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Early Discontinuation of ADHD Drug Treatment: A Danish Nationwide Drug Utilization Study

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Abstract: Knowledge of patterns of treatment discontinuation in ADHD drug treatment is of importance, both for 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 six 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 six months of eligible follow-up were identified. Overall, 12.6% (n=7,441) failed to fill a second prescription within six 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 18-49-year-olds throughout the study period (22.6% in 2012).

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 outcomes 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, both for clinical practice and the future study of long-term treatment outcomes. Early discontinuation patterns are likely to be related to factors 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

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psychiatric co-morbidities (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, e.g. within the first six months.

We expect 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 anticipate early discontinuation to vary across drug formulations, patient age and sex. Finally, we expect 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 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 six months following the index prescription. All ADHD drugs were included, i.e. a subsequent prescription for another ADHD drug than the index drug also counted towards continued use. Individuals were entered 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 1) sex and age group (≤ 12 years, 13-17 years, 18-24 years, 25-49 years and ≥ 50 years); 2) index drug (methylphenidate immediate-release, methylphenidate extended-release and atomoxetine); and 3) region of residence.

Lastly, we estimated the proportion of users who, following their index prescription, failed to fill two or more prescriptions within the first twelve months.

Results

We identified 62,304 first-time users of ADHD drugs between 2000 and 2012, 59,116 (95%) of whom had at least six months of follow-up time (3,188 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% ($n=7,441$) failed to fill a second prescription within six 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).

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We found comparable proportions of early discontinuation when stratifying by index drug, ranging from 11.3% (MPH extended-release), 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 early discontinuation among 18-49-year-olds dropped in all regions, except in the capital region, where it remained at around 20% (22.6% in 2012), i.e. higher than in all other regions (11.1-14.1% in 2012).

Among 54,647 ADHD drugs users who had more than twelve months of follow-up time available, we found that overall 17.5% (n=9,553) failed to fill two or more prescriptions within the first twelve months following 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, i.e. 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 entire nation over a 13-year period. The main limitation is the lack of detailed data on the indication for treatment, e.g. the severity of the underlying disorder, variations in primary diagnoses and the presence of other psychiatric co-morbidities, as well as no information on the underlying reasons for discontinuation.

While not the main objective of the study, we note a marked increase in the annual number of new users of ADHD drugs (table 1). This finding, including the stagnation in the years 2009-2012, is in full accordance with previous studies on the use of ADHD drugs in Denmark (5). Rational use of ADHD drugs, including initiation and discontinuation of treatment, is of major interest given the serious burden of ADHD, as well as the possible adverse effects and abuse potential of the drugs (29–31).

Our finding that the proportion of discontinuation is lower among children and adolescents than among adults is in keeping with the results from earlier studies (25). Possible explanations include that the treatment of young people might be more socially acceptable or that decisions about continued treatment is not made by the patient him- or herself, but by parents or other caretakers. Even though parents are concerned about their children's side effects of medication (32), they might be inclined to be tolerant towards these in favour of the perceived positive effects regarding the child's behaviour and ability to function better socially and academically (33,34). Also, parents may feel pressured by schools or health personnel to keep their children on medication (35).

Compared with the expected proportion of non-responders around 20-30% (15-17), our results suggest that at least some of the patients who continue ADHD drug treatment may have little or no clinical effect of the medication. Side effects to ADHD drug treatment are generally considered to be mild and transient (18,36). Common side effects to ADHD drugs include loss of appetite, insomnia, headaches and cardiovascular and psychological alterations. Side effects are reported in 4-10% of the treated population (18,36), which, in comparison with our results, suggests that at least not all cases of discontinuation can be ascribed to the occurrence of side effects.

In contrast to what we had expected, the proportion of early discontinuation among users of ADHD drugs dropped markedly in the 13-year study period. There are no obvious reasons for this decreasing trend. One possible reason is that the prevalence of ADHD diagnosis has risen markedly in the same period and with that the clinical knowledge and public acceptance of the diagnosis and medical treatment of ADHD. A second possible reason is the fact that in the same period the median daily dose used has increased (37). Higher doses might be more effective and thus contribute to treatment adherence. A third possible reason is the introduction of extended-release MPH formulations in 2003. Although our results did not indicate major differences in the proportion of early discontinuation between types of drug, the availability of additional drug treatment options might facilitate drug persistence (38). Once-a-day medication is easier to administer and generally more acceptable as the patient does not need to take medication at school or at work (39,40).

