DOI:
10.1016/j.eurpsy.2017.05.021

Document Version
Peer reviewed version

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

Talar R Moukhtarian*[a]MSc, Ruth E Cooper*[a,b]PhD, Evangelos Vassos[a]PhD, Paul Moran[c]PhD and Philip Asherson[a]PhD.

[a]King's College London, MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, UK

[b]Newham Centre for Mental Health, Unit for Social and Community Psychiatry, Queen Mary University of London, UK

[c]Centre for Academic Mental Health, School of Social & Community Medicine, University of Bristol, UK

[*]Co-first authors.

Corresponding author:
Talar R Moukhtarian, King's College London, MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, London, SE5 8AF, UK.
E-mail: talar_rita.moukhtarian@kcl.ac.uk, Tel: 0747 931 0755

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.

Funding*:* None

Keywords: Attention-deficit/hyperactivity disorder; Emotional lability; Stimulants; Atomoxetine; Systematic review; Meta-analysis

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 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.

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

[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.

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 (see table 1 in appendix 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] (see table 2 and 3 in appendix 1). 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 (in appendix 1) 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]

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

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

$$C_p = 1-\frac{3}{4(n_T+n_C-2)-1}$$

Note. d_{ppc2}=Standardised Mean Difference (SMD), C_p=bias adjustment, M=Mean, T=treatment, C = Control, Post = Post-treatment, Pre = Pre-treatment, SD = Standard deviation, n = number of participants.

Given the between-study heterogeneity in terms of study design, trial duration, outcome measures and participant characteristics we chose *apriori* to use random-effects models.[28] A nominal level of significance was set at $p < .05$. The I^2 statistic assessed heterogeneity between studies. Publication bias was investigated on the basis of funnel plots using Begg & Mazumdar's rank correlation approach and the Egger regression asymmetry test.

2.3.2 Subgroup analyses: Additional analyses were conducted in subsets of the total sample to investigate the stability of the results to the scale used to measure EL (WRAADS-EDS versus BRIEF-A) and the class of study medication (stimulants versus atomoxetine).

2.3.2.1 Outcome measure: EL was measured by either BRIEF-A the emotion control subscale[23] or the WRAADDS-EDS.[11] Analyses were performed separately on the trials using the BRIEF-A (*n*=3) and WRAADDS-EDS (*n*=6).

2.3.2.2 Medication class: Included trials medicated participants with either stimulants or atomoxetine. Analyses were conducted separately on studies which used stimulants (*n*=6) and atomoxetine (*n*=3).

2.3.2.3 Medication class and outcome measure: To check whether the medication gave different effect size estimates when controlling for the EL scale (BRIEF-A or WRAADDS-EDS) used: we compared the effects of stimulants set against atomoxetine, first when EL was measured by the WRAADDS-EDS and then when it was measured by the BRIEF-A.

3. RESULTS

3.1 Selection of studies

The initial database search identified 3864 unique publications. 403 abstracts were screened against the inclusion criteria, of which 385 were excluded because: the data were already used or reported in another publication (*n*=18); the outcomes were unsuitable (*n*=44); the studies were not randomised controlled trials (*n*=61), failed to report a placebo group (*n*=4); were open label trials (*n*=5); used unsuitable medication (medications other than stimulants or atomoxetine) (*n*=14) or population (*n*=6); were not published in English (*n*=5); requests for data from unpublished trials were not returned successfully (*n*=24); or the trial was conducted on children (*n*=204). Eighteen full-text articles were subsequently quality appraised and eight were excluded because of: an open label design (*n*=1), unsuitable population (*n*=2), unsuitable design (*n*=2) and unsuitable outcome (*n*=3). Ten studies met the inclusion criteria, but one of these had to be excluded on the grounds of missing statistics, leaving nine studies for inclusion in the final pool for the meta-analysis (see fig. 1 and tables 5, 6 and 7 in appendix 1).

