ORIGINAL REPORT

Deviant patterns of methylphenidate use in adults: a Danish nationwide registry-based drug utilization study

Lotte Rasmussen[1]*, Helga Zoëga[2], Jesper Hallas[1] and Anton Pottegård[1]

[1]*Clinical Pharmacology, Department of Public Health, University of Southern Denmark, Odense C, Denmark*
[2]*Centre of Public Health Sciences, Faculty of Medicine, University of Iceland, Reykjavík, Iceland*

ABSTRACT

Purpose   Several survey studies have documented misuse of methylphenidate defined as the use of non-prescribed methylphenidate or use different from what was prescribed. We aimed to identify and characterize adults with deviant patterns of methylphenidate use in Denmark during 2007–2012. Further, we aimed to identify risk factors associated with deviant patterns of use.
Methods   Based on individual-level prescription data, new users of methylphenidate were followed for one year after filling their first prescription on methylphenidate. Adult patients were identified with deviant patterns of use if they had ≥4 different prescribers and filled ≥1095 defined daily doses of methylphenidate during the year of follow-up. Risk factors were estimated by using logistic regression.
Results   Among 20 829 new users of methylphenidate, we identified 82 (0.39%) patients displaying deviant patterns of use. Characteristics associated with deviant patterns of use included an initial prescription for extended-release methylphenidate (OR2 4.35), age 25–49 years at first prescription (OR2 2.49), general practitioners or hospital doctors as initial prescribers (OR2 3.06 and OR2 4.07) and prior use of drugs used in addictive disorders (OR2 2.08) or opioids (OR2 1.75). Sensitivity analyses revealed that the number of different prescribers alone does not seem to effectively identify deviant users of methylphenidate.
Conclusion   We have identified characteristics associated with deviant patterns of methylphenidate use. Our results do not allow us to conclude if deviant users truly represent medical misusers. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—ADHD; methylphenidate; prescription drug misuse; database; doctor shopping; drug utilization; Denmark; pharmacoepidemiology

INTRODUCTION

Methylphenidate has a widespread use as first-line treatment for moderate to severe attention-deficit/hyperactivity disorder (ADHD). Over the past decade there has been a global increase in the use of methylphenidate,[1–6] and in Denmark an increasing off-label use of methylphenidate among adults has been observed[1,7] with a more than tenfold increase from 2000 to 2009.[8] A study showed that this increase was highest among young adults with a slightly higher increase among males than females.[7]

Methylphenidate has been shown to have an abuse potential, with oral immediate-release formulations having a greater risk of abuse or misuse over oral extended-release formulations.[9–11] This may in part be explained by the tamper resistant feature of the osmotic-controlled extended-release formulation of methylphenidate.[9] In recent years, several survey studies have documented misuse of methylphenidate, defined as the use of non-prescribed methylphenidate (non-medical use) or use different from what was prescribed (medical misuse), e.g. larger or more frequent doses.[4,12] Non-medical use of methylphenidate has been widely reported among adolescents and young adults[4,12], for example among student populations, where methylphenidate is used to enhance concentration, improve alertness or to "get high". Medical misuse of methylphenidate has been reported among individuals with ADHD, especially among adults and those with associated psychiatric disorders.[4,12] One study showed an estimated 22% prevalence of medical misuse of methylphenidate including other psychotropic medications among these individuals; this

*Correspondence to: L. Rasmussen, Clinical Pharmacology, University of Southern Denmark, JB Winsløws Vej 19, 2, 5000 Odense C, Denmark. Email: lorasmussen@health.sdu.dk

high prevalence was mainly because of misuse in those patients having conduct or substance use disorders.[13]

Studies on demographic and clinical characteristics associated with deviant use of methylphenidate among the general population are limited, and knowledge is needed to help clinicians identify individuals who might be at risk of a medical misuse.

Different methods have previously been used to identify deviant patterns of drug use with data from prescription databases,[14–24] such as individuals visiting multiple prescribers and/or multiple pharmacies (doctor/pharmacy shopping), high levels of dispensed drugs and simultaneous dispensings of drugs with a known abuse potential.[21] Some may be used as proxy measures of medical misuse of prescription drugs.

The aim of this study was to gain information about deviant users of methylphenidate in Denmark based on national prescription data. Specifically, we aimed to identify and characterize individuals with deviant patterns of methylphenidate use and to assess potential predictors associated with deviant patterns of use.

