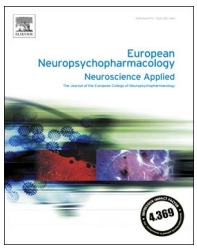
European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

www.elsevier.com/locate/euroneuro



REVIEW

# Efficacy of adding nutritional supplements in unipolar depression: A systematic review and meta-analysis

**Cora Schefft**[a], **Laura L. Kilarski**[b], **Tom Bschor**[c], **Stephan Köhler**[a,*]

[a]*Charité Universitätsmedizin Berlin, Campus Mitte, Department for Psychiatry and Psychotherapy, Charitéplatz 1, 10117 Berlin, Germany*
[b]*University Hospital of Cologne, Department of Psychosomatic Medicine and Psychotherapy, Cologne, Germany*
[c]*Schlosspark-Klinik, Department of Psychiatry, Berlin, Germany and Department of Psychiatry and Psychotherapy, Technical University Dresden, Dresden, Germany*

Received 14 March 2017; received in revised form 16 June 2017; accepted 5 July 2017

**KEYWORDS**
Unipolar depression;
Augmentation;
Nutritional supplements;
Efficacy;
Systematic review

**Abstract**
In this article, we aimed to assess the efficacy of adjunctive administration of nutritional supplements to antidepressants by means of a systematic review and meta-analysis. The supplements included were inositol, vitamin D, folic acid, vitamin B12, S-adenosyl-L-methionine (SAMe), omega-3 polyunsaturated fatty acids (n-3 PUFA) and zinc.
A structured database search (MEDLINE, EBSCO, CENTRAL, Web of Science) was performed using terms for the respective substances in conjunction with terms for depression and the mode of treatment ("add-on" OR "adjunctive" OR "augmentation"). Meta-analyses, randomized controlled trials (RCTs) and non-randomized comparative studies that investigated the supplements as an add-on in the treatment of clinically diagnosed MDD were included. Agents had to be added to an existing antidepressant regime (augmentation) or started simultaneously with the antidepressant (acceleration). For n-3 PUFAs, folic acid and zinc, new meta-analyses were performed as part of this work. Our meta-analyses of 10 articles on n-3 PUFAs and four on zinc support their efficacy. For folic acid, our meta-analysis does not support efficacy. For n-3 PUFAs, sensitivity analysis showed no difference between acceleration and augmentation designs, but significant differences between individuals with or without comorbidities. For the remaining substances, only a few RCTs were available. The preliminary data on inositol was negative, while one RCT for vitamin D demonstrated positive results. For vitamin B12 one and for SAMe

*Corresponding author. Fax: +49 30450517944.
*E-mail address:* stephan.koehler@charite.de (S. Köhler).

http://dx.doi.org/10.1016/j.euroneuro.2017.07.004


Please cite this article as: Schefft, C., et al., Efficacy of adding nutritional supplements in unipolar depression: A systematic review and meta-analysis. European Neuropsychopharmacology (2017), http://dx.doi.org/10.1016/j.euroneuro.2017.07.004

two RCTs and a few open trials are available reporting positive and mixed results. To summarize, for most of the substances, the available data is not yet sufficient or inconclusive.


## 1. Introduction

### 1.1. Background

In about 50% of patients the initiation of antidepressant treatment does not lead to a satisfactory response, and even after several treatment approaches, rates of non-remitted patients are still around 30% (Rush et al., 2006; Trivedi et al., 2006; Walsh et al., 2002). In case of a non-response to an antidepressant treatment, adding a drug from a different pharmaceutical class to the antidepressant has been shown to have an augmentative effect (Bschor, 2010; Bschor et al., 2014; Bschor et al., 2003; Crossley and Bauer, 2007; Köhler et al., 2013; Nelson and Papakostas, 2009). Most evidence has been demonstrated for augmentation with lithium (Bschor, 2014) and atypical antipsychotics (Nelson and Papakostas, 2009). However, augmenting with one of these drugs might also increase undesired side effects and thus make discontinuation of treatment more likely (Shine et al., 2015). It is therefore desirable to find new agents that augment or accelerate response to antidepressant therapy yet do not inflict an additional systemic burden on the patient.

Over the past two decades, the influence of nutritional factors on mental health conditions received growing attention through epidemiological and experimental findings, coining the name *nutritional psychiatry* for this nascent field of research (Sarris et al., 2015a). In this review, we analyzed the literature on nutritional supplements as add-on agents for the treatment of major depressive disorder (MDD) that include essential nutrients and nutritional supplements. Our aim was to systematically review the evidence from original studies and collate data into meta-analyses where appropriate. Herein, we describe details and limitations of the respective studies and report standardized effect sizes for each data set. Previous reviews and meta-analyses have summarized data relevant to this review (Almeida et al., 2015; Mocking et al., 2016; Sarris et al., 2016). However, none of these were designed to include data exclusively from patients fulfilling criteria for unipolar depression based on DSM or ICD-10 criteria in adjunctive trials. We furthermore distinguished between acceleration and augmentation designs, since these can address two different issues of antidepressant treatment: 1) time lapse between treatment initiation and response and 2) non-response to treatment, respectively. Contrary to previous analyses, we assessed trials for potential risks of bias and corrected accordingly where possible.

## 2. Experimental procedures

### 2.1. Study inclusion criteria

We conducted a systematic review of randomized controlled trials (RCTs) and open-label trials investigating the efficacy of adjunctive nutritional supplements in classic antidepressant treatments. Therein, we defined augmentation as the addition of a supplement to an ongoing antidepressant monotherapy. The simultaneous initiation of a common antidepressant and a supplement was termed acceleration (Fig. 1). In RCTs the comparator had to be the antidepressant only or a placebo added to the antidepressant. The selected substances were classified as non-prescription nutritional supplements, which have previously been studied in clinical trials as add-on substances to antidepressants. The authors agreed to focus on the following substances for which at least one RCT was available and which were most commonly reported as adjunctive agents in the therapy of unipolar depression (Freeman et al., 2010; Rechenberg, 2015):

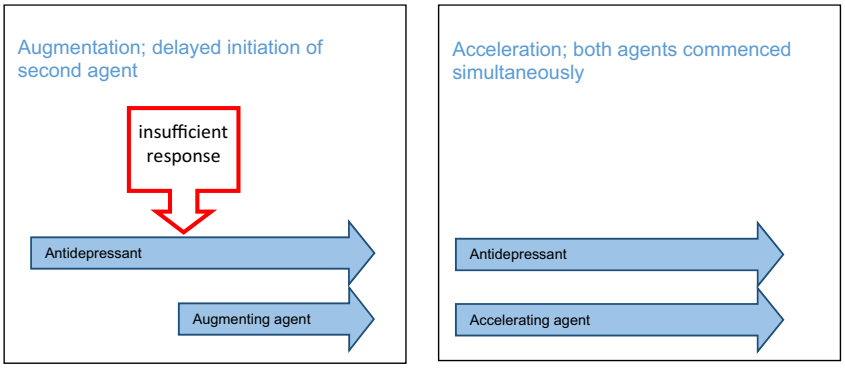



**Fig. 1** Augmentation and acceleration trials.

Please cite this article as: Schefft, C., et al., Efficacy of adding nutritional supplements in unipolar depression: A systematic review and meta-analysis. European Neuropsychopharmacology (2017), http://dx.doi.org/10.1016/j.euroneuro.2017.07.004