Atomoxetine for attention deficit hyperactivity disorder in the adulthood: a meta-analysis and meta-regression

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ABSTRACT

Purpose Atomoxetine is a non-stimulant drug that could be an alternative to methylphenidate, whose benefit : risk balance for the treatment of adults with attention deficit hyperactivity disorder (ADHD) has recently been shown to be unclear. This study aimed to compare all-cause discontinuation rate between atomoxetine and placebo in adults with ADHD. Secondarily, efficacy and safety were investigated.

Methods Systematic review and meta-analysis of randomized controlled trials comparing atomoxetine with placebo in adults with ADHD were performed. All-cause treatment discontinuation was the primary endpoint. Efficacy in reducing ADHD symptoms and safety were the secondary endpoints. Odds ratio (OR) and the standardized mean difference (SMD) were calculated for dichotomous and continuous outcomes, respectively. Data were pooled using the fixed and random effects model. The influence of study design-related, intervention-related and patient-related co-variables over the primary endpoint was investigated by means of meta-regression. This study is registered with the international prospective register of systematic reviews (PROSPERO): CRD 42012002042.

Results Twelve studies (3375 patients) were included. Treatment discontinuation was larger with atomoxetine than with placebo (OR = 1.39). No co-variable was found to modify the effect of atomoxetine over treatment discontinuation. Atomoxetine showed modest efficacy in reducing ADHD symptoms irrespective of the assessor: patient (SMD = −0.33); clinician (SMD = −0.40). The rate of adverse events-induced discontinuation was higher with atomoxetine than with placebo (OR = 2.57).

Conclusion This study suggests that atomoxetine has a poor benefit–risk balance for the treatment of adults with ADHD. The recommendation of atomoxetine use in this population is weak. Copyright © 2013 John Wiley & Sons, Ltd.

KEY WORDS—attention deficit hyperactivity disorder; atomoxetine; discontinuation; efficacy; safety; meta-analysis; meta-regression; pharmacoepidemiology

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) in the adulthood has a prevalence of 2.5%–4%1–3 and significant clinical and psychosocial consequences, such as an increased risk of mood, anxiety and substance use disorders;4–5 fewer years of schooling; lower employment rates; more difficulties with family relationships and social interactions;6 and increased legal problems7 and car accidents8 than adults without ADHD. For these reasons, adult ADHD is considered to be a relevant health problem.

Various medications have been investigated for the treatment of adults with ADHD, including psychostimulants (e.g. methylphenidate and amphetamines) and non-stimulants (e.g. atomoxetine and alpha adrenergic agonists). Pharmacological treatment is frequently recommended as first-line treatment for adult ADHD because of its efficacy in reducing ADHD symptom severity.9–14 Nevertheless, the use of symptom improvement has been criticized because it is a subjective outcome that does not necessarily correlate with the clinical consequences.15,16 For this reason, hard objective endpoints such as traffic accidents, family, work or legal problems should be considered when investigating the efficacy of any intervention for ADHD. However, these types of endpoints are infrequently used, probably because they are not required by regulatory authorities to license drugs to treat adults with ADHD.17 Furthermore, the validity of ‘ADHD symptom improvement’ may be hampered by attrition
bias, which occurs because the patients dropping out from the study differ systematically between the study groups. Given the limitations of this efficacy endpoint, it is difficult to establish the benefit: risk balance of these medications. This difficulty can, in part, be overcome using the endpoint ‘all-cause treatment discontinuation’ because it is an objective endpoint that combines the evaluation of both efficacy and safety and has a straightforward interpretation. If symptomatic improvement outweighs medication-induced side effects, this is expected to result in a lower rate of treatment discontinuation than with placebo, suggesting a favourable benefit: risk balance. Furthermore, treatment discontinuation, by definition, is not affected by attrition bias. All cause-treatment discontinuation has been used to assess the benefit: risk balance of pharmacological interventions for the treatment of several psychiatric disorders.18–22