METHODS

We identified and characterized individuals with deviant patterns of methylphenidate use in Denmark during 2007–2012 by using a proxy for deviant use defined by a large quantity of dispensed drugs and doctor shopping. In addition, we assessed potential predictors of deviant patterns of use.

Data source

Data on prescriptions were extracted from the Danish National Prescription Registry,[25] which holds complete data on all prescription drugs dispensed to Danish residents at community pharmacies from 1995 and onwards. Using a unique personal identification number (CPR-number),[26] the registry allows tracking of every redeemed prescription by an individual over time. Drugs are categorized according to the Anatomical Therapeutic Chemical (ATC) classification system and the amount of dispensed drug is expressed as the number of defined daily doses (DDDs),[27] i.e. "the assumed average daily maintenance dose for a drug for its main indication in adults".[27] For every prescription we extracted the following variables: encrypted CPR-number, age, sex, ATC code, product name, product code, date of dispensing, dispensed quantity in DDDs, the dispensing pharmacy, a unique identifier for the prescribing physician and type of prescriber (general practitioner, practicing specialist and hospital

doctor).[25] Information on migrations and death was extracted from the Danish Civil Registration System.[26]

ADHD medication in Denmark

Methylphenidate is indicated for the treatment of ADHD in children and adolescents aged 6–17 years[28] and for the treatment of narcolepsy.[29] According to Danish guidelines, treatment with methylphenidate should be initiated by a specialist in child or adolescent psychiatry.[28] Methylphenidate is listed under drugs with special restrictions, and therefore a prescription can only be filled once. At the end of 2006 atomoxetine was marketed in Denmark and approved for the treatment of ADHD in children and adolescents.[30]

Study population and study drugs

We included all ADHD drugs belonging to the ATC group N06BA.[27] Prescription data were obtained for all individuals who redeemed at least one prescription for an ADHD drug from January 1995 and onwards. In the present paper, the term "ADHD drugs" refers to methylphenidate (N06BA04), modafinil (N06BA07) and atomoxetine (N06BA09) as one group. Individuals were included in the study if they were ≥18 years and started treatment with methylphenidate between 1 January 2007 and 30 June 2012. This study period was chosen because of preplanned analysis including atomoxetine and therefore taking into account the date of market approval of atomoxetine. Individuals were only included if they had not had any ADHD drugs, amphetamine (N06BA01) or dexamphetamine (N06BA02) dispensed at any time prior to their first methylphenidate prescription (index date). In this way we only included incident users of methylphenidate, and patients treated before entering adulthood were therefore not included. Individuals were excluded if they filled two different ADHD drugs or formulations of methylphenidate at index date. In addition, individuals were excluded if they had index prescriptions with different types of prescribers. Individuals were excluded if they could not be followed for one full year after methylphenidate initiation, i.e. because of migration or death. Finally, individuals were excluded if they had any record of emigration from or immigration to Denmark before the index date, as we would thus be unable to account for their full prescription history. One DDD of methylphenidate corresponds to 30 mg.[31]

Definition of deviant use

Individuals were followed for one full year after their first dispensing of methylphenidate. Based on use patterns during this year, they were identified as having either deviant or non-deviant patterns of methylphenidate use. Deviant patterns of methylphenidate use were defined as having ≥4 different prescribers for methylphenidate prescriptions and filling ≥1095 DDD of methylphenidate during the first year after treatment initiation (corresponding to 3 DDD/day). These criteria were based on the results from a recently published study,[16] where deviant users of methylphenidate consulted multiple prescribers and had been dispensed a large quantity during a 9-month follow-up period. However, no consensus exists for the threshold values of these criteria; they were thus largely arbitrarily set, but subject to multiple sensitivity analyses.

Analysis

Users were characterized according to baseline characteristics and characteristics of methylphenidate use during the first year.

Baseline characteristics. Baseline characteristics included sex, age at first dispensing, whether the first prescription of methylphenidate was an immediate-release or extended-release formulation, initial type of prescriber and use of other drugs related to the nervous system (ATC group N) in the six months prior to the first methylphenidate prescription (at least one dispensing). Drugs of interest were benzodiazepine derivatives (N05BA, N05CD and N03AE01), benzodiazepine-related drugs (N05CF) and opioids (N02A and R05DA04), which are all potential drugs of abuse.[21] Antipsychotics (N05A), antiepileptics (N03A), antidepressants (N06A) and drugs used in addictive disorders (N07B: buprenorphine, methadone and naltrexone) were also included as indicators of psychiatric comorbidity.

