# Effects of vitamins, fatty acids, minerals, and other dietary supplements on schizophrenic symptoms in people with schizophrenia

Report from Kunnskapssenteret (Norwegian Knowledge Centre for the Health Services)
No 19–2011
Systematic Review

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Norwegian Knowledge Centre for the Health Services

**Background:** There is considerable scientific disagreement about the possible effects of dietary supplements on mental health and illness. Do dietary supplements (possibly in megadoses) have an effect on symptoms and consequences of schizophrenia? **Method:** We critically appraised randomized controlled trials about supplemental vitamins, fatty acids, and other dietary supplements given to people diagnosed with schizophrenia. The primary outcome was symptoms of schizophrenia. **Results:** We included 33 randomized controlled trials published between 1957 and 2008. They studied vitamins B, C, E, multivitamins, fatty acids, and other dietary supplements (Mianserin, Benzopyrone). We evaluated the evidence to be of low or very low quality. It is therefore difficult to draw strong conclusions about the effects of vitamins, minerals and other dietary supplements on symptoms of schizophrenia. The evidence shows the following: • Vitamin C and the fatty acid EPA may have a beneficial effect on schizophrenic symptoms (low quality evidence) • Vitamin B6 and the fatty acid DHA may have no effect on schizophrenic symptoms (low quality evidence)

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• We are uncertain of the effect of the fatty acid GLA and of vitamin E on schizophrenic symptoms (very low quality evidence). • No studies about minerals fulfilled our inclusion criteria.

Patients in most studies had few symptoms as a result of using antipsychotic medications. It was, thus, not much room for improvement, and this could have caused an underestimation of the effects of dietary supplements. The risk of adverse effects from the supplements is uncertain. Some adverse effects have been reported, but we could not tell whether the adverse effects were caused by the supplements. • No evidence of effect does not imply evidence of no effect. The included studies did not provide the highly individualized and long-term treatment regimens typically provided by orthomolecular medicine.

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|---|---|
| Title | Effects of vitamins, fatty acids, minerals, and other dietary supplements on schizophrenic symptoms in people with schizophrenia |
| Norwegian title | Effekter av vitaminer, fettsyrer, mineraler og andre kosttilskudd på schizofrenisymptomer hos mennesker med schizofreni |
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Norwegian Knowledge Centre for the Health Services
Oslo, November 2011

# Key messages

There is considerable scientific disagreement about the possible effects of dietary supplements on mental health and illness. Do dietary supplements (possibly in megadoses) have an effect on symptoms and consequences of schizophrenia?

We critically appraised randomized controlled trials about supplemental vitamins, fatty acids and other dietary supplements given to people diagnosed with schizophrenia. The primary outcome was symptoms of schizophrenia.

We evaluated the evidence to be of low or very low quality. It is therefore difficult to draw strong conclusions about the effects of vitamins, minerals and other dietary supplements on symptoms of schizophrenia. The evidence shows the following:

- Vitamin C and the fatty acid EPA may have a beneficial effect on schizophrenic symptoms (low quality evidence)
- Vitamin B6 and the fatty acid DHA may have no effect on schizophrenic symptoms (low quality evidence)
- We are uncertain of the effect of the fatty acid GLA and of vitamin E on schizophrenic symptoms (very low quality evidence)
- No studies about minerals fulfilled our inclusion criteria

Patients in most studies had few symptoms as a result of using antipsychotic medications. It was, thus, not much room for improvement, and this could have caused an underestimation of the effects of dietary supplements. The risk of adverse effects from the supplements is uncertain. Some adverse effects have been reported, but we could not tell whether the adverse effects were caused by the supplements.

No evidence of effect does not imply evidence of no effect. The included studies did not provide the highly individualized and long-term treatment regimens typically provided by orthomolecular medicine.

Title:
Effects of vitamins,fatty acids, minerals, and other supplements on schizophrenic symptoms in people with schizophrenia

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Type of publication:

## Systematic review

A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.

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## Doesn't answer everything:

- Excludes studies that fall outside of the inclusion criteria
- No health economic evaluation
- No recommendations

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## Publisher:

Norwegian Knowledge Centre for the Health Services

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## Updated:

Last search for studies: September 2010.

# Executive summary

## Background

There is considerable scientific disagreement about the importance of dietary supplements in relation to mental health and illness. Do dietary supplements (possibly in megadoses) have an effect on symptoms and consequences of schizophrenia? The Norwegian Directorate of Health commissioned a summary of available research on the effects of dietary supplements for people diagnosed with mental illnesses.

## Objective

This report collects, critically appraises and summarizes the available knowledge from randomized controlled clinical trials on the effects of dietary supplements on schizophrenic symptoms in people diagnosed with schizophrenia or schizoaffective disorder. The review is part of a larger project about dietary supplements for mental health.

## Method

We systematically searched for randomized controlled trials in the Cochrane Library, Medline, Embase, and PsycINFO up to September 2010. In addition, we searched reference lists of included studies and reviews and hand searched all issues of the Journal of Orthomolecular Medicine (1967-2007). We also hand searched the book "Nutritional Influences on Mental Illness" by Melvyn R. Wehrbach. Inclusion criteria were studies with people who were diagnosed with schizophrenia or schizoaffective disorder and who received dietary supplements in the form of vitamins, minerals, fatty acids or other dietary supplements thought to relieve symptoms of schizophrenia. Outcomes were the Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Symptoms Scale (PANSS) plus other measures of severity of schizophrenia. Positive symptoms are those that most individuals do not normally experience but are present in people with schizophrenia (delusions, disordered thoughts, and speech, and hallucinations. Negative symptoms are deficits of normal emotional responses or of other thought processes. They commonly include flat or blunted affect and emotion; poverty of speech, inability to experience pleasure, lack

of desire to form relationships, and lack of motivation. We assessed risk of bias with the Cochrane Collaboration's risk of bias tool, and graded the documentation using GRADE (Grading of Recommendations Assessment, Development, and Evaluation). Results are represented as forest plots, and meta-analyses were performed when two or more studies assessed the same supplement and the same outcome.

## Results

We included 33 randomized controlled trials published between 1957 and 2008. They studied vitamins B, C, E, multivitamins, fatty acids, and other dietary supplements (Mianserin, Benzopyrone).

The main results are listed below: We evaluated the evidence to be of low or very low quality. It is therefore difficult to draw strong conclusions about the effects of vitamins, minerals and other dietary supplements on symptoms of schizophrenia. The evidence shows the following:

- Vitamin C and the fatty acid EPA may have a beneficial effect on schizophrenic symptoms (low quality evidence)
- Vitamin B6 and the fatty acid DHA may have no effect on schizophrenic symptoms (low quality evidence)
- We are uncertain of the effect of the fatty acid GLA and of vitamin E on schizophrenic symptoms (very low quality evidence)
- No studies about minerals fulfilled our inclusion criteria

The risk of adverse effects from the supplements is uncertain. Some adverse effects have been reported, but we could not tell whether the adverse effects were caused by the supplements.

## Discussion

We summarized the evidence for possible effects of dietary supplements on symptoms of schizophrenia in people diagnosed with schizophrenia or schizoaffective disorder. We searched for randomized, placebo-controlled trials that had adhered to the instructions described by the adherents of orthomolecular psychiatry. The included studies had a treatment duration ranging from five days to two years. Only three studies used individual doses of supplements, and only six studies delivered more than one supplement. In sum, most studies delivered only one supplement in equal doses to all participants regardless of their individual needs, and the duration of treatment might have been too short in many of the studies.

From the electronic searches we found only 20 of the 33 studies. The remaining studies were located in the book by Wehrbach (n=4), in the review by Kleijnen (n=4), from personal contact with authors (n=2) and from reference lists (n=3). This might indicate that much of the literature in this field is not published in journals that are indexed in the common electronic databases. The hand search of the Journal of Orthomolecular Medicine failed to find any additional studies. We may have missed some studies because they are hard to locate.

There are few studies evaluating the effects of each supplement, and the trials are typically very small. Many of the trials are old. Patients in most studies had few symptoms as a result of using antipsychotic medications. It was, thus, not much room for improvement, and this could have resulted in an underestimation of the effects of supplements.

We do not have sufficient information to assess the risk for adverse effects.

## Conclusion

The documentation on dietary supplements for schizophrenia is of low to very low quality. There are randomized controlled trials on a number of supplements, but the trials are few and small, and most have a number of methodological shortcomings. However, the lack of evidence for an effect must not be equated with evidence of no effect. There is a need for large, randomized, blinded, placebo-controlled trials that follow the CONSORT (CONsolidated Standards of Reporting Trials) criteria for reporting of trials. The intervention delivery should follow the principles of orthomolecular medicine which suggest that the treatment duration should be individually adjusted and the supplements should be delivered in individual combinations and doses.

# **Hovedfunn** (norsk)

Det er stor vitenskapelig uenighet om betydningen av kosttilskudd for psykisk helse og psykiske lidelser. Har kosttilskudd (kanskje i megadoser) effekt på symptomer og konsekvenser av schizofreni?

Vi vurderte kritisk randomiserte kontrollerte studier med tilskudd av vitaminer, fettsyrer og andre kosttilskudd gitt til pasienter diagnostisert med schizofreni. Primærutfallsmålet var symptomer på schizofreni.

Vi vurderte dokumentasjonen til å være av lav eller svært lav kvalitet. Det er derfor vanskelig å trekke sterke konklusjoner om effekter av vitaminer, fettsyrer, mineraler og andre kosttilskudd på symptomer på schizofreni. Dokumentasjonen viser følgende:

- Vitamin C og omega-3-fettsyren EPA har muligens en gunstig effekt på schizofrenisymptomer (lav kvalitet på dokumentasjonen)
- Vitamin B6 og omega-3-fettsyren DHA har muligens ingen effekt på schizofrenisymptomer (lav kvalitet på dokumentasjonen)
- Vi er usikre på effekten av omega-6-fettsyren GLA og vitamin E på schizofrenisymptomer (svært lav kvalitet på dokumentasjonenen)
- Ingen studier om mineraler oppfylte våre inklusjonskriterier

Pasientene i de fleste studiene hadde få symptomer på grunn av antipsykotiske medisiner. Det var derfor vanskelig å oppnå stor forbedring, og dette kan ha ført til underestimering av effektene. Manglende dokumentasjon på effekt er ikke det samme som dokumentasjon på manglende effekt.

Risikoen for uønskede effekter av tilskuddene er usikker. Noen uønskede effekter har blitt rapportert, men vi kunne ikke avgjøre hvorvidt disse var forårsaket av tilskuddene.
De inkluderte studiene tilbød ikke den sterkt invididualiserte langtidsbehandlingen som typisk blir gitt innenfor ortomolekylær medisin.

Tittel:
Effekter av vitaminer, fettsyrer, mineraler og andre kosttilskudd på schizofreni-symptomer hos mennesker med schizofreni

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**Publikasjonstype:**

## Systematisk oversikt

En systematisk oversikt er resultatet av å
- innhente
- kritisk vurdere og
- sammenfatte relevante forskningsresultater ved hjelp av forhåndsdefinerte og eksplisitte metoder.

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## Svarer ikke på alt:

- Ingen studier utenfor de eksplisitte inklusjonskriteriene

- Ingen helseøkonomisk evaluering

-Ingen anbefalinger

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## Hvem står bak denne rapporten?

Kunnskapssenteret har skrevet rapporten på oppdrag fra Helsedirektoratet.

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## Når ble litteratursøket utført?

Søk etter studier ble avsluttet september 2010.

# **Sammendrag** (norsk)

***Effekter av vitaminer, fettsyrer, mineraler og andre kosttilskudd på schizofrenisymptomer hos mennesker med schizofreni***

## Bakgrunn

Det er stor vitenskapelig uenighet om betydningen av riktig ernæring når det gjelder psykisk helse og psykiske lidelser. Helsedirektoratet bestilte en oppsummering av tilgjengelig forskning på effekter av kosttilskudd for mennesker med psykiske lidelser. Denne rapporten tar for seg effekter på schizofrenisymptomer hos personer med schizofreni.

## Problemstilling

Har tilskudd (kanskje i megadoser) en effekt på symptomer og konsekvenser av schizofreni? Vi har i denne rapporten samlet inn, kritisk vurdert og sammenstilt den tilgjengelige kunnskapen fra kliniske studier om effektene av tilskudd på schizofrenisymptomer hos personer med schizofreni eller schizoaffektiv lidelse. Oversikten er del av et større prosjekt om kosttilskudd ved psykiske lidelser.

## Metode

Vi søkte systematisk etter randomiserte kontrollerte studier i Cochrane Library, Medline, Embase og PsycINFO fram til september 2010. I tillegg lette vi gjennom referanselistene i inkluderte studier og oversikter og håndsøkte alle numrene av Journal of Orthomolecular Medicine (1967-2007). Vi lette også gjennom boken "Nutritional Influences on Mental Illness" av Melvyn R. Wehrbach. Inklusjonskriterier var personer som var diagnostisert med schizofreni eller schizoaffektiv lidelse og som mottok kosttilskudd i form av vitaminer, mineraler, fettsyrer eller andre tilskudd med mulig effekt på symptomer ved schizofreni. Utfallsmål var Brief Psychiatric Rating Scale (BPRS) og Positive and Negative Symptoms Scale (PANSS) pluss andre mål på alvorlighetsgrad av schizofreni. Positive symptomer er slike som de fleste individer normalt ikke opplever, men som er til stede hos mennesker med schizofreni, som vrangforestillinger, forstyrrelser av tanker og tale samt hallusina-

sjoner. Negative symptomer omfatter mangel på normale emosjonelle responser eller på andre tankeprosesser. De inkluderer vanligvis avflating og sløvhet i affekter og emosjoner i form av ordfattigdom, manglende evne til å oppleve glede, manglende ønske om å forme relasjoner og manglende motivasjon.
Vi brukte Cochrane Collaboration sitt verktøy for å vurdere risiko for systematiske feil og graderte dokumentasjonen ved hjelp av GRADE (Grading of Recommendations Assessment, Development, and Evaluation). Resultater ble presentert som forest plots, og meta-analyser ble brukt når to eller flere studier hadde undersøkt det samme tilskuddet og brukt det samme utfallsmålet.

## Resultat

Vi inkluderte 33 randomiserte kontrollerte studier publisert mellom 1957 og 2008. De studerte vitamin B, C, E, fettsyrer og andre tilskudd (mianserin, benzo-pyron). Hovedresultatene er listet opp nedenfor:

- Vitamin C og omega-3-fettsyren EPA har muligens en gunstig effekt på schizofrenisymptomer (lav kvalitet på dokumentasjonen)
- Vitamin B6 og omega-3-fettsyren DHA har muligens ingen effekt på schizofrenisymptomer (lav kvalitet på dokumentasjonen)
- Vi er usikre på effekten av omega-6-fettsyren GLA og vitamin E på schizofrenisymptomer (svært lav kvalitet på dokumentasjonenen)
- Ingen studier om mineraler oppfylte våre inklusjonskriterier

Risikoen for uønskede effekter av kosttilskuddene er usikker. Noen uønskede effekter har blitt rapportert, men vi kunne ikke avgjøre hvorvidt disse var forårsaket av tilskuddene.

## Diskusjon

Vi har oppsummert dokumentasjonen for mulige effekter av kosttilskudd på symptomer på schizofreni hos mennesker som er diagnostisert med schizofreni eller schizoaffektiv lidelse. Vi søkte etter randomiserte, placebo-kontrollerte studier som hadde fulgt instruksjonene beskrevet av tilhengerne av ortomolekylær psykiatri. De 33 inkluderte studiene i vår oversikt hadde en varighet på behandlingen fra fem dager til to år. Bare tre studier brukte individuelle doser av tilskudd, og bare syv studier gav mer enn ett tilskudd. Oppsummert så gav de fleste studiene bare ett kosttilskudd i den samme dosen til alle deltakerne uavhengig av deres individuelle behov, og varigheten av behandlingen kan ha vært for kort i mange av studiene.

Bare 20 av de 33 studiene ble identifisert gjennom de elektroniske søkene. Resten av studiene fant vi i boken av Wehrbach (n=4), i oversikten av Kleijnen (n=4), gjennom personlig kontakt med forfattere (n=2) og fra referanselister (n=3). Dette kan indi-

kere at mye av litteraturen på feltet ikke publiseres i tidsskrifter som er indeksert i de vanlige elektroniske litteraturdatabasene. Håndsøket i Journal of Orthomolecular Medicine resulterte ikke i flere studier. Vi kan ha gått glipp av noen studier fordi de er vanskelige å finne og få tak i.

Det er få studier på hvert kosttilskudd, og studiene er oftest veldig små. Mange av studiene er gamle. Pasientene i de fleste studiene hadde få symptomer på grunn av antipsykotiske medisiner. Det var derfor vanskelig å oppnå stor forbedring, og dette kan ha ført til underestimering av effektene.

Vi har ikke tilstrekkelig informasjon til å vurdere risikoen for uønskede virkninger.

De inkluderte studiene tilbød ikke den sterkt invididualiserte langtidsbehandlingen som typisk blir gitt innenfor ortomolekylær medisin.

## Konklusjon

Dokumentasjonen på effekten av kosttilskudd ved schizofreni er av lav eller svært lav kvalitet. Det finnes randomiserte kontrollerte studier av noen tilskudd, men studiene er få og små, og de har mange metodologiske svakheter. Imidlertid må mangel på dokumentert effekt ikke forstås som dokumentasjon på at det ikke er effekt.

Det er behov for store, randomiserte, blindete, placebo-kontrollerte studier som følger CONSORT-kriteriene (CONsolidated Standards of Reporting Trials) for rapportering av studier. Studiene bør følge anbefalingene fra tilhengerne av ortomolekylær medisin om at kosttilskuddene bør gis i individuelle sammensetninger og doser. Behandlingstiden bør også være individuelt tilpasset den enkelte.

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# Preface

The Standing Committee on Health and Social Affairs in the Norwegian Parliament has produced a recommendation about drug policies labeled ”Rett kurs mot riktigere legemiddelbruk” [More correct use of medicine] (Innst.S.nr.197 2004-2005) which resulted in Resolution no. 373, 30. May 2005: ”Stortinget ber Regjeringen om å medvirke til at det igangsettes forskning samt at internasjonal forskning gjennomgås, knyttet til bruken av mineraler og vitaminer i behandlingen av mennesker med psykiske lidelser.” [The Parliament asks the Government to contribute to the initiation of research, and also that international research is reviewed, regarding the use of minerals and vitamins in the treatment of people with mental illnesses]. The Ministry of Health and Care Services declared in a letter dated 22. September 2005: ”… Nasjonalt kunnskapssenter for helsetjenesten skal foreta en gjennomgang av internasjonal forskning på feltet.” [The Norwegian Knowledge Centre for the Health Services shall conduct a review of international research in the field].

The Norwegian Directorate of Health commissioned a summary of available research on the effects of dietary supplements for people diagnosed with mental illnesses.

