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Original article

Patterns of long-term and short-term responses in adult patients with attention-deficit/hyperactivity disorder in a completer cohort of 12 weeks or more with atomoxetine

E. Sobanski [a,*], S. Leppämäki [b,c], C. Bushe [d], L. Berggren [e], M. Casillas [f], W. Deberdt [g]

[a] Central Institute of Mental Health Mannheim, Medical Faculty Mannheim, University of Heidelberg, J5, 68159 Mannheim, Germany
[b] Finnish Institute of Occupational Health, PL40, FIN-00250 Helsinki, Finland
[c] Department of Psychiatry, Helsinki University Central Hospital, PL590, FIN-00250 HUS, Helsinki, Finland
[d] Medical Department, Eli Lilly & Co. Ltd, Erl Wood Manor, Sunninghill Road, Windlesham, Surrey, GU20 6PH, United Kingdom
[e] Global Statistical Sciences, Lilly Deutschland GmbH, Werner Reimers Str. 2-4, 61350 Bad Homburg, Germany
[f] Medical Department, Lilly S.A., Avenida de la Industria, 30, 28108 Alcobendas, Madrid, Spain
[g] Medical Department, S.A Eli Lilly Benelux N.V., Markiesstraat 1/4B, B - 1000 Brussel, Belgium

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ABSTRACT

Background: Atomoxetine is a well-established pharmacotherapy for adult ADHD. Long-term studies show incremental reductions in symptoms over time. However, clinical experience suggests that patients differ in their response patterns.
Methods: From 13 Eli Lilly-sponsored studies, we pooled and analyzed data for adults with ADHD who *completed* atomoxetine treatment at long-term (24 weeks; $n = 1443$) and/or short-term (12 weeks; $n = 2830$) time-points, and had CAARS-Inv:SV total and CGI-S data up to or after these time-points and at Week 0 (i.e. at baseline, when patients first received atomoxetine). The goal was to identify and describe distinct trajectories of response to atomoxetine using hierarchical clustering methods and linear mixed modelling.
Results: Based on the homogeneity of changes in CAARS-Inv:SV total scores, 5 response clusters were identified for patients who completed long-term (24 weeks) treatment with atomoxetine, and 4 clusters were identified for patients who completed short-term (12 weeks) treatment. Four of the 5 long-term clusters (comprising 95% of completer patients) showed positive trajectories: 2 faster responding clusters (L1 and L2), and 2 more gradually responding clusters (L3 and L4). Responses (i.e. $\geq 30\%$ reduction in CAARS-Inv:SV total score, and CGI-S score ≤ 3) were observed at 8 and 24 weeks in 80% and 95% of completers in Cluster L1, versus 5% and 48% in Cluster L4.
Conclusions: While many adults with ADHD responded relatively rapidly to atomoxetine, others responded more gradually without a clear plateau at 24 weeks. Longer-term treatment may be associated with greater numbers of responders.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) symptoms persist into adulthood in 29–84% of patients, depending on the definition of adult ADHD [8,11,12,24,27,29]. Adults with ADHD typically experience various personal and socioeconomic burdens [1,8,10,16,17,24,27,29,30], at least some of which are relieved by appropriate pharmacological treatment [16,30,32,37,40].

Currently recommended pharmacotherapies for ADHD in adults include stimulants such as methylphenidate and amphetamines, and the non-stimulant medication atomoxetine [15,28,35,36]. Notably, while responses may be detected within about 4 weeks of starting treatment with atomoxetine [14,26,31,47], the time taken to reach maximum improvement tends to be greater than with stimulants. For instance, in adult patients, reductions in ADHD symptoms may be maximal at about 5 weeks of treatment with methylphenidate [39], whereas atomoxetine is associated with incremental reductions that are generally not maximal until ≥ 24 weeks and possibly ≥ 60 weeks of treatment [26,31,47]. Thus short-term comparisons of these

* Corresponding author. Tel.: +49 0 621 1703 2852.
E-mail address: Esther.Sobanski@zi-mannheim.de (E. Sobanski).

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medications have led to potentially erroneous assessments of the relative efficacy of atomoxetine versus stimulants. Furthermore, there is little published data addressing whether short- and long-term trajectories of response to atomoxetine are homogenous among adult patients, or whether subgroups of adult patients with different response trajectories may exist.