Despite the advantages of all-case treatment discontinuation, it is usually a secondary endpoint in most clinical trials, usually being ADHD symptom severity the primary endpoint. Accordingly, the sample size is calculated to demonstrate differences over this study endpoint between the studied interventions. This sample size is usually too small to find differences in treatment discontinuation. This statistical limitation can be overcome by pooling the results of the available data using meta-analytical techniques. We have recently applied this methodology to primarily compare all-cause treatment discontinuation rate between methylphenidate and placebo in adults with ADHD.23 In this study, we found that methylphenidate improved ADHD symptoms but showed no advantage over placebo in terms of treatment discontinuation and was associated with a higher proportion of patients dropping out as a result of adverse events (AEs). Indeed, some analyses pointed to a higher discontinuation rate with methylphenidate, suggesting that methylphenidate’s efficacy for reducing ADHD symptoms did not compensate for its side effects. In view of these findings, it is relevant to investigate other interventions for the treatment of adult ADHD.

Atomoxetine is a norepinephrine (NE) reuptake blocker, which has different behavioural effects to methylphenidate.24,25 By binding to the NE transporter, atomoxetine restores the catecholaminergic deficits that have been suggested to contribute to the pathophysiology of ADHD.26 This study aimed to compare all-cause treatment discontinuation between atomoxetine and placebo in adults with ADHD. Secondarily, we investigated atomoxetine’s efficacy in reducing ADHD symptoms, along with its safety.

METHODS

Design

Systematic review and meta-analysis (SRMA) of randomized placebo-controlled clinical trials (RPCCTs) comparing atomoxetine with placebo for adult ADHD were carried out. Studies that were not conducted in an outpatient setting were excluded, as were those with economic compensation for patient participation. In addition, those studies for which all-cause treatment discontinuation rate was not available were also excluded. No language restrictions were applied. The study was registered with the international prospective register of systematic reviews (PROSPERO): CRD 42012002042.

Procedures

The following databases were searched (the last search was performed on 1 June 2012): Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, psycINFO, www.clinicaltrialsregister.eu, and www.clinicaltrials.gov and www.lillytrials.com (Electronic Supplementary Material (ESM) Table 1 for search strategies). Abstracts of potentially relevant studies were inspected, and the full articles of those studies deemed to be suitable were acquired. The reference list of retrieved studies and relevant review articles27–30 and guidelines9–14 were examined to identify any further studies. Food and Drug Administration (FDA) approval packages31 for atomoxetine were inspected to look for unpublished studies.

Data extraction from the articles selected was performed independently by two reviewers (R.C., X.C.). Because the results of RPCCTs are often posted on Lillytrials.com and clinicaltrials.gov, these databases were also inspected for non-published information. Where relevant information was not available, study authors were e-mailed and missing information was requested.

The primary study outcome was all-cause treatment discontinuation, defined as the proportion of patients randomized who did not complete the study for any reason. Secondary outcomes were the following: (1) efficacy of atomoxetine for ADHD, defined as (a) self-rated baseline-to-endpoint change in ADHD symptom severity, (b) investigator-rated baseline-to-endpoint change in ADHD symptom severity and (c) proportion of responders; (2) proportion of patients who discontinued because of lack of efficacy (LOE); (3) proportion of patients who discontinued due to AEs; and (4) efficacy of atomoxetine on neuropsychological function. Intention to treat data was preferred to
per protocol. Finally, proportion of responders and the efficacy of atomoxetine on neuropsychological function were not analysed because only two studies reported these data.

The risk of bias was ascertained with the Cochrane Collaboration instrument, which is based on the description and suitability of seven domains, as follows: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other sources of bias. Some domains are assessed at study level (sequence generation, allocation concealment, selective outcome reporting and other sources of bias) and the remaining ones at outcome level (blinding, incomplete outcome data). This tool involves assigning a judgement relating to the risk of bias for each entry in terms of ‘low’, ‘high’ or ‘unclear’ risk.