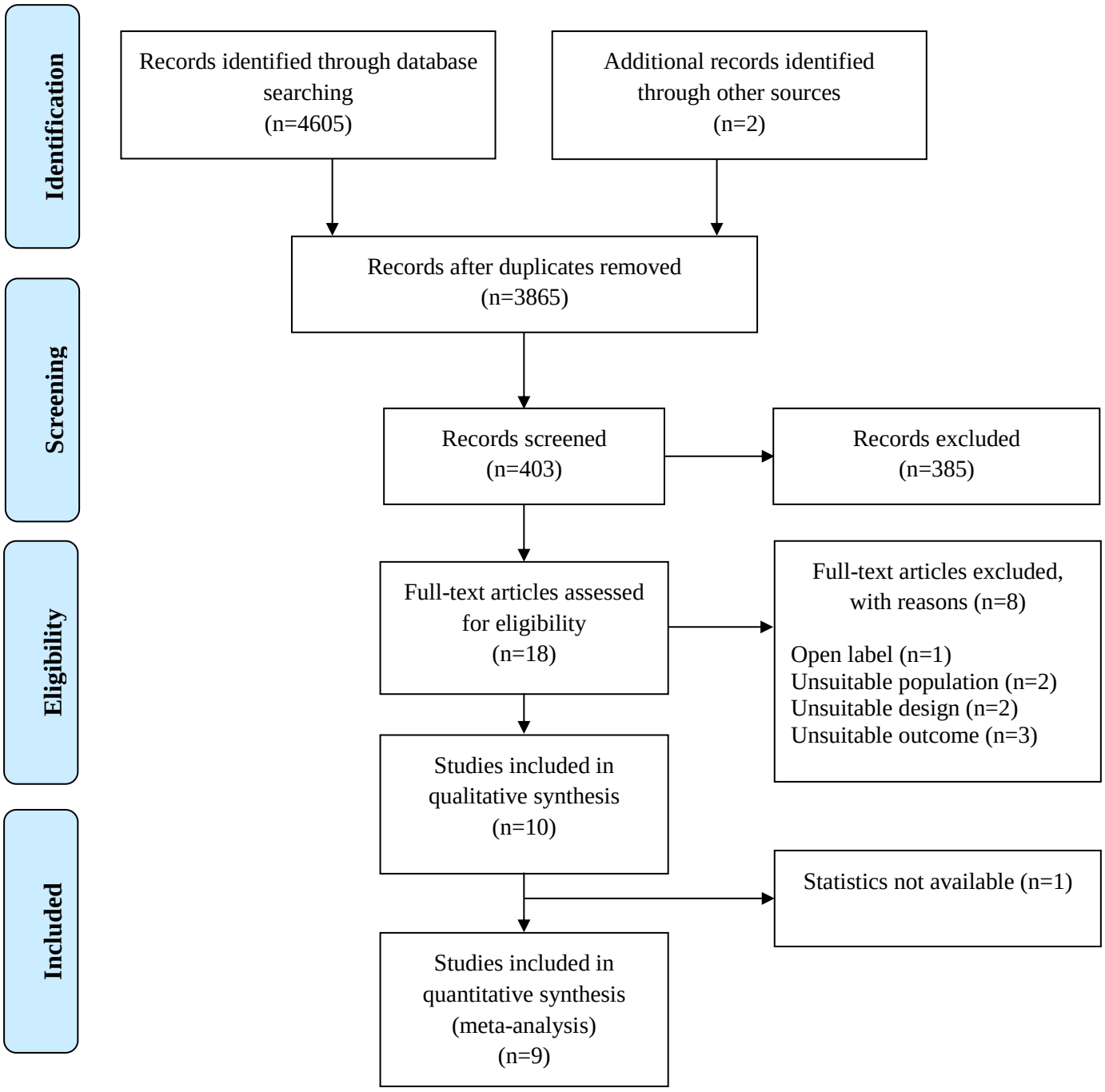


Fig 1. Prisma flow diagram.

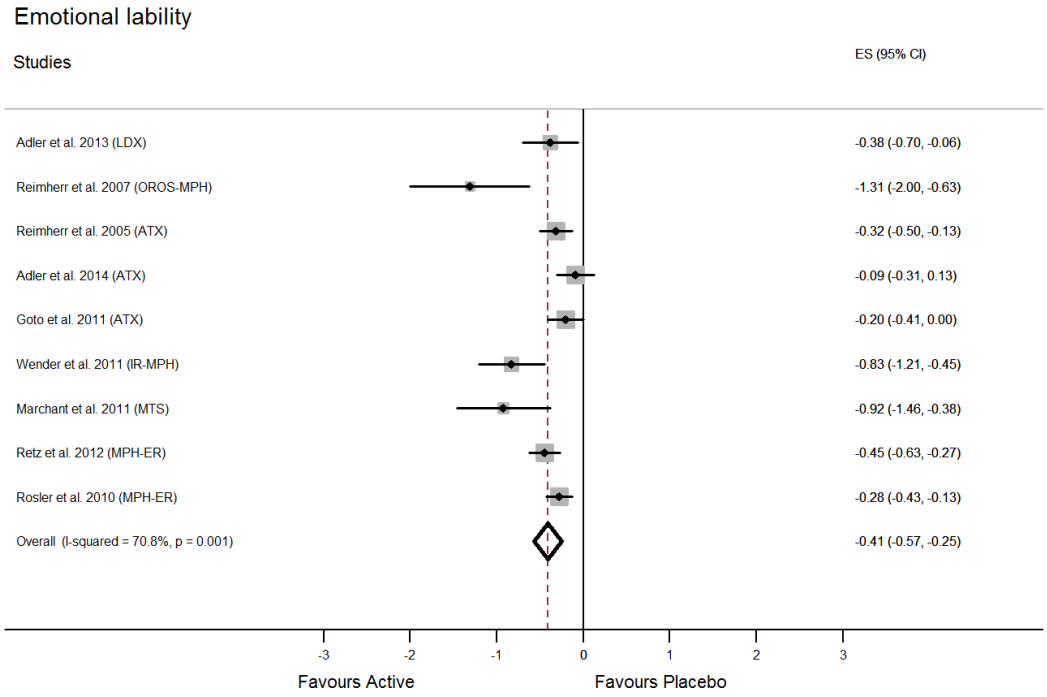
3.2 Quality and characteristics of studies included in qualitative synthesis

Nine studies were judged to be of sufficient quality and suitability to be included in the quantitative synthesis (see supplementary tables 2 and 3). Randomisation and allocation concealment were explicitly described in only one study.[29] In the remainders, this was absent or unclear. Means of blinding the participants, personnel and outcome assessment were unclear in seven studies, and were only clearly stated in three studies. In one study, 25.5% of the initially recruited participants dropped out prior to randomisation and another 12% following randomisation,[19] and in another study, four subjects were eliminated after randomisation,[30] raising concerns about the likelihood of selection bias. Study characteristics are outlined in supplementary table 5.

3.3 Quantitative meta-analysis

Main effects from the meta-analysis of the nine included studies are summarised in fig. 2. A detailed description of these results is available in appendix 2.

