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Tryptophan and 5-Hydroxytryptophan for depression

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Editorial group: Cochrane Common Mental Disorders Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2010.
Review content assessed as up-to-date: 11 February 2008.

Citation: Shaw KA, Turner J, Del Mar C. Tryptophan and 5-Hydroxytryptophan for depression. Cochrane Database of Systematic Reviews 2002, Issue 1. Art. No.: CD003198. DOI: 10.1002/14651858.CD003198.

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 methods
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 Experts and trialists were contacted for unpublished studies.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, phenylalanine, 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-hydroxytryptophan or Hydroxytryptophan
   and
   Intervention = Placebo
   CCDANICTR-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-hydroxytryptophan 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: 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

ACKNOWLEDGEMENTS
Thanks to Anneliese Spinks (Research Officer, Department of Social and Preventive Medicine, University of Queensland) for assistance with computer software and data editing. Thanks to Li Chen (PhD student, Department of Psychiatry, University of Queensland) and Anabel Bardossy for their assistance with translating non-English language articles.
REFERENCES

References to studies included in this review

Thomson 1982 [published data only]

Van Praag 1972 [published data only]

References to studies excluded from this review

Alino 1976 [published data only]

Angst 1977 [published data only]

Ashechik 1989 [published data only]

Ayuso 1971 a [published data only]

Barker 1987 [published data only]

Barr 1994 [published data only]

Brewerton 1992 [published data only]

Carroll 1970 [published data only]

Chouinard 1978 [published data only]

Coppen 1970 [published data only]

D’Elia 1977 b [published data only]

Dunner 1972 [published data only]

Dunne 1975 [published data only]
Farkas 1976 {published data only}  

Glassman 1969 {published data only}  

Harris 1980 a {published data only}  

Herrington 1976 {published data only}  

Hoes 1981 {published data only}  

Honore 1982 {published data only}  

Jacobsen 1987 a {published data only}  

Jensen 1975 {published data only}  

Kirkegaard 1978 {published data only}  

Kline 1964 {published data only}  

Kline 1973 {published data only}  

Levitan 2000 {published data only}  

Lindberg 1979 a {published data only}  

Linnoila 1980 {published data only}  

Lopez Ibor 1973 {published data only}  

Lucca 1995 {published data only}  

MacSweeney 1975 {published data only}  

Matussek 1974 {published data only}  

McCance-Katz 1992 {published data only}  

McGrath 1990 {published data only}  

Meltzer 1984 {published data only}  

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Mendels 1975 b [published data only]

Mendlewicz 1980 b [published data only]

Nolen 1985 [published data only]

Nolen 1988 a [published data only]

Nolen 1988 b [published data only]

Poldinger 1991 [published data only]

Prange 1974 a [published data only]

Price 1998 [published data only]

Quadbeck 1984 [published data only]

Rao 1976 [published data only]

Rao 1978 [published data only]

Rousseau 1987 [published data only]

Russ 1990 [published data only]

Salomon 1994 [published data only]

Seppala 1978 [published data only]

Shaw 1970 [published data only]

Shaw 1972 [published data only]

Smith 1984 [published data only]
Additional references

Beckmann 1983

Blackburn 1997

Bourne 1968

Coppen 1963

D’Elia 1978

Edgell 1972

Gelenberg 1982

Horowitz 1996

Jorm 1997

Lader 1981

Michelson 1994

Murphy 1978

Pare 1959

Pare 1969

Praag 1981

Rousseau 1987

Shaw 1967
Toyo’oka 1991

Trindade 1997

Wurtman 1976

Wurtman 1981

* Indicates the major publication for the study
### Characteristics of included studies  
**[ordered by study ID]**

**Thomson 1982**

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<tr>
<td><strong>Methods</strong></td>
<td>Randomized, double blind placebo-controlled trial</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Placebo for 1 week followed by 12 weeks of L-Tryptophan 1 gram tds, placebo group received identical placebo capsules for 13 weeks</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Hamilton Depression Rating Scale, Global Rating Scale, and Visual Analogue Scale</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Over 15% dropout rate, 7 withdrawals in active treatment group, 1 due to epigastric pain and 2 due to dizziness</td>
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**Risk of bias**

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<tr>
<td>Allocation concealment?</td>
<td>Low risk</td>
<td>A - Adequate</td>
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**Van Praag 1972**