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 exams) (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 conflicts of interest.

Tables

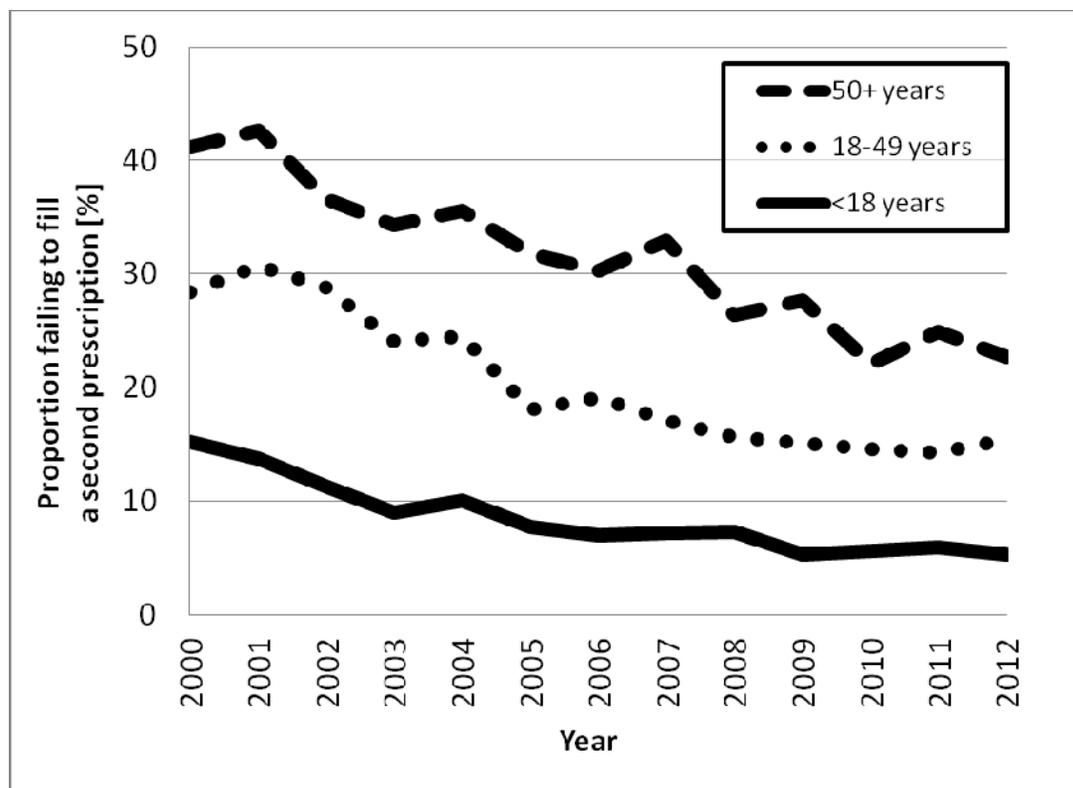
Table 1: Number of first-time users of ADHD drugs according to type of drug issued, specified by calendar year.

Year	Methylphenidate immediate-release n (%)	Methylphenidate extended-release n (%)	Atomoxetine n (%)
2000	720 (100.0)		
2001	700 (100.0)		
2002	915 (100.0)		
2003	1,217 (99.5)	6 (0.5)	
2004	1,536 (86.9)	231 (13.1)	
2005	2,097 (88.5)	272 (11.5)	
2006	2,604 (86.4)	332 (11.0)	77 (2.6)
2007	3,600 (82.2)	582 (13.3)	199 (4.5)
2008	5,008 (77.5)	1,158 (17.9)	299 (4.6)
2009	6,918 (74.7)	1,921 (20.7)	427 (4.6)
2010	7,181 (70.4)	2,288 (22.4)	728 (7.1)
2011	5,683 (65.0)	2,188 (25.0)	873 (10.0)
2012	5,131 (61.1)	2,285 (27.2)	987 (11.7)

NOTE: 953 (1.6%) users were excluded from this analysis as they filled two different ADHD drugs on the date of their index prescription.

Figures

Figure 1: The proportion of first-time users of ADHD drugs who failed to fill a second prescription within six months, specified by age category.



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