

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

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Abstract Treatment options for ADHD in the Netherlands have increased with the introduction of the extended-release formulations of methylphenidate (MPH ER, Concerta®) in 2003 and atomoxetine (ATX, Strattera®) in 2005, but data on the effect on drug usage patterns are scarce. The objective of the present study was to describe changes in the patterns of ADHD medication use and determinants thereof among children, adolescents and adults (<45 years) starting ADHD medication since the introduction of MPH ER and ATX. Data were obtained from Dutch community pharmacies as collected by the Foundation for Pharmaceutical Statistics, covering 97% of all dispenses for prescription medicines to outpatients in

the Netherlands. Usage patterns (continuation, discontinuation, switching and addition) of ADHD drugs were evaluated at 3, 6 and 12 months after initiation for three separate time cohorts (patients starting ADHD medication in Jan-Dec 2002, Jan 2003–June 2004, respectively July 2004–Dec 2005). It was found that between 2002 and 2006, most ADHD drug users were initiated on methylphenidate IR. Discontinuation of any ADHD drug treatment decreased over time partly in favour of switching and addition. Discontinuation at 3 months decreased from around 33% to around 25%, at 6 months from less than 50% to almost 35%, and at 12 months from just fewer than 60% to less than 45%. Discontinuation was higher among females and in adults >18 years. After the introduction of MPH ER and ATX (time cohort III), 16.5% of the incident ADHD drug users switched their medication and almost 9% added an ADHD drug to the prior ADHD drug. In conclusion, discontinuation of incident ADHD drug use is high after 3, 6 and 12 months. During the study period, the incidence of discontinuation decreased because of the availability of extended-release methylphenidate and atomoxetine.

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Abbreviations

ADHD Attention deficit hyperactivity disorder
MPH IR Methylphenidate immediate release
MPH ER Methylphenidate extended release
ATX Atomoxetine

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a neurobiological psychiatric disorder that occurs in childhood, adolescence and adulthood. The prevalence of ADHD has been estimated at 3.0–7.5% among youth (Buitelaar 2002) and between 1.0 and 4.7% among adults (Ten Have et al. 2006; Murphy and Barkley 1996; Kessler et al. 2005; de Ridder et al. 2008). Many patients are not outgrowing their ADHD, indicating that it is a lifetime disorder requiring chronic treatment (Faraone et al. 2006). Psychopharmacological treatment is one of the most effective currently available treatment options in ADHD (Practice Parameter for the use of stimulant medications in the treatment of children, adolescents and adults 2002; Multidisciplinaire Richtlijn ADHD 2005). During the last decade, the pharmacotherapeutic options for the treatment of ADHD in the Netherlands have widened by the introduction of extended-release formulations of methylphenidate (MPH ER, Concerta[®]) in 2003 and the new active molecule atomoxetine (ATX, Strattera[®]) in 2005. Before 2003, only methylphenidate immediate release (MPH IR, Ritalin[®]) was approved in the Netherlands for the treatment of patients 6–18 years old with ADHD, while dexamphetamine (Dexedrin[®]), nortryptilin (Nortrilen[®]) and clonidine (Dixarit[®]) were used off-label for this indication.

Studies in several countries, including The Netherlands, have shown a strong increase during the last two decades in prevalence and incidence in the use of ADHD medication among preschoolers, children and adults (Robison et al. 1999, 2005; Zito et al. 2000, 2007, 2008; Miller et al. 2001; Schirm et al. 2001; Reid et al. 2002; DeBar et al. 2003; Hugtenburg et al. 2005; DosReis et al. 2005; Faber et al. 2005; Vinker et al. 2006; Castle et al. 2007; Winterstein et al. 2008; Mitchell et al. 2008; Trip et al. 2009; van den Ban et al. 2010). US data have suggested that the average duration of psychostimulant use ranges from 5 years for middle school students (Safer and Krager 1994; Angold et al. 2000) to 8 years for high school students. Dutch studies have shown a shift towards longer duration of use from 1995 to 2006 (Schirm et al. 2001; Faber et al. 2005; Trip et al. 2009). Incidences and usage patterns differ between countries and within countries because there are differences regarding use of diagnostic classification systems, practice guidelines, cultural beliefs about use of medication, reimbursement possibilities, government regulations and drug advertising (Scheffler et al. 2007; Mitchell et al. 2008; Vitiello 2008; Zito 2008). However, little is known how treatment patterns like continuation or discontinuation, switching and combining ADHD drugs have changed after the introduction of the newer ADHD drugs.

