BCPT Basic & Clinical Pharmacology & Toxicology

Basic & Clinical Pharmacology & Toxicology, 2015, **116**, 349–353 Doi: 10.1111/bcpt.12325

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

Anton Pottegård[1], Bine Kjøller Bjerregaard[2], Lisbeth Sandal Kortegaard[3] and Helga Zoëga[4]

[1]Clinical Pharmacology, Institute of Public Health, University of Southern Denmark, Odense, Denmark, [2]Data Deliveries and Medicinal Products Statistics, Sector for National Health Surveillance and Research, Statens Serum Institut, Copenhagen, Denmark, [3]Solvang Child and Adolescent Psychiatry, Private Practice, Højbjerg, Denmark and [4]Centre of Public Health Sciences, Faculty of Medicine, University of Iceland, Reykjavík, Iceland

(Received 5 July 2014; Accepted 4 September 2014)

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).

Author for correspondence: Anton Pottegård, Clinical Pharmacology, Institute of Public Health, University of Southern Denmark, J.B. Winsløws Vej 19, 2, DK-5000 Odense C, Denmark (e-mail apottegaard@health.sdu.dk).

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).

Table 1.
Number of first-time users of ADHD drugs according to the 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	1217 (99.5)	6 (0.5)	
2004	1536 (86.9)	231 (13.1)	
2005	2097 (88.5)	272 (11.5)	
2006	2604 (86.4)	332 (11.0)	77 (2.6)
2007	3600 (82.2)	582 (13.3)	199 (4.5)
2008	5008 (77.5)	1158 (17.9)	299 (4.6)
2009	6918 (74.7)	1921 (20.7)	427 (4.6)
2010	7181 (70.4)	2288 (22.4)	728 (7.1)
2011	5683 (65.0)	2188 (25.0)	873 (10.0)
2012	5131 (61.1)	2285 (27.2)	987 (11.7)

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

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

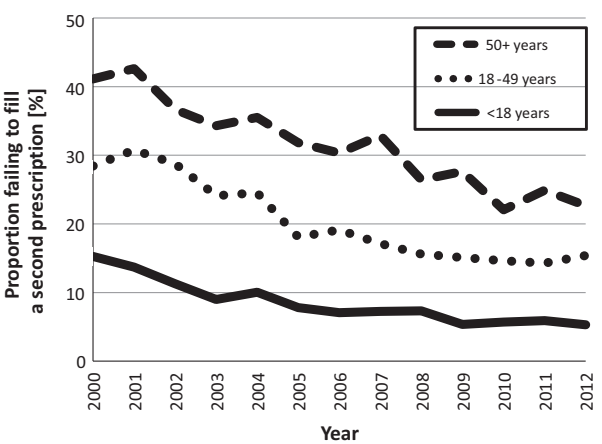

Fig. 1. The proportion of first-time users of ADHD drugs who failed to fill a second prescription within 6 months, specified by age category.

entire nation over a 13-year period. The main limitation is the lack of detailed data on the indication for treatment, for example the severity of the underlying disorder, variations in primary diagnoses and the presence of other psychiatric comorbidities, 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 the 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 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.

Acknowledgements

The authors would like to acknowledge Margit Anne Petersen for valuable comments on the manuscript.

Conflicts of Interest

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

References

1 Zuvekas SH, Vitiello B, Norquist GS. Recent trends in stimulant medication use among U.S. children. Am J Psychiatry 2006;**163**:579–85.
2 Zuvekas SH, Vitiello B. Stimulant medication use in children: a 12-year perspective. Am J Psychiatry 2012;**169**:160–6.
3 Castle L, Aubert RE, Verbrugge RR, Khalid M, Epstein RS. Trends in medication treatment for ADHD. J Atten Disord 2007;**10**:335–42.
4 McCarthy S, Wilton L, Murray ML, Hodgkins P, Asherson P, Wong ICK. The epidemiology of pharmacologically treated attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults in UK primary care. BMC Pediatr 2012;**12**:78.

5 Pottegård A, Bjerregaard BK, Glintborg D, Hallas J, Moreno SI. The use of medication against attention deficit hyperactivity disorder in Denmark: a drug use study from a national perspective. Eur J Clin Pharmacol 2012;**68**:1443–50.

