Early Discontinuation of Attention-Deficit/Hyperactivity Disorder Drug Treatment: A Danish Nationwide Drug Utilization Study

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Abstract: Knowledge of patterns of treatment discontinuation in attention-deficit/hyperactivity disorder (ADHD) drug treatment is of importance, for both the clinical practice and the study of long-term treatment outcomes. The purpose of this study was to describe early discontinuation of ADHD drug treatment. Using the Danish National Prescription Registry, all first-time users of the ADHD drugs methylphenidate and atomoxetine were identified between 2000 and 2012. Early discontinuation was defined as failing to fill a second prescription for any ADHD drug within 6 months. Analyses were conducted stratified by calendar year, drug formulation, patient sex, age and region of residence. 59,116 first-time users of methylphenidate and atomoxetine with at least 6 months of eligible follow-up were identified. Overall, 12.6% (n = 7441) failed to fill a second prescription within 6 months. This proportion changed over time, dropping from 20.8% in 2000 to 12.5% in 2012. The proportion of early discontinuation was considerably lower among children than among adults. Proportions were comparable when stratifying by index drug. Proportions of early discontinuation were similar between regions of Denmark, except in the capital region, where it remained at around 20% among 18- to 49-year-olds throughout the study period (22.6% in 2012). In conclusion, we found that the proportion of early discontinuation among ADHD drug users in Denmark dropped markedly during the past decade for both sexes, all age groups and all regions, except for adults in the capital region. Overall, early discontinuation was somewhat lower than expected, considering rates of side effects or non-response to ADHD drug treatment.

The use of pharmacotherapeutics to treat attention-deficit/hyperactivity disorder (ADHD) has grown notably over the past decades [1–10]. Randomized clinical trials have shown positive effects of stimulants, such as amphetamines and methylphenidate, as well as the non-stimulant atomoxetine, in reducing the core symptoms of ADHD in children [11] and young- to middle-aged adults [12,13]. Data on drug efficacy in older patients and on long-term outcome of drug treatment are to a large extent, however, lacking [12–14].

Determination of the long-term benefits and risks of ADHD drugs is often distorted in observational studies by non-adherence and discontinuation of treatment. Knowledge of the patterns of treatment discontinuation is thus of major importance, for both the clinical practice and the future study of long-term treatment outcomes. Early discontinuation patterns are likely to be related to factors such as side effects or lack of treatment response, experienced by approximately 20–30% of patients [15–18], societal stigma of using stimulants [19–21], as well as patients’ underlying attention-deficit or psychiatric comorbidities [22–24]. While previous studies indicate that discontinuation of drug treatment for ADHD is relatively common [7,20,25,26], changes in discontinuation patterns over calendar time have not been studied before. Further, very few of the previous estimates have included adult populations and almost none account for early discontinuation, for example within the first 6 months.

We expected the proportion of users of ADHD drugs who discontinue treatment early to be at least as high as the reported rate of side effects and non-response. Further, we anticipated early discontinuation to vary across drug formulations, patient age and sex. Finally, we expected early treatment discontinuation to have increased over the past decade alongside the growing use of drugs for ADHD. Using nationwide prescription data including both children and adults from Denmark, we conducted an observational drug utilization study to assess our hypotheses.

Materials and Methods

In this study, we described early discontinuation of ADHD drug treatment using basic descriptive statistics. In brief, we identified first-time users of ADHD drugs and followed them over time to estimate the proportion who failed to fill a second prescription, along with a range of supplementary analyses.

Data source. National data on drug use in Denmark were extracted from the Danish National Prescription Registry [27]. The registry contains complete information, from 1 January 1995 onwards, on all prescriptions filled by Danish residents at outpatient pharmacies. Drugs are categorized according to the Anatomic Therapeutic Chemical (ATC) index [28]. The registry is found to have a high completeness and validity [27].

Drugs included in the analysis. We included all prescriptions for methylphenidate (ATC, N06BA04) and atomoxetine (N06BA09),
Prescriptions for modafinil (N06BA07) were only included if the user had previously filled prescriptions for either methylphenidate or atomoxetine, as modafinil is only used as a third-line treatment against ADHD. Throughout the text, the term ADHD drugs refer to these three substances as a group.

**Analysis.** In the main analysis, we estimated the proportion of users who failed to fill a second prescription within the first 6 months after the index prescription. All ADHD drugs were included, that is a subsequent prescription for another ADHD drug than the index drug also counted towards continued use. Individuals entered the study at the time of filling their first-ever prescription (i.e. with no previous prescription registered since the beginning of the prescription registry in 1995) for an ADHD drug between 1 January 2000 and 31 December 2012. The proportion of early discontinuation was given per calendar year (year of index prescription).

We performed supplementary analyses, stratifying users by (i) sex and age group (<12 years, 13–17 years, 18–24 years, 25–49 years and ≥50 years); (ii) index drug (methylphenidate immediate release, methylphenidate extended release and atomoxetine); and (iii) region of residence. Lastly, we estimated the proportion of users who, after their index prescription, failed to fill two or more prescriptions within the first 12 months.

**Results**

We identified 62,304 first-time users of ADHD drugs between 2000 and 2012, 59,116 (95%) of whom had at least 6 months of follow-up time (3188 excluded due to death). Methylphenidate as immediate-release formulation was the dominant first-line treatment throughout the period, although the proportion of users using methylphenidate extended-release formulations as well as atomoxetine increased over the period (table 1).