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<tr>
<td><strong>Methods</strong></td>
<td>Randomized, double blind placebo-controlled trial</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>10 severely depressed inpatients for whom ECT therapy was being contemplated</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Hamilton Depression Rating Scale, Venables Scale and Zung Rating Scale</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Patients also received barbiturates as needed</td>
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**Risk of bias**

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<td>A - Adequate</td>
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## Characteristics of excluded studies  

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<tr>
<td>Alino 1976</td>
<td>No group treated with 5-hydroxytryptophan alone</td>
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<tr>
<td>Angst 1977</td>
<td>No placebo</td>
</tr>
<tr>
<td>Asheychik 1989</td>
<td>Alcoholic patients</td>
</tr>
<tr>
<td></td>
<td>No intention to treat analysis performed</td>
</tr>
<tr>
<td>Ayuso 1971 a</td>
<td>No placebo, no group treated with tryptophan alone</td>
</tr>
<tr>
<td>Barker 1987</td>
<td>No placebo, no group treated with tryptophan alone</td>
</tr>
<tr>
<td>Barr 1994</td>
<td>Patients had obsessive-compulsive disorder and not depression</td>
</tr>
<tr>
<td>Brewerton 1992</td>
<td>Patients had bulimia, no clinically useful measurement of change in depressive symptoms made</td>
</tr>
<tr>
<td>Carroll 1970</td>
<td>Not randomized, no placebo</td>
</tr>
<tr>
<td>Chouinard 1978</td>
<td>No placebo</td>
</tr>
<tr>
<td>Cooper 1980</td>
<td>Unable to extract data for unipolar patients alone, patients had major medical comorbidities</td>
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<tr>
<td>Coppen 1970</td>
<td>No placebo</td>
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<tr>
<td>Coppen 1976 c</td>
<td>No placebo</td>
</tr>
<tr>
<td>D’Elia 1977 b</td>
<td>Republication of previous study</td>
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<td>Dunner 1972</td>
<td>No placebo</td>
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<tr>
<td>Dunner 1975</td>
<td>No placebo</td>
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<td>Farkas 1976</td>
<td>Crossover study</td>
</tr>
<tr>
<td>Glassman 1969</td>
<td>No randomisation performed</td>
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<tr>
<td>Harris 1980 a</td>
<td>Patients had maternity blues and not depression</td>
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<tr>
<td>Herrington 1976</td>
<td>No placebo</td>
</tr>
<tr>
<td>Hoes 1981</td>
<td>No randomisation, not double blind, no intention to treat analysis</td>
</tr>
<tr>
<td>Honore 1982</td>
<td>No placebo, no patients treated with tryptophan alone</td>
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<tr>
<td>Jacobsen 1987 a</td>
<td>Patients had seasonal affective disorder and not depression</td>
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<td>Study</td>
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<td>Jensen 1975</td>
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<td>Kirkegaard 1978</td>
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<tr>
<td>Kline 1964</td>
<td>No randomisation, no intention to treat, no standardised assessment, no placebo</td>
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<tr>
<td>Kline 1973</td>
<td>No placebo group</td>
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<td>Levitan 2000</td>
<td>Tryptophan given in combination with fluoxetine</td>
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<td>Lindberg 1979 a</td>
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<tr>
<td>MacSweeney 1975</td>
<td>Not randomized controlled trial</td>
</tr>
<tr>
<td>Matussek 1974</td>
<td>Open study - no randomisation, no blinding and no placebo</td>
</tr>
<tr>
<td>McCance-Katz 1992</td>
<td>Not about primary outcome of our study, not randomized, IV tryptophan as single dose</td>
</tr>
<tr>
<td>McGrath 1990</td>
<td>Patients had seasonal affective disorder and not depression</td>
</tr>
<tr>
<td>Meltzer 1984</td>
<td>Not randomized, no placebo</td>
</tr>
<tr>
<td>Mendels 1975 b</td>
<td>Unable to extract data for unipolar patients alone</td>
</tr>
<tr>
<td>Mendlewicz 1980 b</td>
<td>Unable to extract data for unipolar patients alone</td>
</tr>
<tr>
<td>Murphy 1974</td>
<td>Crossover study</td>
</tr>
<tr>
<td>Nolen 1985</td>
<td>No blinding</td>
</tr>
<tr>
<td>Nolen 1988 a</td>
<td>No placebo</td>
</tr>
<tr>
<td>Nolen 1988 b</td>
<td>No Placebo</td>
</tr>
<tr>
<td>Poldinger 1991</td>
<td>No placebo</td>
</tr>
<tr>
<td>Prange 1974 a</td>
<td>Patients had mania and not depression</td>
</tr>
<tr>
<td>Price 1998</td>
<td>Tryptophan depletion was the subject of study, not tryptophan administration to treat depression</td>
</tr>
<tr>
<td>Study Date</td>
<td>Description</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Quadbeck 1984</td>
<td>No randomisation, no placebo</td>
</tr>
<tr>
<td>Rao 1976</td>
<td>No placebo</td>
</tr>
<tr>
<td>Raotma 1978</td>
<td>No measurement of depressive symptoms</td>
</tr>
<tr>
<td>Rousseau 1987</td>
<td>No treatment group administered tryptophan alone</td>
</tr>
<tr>
<td>Russ 1990</td>
<td>Case-control study</td>
</tr>
<tr>
<td>Salomon 1994</td>
<td>Not randomized, no placebo</td>
</tr>
<tr>
<td>Seppala 1978</td>
<td>No placebo</td>
</tr>
<tr>
<td>Shaw 1970</td>
<td>No placebo</td>
</tr>
<tr>
<td>Shaw 1972</td>
<td>No placebo</td>
</tr>
<tr>
<td>Smith 1984</td>
<td>Crossover study</td>
</tr>
<tr>
<td>Steinberg 1999</td>
<td>Patients had premenstrual dysphoria and not depression</td>
</tr>
<tr>
<td>Walinder 1975</td>
<td>No treatment group administered tryptophan alone</td>
</tr>
<tr>
<td>Worrall 1979 b</td>
<td>No placebo</td>
</tr>
<tr>
<td>Zarcone 1977</td>
<td>Not randomized</td>
</tr>
<tr>
<td>Zhao 1989</td>
<td>Crossover study</td>
</tr>
</tbody>
</table>
## DATA AND ANALYSES