The objective of this study was to assess changes in ADHD medication usage patterns (continuation,

discontinuation, switching and addition) and determinants thereof in children, adolescents and adults <45 years initiated on ADHD drugs in the Netherlands since the availability of the long-acting ADHD drugs MPH ER and ATX.

Methods

Setting and study population

Drug-dispensing data for this study were obtained from the Foundation for Pharmaceutical Statistics (Stichting Farmaceutische Kengetallen, SFK). As of 1990, SFK has been collecting dispensing data from a growing number of community pharmacies in the Netherlands. In 2001, the catchment area of SFK comprised 1,629 community pharmacies in both rural and urban areas all over the Netherlands, representing 90.7% of the total number of Dutch pharmacies. In 2006, coverage had increased to 92% of the total number of Dutch pharmacies and 97% of the Dutch population (<http://www.sfk.nl>). For this study, we used data from those 745 pharmacies with a complete medication history of the patients from 2001 to 2006. As the majority of patients in the Netherlands designate a single pharmacy to fill prescriptions from general practitioners or medical specialists, dispensing histories provide an almost complete account of prescription drug exposure in time (Buurma et al. 2008). Information about the prescribed medication contained patient data (anonymous ID, gender, year of birth), dispensing date, number of units dispensed and prescribed daily dose. From the SFK database, all patients born after 1960 (i.e. <45 years of age) were identified with at least one prescription dispensed between January 2002 and December 2005 for a drug approved for the treatment of ADHD (methylphenidate IR and ER, atomoxetine). From here on, these drugs will be referred to as 'ADHD drugs'. The date of the first dispensing of an ADHD drug marked the start of follow-up. Only incident users of an ADHD drug were included in this study, where an incident user was defined as a patient having no ADHD drug dispensed during the 12 months prior. All patients were therefore required to have at least 12 months of history in the SFK database prior to this prescription date and also 12 months of follow-up after cohort-entry in order to be able to evaluate medication usage patterns. Three time cohorts were defined according to the year of ADHD drug initiation: I: January 2002–December 2002, II: January 2003–June 2004 and III: July 2004–December 2005.

ADHD drug usage patterns

For each included patient, all prescriptions for ADHD drugs were identified. The theoretical duration of use of

each prescription was calculated by using information about the dispensing date, the number of units dispensed and the prescribed dosage regimen. For each subsequent dispensed prescription for an ADHD drug, the drug usage pattern was classified as continuation, discontinuation, switching or addition. Continuation was defined as continuing the initially prescribed ADHD drug. Discontinuation of ADHD treatment was defined as not having refilled a new prescription for any ADHD drug within 3 months after the theoretical end date of the previous prescription. Switching was defined as changing from one type of ADHD drug to another. Addition was defined as starting another type of ADHD drug while continuing the initially prescribed drug.

Data analysis

Demographic characteristics at baseline were compared between the three time cohorts. Age was categorized in four age strata: 0–5, 6–11, 12–17 and 18–45 years.

Patients were followed up from cohort-entry to the first change in ADHD treatment (discontinuation, switch, addition,) or censoring, whichever came first. The frequency of study outcomes for each time cohort was assessed at 3, 6 and 12 months after cohort-entry. Cox regression analysis was conducted to assess the strength of the association between determinants and discontinuation and was expressed as a hazard ratio (HR) with 95% confidence interval (CI). The association between determinants (gender, age, initial ADHD drug) and switching and addition was studied for time cohort III only, because by

that time both MPH ER formulations as well as atomoxetine were available on the Dutch market.

Results

We identified 62,098 unique patients and our study population comprised 13,489 incident users of ADHD drugs (Table 1). Overall, 72.6% were male and 44.2% were aged between 6 and 11 years of age. There were no major differences in the male/female ratio and age distribution between the three time cohorts. The absolute number of patients initiating ADHD drug treatment increased over time. The vast majority of patients (93.7%) were initiated on methylphenidate IR.

