutic use]

MeSH check words

Humans