Statistical analysis

Odds ratios (OR) were calculated for binary outcomes and standardized mean differences (SMD) for continuous outcomes. To combine parallel group with crossover studies, only the first phase of crossover trials was included in the meta-analysis. Heterogeneity between studies was assessed using the Cochran’s Q-test for homogeneity, jointly with the $I^2$ index to establish the percentage of variation in the combined estimate that could be attributed to Between-study heterogeneity ($<25%$: low heterogeneity, 25% to 50%: moderate; 50% to 75%: high, $>75%$: very high). The study-specific estimates were pooled using both the fixed and random effects models by means of the inverse variance method. A post-hoc cumulative meta-analysis was performed for the primary outcome to display the pattern of evidence over time. Publication bias was evaluated using the funnel plot together with the Begg’s test.

Subgroup analyses for the primary outcome were performed for the following characteristics: (1) treatment duration; (2) dose regimen; (3) inclusion of patients with a specific comorbid diagnosis; (4) lead-in phase; and (5) recruitment of participants by advertisement. Specific-stratum ORs for each characteristic were calculated from subgroup meta-analysis, and comparison between each subgroup was performed using random-effects meta-regression.

Sensitivity analyses of the primary outcome were performed as follows: (1) repeating the analysis with the inclusion of patients who took at least one dose of treatment instead of all randomized ones and (2) excluding those studies for which at least one domain that could affect the primary outcome was rated as having ‘high risk of bias’ by means of the Cochrane instrument. Statistical analyses were performed using Stata statistical software, (version 12; StataCorp, College Station, TX, 2012) by using the metan and metareg commands.

RESULTS

Description of studies

Twelve studies were included (ESM Figure 1 for flow diagram), which randomized 3375 patients—1796 of them to atomoxetine and 1579 to placebo. A description of the studies’ characteristics can be found in ESM Table 2. All studies but one had a parallel-group design. Two studies (described together in the same article) used a pre-randomization placebo lead-in phase, which lasted 2 weeks. All the studies were sponsored by the pharmaceutical industry and were carried out in the USA, two of them with additional participation from Canada and Puerto Rico. ADHD diagnosis was performed using DSM-IV/DSM-IV TR diagnostic criteria in all studies but one, which used DSM-III-R criteria. The presence of a comorbid disorder was an inclusion criterion in three studies, as follows: marijuana dependence ($n=78$), alcohol abuse/dependence ($n=147$) and social anxiety ($n=442$). The mean age of patients was 36.5 years, and 57.2% of them were men.

Atomoxetine was administered in equal doses twice daily in six studies ($n=822$) and once daily in four ($n=631$). In two studies ($n=343$), atomoxetine was administered either once or twice daily. Mean atomoxetine dose was 87.5 mg/day. Treatment length ranged from 3 to 26 weeks (weighted mean = 17 weeks). No study specified if psychotherapy for ADHD was provided.

No study was deemed to be free of bias in all Cochrane tool domains (ESM Figure 2), mainly because the treatment discontinuation rate was rather high in most studies, yielding the possibility of attrition bias, except for the outcome ‘all-cause treatment discontinuation’, which is not affected by this bias. Additionally, the possibility of blinding failure was judged to be likely because atomoxetine has been associated with a constellation of behavioural effects that may reveal the assigned intervention. Two studies were scored as high risk of bias in one domain. The study by McRae et al. was deemed to be at risk of biased results because patients’ baseline ADHD severity was different between the atomoxetine and placebo groups. The study by Young et al. was judged to have a high risk of selection bias because a randomization error occurred, leading to unbalanced groups at baseline.
These two studies were subsequently withdrawn from one of the sensitivity analyses.

All-cause treatment discontinuation

Almost 50% of patients (865 out of 1796) treated with atomoxetine discontinued treatment, being the discontinuation rate higher with atomoxetine than with placebo (OR = 1.39 [1.17, 1.64]) (Figure 1). Statistical heterogeneity was low ($I^2 = 20.8\%$), and no differences between subgroups were found (ESM table 3). Cumulative meta-analysis showed that higher all-cause treatment discontinuation with atomoxetine became evident after the fourth study, which was published in 2008 (Figure 2).