Figure 1 shows the proportion of patients having one of the medication usage pattern events at 3, 6 and 12 months for the three time cohorts. The number of patients continuing the initial ADHD medication decreased over time of follow-up, and this pattern was not different between the three time cohorts. After 3 months, around two-thirds of patients were still using the *original* ADHD drug, but at 1 year this proportion had dropped just under 40%. In contrast, continuation of *any* ADHD drug treatment increased from time cohort I to time cohort III with at each measurement point (3, 6, 12 months after initiation) a relative increase in the continuation of 30–40%. The incidence of discontinuation of *any* ADHD drug was lower in the later time cohorts due to increased switching to and addition of the newer ADHD drugs. In time cohort III, 25% of patients had an alteration of their initial treatment: in

Table 1 Characteristics of incident users of ADHD drugs during 2002–2005 ($N = 13,489$)

Characteristics	Time cohort I Jan 2002–Dec 2002		Time cohort II Jan 2003–June 2004		Time cohort III July 2004–Dec 2005		Overall 2002–2005	
	N	%	N	%	N	%	N	%
Sex								
Male	1,288	69.7	4,089	73.6	4,412	72.5	9,789	72.6
Female	561	30.3	1,466	26.4	1,673	27.5	3,700	27.4
Age								
0–5 years	95	5.1	199	3.6	256	4.2	550	4.1
6–11 years	710	38.4	2,489	44.8	2,767	45.5	5,966	44.2
12–17 years	396	21.4	988	17.8	1,126	18.5	2,510	18.6
18–45 years	648	35.0	1,879	33.8	1,936	31.8	4,463	33.1
Type of initial ADHD drug								
MPH IR	1,849	100	5,372	96.7	5,420	89.1	12,641	93.7
MPH ER	NA	NA	183	3.3	549	9.0	732	5.4
ATX	NA	NA	NA	NA	116	1.9	116	0.9

NA not available at that time

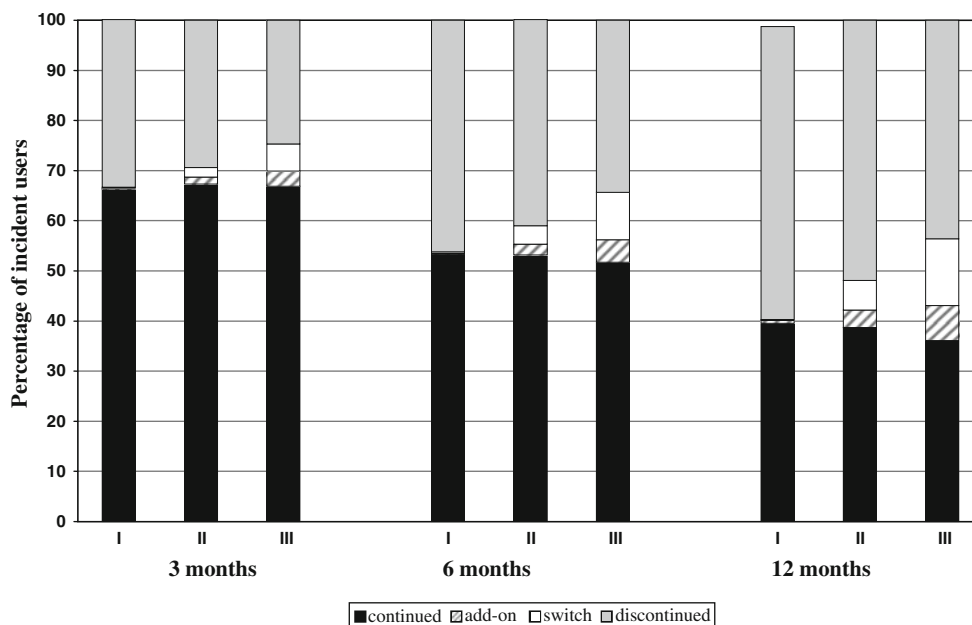


Fig. 1 Percentage of incident users having encountered one of the outcome events at 3, 6 and 12 months for the three time cohorts I, II, III. *Time cohort I* January 2002–December 2002, *time cohort II* January 2003–June 2004, *time cohort III* July 2004–December 2005

16.5%, the medication was switched, and in almost 9%, another ADHD drug was added to the initially prescribed drug. Overall, 90% of the switchers comprised MPH IR users, of whom almost 94% switched to MPH ER and 6% switched to ATX. Of the patients having an addition, 83% were MPH IR users and most of them were added MPH ER (data not shown).

Table 2 shows that the proportion of patients of discontinuing of ADHD drug users was higher among females (72.0%) than among men (60.3%), yielding an adjusted HR of 1.09 (95% CI 1.04–1.15) and among adults >18 years (adjusted HR 1.13, 95% CI: 1.06–1.19 vs. 12–17 year olds) in this particular study period. The influence of the determinants did not differ between the three time cohorts.