The project team was composed of:

- Project coordinator: Geir Smedslund , Senior Researcher (Kunnskapssenteret), the Norwegian Knowledge Centre for the Health Services
- Rigmor C Berg, Researcher, the Norwegian Knowledge Centre for the Health Services

This report is meant to help decision makers in health care to arrive at well-informed decisions that can improve quality of care. When dealing with an individual patient, the evidence must be considered in the context of other relevant conditions, the patients’ needs and preferences and one’s own clinical experience.

| | | |
|---|---|---|
| Gro Jamtvedt | Brynjar Fure | Geir Smedslund |
| *Department director* | *Unit director* | *Project coordinator* |

# Objective

This report is part of a larger project about dietary supplements for mental illnesses. We have already published an overview of overviews (OoO) about the effectiveness of dietary supplements for schizophrenia (1). We have also published another OoO about the effectiveness of dietary supplements for anxiety, depression, bipolar disorder and ADHD (2).

This systematic review sums up the evidence for effects of supplements on schizophrenic symptoms and adverse effects in people diagnosed with schizophrenia.

# Background

The present report is part of a series about effects of dietary supplements on mental disorders. One of the previous reports had the same research question as the present report: what are the effects of dietary supplements on symptoms of schizophrenia? The difference is that whereas our previous report was a rapid overview of overviews, the present report is a systematic review of primary studies. We refer to our previous report regarding the background section about definition, prevalence and treatment of schizophrenia: (http://www.kunnskapssenteret.no/Publikasjoner/Effekten+av+vitaminer%2C+mineraler+og+andre+kosttilskudd+p%C3%A5+mental+helse+hos+mennesker+med+schizofreni.10207.cms

This report contains a number of technical terms, and we refer to the glossary in Appendix 1 for descriptions of some of these terms. Use of vitamins, minerals and other supplements are usually an add-on therapy to traditional treatments of mental disorders, but it is widespread within the alternative
treatment tradition (3).

## How the interventions might work

**Vitamin B:** Osmond and Smythies (4) claimed that schizophrenia is the result of stress-induced anxiety and a failure of metabolism which results in highly toxic mescaline-like compounds. Hoffer (5) has stated that epinephrine can be oxidized to adenochrome which can produce schizophrenic like symptoms. He believed that patients with schizophrenia lack the ability to eliminate adenochrome from their brain. Carl Pfeiffer (6) has suggested that patients with schizophrenia have an abnormal production of a group of chemicals called pyrroles. These have been found in the urine of 30% of patients with schizophrenia and are accompanied by a serious lack of vitamin B6 and zinc (6).

**Vitamin C:** Abnormal activities of important redox-regulatory enzymes and biomarkers of lipid peroxidation have repeatedly been detected in different tissues of schizophrenic patients (7). Vitamin C plays an important role in protecting against

free radical-induced damage to the brain, mainly by reducing and thus detoxifying oxidized vitamin E (8).

**Vitamin E** is the principal protector of polyunsaturated fatty acids against peroxidation. In addition, it has several other regulatory effects not directly related to antioxidation, which may be relevant for its effects on schizophrenia (9-11).

**Polyunsaturated fatty acids (PUFA):** One hypothesis suggests that the symptoms of schizophrenia may be the result of altered neuronal membrane structure and metabolism (7). Several studies have shown that people with schizophrenia generally have lower levels of the particular PUFA necessary for normal nerve cell function (12).

**Benzo-pyrones:** A virus infection has been suggested as a possible cause of schizophrenia (13). Benzo-pyrones, such as coumarin and biflavonoids, have the ability to increase the normal proteolysis by macrophages and hence remove high-protein edema anywhere in the body (14). There is also some evidence that these drugs assist in immune reactions and speed the resolution of many infections. Benzo-pyrones can also replace certain of the B group vitamins and potentiate the effect of vitamin C.

## Critique of the orthomolecular approach

In the early 1970s, the American Psychiatric Association commissioned a report that was to critically examine the claims that orthomolecular therapy could be effective in the treatment of schizophrenia. In July 1973, the American Psychiatric Association's Task Force Report (15) concluded:

"This review and critique has carefully examined the literature produced by megavitamin proponents and by those who have attempted to replicate their basic and clinical work. It concludes in this regard that the credibility of the megavitamin proponents is low. Their credibility is further diminished by a consistent refusal over the past decade to perform controlled experiments and to report their new results in a scientifically acceptable fashion. Under these circumstances this Task Force considers the massive publicity which they promulgate via radio, the lay press and popular books, using catch phrases which are really misnomers like "megavitamin therapy" and "orthomolecular treatment," to be deplorable."

There is still considerable scientific disagreement about the effects of nutrition in relation to mental health and illness. Do dietary supplements (possibly in megadoses) have an effect on symptoms and consequences of schizophrenia? This report collects, critically appraises and summarizes the available knowledge in the field. The review is part of a larger project about dietary supplements for mental health.

### Relation to traditional treatment

The treatment of mental illnesses generally involves pharmaceuticals and psychotherapy. Some professionals have claimed that malnutrition in vulnerable individuals to a large extent contributes to the maintenance of these illnesses, and that it is possible to achieve symptom reduction by supplying the correct amounts of vitamins and minerals (16). Researchers within orthomolecular medicine maintain that very large doses (megadoses) over long periods of time and individually adjusted may be necessary for obtaining the desired effects (17).

# Method

## Literature search

We systematically searched for literature in the following databases:

- Cochrane Library (CDSR, DARE, CENTRAL, Cochrane Methodology Register, Issue 8, 2010)
- Medline (1950 to September 2010)
- Embase (1980 to 2010, week 35)
- PsycINFO (1806 to August Week 5, 2010)

In addition, we searched reference lists of reviews obtained as part of our larger project. After consulting with a local expert in the field (Dr. Håvard Bentsen, personal communication), we also hand searched the book "Nutritional Influences on Mental Illness" by Melvyn R. Wehrbach (18). Because much of the literature on orthomolecular psychiatry is published in the Journal of Orthomolecular Medicine, we hand-searched every issue of this journal from 1967-2007 (the years available at www.orthomolecular.org). The research librarians Hege Sletsjøe and Malene W. Gundersen planned and executed all the searches. The complete search strategy is available in Appendix 2.

## Inclusion criteria

Study design (in order of priority):

1. Randomized controlled trials, including cross-over trials
2. Quasi-randomized controlled trials (e.g. alternation) including cross-over trials

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|---|---|
| **Population:** | People diagnosed as having schizophrenia (ICD-10 code: F20). We also included mixed populations of schizophrenia and schizoaffective disorder (F25) |
| **Intervention:** | Supplements (oral or injections) containing vitamins, minerals, fatty acids or other dietary supplements studied for a possible effect on schizophrenia |
| **Comparison:** | Standard antipsychotic medication and placebo, placebo only, or no intervention |
| **Outcome**: | Positive and negative mental symptoms typically measured with |

| | |
|---|---|
| | Positive and Negative Symptom Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), as well as other validated scales for assessing symptoms of schizophrenia, adverse effects |
| **Language**: | No language restriction |

## Exclusion criteria

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|---|---|
| **Study design:** | Controlled trials without any reported random or quasi-random allocation, studies without a control group |
| **Population**: | Other diagnoses than schizophrenia/schizoaffective disorder, studies with several diagnoses without separate results for schizophrenia. People without a diagnosis of schizophrenia |
| **Intervention:** | Elimination of dietary factors, supplements with herbs |
| **Outcome**: | Cognitive function |

## Article selection

Two authors (Smedslund and Berg) independently read all titles/and or abstracts resulting from the electronic searches and the book by Wehrbach. Smedslund hand searched the Journal of Orthomolecular Medicine. Smedslund and Berg eliminated any obviously irrelevant studies resulting from the search process. We obtained full copies of the remaining potentially relevant studies. The same pair of authors, acting independently, classified these as clearly relevant, that is, meeting all the inclusion criteria and therefore to be included, or clearly irrelevant and therefore to be excluded. Pre-designed inclusion/exclusion forms were used for each screening level.

## Data extraction and analysis

The two authors independently extracted data from the published sources using a predesigned data recording form. Where differences in data extracted occurred, this was resolved through discussion. To assess the quality of the evidence, we used the Cochrane Collaboration's tool for assessing risk of bias, as described in chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions, version 5.0.1 (19). We discussed and agreed about the adequacy of each risk of bias study domain by assigning a judgment of 'Yes' indicating low risk of bias, 'No' indicating high risk of bias, and 'Unclear' indicating unclear or unknown risk of bias. As a supplemental analysis, we compared the risk of bias assessments for studies published before the introduction of the CONSORT (CONsolidated Standards of Reporting Trials) guidelines for reporting of trials (20) with the studies published after these guidelines were published. Further, we applied the instrument: Grading of Recommendations

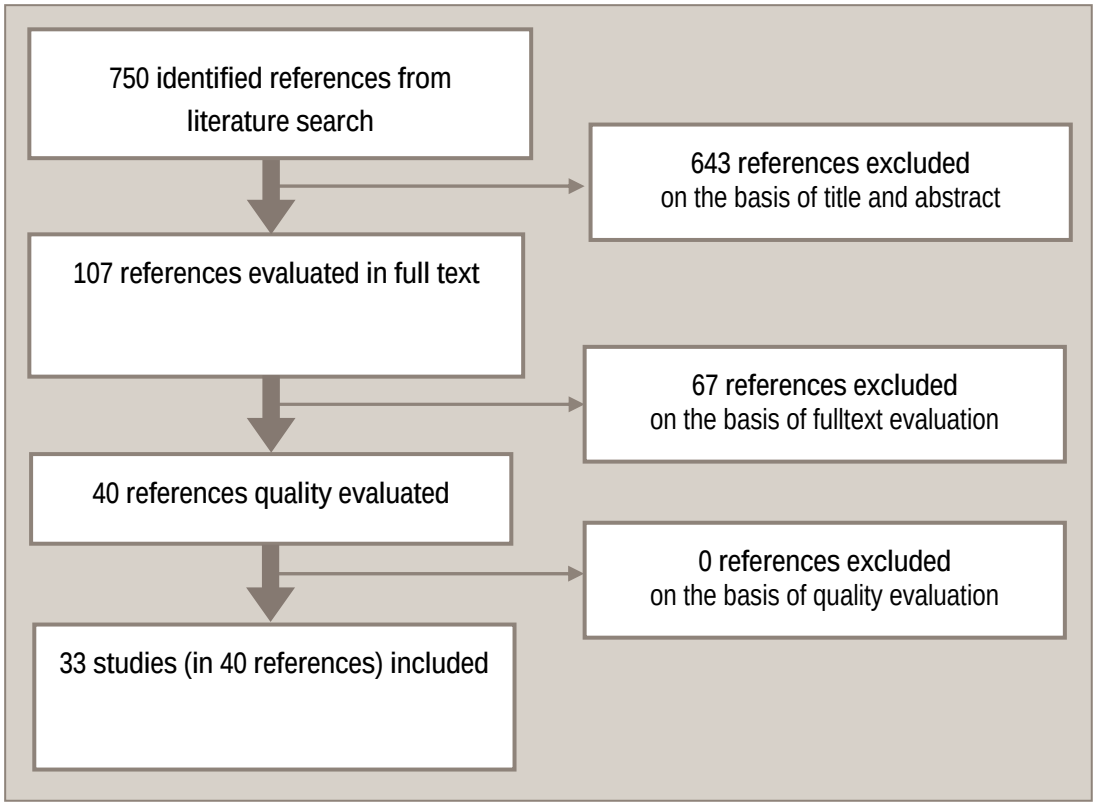
Assessment, Development and Evaluation (GRADE) (21) to assess the extent to which we should be confident that estimates of effect were correct. Eight comparisons were selected for grading according to the following criteria:

- Full scales were preferred before subscales and change scores (e.g. PANSS total was preferred before PANSS positive subscale).
- Simple comparisons were preferred before comparisons involving several interventions (e.g. nicotinamide vs. placebo was preferred before nicotinamide + pyridoxine vs. nicotinamide).
- Comparisons between supplement and placebo were preferred before comparisons between different supplements (we had one exception. There is an interest among experts in the relative effects of EPA and DHA, so we graded this comparison).
- Validated scales were preferred as outcomes before unvalidated scales.

We also decided, *a priori*, to perform meta-analyses to estimate effects across studies. We decided to use inverse-variance random effects meta-analyses because it was assumed that the studies would estimate different, but related, intervention effects. Further, we used RevMan 5, the latest version of the Cochrane Collaboration's meta-analysis software (22). For continuous scales, we calculated mean differences, and for dichotomous data we calculated risk ratios. We analyzed results from parallel-group trials and cross-over trials together. However, for some cross-over trials we used only the first phase of the trial (until the cross-over), because the means and standard deviations (or standard errors) of the participant-specific differences between experimental intervention and control intervention were missing. We also had some concern about possible carry-over effects. By using only data from the first phase, the data were as taken from a parallel-group design.

# Results

Figure 1. Flow chart of the literature review process




Studies formally considered but excluded are listed in Appendix 3, and reasons for exclusion are provided.

## Description of included studies

We included 33 studies reported in 40 journal articles (5;8;10;11;14;23-57). One article (48) reported results from two studies. We categorized the studies according to the supplements given (Tables 1-6). There were 14 studies in which different types of vitamin B were given. One study provided vitamin C. Five studies provided vitamin E. Two studies provided a combination of different vitamins. Ten studies provided different types of polyunsaturated fatty acids. Finally one study provided other sup-

plements. The supplements were mostly given as capsules to be swallowed, but in one study (37) the vitamins were injected.

Seven studies were from the USA, and six were from Israel (from the same group of researchers). There were five studies from Canada, and four from the UK. Other countries were India (n=3), Australia (n=2), South-Africa (n=2), Ireland (n=1), Iran (n=1), Hong Kong (n=1), and Italy (n=1). The studies were published between 1957 and 2008.

In thirty-two of the 33 studies, patients continued with their usual antipsychotic medication during the study, so the results show the effects of adding a supplement to the usual medication. The exception was the study by Peet (48) in India reporting that "EPA was used as a sole treatment, though the use of antipsychotic drugs was still permitted if this was clinically imperative".

Sample sizes ranged between 12 and 265 patients and follow-up times ranged between 5 days and 2 years.

Table 1. Included studies with vitamin B (n=14)

| Study/ Country | Patients | Intervention(s) | Comparison(s) | Outcomes |
|---|---|---|---|---|
| Ananth 1972 /Canada (25) | 30 newly admitted patients. Mean age: 27 years. 60 % males. | Individually tailored vitamin B3 (1) nicotinic acid 500 mg/2-4 times a day (n=9), (2) nicotinamide 500 mg 2-4 times a day (n=10). Duration: 2 years | Placebo (n=11) | BPRS (see appendix 1 for abbreviations) |
| Ananth 1973 /Canada (26;50) | 30 patients with chronic schizophrenia. Mean age: 42 years. 50 % males. | (1) Vitamin B3 (Nicotinic acid) 3000 mg/day + vitamin B6 (pyridoxine) 75 mg/day (n=10), (2) Nicotinic acid + placebo (n=10), (3) Pyridoxine + placebo (n=10). Duration: 48 weeks | No group without active treatment | NOSIE, BPRS, improvement |
| Deutsch 1977 /Canada (27) | 30 patients with chronic schizophrenia. Mean age: 48 years. 50% males. | (1) Nicotinic acid 3150 mg/day (n=10), (2) Nicotinamide 3150 mg/day (n=10). Duration: 48 weeks | Placebo (n=10) | PDI, DDR, TESS, BPRS, NOSIE, CGI, DSR |
| Godfrey 1990 /UK (33) | 17 patients. Mean age: 44 years. 53% males. | Vitamin B9 (methylfolate) 15 mg/day (n=9). Duration: 26 weeks | Placebo (n=8) | Clinical rating scale + clinical outcome scores |
| Hoffer 1957 /Canada (5;36) | 30 patients (mix of chronic and newly diagnosed). Mean age not reported. % males not reported. | (1) Nicotinic acid 3000 mg/day (n=10), (2) Nicotinamide 3000 mg/day (n=11). Duration: 4 weeks | Placebo (n=9) | Adjustment score |
| Joshi 1980 /India (37) | 60 newly diagnosed patients. | Injected vitamin B1 100 mg/day, vitamin B6 50 | Placebo injections (n=30) | Rockland and Pollin Beha- |

| | | | | |
|---|---|---|---|---|
| | Mean age: 25 years. 66 % males. | mg/day, vitamin B12 1000 mg/day (n=30). Duration: 4 weeks | | vior Scale. Need for modified ECT (MECT) |
| Lerner 2002 /Israel (39) | 15 patients with chronic disease (mix of schizophrenia and schizoaffective disorder). Mean age: 50 years. 27% males. | Crossover with vitamin B6 up to 400 mg/day for 8 weeks. Washout period of 1 week. Vitamins first: (n=8) Duration: 8 weeks | Placebo first: (n=7) | PANSS, CGI |
| Lerner 2004 /Israel (40) | 20 patients with chronic disease (mix of schizophrenia and schizoaffective disorder). n=10. Mean age: 42 years. 70% males. | Vitamin B6 600 mg/day for 5 days. (n=10). Duration: 5 days | Placebo (n=10) | BPRS, CGI |
| Lerner 2007 /Israel (41) | 50 patients with chronic disease (mix of schizophrenia and schizoaffective disorder). Mean age: 47 years. 56% males. | Crossover with vitamin B6 1200 mg/day. Washout period of 2 weeks. Vitamins first: (n=28). Duration: 12 weeks | Placebo first: (n=22) | CGI |
| Levine 2006 /Israel (42) | 55 patients with chronic schizophrenia. Mean age: 40 years. 95% males. | Crossover with vitamin B9 (folic acid) 2 mg/day, vitamin B12 (cobalamin) 400 µg/day, vitamin B6 25 mg/day. Probably no washout period. Vitamins first: (n=20). Duration: 12 weeks | Placebo first: (n=22) | PANSS |
| McGrath 1973 /Ireland (46) | 265 patients with a mix of newly diagnosed and patients with chronic disease. Mean age: 32 years. 72% males. | Vitamin B3 (nicotinamide) 3000 mg/day (n=132) Duration: 52 weeks | Placebo (n=133) | Judgement of recovery and improvement |
| Miodownik 2006 /Israel (47) | 60 patients with chronic disease (mix of schizophrenia and schizoaffective disorder). Mean age: 42 years. 58% males. | (1) Vitamin B6 1200 mg/day (n=23), (2) Mianserin 15 mg/day (n=20). Duration: 5 days | Placebo (n=17) | BPRS, CGI |
| Ramsey 1970 /Canada (51) | 30 acute or sub-acute patients. Mean age: 29 years. 50 % males. | (1) Nicotinic acid up to 3000 mg/day (n=10). (2) Nicotinamide up to 3000 mg/day (n=10). Duration: 26 weeks | Placebo (n=10) | BPRS, Hoffer-Osmond Diagnostic Test, MMPI schizophrenia |

| | | | | |
|---|---|---|---|---|
| | | | | scale |
| Wittenborn 1973 /USA (55;56) | 86 patients. Mean age: 29 years. 100% males. | Vitamin B3 (niacin) 3000 mg/day for 2 years. Only data for 18 months (n = not reported) | Placebo group received niacin 6 mg/day (n=not reported) | WPRS, Rutgers Nurses Rating Scale, Today's Mood Inventory |

Table 2. Included study with vitamin C (L-ascorbic acid)

| Study/ Country | Patients | Intervention | Comparison | Outcomes |
|---|---|---|---|---|
| Dakhale 2005/India (8) | 40 newly diagnosed patients. Mean age: 39 years. % males not reported. | Vitamin C 500 mg/day + atypical antipsychotics (n=20). Duration: 8 weeks | Placebo (n=20) | BPRS |

