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Review

Comparative efficacy and acceptability of atomoxetine, lisdexamfetamine, bupropion and methylphenidate in treatment of attention deficit hyperactivity disorder in children and adolescents: A meta-analysis with focus on bupropion

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ABSTRACT

Objectives: There is a lack of comparative effectiveness research among attention deficit hyperactivity disorder (ADHD) drugs in terms of efficacy and acceptability, where bupropion is compared with atomoxetine, lisdexamfetamine and methylphenidate. The main aim of this work was to compare the efficacy and acceptability of these drugs in children and adolescents using a metaanalysis.
Methods: A literature search was conducted to identify double-blind, placebo-controlled, noncrossover studies of ADHD. PubMed/Medline and Clinicaltrials.gov were searched. Comparative drug efficacy to placebo was calculated based on the standardized mean difference (SMD), while the comparative drug acceptability (all cause discontinuation) to placebo was estimated on the odds ratio (OR).
Results: In total 28 trials were included in the meta-analysis. Efficacy in reducing ADHD symptoms compared to placebo was small for bupropion (SMD= −0.32, 95% CI; −0.69, 0.05), while modest efficacy was shown for atomoxetine (SMD= −0.68, 95% CI; −0.76, −0.59) and methylphenidate (SMD= −0.75, 95% CI; −0.98, −0.52) and high efficacy was observed for lisdexamfetamine (SMD= −1.28, 95% CI; −1.84, −0.71). Compared to placebo treatment discontinuation was statistically significantly lower for methylphenidate (OR=0.35, 95% CI; 0.24, 0.52), while it was not significantly different for atomoxetine (OR=0.91, 95% CI; 0.66, 1.24), lisdexamfetamine (OR=0.60, 95% CI, 0.22, 1.65), and bupropion (OR=1.64, 95% CI; 0.5, 5.43).
Limitations: The heterogeneity was high, except in atomoxetine trials. The crossover studies were excluded. The effect sizes at specific time points were not computed. Studies with comorbid conditions, except those reporting on oppositional defiant disorder, were also excluded. All studies involving MPH were combined.
Conclusions: The results suggest that lisdexamfetamine has the best benefit risk balance and has promising potential for treating children and adolescents with ADHD. More research is needed for a better clinical evaluation of bupropion.

Contents

Abbreviations: ADHD, Attention deficit hyperactivity disorder; ATX, Atomoxetine; BUP, Bupropion; IR, Immediate-release; LDX, Lisdexamfetamine; MPH, Methylphenidate; MR, Modified-Release; OROS, Osmotic-release oral system; SMD, standardized mean difference

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1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder. Its core symptoms are inattention, impulsivity and hyperactivity. Its worldwide prevalence in the children and adolescents is between 8% and 10% and in adults 2.5–4% (Faraone et al., 2003; Fayyad et al., 2007; McCarthy et al., 2012). About 30–50% of children diagnosed in childhood continue to have symptoms into adulthood (Bálint et al., 2008). The exact cause of ADHD is not known, however the most likely cause of ADHD is an imbalance in catecholamine metabolism in the cerebral cortex, with inhibitory dopaminergic and noradrenergic activities decreased (Russell et al., 2000). ADHD is a disorder with a high impact on the healthcare system and the community in terms of economic costs, family stress, academic and vocational adversity (Matza et al., 2005). From an economic perspective, healthcare costs are greater for children and adults with ADHD compared with those without (Pelham et al., 2007). According to the European guidelines, the management of ADHD consists of nonpharmacological options, including behavioral therapy, and pharmacological options, including stimulants and nonstimulants. Pharmacotherapy is essential for the treatment of children and adolescents with ADHD (Swanson et al., 1998). Medications are not recommended for preschool children, as the long-term effects in this age group are not known (Greenhill et al., 2008).

ADHD is treated with the drugs acting through dopaminergic and noradrenergic pathways, which are commonly stimulants. An alternative is usually the nonstimulant atomoxetine (ATX), a selective norepinephrine reuptake inhibitor. Stimulants show greater efficacy in treating youth with ADHD compared with nonstimulants (Faraone, 2009; Faraone et al., 2006). Although both stimulant and nonstimulant drugs also treat ADHD in adults effectively, stimulant drugs show greater short-term efficacy (Faraone and Glatt, 2010). The choice group of drugs are stimulants, primarily immediate-release methylphenidate (IR-MPH). The controlled release formulations should be available and used but they should not entirely replace the IR formulations (Banaschewski et al., 2006). Results from clinical studies indicate that the MPH-osmotic release oral delivery system (OROS-MPH) is effective as IR-MPH in three daily doses. The pharmacokinetic profile of OROS-MPH is the main reason for the long-term effect (Swanson et al., 2003).

In addition, ADHD is also occasionally treated with BUP, tricyclic antidepressants and some other drugs (Harpin, 2008). The Texas Department of State Health Services guideline recommends considering BUP or tricyclic antidepressants as a fourth-line treatment, used after trying two different stimulants and ATX (Pliszka et al., 2006). According to the ADHD treatment guidelines from the American Academy of Child and Adolescent Psychiatry, the evidence for BUP is weaker than for the FDA-approved treatments (Pliszka, 2007). However, several studies report positive results of BUP in treating ADHD in children and adolescents (Barrickman et al., 1995; Casat et al., 1987; Conners et al., 1996). Although individual drugs are typically thoroughly investigated during placebo-controlled studies, comparative effectiveness research is scarce and often involves smaller samples. In the absence of direct comparative head-to-head trials, the best evidence comes from comparing the individual randomized, double-blind, placebo-controlled studies of each treatment using the method of meta-analysis, which provides a systematic quantitative framework for assessing the effects of drugs reported in different studies (Faraone, 2009).

Because of few nonstimulant medications available in ADHD treatment, BUP may be a useful addition to available ADHD treatments. However, new research on BUP effectiveness and acceptability in ADHD treatment is needed before it could be considered for clinical use. Individual ADHD medications have been well researched until now, but there is a lack of comparative effectiveness research among medications in terms of efficacy and acceptability, which compare BUP with ATX, lisdexamfetamine (LDX) and MPH. Only two meta-analyses are available in the literature where BUP was also included and compared to ATX and MPH in the treatment of ADHD in children and adolescents, and both were sponsored without reported treatment acceptability (Faraone, 2009; Faraone et al., 2006). Consequently, a non-sponsored meta-analysis was performed, comparing the efficacy and acceptability of MPH, LDX, BUP and ATX for treating ADHD symptoms in children and adolescents. This meta-analysis will be the third to compare BUP with LDX by their efficacy and the second to further compare BUP with LDX. It will be also the first nonsponsored meta-analysis that analyses and reports on discontinuations of ATX, BUP, LDX, and MPH. The main aim of our work was to compare the efficacy and acceptability of MPH, LDX, BUP and ATX for the treatment of ADHD symptoms.

2. Materials and methods

2.1. Searching strategy

A systematic electronic literature search of PubMed (1975–April 2014) and Clinicaltrials.gov with full text (1981–April 2014) was conducted with the following search strategy limited to human studies in children and adolescents only:

(MPH OR BUP OR MPH-OROS OR MPH-IR OR MPH OR ATX OR BUP OR LDX) AND (effect OR effect size OR size OR efficacy OR effectiveness) AND (ADHD OR hyperkinetic syndrome OR ADH OR attention deficit hyperactivity disorder). Another search was followed in the same databases with the same limitations as previously, but with only two terms: “ADHD” AND “Name of the drug”, (e.g. “ADHD” AND “ATX”). Also, the references of selected full text articles were searched.