Discussion

First, this study showed that the discontinuation rate of treatment with ADHD drugs is high in all three time cohorts after 3, 6 and 12 months, especially among women and adults. Second, over time the discontinuation rate of any ADHD drug use decreased because of increased switching and addition following the availability of the newer ADHD drugs MPH ER and ATX.

The discontinuation frequency in our study is within the same range as found in other studies. Between 36 and 51% of the children discontinued their ADHD medication within 1 year after start (Bussing et al. 2005; Winterstein et al. 2008). Only half of the children received their ADHD

Table 2 Risk of ADHD treatment discontinuation during total follow-up (N = 13,489)

Characteristics	Number	% Discontinued	Crude HR (95% CI)	Adjusted HR (95% CI) ^a
Time cohort				
Jan 2002–Dec 2002	1,458	78.9	1.00 (reference)	1.00 (reference)
Jan 2003–June 2004	3,864	69.6	0.86 (0.81–0.91)	0.98 (0.92–1.04)
July 2004–Dec 2005	3,248	53.4	0.70 (0.66–0.75)	0.86 (0.81–0.92)
Sex				
Male	5,907	60.3	1.00 (reference)	1.00 (reference)
Female	2,663	72.0	1.39 (1.32–1.45)	1.09 (1.04–1.15)
Age category				
0–5 years	294	53.5	0.64 (0.57–0.72)	0.67 (0.59–0.75)
6–11 years	2,910	48.8	0.52 (0.49–0.56)	0.53 (0.50–0.56)
12–17 years	1,810	72.1	1.00 (reference)	1.00 (reference)
18–45 years	3,556	79.7	1.37 (1.29–1.45)	1.13 (1.06–1.19)

^a Adjusted for other characteristics in Table 2

medication for less than 3 years (Prosser and Reid 2009). On the other hand, 77% of the parents of children (6–18 years) diagnosed with ADHD reported in an online questionnaire that the length of treatment was more than 1 year (Coghill et al. 2008). In the Netherlands, a retrospective study of patients aged 6–21 years in an outpatient clinic for child and adolescent psychiatry showed that less than 10% discontinued their medication and half of the patients switched at least once between 2005 and 2006 (Pauw et al. 2008). Studies in adults also report high discontinuation rates. Only 24% of the patients initiated on methylphenidate were still on treatment after 7 months (Capone and McDonnell 2006). About 20% of the adult ADHD patients in Norway still used their medication after 2 years between 1997 and 2003 (Aanonsen et al. 2004).

In our study, risk of discontinuation was higher among females. This finding is in contrast with results from Faber et al. (2005), who found no difference in duration of stimulant use between boys and girls, but supports data from Trip et al. (2009), who found that boys tended to use their ADHD medication longer than girls. A recent Australian study (Prosser and Reid 2009) found a decline in the duration of treatment with ADHD drugs from 2.5 years in 1990–2000 to 2 years in 2000–2006 with no difference between boys and girls aged less than 18 years. Their finding is consistent with studies by Reid et al. (2002) and Barbaresi et al. (2006). Differences in outcome of discontinuation rates can be caused by study design, inclusion of different ages, the prescriber, the treatment setting, the motivation of patient and parents, duration of follow-up and as in our study the introduction of newer ADHD drugs.

In time cohort III, after the introduction of MPH ER and ATX, 16.5% of the incident ADHD drug users switched their medication, mainly MPH IR to ER and almost 9%, of whom 17% was adult, added an ADHD drug to the prior ADHD drug, mainly MPH ER to IR. This is consistent with the study of Pauw et al (2008) in which eighty per cent switched from MPH IR to ER. Our hypothesis is that switching from MPH IR to ER is associated with a greater continuity of treatment than MPH IR. This is confirmed in studies in youth (Marcus et al. 2005; Lage and Hwang 2004) and adults (Olfson et al. 2007). Switching to the non-stimulant drug ATX is probably because of side effects or too little effect of MPH IR.