In adults with ADHD treatment with stimulants (OROS-methylphenidate, IR-methylphenidate, Lis-dexamphetamine, methylphenidate-ER, methylphenidate transdermal system) and atomoxetine had a moderate effect on EL (9 studies, SMD = -0.41; 95% CI: -0.57 to -0.25, z= 5.14, p= 2.7x10^{-7}) and a large effect on ADHD symptoms (9 studies, SMD= -0.8; 95% CI: -1.07 to -0.53, z= 5.85, p= 4.9x10^{-9}). There was evidence of high heterogeneity in both analyses (X^2= 27.40, I^2= 70.8%, p= 0.001; X^2= 72.09, I^2 = 88.9%, p < 0.001, respectively). There was no evidence of publication bias.



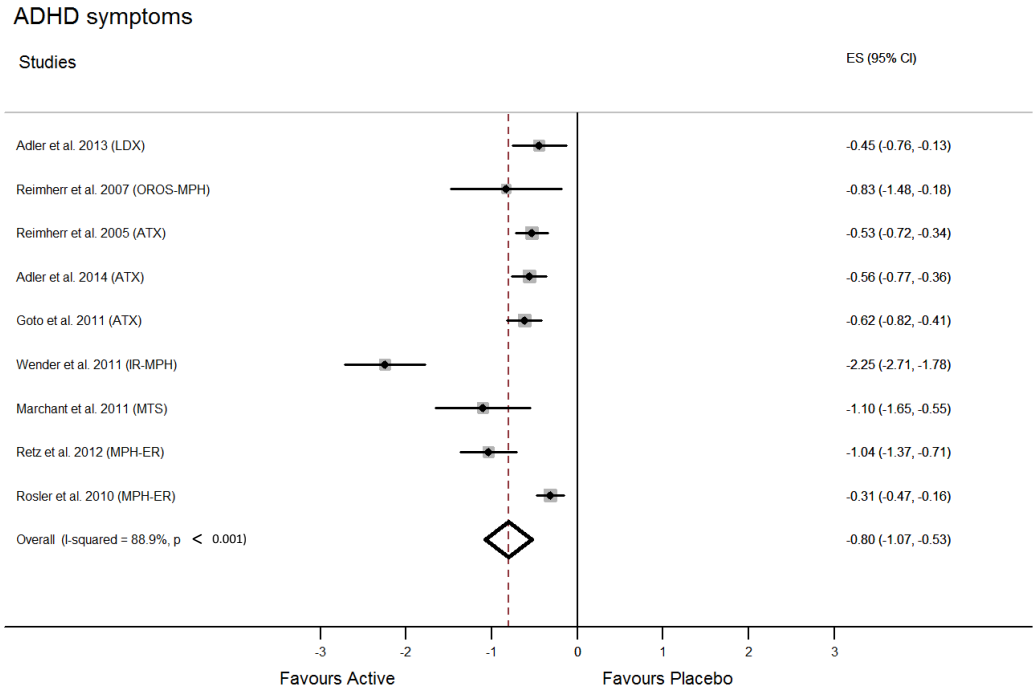


Fig 2. Forests plots for meta-analyses across the two main outcome domains ES= Effect size

3.4 Subgroup analysis

Main effects from the sub-group analyses are shown in table 8.

3.4.1 Outcome measure: In the subgroup analysis of studies using the WRAADDS-EDS as a measure of EL, a higher treatment effect was found for EL symptoms (6 studies, SMD= -0.54; 95% CI: -0.75 to -0.33, z= 5.02, p= $5.2x10^{-7}$), compared to the treatment effect of ADHD medication on EL measured by the BRIEF-A (3 studies, SMD= -0.19; 95% CI: -0.33 to -0.05, z= 2.66, p= 0.008).

3.4.2 Medication class: In the subgroup analysis of stimulants only, a higher effect size was found on EL symptoms (6 studies, SMD= -0.57; 95% CI: -0.80 to -0.34, z= 4.90, p= $9.6x10^{-7}$), compared to the small effect of atomoxetine on EL (3 studies, SMD= -0.21; 95% CI: -0.34 to -0.08, z= 3.25, p= 0.001).
We also looked at the effects of stimulants and atomoxetine on core ADHD symptoms. There was a large treatment effect of stimulants on core ADHD symptoms (6 studies, SMD= -0.98; 95 % CI: -1.51 to -0.44, z= 3.58, p= $3.4x10^{-4}$) and a moderate to large treatment effect of atomoxetine (3 studies, SMD= -0.57; 95% CI: -0.68 to -0.45, z= 9.76, p= $1.7x10^{-22}$).

3.4.3 Medication class and outcome measure: There was a large treatment effect of stimulants on EL symptoms when the latter was measured by the WRAADDS-EDS (5 studies, SMD= -0.64; 95% CI: -0.91 to -0.36, z= 4.46, p= $8.2x10^{-6}$).
Atomoxetine had a small effect on EL when this was measured by the BRIEF-A (2 studies, SMD= -0.15; 95% CI: -0.3 to 0, z= 1.97, p= 0.049).

Table 8

Subgroup meta-analyses of studies based on: (1) Outcome measure (2) medication class and (3) medication class and outcome measure

	Sub-analyses domain	Studies	*p*	SMD[2]	95% CI
1	WRAADDS-EDS	2,3,6-9	$5.2x10^{-7}$	-0.54	-0.75 to -0.33
	BRIEF-A-BRI	1,4,5	0.008	-0.19	-0.33 to -0.05
2	Stimulants on EL	1,2,6-9	$9.6x10^{-7}$	-0.57	-0.80 to -0.34
	Atomoxetine on EL	3-5	0.001	-0.21	-0.34 to -0.08
	Stimulants on ADHD	1,2,6-9	$3.4x10^{-4}$	-0.98	-1.51 to -0.44
	Atomoxetine on ADHD	3-5	$1.7x10^{-22}$	-0.57	-0.68 to -0.45
3	WRAADDS-EDS +Stimulants	2,6-9	$8.2x10^{-6}$	-0.64	-0.91 to -0.36
	BRIEF-A-BRI+Atomoxetine	4,5	0.049	-0.15	-0.3 to 0

