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Review

Effects of stimulants and atomoxetine on emotional lability in adults: A systematic review and meta-analysis

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ABSTRACT

Background: Emotional lability (EL) is an associated feature of attention-deficit/hyperactivity disorder (ADHD) in adults, contributing to functional impairment. Yet the effect of pharmacological treatments for ADHD on EL symptoms is unknown. We conducted a systematic review and meta-analysis to examine the effects of stimulants and atomoxetine on symptoms of EL and compare these with the effects on core ADHD symptoms.

Methods: A systematic search was conducted on the databases Embase, PsychInfo, and Ovid Medline® and the clinicaltrials.gov website. We included randomised, double-blind, placebo-controlled trials of stimulants and atomoxetine in adults aged 18–60 years, with any mental health diagnosis characterised by emotional or mood instability, with at least one outcome measure of EL. All identified trials were on adults with ADHD. A random-effects meta-analysis with standardised mean difference and 95% confidence intervals was used to investigate the effect size on EL and compare this to the effect on core ADHD symptoms.

Results: Of the 3,864 publications identified, nine trials met the inclusion criteria for the meta-analysis. Stimulants and atomoxetine led to large mean weighted effect-sizes for on ADHD symptoms ($n = 9$, SMD = −0.8, 95% CI: −1.07 to −0.53). EL outcomes showed more moderate but definite effects ($n = 9$, SMD = −0.41, 95% CI: −0.57 to −0.25).

Conclusions: In this meta-analysis, stimulants and atomoxetine were moderately effective for EL symptoms, while effect size on core ADHD symptoms was twice as large. Methodological issues may partially explain the difference in effect size. Reduced average effect size could also reflect heterogeneity of EL with ADHD pharmacotherapy responsive and non-responsive sub-types. Our findings indicate that EL may be less responsive than ADHD symptoms overall, perhaps indicating the need for adjunctive psychotherapy in some cases. To clarify these questions, our findings need replication in studies selecting subjects for high EL and targeting EL as the primary outcome.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental condition affecting around 5% of children [1]. Longitudinal follow-up studies show that ADHD frequently persists into adulthood, either as the full blown disorder, or as persistent subthreshold levels of symptoms causing impairment [2,3], with epidemiological surveys suggesting an estimated prevalence in adults of around 3–4% [4]. Although inattention, hyperactivity and impulsivity are considered to be the core symptoms of ADHD [5], emotional lability (EL), characterised by low frustration tolerance, irritability and mood lability, is a commonly associated feature that causes considerable distress to individuals and their families [6]. Clinically significant levels of EL are present in around 70–90% of adults with ADHD, and is an independent predictor of functional impairments beyond those accounted for by inattention and hyperactivity-impulsivity [7–10].

The importance of EL in adult ADHD was established by Wood, Wender and colleagues, who were among the first to describe the syndrome and included affective lability, hot temper, and stress intolerance as core symptoms of the disorder [11,12]. The current diagnostic and statistical manual of mental disorders (DSM-5) describes such emotional symptoms as associated features of ADHD that support the diagnosis [13]. Furthermore, high levels of EL are also observed in ADHD patients who do not present with co-occurring mental health disorders [7], indicating that the association

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of EL with ADHD cannot always be accounted for by the presence of comorbid disorders such as bipolar or borderline personality disorders [14].

Debate as to whether EL reflects a core domain of ADHD in adults is ongoing [5,15,16]. In particular it is unclear whether medications such as stimulants and atomoxetine, used in the treatment of ADHD, also lead to reductions in EL. Randomized placebo controlled trials in adults with ADHD conclusively show that both groups of medications lead to clinically significant reductions in symptoms of ADHD symptoms [9,17–20]. However, the effects of drugs used to treat ADHD on EL are yet to be established.

In order to assess the effects of stimulants and atomoxetine on EL in adults we conducted a systematic review and meta-analysis of randomised placebo-controlled trials. Our primary aim was to quantify the effects of stimulants and atomoxetine on EL. Our secondary aim was to contrast the effects of stimulants and atomoxetine on EL with the effects on the core ADHD symptoms of inattention and hyperactivity-impulsivity in the same studies.

Table 1
Search strategy.