Table 3. Included studies with vitamin E (alpha-tocopherol) (n=5)

| Study/ Country | Patients | Intervention | Comparison | Outcomes |
|---|---|---|---|---|
| Adler 1999 /USA (10) | 158 outpatient veterans. Mean age: 50 years. 97 % males. | Vitamin E 1600 IU/day (n=73). Duration: up to 2 years | Placebo (n=85) | BPRS, GAF |
| Dorfman-Etrog 1999 /Israel (11) | 39 patients with chronic schizophrenia and acute exacerbation. Mean age: 35 years. 49% males. | Vitamin E 600 IU/day (n=19). Duration: 2 weeks | Placebo (n=20) | BPRS |
| Lam 1994 /Hong Kong (38) | 16 patients with chronic schizophrenia. Mean age: 62 years. 42% males. | Crossover with vitamin E up to 1200 IU/day. Washout period of 2 weeks. Vitamin E first: (n=not reported). Duration: 12 weeks | Placebo first: n= not reported | BPRS |
| Lohr 1988 /USA (44) | 15 patients with chronic disease (mix of schizophrenia and schizoaffective disorder). Mean age: 44 years. 73% males. | Crossover with vitamin E up to 12 mg/day. Washout period not reported. Vitamin E first: n=not reported. Duration: 8 weeks | Placebo first: n not reported | BPRS |
| Lohr 1996 /USA (43) | 35 patients (mix of schizophrenia and mood disorder). Mean age: 49 years. 93 % males. | Vitamin E 1600 IU/day (n=14) Duration: 8 weeks | Placebo: n= 15 | BPRS |

Table 4. Included studies with multiple vitamins (n=2)

| Study/ Country | Patients | Intervention | Comparison | Outcomes |
|---|---|---|---|---|
| Altman | 132 patients. | Vitamin B1 (thiamine) 15 | Placebo | MIBS hostili- |

| | | | | |
|---|---|---|---|---|
| 1973/ USA (23;24) | Mean age: 72 years. 46% males. | mg, vitamin B2 (riboflavin) 10mg, vitamin B3 (niacinamide) 50mg, vitamin B6 (pyridoxine) 5mg +vitamin C 300mg, calcium pantothenate 10mg (n=75). Duration: 6 weeks | (n=76) | ty, excitement, anxiety/depression and total |
| Vaughan 1999 /Australia (54) | 22 patients with chronic schizophrenia. Mean age: 31 years. 64% males. | Individually tailored megavitamins. Daily doses: (vitamin A 6000 IU, vitamin B1 1345 mg, vitamin B3 3520 mg, vitamin B6 6223 mg, vitamin B12 25 mg, vitamin C 2852 mg, vitamin E 204 mg + dietary supplements (n=10). Duration: 20 weeks | Placebo group received 25 mg of vitamin C (n=8). | BSI, BDI |

Table 5. Included studies with polyunsaturated fatty acids (n=10)

| Study/ Country | Patients | Intervention(s) | Comparison | Outcomes |
|---|---|---|---|---|
| Emsley 2002 /South Africa (28;29;31) | 40 patients with chronic schizophrenia. Mean age: 45 years. % males not reported. | E-EPA 3000 mg/day. Duration: 12 weeks (n=20) | Placebo (n=20) | PANSS |
| Emsley 2006 /South Africa (30) | 84 patients with chronic disease (mix of schizophrenia and schizoaffective disorder). Mean age: 43 years. 66% males. | E-EPA 2000 mg/day (n=42). Duration: 12 weeks | Placebo (n=42) | ESRS, CGI, PANSS |
| Fenton 2001 /USA (32;34) | 30 patients with chronic disease (mix of schizophrenia and schizoaffective disorder). Mean age: 40 years. 61% males. | E-EPA 3000 mg/day (n=43) Duration: 16 weeks | Placebo: (n=44) | PANSS, CGI |
| Manteghiy 2008 /Iran (45) | 85 patients with chronic schizophrenia. Mean age: 38 years. 89% males. | Fish oil 6000 mg/day + EPA 1080 mg/day + DHA 360 mg/day (n=42). Duration: 6 weeks | Placebo (n=43) | PANSS |
| Peet 2001 /UK (48) | 31 patients. Mean age: 43 years. 67% males. | (1) EPA 2000 mg/day (n=15), (2) DHA 2000 mg/day (n=14). Duration: 12 weeks | Placebo (n=14) | PANSS |
| Peet 2001 /India (48) | 26 patients with chronic schizophrenia. Mean age: 35 | EPA 2000 mg/day (n=14) Duration: 12 weeks | No intervention control group (n=12) | PANSS |

| | | | | |
|---|---|---|---|---|
| | years. 60% males. | | | |
| Peet 2002 /UK (49) | 122 patients. Mean age: 37 years. 66% males. | (1) E-EPA 1000 mg/day (n=32), (2) E-EPA 2000 mg/day (n=32), (3) E-EPA 4000 mg/day (n=27). Duration: 12 weeks | Placebo (n=31) | PANSS MADRS |
| Rapisarda 2000 /Italy (52) | 6 patients. Mean age: 39 years. 67% males | Omega-3 4000 mg/day (n=3). Duration: 4 weeks | Placebo (n=3) | SANS |
| Vaddadi 1986 /UK (53) | 21 patients with chronic schizophrenia. Age range: 20-55 years. % males not reported but both genders were represented. | Individually tailored (1) DHLA up to 1000 mg/day + medications (n=not reported), (2) DHLA up to 1000 mg/day + placebo medications (n=not reported). Duration: 16 weeks | Placebo DHLA + placebo medications (n=not reported) | BPRS, PIP, Bannister-Fransella grid test for measurement of thought disorder |
| Wolkin 1986/USA (57) | 15 patients with chronic schizophrenia. Mean age: 55 years. 100% males. | GLA, omega-6 600 mg/day (n=8). Duration: 6 weeks | Placebo (n=8) | BPRS |

Table 6. Included study with other supplements

| Study/ Country | Patients | Intervention | Comparison | Outcomes |
|---|---|---|---|---|
| Casley-Smith 1986 / Australia (14) | 16 patients with chronic schizophrenia. Mean age: 36 years. 63% males. | Crossover with benzopyrone (Paroven/Venoruton [Zyma]) 3000 mg/day. Probably no washout period. Active first (n=3). Duration: 12 weeks | Placebo first (n=8) | BPRS |

The risk-of-bias assessments are reported in Appendix 4. In Table 7 we report the number of studies in which the risk of bias is judged as low. We report this for each item of the risk of bias tool, and we compare studies that were published before (n=17) and after (n=16) the introduction of CONSORT in 1996.

Table 7. Risk of bias in studies published before and after the CONSORT statement in 1996

| Risk of bias item | Number (percent) of studies with low risk of bias before CONSORT (n=17) | Number (percent) of studies with low risk of bias after CONSORT (n=16) |
|---|---|---|
| Adequate sequence generation? | 1 (6%) | 3 (19%) |
| Allocation concealment? | 2 (12%) | 7 (44%) |
| Blinding of patients and | 8 (47%) | 10 (63%) |

| | | |
|---|---|---|
| providers? | | |
| Incomplete outcome data addressed? | 4 (24%) | 12 (75%) |
| Free of selective reporting? | 8 (47%) | 16 (100%) |
| Free of other bias? | 6 (35%) | 5 (31%) |
| Blinding of assessor? | 4 (24%) | 7 (44%) |

According to Table 7, the risk of bias in trials has been reduced for all risk of bias domains except for "other bias" after the introduction of CONSORT.

## Effects of vitamin B

Below we have computed mean differences for continuous variables and risk ratios for categorical variables. We list results for different outcomes/scales.

### Vitamin B3: Nicotinic acid (niacin), nicotinamide, and vitamin B6: pyridoxine

Ananth and colleagues (26) studied whether effects of nicotinic acid (vitamin B3) could be improved by adding pyridoxine (vitamin B6) and whether effects of pyridoxine could be improved by adding nicotinic acid (Figures 2-4).

Figure 2. Nicotinic acid versus pyridoxine +nicotinic acid on improvement on BPRS

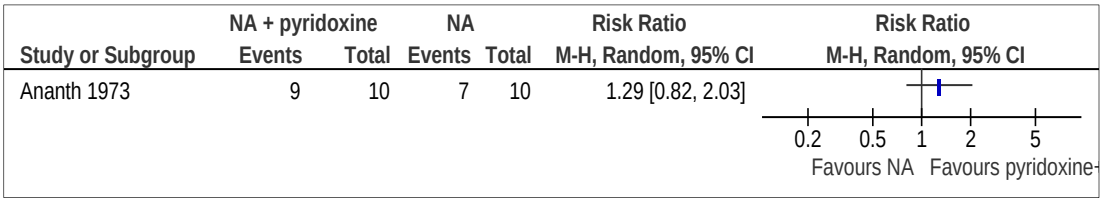



Figure 3. Nicotinic acid + pyridoxine versus pyridoxine on improvement on BPRS

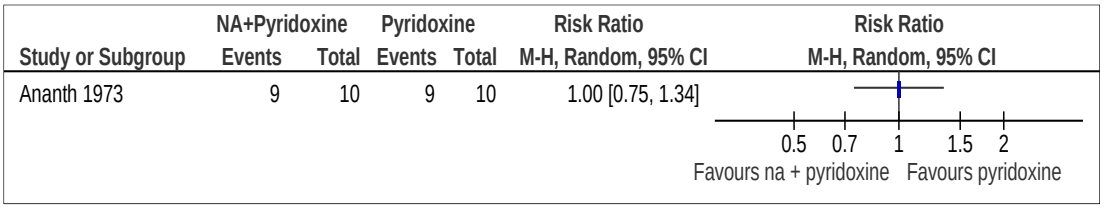
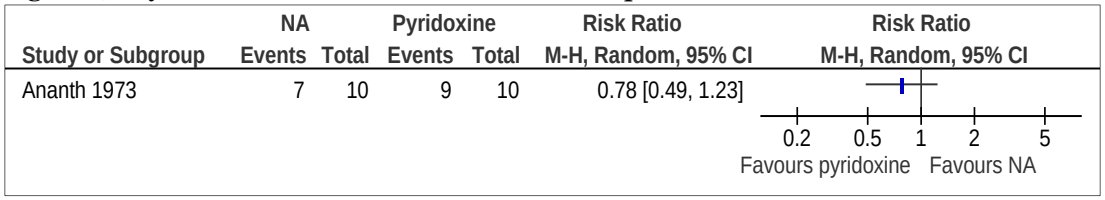



Figure 4. Pyridoxine versus nicotinic acid on improvement on BPRS




The researchers also performed a head-to-head comparison between the two vitamins. The study was underpowered and produced no significant effects. Hoffer and

colleagues (5) found a large (MD: 1.02), but marginally significant positive effect of nicotinic acid on what the researchers labeled “adjustment on the ward”. This referred to the patient’s adjustment in terms of physical health, work, social activities, family, and interpersonal relationships. According to Figure 5, 79 percent of the patients on nicotinic acid showed good adjustment, compared to only 33 percent on placebo. They found a similar effect size (MD: 0.49) for nicotinamide (Figure 6). In a head-to-head comparison, they found that the two substances had similar effects (Figure 7).

Figure 5. Placebo versus nicotinic acid on adjustment score

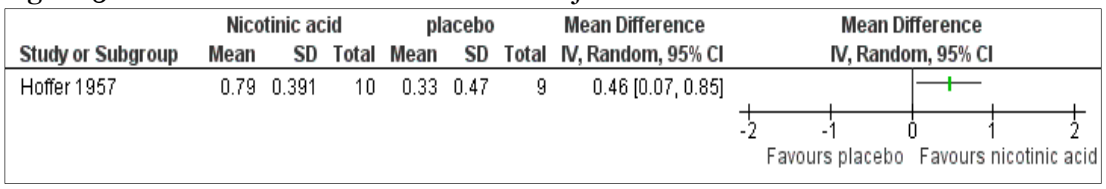



Figure 6. Placebo versus nicotinamide on adjustment score

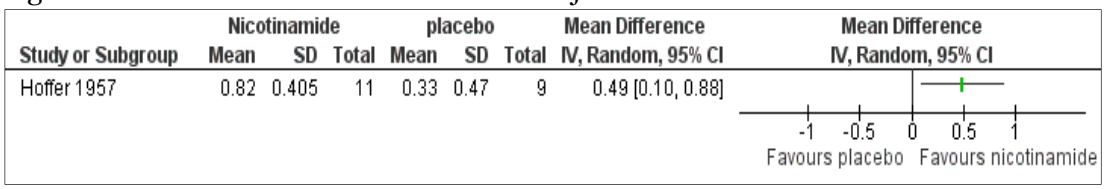
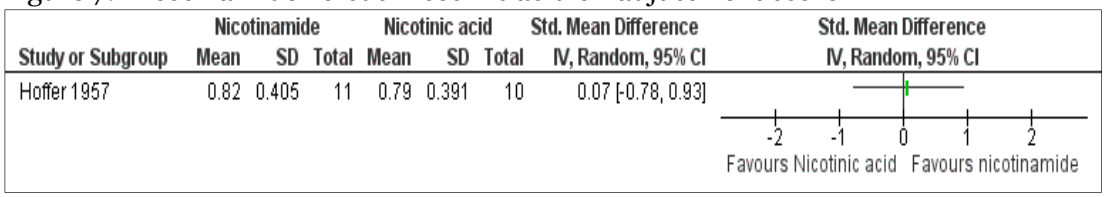
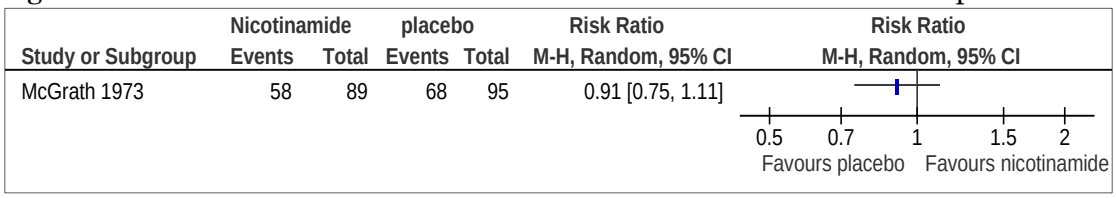



Figure 7. Nicotinamide versus nicotinic acid on adjustment score



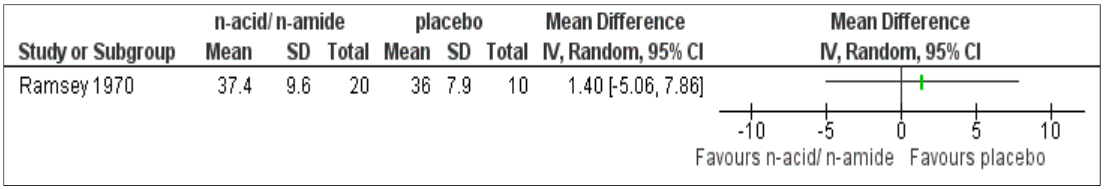

McGrath and colleagues (46) did not find that nicotinamide had any effect on the number of patients who were recovered or much improved (Figure 8).

Figure 8. Placebo versus nicotinamide on number recovered and much improved




Ramsey and colleagues (51) had three groups, of which one received nicotinic acid, another nicotinamide, and a third placebo for 26 weeks. When the two active groups were combined, they did not show significantly different results from the placebo group on the MMPI SCH subscale (Figure 9).

Figure 9. Nicotinic acid/nicotinamide (combined group) versus placebo on MMPI SCH scale




We did not grade any of the studies of vitamin B3.

**Vitamin B6**

All the five included studies on vitamin B6 were published by the same Israeli research team (39-42;47) (Figures 10-14).

There were no significant effects of vitamin B6 on PANSS, but a meta-analysis of three of their studies (Figures 10-13) shows a large and significant effect on CGI. The participants in both groups were rated as "moderately ill" before the intervention. After the intervention, participants in the placebo group were still moderately ill, but the participants in the B6 group were now rated as "borderline normal". Two of the three studies (40;47) lasted only 5 days.

Figure 10. Vitamin B6 versus placebo on PANSS positive

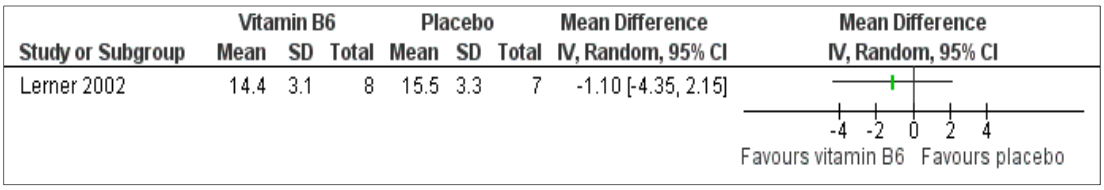



Figure 11. Vitamin B6 versus placebo on PANSS negative

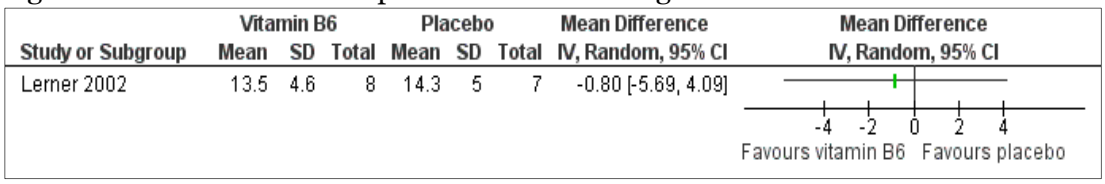



Figure 12. Vitamin B6 versus placebo on BPRS

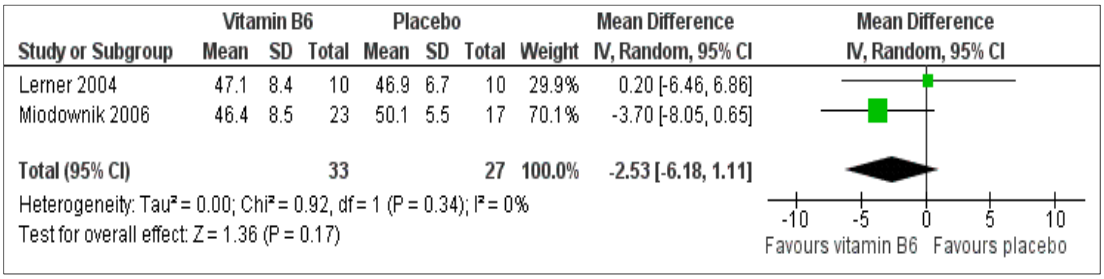
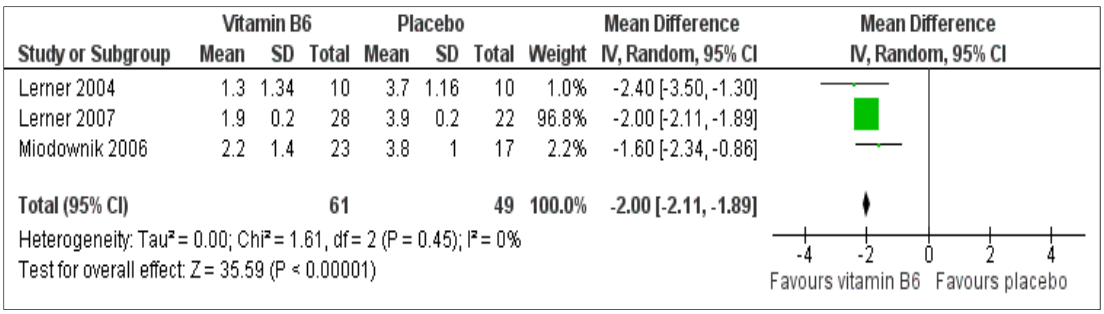
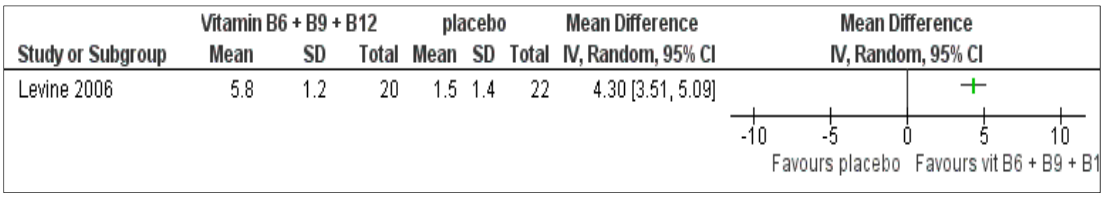


Figure 13. Vitamin B6 versus placebo on CGI




The fifth study by Levine 2006 (42) also included vitamin B9 and vitamin B12 and found a large significant positive effect on PANSS improvement with only 25mg/day of vitamin B6 (Figure 14).