In a database of all Eli Lilly-sponsored atomoxetine studies in adults with ADHD, a large number of patients have efficacy data for up to 24 weeks of treatment [3–6,19,25,26,31,42–44,47]. In these studies, treatment effects on ADHD symptoms and associated functioning have been assessed using various scales, including the Conners' Adult ADHD Rating Scales (CAARS) for ADHD symptoms, the Clinical Global Impressions of ADHD Severity (CGI-S) scale for overall clinical severity, and the Adult ADHD Quality of Life (AAQoL) scale [4–6,19,25,26,32,42,44]. In the current study, we used this integrated database to evaluate patterns of ADHD symptom reduction up to 24 weeks because long-term treatment typically reflects the clinical reality of treating adult ADHD patients when there is evidence of successful treatment [16,20,22,23,30]. Accordingly, we performed cluster analyses for all adult patients in the database who *completed* 24 weeks (the 'long-term analysis') and/or 12 weeks (the 'short-term analysis') of treatment with atomoxetine, and had CAARS total scores available up to or after these time-points and at baseline. Our aims were to determine whether distinct clusters of different types of response trajectory were present, and to describe the number of clusters and their individual trajectories.

2. Methods

2.1. Selection of source studies

The integrated database contains data from all 16 clinical trials of atomoxetine in adults that have been performed by Eli Lilly. From this database we pooled atomoxetine efficacy data for all patients who *completed* $\geq$ 12 weeks of treatment (regardless of whether or not the patient had responded) in studies that addressed ADHD as the primary disease and used CAARS Investigator-Rated: Screening Version (CAARS-Inv:SV) total and CGI-S scores. These efficacy data were available from 13 studies. Atomoxetine efficacy data were also pooled for patients who *completed* $\geq$ 24 weeks of treatment (regardless of whether or not the patient had responded). These data were available from 9 of the 13 studies.

As shown in Table 1, 7 of the 13 source studies had $\geq$ 2 treatment phases (double-blind and open-label), and another 3 source studies (randomized controlled trials [RCTs]) were followed by 2 open-label extension studies that were also used as source studies. In the current analyses, baseline (i.e. Week 0) was the start of the first atomoxetine treatment phase/study for each patient.

All 13 of the source studies required patients to have ADHD defined using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), with the clinical diagnosis established using the Connors Adult ADHD Diagnostic Interview from DSM-IV (CAADID) [21] or using the Adult ADHD Clinical Diagnostic Scale version 1.2 (ACDS v1.2) [2]. A complete list of the key design features of the 13 source studies included in the present analysis, together with the reasons for excluding the other 3 of the 16 studies in the integrated database, are shown in Table 1. Ethical approval for each source study was granted by the appropriate institutional review boards, informed consent was provided by all patients included, and all studies complied with the Declaration of Helsinki.

2.2. Identification of response clusters

Using the completer patients' pooled CAARS-Inv:SV total scores, 2 separate hierarchical cluster analyses were performed. One was the 'long-term analysis', i.e. for patients with CAARS-Inv:SV total scores at 24 weeks, as well as at baseline and at 2, 4, 6, 8, 10, 12, 14, 18, and 22 weeks. The other was the 'short-term analysis', i.e. for patients with CAARS-Inv:SV total scores at 12 weeks, as well as at baseline and at 2, 4, 6, 8, and 10 weeks. Linear interpolation was used to impute a missing value at any time-point, including at 12 and 24 weeks, based on the patient's closest non-missing observations before and after the missing time-point. The 2 cluster analyses were not mutually exclusive, i.e. patients included in the long-term analysis were also included in the short-term analysis.

In both cluster analyses, each cluster of patients that was identified had a pattern of CAARS-Inv:SV total scores that was specific to that cluster. Thus, the number of clusters identified was based on the homogeneity of CAARS-Inv:SV total scores within each cluster at the time-points up to 12 or 24 weeks.

The 2 hierarchical cluster analyses were conducted using the Spotfire program (TIBCO, Boston, MA, USA). The following methods/parameters were also used for clustering in Spotfire:

- clustering method: Wards method;
- distance measure: half square Euclidean;
- ordering weight: average value.

The clusters identified were analyzed further using Statistical Analysis System software (SAS, Cary, NC, USA).

2.3. Efficacy analyses

Changes in efficacy measures, compared between clusters over time, were analyzed using mixed model repeated measures (MMRM) for the long- and short-term analyses.

The efficacy measures were mean change to endpoint (12 and 24 weeks) in:

- CAARS-Inv:SV total score (lower scores indicate lower ADHD symptom severity);
- CGI-S score (scored using a 7-point scale; 1: normal, not at all ill; 7: extremely ill);
- AAQoL total score (higher scores indicate better functioning).

Fixed effects for MMRM were:

- cluster;
- study;
- visit window (including baseline as a visit);
- interactions:
  - cluster* visit window.

Least square (LS) means are presented by cluster and visit window.

In addition to investigating LS mean changes in efficacy measure scores in each cluster, we also calculated the proportions of patients meeting categorical response criteria, as we wanted to determine whether the different CAARS-Inv:SV score trajectories were associated with a specific likelihood of patients meeting a certain threshold of response. Two categorical definitions of response were used, i.e. the percentages of responders were calculated based on a single criterion definition ($\geq$ 30% reduction in CAARS-Inv:SV total score from baseline), which includes patients with partial responses, and a more rigorous combined definition of response requiring reductions in core ADHD symptom