Studies
1= Adler et al. (2013),[31] 2 = Reimherr et al. (2007),[30] 3 = Reimherr et al. (2005),[17] 4 = Adler et al. (2014),[29] 5 = Goto et al. (2011),[32] 6 = Wender et al. (2011),[33] 7 = Marchant et al. (2011),[19] 8 = Retz et al. (2012),[18] 9 = Rösler et al. (2010)[9]

[2] Negative SMD favours a treatment effect for the active medication (stimulants or atomoxetine); Positive SMD favours a treatment effect for the placebo group

4. DISCUSSION

We conducted a systematic review and meta-analysis examining the efficacy of stimulants (methylphenidate and dexamphetamine/lisdexamfetamine) and atomoxetine on EL in adults. In addition, we reported on the effects on ADHD symptoms in the same studies to enable a comparison of medication effects on ADHD and EL. Overall we found an effect of stimulants and atomoxetine of d=0.41 (CI: -0.57 to -0.25) for EL symptoms and d=0.8 (CI: -1.07 to -0.53) for ADHD symptoms. Our findings suggest that medications used to treat ADHD also have a significant effect on EL, although the effect appears to be more modest on EL compared to the effect on the core ADHD symptoms of inattention and hyperactivity-impulsivity.

Subgroup analyses indicated that use of the WRAADDS-EDS as an outcome measure might lead to greater estimates of clinical effectiveness of ADHD medications on EL than use of the BRIEF-A-BRI scale. Subgroup analyses also indicated that stimulants might have a stronger effect on reducing EL symptoms than atomoxetine. The greater effects of stimulants compared to atomoxetine on EL is in line with independent findings from meta-analyses of these medication on core ADHD symptoms.[34,35]
Consistent with this, the greatest effect on EL was found when analysing the subgroup of 5 studies which examined the effects of stimulants on EL measured by the WRAADDS-EDS (d=0.64). These findings suggests that the effect sizes on EL found in this meta-analysis may have been affected by measurement bias or differences in the effects of medication class (i.e. stimulants compared to atomoxetine).

In this meta-analysis stimulants and atomoxetine had a two-fold higher treatment effect on core ADHD than on EL symptoms. Nevertheless, the moderate treatment effect shows clinically significant improvement in the symptoms of EL. One study that was included in the qualitative but not the quantitative analysis also found a significant treatment effect of atomoxetine compared with placebo on EL. Patients receiving atomoxetine had a significant reduction of EL symptoms measured by the BRIEF-A self-rated and informant-rated scales.[36]

There were a number of limitations associated with this systematic review. First, despite adopting a broad approach towards the selection of studies, many did not meet the eligibility criteria and we were only able to include half of those assessed for eligibility (9 studies) in the meta-analysis. Secondly, there was substantial heterogeneity with regard to patient groups, assessment measures (including differecnes in informant versus self-report vs investigator-rated measures) and quality of studies and we therefore had to use random-effects models that produced wide confidence intervals. Thirdly, all the studies included in the meta-analysis relied on participants who were selected on the grounds of having high levels of core ADHD symptoms, not EL symptoms and this may have contributed to the differential effect sizes. No studies of stimulants or atomoxetine on EL symptoms were found for conditions other than ADHD, and none of the trials examined the effects of ADHD medication on EL as a primary outcome. Finally, none of the studies reported standard deviation of the change (the difference before and after the intervention) in their effect size calculations[26] and so we had to rely on the pre-treatment standard deviation in our calculations. This may also have contributed to an underestimation of the true effect size associated with EL.[37]
Another limitation was in relation to the different duration of the included trials that may have influenced the result on EL. Therefore a meta-regression of trial duration on both

ADHD and EL symptoms has been conducted. However, due to the small number of studies and heterogeneity of study characteristic, the results were inadequate.

In conclusion, our findings indicate that EL in patients with ADHD can be treated with stimulants or atomoxetine. Although these medications reduce EL, the effects appear to be modest by comparison with the effects on the core ADHD symptoms of inattention and hyperactivity-impulsivity. Our findings require replication, particularly in patients selected for high baseline levels of EL and addressing methodological issues such as measurement bias and the potential differential effects of stimulants and atomoxetine.

With regard to the clinical implications of our findings, there are two main possibilities to consider. First, that EL reflects a heterogeneous domain of psychopathology that results from a number of distinct processes requiring different treatments, much in the same way there are different causes for fever or headache. In this scenario it would be important to distinguish between stimulant and atomoxetine responsive and non-responsive forms of EL particularly in ADHD. An alternative explanation is that stimulants and atomoxetine may have a more modest effect on EL overall, perhaps indicating the need for additional targeted psychological treatments in some cases. For example, dialectical behaviour therapy has proven efficacy in the treatment of emotional instability in people with borderline personality disorder,[38] and may also have similar effects in ADHD accompanying pharmacological treatments.[39] Further investigations are required using individual patient level data to address these questions.

Finally, we did not find any studies of ADHD drug treatments in adult ADHD patients with comorbid conditions in which emotional symptoms are also prominent. Further studies are therefore required to clarify the role that stimulants or atomoxetine play in the treatment of EL in patients with ADHD and co-occurring conditions such as borderline personality disorder, or bipolar disorder. Notwithstanding, clinicians should be aware that symptoms of EL are often reduced when treating patients with stimluants or atomoxetine who meet diagnostic criteria for ADHD.

