Safety and tolerability of atomoxetine in treatment of attention deficit hyperactivity disorder in adult patients: An integrated analysis of 15 clinical trials

Angelo Camporeale¹, Vibeke Porsdal², Katrien De Bruyckere³, Yoko Tanaka⁴, Himanshu Upadhyaya⁴, Claudia Deix⁵ and Walter Deberdt³

Abstract
The safety profile of atomoxetine in the treatment of attention deficit hyperactivity disorder has been studied in many clinical trials. We performed an integrated safety analysis of 15 clinical trials in adults with attention deficit hyperactivity disorder. The analysis pooled patient data into three groups: acute placebo-controlled trials; long-term placebo-controlled trials; all trials. In total, 4829 adults (18–77 years, median: 36 years) were exposed to atomoxetine. Statistically significantly more atomoxetine-treated than placebo-treated patients experienced treatment-emergent adverse events (81.3% vs. 68.3% acute; 90.6% vs. 76.8% long term) and discontinued due to adverse events (8.9% vs. 4.0% acute; 17.9% vs. 6.3% long term). No statistically significant differences were observed in the proportion of patients experiencing serious adverse events. No previously unknown adverse events were identified. The most common adverse events included nausea, dry mouth, decreased appetite, insomnia and erectile dysfunction. Mean increases in heart rate (+5.2 beats per min) and blood pressure (systolic +2 mmHg, diastolic +1.9 mmHg) were modest. The proportion of patients experiencing clinically significant increases in blood pressure and heart rate at any time was statistically significantly higher with atomoxetine (systolic blood pressure 13–17%, diastolic blood pressure 37–40%, heart rate 42–43%) compared to placebo (systolic blood pressure 8–13%, diastolic blood pressure 29–34%, heart rate 21–26%). There was no increased risk of suicidal ideation or behaviour. Our findings confirm atomoxetine’s known safety profile. From a safety perspective, atomoxetine is a useful treatment option for adults with attention deficit hyperactivity disorder.

Keywords
Atomoxetine, safety, attention deficit hyperactivity disorder, adult, integrated analysis

Background
Attention deficit hyperactivity disorder (ADHD) is widely recognized as a psychiatric disorder in childhood and adolescence, potentially related to genetic factors (Faraone et al., 2005) and it has become more widely recognized that ADHD frequently persists into adulthood (Asherson, 2005; Faraone et al., 2006; Wender et al., 2001).

Current estimates suggest that ADHD may affect 4.4% of the adult population in the USA (Faraone et al., 2005; Kessler et al., 2006); estimates for European countries range from 1.0% to 7.3%, depending on diagnostic criteria (Bitter et al., 2010; Fayyad et al., 2007; Kooij et al., 2005; Simon et al., 2009) and the worldwide prevalence in adults is estimated to be 3.4% (Fayyad et al., 2007).

ADHD in adults is often associated with comorbid psychiatric disorders, such as mood and anxiety disorders, or substance abuse (Fayyad et al., 2007; Kessler et al., 2006). Furthermore, adult patients with ADHD tend to suffer from major socioeconomic and functional impairment (Sobanski et al., 2007), as well as diminished quality of life (Able et al., 2007; Biederman and Faraone, 2006; de Graaf et al., 2008).

Treatment guidelines for adult ADHD (Kooij et al., 2010; NICE, 2008) recommend a multimodal approach. A comprehensive treatment programme should include both pharmacological and non-pharmacological interventions, addressing psychological, behavioural, educational and occupational needs. Pharmacological treatment includes stimulant and non-stimulant options. Stimulants (such as methylphenidate) act primarily by enhancing the neurotransmission of dopamine and, to a lesser extent, norepinephrine (Biederman and Spencer, 2008). Atomoxetine is a non-stimulant and a potent and selective inhibitor of the presynaptic noradrenaline transporter. Preclinical data suggest that atomoxetine has minimal affinity for either the serotonin or dopamine transporters or other neurotransmitter receptors (Bymaster et al., 2002). However,
Overall group (N=4892) & 15 trials & • Atomoxetine & • Atomoxetine (n=926): 85.6 mg/day, 163 days.

Table 1. Analysis groups.

<table>
<thead>
<tr>
<th>Analysis groups</th>
<th>Number of trials included</th>
<th>Treatment group(s)</th>
<th>Drug exposure, mean dose of atomoxetine and duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute controlled group (N=932)</td>
<td>6 trials</td>
<td>• Atomoxetine</td>
<td>• Atomoxetine (n=926): 85.6 mg/day, 163 days.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Placebo</td>
<td>• Placebo (n=931): 73 days.</td>
</tr>
<tr>
<td>Long-term controlled group (N=765)</td>
<td>3 trials</td>
<td>• Atomoxetine</td>
<td>• Atomoxetine (n=765): 84.3 mg/day 127 days.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Placebo</td>
<td>• Placebo (n=617): 133 days.</td>
</tr>
</tbody>
</table>

N: number of patients in analysis set; n: number of enrolled patients who received at least one dose of study drug.

in the forebrain of the rat, dopaminergic levels are also increased by atomoxetine (Bymaster et al., 2002), perhaps because of non-specific reuptake of dopamine by the noradrenaline transporter in that brain region (Carboni et al., 1990). Atomoxetine does not increase dopamine, either in the striatum or in the nucleus accumbens in rats (Bymaster et al., 2002). In contrast to methylphenidate, the pharmacological profile of atomoxetine indicates that it is less likely to have drug abuse potential. Drug abuse liability studies have provided evidence that atomoxetine is unlikely to be abused (Bymaster et al., 2002; Carboni et al., 1990; Heil et al., 2002; Jasinski et al., 2008; Upadhyaya et al., 2013a; Wee and Woolverton, 2004). Thus, atomoxetine is pharmacologically distinct from stimulants.

The efficacy of atomoxetine for ADHD in adults has been consistently demonstrated in various clinical trials, including six placebo-controlled short-term trials of 10–16 weeks duration, three placebo-controlled 6-month trials and one long-term maintenance of response trial of 1 year duration (Adler et al., 2008, 2009a, 2009b; Durell et al., 2013; Hirata et al., 2012; Michelson et al., 2003; Upadhyaya et al., 2013b; Wilens et al., 2008; Young et al., 2011).

Atomoxetine is metabolized by the cytochrome P450 2D6 (CYP2D6) pathway. Approximately 7% of Caucasians have a genotypic corresponding to a non-functional CYP2D6 enzyme (called CYP2D6 poor metabolizers). Patients with this genotype have a higher exposure to atomoxetine when compared to patients with a functional enzyme. Poor metabolizers are therefore potentially at higher risk of adverse events (AEs). For patients with a known poor metabolizer genotype or for patients who are concomitantly receiving CYP2D6 inhibitors (selective serotonin-reuptake inhibitors (e.g. fluoxetine, paroxetine), quinidine, terbinafine), a lower starting dose and slower up titration of the dose may be considered.