Overall, 12.6% (n = 7441) failed to fill a second prescription within 6 months. This proportion changed over time, dropping from 20.8% in 2000 to 12.5% in 2012. Supplementary analyses showed a similar proportion of early discontinuation when comparing males with females, individuals aged ≤12 with 13–17 years, and individuals aged 18–24 with 25–49 years (data not shown). For simplicity, we display the data with these age strata pooled into one, as well as the sex strata pooled together. For all age categories, we observed a similar trend of decreasing early discontinuation with calendar time. Further, the proportion of first-time users of ADHD drugs ceasing treatment early was lower among children than among adults (fig. 1).

We found comparable proportions of early discontinuation when stratifying by index drug, ranging from 11.3% (MPH extended release) and 12.7% (MPH immediate release) to 13.7% (atomoxetine) in 2012 (data not shown in full).

When stratifying by users’ region of residence in Denmark, we found similar proportions of early discontinuation between regions with one notable exception. During the study period, the proportion of early discontinuation among 18- to 49-year-olds dropped in all regions, except in the capital region, where it remained at around 20% (22.6% in 2012), that is higher than in all other regions (11.1–14.1% in 2012).

Among 54,647 ADHD drugs users who had more than 12 months of follow-up time available, we found that overall 17.5% (n = 9553) failed to fill two or more prescriptions within the first 12 months after their index prescription. This figure dropped from 26-27% in 2000–2001 to 18% in 2005 and remained reasonably stable thereafter (16–18% in 2006–2012) (data not shown in full).

**Discussion**

Using nationwide Danish data on drug use, we found that the proportion of early discontinuation among users of ADHD drugs dropped markedly during the last decade. The proportion of discontinuation reported in earlier studies [7,20,25,26] varies considerably, that is from 13% to 64%. With reference to previous findings and reported rates of side effects and non-response, the overall proportion of early discontinuation of ADHD drug treatment in this study is lower than expected.

The main strength of the study is the nationwide approach, effectively capturing all incident users of ADHD drugs of an

Table 1.

<table>
<thead>
<tr>
<th>Year</th>
<th>Methylphenidate immediate release n (%)</th>
<th>Methylphenidate extended release n (%)</th>
<th>Atomoxetine n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>720 (100.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>700 (100.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>915 (100.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>1217 (99.5)</td>
<td>6 (0.5)</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>1536 (86.9)</td>
<td>231 (13.1)</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>2097 (88.5)</td>
<td>272 (11.5)</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>2604 (86.4)</td>
<td>332 (11.0)</td>
<td>77 (2.6)</td>
</tr>
<tr>
<td>2007</td>
<td>3600 (82.2)</td>
<td>582 (13.3)</td>
<td>199 (4.5)</td>
</tr>
<tr>
<td>2008</td>
<td>5008 (77.5)</td>
<td>1158 (17.9)</td>
<td>299 (4.6)</td>
</tr>
<tr>
<td>2009</td>
<td>6918 (74.7)</td>
<td>1921 (20.7)</td>
<td>427 (4.6)</td>
</tr>
<tr>
<td>2010</td>
<td>7181 (70.4)</td>
<td>2288 (22.4)</td>
<td>728 (7.1)</td>
</tr>
<tr>
<td>2011</td>
<td>5683 (65.0)</td>
<td>2188 (25.0)</td>
<td>873 (10.0)</td>
</tr>
<tr>
<td>2012</td>
<td>5131 (61.1)</td>
<td>2285 (27.2)</td>
<td>987 (11.7)</td>
</tr>
</tbody>
</table>

933 (1.6%) users were excluded from this analysis as they filled two different ADHD drugs on the date of their index prescription.

Fig. 1. The proportion of first-time users of ADHD drugs who failed to fill a second prescription within 6 months, specified by age category.
EARLY DISCONTINUATION OF ADHD DRUG TREATMENT

We found that the proportion of discontinuation dropped in all regions in Denmark except for the capital region. There are no obvious explanations for this difference. The demography of the capital region differs from the general population with more young people, many of whom are students. Studies have shown considerable use of non-medical use of stimulants among students, both prescribed and non-prescribed [41–44], and that such use is especially prevalent in periods of high stress (e.g., during examinations) [45]. The nature of our data does not allow us to conclude whether ADHD medications are in fact increasingly used as ‘study drugs’ in the capital area. To this end, further studies are needed.

We did not find any significant variation in proportion of discontinuation according to the drug with which treatment has been initiated. It is conceivable that the group of patients who receive atomoxetine as first-line treatment differ from those using MPH regarding ADHD severity and psychiatric comorbidity. Clinical experience shows that atomoxetine is often used as first-line treatment for patients with other neuropsychiatric disorders or problems of addiction.

Conclusion

Our study showed a decrease in early discontinuation of ADHD drug treatment over the last thirteen years. This could be due to an accumulated experience among prescribers regarding diagnosis and dosages for treatment. Also, alongside considerable increases in the use of ADHD drugs and introduction of longer-acting preparations, the use of ADHD drugs may have become more accepted than before. The lower proportion of early discontinuation among children compared with adults might be because children do not themselves make decisions about discontinuation. Further studies are needed to investigate why early discontinuation among adults is more common in the capital region than in the rest of Denmark.

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Conflicts of Interest

No specific funding was obtained in relation to this work. The authors report no conflict of interests.

References


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31 FDA Drug Safety Communication. Safety Review Update of Medications used to treat Attention-Deficit/Hyperactivity Disorder (ADHD) in children and young adults [Internet]. Available from: http://www.fda.gov/drugsafety/ucm277770.htm#data (last accessed on 1 September 2014).


40 Van den Ban E, Souverein PC, Swaab H, van Engelhard H, Egberts TCG, Heerdink ER. Less discontinuation of ADHD drug use since the availability of long-acting ADHD medication in children,