Contributors

TRM, PA and PM conceived the study; TRM, REC and EV conducted the literature search and statistical analysis. TRM, REC, PA and PM were involved in the selection of papers. TRM, REC, PA, PM and EV interpreted the data. The manuscript was drafted by TRM and thoroughly revised by PA, PM, EV and REC.

Declaration of interests

Philip Asherson, on behalf of King's College London (non-personal pecuniary funds), has served as consultant for Janssen-Cilag, Eli Lilly, Shire, Novartis and has received educational or research grants from or has spoken at sponsored talks from Janssen, GW Pharma, Vifor Pharma, and QbTech. Paul Moran has received funds for sponsored talks for Wiley. Talar Moukhtarian, Ruth Cooper and Evangelos Vassos declare no conflicts of interest.

Acknowledgements

We would like to thank Kate Williams, Dan Woodcock and Jessica Peixinho for their assistance with data extraction and proof reading.

Funding

This research was conducted at King’s College London and did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Polanczyk G, De Lima MS, Lessa Horta B, Biederman J, Rohde LA. The Worldwide Prevalence of ADHD: A Systematic Review and Metaregression Analysis. American Journal of Psychiatry. 2007;164(6):942-8.
2. Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Psychol Med. 2006;36(2):159-65.
3. Cheung CHM, Rijsdijk F, McLoughlin G, Brandeis D, Banaschewski T, Asherson P, et al. Cognitive and neurophysiological markers of ADHD persistence and remission. The British Journal of Psychiatry. 2016;208(6):548-55.
4. Fayyad J, De Graaf R, Kessler R, Alonso J, Angermeyer M, Demyttenaere K, et al. Cross–national prevalence and correlates of adult attention–deficit hyperactivity disorder. The British Journal of Psychiatry. 2007;190(5):402-9.
5. Posner J, Kass E, Hulvershorn L. Using stimulants to treat ADHD-related emotional lability. Curr Psychiatry Rep. 2014;16(10):478.
6. Association AP. Diagnostic and statistical manual of mental disorders. 5th edition ed. Arlington VA2013.
7. Skirrow C, Asherson P. Emotional lability, comorbidity and impairment in adults with attention-deficit hyperactivity disorder. J Affect Disord. 2013;147(1-3):80-6.
8. Barkley RA, Fischer M. The Unique Contribution of Emotional Impulsiveness to Impairment in Major Life Activities in Hyperactive Children as Adults. Journal of the American Academy of Child & Adolescent Psychiatry. 2010;49(5):503-13.
9. Rosler M, Retz W, Fischer R, Ose C, Alm B, Deckert J, et al. Twenty-four-week treatment with extended release methylphenidate improves emotional symptoms in adult ADHD. World J Biol Psychiatry. 2010;11(5):709-18.
10. Asherson P, Stes S, Nilsson Markhed M, Berggren L, Svanborg P, Kutzelnigg A, et al. The effects of atomoxetine on emotional control in adults with ADHD: An integrated analysis of multicenter studies. European Psychiatry. 2015;30(4):511-20.
11. Wender PH. Attention-Deficiti Hyperactivity Disorder in Adults. Psychiatr Clin North Am. 1998;21:761-74.
12. Wood DR, Reimherr FW, Wender PH, Johnson GE. Diagnosis and treatment of minimal brain dysfunction in adults: A preliminary report. Arch Gen Psychiatry. 1976;33:1453-60.
13. Asherson P, Buitelaar J, Faraone SV, Rohde LA. Adult attention-deficit hyperactivity disorder: key conceptual issues. The lancet Psychiatry. 2016;3(6):568-78.
14. Asherson P, Young AH, Eich-Hochli D, Moran P, Porsdal V, Deberdt W. Differential diagnosis, comorbidity, and treatment of attention-deficit/hyperactivity disorder in relation to bipolar disorder or borderline personality disorder in adults. Current medical research and opinion. 2014;30(8):1657-72.
15. Skirrow C, Hosang GM, Farmer AE, Asherson P. An update on the debated association between ADHD and bipolar disorder across the lifespan. J Affect Disord. 2012;141(2-3):143-59.
16. Skirrow C, McLoughlin G, Kuntsi J, Asherson P. Behavioral, neurocognitive and treatment overlap between attention-deficit/hyperactivity disorder and mood instability. Expert Review of Neurotherapeutics. 2009;9(4):489-503.
17. Reimherr FW, Marchant BK, Strong RE, Hedges DW, Adler L, Spencer TJ, et al. Emotional dysregulation in adult ADHD and response to atomoxetine. Biol Psychiatry. 2005;58(2):125-31.
18. Retz W, Rosler M, Ose C, Scherag A, Alm B, Philipsen A, et al. Multiscale assessment of treatment efficacy in adults with ADHD: a randomized placebo-controlled, multi-centre study with extended-release methylphenidate. World J Biol Psychiatry. 2012;13(1):48-59.
19. Marchant BK, Reimherr FW, Robison RJ, Olsen JL, Kondo DG. Methylphenidate transdermal system in adult ADHD and impact on emotional and oppositional symptoms. J Atten Disord. 2011;15(4):295-304.