Characteristics of use during the first year. Characteristics included number of different pharmacies and prescribers visited for the dispensing/prescription of methylphenidate, proportion of methylphenidate prescriptions accounted for by different type of prescriber, total number of dispensings of methylphenidate, total number of DDDs of methylphenidate, percentage of users with a prescription of atomoxetine or modafinil and concurrent use of other drugs related to the nervous system. Concurrent drug use was defined as at least one dispensing of a drug in the categories as described above (ATC N) within the first year. In addition, we calculated the prescriber- and pharmacy loyalty coefficients. The prescriber loyalty coefficient is calculated as the proportion of an individual's prescriptions that is prescribed by the dominant prescriber for that individual, while the pharmacy loyalty coefficient is calculated similarly as the proportion of prescriptions redeemed at the dominant pharmacy.[32] In 6.0% of the prescriptions the type of prescriber was unknown and therefore these prescriptions were ignored in the calculation of the prescriber loyalty coefficient and in the number of different prescribers.

Factors associated with deviant patterns of methylphenidate use. Baseline characteristics associated with deviant patterns of methylphenidate use were identified using logistic regression and the corresponding odds ratios (ORs) with 95% confidence intervals were calculated. Both univariate (OR1) and multivariate analysis (OR2) were performed.

Supplementary analyses

We performed supplementary analyses stratifying users by sex, age, formulation of first dispensing of methylphenidate, type of initial prescriber and prior use of benzodiazepines or opioids.

Sensitivity analyses

Because there is a high drop-out rate among adults after filling only one prescription of ADHD-medication,[1,33] we performed a sensitivity analysis excluding individuals from our analysis with only one prescription for methylphenidate along with those initiating atomoxetine or modafinil within the first year, because these are expected to have changed their treatment regimens.

Sensitivity analyses were carried out regarding our definition of deviant use by varying the definition of deviant patterns of methylphenidate use. First by considering doctor shopping or high use separately and then by varying thresholds for doctor shopping and large dispensed quantity.

Other

All calculations were performed using STATA Release 13.0 (StataCorp, College Station, Texas, USA). The study was approved by the Danish Data Protection Agency and Statistics Denmark's Scientific Board. According to Danish law, ethical approval is not required for purely registry-based studies.[34]

RESULTS

We identified 42 694 individuals who started treatment with methylphenidate during the period 1 January 2007 to 30 June 2012. We excluded 17 215 individuals aged < 18 years, 357 individuals who filled two different ADHD drugs (inclusive amphetamine and dexamphetamine) at index date and 18 individuals who had at least two different types of prescribers at the index date. A total of 2144 individuals were excluded because of migration, and last, 2131 individuals were excluded because of death during the first year of follow-up, 89% of which were aged 50 or more. The final study population thus consisted of 20 829 individuals filling a total of 197 062 prescriptions for methylphenidate during the first year of follow-up.

Baseline characteristics of the study participants are presented in Table 1. The study participants had a median age of 31 years and were predominantly male (57.7%). A large proportion of the participants had prior use of drugs related to the nervous system with antidepressant use being dominant (37.9%).

A total of 82 (0.39%) individuals displayed deviant patterns of methylphenidate use according to the predefined criteria. This proportion was stable throughout the study period, going from 0.47% in 2007 to 0.44% in 2012 (range 0.26% to 0.47%). This group had a slightly greater proportion of males (65% vs. 57.7%) and had a greater proportion of individuals initiating treatment with extended-release methylphenidate compared to the group of non-deviant users (60% vs. 22.5%). Hospital doctors most frequently initiated treatment among deviant users (50%) and practicing specialist most often initiated treatment among non-deviant users (47.1%). A markedly higher proportion of deviant users had baseline use of drugs related to the nervous system compared with non-deviant users, with the exception of antidepressants (Table 1).

During the first year following index date, deviant users were characterized by a greater number of different pharmacies, a greater number of different prescribers and lower median loyalty to both prescriber (0.6 vs. 1.00) and pharmacy (0.7 vs. 1.00). The median number of dispensings was almost seven times higher among deviant users. Further, the dispensed quantities of extended-release methylphenidate were higher among deviant users (1260 DDD vs. 40 DDD) (Table 2).