Sensitivity analyses including patients who took at least one dose of treatment (OR = 1.37 [1.16, 1.62]) and excluding those studies rated as having ‘high risk of bias’ (OR = 1.33 [1.10, 1.61]) yielded similar results to the main analysis.

Efficacy and safety

Atomoxetine was more efficacious than placebo in reducing ADHD symptom severity irrespective of the assessor being the patient (SMD = −0.33 [−0.43, −0.23], $I^2 = 0\%$) (Figure 3) or clinician (SMD = −0.40 [−0.48, −0.32], $I^2 = 0\%$) (Figure 4). This improvement in ADHD symptoms with atomoxetine was found to be modest.

Few patients discontinued because of LOE in both study arms (5% with atomoxetine and 6% with placebo). Still, the proportion of patients who discontinued because of LOE was slightly lower with atomoxetine (OR = 0.73 [0.53, 0.99], $I^2 = 0\%$) (Figure 5). Conversely, dropping out due to AEs was rather frequent (13% vs 5%), and the rate of patients who discontinued for this reason was clearly higher with atomoxetine than with placebo (OR = 2.57 [1.78, 3.71], $I^2 = 34.1\%$) (Figure 6).

Publication bias analysis

No publication bias was detected using the Begg’s test ($p = 0.640$). Neither did the funnel plot (ESM Figure 3) show asymmetries, providing no evidence for publication bias.

DISCUSSION

In this SRMA, we found that all-cause treatment discontinuation was higher with atomoxetine than with placebo in adults with ADHD. Furthermore, although atomoxetine was efficacious in reducing the severity of ADHD symptoms, the effect size was modest when assessed either by clinicians (SMD = −0.40) or patients (SMD = −0.33). When symptom improvement is small, it is likely that the efficacy does not compensate for the side effects, leading patients to discontinue medication. In support of this hypothesis, we found that whilst atomoxetine was associated with slightly lower LOE-induced discontinuation than placebo, the proportion of patients who discontinued because of AEs was
clearly larger amongst those treated with atomoxetine. Overall, these results suggest that atomoxetine has a poor benefit: risk balance.

Atomoxetine was the first non-stimulant drug approved by the FDA and the EMA to treat children and adolescents with ADHD. It was also the first drug approved by the FDA to treat adults with ADHD and by the EMA to treat adults with ADHD who initiated atomoxetine before the age of 18 years. It is usually recommended as second-line pharmacologic treatment for adults with ADHD. From the results of our study, the recommendation to use atomoxetine to treat adults with ADHD should be considered weak. This opinion might be more favourable to the drug if, despite its low efficacy in reducing ADHD symptoms and its negative results with regard to treatment discontinuation, atomoxetine had been shown to improve objective clinically meaningful outcomes such as...
as work, legal or family problems. However, to our knowledge, no controlled clinical trial has investigated this issue.

It is likely that for some groups of patients or under certain circumstances, atomoxetine is associated with lower treatment discontinuation than placebo. The meta-regression analysis examined the influence of study design, intervention-related variables and patients’ characteristics over the primary endpoint and found no between-group differences, indicating that the effect of atomoxetine on treatment discontinuation is consistent across the subgroups pre-specified. It must be noted that the statistical heterogeneity was small, lowering the possibility of identifying the effect of any co-variables on this endpoint. Furthermore, meta-regression analysis is an indirect methodology for investigating the influence of co-variables. Therefore, these findings should be confirmed in the future.
The results of this SRMA highlight the need not to rely excessively on subjective endpoints such as symptom improvement. Objective clinically meaningful endpoints should be preferred. In the absence of these endpoints, all-cause treatment discontinuation can be a useful endpoint with which to appraise the benefit: risk balance of interventions for ADHD. However, regulatory agencies such as the EMA require the demonstration of efficacy on ADHD symptoms as the primary endpoint in regulatory trials. The sample sizes of clinical trials are, therefore, calculated to accomplish this objective. This results in a lack of statistical power to rule out the possibility of a negative outcome on all-cause treatment discontinuation. For this reason, it was not until the fourth published study that it was evident that atomoxetine was associated with greater treatment discontinuation than placebo. Future studies should have enough statistical power to detect clinically important differences concerning this endpoint.