20. Reimherr FW, Marchant BK, Gift TE, Steans TA, Wender PH. Types of adult attention-deficit hyperactivity disorder (ADHD): baseline characteristics, initial response, and long-term response to treatment with methylphenidate. Atten Defic Hyperact Disord. 2015;7(2):115-28.
21. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Journal of Clinical Epidemiology.62(10):1006-12.
22. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Hoboken: Wiley; 2008. Available from: http://kcl.eblib.com/patron/FullRecord.aspx?p=366838.
23. Roth RM, Isquith PK, Gioia GA. Behavior Rating Inventory of Executive Function–Adult Version (BRIEF-A). Parinc; 2000.
24. Conners CK, Erhardt D, Sparrow MA. Conners' Adult ADHD Rating Scales (CAARS). New York1999.
25. Corp S. Stata Statistical Software. Release 11 ed. College Station, TX: STATACorp LP 2009.
26. Morris SB. Estimating Effect Sizes From Pretest-Posttest-Control Group Designs. Organizational Research Methods. 2008;11(2):364-86.
27. Cohen J. A power primer. Psychological Bulletin. 1992;112(1):155-9.
28. Field AP, Gillett R. How to do a meta-analysis. British Journal of Mathematical and Statistical Psychology. 2010;63(3):665-94.
29. Adler LA, Clemow DB, Williams DW, Durell TM. Atomoxetine effects on executive function as measured by the BRIEF--a in young adults with ADHD: a randomized, double-blind, placebo-controlled study. PLoS One. 2014;9(8):e104175.
30. Reimherr FW, Williams ED, Strong RE, Mestas R, Soni P, Marchant BK. A double-blind, placebo-controlled, crossover study of Osmotic release oral system Methylphenidate in adults with ADHD with assessment of oppositional and emotional dimensions of the disorder. J Clin Psychiatry. 2007;68(1):93-101.
31. Adler LA, Dirks B, Deas PF, Raychaudhuri A, Dauphin MR, Lasser RA, et al. Lisdexamfetamine dimesylate in adults with attention-deficit/ hyperactivity disorder who report clinically significant impairment in executive function: results from a randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2013;74(7):694-702.
32. Goto T, Hirata Y, Takita Y, Trzepacz PT, Allen AJ, Song DH, et al. Efficacy and Safety of Atomoxetine Hydrochloride in Asian Adults With ADHD: A Multinational 10-Week Randomized Double-Blind Placebo-Controlled Asian Study. J Atten Disord. 2013.
33. Wender PH, Reimherr FW, Marchant BK, Sanford ME, Czajkowski LA, Tomb DA. A one year trial of methylphenidate in the treatment of ADHD. J Atten Disord. 2011;15(1):36-45.
34. Castells X, Ramos-Quiroga JA, Rigau D, Bosch R, Nogueira M, Vidal X, et al. Efficacy of Methylphenidate for Adults with Attention-Deficit Hyperactivity Disorder. CNS Drugs. 2011;25(2):157-69.
35. Cunill R, Castells X, Tobias A, Capellà D. Atomoxetine for attention deficit hyperactivity disorder in the adulthood: a meta-analysis and meta-regression. Pharmacoepidemiology and Drug Safety. 2013;22(9):961-9.
36. Adler LMD, Tanaka YP, Williams DM, Trzepacz PTMD, Goto TMDP, Allen AJMDP, et al. Executive Function in Adults With Attention-Deficit/Hyperactivity Disorder During Treatment With Atomoxetine in a Randomized, Placebo-Controlled, Withdrawal Study. Journal of Clinical Psychopharmacology. 2014;34(4):461-6.
37. Ortego C, Botella J. The hard but necessary task of gathering order-one effect size indices in meta-analysis. Psicológica. 2010;31(2):291-315.
38. Stoffers JM, Völlm BA, Rücker G, Timmer A, Huband N, Lieb K. Psychological therapies for people with borderline personality disorder. Cochrane Database of Systematic Reviews. 2012(8).
39. Philipsen A, Richter H, Peters J, Alm B, Sobanski E, Colla M, et al. Structured Group Psychotherapy in Adults With Attention Deficit Hyperactivity Disorder: Results of An Open Multicentre Study. The Journal of Nervous and Mental Disease. 2007;195(12):1013-9.

Appendix 1

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")

Table 2

Study quality appraisal (scored as low, high or unclear risk)

First Author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall risk	Other limitations
Reimherr et al. (2007)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	N/A	Unclear	No
Wender et al. (2011)	Low	Unclear	Low	Low	Low	Low	N/A	Unclear	No
Reimherr et al. (2005)	Unclear	Unclear	Unclear	Low	Low	Low	N/A	Unclear	No
Adler et al. (2013)	Unclear	Low	Low	Unclear	Low	Low	N/A	Unclear	No
Adler et al. (2014)	Low	Low	Low	Unclear	Low	Low	Low	Unclear	No
Rosler et al. (2010)	Unclear	Unclear	Unclear	Unclear	Low	Low	N/A	Unclear	No
Marchant et al. (2011)	Low	Unclear	Unclear	Unclear	Unclear	Low	N/A	Unclear	No
Goto et al. (2011)	Unclear	Unclear	Unclear	Unclear	Low	Low	N/A	Unclear	No
Retz et al. (2012)	Low	Unclear	Unclear	Unclear	Low	Low	N/A	Unclear	No

Table 3
Study quality appraisal

First Author	Reason if not low risk?	Other limitations
Reimherr et al. (2007)	Random sequence generation: Insufficient information Allocation concealment: Insufficient information Blinding of participants and personnel: Procedure unspecified Blinding of outcome: Procedure unspecified Incomplete outcome data: 6 drop-outs, reasons not stated	N/A
Wender et al. (2011)	Allocation concealment: Insufficient information	N/A
Reimherr et al. (2005)	Random sequence generation: Insufficient information Allocation concealment: Unspecified Blinding participants and personnel: Insufficient information	N/A
Adler et al. (2013)	Random sequence generation: Unspecified Blinding of outcome assessment: Unspecified	N/A
Adler et al. (2014)	Blinding of outcome assessment: Insufficient information	N/A
Rosler et al. (2010)	Random sequence generation: Randomised Allocation concealment: Insufficient information Blinding of participants: Double-blind Blinding of outcome assessment: Insufficient information.	N/A
Merchant et al. (2011)	Allocation concealment: Unspecified Blinding of participants and personnel: Unspecified Binding of outcome assessment: Unspecified Incomplete outcome data: High drop-out rate with no explanations	N/A
Goto et al. (2011)	Random sequence generation: Unspecified Allocation concealment: Unspecified Blinding of participants and personnel: Insufficient information. Blinding of outcome assessment: Unspecified	N/A
Retz et al. (2012)	Allocation concealment: Insufficient information Blinding of participants and personnel: Unspecified Binding of outcome assessment: Unspecified	N/A