There are several studies on pharmacological monotherapy versus combined therapy for ADHD in youth. Combined use of methylphenidate IR, ER or atomoxetine has not been the main subject of a study, although some data are available. Only 7% of the Australian children, 3–17 years old, received a combination of MPH IR and ER in 2004 (Preen et al. 2007). Less than 2% of the children between 2006 and 2008 used more than one psychostimulant (Thompson et al. 2009). In adults, combined use of

ADHD drugs was determined in 19.7% of initial atomoxetine users, in 21.0% of initial extended-release stimulant users and in 23.1% of the initial immediate-release stimulant users between July 2003 and June 2004 (Pohl et al. 2009). Hyperactivity predicted the combined use of ADHD medication in adults initiated on atomoxetine.

As if ADHD can be seen as a lifetime disorder, it should need chronic treatment. Medication is one of the most powerful treatment options in ADHD (Faraone et al. 2006). The high discontinuation rate in our study may reflect suboptimal treatment for ADHD. Untreated ADHD is a risk factor for traffic accidents, emergency room visits, school, work and marital problems, substance abuse and psychopathology (Fischer et al. 1990; Barkley et al. 1993, 1996; Mannuzza et al. 1993; DiScala et al. 1998; Leibson et al. 2001; Wilens 2004; Sobanski et al. 2008a, b). Probably with the introduction of long-acting ADHD medication continuation of treatment can be optimized. In children (6–17 year) and adults, initial use of MPH ER was associated with a longer duration of treatment compared to the initial use of MPH IR (Lage and Hwang 2004; Marcus et al. 2005; Olfson et al. 2007). There are indications that patients with more severe ADHD symptoms switch more rapidly to long-acting drugs (Gau et al. 2008). There are several reasons for discontinuation. Psychostimulants can have a rapid effect on ADHD symptoms, and ADHD drug users can think that they are cured by the medication and stop. They can suffer from side effects or they disbelieve in the effects of medication. The type of prescriber or setting can influence their compliance. Probably, the ADHD drug user did not suffer from ADHD or other treatment opportunities were available and effective in reducing the ADHD symptoms.

Strengths of this study were that it was population based and involved a large sample of persons using ADHD medication. There are several limitations. We had no information on the indication for which ADHD drugs were prescribed. Although methylphenidate is the first-choice pharmacotherapeutic intervention in the treatment of ADHD for children, adolescents (Practice Parameter for the use of stimulant medications in the treatment of children, adolescents and adults 2002; Multidisciplinaire Richtlijn ADHD 2005) and adults (Kooij 2003; Spencer et al. 2005), it can also be prescribed to adults for somatic problems (Donker et al. 2005; Gagnon et al. 2005). Furthermore, persistence of ADHD treatment might have been affected by the prescriber, treatment setting or high costs of long-acting medication, which are not always covered by health insurance companies. Little is known about the influence of studies or guidelines on ADHD drug treatment published in professional journals (inter)national conventions or marketing strategies of pharmaceutical companies on the prescribing behaviour of health care professionals or the

perception on ADHD symptoms and medication of patients, parents or teachers (Layton et al. 2008). These factors may contribute to a more or less tolerant attitude towards ADHD drugs. The Dutch clinical guideline was presented just before the introduction of atomoxetine in the Netherlands and could have influenced prescription behaviour.

In conclusion, discontinuation of ADHD drugs use is high within 1 year after initiation. It decreased over calendar time since the availability of long-acting ADHD drugs, which make it possible to switch or use more than one ADHD drug at the same time. Combined ADHD drug therapy is not very common in the Netherlands. More research on continuation, discontinuation, switching and addition must be performed after 2006 to investigate whether prescription of long-acting drugs further decreases the rate of discontinuation. Backgrounds of switching to MPH ER or ATX and effects of discontinuation of ADHD drugs on school performance, comorbidity, marital and family stress should be subject of future research.

Conflict of interest E van den Ban: Janssen-Cilag BV: lecture, reimbursed travel to convention; Lilly Nederland BV: scientific research (no personal grant), lecture, advisory board, reimbursed travel to convention; UCB Pharma BV: advisory board, reimbursed travel to convention; Eurocept BV: lecture (no personal grant), reimbursed travel to convention. The division of Pharmacoepidemiology & Clinical Pharmacology employing authors PS, RH and TE has received unrestricted funding for pharmacoepidemiological research from GlaxoSmithKline, Novo Nordisk, the private-public funded Top Institute Pharma (<http://www.tipharma.nl>, includes co-funding from universities, government, and industry), the Dutch Medicines Evaluation Board, and the Dutch Ministry of Health. No support or funding for this manuscript.

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