Figure 14. Placebo versus vitamin B6 + B9 + B12 on PANSS improvement

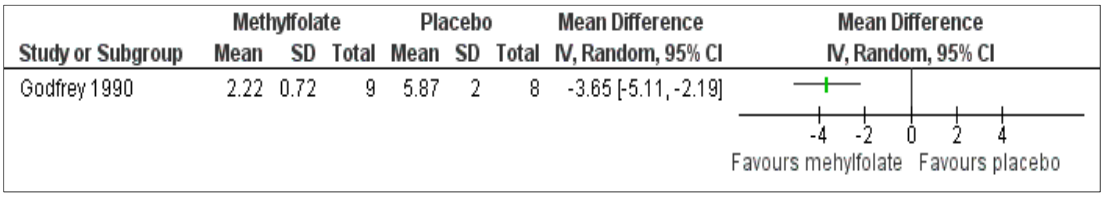



We graded the documentation regarding BPRS as low quality (Appendix 5, Table 5.1). Vitamin B6 possibly has no effect on BPRS, but further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. We did not grade the other outcomes from vitamin B6 studies.

### Methylfolate (vitamin B9)

One small study by Godfrey et al (33) found a significant positive effect on a clinical rating scale (Figure 15). The diagnoses were a mix of schizophrenia and major depression, and the supplements were provided for 26 weeks. We did not grade the documentation on vitamin B9.

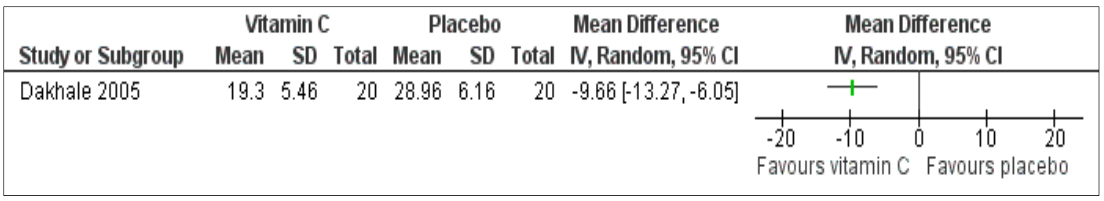
Figure 15. Methylfolate versus placebo on clinical rating scale




## Effects of vitamin C

One study by Dakhale et al (8) compared vitamin C with a placebo and found a significant improvement in BPRS score after 8 weeks (Figure 16). In fact, a score of 19.3 means almost symptom-free on the BPRS scale with a range of 18 to 126.

Figure 16. Vitamin C versus placebo on BPRS

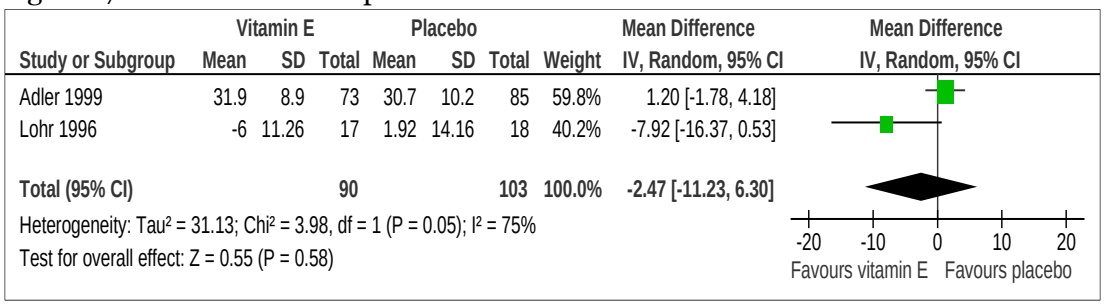



We graded the documentation on vitamin C for BPRS as low quality (Appendix 5, Table 5.2). Vitamin C may possibly have a positive effect on BPRS, but further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

## Effects of vitamin E

We included two studies about the effects of vitamin E compared to a placebo (10;43). They showed different results on the BPRS ($I^2$= 75%), but none of the individual effect sizes are statistically significant (Figure 17). The meta-analysis result is compatible both with a favorable effect and an adverse effect. Both studies used the same dose (1600 IU), but Adler and colleagues followed patients for much longer (up to 2 years) than Lohr and colleagues (8 weeks).

Figure 17. Vitamin E versus placebo on BPRS




Lohr and colleagues found a significant effect favoring vitamin E on positive symptoms using the BPRS (Figure 18). The result from this study on the BPRS negative symptoms subscale was not significant (Figure 19).

Figure 18. Vitamin E versus placebo on BPRS positive

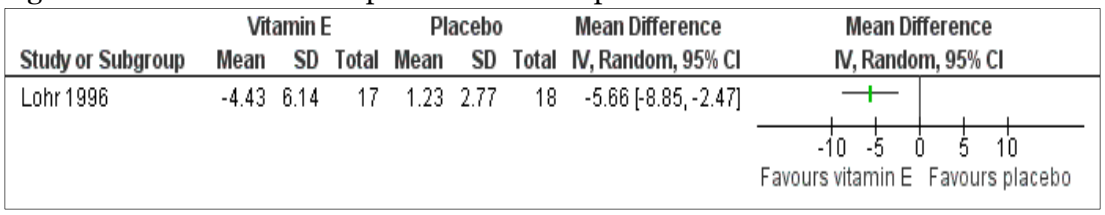
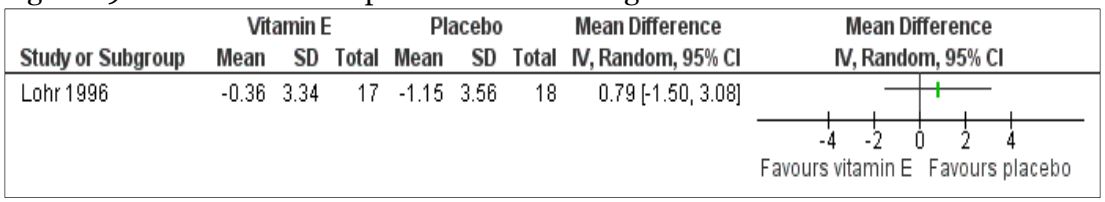
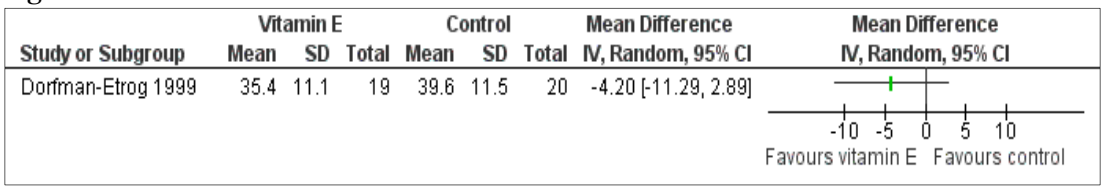


Figure 19. Vitamin E versus placebo on BPRS negative




One study (11) compared vitamin E to a no-treatment control. The result was non-significant (Figure 20). We graded the documentation for vitamin E on BPRS to very low quality (Appendix 5, Table 5.3): We are very uncertain about the estimate. No other comparison regarding vitamin E was graded.

Figure 20. Vitamin E versus control on BPRS




## Effects of multivitamins

We included two studies (23;54) of the effects of multivitamins with non-significant positive and negative results on the Missouri Inpatient Behavior Scale (MIBS), the Brief Symptom Inventory (BSI), and the Behavior Disturbance Inventory (BDI) (Figures 21-26).

Figure 21. Placebo versus multivitamins on MIBS anxiety/depression

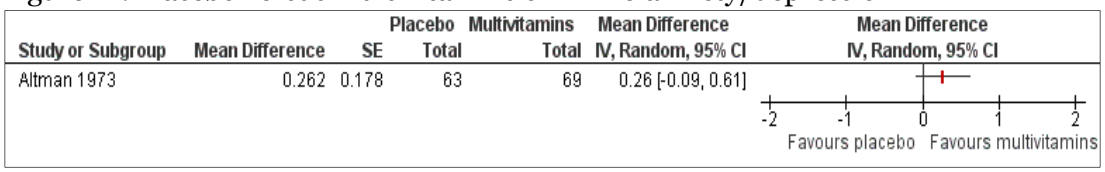



Figure 22. Placebo versus multivitamins versus placebo on MIBS excitement

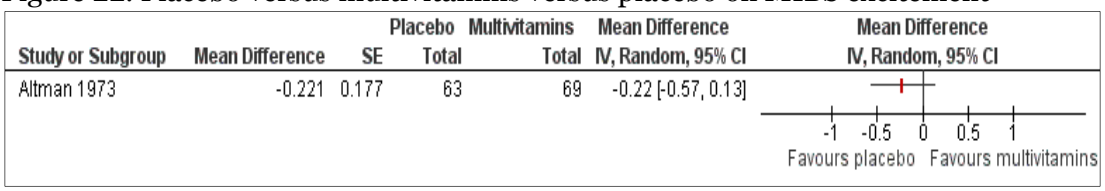



Figure 23. Placebo versus multivitamins on MIBS hostility

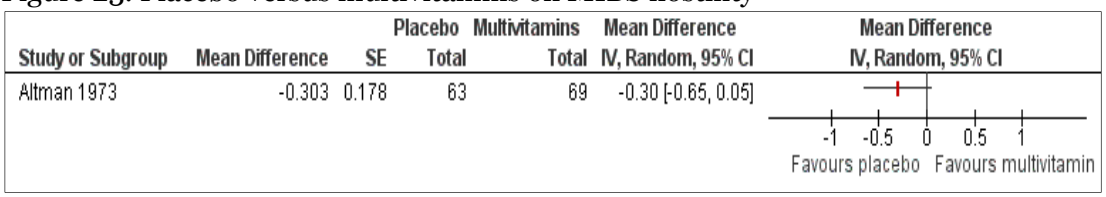


Figure 24. Placebo versus multivitamins on MIBS total

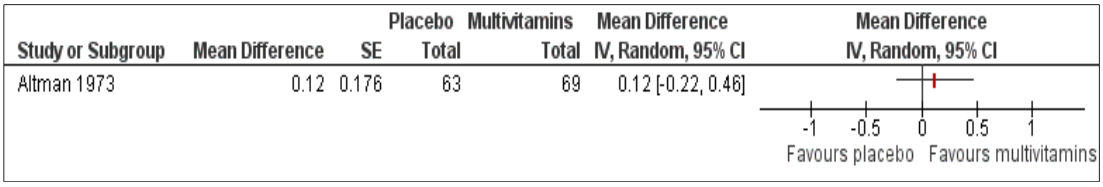



Figure 25. Multivitamins versus placebo on number improved on BSI

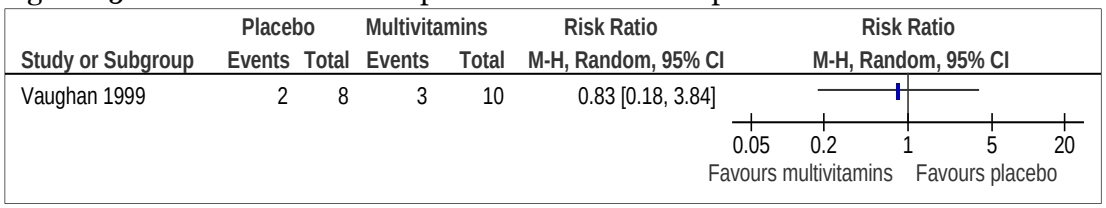
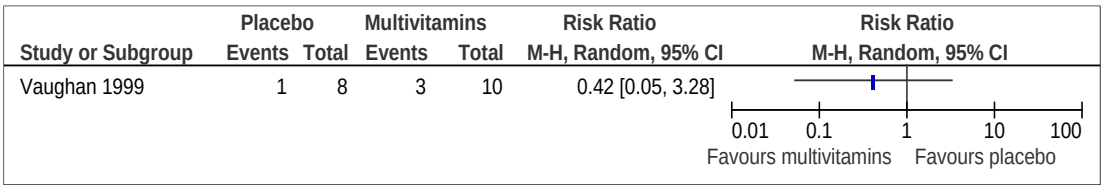



Figure 26. Multivitamins versus placebo on number improved on BDI



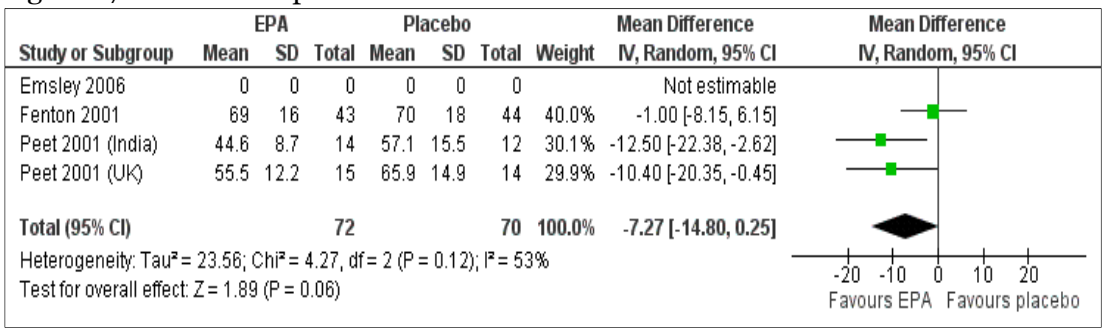

The documentation on multivitamins was not graded.

## Effects of polyunsaturated fatty acids

### EPA (Eicosapentaenoic acid)

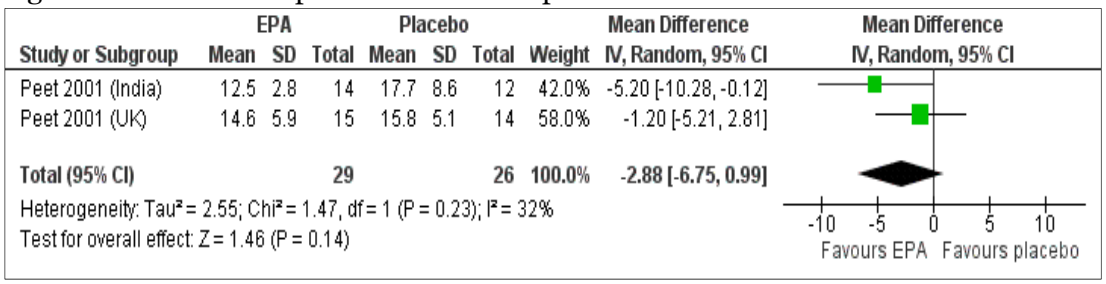
A meta-analysis of three studies (reported in two articles) (32;48) found an almost significant effect in favor of EPA on PANSS (Figure 27). The results were heterogeneous ($I^2$ = 53%). The studies had similar durations (12-16 weeks). The doses ranged between 2 and 3 grams per day with the study with the highest dose having the smallest effect, and the studies were performed in three different countries (USA, UK, and India).

Figure 27. EPA versus placebo on PANSS



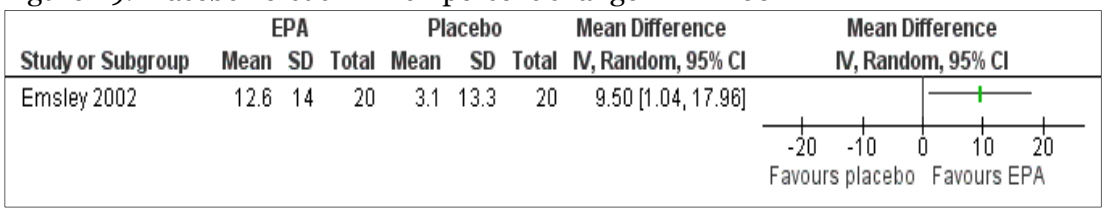

Two of the three studies also looked at the PANSS positive scale and also found a non-significant result (Figure 28).

Figure 28. EPA versus placebo on PANSS positive



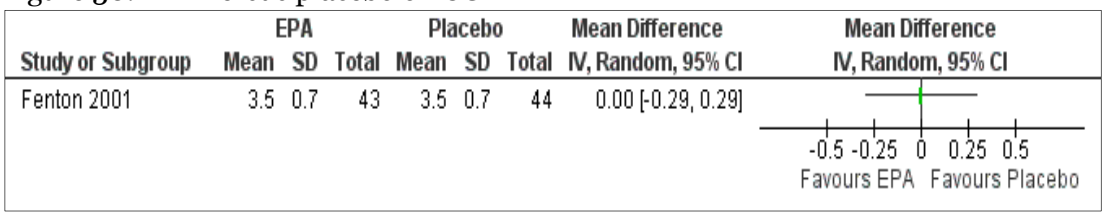

A fourth study by Emsley et al from 2002 (29) found a significant effect in favor of the EPA group on the PANSS change score with similar doses/duration in South Africa (Figure 29).

Figure 29. Placebo versus EPA on percent change in PANSS




Finally, a study by Fenton and colleagues (32) found equal results for EPA and placebo on CGI (Figure 30).

Figure 30. EPA versus placebo on CGI




We graded the documentation regarding the effect of EPA on PANSS to low quality (Appendix 5, Table 5.4): there may be a possible effect of EPA on PANSS (technically the effect is not statistically significant, but almost all of the diamond is on the side favoring EPA, and with a larger sample size the same effect size would have been significant) but further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**EPA + DHA + fish oil**

The documentation comes from one Iranian study (45) that found almost identical results for the active treatment and placebo on PANSS and general psychopathology after a 6-week treatment period (Figures 31-33).