Table 4

Detailed breakdown of behavioural rating scales included in the meta-analysis per study by the two outcome measures

First author	Domain(s) investigated	Rating scale	Measure included in meta-analysis[a]	Numbers in Analysis in FU	
				Active	Placebo
Reimherr et al. (2007)	Emotional lability	WRAADDS-EDS	Emotional lability	20	20
	ADHD symptoms	ADHD-RS	ADHD DSM-IV domains	20	20
Wender et al. (2011)	Emotional lability	WRAADDS-EDS	Emotional lability	58	57
	ADHD symptoms	WRAADDS	ADHD DSM-IV domains	58	57
Reimherr et al. (2005)	Emotional lability	WRAADDS-EDS	Emotional lability	225	226
	ADHD symptoms	CAARS- Investigator rated	ADHD DSM-IV domains	225	226
Adler et al. (2013)	Emotional control	BRIEF-A (BRI-emotional control subscale)- self-report	Emotional lability	79	75
	ADHD symptoms	CAARS- Informant rated	ADHD DSM-IV domains	79	80
Adler et al. (2014)	Emotional control	BRIEF-A (BRI-emotional control subscale)	Emotional lability	161	167
	ADHD symptoms	CAARS- Investigator rated	ADHD DSM-IV domains	192	199
Rösler et al. (2010)	Emotional lability	WRAADDS-EDS	Emotional lability	241	118
	ADHD symptoms	CAARS- Self report	ADHD DSM-IV domains	239	118
Marchant et al. (2011)	Emotional lability	WRAADDS-EDS	Emotional lability	26	33
	ADHD symptoms	CAARS- Investigator rated	ADHD DSM-IV domains	26	33
Goto et al. (2011)	Emotional control	BRIEF-A (BRI-emotional control subscale)- self-report	Emotional lability	178	190
	ADHD symptoms	CAARS- Investigator rated	ADHD DSM-IV domains	191	195
Retz et al. (2012)	Emotional lability	WRAADDS-EDS	Emotional lability	84	78
	ADHD symptoms	CAARS- Self report	ADHD DSM-IV domains	83	76

Note. BRIEF-A (BRI)= Behaviour Rating Inventory of Executive Function, behavioural regulation scales (Roth et al., 1996); WRAADDS= Wender-Reimherr Adult Attention Deficit Disorder Scale (Wender, 1995); CAARS= Conners' Adult ADHD Rating Scale (Conners, 1998); ADHD-RS= ADHD- Rating Scale

Table 5
Description of studies included in quantitative and qualitative synthesis

First Author Disorder Country	Mean age, years (% male) Meds	Supplements (dose/day)		Study duration	Design % completed	Domain(s) investigated	Numbers recruited	
		Active 1	Placebo				Active	Placebo
Reimherr et al. (2007) Clinical ADHD US	30.6 Mixed (66)	OROS- MPH (18/27-90mg)	Unspecified	4 weeks	RCT 87.24%	Emotional lability ADHD Symptoms	20 20	20 20
Wender et al. (2011) **ADHD** **USA**	36.9 (72.41) Unmedicated	Immediate release MPH 45 +/- 14mg day	Unspecified 49 +/- 13 mg/day	2 weeks	RCT 90.5%	Emotional lability ADHD symptoms	58 58	57 57
Reimherr et al. (2005) Clinical ADHD USA/Canada	41.2 (65) Unmedicated	ATX (60mg, 90mg, 120mg)	Unspecified	10 weeks	RCT 84.2%	Emotional lability ADHD symptoms	225 225	226 226
Adler et al. (2013) ADHD symptoms USA	34.2 (active) 34.9 (placebo) (50.6) Unmedicated	Lisdexamphetamine 30mg, 50mg, 70mg (titration)	Unspecified	10 weeks	RCT 78.5 %(active) 66.2% (placebo)	Emotional lability ADHD symptoms	79 79	75 80
Adler et al. (2014) Clinical ADHD USA	24.7 (57.30) Unmedicated	ATX 40mg/dayfor min 7 days (20mg BID), 80mg/day for min 7 days (40mg BID). Up to 100mg/ day (50mg BID) titration	Unspecified	12 weeks	RCT 79.73%	Emotional lability ADHD symptoms	161 192	167 199
Rosler et al. (2010) ADHD symptoms Germany	35.2 (active) 33.8 (placebo) (50) Unmedicated	MPH-ER 10-60mg/day	10mg capsules	24 weeks	RCT 30.64% (24% active group, 43% placebo group)	Emotional lability ADHD symptoms	241 239	118 118
Merchant et al. (2011) Clinical ADHD USA	18-65 years (unspecified but mixed) Unmedicated	MTS 22% 10-15mg, 28% 20-25mg, 50% 30mg	Unspecified	4 Weeks	RCT 86.5%	Emotional lability ADHD symptoms	26 26	33 33
Goto et al. (2011) ADHD Asia	32.3 (47.70) unmedicated	ATX 40-120mg/ once daily	Unspecified	10 weeks	RCT 79.49% ATX 87.25% Placebo	Emotional lability ADHD symptoms	178 191	190 195
Retz et al. (2012) Clinical ADHD Germany	36.6 (MPH), 38.2 (PL) (38- MPH), (56- PL) Unmedicated	MPH-ER 40,60,80,120 md/day	Unspecified	8 weeks	RCT 95.68%	Emotional lability ADHD symptoms	84 83	78 76