To be able to assess the clinical value of atomoxetine for ADHD in adults, a comprehensive understanding of its efficacy and safety profiles is required. While the efficacy of atomoxetine for ADHD in the adult patient population is discussed elsewhere (see references above), the objective of this paper is to provide a comprehensive assessment of the safety and tolerability of atomoxetine for treatment of adult patients with ADHD. This is of particular interest as the indication of atomoxetine for adult patients with ADHD has recently been granted in the European Union and other countries worldwide. The potential association between medications approved for treating patients with ADHD and the risk of serious cardiovascular problems is still being investigated (Martinez-Raga et al. 2013; Olsson et al. 2012), and recent guidance on the management of the most common AEs during treatment with ADHD medications in children and adolescents has been published (Cortese et al. 2013). However, an overview of all safety data including cardiovascular parameters and their relevance in adult patients for this drug – as presented in this paper – has not yet been published and will improve the current knowledge on atomoxetine’s safety in adults and help physicians make informed decisions in their clinical practice.

Methods

In the present analysis, 15 trials were included, all sponsored by Eli Lilly, studying atomoxetine in adult patients (≥18 years) with a diagnosis of ADHD (see Table 1 in Supplementary Material).

Trial designs

Six of the 15 trials were acute, double-blind trials evaluating acute efficacy as primary end-point and safety as secondary, with durations between 10 and 16 weeks. Two of these acute trials included a comorbid condition (alcohol abuse and social anxiety disorder). Three of the 15 trials were long-term, evaluating long-term efficacy as primary end-point and safety as secondary; they included double-blind phases and had durations of at least 6 months. In addition, there was one long-term maintenance of response trial evaluating efficacy as primary end-point and safety as secondary, with a duration of up to 49 weeks (data from a subsequent 2 year extension study were not included here because the extension study had not been completed at the time of this analysis). Safety was also evaluated in four open-label trials ranging in duration from 8 weeks to nearly 4.5 years and in another double-blind trial comparing two atomoxetine dose regimens.

Patients

Inclusion criteria. All 15 trials required patients to have ADHD as defined by Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) or 4th edition, text revision (DSM-IV-TR) as assessed through a structured diagnostic interview, such as the Conners’ Adult ADHD Diagnostic Interview for DSM-IV. Patients were required to have ADHD symptoms or overall illness disturbance of at least moderate severity across all trials (e.g. at least four on the Clinical Global Impressions-Severity scale).

Two trials were designed to compare atomoxetine and placebo with regard to relapse to alcohol abuse or worsening of anxiety, therefore one trial required patients to have comorbid alcohol abuse problems (Wilens et al., 2008) and the other required patients to have comorbid social anxiety disorder (Adler et al., 2009a).
Address the overall safety profile. In addition, results specifically related to safety and tolerability in the comorbid conditions are presented as single-trial results.

### Exclusion criteria

All trials used a core set of exclusion criteria, of which most were intended to ensure patient safety and minimize risk in a research setting. Patients with serious acute medical conditions were generally excluded, as were patients with a history of a seizure disorder, patients with uncontrolled hypertension and patients at serious risk for suicide. Women who were pregnant or breastfeeding were also generally excluded. A number of medications were grounds for exclusion, including primarily medications with psychoactive effects that could confound efficacy analyses (e.g. antidepressants or antipsychotics) and medications that could have unwanted pharmacodynamic or other interactions with atomoxetine, such as additive sympathomimetic effects. Patients with relevant psychiatric disorders such as bipolar or psychotic disorder were generally excluded. Most trials (except for the Adler and colleagues trial (Adler et al., 2009a)) excluded patients who met DSM-IV diagnostic criteria for current major depression or a current anxiety disorder (including generalized anxiety disorder, panic disorder and social phobia).

### Statistical analyses

An integrated analysis of individual patient-level data (or pooled analysis) was performed. An integrated analysis can be viewed as a meta-analysis of individual patient-level data as opposed to trial-level summary data used in meta-analyses. This allows investigation of patient characteristics using within-subgroup analyses that were not part of the original trial analyses.

### Analysis groups

As detailed in Table 1, three analysis groups were established:

- The ‘acute controlled group’ comprising all six acute, double-blind, placebo-controlled trials with a length of 10–16 weeks.
- The ‘long-term controlled group’ comprising all three long-term, double-blind, placebo-controlled trials with 6 months duration.
- The ‘overall group’ comprising all 15 trials (i.e. the trials in the two above groups and six other trials with varying durations, from 7 months up to nearly 4.5 years).

### Single-trial results for safety in comorbid conditions

Safety data from the two trials in patients with comorbid anxiety and comorbid alcohol abuse were part of the integrated analysis to address the overall safety profile. In addition, results specifically related to safety and tolerability in the comorbid conditions are presented as single-trial results.

### Safety measures

Treatment-emergent AEs (TEAEs) were collected as spontaneously reported (i.e. no solicited reporting using check-lists of potential AEs) at each study visit. Vital signs were measured according to the procedures specified in the respective study protocols.

All analyses were done on the safety population (i.e. all enrolled patients receiving at least one dose of atomoxetine as study drug). The following analyses were performed on the overall group: duration of exposure; modal dose by geographic region; demographics, disposition; AEs; laboratory tests; vital signs and weight; electrocardiogram (ECG). Subgroup analyses (age, gender, ethnic origin, dose regimen and CYP2D6 genotype) were conducted for atomoxetine exposure, TEAEs, serious AEs (SAEs), AEs leading to discontinuation, laboratory analyses, vital signs and weight, and ECG parameters.

For the analysis of continuous measures, unless otherwise specified, when an analysis of variance (ANOVA) model was used, it contained the main effects of treatment and trial. An analysis of covariance model consists of the terms used in the ANOVA with baseline added as a covariate. The last observation carried forward method was used for these analyses.

Within treatment group comparisons were conducted using the Wilcoxon signed-rank test.

For categorical/frequency data, the significance of overall treatment group differences was assessed using Fisher’s exact test.

Clinically significant criteria for diastolic blood pressure (DBP), systolic blood pressure (SBP), heart rate (HR) and weight are defined as shown in Table 2. The criteria for blood pressure (BP) and HR in Table 2 were chosen for our analyses because, although from an individual patient management perspective it is appropriate to consider values of ≥140/90 mmHg for BP and ≥100 for HR, when determining in clinical trials the occurrence of an adverse phenomenon whose measurement is subject to significant random variability (such as an increase in BP or HR), it is advisable to use a threshold or reference limit that will improve specificity for a given number of patients and incur fewer false positives.

