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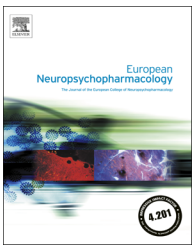

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REVIEW

Guanfacine for attention deficit and hyperactivity disorder in pediatrics: A systematic review and meta-analysis

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Abstract
To review the evidence from randomized controlled trials (RCTs) on the safety and efficacy of guanfacine in pediatric attention deficit hyperactivity disorder (ADHD), a bibliographic search up to May 2014 was performed using the Cochrane Library's Central Register of Controlled Trials, the Embase, PsycINFO, and Medline databases, and clinical trials registers. The search terms used were: ["guanfacine"] and ["child" or "adolescent" or "pediatrics"] and ["randomized controlled trial"] and ["Attention Deficit Disorder with Hyperactivity" or "Attention Deficit Disorder" or "Attention Hyperactivity Disorder" or "Hyperactivity" or "ADHD"]. A meta-analysis was performed using response, defined as a score ≤ 2 on the Clinical Global Impression Improvement score, as the outcome measure. In all, 7 out of 48 studies were included, for a total of 1752 participants. All studies compared guanfacine versus placebo, with a duration ranging from 6 to 16 weeks. In all, the Clinical Global Impression Improvement score was reported as a secondary measure. Overall, 694/1177 (59.0%) participants in the guanfacine group benefited from the treatment compared to 192/575 (33.3%) in the placebo group (pooled OR 3.2; 95%CI 2.4–4.1). The participants with at least one adverse event were 948 (82.4%) in the guanfacine and 376 (67.9%) in the placebo group (OR 2.6; 95%CI 1.6–4.4). Somnolence (OR 4.9), sedation (OR 2.8), and fatigue (OR 2.2), were the adverse events with the greatest risk of

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occurrence in the guanfacine versus the placebo group. On the basis of seven randomized, placebo controlled trials guanfacine resulted safe and effective in treating children and adolescents with ADHD

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder in children and adolescents that comprises core symptoms of developmentally inappropriate levels of inattention and/or hyperactivity and impulsivity. (American Psychiatric Association.Task force on DSM-IV., 2010) Recommendations in the international guidelines on the treatment of ADHD vary. However, there is a general consensus on recommending psychostimulant drugs as first line treatment because of their documented efficacy in about 80% of children. (American Academy of Pediatrics, 2011; National Collaborating Centre For Mental Health, 2008) In particular, methylphenidate is preferred to amphetamines, which are generally less used in Europe. Atomoxetine is a non-stimulant medication that, although generally less effective than stimulants, is also widely available and may be recommended as an alternative to methylphenidate (Hanwella et al., 2011; National Collaborating Centre For Mental Health, 2008; Newcorn et al., 2008). Since their approval, several issues have affected the use of ADHD medications, such as tolerability, comorbidity, and potential substance abuse risk.. This has enhanced the need for alternative treatment options, such as the α2 adrenergic receptor agonists, clonidine and guanfacine. Clonidine and guanfacine are two older antihypertensive drugs, licensed for use in adults, that induce peripheral sympatho-inhibition via the stimulation of receptors located in the brainstem. (van Zwieten and Chalmers, 1994) Despite their proven efficacy in lowering blood pressure, these two drugs are no longer widely used as antihypertensive agents. Nevertheless, they have been found to be useful in the treatment of different neuropsychiatric disorders, including ADHD, with the first studies in ADHD dating back to 30 years ago. (Hunt et al., 1985; Hunt et al., 1995) For a long time these drugs have been used as off-label alternatives to stimulant therapies, in particular in children and adolescents who continued to show behavioral problems, tics, or sleep disturbances during treatment with stimulants or atomoxetine.(Posey and McDougle, 2007) Although clonidine, used alone or in combination with methylphenidate, has been shown to be effective in reducing symptoms of ADHD in children, its clinical usefulness is limited by adverse effects, including sedation, bradycardia, and hypotension, especially at the start of treatment.(Hunt et al., 1990) Guanfacine is a more selective α 2-adrenoceptor agonist than clonidine.(Horrigan and Barnhill, 1995) Whereas clonidine binds equally to α 2A-, α 2B-, and α 2C-adrenoceptors (as well as to α 1-adrenoceptors, β-adrenoceptors, histamine receptors, and possibly dopamine receptors), guanfacine binds preferentially to postsynaptic α 2A-adrenoceptors in the prefrontal cortex (PFC), which have been implicated in attentional and organizational functions.(Wang et al., 2007) The mechanism through which α 2-adrenoceptor agonists works in ADHD patients is unclear, but abnormal PFC functioning is posited to be a key contributor to the impairments observed in ADHD.(Arnsten and Li, 2005; Arnsten et al., 2007; Franowicz et al., 2002) The guanfacine selectivity for α 2A receptors in PFC may more efficiently target ADHD symptoms while minimizing the risk of adverse effects. Compared with clonidine, guanfacine has less central nervous system depressant and less hypotensive activity (Yamadera et al., 1985; Kugler et al., 1980) and may have a more favorable pharmacokinetic profile. (Newcorn et al., 1998; Sorkin and Heel, 1986) In USA, a long acting formulation of guanfacine was approved in February 2009 by the Food and Drug Administration (FDA) for the treatment of ADHD in the pediatric population aged 6 to 7 years as monotherapy, and in 2011 as adjunctive therapy to psychostimulant treatment. In 2013 the drugs was approved also in Canada for use in children 6–12 years old. In Europe, a Pediatric Investigation Plan was submitted to the EMA from the drug company (EMEA-000745-PIP01-09-M01), but, until now the use of guanfacine is still limited to the treatment of hypertension in adults. Given the increasing interest for this drug in the clinical, research and regulatory settings, a review of published and unpublished studies on the safety and efficacy of guanfacine in the treatment of ADHD symptoms in the pediatric population was performed.

2. Experimental procedures

2.1. Definitions and inclusion/exclusion criteria

The systematic review was restricted to studies evaluating guanfacine therapy in children and adolescents with a diagnosis of ADHD. The search was limited to humans and only original articles were considered. Studies were eligible if they were randomized controlled trials. Studies involving adults, reviews, letters, editorials, follow-up studies, n-of-1 studies (i.e. studies in which random allocation is used to determine the order in which an experimental and a control intervention are given to a single patient who represents the trial population), comments, or published errata were excluded.

2.2. Search strategy

The search was performed independently by 2 reviewers (SR, AC) using the Medline (1950-May 2014), Embase (1974-May 2014), and PsycINFO (1967-May 2014) databases, and the Cochrane Central Register of Controlled Trials (Issue 5 of 12, May 2014).

The search strategy used both terms included in the title/abstract and in the subject headings, i.e. Medical Subject Headings (MeSH) for Medline and Cochrane, Emtree for Embase, and thesaurus for PsycINFO. The search terms used were: [“guanfacine”]