Figure 31. EPA + DHA + fish oil versus placebo on PANSS positive

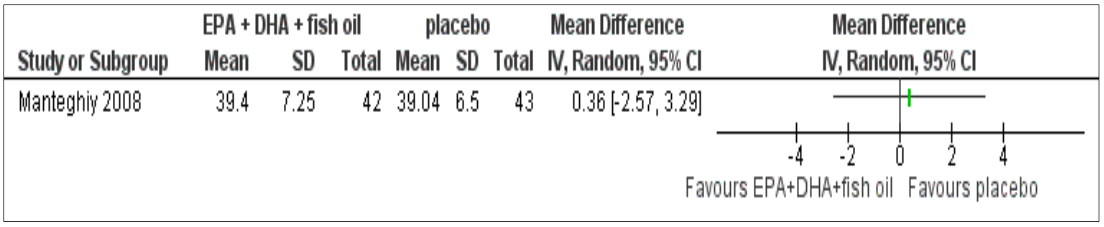



Figure 32. EPA + DHA + fish oil versus placebo on PANSS negative

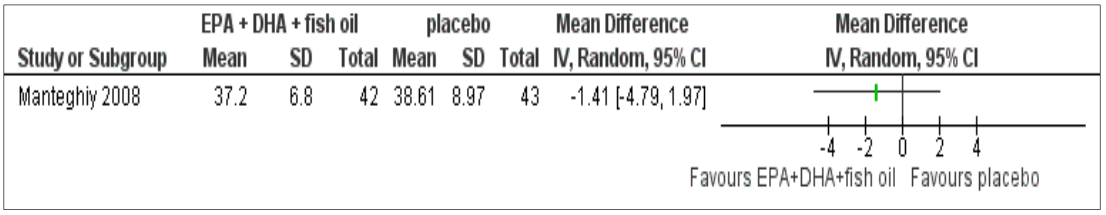
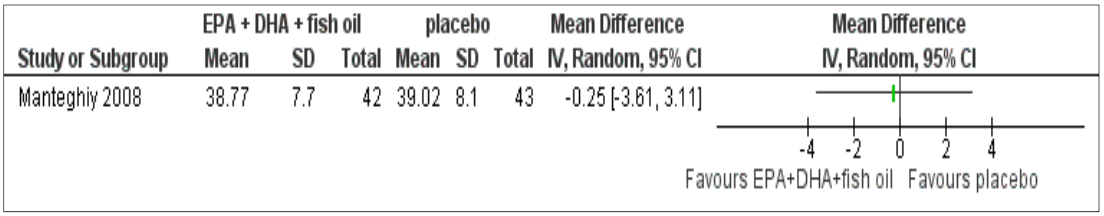



Figure 33. EPA + DHA + fish oil versus placebo on general psychopathology




We graded the documentation regarding EPA + DHA + fish oil on PANSS positive as low quality (Appendix 5, Table 5.5): EPA may possibly have no effect on PANSS positive, but further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. We graded the documentation regarding EPA + DHA + fish oil on PANSS negative as low quality (Appendix 7.5): EPA may possibly have no effect on PANSS negative, but further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

### DHA

The documentation is a study by Peet et al in the UK from 2001 (48). They found that a treatment of 2 grams of DHA per day for six weeks produced almost the same results as in the placebo group on PANSS and its positive subscale (Figures 34-35).

Figure 34. DHA versus placebo on PANSS

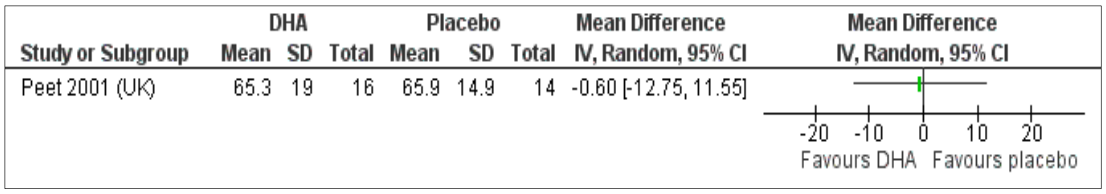
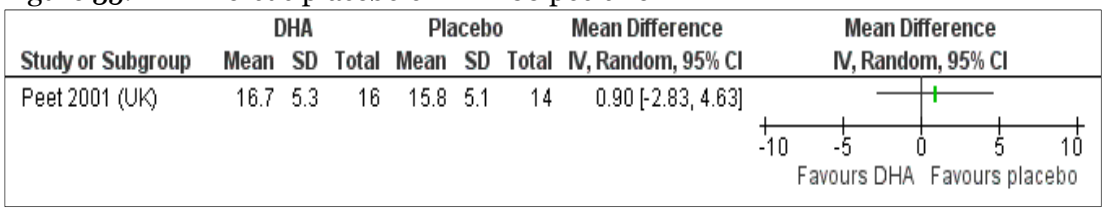



Figure 35. DHA versus placebo on PANSS positive




We graded the documentation regarding effects of DHA on PANSS to low quality (Appendix 5, Table 5.6): DHA has possibly no effect on PANSS, but further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

### EPA versus DHA

The documentation is a study by Peet and colleagues (48) in which a head-to-head comparison of EPA and DHA favored EPA, but not significantly so (Figure 36). Peet 2001 also found similar results on the PANSS positive subscale (Figure 37).

Figure 36. EPA versus DHA on PANSS

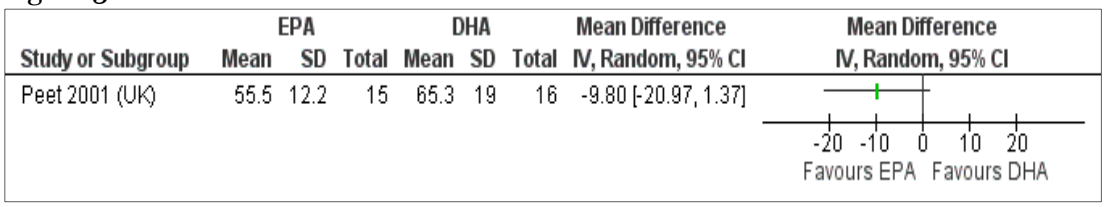
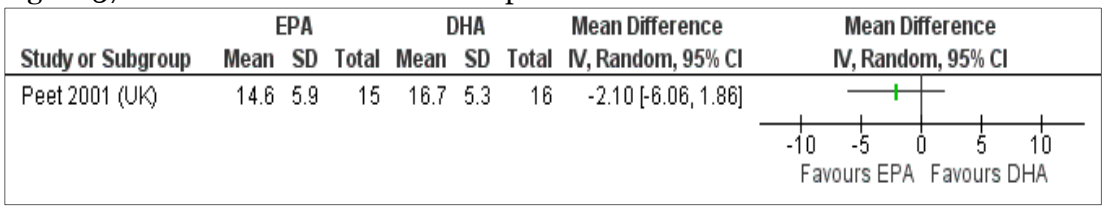



Figure 37. EPA versus DHA on PANSS positive scale

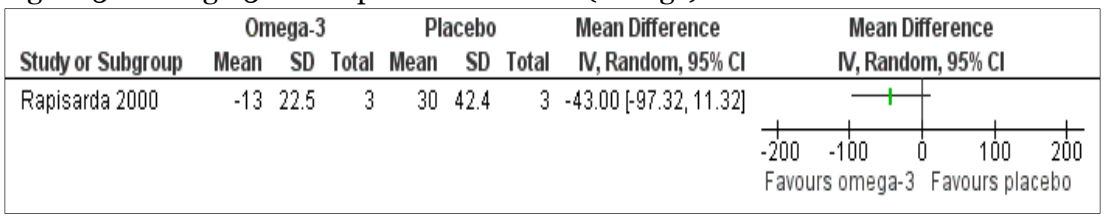


We graded the effects of EPA versus DHA on PANSS to low quality (Appendix 5, Table 5.7): EPA and DHA may possibly have similar effects on PANSS, but further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

### Omega-3

One study by Rapisarda et al (52) gave omega-3 (Figure 38). It was not reported what kind of omega-3 that was provided. The omega-3 group had a significant decrease in SANS scores after the intervention, while the placebo group had an increase. This was a very small study with only 3 schizophrenic patients in each study arm, and the difference in SANS change scores was not statistically significant. We did not grade this documentation.

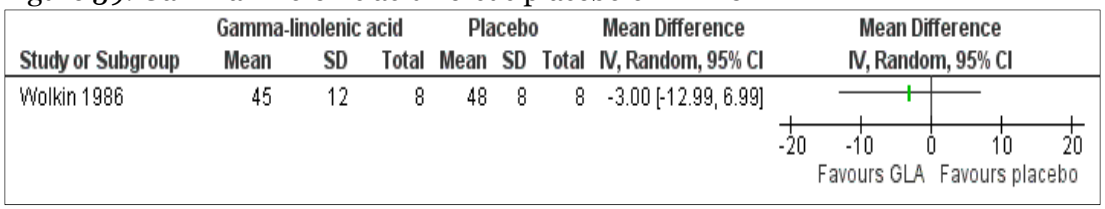
Figure 38. Omega-3 versus placebo on SANS (change)




### Gammalinolenic acid (GLA) versus placebo

One small study by Wolkin et al (57) did not find a statistically significant difference between GLA and placebo on BPRS scores (Figure 39).

Figure 39. Gamma-linolenic acid versus placebo on BPRS




We graded the documentation regarding effects of GLA on BPRS to very low quality (Appendix 5, Table 5.8): we are very uncertain about the estimate.

### DHLA

One study by Vaddadi et al (53) studied effects of DHLA, but they did not report their results in a form that could be used to compute effect sizes. Therefore, we report the authors' own statements (Table 8). We did not grade this documentation.

Table 8. Effects of DHLA in Vaddadi and colleagues' study

| Comparison and out- | Study conclusions |
|---|---|

| come | |
|---|---|
| DHLA plus medications versus placebo on BPRS | Total BPRS increased from 9.8 to 27.8 from pre-trial to 3rd month in the active group, while it decreased from 39.0 to 35.7 in the placebo group (no SDs reported). |
| DHLA plus medications versus placebo on PIP | "There were no significant occasion effects nor were there any treatment group by occasion effects." |
| DHLA + placebo medications versus placebo on BPRS | Total BPRS decreased from 31.8 to 21.2 from pre-trial to the 3rd month in the DHLA group, while it decreased from 39.0 to 35.7 in the placebo group (no SDs reported). |
| DHLA + placebo medications versus placebo on PIP | "There were no significant occasion effects nor were there any treatment group by occasion effects." |

## Effects of other dietary supplements

### Benzo-pyrone versus placebo

One study by Casley-Smith et al (14) studied effects of benzo-pyrone, but they did not report their results in a form that could be used to compute effect sizes. Therefore, we report the authors' own statements. Regarding benzo-pyrone versus placebo on BPRS improvement, the authors stated: "When on the active substance, they showed as compared with the placebo, a mean improvement of 27% (significant at the 1% level)." We did not grade this documentation.

## Adverse effects

Below we list all adverse effects that were reported in the studies. The adverse effects are, if possible, detailed under the appropriate arm of the study. The adverse effects per supplement are listed in Tables 9-18. These are estimated absolute probabilities of experiencing adverse effects while being in the study (This is also reported in Figure 43). For example, the first study in Table 13 by Adler et al shows that there was a 22% risk of having diarrhea while taking part in the study. We do not know whether the patients on vitamin E had a different risk than the patients on placebo. Figure 43 (fourth row from the bottom) shows e.g. that the combined risk from taking part in the study of developing either diarrhea, flu syndrome, headache, or psychosis was 13.4% with a 95% confidence interval from 8.8% to 19.9%.

We were not able to report the relative risks of adverse effects because the data were too sparse. In a typical study, about 1 out of 10 in the intervention group experienced an adverse effect compared to zero in the placebo group. And in many of the studies, no adverse effects were reported in either arm of the study.

**Adverse effects in studies with vitamin B**

According to Table 9 there are some reported adverse effects in patients who were randomised to nicotinic acid, nicotinamide, or pyridoxine. No adverse effects were reported in any of these studies for patients randomised to a placebo. This is, however, uncertain because of poor reporting in some of the studies.

Table 9. Adverse effects in studies with nicotinic acid (vitamin B3), pyridoxine (vitamin B6), and/or nicotinamide (vitamin B3)

| Study | Supplement | Reported adverse effects | Treatment group | Placebo group |
|---|---|---|---|---|
| Ananth 1973 | Nicotinic acid Pyridoxine | 26 adverse outcomes in 21 patients (21/30) | Nicotinic acid: abnormal liver function (2/10); leukopenia (1/10); weight loss (1/10) | There was no placebo group |
| | | | Pyridoxine: nausea & vomiting (1/10); dizziness (1/10); tachycardia (1/10); weight gain (1/10); flushing of skin (2/10); dermatitis (1/10) | |
| | | | Combined treatment: abnormal liver function (5/10); hypotension (1/10); leukopenia (1/10); weight loss (2/10); weight gain (1/10) | |
| Ananth 1972 | Nicotinic acid/ nicotinamide | Rash, toxicity, hypertension. 3/30 | Nicotinic acid: suicidal attempt (1/9); persistent rash and hypertension (1/9) | 0/11 |
| | | | Nicotinamide: toxicity (1/10) | |
| Deutsch 1977 | Nicotinic acid/ nicotinamide | Lupus erythamosus, vomiting, weight loss and swelling of lower extremities, coronary thrombosis, dizziness, anorexia, and weight loss. 4 persons in total | Nicotinic acid: vomiting, swelling (1/10); coronary thrombosis (1/10); dizziness, anorexia and weight loss (1/10) | 0/10 |
| | | | Nicotinamide: Lupus erythamosus (1/10) | |

| | | | | |
|---|---|---|---|---|
| | | with adverse effects. (4/30) | | |
| Ramsey 1970 | Nicotinic acid/ nicotinamide | 2/30 | Nicotinic acid: Flushing (1/10) | |
| | | | Nicotinamide: Suicidal tendencies (1/10) | 0/10 |
| Hoffer 1957 | Nicotinic acid/ Nicotinamide | | Nicotinic acid: Flushing of face, congestion in the ears, tension headache (rare=not stated number of persons). Suicide (1 person [1/10]), ankle edema (1person [1/10]). | Not reported |
| | | | Nicotinamide: Gastric disturbances on rare occasions. | |
| Wittenborn 1973 | Nicotinic acid | Pigmented hyperkeratosis in 20 persons (20/86). | Not reported | Not reported |
| McGrath 1973 | Nicotinamide | Not reported | Not reported | Not reported |

Table 10 shows that the presence or absence of adverse effects was reported in all our included studies of vitamin B6. No adverse effects were reported in any placebo patient. The only adverse effects in a group receiving vitamin B6 were acne and allergic reactions in 2 percent.

Table 10. Adverse effects in studies with vitamin B6

| Study | Reported adverse effects | Treatment group | Placebo group |
|---|---|---|---|
| Lerner 2002 | Reported that there were no adverse effects. (0/15) | 0/8 | 0/7 |
| Lerner 2004 | Reported that there were no adverse effects. 0/20 | 0/10 | 0/10 |
| Lerner 2007 | Acne (1/50). Allergic reaction (light itch [1/50]). | Acne (1/28); Allergic reaction (1/28) | 0/22 |
| Miodownik 2006 | Reported that there were no adverse effects (0/60) | 0/23 on vitamin B6; 0/20 on Mianserin | 0/17 |

Table 11 shows that the study by Godfrey et al did not report adverse effects. The study by Levine et al (see Table 13) also included vitamin B9 as a supplement and reported that 5 percent (one out of 20) of their patients developed serious medical illness. They did not, however, report whether the patient who became ill was in the active or placebo group.

Table 11. Adverse effects in studies with methylfolate (vitamin B9)

| Study | Reported adverse effects | Treatment group | Placebo group |
|---|---|---|---|
| Godfrey 1990 | Not reported | Not reported | Not reported |

Table 12 shows that Joshi and colleagues did not report any adverse effects.

Table 12. Adverse effects in studies with vitamin B1, B6, and B12

| Study | Reported adverse effects | Treatment group | Placebo group |
|---|---|---|---|
| Joshi 1980 | Not reported | Not reported | Not reported |

Table 13 shows that Levine and colleagues reported one adverse effect, but they did not state whether this was in the treatment or in the placebo group.

Table 13. Adverse effects in studies with vitamin B6, B9, and B12

| Study | Reported adverse effects | Treatment group | Placebo group |
|---|---|---|---|
| Levine 2006 | "Serious medical illness" (1/20) | Not reported | Not reported |

### Adverse effects in studies with vitamin C

Dakhale et al reported no serious side effects in their vitamin C study, but there might have been some non-serious side effects (Table 12).

Table 12. Adverse effects in studies with vitamin C

| Study | Reported adverse effects | Treatment group | Placebo group |
|---|---|---|---|
| Dakhale 2005 | Reported that there were no serious side effects. | 0/20 | 0/20 |

### Adverse effects in studies with vitamin E

There was no information about differences between active and placebo conditions on adverse effects in vitamin E studies (Table 13).

Table 13. Adverse effects in studies with vitamin E

| Study | Reported adverse effects | Treatment group | Placebo group |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Adler 1999 | diarrhea: 22% (35/158), flu syndrome: 14% (22/158), headache: 11% (18/158), psychosis: 9% (14/158). Stated that there were no differences between groups in percent of people reporting adverse events. | Not reported | Not reported |
| Lam 1994 | Death from unrelated medical illness (1/16), deteriorated mental state (1/16), bacillary dysentery (1/16). | Not reported | Not reported |
| Lohr 1988 | Reported that there were no side effects. (0/15) | Not reported | Not reported |
| Lohr 1996 | Not reported | Not reported | Not reported |
| Dorfman-Etrog 1999 | Not reported | Not reported | Not reported |

### Adverse effects in studies with multivitamins

There were almost no reported adverse effects in studies with multivitamins (Table 14).

Table 14. Adverse effects in studies with multivitamins

| Study | Reported adverse effects | Treatment group | Placebo group |
|---|---|---|---|
| Altman 1973 | Tremors, restless, faint, dizzy. Stated that there were no differences between groups in percent of people reporting adverse events. | Not reported | Not reported |
| Vaughan 1999 | Few: One woman in the vitamin group with a previous diagnosis of hiatus hernia experienced several episodes of vomiting over the course of three days (1/18). | 1/10 | 0/8 |

### Adverse effects in studies with polyunsaturated fatty acids

Table 15 shows that the reporting of adverse effects of fatty acids is generally poor.

Table 15. Adverse effects in studies with EPA/DHA/omega-3/fish oils

| Study | Supplement | Reported adverse effects | Treatment group | Placebo group |
|---|---|---|---|---|
| Emsley 2002 | EPA | No serious adverse events were recorded | 0/20 | 0/20 |
| Emsley 2006 | EPA | In the placebo group: congestive cardiac failure (1/84), nose bleed (1/84). | 0/42 | 2/42 |
| Fenton 2001 | EPA | Upper respiratory infection (8/43), diarrhea (8/43. | Range: 8-16/43 | Not reported |

| | | | | |
|---|---|---|---|---|
| Peet 2001 (India) | EPA | Reported that no side effects occurred. | 0/14 | 0/12 |
| Peet 2002 | EPA | | 16/32 in 1g group; 11/32 in 2g group; 16/27 in 4g group | 16/31 |
| Manteghiy 2008 | EPA + DHA + fish oils | Extra pyramidal (n=6/85). Gastrointes-tinal (n=3/85). | Not reported | Not reported |
| Peet 2001 (UK) | DHA | Not reported | Not reported | Not reported |
| Peet 2001 (UK) | EPA/DHA | Not reported | Not reported | Not reported |
| Rapisarda 2000 | Omega-3 | Not reported | Not reported | Not reported |
| Wolkin 1986 | Gamma-linolenic acid | Not reported | Not reported | Not reported |
| Vaddadi 1988 | DHLA | Not reported | Not reported | Not reported |

**Adverse effects in studies with other dietary supplements**

Joshi and colleagues (37) and Altman and colleagues (23;24) included thiamine in their studies but did not report adverse effects. Vaughan and McConaghy (54) also included thiamine and reported that one woman on multivitamins (including thia-mine) “vomited for three days”.