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

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Numbers of responders</td>
<td>2</td>
<td>46</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>4.10 [1.28, 13.15]</td>
</tr>
</tbody>
</table>

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

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

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

Outcome: Numbers of responders

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio Peto,Fixed,95% CI</th>
<th>Weight</th>
<th>Peto Odds Ratio Peto,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson 1982</td>
<td>13/21</td>
<td>5/15</td>
<td></td>
<td>79.4 %</td>
<td>3.04 [0.82, 11.22]</td>
</tr>
<tr>
<td>Van Praag 1972</td>
<td>3/5</td>
<td>0/5</td>
<td></td>
<td>20.6 %</td>
<td>13.08 [1.01, 170.31]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>26</strong></td>
<td><strong>20</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td>4.10 [1.28, 13.15]</td>
</tr>
</tbody>
</table>

Total events: 16 (Treatment), 5 (Control)

Heterogeneity: $\chi^2 = 0.99$, df = 1 ($P = 0.32$), $I^2 = 0.0 %$

Test for overall effect: $Z = 2.38$ ($P = 0.017$)

Test for subgroup differences: Not applicable
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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson 1982</td>
<td>3/28</td>
<td>0/26</td>
<td>74.2 %</td>
<td>7.42   [ 0.74, 74.66 ]</td>
<td></td>
</tr>
<tr>
<td>Van Praag 1972</td>
<td>1/5</td>
<td>0/5</td>
<td>25.8 %</td>
<td>7.39   [ 0.15, 372.38 ]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>33</td>
<td>31</td>
<td>100.0 %</td>
<td>7.41   [ 1.01, 54.19 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 4 (Treatment), 0 (Control)
Heterogeneity: $\chi^2 = 0.00$, df = 1 ($P = 1.00$); $I^2 = 0.0$
Test for overall effect: $Z = 1.97$ ($P = 0.048$)
Test for subgroup differences: Not applicable

FEEDBACK

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 Tranquility 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

Tryptophan and 5-Hydroxytryptophan for depression (Review)
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WHAT'S NEW

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

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>6 November 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
</tr>
</tbody>
</table>

HISTORY

Protocol first published: Issue 2, 2000

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 November 2001</td>
<td>New citation required and conclusions have changed</td>
<td>Substantive amendment</td>
</tr>
</tbody>
</table>

CONTRIBUTIONS OF AUTHORS

KELLY SHA W: 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