Suicide-related events were analysed using the Mantel–Haenszel incidence difference test, stratified by trial and Mantel–Haenszel risk ratio.

Regarding first occurrence and persistence of TEAEs, a TEAE was considered to be a persistent occurrence at a time-point if it first occurred prior to the time-point and was not yet resolved. For each time-point, patients who had not discontinued the trial prior to
to the time-point were included. For male sexual events, time to event analysis was conducted using Kaplan–Meier estimates. Between-treatment comparison was tested using Wilcoxon’s test.

**Results**

**Patient characteristics**

A total of 4829 adult patients from the 15 source studies, exposed to atomoxetine for a mean of 163 days and 2152 patient-years of exposure, were included.

In general, demographic characteristics of patients across the trials were comparable; however, there were differences for a few trials (for example, one trial only included patients aged 18–30 years; two trials that included patients with comorbidities). Key demographic information (age, gender, sample size) is listed in Table 3. Overall, the majority of atomoxetine-treated patients were white (79.1%) and male (57.7%); mean age was 35.6 years.

The majority of atomoxetine-treated patients were CYP2D6 extensive metabolizers (94.7%) and were classified as combined ADHD subtype (69.1%).

**Patient disposition**

Discontinuation rates (due to any reason, lost to follow-up and AE) for all three analysis groups are presented in Table 4. Overall, 747 atomoxetine-treated patients (15.3%) discontinued because of an AE. Nausea (n=107, 2.2%) was the most frequently reported TEAE as a reason for discontinuation, followed by erectile dysfunction (ED; n=40, 1.4%), fatigue (n=33, 0.7%) and insomnia (n=28, 0.6%). Two AEs leading to discontinuation were considered serious and likely to be related to study drug by the investigators: one event in the acute placebo-controlled group (diverticulitis); one event in the long-term placebo-controlled group (atrial fibrillation). Both of these cases recovered from these events.
The median duration of exposure in the acute controlled group was 74 days in the atomoxetine (N=932) and 75 days in the placebo (N=943) group. In the long-term controlled group, the median duration of exposure was 147 days in the atomoxetine (N=765) and 159 days in the placebo (N=617) group.

Adverse events

In both the acute and long-term controlled groups, statistically significantly more atomoxetine-treated patients than placebo-treated patients experienced at least one TEAE (81.3% vs. 68.3%, p<0.001 for acute; 90.6% vs. 76.8%, p<0.001 for long term). In the overall group, the most frequent TEAEs of atomoxetine-treated patients were nausea (26.7%), dry mouth (18.4%), headache (16.3%), decreased appetite (14.9%), insomnia (11.3%) and fatigue (10.8%). An overview of common TEAEs (defined as with a frequency ≥5%) in all three analysis groups is given in Table 5. Overall, all of the common TEAEs (with the exception of nasopharyngitis) occurred more frequently during the initial acute treatment with atomoxetine (within the first 5 weeks), with few new reports occurring during long-term treatment. Most of the TEAEs showed the pattern of persistence seen for nausea: the events were reported early and tended to resolve fairly consistently during ongoing atomoxetine treatment (see Figure 1).

Subgroup analysis of adverse events

Analyses of TEAEs by subgroups were performed on the overall group to determine whether a particular subgroup experienced differences when treated with atomoxetine.

Table 4. Patient disposition.

<table>
<thead>
<tr>
<th></th>
<th>Acute controlled group</th>
<th></th>
<th>Long-term controlled group</th>
<th></th>
<th>Overall group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atomoxetine</td>
<td>Placebo</td>
<td>p-value</td>
<td>Atomoxetine</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>N=932 n (%)</td>
<td>N=943 n (%)</td>
<td>N=765 n (%)</td>
<td>N=617 n (%)</td>
<td>N=4892 n (%)</td>
</tr>
<tr>
<td>Discontinued due to any reason</td>
<td>318 (34.1)</td>
<td>262 (27.8)</td>
<td>.003</td>
<td>448 (58.6)</td>
<td>303 (49.1)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>102 (10.9)</td>
<td>96 (10.2)</td>
<td>.600</td>
<td>99 (12.9)</td>
<td>75 (12.2)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>83 (8.9)</td>
<td>38 (4.0)</td>
<td>&lt;.001</td>
<td>137 (17.9)</td>
<td>39 (6.3)</td>
</tr>
</tbody>
</table>

N: number of enrolled patients who received at least one dose of study drug; n (%): number/percentage of patients in each category.

Table 5. Overview of TEAEs with a frequency ≥5% in atomoxetine, all analysis groups.

<table>
<thead>
<tr>
<th>System organ class preferred term</th>
<th>Acute controlled group</th>
<th></th>
<th>Long-term controlled group</th>
<th></th>
<th>Overall group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atomoxetine</td>
<td>Placebo</td>
<td>p-value</td>
<td>Atomoxetine</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(N=932) n (%)</td>
<td>(N=943) n (%)</td>
<td>N=765 n (%)</td>
<td>N=617 n (%)</td>
<td>N=4892 n (%)</td>
</tr>
<tr>
<td>Patients with ≥1 TEAE</td>
<td>758 (81.3)</td>
<td>644 (68.3)</td>
<td>&lt;.001</td>
<td>693 (90.6)</td>
<td>474 (76.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>194 (20.8)</td>
<td>46 (4.9)</td>
<td>&lt;.001</td>
<td>249 (32.5)</td>
<td>47 (7.6)</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>137 (14.7)</td>
<td>37 (3.9)</td>
<td>&lt;.001</td>
<td>195 (25.5)</td>
<td>40 (6.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>119 (12.8)</td>
<td>107 (11.3)</td>
<td>.357</td>
<td>124 (16.2)</td>
<td>121 (19.6)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>134 (14.4)</td>
<td>26 (2.8)</td>
<td>&lt;.001</td>
<td>140 (18.3)</td>
<td>22 (3.6)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>97 (10.4)</td>
<td>50 (5.3)</td>
<td>&lt;.001</td>
<td>88 (11.5)</td>
<td>40 (6.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>57 (6.1)</td>
<td>39 (4.1)</td>
<td>&lt;.001</td>
<td>109 (14.2)</td>
<td>47 (7.6)</td>
</tr>
<tr>
<td>Erectile dysfunction*</td>
<td>37 (6.8)</td>
<td>4 (0.7)</td>
<td>&lt;.001</td>
<td>38 (9.5)</td>
<td>5 (1.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>61 (6.5)</td>
<td>16 (1.7)</td>
<td>&lt;.001</td>
<td>68 (8.9)</td>
<td>31 (5.0)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>58 (6.2)</td>
<td>68 (7.2)</td>
<td>.408</td>
<td>31 (4.1)</td>
<td>45 (7.3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>70 (7.5)</td>
<td>25 (2.7)</td>
<td>&lt;.001</td>
<td>57 (7.5)</td>
<td>18 (2.9)</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>32 (3.4)</td>
<td>7 (0.7)</td>
<td>&lt;.001</td>
<td>35 (4.6)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>56 (6.0)</td>
<td>40 (4.2)</td>
<td>&lt;.001</td>
<td>49 (6.4)</td>
<td>21 (3.4)</td>
</tr>
<tr>
<td>Irritability</td>
<td>35 (3.8)</td>
<td>22 (2.3)</td>
<td>.081</td>
<td>50 (6.5)</td>
<td>31 (5.0)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>39 (4.2)</td>
<td>61 (6.5)</td>
<td>.031</td>
<td>44 (5.8)</td>
<td>37 (6.0)</td>
</tr>
<tr>
<td>Urinary hesitation</td>
<td>22 (2.4)</td>
<td>2 (0.2)</td>
<td>&lt;.001</td>
<td>49 (6.4)</td>
<td>6 (1.0)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>35 (3.8)</td>
<td>21 (2.2)</td>
<td>.058</td>
<td>42 (5.5)</td>
<td>15 (2.4)</td>
</tr>
<tr>
<td>Ejaculation disorder*</td>
<td>6 (1.1)</td>
<td>2 (0.4)</td>
<td>.175</td>
<td>20 (5.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