6 Zoëga H, Baldursson G, Halldórsson M. Use of methylphenidate among children in Iceland 1989–2006. Læknablaðið 2007;**93**: 825–32.

7 Garbe E, Mikolajczyk RT, Banaschewski T, Petermann U, Petermann F, Kraut AA *et al.* Drug treatment patterns of attention-deficit/hyperactivity disorder in children and adolescents in Germany: results from a large population-based cohort study. J Child Adolesc Psychopharmacol 2012;**22**:452–8.

8 Zetterqvist J, Asherson P, Halldner L, Långström N, Larsson H. Stimulant and non-stimulant attention deficit/hyperactivity disorder drug use: total population study of trends and discontinuation patterns 2006-2009. Acta Psychiatr Scand 2013;**128**:70–7.

9 Van den Ban E, Souverein P, Swaab H, van Engeland H, Heerdink R, Egberts T. Trends in incidence and characteristics of children, adolescents, and adults initiating immediate- or extended-release methylphenidate or atomoxetine in the Netherlands during 2001-2006. J Child Adolesc Psychopharmacol 2010;**20**:55–61.

10 Scheffler RM, Hinshaw SP, Modrek S, Levine P. The global market for ADHD medications. Health Aff (Millwood) 2007; **26**:450–7.

11 Parker J, Wales G, Chalhoub N, Harpin V. The long-term outcomes of interventions for the management of attention-deficit hyperactivity disorder in children and adolescents: a systematic review of randomized controlled trials. Psychol Res Behav Manag 2013;**6**:87–99.

12 Volkow ND, Swanson JM. Clinical practice: adult attention deficit-hyperactivity disorder. N Engl J Med 2013;**369**:1935–44.

13 Molina BSG, Hinshaw SP, Swanson JM, Arnold LE, Vitiello B, Jensen PS *et al.* The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. J Am Acad Child Adolesc Psychiatry 2009;**48**:484–500.

14 Shaw M, Hodgkins P, Caci H, Young S, Kahle J, Woods AG *et al.* A systematic review and analysis of long-term outcomes in attention deficit hyperactivity disorder: effects of treatment and non-treatment. BMC Med 2012;**10**:99.

15 Greenhill LL, Halperin JM, Abikoff H. Stimulant medications. J Am Acad Child Adolesc Psychiatry 1999;**38**:503–12.

16 Moriyama TS, Polanczyk GV, Terzi FS, Faria KM, Rohde LA. Psychopharmacology and psychotherapy for the treatment of adults with ADHD-a systematic review of available meta-analyses. CNS Spectr 2013;**18**:296–306.

17 Santosh PJ, Taylor E. Stimulant drugs. Eur Child Adolesc Psychiatry 2000;**9**(Suppl 1):I27–43.

18 Barkley RA, McMurray MB, Edelbrock CS, Robbins K. Side effects of methylphenidate in children with attention deficit hyperactivity disorder: a systemic, placebo-controlled evaluation. Pediatrics 1990;**86**:184–92.

19 Ahmed R, Aslani P. Attention-deficit/hyperactivity disorder: an update on medication adherence and persistence in children, adolescents and adults. Expert Rev Pharmacoecon Outcomes Res 2013;**13**:791–815.

20 Swanson J. Compliance with stimulants for attention-deficit/hyperactivity disorder: issues and approaches for improvement. CNS Drugs 2003;**17**:117–31.

21 Pescosolido BA. Culture, children, and mental health treatment: special section on the national stigma study-children. Psychiatr Serv 2007;**58**:611–2.

22 Torgersen T, Gjervan B, Nordahl HM, Rasmussen K. Predictive factors for more than 3 years' duration of central stimulant treatment in adult attention-deficit/hyperactivity disorder: a retrospective, naturalistic study. J Clin Psychopharmacol 2012;**32**: 645–52.

23 Gau SS-F, Chen S-J, Chou W-J, Cheng H, Tang C-S, Chang H-L *et al.* National survey of adherence, efficacy, and side effects of methylphenidate in children with attention-deficit/hyperactivity disorder in Taiwan. J Clin Psychiatry 2008;**69**:131–40.

24 Thiruchelvam D, Charach A, Schachar RJ. Moderators and mediators of long-term adherence to stimulant treatment in children with ADHD. J Am Acad Child Adolesc Psychiatry 2001;**40**: 922–8.