Table 6

Characteristics of studies included in qualitative synthesis

Characteristic	**Frequencies**
N (studies)	9
N (participants)	2,122
% Male[1]	57
Completion rate	77.8%
Medication	Unmedicated:8
	Unspecified: 1
	Weighted mean
Age (years)[2]	34.02
Trial duration (weeks)	8.9
MPH (daily dose)	Ranging from 10mg to 120mg/day
ATX (daily dose)	Ranging from 40mg to 120mg/day

1. One study did not specify sex ratio's and was therefore not included in this calculation (Marchant et al., 2011).

2. One study did not specify the mean age but only gave an age range of the participants eligible to take part in the trial, therefore not included in this calculation (Marchant et al., 2011).

Table 7
Studies excluded at full text stage with reasons (*n*=8)

Reason for exclusion	**Studies**
Open label	Sobanski et al. (2012)
Unsuitable population	Drijgers et al. (2012)
	Young et al. (2013)
Unsuitable design	Kavoussi et al. (1993)
	Du Paul et al. (2012)
Unsuitable outcome	Brown et al. (2011)
	Wender et al. (1985)
	Medori et al. (2008)
Statistics not available	Adler et al. (2014)

Appendix 2

Detailed description of meta-analyses results

Emotional lability

Nine trials in 2,036 adults with ADHD examined emotional lability. There was a moderate effect of stimulants and atomoxetine on EL (SMD= -0.41; 95% CI: -0.57 to -0.25, *z*= 5.14, *p*= $2.7x10^{-7}$) with evidence of significant high heterogeneity (X^2= 27.40, I^2= 70.8%, *p*= 0.001).

ADHD symptoms

Nine trials in 2,097 adults with ADHD examined combined ADHD symptoms. There was a large effect of stimulants and Atomoxetine on core ADHD symptoms (SMD= -0.8; 95% CI: -1.07 to -0.53, z= 5.85, p= $4.9x10^{-9}$) with evidence of high significant heterogeneity (X^2= 72.09, I^2 = 88.9%, *p* < 0.001).

Emotional lability (WRAADDS-EDS)

Six trials in 1,186 adults with ADHD examined EL using the emotion dysregulation subscale (EDS) of the WRAADDS. There was a medium effect of stimulants and ATX on EL (SMD= -0.54; 95% CI: -0.75 to -0.33, z= 5.02, *p*= $5.2x10^{-7}$) with evidence of significant heterogeneity (X^2= 18.78, I^2= 73.4%, *p*= 0.002).

Emotional lability (BRIEF-A-BRI, emotional control subscale)

Three trials in 850 adults with ADHD examined EL using the emotional control subscale of the BRIEF-A. There was a small significant effect of stimulants and ATX on EL (SMD= -0.19; 95% CI: -0.33 to -0.05, z= 2.66, *p*= 0.008) with no evidence of heterogeneity (X^2= 2.17, I^2= 7.9%, *p*= 0.337).

Emotional lability (Stimulants)

Six trials in 889 adults with ADHD examined effects of stimulants on EL. There was a medium to large effects of stimulant medication on EL (SMD= -0.57; 95% CI: -0.80 to -0.34, z= 4.90, p= $9.6x10^{-7}$), with evidence of heterogeneity (X^2= 17.76, I^2= 71.8%, *p*= 0.003).

Emotional lability (Atomoxetine)

Three trials in 1,147 adults with ADHD examined effects of Atomoxetine on EL. There was small significant effect of ATX on EL (SMD= -0.21; 95% CI: -0.34 to -0.08, z= 3.25, *p*= 0.001) with no evidence of heterogeneity (X^2= 2.42, I^2= 17.3%, *p*= 0.298).

ADHD symptoms (Stimulants)

Six trials in 889 adults with ADHD examined effects of stimulants on core ADHD symptoms. There was a large treatment effect of stimulants on ADHD symptoms (SMD= -0.98; 95% CI: -1.51 to -0.44, z= 3.58, *p*= $3.4x10^{-4}$), with evidence of significant heterogeneity (X^2= 71.47, I^2= 93%, *p* < 0.001).

ADHD symptoms (Atomoxetine)

Three trials in 1,228 adults with ADHD examined effects of Atomoxetine on core ADHD symptoms. There was a moderate to large treatment effect of ATX on ADHD symptoms (SMD= -0.57; 95% CI: -0.68 to -0.45, z= 9.76, *p*= $1.7x10^{-22}$) with no evidence of heterogeneity (X^2= 0.4, I^2= 0%, *p*= 0.817).

Emotional lability (WRAADDS-EDS+stimulants)

Five trials in735 adults examined the effects of stimulants on EL when measured by the WRAADDS-EDS. There was a large treatment effect of stimulants on EL (SMD= -0.64; 95% CI: -0.91 to -0.36, z= 4.46, *p*= $8.2x10^{-6}$) with evidence of significant heterogeneity (X^2= 17.66, I^2 = 77.4%, *p*= 0.001).

Emotional lability (BRIEF-A+Atomoxetine)

Two trials in 696 adults examined the effects of atomoxetine on EL when this was measured by the BRIEF-A-BRI. There was a small treatment effect of ATX on EL (SMD= -0.15; 95% CI: -0.3 to 0, z= 1.97, *p*= 0.049), with no evidence of heterogeneity (X^2= 0.56, I^2= 0%, *p*= 0.45).