N: number of enrolled patients who received at least one dose of study drug; n (%): number/percentage of patients in each category; TEAE: treatment-emergent adverse event.

*Event for males.

aN=545 (atomoxetine), N=553 (placebo).
bN=398 (atomoxetine), N=316 (placebo).
cN=2820 (atomoxetine).
Many of the common TEAEs were comparable or only slightly different in frequency among age, gender, once-daily (q.d.) or twice-daily (b.i.d.) dosing, and poor vs. extensive metabolizer subgroups. However, the following differences were noted: dry mouth (26.4% vs. 12.7%), constipation (12.3% vs. 4.1%) and ED (18.6% vs. 5.1%) were more than twice as likely in older patients (≥51 years) than in younger patients (18–30 years). The frequencies of nausea and dry mouth observed in females were notably higher than in males (33.4% vs. 21.7% and 22.6% vs. 15.2%, respectively). Dry mouth (34.5% vs. 17.4%), ED (20.9% vs. 8.9%) and hyperhidrosis (14.8% vs. 6.8%) were more than twice as likely to be reported in poor metabolizers relative to extensive metabolizers. Comparing q.d. and b.i.d. dosing showed that nausea was more than twice as likely to be reported in patients receiving atomoxetine q.d. (33.8%) compared to b.i.d. (16.7%). Somnolence was nearly twice as likely to be reported in patients receiving atomoxetine q.d. (8.8%) compared to b.i.d. (4.5%). On the other hand, insomnia was more frequently reported with b.i.d. (17.0%) than with q.d. (9.5%). Among the 13 most common AEs, six TEAEs were numerically higher in b.i.d. patients compared with seven in q.d. patients; therefore, no specific pattern was identified when comparing dose regimens.

**Serious adverse events**

In both the acute and long-term controlled groups, no statistically significant differences in the proportion of patients experiencing SAEs were observed between patients receiving atomoxetine and those receiving placebo (0.8% vs. 0.7% for acute, 0.5% vs. 1.3% for long term). No single event was predominant and the events did not fit into a pattern and did not suggest systemic drug toxicity.

Overall, 81 atomoxetine-treated patients (1.7%) experienced at least one SAE, with some patients experiencing more than one SAE. Among all reported SAEs, 12 events were considered likely to be related to study drug by the investigators. Of these, the outcome for seven events were reported as recovered following atomoxetine discontinuation (atrial fibrillation, restlessness, alcohol abuse, bradykinesia, haemorrhage, auditory hallucination, and diverticulitis), one was reported as recovering/resolving (palpitations), three were reported as not recovered (suicidal ideation, paresthesia, and palpitations) and one was reported as unknown (headache).

In all 15 trials, one death (suspected myocardial infarction) was reported. It occurred in the long-term maintenance of response trial (Upadhyaya et al., 2013b) in a 38-year-old male patient, 220 days after the initiation of atomoxetine treatment. The investigator was unable to assess the relatedness between this event and blinded study drug. The patient had very minor above-normal limits values at baseline for creatine phosphokinase and cholesterol, and pre-existing partial right bundle branch block. The patient had normal BP and HR at the beginning and throughout the trial. No conclusions could be drawn regarding possible causality.

**Laboratory**

In the acute treatment group, atomoxetine-treated patients experienced statistically significant mean changes in the following laboratory tests compared with placebo-treated patients: increased platelet count (+6.34 vs. –1.51); increased alkaline phosphatase (AP) (+0.84 vs. –1.74); decreased chloride (–0.61 vs. –0.03); less decreased albumin (–0.66 vs. –1.05); decreased uric acid (–2.44 vs. –5.84); increased prolactin (+2.68 vs. +0.42). In the long-term treatment group, statistically significant differences for increased monocytes (+0.01 vs. +0.03), decreased chloride (–1.01 vs. –0.66), and decreased uric acid (–2.20 vs. –8.69) were found. The changes and rates of treatment-emergent abnormal values were small and not clinically relevant and these differences in the laboratory data do not appear to be representative of systemic drug toxicities or of safety issues. These findings are consistent with laboratory value findings in paediatric trials with atomoxetine, which similarly were not clinically relevant.

**Weight**

As expected from the known safety profile of atomoxetine and its pharmacology, mean decreases in weight were observed in atomoxetine-treated patients (overall −1.01 kg). In both the acute
and the long-term controlled groups, the proportion of atomoxetine-treated patients experiencing significant weight loss (≥7%) at any time post-baseline was statistically significantly greater compared to placebo-treated patients (5.6% vs. 0.9% for acute; 10.0% vs. 3.3% for long term). In the long-term treatment analysis (patients from the overall group who received atomoxetine for at least 1 year, N=269), approximately one-third of patients experienced a significant weight loss. However, the stratified analysis of weight and body mass index (BMI) showed that on average they were overweight at baseline (BMI 27.6) and that those who experienced significant weight loss during treatment were actually heavier at baseline (BMI 29.8) than those who did not (BMI 26.6).

**Safety measures of special interest**

**Cardiovascular events and parameters.** In the acute controlled group, palpitations (2.9% vs. 1.0%, p=0.002), tachycardia (1.3% vs. 0.3%, p=0.020) and HR increased (2.0% vs. 0.2%, p<0.001) were reported statistically significantly more often in atomoxetine-treated patients compared to placebo. In the long-term controlled group, HR increased was the only AE reported statistically significantly more in atomoxetine-treated patients compared to placebo (2.1% vs. 0.%, p=0.001).