25 Adler LD, Nierenberg AA. Review of medication adherence in children and adults with ADHD. Postgrad Med 2010;**122**:184–91.

26 Olfson M, Marcus SC, Zhang HF, Wan GJ. Continuity in methylphenidate treatment of adults with attention-deficit/hyperactivity disorder. J Manag Care Pharm 2007;**13**:570–7.

27 Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011;**39**(7 Suppl): 38–41.

28 WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2013. 2012 Oslo. [Internet]. Available from: http://www.whocc.no/filearchive/publications/1_2013guidelines.pdf (last accessed 5 July 2014).

29 Cooper WO, Habel LA, Sox CM, Chan KA, Arbogast PG, Cheetham TC *et al.* ADHD drugs and serious cardiovascular events in children and young adults. N Engl J Med 2011 Nov 17;**365**:1896–904.

30 Graham J, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, Dittmann RW *et al.*, (for the European Guidelines Group) European guidelines on managing adverse effects of medication for ADHD. Eur Child Adolesc Psychiatry 2011;**20**:17–37.

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/drugs/drugsafety/ucm277770.htm#data (last accessed on 1 September 2014).

32 Ahmed R, McCaffery KJ, Aslani P. Factors influencing parental decision making about stimulant treatment for attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 2013;**23**: 163–78.

33 dosReis S, Myers MA. Parental attitudes and involvement in psychopharmacological treatment for ADHD: a conceptual model. Int Rev Psychiatry 2008;**20**:135–41.

34 DosReis S, Mychailyszyn MP, Evans-Lacko SE, Beltran A, Riley AW, Myers MA. The meaning of attention-deficit/hyperactivity disorder medication and parents' initiation and continuity of treatment for their child. J Child Adolesc Psychopharmacol 2009;**19**: 377–83.

35 Brinkman WB, Sherman SN, Zmitrovich AR, Visscher MO, Crosby LE, Phelan KJ *et al.* Parental angst making and revisiting decisions about treatment of attention-deficit/hyperactivity disorder. Pediatrics 2009;**124**:580–9.

36 Wigal SB. Efficacy and safety limitations of attention-deficit hyperactivity disorder pharmacotherapy in children and adults. CNS Drugs 2009;**23**(Suppl 1):21–31.

37 Pottegård A, Bjerregaard BK, Glintborg D, Kortegaard LS, Hallas J, Moreno SI. The use of medication against attention deficit/hyperactivity disorder in Denmark: a drug use study from a patient perspective. Eur J Clin Pharmacol 2013 Mar;**69**:589–98.

38 Marcus SC, Wan GJ, Kemner JE, Olfson M. Continuity of methylphenidate treatment for attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med 2005;**159**:572–8.

39 Kemner JE, Lage MJ. Effect of methylphenidate formulation on treatment patterns and use of emergency room services. Am J Health Syst Pharm 2006;**63**:317–22.

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

adolescents and adults under the age of 45 years in the Netherlands. Atten Defic Hyperact Disord 2010;**2**:213–20.

41 Kudlow PA, Naylor KT, Xie B, McIntyre RS. Cognitive enhancement in Canadian medical students. J Psychoactive Drugs 2013 Oct;**45**:360–5.

42 McCabe SE, West BT, Teter CJ, Boyd CJ. Trends in medical use, diversion, and nonmedical use of prescription medications among college students from 2003 to 2013: connecting the dots. Addict Behav 2014;**39**:1176–82.

43 Franke AG, Bonertz C, Christmann M, Huss M, Fellgiebel A, Hildt E *et al.* Non-medical use of prescription stimulants and illicit use of stimulants for cognitive enhancement in pupils and students in Germany. Pharmacopsychiatry 2011;**44**:60–6.

44 Castaldi S, Gelatti U, Orizio G, Hartung U, Moreno-Londono AM, Nobile M *et al.* Use of cognitive enhancement medication among northern Italian university students. J Addict Med 2012;**6**: 112–7.

45 Moore DR, Burgard DA, Larson RG, Ferm M. Psychostimulant use among college students during periods of high and low stress: an interdisciplinary approach utilizing both self-report and unobtrusive chemical sample data. Addict Behav 2014;**39**:987–93.