In the cross-over trial by Casley-Smith et al, there were two patients with adverse effects (Table 18). One patient complained of nausea while on placebo. One patient developed hepatitis, but it is not reported whether this happened on placebo or on benzo-pyrone.

Table 18. Adverse effects in study with benzo-pyrone

| Study | Reported adverse effects | Treatment group | Placebo group |
|---|---|---|---|
| Casley-Smith 1986 | Infectious hepatitis (1/16) | Not reported | Nausea (1/16) |

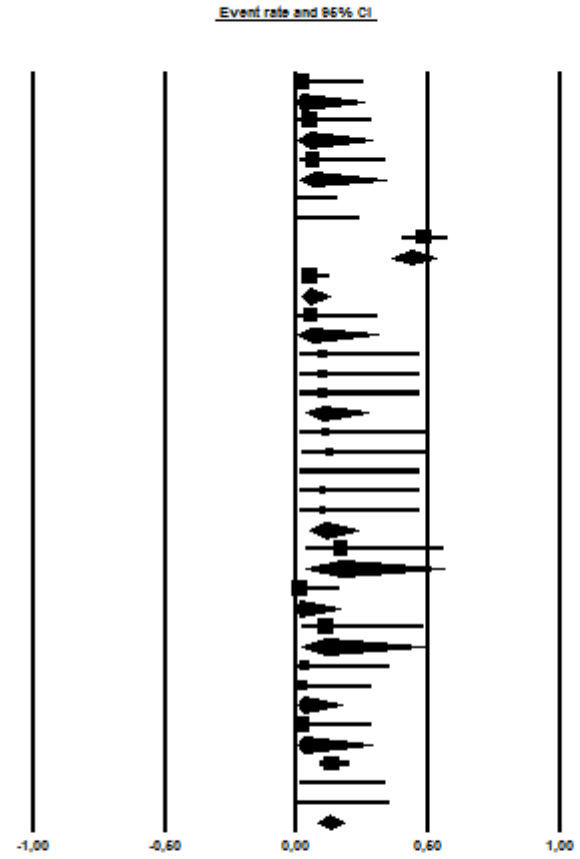
As Figure 43 shows, reporting of adverse effects was generally poor. The probability of experiencing an adverse event while taking part in a study of supplements for schizophrenia might be, for some supplements, close to zero, but it might also be 50

percent. The reported results were insufficient for calculating relative risks of developing adverse effects on active treatment compared with placebo.

Figure 43 (next page). Estimated probabilities of experiencing adverse effects when taking part in the included studies.

# Adverse effects event rate

| Group by Comparison | Study name | Comparison | Outcome | Statistics for each study: Event rate | Lower limit | Upper limit | Total |
|---|---|---|---|---|---|---|---|
| acetazolamide + thiamine | sacks 1989 | acetazolamide + thiamine | side effects | 0,020 | 0,001 | 0,251 | |
| acetazolamide + thiamine | | | | 0,020 | 0,001 | 0,251 | |
| B6+B9+B12 | levine 2006 | B6+B9+B12 | serious medical illness | 0,050 | 0,007 | 0,282 | 1 / 20 |
| B6+B9+B12 | | | | 0,050 | 0,007 | 0,282 | |
| benzopyrone | caseley-smith 1986 | benzopyrone | infectious hepatitis | 0,063 | 0,009 | 0,335 | 1 / 16 |
| benzopyrone | | | | 0,063 | 0,009 | 0,335 | |
| EPA | emsley 2002 | EPA | overdose of medication | 0,025 | 0,004 | 0,157 | 1 / 40 |
| EPA | peet 2001 (india) | EPA | side effects | 0,019 | 0,001 | 0,236 | |
| EPA | peet 2002 | EPA | side effects | 0,484 | 0,396 | 0,572 | 59 / 122 |
| EPA | | | | 0,441 | 0,358 | 0,528 | |
| epa + dha + fish oil | mantegihi 2008 | epa + dha + fish oil | Combined | 0,050 | 0,019 | 0,126 | 5 / 85 |
| epa + dha + fish oil | | | | 0,050 | 0,019 | 0,126 | |
| multivitamins | vaughan 1999 | multivitamins | vomiting | 0,056 | 0,008 | 0,307 | 1 / 18 |
| multivitamins | | | | 0,056 | 0,008 | 0,307 | |
| nicotinamide | ananth 1972 | nicotinamide | toxicity | 0,100 | 0,014 | 0,467 | 1 / 10 |
| nicotinamide | deutsch 1977 | nicotinamide | lupus erythamosus | 0,100 | 0,014 | 0,467 | 1 / 10 |
| nicotinamide | ramsey 1970 | nicotinamide | suicidal tendencies | 0,100 | 0,014 | 0,467 | 1 / 10 |
| nicotinamide | | | | 0,100 | 0,033 | 0,268 | |
| nicotinic acid | ananth 1972 | nicotinic acid | Combined | 0,111 | 0,015 | 0,500 | 1 / 9 |
| nicotinic acid | ananth 1973 | nicotinic acid | Combined | 0,127 | 0,021 | 0,496 | 1 / 10 |
| nicotinic acid | deutsch 1977 | nicotinic acid | Combined | 0,100 | 0,014 | 0,467 | 1 / 10 |
| nicotinic acid | hoffer 1957 | nicotinic acid | suicide | 0,100 | 0,014 | 0,467 | 1 / 10 |
| nicotinic acid | ramsey 1970 | nicotinic acid | flushing of skin | 0,100 | 0,014 | 0,467 | 1 / 10 |
| nicotinic acid | | | | 0,108 | 0,046 | 0,231 | |
| nicotinic acid + pyridoxine | ananth 1973 | nicotinic acid + pyridoxine | Combined | 0,169 | 0,032 | 0,558 | 2 / 10 |
| nicotinic acid + pyridoxine | | | | 0,169 | 0,032 | 0,558 | |
| piracetam | lilov 2007 | piracetam | side effects | 0,012 | 0,001 | 0,167 | |
| piracetam | | | | 0,012 | 0,001 | 0,167 | |
| pyridoxine | ananth 1973 | pyridoxine | Combined | 0,113 | 0,017 | 0,482 | 1 / 10 |
| pyridoxine | | | | 0,113 | 0,017 | 0,482 | |
| vitamin b6 | lerner 2002 | vitamin b6 | side effects | 0,031 | 0,002 | 0,350 | |
| vitamin b6 | lerner 2004 | vitamin b6 | side effects | 0,024 | 0,001 | 0,287 | |
| vitamin b6 | | | | 0,027 | 0,004 | 0,170 | |
| vitamin c | dakhale 2005 | vitamin c | side effects | 0,024 | 0,001 | 0,287 | |
| vitamin c | | | | 0,024 | 0,001 | 0,287 | |
| vitamin E | adler 1999 | vitamin E | Combined | 0,134 | 0,088 | 0,199 | 22 / 158 |
| vitamin E | lam 1994 | vitamin E | Combined | 0,063 | 0,009 | 0,335 | 1 / 16 |
| vitamin E | lohr 1988 | vitamin E | side effects | 0,031 | 0,002 | 0,350 | |
| vitamin E | | | | 0,125 | 0,083 | 0,183 | |



# Discussion

In the present systematic review, we summarized the evidence for possible effects of dietary supplements on symptoms of schizophrenia in people diagnosed with schizophrenia or schizoaffective disorder. We included only randomized controlled trials. A main finding was that the included studies were generally not aligned with the principles of orthomolecular psychiatry. According to these principles, supplements should be individually tailored, based on present deficiencies. An individual should receive a number of vitamins and other dietary supplements in sufficiently large doses and for a sufficient duration of time. The sufficient duration required for treatment effects of vitamin B3 may be as long as five to six years according to Abram Hoffer (16). The included studies in our review had a treatment duration ranging from 5 days to 2 years. Only three studies used individual doses of supplements (25;53;54), and only six studies delivered more than one supplement (23;26;37;42;45;54). In short, most studies delivered only one supplement in equal doses to all participants regardless of their individual needs, and the duration of treatment might have been too short in many of the studies.

The electronic searches found only 20 of the 33 studies. The remaining studies were located in the book by Wehrbach (17) (n=4), in the review by Kleijnen (57) (n=4), from personal contact with authors (n=2) and from reference lists (n=3). This might indicate that much of the literature in this field is not published in journals that are indexed in the common electronic databases. Therefore, we hand-searched all issues of the Journal of Orthomolecular Medicine for possible publications. Full text content of this journal covering the years 1967 to 2007 is freely available at www.orthomolecular.org/library. We found no articles fulfilling our inclusion criteria in this journal. As a consequence of the results of our literature search, we may have missed some studies because they are hard to locate.

Although there are at least 33 randomized controlled trials on dietary supplements for schizophrenic symptoms in people diagnosed with schizophrenia, there are few on each supplement, and the trials are typically very small. Many of the trials are old – 16 trials were published before the introduction of the CONSORT guidelines for reporting of trials in 1996 (20). But 17 trials were published after the introduction of these guidelines. We have shown that the quality of reporting has improved in this field after the introduction of CONSORT.

Low scores on BPRS and PANSS in the included studies indicate that symptoms were well controlled by the antipsychotic medications with not much room for improvement. This is sometimes called floor effects and might have caused an underestimation of the effects of supplements.

Our main finding is that although there are a number of randomized controlled trials on effects of dietary supplements to possibly reduce schizophrenic symptoms, the effects are small and imprecise.

One of the external reviewers pointed out certain weaknesses of this review:

- Schizophrenia is not one disease but an "umbrella diagnosis" consisting of several different phenotypes
- Minerals like zink, magnesium, calsium, copper, and selenium has not been evaluated in this review. Other central substances that have not been evaluated are SAMe, L-methionin, Sarcosin (n-metylglycin), D-Serin, D-Cycloserin, and Glycine.
- Researchers should measure the amounts of substances in the body of the patients before the supplementation begins.

Although these comments are highly relevant, it was not possible to incorporate them because they were not dealt with in the primary studies. Hence, it is not a weakness of this review.

Effects of elimination of certain substances such as gluten and casein as well as providing herbal supplements were not covered by our mandate, but these interventions might be effective alone or in combination with the supplements described in the present report.

We think that two findings are worth discussing: How could EPA have a beneficial effect, while a combination of EPA, DHA, and fish oil has not? And how can EPA and DHA be equally beneficial, while EPA is beneficial and DHA is not? We do not have the answer to these questions, but one explanation might be that DHA and fish oil somehow cancel out a beneficial effect of EPA. Another explanation has to do with the low quality of evidence. The effects of methodological biases may be larger than the effects of the supplements.

We do not have sufficient information to assess the risk for adverse effects. There are two main reasons for this: The first is that we cannot know whether there was a causal effect or whether the symptoms just happened to coincide with the treatment period. This is when we look at all study participants as a whole. The second is that the studies rarely reported whether the adverse effects occurred on the active treatment or on placebo. It is well known that placebo capsules can produce large nocebo effects (59).

We did not involve user participants in the production of this review. Such involvement might have made the review more relevant to patients diagnosed with schizophrenia, health personnel involved with treating these patients, and decision makers.

# Conclusion

The documentation on dietary supplements for schizophrenia is of low to very low quality. There are randomized controlled trials on a number of supplements, but the trials are few and small, and they have a number of methodological shortcomings. However, the lack of evidence for an effect must not be equated with evidence of no effect.

## Need for further research

There is a need for large, randomised, well-blinded, placebo-controlled trials that follow the CONSORT criteria for reporting of trials. In order to investigate the claims of orthomolecular medicine, researchers should provide individual combinations of dietary supplements and in individual amounts for individual durations of time. Researchers should improve reporting of adverse effects. They should report whether the adverse effects occurred in the intervention or placebo group, and whether they believe that there was a causal relation between intake of supplement and adverse effect.

## Implications for practice

The documentation for effects of dietary supplements on schizophrenic symptoms in people diagnosed with schizophrenia is not strong enough to recommend practitioners to provide supplements as part of their treatment. On the other hand, there is no evidence that intake of the supplements described in the present report has any serious, common side effects. When dealing with an individual patient, the evidence must be considered in the context of other relevant conditions, the patients' needs and preferences and one's own clinical experience.

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# Appendix

## 1 Glossary

| | |
|---|---|
| **Alpha-tocopherol** | Vitamin E |
| **BDI** | Behavior Disturbance Inventory |
| **BPRS** | Brief Psychiatric Rating Scale |
| **BSI** | Brief Symptom Inventory |
| **CGI** | Clinical Global Impression |
| **Cobalamin** | Vitamin B12 |
| **CONSORT** | CONsolidated Standards of Reporting Trials |
| **DDR** | Drug Dosage Record |
| **DHA** | Docosahexaenoic acid. A type of omega-3 polyunsaturated fatty acid |
| **DHLA** | Dihomo-Gammalinolenic Acid |
| **DSR** | Drug Study Résumé |
| **ECT** | Electroconvulsive Therapy |
| **EPA** | Eicosapentaenoic acid (E-EPA is Ethyl-EPA). A type of omega-3 polyunsaturated fatty acid |
| **ESRS** | Extrapyramidal Symptom Rating Scale |
| **Floor effects** | When data cannot take on a value lower than some particular number, called the floor. |
| **Folate** | Vitamin B9 |
| **GAF** | The Global Assessment of Functioning Scale |
| **GLA** | Gamma-linolenic acid |
| **GRADE** | Grading of Recommendations Assessment, Development and Evaluation. Tool for assessing the quality of evidence. |

| | |
|---|---|
| **IU** | International Units |
| **MADRS** | Montgomery-Åsberg Depression Rating Scale |
| **MECT** | Modified Electroconvulsive Therapy |
| **Methylfolate** | Vitamin B9 |
| **MD** | Mean difference. In meta-analysis: a method used for combining measures on a continuous scale, where mean, standard deviation and sample size in each group are known |
| **MIBS** | Missouri Inpatient Behavior Scale |
| **MMPI** | Minnesota Multiphasic Personality Inventory |
| **Negative symptoms** | Negative symptoms are deficits of normal emotional responses or of other thought processes. They commonly include flat or blunted affect and emotion, poverty of speech, inability to experience pleasure, lack of desire to form relationships, and lack of motivation. |
| **Niacin** | Vitamin B3 (nicotinic acid and nicotinamide are also vitamin B3 |
| **Nocebo effect** | A real, adverse physical reaction that people sometimes experience when they discover that they have been exposed to something, despite that there are no evidence for the exposure being harmful. |
| **NOSIE** | Nurses' Observation Scale for Inpatient Observation |
| **Orthomolecular medicine** | A form of alternative medicine that aims to prevent and cure disease by using specific doses of vitamins, amino acids, fatty acids, trace minerals, electrolytes, and other natural substances. |
| **PANSS** | Positive and Negative Symptoms Scale |
| **PDI** | Patient Data Inventory |
| **PIP** | Psychotic Inpatient Profile |
| **Positive symptoms** | Positive symptoms are those that most individuals do not normally experience but are present in people with schizophrenia (delusions, disordered thoughts and speech, and hallucinations. |
| **Pyridoxine** | Vitamin B6 |
| **Riboflavin** | Vitamin B2 |
| **SANS** | Scale for the Assessment of Negative Symptoms |
| **SAPS** | Scale for the Assessment of Positive Symptoms |

| | |
|---|---|
| **Schizophrenia** | Schizophrenia is a mental disorder characterized by disintegration of thought processes and of emotional responsiveness. It most commonly manifests as auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking, and it is accompanied by significant social or occupational dysfunction. |
| **TESS** | Treatment Emergent Symptoms Scale |
| **Thiamine** | Vitamin B1 |
| **WPRS** | Wittenborn Psychiatric Rating Scale |

## 2 Search strategy

**Search:** Malene W. Gundersen, based on original search by Hege Sletsjøe
**Database:** Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present
**Date:** 08.09.2010
**Number of hits:** 281
**Comment:** Used RCT filter (CRD and Cochrane Highly Sensitive Search Strategy-Max Sensitivity)

Vitamins and schizophrenia-update-rct-medline-2010

1. exp Schizophrenia/
2. (schizophren*).tw.
3. or/1-2
4. exp fish oils/ or exp plant oils/
5. exp dietary fats, unsaturated/ or fatty acids, omega-3/
6. fatty acids/ or exp fatty acids, unsaturated/
7. exp Nutrition Therapy/
8. exp Diet Therapy/
9. exp Vitamins/
10. exp Minerals/
11. (supplement* or therapy*).tw.
12. therapy.fs.
13. or/9-10
14. or/11-12
15. 13 and 14
16. ((fish or flax or linseed or plant) adj1 oil).tw.
17. (fatty adj1 acid* adj1 (n-3 or n-6)).tw.
18. ((vitamin* or diet* or mineral*) adj1 (supplement* or therapy)).tw.
19. (omega-3 or omega-6).tw.
20. Orthomolecular Therapy/
21. (megavitamin* or orthomolecular*).tw.
22. or/4-8,15-21
23. 3 and 22
24. randomised controlled trial.pt.
25. controlled clinical trial.pt.
26. randomised.ab.
27. placebo.ab.
28. drug therapy.fs.
29. randomly.ab.
30. trial.ab.