The continuous analysis of mean baseline-to-end-point changes in SBP, DBP and HR showed that they were statistically significantly greater in atomoxetine-treated patients compared to placebo in both the acute and long-term controlled groups (see Table 6). To assess cardiovascular parameters in patients with a higher age, the mean changes for the 51–65 year old atomoxetine patients (N=268) in the overall atomoxetine group were SBP +3.90 mmHg, DBP +3.18 mmHg and HR +5.31 beats per minute (bpm). The respective values for patients of all age groups in the overall atomoxetine group were: SBP: +1.96 mmHg; DBP: +1.87 mmHg; HR: +5.23 bpm.

In order to analyse the pattern during treatment, mean changes over time were also calculated for the overall group, with patients with at least 1 year of atomoxetine treatment being included in the analysis. Mean baseline SBP (N=308, 118.1 mmHg, SD=11.0), DBP (N=308, 75.9 mmHg, SD=8.7) and HR (N=229, 73.4 bpm, SD=9.6) started to increase early after treatment initiation up to 3–6 months and then remained substantially stable for up to 12 months, with slight further increases for DBP and SBP in the long-term period of more than 12 months.

In both the acute and long-term controlled groups, the categorical analysis of the clinically significant criteria as defined in Table 2 did not show statistically significant differences between atomoxetine and placebo for the three haemodynamic parameters. Also, no statistically significant differences compared to placebo were observed in the proportion of atomoxetine-treated patients exceeding clinically significant absolute value limits for SBP (160 mmHg), DBP (100 mmHg) and HR (120 bpm). However, the proportion of patients exceeding the clinically significant change from baseline at any time was statistically significantly different compared to placebo (Table 6). Of the overall atomoxetine group patients of 51–65 years of age, 2.6% (7/268) showed clinically significant higher SBP, 4.9% clinically significant higher DBP and no patient showed a clinically significant change in HR. The respective values for patients of all age groups in the overall atomoxetine group were: SBP: 1.2%; DBP: 2.9%; HR: 0.3%.

With regard to ECGs, for the data-derived QTc correction method (QTcD), proportions of atomoxetine-treated patients with important prolongation did not statistically significantly differ between atomoxetine and placebo groups in either the acute or long-term controlled groups. Overall, assessment of mean (SD) change in QTcD of atomoxetine-treated patients showed statistically significant increases from baseline (1.92 msec (15.55), p<0.001), but the resulting mean QTcD interval value remained within normal limits (404.51 (19.30) msec at baseline, 406.43 (18.37) msec at end-point).

In both the acute and long-term controlled groups, mean changes in cardiac- and vascular-related laboratory values were minimal and not considered clinically meaningful.

**Hepatic safety.** In both the acute and long-term controlled groups, mean changes in hepatic-related laboratory values were minimal and not considered clinically meaningful. In the acute controlled group, there were statistically significant differences in mean changes in alkaline phosphatase (ALP) (+0.88 vs. –1.74, p<0.001) and albumin (–0.66 vs. –1.05, p=0.003) when comparing atomoxetine-treated patients to placebo. Mean changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and total bilirubin showed no statistically significant differences between atomoxetine and placebo groups. In the long-term controlled group, mean changes in ALT, AST, GGT, ALP, total bilirubin and albumin showed no statistically significant differences between atomoxetine and placebo groups.

In terms of hepatic-related TEAEs, no statistically significant differences between treatment and placebo groups were found in controlled trials. Overall, in all trials, a total of 28 hepatic-related TEAEs were reported for atomoxetine-treated patients. Of these, three events were serious (one case reported alcoholic hepatitis in a patient with a history of heavy alcohol binges several times per year, and two cases reported cholelithiasis and biliary dyskinesia, with resultant cholelithotomy and cholecystectomy, respectively). All three cases recovered, had normal laboratory values and were considered not related to study drug. The remaining 25 events were non-serious and mild to moderate in severity. Most of them represented increases in hepatic-related laboratory values with no associated hepatic-related TEAEs.

**Aggression and hostility.** In both the acute and long-term controlled groups, few aggression- and hostility-related TEAEs were reported. Six events were reported in acute trials: four in atomoxetine-treated patients (all anger); two in placebo patients (aggression and anger). Four events were reported in long-term trials: two in atomoxetine-treated patients (both anger); two in placebo patients (both aggression). No statistically significant differences between atomoxetine and placebo groups were observed. In the overall group, the incidence of aggression- and hostility-related TEAEs in atomoxetine-treated patients reported was low, with a total of 16 patients (0.3%) reporting aggression, 17 (0.3%) reporting anger, one reporting disinhibition, one reporting disturbance in social behaviour and one reporting violence-related symptoms.

A risk ratio (relative risk) analysis of aggression related terms in both the acute and long-term controlled groups has shown that aggression/hostility events, although not statistically different, are reported more frequently in the atomoxetine than in the placebo arm (risk ratio of 1.38 (95% confidence interval (CI): 0.39, 4.88; p=0.756)).
Suicidal or self-injurious behaviour. In general, patients at serious suicidal risk were excluded from the trials. A meta-analysis for unsolicited suicide-related events in all placebo-controlled trials of ADHD in adults using the combined FDA codes of 1–6 and 9 (Gassmann-Mayer et al., 2011), which involve all events related to either suicide-related ideation and/or possible suicide-related behaviours, identified four events meeting criteria for suicidal behaviour or ideation (categories 1–4), two in atomoxetine-treated patients and two in placebo-treated patients. The risk ratio (Mantel–Haenszel) was 0.96 (95% CI; 0.24, 3.79; p = 0.953) and the incidence difference (Mantel–Haenszel) was −0.01 (95% CI; −0.27, 0.26; p = 0.967) when the atomoxetine-treated group was compared with the placebo-treated group.

In addition, AEs potentially related to suicidality were analysed. Irritability was reported in the long-term placebo-controlled ADHD analysis by 6.5% patients in the atomoxetine and 5.0% in the placebo group (Fisher’s exact test; p = 0.251). Two patients (0.3%) in the atomoxetine group discontinued due to irritability vs. five patients (0.8%) in the placebo group (Mantel–Haenszel test; p = 0.253). In the acute analysis, 3.8% of the patients in the atomoxetine group and 2.3% in the placebo group reported irritability (Fisher’s exact test; p = 0.081). Two patients discontinued in the atomoxetine and none in the placebo group (Fisher’s exact test; p = 0.247).

Depression was reported in the long-term placebo-controlled ADHD analysis by 1.2% patients in the atomoxetine group vs. 1.8% in the placebo group (Fisher’s exact test; p = 0.373).