Study limitations are closely related to the quality of the included studies. Our study warns of the difficulty of carrying out clinical trials that are free of the risk of bias when atomoxetine is investigated. Two potential sources of bias were identified. The first was blinding failure, which may yield performance and detection bias. This can happen when medications with powerful behavioural effects are compared with placebo. The possibility of blinding failure highlights the importance of using objective outcomes to hinder the influence of detection bias instead of relying on subjective outcomes. The second potential source of bias was attrition bias. Most studies had high discontinuation rates making attrition bias rather likely, except for all-cause treatment discontinuation, which is not affected by this bias.

The external validity of this study may be limited by the fact that all clinical trials were carried out in North America. However, it is unlikely that the results of studies conducted in other regions of the world would differ substantially from those conducted in North America. Indeed, the results of clinical trials comparing methylphenidate with placebo in adults with ADHD in the USA and in the EU were similar.23 The study length of most clinical trials was short, and the long-term efficacy of atomoxetine is, therefore, unknown. Although it must be stressed that, on average, clinical trials investigating atomoxetine treatment in adults with ADHD was longer (17 weeks) than those of methylphenidate (10 weeks) or amphetamine derivatives (8 weeks).53

Reporting bias can threaten the validity of any meta-analysis. However, we found no evidence of reporting bias in this study as shown by the fact that the funnel plot was symmetrical and the Begg’s test provided no evidence of small study effects.
Strengths must also be highlighted. This is the first study to compare treatment discontinuation between atomoxetine and placebo using meta-analytical techniques. A large number of patients were included. No other medicine has been investigated in such a large sample of adults with ADHD. This provides us with considerable statistical power, enabling the calculation of reasonably precise effect estimates. In addition to this, statistical heterogeneity was low in all analyses performed, as shown by the small $I^2$ index in all analyses and the almost identical results obtained when the meta-analysis was performed using a fixed effect or random effects model. Unlike methylphenidate or amphetamine derivatives, which have been studied in a wide range of doses using numerous distinct pharmaceutical formulations, atomoxetine has a unique formulation, and the dose studied was similar in all studies. This may have helped to obtain results with considerable homogeneity. For the reasons listed earlier, it is unlikely that further research would substantially change the results of this study.

In conclusion, this SRMA found that atomoxetine shows a higher discontinuation rate than placebo, probably because its low efficacy in reducing ADHD does not compensate for its side effects, providing weak support for the use of atomoxetine to treat adults with ADHD. These results, added to those of our previous study, stress that ‘all-cause treatment discontinuation’ can be a useful endpoint for assessing pharmacological interventions for ADHD in adulthood.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

ESM Table 1. Bibliographic search syntax that was used in the following datasets: PubMed, CENTRAL, PsycINFO, clinicaltrials.gov and clinicaltrialsregister.eu and Lillytrials.com.

ESM Table 2. Characteristics of studies included in the SRMA.

ESM Table 3. Subgroup-analysis of the effect of dose regimen, treatment length, comorbidity as inclusion criterion, lead-in phase and type of recruitment on the effect of atomoxetine on treatment discontinuation.

ESM Figure 1. Flow chart for selection of studies.

ESM Figure 2. Risk of bias summary review. The risk of selection, performance, detection, attrition, reporting and other biases is appraised for each study using the Cochrane risk of bias instrument. Green indicates “low”, yellow “unclear” and red “high” risk of bias.

ESM Figure 3. Funnel plot of the effect of atomoxetine on all-cause treatment discontinuation in adults with attention deficit disorder.

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