31. groups.ab.
32. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33. Animals.sh.
34. Humans.sh.
35. 33 not (33 and 34)
36. 32 not 35
37. 23 and 36

**Database:** EMBASE 1980 to 2010 Week 35
**Date:** 08.09.2010
**Number of hits:** 381
**Comment:** RCT Filter based on SIGN

Vitamins and schizophrenia-update-rct-embase-2010

1. exp schizophrenia/
2. (dementi* or schizophren*).tw.
3. or/1-2
4. exp diet supplementation/ or exp vitamin supplementation/
5. ((vitamin* or diet* or mineral*) adj1 (supplement* or therapy)).tw.
6. exp vegetable oil/
7. exp fish oil/
8. fatty acid/ or essential fatty acid/
9. exp omega 3 fatty acid/
10. exp mineral/
11. ((fish or flax or linseed or plant) adj1 oil).tw.
12. (fatty adj1 acid* adj1 (n-3 or n-6)).tw.
13. (omega-3 or omega-6).tw.
14. (supplement* or therapy*).tw.
15. (dt or dm).fs.
16. 14 or 15
17. or/6-13
18. 17 and 16
19. or/4-5,18
20. 3 and 19
21. Clinical trial/
22. Randomised controlled trial/
23. Randomization/
24. Single blind procedure/
25. Double blind procedure/
26. Crossover procedure/
27. Placebo/

28. Randomi?ed controlled trial$.tw.
29. Rct.tw.
30. Random allocation.tw.
31. Randomly allocated.tw.
32. Allocated randomly.tw.
33. (allocated adj2 random).tw.
34. Single blind$.tw.
35. Double blind$.tw.
36. ((treble or triple) adj blind$).tw.
37. Placebo$.tw.
38. Prospective study/
39. or/21-38
40. Case study/
41. Case report.tw.
42. Abstract report/ or letter/
43. human/
44. nonhuman/
45. animal/
46. animal experiment/
47. 44 or 45 or 46
48. 47 not (43 and 47)
49. or/40-42,48
50. 39 not 49
61. 20 and 50

**Database:** Cochrane Issue 8 of 12, Aug 2010
**Date:** 08.09.2010
**Number of hits:** Review:3 // Other Reviews:1 // Clinical Trials:94 // Method studies:1

Vitamins and schizophrenia-update-rct-Cochrane-2010

| ID | Search | Hits |
|---|---|---|
| #1 | MeSH descriptor **Schizophrenia** explode all trees | 4253 |
| #2 | (schizophren*):ti,ab | 10553 |
| #3 | (#1 OR #2) | 11234 |
| #4 | MeSH descriptor **Fish Oils** explode all trees | 1560 |
| #5 | MeSH descriptor **Plant Oils** explode all trees | 1051 |
| #6 | MeSH descriptor **Dietary Fats, Unsaturated** explode all trees | 1829 |
| #7 | MeSH descriptor **Fatty Acids, Omega-3** explode all trees | 1337 |

| | | |
|---|---|---|
| #8 | MeSH descriptor **Fatty Acids**, this term only | 1032 |
| #9 | MeSH descriptor **Fatty Acids, Unsaturated** explode all trees | 7875 |
| #10 | MeSH descriptor **Nutrition Therapy** explode all trees | 5601 |
| #11 | MeSH descriptor **Diet Therapy** explode all trees | 3064 |
| #12 | MeSH descriptor **Vitamins** explode all trees | 9322 |
| #13 | MeSH descriptor **Minerals** explode all trees | 2236 |
| #14 | (supplement* or therapy*):ti,ab | 117979 |
| #15 | (( #12 OR #13 ) AND #14) | 5098 |
| #16 | ((fish or flax or linseed or plant) NEAR/1 oil):ti,ab | 1062 |
| #17 | ((fatty NEAR/1 acid*) or (n-3 or n-6 or omega-3 or omega-6)):ti,ab | 8357 |
| #18 | ((vitamin* or diet* or mineral*) NEAR/1 (supplement* or therapy)):ti,ab | 2242 |
| #19 | (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #15 OR #16 OR #17 OR #18) | 26213 |
| #20 | (#3 AND #19) | 99 |

**Database:** PsycINFO 1806 to August Week 5 2010
**Date:** 08.09.2010
**Number of hits:** 49
**Comment:** Used RCT filter

Vitamins and schizophrenia-update-rct-PsycINFO-2010

1. exp schizophrenia/
2. (schizophren*).tw.
3. or/1-2
4. vitamin therapy/
5. dietary supplements/
6. exp fatty acids/
7. exp Diets/
8. exp Nutrition/
9. exp vitamins/
10. ((fish or flax or linseed or plant or vegetable) adj1 oil).tw.
11. (fatty adj1 acid* adj1 (n-3 or n-6)).tw.
12. (vitamin* or diet* or mineral*).tw.
13. (omega-3 or omega-6).tw.
14. (megavitamin* or orthomolecular*).tw.
15. (supplement* or therapy*).tw.
16. or/6-14
17. 15 and 16

18. or/4-5,17
19. 3 and 18
20. empirical methods/
21. Experimental methods/
22. Quasi experimental methods/
23. experimental design/
24. between groups design/
25. followup studies/
26. repeated measures/
27. experiment controls/
28. experimental replication/
29. exp "sampling (experimental)"/
30. placebo/
31. clinical trials/
32. treatment effectiveness evaluation/
33. experimental replication.md.
34. followup study.md.
35. prospective study.md.
36. treatment outcome clinical trial.md.
37. placebo$.tw.
38. randomi?ed controlled trial$.tw.
39. rct.tw.
40. random allocation.tw.
41. (randomly adj1 allocated).tw.
42. (allocated adj2 random).tw.
43. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
44. (clinic$ adj (trial? or stud$3)).tw.
45. or/20-44
46. comment reply.dt.
47. editorial.dt.
48. letter.dt.
49. clinical case study.md.
50. nonclinical case study.md.
51. animal.po.
52. human.po.
53. 51 not (51 and 52)
54. or/46-50,53
55. 45 not 54
56. 55 and 19

## 3 Table of excluded studies (n=67)

| Study<br>First author<br>(reference no.) | Cause for exclusion of study |
|---|---|
| Adler 1993a (60) | Did not report outcomes about symptoms of schizophrenia. |
| Adler 1993b (61) | Did not report outcomes about symptoms of schizophrenia. |
| Adler 1998 (62) | Did not report outcomes about symptoms of schizophrenia. |
| Affleck 1969 (63) | Intervention not relevant. |
| Akhtar 1993 (64) | Population was unclear. |
| Amminger 2010 (65) | Participants did not have diagnosis of schizophrenia. |
| Ashby 1960 (66) | Did not report outcomes about symptoms of schizophrenia. |
| Ban 1977 (67) | Not a randomised trial. |
| Ban 1971 (68) | Letter. |
| Ban 1974 (69) | Review. |
| Beauclair 1987 (70) | Not a controlled trial. |
| Berger 2007 (71) | Participants did not have diagnosis of schizophrenia. |
| Berger 2008 (72) | Participants did not have diagnosis of schizophrenia. |
| Bockenheimer 1976 (73) | Not a randomised trial. |
| Carney 1970 (74) | Not a randomised trial. |
| Carney 1979 (75) | Not a randomised trial. |
| Dabiri 1994 (76) | Participants did not have diagnosis of schizophrenia. |
| Denson 1962 (77) | Did not report outcomes about symptoms of schizophrenia. |
| Domino 1985 (78) | Intervention not relevant. |
| Dorevitch 1997a (79) | Did not report outcomes about symptoms of schizophrenia. |
| Dorevitch 1997b (80) | Did not report outcomes about symptoms of schizophrenia. |
| Egan 1992 (81) | Not separate results for schizophrenia. |
| Elkashef 1990 (82) | Not separate results for schizophrenia. |
| Emsley 2008 (83) | Did not report outcomes about symptoms of schizophrenia. |
| Gelenberg 1990 (84) | Not separate results for schizophrenia. |
| Gelenberg 1989 (85) | Participants did not have diagnosis of schizophrenia. |
| George 1981 (86) | Participants did not have diagnosis of schizophrenia. |
| Gillin 1976 (87) | Not a randomised trial. |
| Growdon 1977 (88) | Not a randomised trial. |
| Heresco-Levy 1996 (89) | Intervention not relevant. |

| Study<br>First author<br>(reference no.) | Cause for exclusion of study |
|---|---|
| Hoffer 1971 (90) | Review. |
| Hoffer 2008 (91) | Review. |
| Hoffer 1954 (92) | Not a randomised trial. |
| Holman 1983 (93) | Not a randomised trial. |
| Jackson 1981 (94) | Not a randomised trial. |
| Jackson 1979 (95) | Participants did not have diagnosis of schizophrenia. |
| Javitt 1994 (96) | Intervention not relevant. |
| Junker 1992 (97) | This is only a meeting abstract. We did not find a fulltext in PubMed or ISI Web of Knowledge (search date: 04.02.11). |
| Kabes 1983 (98) | Not separate results for schizophrenia. |
| Kai 1976 (99) | Not a randomised trial. |
| Kanofsky 1989 (100) | Not a randomised trial. |
| Lerner 2001 (101) | Did not report outcomes about symptoms of schizophrenia. |
| Libov 2007 (125) | Intervention not relevant. |
| Lohr 1987 (102) | Not separate results for schizophrenia. |
| Milner 1963 (103) | Not separate results for schizophrenia. |
| Morand 1983 (104) | Not a randomised trial. |
| Nasrallah 1984 (105) | Not a randomised trial. |
| Nicholson 1966 (106) | Intervention not relevant. |
| Osmond 1962 (107) | Did not report outcomes about symptoms of schizophrenia. |
| Peet 1996 (108) | Review. |
| Peet 1997 (109) | Abstract. |
| Peet 2003 (110) | Review. |
| Penovich 1978 (111) | Participants did not have diagnosis of schizophrenia. |
| Pfeiffer 1979 (112) | Not a randomised trial. |
| Potkin 1981 (113) | No supplements were given. |
| Procter 1991 (114) | Not a report of a study. |
| Reed 1929 (115) | Not a controlled study. |
| Sacks 1988 (116) | Did not report outcomes about symptoms of schizophrenia. |
| Sacks 1989 (126) | Intervention not relevant. |
| Saijad 1998 (117) | Did not report outcomes about symptoms of schizophrenia. |
| Schmidt 1991 (118) | Did not report outcomes about symptoms of schizophrenia. |
| Sehdev 1974 (119) | Not a randomised trial. |
| Shriqui 1992 (120) | Not separate results for schizophrenia. |

| Study<br>First author<br>(reference no.) | Cause for exclusion of study |
|---|---|
| Simpson 1977 (121) | Participants did not have diagnosis of schizophrenia. |
| Storms 1982 (122) | No supplements were given. |
| Straw 1989 (123) | Not a controlled study. |
| Vaddadi 1989 (124) | Not separate results for schizophrenia. |

## 4 Risk of bias assessments

Adler 1999

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Yes | Adaptive allocation. Unbiased coin. |
| Allocation concealment? | Unclear | "central randomization". |
| Blinding? | Unclear | "double blind". |
| Incomplete outcome data addressed? | Yes | 32.2% attrition at 1 year. Balanced and reasons provided. ITT performed. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Yes | Clinicians were allowed to change doses of neuroleptics. |
| Blinding of assessors? | Yes | "blinded assessment." |

Altman 1973

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "randomly assigned". |
| Allocation concealment? | Unclear | Insufficient information about concealment. |
| Blinding? | Unclear | Insufficient information about blinding. |
| Incomplete outcome data addressed? | Unclear | 12.6% attrition. Balanced. No reasons provided. Not ITT. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Unclear | Researchers did not expect supplements to work. |
| Blinding of assessors? | Unclear | Insufficient information about blinding of assessors. |

Ananth 1972

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "randomly assigned". |
| Allocation concealment? | Unclear | Insufficient information about concealment. |
| Blinding? | Unclear | Insufficient information about blinding. |
| Incomplete outcome data addressed? | No | 80% attrition. Balanced. Reasons. Not ITT. |

| | | |
|---|---|---|
| Free of selective reporting? | No | Some outcomes have only p-levels. |
| Free of other bias? | Unclear | Clinicians administered chlorpromazine in individual doses according to perceived patient need. |
| Blinding of assessors? | Unclear | Insufficient information about blinding of assessors. |

Ananth 1973

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "randomly assigned". |
| Allocation concealment? | Unclear | Insufficient information about concealment. |
| Blinding? | Unclear | "double blind". |
| Incomplete outcome data addressed? | Unclear | 13.3% attrition at 48 weeks. Balanced. Reasons. Not ITT. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Unclear | Clinicians administered chlorpromazine in individual doses according to perceived patient need. |
| Blinding of assessors? | Unclear | Insufficient information about blinding of assessors. |

Casley-Smith 1986

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | Insufficient information about method of sequence generation. |
| Allocation concealment? | Unclear | Insufficient information about concealment. |
| Blinding? | Unclear | "double blind." |
| Incomplete outcome data addressed? | No | 31.3% attrition at 6 months. Reasons. Not ITT. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | No | Two of the authors had a schizophrenic son who improved after having received two of the benzo-pyrone group of drugs which led them to initiate the study. Zyma provided supplements and financial support. Seemingly no washout period. |
| Blinding of assessors? | Yes | Assessors "did not know whether the patient was taking the active drug or the placebo." |

Dakhale 2005

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Yes | "Randomization was blocked and done by using computer program to generate sequence of random numbers and assign each patient randomly to either group A or group B." |
| Allocation concealment? | Unclear | Insufficient information about concealment. |
| Blinding? | Yes | "All medicines were identical in formulation, shape, size, weight, color and packing." |
| Incomplete outcome data addressed? | Yes | 12.5% attrition at 2 months. Reasons. ITT performed. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Yes | No other sources of bias were detected. |
| Blinding of assessors? | Yes | Coding was not broken until the end of the trial. |

Deutsch 1977

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "randomly assigned." |
| Allocation concealment? | Unclear | Insufficient information about concealment. |
| Blinding? | Yes | "All three substances were supplied in capsules identical in appearance, taste and smell." |
| Incomplete outcome data addressed? | No | 20% attrition at 48 weeks. Not balanced. Reasons. Not ITT. |
| Free of selective reporting? | No | Some scales (PDI, DDR) have missing reported outcomes. |
| Free of other bias? | Yes | No other sources of bias were detected. |
| Blinding of assessors? | Unclear | Insufficient information about blinding of assessor. |

Dorfman-Etrog 1999

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "randomly allocated." |
| Allocation concealment? | Unclear | Insufficient information about concealment. |
| Blinding? | No | It was an open label study. |
| Incomplete outcome data addressed? | Unclear | Insufficient information about incomplete outcome data. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have |

| | | |
|---|---|---|
| | | been reported. |
| Free of other bias? | No | Too short duration (2 weeks). |
| Blinding of assessors? | Unclear | Insufficient information about blinding of assessor. |

Emsley 2002

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "Randomised" |
| Allocation concealment? | Unclear | Insufficient information about concealment. |
| Blinding? | Unclear | "double blind." |
| Incomplete outcome data addressed? | Yes | 2.5 % attrition. ITT performed. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Yes | No other sources of bias were detected. |
| Blinding of assessors? | Unclear | Insufficient information about blinding of assessors. |

Emsley 2006

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "randomly assigned." |
| Allocation concealment? | Yes | "Trial supplies were packed by an independent contract clinical trials supplies company (DHP), who prepared the placebo and active packs for the entire trial and assigned the randomization numbers to the packs." |
| Blinding? | Yes | "double blind". "identical capsules". |
| Incomplete outcome data addressed? | No | 24% attrition. Reasons. Not balanced. Not ITT. |
| Free of selective reporting? | No | Only model estimates and results of F-test. |
| Free of other bias? | No | One of the authors was employed by Amarin Neuroscience Limited that supplied the drug. Possible floor effects. Subjects had few symptoms at baseline. |
| Blinding of assessors? | Yes | "The randomization code was broken after completion of the trial." |

Fenton 2001

| Item | Judgement | Description |
|---|---|---|

| | | |
|---|---|---|
| Adequate sequence generation? | Unclear | "randomly assigned." |
| Allocation concealment? | Unclear | Insufficient information about concealment. |
| Blinding? | Yes | Double blind. Patients were unable to distinguish placebo from active treatment. Medication was tasteless. |
| Incomplete outcome data addressed? | Yes | 13.8 % attrition. Balanced. Reasons. ITT. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Yes | No other sources of bias were detected. |
| Blinding of assessors? | Yes | "raters blind to treatment groups." |

Godfrey 1990

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "randomly allocated" |
| Allocation concealment? | Unclear | Insufficient information about concealment. |
| Blinding? | Unclear | "double blind." |
| Incomplete outcome data addressed? | Yes | No attrition at 6 months. |
| Free of selective reporting? | No | Results for Beck Depression self-rating scale was not reported for the three follow-ups. |
| Free of other bias? | Yes | No other sources of bias were detected. |
| Blinding of assessors? | Unclear | Insufficient information about blinding of assessors. |

Hoffer 1957

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "assigned at random." |
| Allocation concealment? | Unclear | Insufficient information about concealment. |
| Blinding? | Unclear | "double blind." "Patients were blinded." |
| Incomplete outcome data addressed? | Unclear | Insufficient information about incomplete outcome data. |
| Free of selective reporting? | Unclear | Results are not represented in a way that allows assessment of effects. |
| Free of other bias? | Unclear | Both authors have personal beliefs in the effects of niacin. |

| | | |
|---|---|---|
| Blinding of assessors? | Yes | "The social worker following the patient did not know which treatment had been given, that is, he did not know whether nicotinic acid or the placebo was used during the hospital stay and after release from the hospital." |

Joshi 1980

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "randomised list" |
| Allocation concealment? | Unclear | Insufficient information about concealment. |
| Blinding? | Unclear | "double blind". |
| Incomplete outcome data addressed? | Yes | 1.7 % attrition. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | No | Vitamins and other assistance supplied by Glaxo Laboratories (India) Ltd. The placebo group received significantly more ECT. |
| Blinding of assessors? | Unclear | Insufficient information about blinding of assessors. |

Lam 1994

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "selected randomly" |
| Allocation concealment? | Unclear | Insufficient information about concealment. |
| Blinding? | Unclear | "double blind" |
| Incomplete outcome data addressed? | No | 25% attrition. Unclear whether it was balanced. Reasons provided. No ITT. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Unclear | Washout period of 1 week is short compared to the half-life of vitamin B6 which is appr. 15-25 days. |
| Blinding of assessors? | Yes | "two independent blind raters". |

Lerner 2002

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | Insufficient information about sequence generation. |
| Allocation concealment? | Unclear | Insufficient information about con- |

| | | |
|---|---|---|
| | | cealment. |
| Blinding? | Unclear | "double blind." |
| Incomplete outcome data addressed? | Yes | No attrition at 8 weeks. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Yes | No other sources of bias were detected. |
| Blinding of assessors? | Yes | "blinded investigators." |

Lerner 2004

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "randomly divided". |
| Allocation concealment? | Yes | "The preparations were made by a professional pharmacist in the same size and colour capsules in individual number-coded packages." |
| Blinding? | Yes | "Both raters and patients were blind to the patients' drug assignment." |
| Incomplete outcome data addressed? | Yes | "All patients completed the trial." |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Unclear | Study duration may have been too short (5 days). |
| Blinding of assessors? | Yes | "Both raters and patients were blind to the patients' drug assignment." |

Lerner 2007

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "randomly assigned". |
| Allocation concealment? | Unclear | Insufficient information about concealment. |
| Blinding? | Unclear | "double-blind". |
| Incomplete outcome data addressed? | No | 28% attrition. Balanced and reasons, but not ITT. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Unclear | Washout period of 2 weeks is short compared to the half-life of vitamin B6 which is appr. 15-25 days. |
| Blinding of assessors? | Unclear | Insufficient information about blinding of assessors. |

Levine 2006

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "randomised". |
| Allocation concealment? | Unclear | Insufficient information about concealment. |
| Blinding? | Unclear | "double blind". |
| Incomplete outcome data addressed? | No | 23.6% attrition. Balanced and reasons, but not ITT. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Unclear | Large carry-over effects. |
| Blinding of assessors? | Unclear | Insufficient information about blinding of assessors. |

Lohr 1988

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "chosen on a random basis". |
| Allocation concealment? | Unclear | Insufficient information about concealment. |
| Blinding? | Yes | "matched placebo". |
| Incomplete outcome data addressed? | Unclear | Insufficient information about incomplete outcome data. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Yes | No other sources of bias were detected. |
| Blinding of assessors? | Yes | "All ratings were performed without knowledge of the patient's medication status by trained raters." |

Lohr 1996

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "randomly assigned". |
| Allocation concealment? | Unclear | Insufficient information about concealment. |
| Blinding? | Yes | "placebo gelcaps, which where indistinguishable from the active gelcaps". |
| Incomplete outcome data addressed? | No | 36.4% attrition. Reasons. Unclear whether balanced. Not ITT. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Yes | No other sources of bias were detected. |

| | | |
|---|---|---|
| Blinding of assessors? | Unclear | Insufficient information about blinding of assessors. |