<table>
<thead>
<tr>
<th>Vital sign</th>
<th>Acute controlled group</th>
<th>Long-term controlled group</th>
<th>Overall group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ATX mean (SD) Placebo mean (SD) p-value</td>
<td>ATX mean (SD) Placebo mean (SD) p-value</td>
<td>ATX mean (SD)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td><strong>N</strong> Baseline 117.7 (11.65) 118.0 (12.11) –</td>
<td><strong>N</strong> End-point 119.6 (11.82) 118.0 (12.40) –</td>
<td><strong>N</strong> Change to end-point 1.86 (10.22) −0.02 (10.28) &lt;.001</td>
</tr>
<tr>
<td></td>
<td>907 919</td>
<td>760 612</td>
<td>4727</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td><strong>N</strong> Baseline 74.6 (8.93) 74.5 (8.71) –</td>
<td><strong>N</strong> End-point 76.6 (9.51) 74.7 (10.21) –</td>
<td><strong>N</strong> Change to end-point 2.00 (8.65) 0.01 (10.02) &lt;.001</td>
</tr>
<tr>
<td></td>
<td>907 919</td>
<td>760 612</td>
<td>4727</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td><strong>N</strong> Baseline 73.1 (10.53) 72.7 (10.28) –</td>
<td><strong>N</strong> End-point 78.6 (11.98) 72.7 (10.21) –</td>
<td><strong>N</strong> Change to end-point 5.50 (11.78) 0.01 (10.02) &lt;.001</td>
</tr>
<tr>
<td></td>
<td>907 919</td>
<td>760 612</td>
<td>4727</td>
</tr>
</tbody>
</table>

**Table 6.** Blood pressure and heart rate values at baseline and endpoint, relative changes and % patients with clinically relevant changes.

<table>
<thead>
<tr>
<th>Vital sign</th>
<th>ATX %</th>
<th>Placebo %</th>
<th>p-value</th>
<th>ATX %</th>
<th>Placebo %</th>
<th>p-value</th>
<th>ATX %</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP Absolute and change limits at any time (160 mmHg and 20 mmHg)*</td>
<td>0.33</td>
<td>0.33</td>
<td>1.000</td>
<td>0.79</td>
<td>0.65</td>
<td>1.000</td>
<td>1.16</td>
</tr>
<tr>
<td>Absolute value limit at any time (160 mmHg)*</td>
<td>0.33</td>
<td>0.44</td>
<td>1.000</td>
<td>0.92</td>
<td>0.82</td>
<td>1.000</td>
<td>1.25</td>
</tr>
<tr>
<td>Change limit at any time (20 mm Hg)*</td>
<td>13.45</td>
<td>7.83</td>
<td>&lt;.001</td>
<td>16.58</td>
<td>13.07</td>
<td>.08</td>
<td>16.52</td>
</tr>
<tr>
<td>DBP*</td>
<td>1.76</td>
<td>0.87</td>
<td>.103</td>
<td>1.45</td>
<td>1.14</td>
<td>.812</td>
<td>2.94</td>
</tr>
<tr>
<td>Absolute and change limits at any time (100 mm Hg and 10 mmHg)*</td>
<td>1.87</td>
<td>0.98</td>
<td>.117</td>
<td>1.84</td>
<td>1.47</td>
<td>.675</td>
<td>3.28</td>
</tr>
<tr>
<td>Absolute value limit at any time (100 mmHg)*</td>
<td>37.38</td>
<td>28.62</td>
<td>&lt;.001</td>
<td>39.87</td>
<td>33.99</td>
<td>.028</td>
<td>41.80</td>
</tr>
<tr>
<td>Change limit at any time (10 mm Hg)*</td>
<td>0.11</td>
<td>0.11</td>
<td>1.000</td>
<td>0.00</td>
<td>0.00</td>
<td>–</td>
<td>0.34</td>
</tr>
<tr>
<td>HR Absolute and change limits at any time (120 bpm and 15 bpm)</td>
<td>0.33</td>
<td>0.11</td>
<td>.371</td>
<td>0.13</td>
<td>0.00</td>
<td>1.000</td>
<td>0.44</td>
</tr>
<tr>
<td>Absolute value limit at any time (120 bpm)</td>
<td>41.68</td>
<td>21.00</td>
<td>&lt;.001</td>
<td>43.03</td>
<td>26.47</td>
<td>&lt;.001</td>
<td>46.78</td>
</tr>
</tbody>
</table>

**ATX**: atomoxetine; **bpm**: beats per minute; **DBP**: diastolic blood pressure; **HR**: heart rate; **N**: number of patients with a baseline and at least one post-baseline result; **SBP**: systolic blood pressure.

*A cut-off of 160/100 mm Hg SBP/DBP was chosen as these values correspond to the 95 percentile of blood pressure (BP) observed in population-based studies and avoids reporting false positive values of high BP.*
Depression was given as a reason for discontinuation in the long-term placebo-controlled ADHD analysis for three patients (0.4%) in the atomoxetine group and for two patients (0.3%) in the placebo group (Fisher’s exact test; p=1.00). In the acute analysis, 1.3% of the patients in the atomoxetine group and 1.2% in the placebo group reported depression (Fisher’s exact test; p=0.837). No patient discontinued due to depression in the acute analysis.

Mood swings were reported in the long-term placebo-controlled ADHD analysis by 0.8% of the patients in the atomoxetine group vs. 0.3% of the patients in the placebo group (Fisher’s exact test; p=0.301). Mood swings were given as a reason for discontinuation for two patients (0.3%) in the atomoxetine group and for one patient (0.2%) in the placebo group (Fisher’s exact test; p=1.00). In the acute analysis, 0.3% of the patients in the atomoxetine group and 0.1% in the placebo group reported mood swings (Fisher’s exact test; p=0.372). No patient discontinued due to mood swings in the acute analysis.

These findings show that the risk of suicidal behaviour or ideation and other events potentially related to suicidality observed in adult patients treated with atomoxetine was not statistically significantly different from placebo.

Male sexual side effects. In the acute controlled group, among all male sexual dysfunction TEAEs included in the Medical Dictionary for Regulatory Activities high-level terms (erection and ejaculation conditions and disorders, orgasmic disorders and disturbances, reproductive tract disorders not elsewhere classified (NEC) (excluding neoplasms), sexual arousal disorders, sexual desire disorders, sexual function and fertility disorders NEC), ED was the only TEAE reported statistically significantly more frequently in atomoxetine-treated patients compared to placebo (6.8% vs. 0.7%, p<0.001). In the long-term controlled group, ejaculation disorder (5.0% vs. 0.0%, p<0.001), ejaculation delayed (2.3% vs. 0.0%, p=0.006) and ED (9.5% vs. 1.6%, p<0.001) were statistically significantly more frequent in atomoxetine patients.

