



Review

Acetylcholinesterase inhibitors and memantine for neuroenhancement in healthy individuals: A systematic review

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ABSTRACT

The term neuroenhancement refers to improvement in the cognitive, emotional and motivational functions of healthy individuals through, inter alia, the use of drugs. Of known interventions, psychopharmacology provides readily available options, such as the anti-dementia drugs, e.g. acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) and memantine. Based on a systematic review we found that expectations about the potential of these drugs exceed their actual effects, as has been demonstrated in randomised controlled trials. Both single and repeated dose trials were included in the systematic review, however repeated dose trials have only been conducted for donepezil. In six small trials lasting 14–42 days, the following results emerged: donepezil improved the retention of training on complex aviation tasks and verbal memory for semantically processed words. In one study episodic memory was improved, whereas in others it remained unaffected by donepezil. In a sleep deprivation trial, donepezil reduced the memory and attention deficits resulting from 24 h of sleep deprivation. Two studies reported even transient negative effects. Regarding the safety profile of donepezil, these studies found that it was rather well tolerated. In any case, since large longitudinal studies are not available no conclusions can be drawn.

Seven small studies about the effects of a single dose of memantine, and one study with a single dose of rivastigmine have been reported. Again, these studies are not adequate to answer our research question. If, as here and elsewhere suggested, the concept of pharmaceutical neuroenhancement is not to be rejected in principle, the decision of healthy individuals to take drugs for the purpose of neuroenhancement should be based on exhaustive information. At the moment, the research that would support or oppose the use of acetylcholinesterase inhibitors and memantine for neuroenhancement by healthy individuals has not yet been performed.

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1. Introduction

The term *neuroenhancement* has been coined to denote interventions by which healthy people improve their cognitive, emotional and motivational functions [21,32]. If psychopharmaceutical substances are used to achieve such improvements, we refer to pharmaceutical neuroenhancement. In the last decade anti-aging medicine has gained importance. Apparently, a number of healthy individuals e.g. those with normal age-related cognitive changes are asking for pharmaceutical neuroenhancement [9,21,22]. Already many use the readily available over-the-counter dietary supplements or other substances e.g. extracts of ginkgo biloba that are sometimes referred to as “nootropics”. The term “nootropics” refers to substances thought to enhance cognitive functions and it is interchangeable with “smart drugs” or “smart pills”. The effects of these substances are questionable and not scientifically proven for patients or healthy individuals.

Prescription drugs currently available for the treatment of dementia provide a further possibility for neuroenhancement. Healthy adults using this kind of drugs should base their decision to do so on the known effects of the drugs. Here, we report the results of a systematic review about the neuroenhancement properties of acetylcholinesterase inhibitors (AChEIs) and memantine. The first category comprises three substances – donepezil, galantamine, rivastigmine – that are widely recommended for clinical use for the treatment of patients with mild to moderate Alzheimer’s disease [27]. Memantine is a NMDA receptor antagonist and is registered for the treatment of moderate to severe Alzheimer’s disease [35].

This systematic review has been conducted according to pre-defined inclusion criteria as stated in a pre-defined protocol and collects the available evidence about the effects of AChEIs or memantine in healthy individuals. If it can be shown that these drugs have positive effects in healthy individuals, this would add urgency to the question how to regulate their potential use for neuroenhancement purposes. If no evidence of neuroenhancement effects can be found in the existing literature, then this fact should be made known to healthy people who are ready to accept the risk of consuming these drugs, although their benefit is not supported empirically.

1.1. Objectives

The aim of this review was to assess the effect of AChEIs and memantine on emotional, cognitive and motivational processes and the safety of their use by healthy individuals. Although these drugs are supposed to mainly affect cognition, they might also have an impact on emotional and motivational functions.

2. Methods

2.1. Criteria for considering studies for this review (inclusion criteria)

2.1.1. Types of studies

Included were all published single- or double-blind randomised or quasi-randomised controlled clinical trials, including crossover clinical trials, which compare memantine or one of the AChEIs donepezil, galantamine and rivastigmine with placebo. We did not consider tacrine in our search, since it is no longer used in clinical practice, because of its hepatic toxicity [11,38].

2.1.2. Types of participants

Eligible studies were those involving individuals of any age and either sex who show no evidence of psychiatric disorder, cognitive decline or other diseases.

2.1.3. Types of interventions

All interventions with AChEIs or memantine in all doses and dosing schedules (single dose or repeated doses) for any duration and by any route of administration in comparison with placebo.

2.1.4. Types of outcome measures

The primary outcomes of interest were measures for emotional, cognitive or motivational parameters. Specifically: mood, wakefulness, motivation, attention, concentration, memory, learning and executive functions. The outcomes were not pre-defined any further. Secondary outcomes of interest were adverse effects and acceptability of the medication, measured by numbers of participants dropping out during the trials and post-randomisation exclusions due to the drugs’ effects.

2.2. Search methods for identification of studies

Supported by a professional librarian an author (DR) developed search strategies (available upon request) including terms such as “acetylcholinesterase inhibitors”, “donepezil”, “galantamine”, “rivastigmine”, “memantine”, “healthy people” and their variants, synonyms, acronyms and the relevant medical subject headings (MeSH) to identify potentially relevant studies. The MEDLINE and EMBASE databases were searched using the WebSPIRS® 5.12 search engine from OVID. No language restriction was applied. The search was performed in the second week of July 2007 (MEDLINE: 1950 to 2007/07-week 2, EMBASE: 1989 to 2007/07). An additional search for newly published articles was performed in the forth week of July 2009. Reference lists from relevant primary and review articles were examined to identify additional studies.

2.3. Methods of the review

2.3.1. Selection of studies

The studies obtained through the search strategy were screened and those being clearly irrelevant were discarded on the basis of

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