Manteghiy 2008

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Yes | "table of random numbers". |
| Allocation concealment? | Unclear | Insufficient information about concealment. |
| Blinding? | Yes | "Omega-3 fatty acids and placebo were started with the dosage of 1 pearl on the first day. They were similar in taste, colour and shape" |
| Incomplete outcome data addressed? | Unclear | Insufficient information about incomplete outcome data. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Yes | No other sources of bias were detected. |
| Blinding of assessors? | Yes | "The psychologist and the psychiatrist who assessed the patients were blind to the treatment groups, so were the treating psychiatrist and the patients." |

McGrath 1973

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Yes | "The allotment of these active and inert tablets was made on the basis of sets of randomised numbers." |
| Allocation concealment? | Yes | "Since the identical-appearing tablets were supplied to the hospitals in containers bearing only the patient's code number, neither hospital staff members nor patients knew who was receiving nicotinamide and who was receiving placebo." |
| Blinding? | Yes | "Since the identical-appearing tablets were supplied to the hospitals in containers bearing only the patient's code number, neither hospital staff members nor patients knew who was receiving nicotinamide and who was receiving placebo." |
| Incomplete outcome data addressed? | No | 30.6% attrition. Reasons provided. Unclear whether it was balanced. No ITT. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | No | Used unvalidated rating scale. |
| Blinding of assessors? | Unclear | Insufficient information about blind- |

| | | |
|---|---|---|
| | | ing of assessors. |

Miodownik 2006

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "randomly assigned". |
| Allocation concealment? | Yes | "The study medications and placebo were prepared by a professional pharmacist in capsules of the same size and colour in number-coded packages." |
| Blinding? | Yes | "Both rater and patient were blinded to the patients' drug assignment." |
| Incomplete outcome data addressed? | Yes | No attrition during 5 days. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Unclear | Study duration may have been too short (5 days). |
| Blinding of assessors? | Yes | "Both rater and patient were blinded to the patients' drug assignment." |

Peet 2001 (India)

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | Insufficient information about sequence generation. |
| Allocation concealment? | Yes | “Patients were allocated at random to be treated double blind…” |
| Blinding? | Yes | “…capsules…in the form of EPA enriched oil (Kirunal) or an identical appearing matching corn oil placebo…” |
| Incomplete outcome data addressed? | Yes | 13.3% attrition. Reasons provided. Unclear whether it was balanced. Not ITT. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Unclear | Laxdale Ltd supplied the supplements and provided financial support. |
| Blinding of assessors? | Unclear | Insufficient information about blinding of assessors. |

Peet 2001 (UK)

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | Insufficient information about sequence generation. |
| Allocation concealment? | Yes | "The oils, which were indistinguish- |

| | | |
|---|---|---|
| | | able by color, texture and taste, were provided in bottles, consecutively numbered, based on a randomization code that was not available to the investigators." |
| Blinding? | Yes | "The oils, which were indistinguishable by color, texture and taste, were provided in bottles, consecutively numbered, based on a randomization code that was not available to the investigators." |
| Incomplete outcome data addressed? | Yes | 18.2% attrition. Reasons provided. Unclear whether it was balanced. Not ITT. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Unclear | Laxdale Ltd supplied the supplements and provided financial support. |
| Blinding of assessors? | Unclear | Insufficient information about blinding of assessors. |

Peet 2002

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | Insufficient information about sequence generation. |
| Allocation concealment? | Yes | "Packing of the medication and randomisation were performed by DHP Ltd, Abergavenny, UK, an organization independent of any other aspect of the trial. Drug packages, coded and with a unique randomisation number were despatched direct from the DHP to each study centre." |
| Blinding? | Yes | "Two types of identical-appearing soft gelatine capsules were packaged into a daily blister pack." |
| Incomplete outcome data addressed? | Yes | 5.7 % attrition and ITT. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Unclear | Supplements provided by Laxdale Limited. Horrobin (one of the authors) worked for Laxdale. |
| Blinding of assessors? | Unclear | Insufficient information about blinding of assessors. |

Ramsey 1970

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "randomly assigned". |

| | | |
|---|---|---|
| Allocation concealment? | Unclear | Insufficient information about allocation concealment. |
| Blinding? | Yes | "identical tablets". |
| Incomplete outcome data addressed? | Yes | 30% attrition. Reasons and balanced and ITT performed using last observation carried forward. |
| Free of selective reporting? | No | Only significance values reported. Not separate results for the 4 follow-ups. |
| Free of other bias? | Unclear | Phenothiazine drugs were given in free doses adjusted according to clinical need. Phenothiazine requirements were significantly lower in the placebo groups than in the active treatment groups. |
| Blinding of assessors? | Unclear | Insufficient information about blinding of assessors. |

Rapisarda 2000

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | Divided randomly and age-matched. |
| Allocation concealment? | Unclear | Insufficient information about allocation concealment. |
| Blinding? | No | The study was not blinded to patients and providers. |
| Incomplete outcome data addressed? | Yes | 16.7 % attrition. No reasons. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Yes | No other sources of bias were detected. |
| Blinding of assessors? | Unclear | Insufficient information about blinding of assessors. |

Vaddadi 1986

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "randomly allocated". |
| Allocation concealment? | Unclear | Insufficient information about allocation concealment. |
| Blinding? | Yes | "The ward doctor, the nursing staff and all those involved in making assessments were unaware of the allocation of treatments. The placebo injections contained either sesame oil or coconut oil to match the pre-trial depot preparations." |
| Incomplete outcome data addressed? | No | 23.8% attrition. Reasons provided. Unclear whether attrition was balanced. Not ITT. |

| | | |
|---|---|---|
| Free of selective reporting? | No | Standard deviations for BPRS not reported. Psychotic inpatient Profile results only reported as not significant. |
| Free of other bias? | No | Three people involved in study design, execution and outcome analysis were employed by Roche Products Limited (the supplier of the supplements). |
| Blinding of assessors? | Yes | "The ward doctor, the nursing staff and all those involved in making assessments were unaware of the allocation of treatments. The placebo injections contained either sesame oil or coconut oil to match the pre-trial depot preparations." |

Vaughan 1999

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "At entry to the study, random allocation was achieved by sealing patients' ID numbers in opaque envelopes, which was later distributed either to a megavitamin or a control group by an independent research worker." |
| Allocation concealment? | Yes | "At entry to the study, random allocation was achieved by sealing patients' ID numbers in opaque envelopes, which was later distributed either to a megavitamin or a control group by an independent research worker." |
| Blinding? | Yes | "Control group subjects were given tablets identical in character and quantity to the mean number given to the vitamin group." |
| Incomplete outcome data addressed? | Yes | 18% attrition. Reasons provided. Unbalanced. No ITT. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Yes | No other sources of bias were detected. |
| Blinding of assessors? | Unclear | Insufficient information about blinding of assessors. |

Wittenborn 1973

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Yes | "assigned in an unbiased double-blind manner to either the high-niacin or the control group in a 60 to 40 ratio." |
| Allocation concealment? | Yes | "Medication was packaged for the individual patient by the hospital |

| | | |
|---|---|---|
| | | pharmacist who followed a prepared assignment schedule and protected the double-blind condition." |
| Blinding? | Yes | "Medication was packaged for the individual patient by the hospital pharmacist who followed a prepared assignment schedule and protected the double-blind condition." |
| Incomplete outcome data addressed? | No | 46.4% attrition. Number randomised is not reported. |
| Free of selective reporting? | No | Incomplete reporting of results from the Wittenborn Psychiatric Rating Scale, the Rutgers Nurses Rating Scale, Today's Mood Inventory, and the Social Workers Follow-up Inventory. |
| Free of other bias? | No | Treatments were interrupted for a number of patients (44/86). |
| Blinding of assessors? | Yes | Insufficient information about blinding of assessors. |

Wolkin 1986

| Item | Judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | "Subjects were assigned on a random, double-blind basis". |
| Allocation concealment? | Unclear | Insufficient information about allocation concealment. |
| Blinding? | Unclear | Insufficient information about blinding of patients and providers. |
| Incomplete outcome data addressed? | Unclear | Insufficient information about incomplete outcome data. |
| Free of selective reporting? | Yes | All relevant outcomes seem to have been reported. |
| Free of other bias? | Yes | No other sources of bias were detected. |
| Blinding of assessors? | Unclear | Insufficient information about blinding of assessors. |

Figure 4.1. Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies.

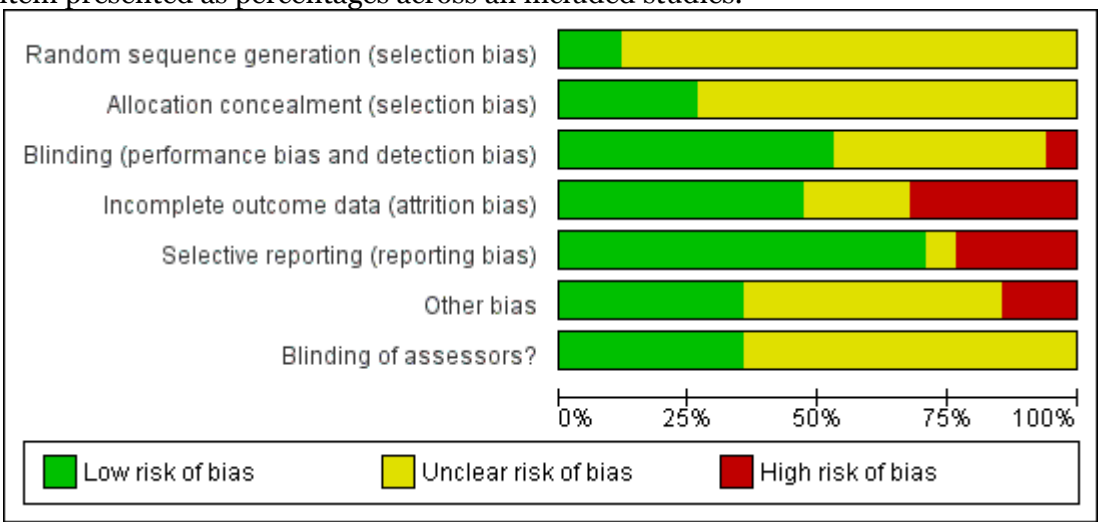
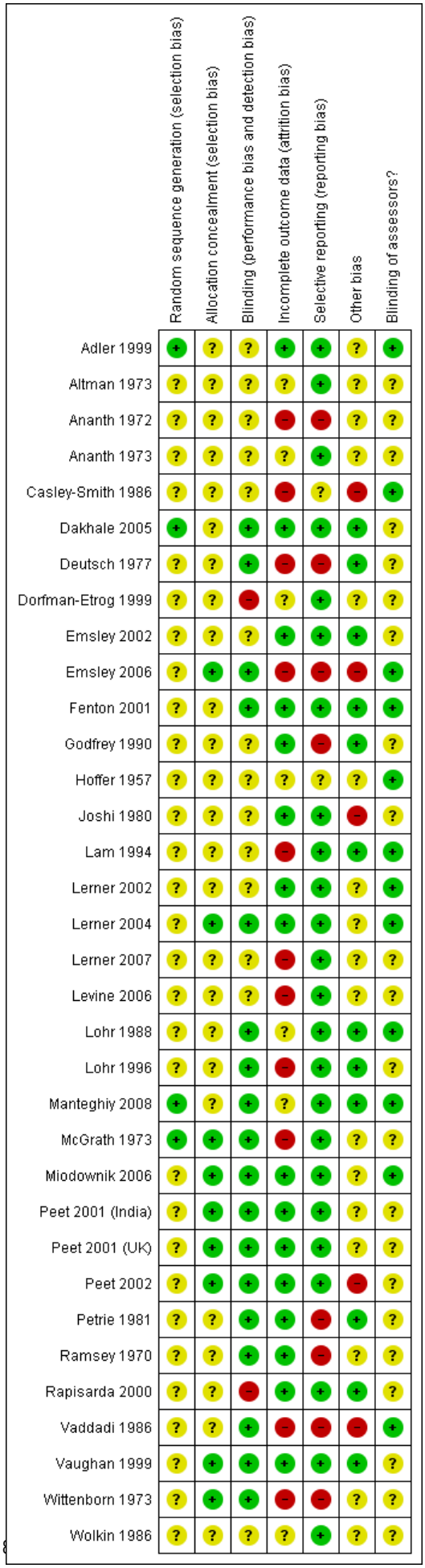



Figure 4.2 (next page). Risk of bias summary: review authors' judgments about each risk of bias item for each included study.


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding (performance bias and detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Blinding of assessors?
Adler 1999
Altman 1973
Ananth 1972
Ananth 1973
Casley-Smith 1986
Dakhale 2005
Deutsch 1977
Dorfman-Etrog 1999
Emsley 2002
Emsley 2006
Fenton 2001
Godfrey 1990
Hoffer 1957
Joshi 1980
Lam 1994
Lerner 2002
Lerner 2004
Lerner 2007
Levine 2006
Lohr 1988
Lohr 1996
Manteghiy 2008
McGrath 1973
Miodownik 2006
Peet 2001 (India)
Peet 2001 (UK)
Peet 2002
Petrie 1981
Ramsey 1970
Rapisarda 2000
Vaddadi 1986
Vaughan 1999
Wittenborn 1973
Wolkin 1986

# 5 Grade

Table 5.1. Grade - vitamin B6 vs. placebo

**Vitamin B6 compared to placebo for schizophrenia**

**Patient or population:** patients with schizophrenia
**Settings:** Israel
**Intervention:** Vitamin B6
**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk<br>**placebo** | Corresponding risk<br>**Vitamin B6** | | | | |
| **BPRS**<br>BPRS. Scale from: 18 to 126.<br>Follow-up: mean 5 days | The mean bprs in the control groups was<br>**48.9 weighted point scores** | The mean BPRS in the intervention groups was<br>**2.53 lower**<br>(6.18 lower to 1.11 higher) | | 60<br>(2 studies) | ⊕⊕⊖⊖<br>**low**[1] | SMD -0.31 (-0.83 to 0.2) |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Total sample size=60.

Table 5.2. Grade - vitamin C vs. placebo

**Vitamin C compared to placebo for schizophrenia**

**Patient or population:** patients with schizophrenia
**Settings:** India
**Intervention:** Vitamin C
**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk<br>**Placebo** | Corresponding risk<br>**Vitamin C** | | | | |
| **BPRS**<br>BPRS. Scale from: 18 to 126.<br>Follow-up: mean 8 weeks | The mean bprs in the control groups was<br>**28.96 point score** | The mean bprs in the intervention groups was<br>**9.66 lower**<br>(13.3 to 6.1 lower) | | 40<br>(1 study) | ⊕⊕⊖⊖<br>**low**[1] | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Single small study (n=40).

Table 5.3. Grade – vitamin E vs. placebo

**Vitamin E compared to placebo for schizophrenia**

**Patient or population:** patients with schizophrenia
**Settings:**
**Intervention:** Vitamin E
**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk placebo | Corresponding risk Vitamin E | | | | |
| **BPRS**<br>BPRS. Scale from: 18 to 126.<br>Follow-up: 2-24 months | The mean bprs in the control groups was **25.7 Weighted mean point score** | The mean BPRS in the intervention groups was **2.47 lower** (11.23 lower to 6.3 higher) | | 193<br>(2 studies) | ⊕⊖⊖⊖<br>**very low**[1,2,3] | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Both studies have unclear assessment in 3 domains. One study not met on criterion of incomplete outcome data.
[2] I-square=75%. Effects are in opposite directions.
[3] Wide confidence interval.

Table 5.4. Grade – EPA vs. placebo

**EPA compared to placebo for schizophrenia**

**Patient or population:** patients with schizophrenia
**Settings:**
**Intervention:** EPA
**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk placebo | Corresponding risk EPA | | | | |
| **PANSS**<br>PANSS. Scale from: 30 to 210.<br>Follow-up: 12-16 weeks | The mean panss in the control groups was **66.97 weighted point scores** | The mean PANSS in the intervention groups was **7.27 lower** (14.8 lower to 0.25 higher) | | 142<br>(3 studies) | ⊕⊕⊖⊖<br>**low**[1,2] | SMD -0.51 (-1.12 to 0.09) |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] I-squared=61%.
[2] Total sample size=142

Table 5.5. Grade – EPA + DHA + fish oil vs. placebo (next page)

**EPA + DHA + fish oil compared to placebo for schizophrenia**

**Patient or population:** patients with schizophrenia
**Settings:** Iran
**Intervention:** EPA + DHA + fish oil
**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk<br>**Placebo** | Corresponding risk<br>**EPA + DHA + fish oil** | | | | |
| **PANSS positive**<br>PANSS positive. Scale from: 7 to 49.<br>Follow-up: mean 6 weeks | The mean panss positive in the control groups was<br>**39.04** | The mean panss positive in the intervention groups was<br>**0.36 higher**<br>(2.57 lower to 3.29 higher) | | 85<br>(1 study) | ⊕⊕⊖⊖<br>**low**[1] | |
| **PANSS negative**<br>PANSS negative. Scale from: 7 to 49.<br>Follow-up: mean 6 weeks | The mean panss negative in the control groups was<br>**38.61 point score** | The mean panss negative in the intervention groups was<br>**1.41 lower**<br>(4.79 lower to 1.97 higher) | | 85<br>(1 study) | ⊕⊕⊖⊖<br>**low**[1] | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Single study with total sample size=85

Table 5.6. Grade – DHA vs. placebo

**DHA compared to placebo for schizophrenia**

**Patient or population:** patients with schizophrenia
**Settings:** UK
**Intervention:** DHA
**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk<br>**Placebo** | Corresponding risk<br>**DHA** | | | | |
| **PANSS**<br>PANSS total. Scale from: 30 to 210.<br>Follow-up: mean 12 weeks | The mean panss in the control groups was<br>**65.9 point score** | The mean panss in the intervention groups was<br>**0.60 lower**<br>(12.75 lower to 11.55 higher) | | 30<br>(1 study) | ⊕⊕⊖⊖<br>**low**[1] | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Single study with sample size=30.

Table 5.7. Grade – EPA vs. DHA (next page)

**EPA compared to DHA for schizophrenia**

**Patient or population:** patients with schizophrenia
**Settings:** UK
**Intervention:** EPA
**Comparison:** DHA

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk<br>**DHA** | Corresponding risk<br>**EPA** | | | | |
| **PANSS**<br>PANSS total. Scale from: 30 to 210.<br>Follow-up: mean 12 weeks | The mean panss in the control groups was<br>**65.3 point score** | The mean panss in the intervention groups was<br>**9.80 lower**<br>(20.97 lower to 1.37 higher) | | 31<br>(1 study) | ⊕⊕⊖⊖<br>**low**[1] | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Single study with sample size=31.

Table 5.8. Grade – GLA vs. placebo (next page)

**Gamma-linolenic acid compared to placebo for schizophrenia**

**Patient or population:** patients with schizophrenia
**Settings:** USA
**Intervention:** Gamma-linolenic acid
**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk<br>**Placebo** | Corresponding risk<br>**Gamma-linolenic acid** | | | | |
| **BPRS**<br>BPRS. Scale from: 18 to 126.<br>Follow-up: mean 6 weeks | The mean bprs in the control groups was<br>**48 point score** | The mean bprs in the intervention groups was<br>**3 lower**<br>(12.99 lower to 6.99 higher) | | 16<br>(1 study) | ⊕⊖⊖⊖<br>**very low**[1,2] | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Unclear risk of bias in 6 domains.
[2] Single study with total sample size=16.