A post hoc analysis of data from the long-term controlled group shows that more atomoxetine- than placebo-treated patients experienced male sexual dysfunction TEAEs (ejaculation disorder, ED, orgasm abnormal, male genital pain, priapism, ejaculation failure, libido decreased) (9.3% vs. 1.8%). However, there was no statistically significant difference in time to onset between atomoxetine and placebo groups, with most analysed events having onset in the first 1 to 2 months of treatment in both the atomoxetine and placebo groups (means of 20 days for atomoxetine and 27 for placebo; medians of 11 and 18). In the analysis of time to resolution, there was no statistically significant difference between atomoxetine and placebo groups. Approximately 50% of the analysed events in both the atomoxetine and placebo groups had resolved as of 3 months after event onset and 81.4% of the analysed events in the atomoxetine treatment group had resolved as of 6 months after event onset. Data for the placebo group at 6 months are limited because all placebo patients had discontinued or had already experienced resolution prior to that time. Mean time to resolution was 73 days for atomoxetine and 71 for placebo, with medians of 54 and 49. ED was the most frequently reported of all sexual dysfunction TEAEs. ED occurred more frequently during the initial acute treatment with atomoxetine, with few new reports occurring during long-term treatment.

Comorbidity. As mentioned above, one trial compared safety of atomoxetine with placebo in a population of adult patients who met DSM-IV-TR criteria for ADHD and social anxiety disorder after up to 16 weeks of treatment. No patients experienced a SAE that was anxiety related, and only two (0.9%) atomoxetine-treated and two (0.9%) placebo-treated patients discontinued due to ‘anxiety’. Atomoxetine-treated patients did not experience worsening of anxiety compared to placebo-treated patients.

One placebo-controlled trial was conducted in patients with ADHD and comorbid alcohol abuse or dependence disorder. AEs were similar to those of other adult populations treated with atomoxetine.

Seizure. In atomoxetine trial protocols, patients with history or current seizure disorders were in general excluded from trials. In the acute controlled group, no seizure-related TEAEs were reported; in the long-term controlled group, convulsion was the only seizure-related TEAE reported, occurring in a placebo-treated patient. In the overall group, the incidence of seizure-related TEAEs reported was low, with a total of 4 (0.1%) atomoxetine-treated patients reporting convulsion.

Overdose. No fatal overdoses occurred in the clinical trials in adults.

Discussion

This is the first integrated analysis focusing on the safety of atomoxetine in adult patients with ADHD. It describes safety findings from 15 clinical trials in adult patients with ADHD, with a total of 4829 patients being exposed to atomoxetine for a mean of 163 days, or 2152 patient-years of exposure. Integrated analysis of data from these patients enabled us to further characterize and confirm the safety and tolerability of atomoxetine for treatment of adult patients with ADHD.

Most of the common AEs that occurred statistically significantly more in adult atomoxetine-treated patients compared to placebo (e.g. nausea, dry mouth, constipation, urinary hesitation and ED) were predictable, based on atomoxetine’s noradrenergic pharmacology, and are listed in the approved label for atomoxetine. When comparing AEs between acute and long-term trials, there appear to be very few differences in the safety profile between acute and long-term treatment (see Table 5). A number of frequently occurring AEs were confirmed to be transient in the majority of patients, e.g. nausea, which is the most common AE and the AE most frequently leading to treatment discontinuation. In controlled trials, statistically significantly more atomoxetine-treated patients discontinued due to AEs compared to placebo. However, the number of events leading to discontinuations that were considered serious was very low.

Due to the known effects on BP and HR, the cardiac safety of drugs used to treat ADHD, including atomoxetine, may be important, particularly for patients with severe cardiovascular disorders whose condition would be expected to deteriorate in case of increases in BP or HR. In our dataset, mean changes in BP and pulse were modest and consistent with increased noradrenergic activity; however a higher proportion of atomoxetine-treated patients showed clinically relevant increases from baseline in BP and HR compared to placebo. This is consistent with a previous
analysis (MHRA, 2012) that was performed for an assessment of the UK Medicines and Healthcare Products Regulatory Agency in 2011. In this analysis, it was also shown that the proportion of atomoxetine patients who experienced clinically important increases in BP or HR ranged from 6 to 10% (increase in SBP ≥20 mmHg; 6%, in DBP ≥15 mmHg; 6.5%, in HR ≥20 bpm: 10%). Of those patients who simultaneously exceeded both clinically important changes from baseline and absolute value limits in BP and HR, approximately 30% had progressive or sustained increases while participating in the atomoxetine trials. The mean changes to end-point for all atomoxetine-treated patients were: SBP +2.0 mmHg; DBP +1.9 mmHg; HR +5.2 bpm. An interesting aspect for clinical practice in this regard is how increases in BP and HR evolve if atomoxetine treatment is stopped. In the 6-month double-blind randomized withdrawal phase of the long-term maintenance of response trial (Upadhyaya et al., 2013b), values were stable under continued atomoxetine treatment and decreased to baseline values when treatment was stopped. Data from our analysis support the current wording in the atomoxetine label regarding potential cardiovascular effects in patients, risk minimization activities (such as routinely monitoring BP before and while taking atomoxetine), as well as contraindications and warnings.

In our analysis, atomoxetine was not associated with adverse effects on cardiac repolarization (QT interval) and the mean QTcD interval value remained within normal limits. This finding is consistent with results of a TQT study in healthy volunteers (Loghin et al., 2013), which showed no clinically significant effect of atomoxetine on QT even at maximum therapeutic dosage. However, there is the possibility that atomoxetine might result in delayed repolarization in overdose (Barker et al., 2004; Kashani and Ruha, 2007; Sawant and Daviss, 2004). Thus, atomoxetine should be used with caution in patients with congenital long QT syndrome, acquired long QT syndrome (for example, due to concomitant use of a drug that prolongs the QT) or a family history of QT prolongation.

Overall, evidence indicates that atomoxetine use is not associated with an increased risk of cardiovascular or cerebrovascular adverse effects (Adler et al., 2008; Holick et al., 2009; Loghin et al., 2013; Wernicke et al., 2003). More recently, a retrospective study used electronic health care records of more than 440,000 patients aged 25–64, more than 150,000 of whom were treated for ADHD with methylphenidate, amphetamine, atomoxetine, and pemoline (Habel et al., 2011). During more than 806,000 person-years of follow-up, the authors did not find any evidence of increased cardiovascular risk associated with current use of the aforementioned ADHD medications compared to non-use or remote use. This suggests that careful selection of patients for treatments and follow-up and management of AEs may decrease the theoretical risk of cardiovascular events in real life.