Database	Search Strategy
Ovid Medline (1946 to June week 1, 2015) Embase (1974 to June 10, 2015) PsychInfo (1806 to June week 2, 2015)	Key Word search: (“affect*” or “oppositional” or “conduct” or “aggression” or “mood” or “emotion*” or “instability” or “lability” or “*regulation” or “bipolar”) and (“stimulants” or “*methylphenidate*” or “*amphetamine*” or “*amfetamine*” or “atomoxetine”) and (“RCT” or “randomized controlled trial” or “randomised controlled trial” or “double blind study” or “clinical trial” or “placebo controlled”)
Clinicaltrials.gov	(“affect*” OR “oppositional” OR “conduct” OR “aggression” OR “mood” OR “emotion*” OR “instability” OR “lability” OR “*regulation” OR “bipolar”) AND (“stimulants” OR “*methylphenidate*” OR “*amphetamine*” OR “*amfetamine*” OR “atomoxetine”)

2. Methods

We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21].

2.1. Search strategy and selection criteria

Studies were included if: (a) they were randomised double-blind placebo-controlled trials of stimulants or atomoxetine; (b) participants were adults aged 18–60 years with any mental health diagnosis associated with EL[1]; (c) the study measured at least one outcome of behavioural change related to EL; (d) for each outcome measure, mean (M) and standard deviation (SD) from baseline and follow-up for the placebo and active group were reported or obtained upon contacting the authors. Trials published in languages other than English were excluded for feasibility reasons of translation.

A literature search was conducted using pre-specified search terms (Table 1) using the following databases: Embase (1974 to 2015 June 10th), PsychInfo (1806 to June week 2, 2015) and Ovid Medline® (1946 to June week 1, 2015). Unpublished or ongoing trials were searched on the clinicaltrials.gov website. Authors were contacted to request missing data.

In spite of the official systematic search being stopped in June 2015, there were no new clinical trials published meeting the selection criteria of this systematic review up until 2nd May, 2017.

To assess for the risk of bias, study quality was assessed by two independent authors (TRM & PM) according to PRISMA guidelines and the Cochrane Handbook of Systematic Reviews [22] (Tables 2 and 3). TRM and PM then met to discuss assessments and reach a consensus on study inclusion. Unresolved classification of studies was arbitrated by PA and REC. Studies were classified overall as unclear, low or high risk. High risk studies were excluded.

Data extraction was performed by TRM and checked by two research assistants. The main outcome measures were raw scores of mean and standard deviation of the pre- and post-treatment measures of EL and DSM-IV ADHD symptoms for active and placebo arms. Intent to treat analysis (ITT) was reported. For trials with a cross-over design, only the initial pre-cross-over data was included, if available, and treated as a parallel group trial. We used this rather conservative approach because there was lack of sufficient data to permit analysis of within-individual change (i.e. correlations of scores between conditions were not given). Missing data that remained unavailable after contacting authors were not imputed.

2.2. Outcome measures

Two outcome domains were included in the meta-analysis: EL and DSM-IV ADHD symptoms. EL was measured using the emotion dysregulation subscale of the Wender Reimherr Adult Attention Deficit Disorder Scale (WRAADDS-EDS) [11], which combined subscales of hot temper, affective lability and emotional over-reactivity, or the emotion control subscale of the Behaviour Rating Inventory of Executive Function (BRIEF-A) [23]. ADHD DSM-IV domains were measured by the investigator-rated, self-rated or informant-rated Conners Adult ADHD Rating Scale (CAARS) [24], ADHD- Rating Scale (ADHD-RS) or the investigator rated WRAADDS [11]. Table 4 contains a detailed list of measures used in these two domains.

2.3. Data analysis

2.3.1. Statistical analyses

Analyses were performed in STATA 11.2 [25]. An initial analysis in the full sample across the two domains of EL and ADHD symptoms was run, following this, subgroup analyses (see below) were conducted.

We report the SMD calculated as the mean pre-to-post-treatment change, minus the mean pre-to-post-placebo group change, divided by the pooled pre-test standard deviation (SD), with a bias adjustment. The equation for this method is presented below [26]. Effects sizes were classified according to Cohen's d as follow: d = 0.2, d = 0.5 and d = 0.8 as small, medium and large respectively [27].

$$d_{ppc2} = C_P\left[\frac{(M_{post,T}-M_{pre,T})-(M_{post,C}-M_{pre,C})}{SD_{pre}}\right]$$

$$SD_{pre} = \sqrt{\frac{(n_T-1)SD^2_{pre,T}+(n_C-1)SD^2_{pre,C}}{n_T+n_C-2}}$$

$$C_P = 1-\frac{3}{4(n_T+n_c-2)-1}$$

[1] ADHD was not specified as a search term, with the intention of including trials of stimulants and atomoxetine on EL in non-ADHD populations. However, all resulting trials were conducted on adults with ADHD.