In terms of hepatic safety, clinical trial data did not identify any serious findings related to atomoxetine in adults. Despite these findings, very rarely liver injury, manifested by elevated hepatic enzymes and bilirubin with jaundice, has been reported. Also very rarely, severe liver injury, including acute liver failure has been reported in patients taking atomoxetine. As noted in the product labelling, atomoxetine should be discontinued in patients with jaundice or laboratory evidence of liver injury and should not be restarted.

In our integrated analysis, the overall incidence of reported aggression- and hostility-related TEAEs in atomoxetine-treated patients was low. Aggressive behaviour or hostility is often observed in patients with ADHD and has been reported in clinical trials and post-marketing experience of some ADHD medications. In our integrated analysis, aggression/hostility events were not reported with a statistically significantly increased frequency in atomoxetine-treated patients than in placebo-treated patients, but were slightly higher in the atomoxetine groups. Although there is no conclusive evidence that atomoxetine causes aggressive behaviour or hostility (Polzer et al., 2007), the atomoxetine label already comprises the warning that patients beginning treatment should be monitored for the appearance or worsening of aggressive behaviour or hostility.

The labelling for atomoxetine includes warnings and precautions to address the potentially increased risk of suicidal thoughts and behaviour. However, adult clinical trial meta-analyses and multiple reviews of spontaneous data sources have not identified an association of atomoxetine use with suicidal or self-injurious behaviour. Indeed, a recently published meta-analysis of adult (N=3365) and paediatric (N=3883) clinical trial data (Bangs et al., 2014), and in a recent randomized study of adults (N=524), using the Columbia Suicide-Severity rating scale (Camporeale et al., 2013), the risk of suicidal behaviour or ideation observed in those treated with atomoxetine is not significantly different from placebo. Data in our analysis do not show an increased risk of suicidal ideation or behaviour in adult patients treated with atomoxetine either. This is in contrast to some data from the paediatric clinical trial setting, where suicidal ideation was more frequently observed among children and adolescents treated with atomoxetine compared to those treated with placebo (Bangs et al., 2008). However, there is evidence that those suffering from ADHD are at greater risk of suicide than the general population. ADHD appears to increase the risk of suicide, especially in males, via increasing severity of comorbid conditions, particularly conduct disorders and depression (Imprey and Heun, 2012; James et al., 2004). In several unpublished post-marketing reviews, no inconsistencies in any trends of spontaneously reported events of suicidal ideation and behaviour, and of self-injurious ideation and behaviour, were identified between atomoxetine-treated patients and the general population for children, adolescents and adults.

More atomoxetine-than placebo-treated patients experienced treatment-emergent male sexual dysfunction AEs in our integrated analysis, but our post hoc analysis showed that more than three-quarters of the events in the atomoxetine treatment group had resolved as of 6 months after event onset. Despite the persistence of dysfunction events in some patients, it is notable that relatively few men discontinued atomoxetine trials for this reason. For example, although the most common sexual dysfunction event, ED, was reported as a TEAE in 9.0% of atomoxetine-treated men in the overall database, it was a reason for discontinuation in only 1.4%, indicating that for most men with this event, the perceived benefit of remaining in the trial outweighed the difficulty of tolerating the event.

A clinically useful finding is the difference in tolerability between q.d. and b.i.d. dosing. Both nausea and somnolence are relatively common AEs and both of these have lower incidences when atomoxetine is dosed in a b.i.d. regimen. On the other hand, insomnia, for example, was more frequent with the b.i.d. regimen. Atomoxetine can be taken once or twice daily. This gives the possibility for the clinician to treat each patient according to his or her needs and tolerability. q.d. dosing is the
recommended regimen, given the importance of patient convenience and adherence, especially for patients with ADHD who may be disorganized and inattentive to routine tasks. On the basis of the available data it does, however, remain appropriate that physicians consider the benefit of b.i.d. dosing in the case of patients with poor tolerability.

To date, the known atomoxetine safety profile has mainly been based on clinical trials and experience from children and adolescents. At present, the estimated number of worldwide exposures of atomoxetine is over 10 million patients, approximately 7 million of whom were children and adolescents and 3 million were adults. To a high degree, tolerability and safety of atomoxetine in adults is similar to its tolerability and safety in children and adolescents. However, some differences are seen between age groups. A post hoc analysis combining data from six randomized, placebo-controlled, parallel-arm atomoxetine trials with durations ranging from 6 to 9 weeks in adolescents (12–17 years) and three trials (10 weeks in duration) that studied young adults (18–30 years) found the AE profile to be similar in both age groups (Adler et al., 2012). Although there was the exception that nausea was significantly more frequent with atomoxetine compared to placebo in young adults (13.7% vs. 4.8%), in contrast to adolescents in which nausea occurred more frequently with placebo (4.5% vs. 10.2%) (Adler et al., 2012). The frequency of nausea observed in this analysis was lower than the 20.8% in our acute trial dataset, comprising patients from 18 years and over, with a mean age of 35.6 years. In our integrated analysis, we found some differences within the group of adult patients with dry mouth and constipation being more common among older adults than younger adults.

Limitations of our analysis are that despite the large number of patients included, the statistical power of the analysis was not suitable to detect differences in rare AEs between atomoxetine and placebo. As more patients on atomoxetine discontinued from the studies, as compared to patients on placebo, there might have been an attrition-bias that led to an underestimation of AEs for atomoxetine. However, the median exposure duration was comparable between both treatment groups. Moreover, the large majority of the possibly drug related AEs occurred in the first weeks of treatment, i.e. before most of the discontinuations happen, and therefore these TEAEs are taken well into account. Furthermore, compared to studies using solicited AE reporting for ADHD, the present study might have lower estimates for AEs because of their collection via spontaneous reporting. However, standard solicited AE questionnaires for ADHD are tailored for the typical side effects for stimulant medications, and might not have captured all atomoxetine-related side effects. In addition, the all-cause discontinuation rate in randomized controlled clinical trials, such as those included in the present analyses, cannot be considered as a proxy for a benefit-risk measurement, as study conduct-related reasons for discontinuation are frequent. As all studies included in this analysis were clinical trials and do not include results from non-interventional studies, the application of inclusion/exclusion criteria limits generalization of the results.

Conclusion

This integrated analysis confirmed atomoxetine’s known safety profile. No new potential or identified important risks were found during treatment with atomoxetine in adults beyond those already known. The known risks are appropriately described in the atomoxetine label, and they can be managed through appropriate screening and monitoring of patients before and during treatment. No particular safety issues in patients with comorbid social anxiety disorder or alcohol abuse and the lack of abuse potential all suggest that, based on the published efficacy data and the current integrated analysis of safety data, atomoxetine is a useful treatment option for adults with ADHD.

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Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: All authors are employees of Eli Lilly and Company. A.C., Y.T., H.U. and W.D. are stockholders of Eli Lilly and Company.

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References