With the exception of female sex, the univariate analysis yielded higher ORs for all variables compared to the multivariate analysis. The age stratum 25–49 years (OR2 2.49), extended-release methylphenidate as

Table 1. Baseline characteristics of incident users of methylphenidate from 1 January 2007 to 30 June 2012

Baseline characteristics			
	All (n = 20 829)	Deviant (n = 82)	Non-deviant (n = 20 747)
Median age at first dispensing (IQR)*	31 (23–41)	34 (28–40)	31 (23–41)
Sex			
Male	12 023 (57.7%)	53 (65%)	11 970 (57.7%)
Female	8806 (42.3%)	29 (35%)	8777 (42.3%)
Formulation of first dispensing of methylphenidate			
Immediate release	16 105 (77.3%)	33 (40%)	16 072 (77.5%)
Extended release	4724 (22.7%)	49 (60%)	4675 (22.5%)
Type of initial prescriber			
Practicing specialist	9781 (47.0%)	15 (18%)	9766 (47.1%)
General practitioner	3656 (17.6%)	21 (26%)	3635 (17.5%)
Hospital doctor	5688 (27.3%)	41 (50%)	5647 (27.2%)
Unknown	1704 (8.2%)	5 (6%)	1699 (8.2%)
Prior use of†			
Benzodiazepines and benzodiazepine-related drugs	3531 (17.0%)	31 (38%)	3500 (16.9%)
Opioids	2366 (11.4%)	19 (23%)	2347 (11.3%)
Antipsychotics	3199 (15.4%)	29 (35%)	3170 (15.3%)
Antidepressants	7886 (37.9%)	38 (46%)	7848 (37.8%)
Antiepileptics	1929 (9.3%)	18 (22%)	1911 (9.2%)
Drugs used in addictive disorders	907 (4.4%)	13 (16%)	894 (4.3%)

*IQR; interquartile range (Q25–Q75).
†For ATC codes see materials and methods.

first-line treatment (OR2 4.35) and general practitioners (OR2 3.06) and hospital doctors (OR2 4.07) as initial prescribers were all significant and relatively strong predictors of deviant use. The ORs of prior use of drugs related to the nervous system all had confidence intervals overlapping 1, with the exception of drugs used in addictive disorders (OR2 2.08) and opioids (OR2 1.75) (Table 3).

Stratification by sex revealed that deviant use among females was associated with prior use of benzodiazepines and benzodiazepine-related drugs (OR2 2.48), opioids (OR2 2.60) and drugs used in addictive disorders (OR2 5.36). Among males, these associations were non-significant (data shown in supplementary material, Tables S1 and S2).

Excluding individuals with only one prescription for methylphenidate (n = 3354) along with those initiating atomoxetine or modafinil only caused small changes in ORs (data not shown in full).

Changing our definition of deviant use, i.e. the thresholds of number of different prescribers and number of DDDs of methylphenidate, markedly changed the number of users displaying deviant

Table 2. Characteristics of use during the first year after first dispensing of methylphenidate

Characteristics during the first year	All (n = 20 829)	Deviant (n = 82)	Non-deviant (n = 20 747)
Median number of different pharmacies (IQR)[*]	1 (1–2)	3 (2–4)	1 (1–2)
Median number of different prescribers (IQR)[*]	1 (1–2)	5 (4–7)	1 (1–2)
Median number of dispensings (IQR)[*]	7 (3–14)	44 (35–59)	7 (3–14)
Median number of DDDs (IQR)[*]			
Methylphenidate	130 (40–313)	1387 (1254–1677)	130 (38–310)
Immediate-release	30 (10–80)	25 (0–297)	30 (10–80)
Extended-release	40 (0–230)	1260 (1110–1436)	40 (0–224)
Users with a prescription of			
Atomoxetine	2270 (10.9%)	9 (11%)	2261 (10.9%)
Modafinil	395 (1.9%)	1 (1%)	394 (1.9%)
Concurrent use of[†]			
Benzodiazepines and benzodiazepine-related drugs	4204 (20.2%)	35 (43%)	4169 (20.1%)
Opioids	3371 (16.2%)	33 (40%)	3338 (16.1%)
Antipsychotics	4584 (22.0%)	46 (56%)	4538 (21.9%)
Antiepileptics	2846 (13.7%)	32 (39%)	2814 (13.6%)
Antidepressants	8756 (42.0%)	46 (56%)	8710 (42.0%)
Drugs used in addictive disorders	1298 (6.2%)	25 (30%)	1273 (6.1%)
Median prescriber loyalty (IQR)[*]	1.00 (0.70–1.00)	0.6 (0.5–0.8)	1.00 (0.71–1.00)
Median pharmacy loyalty (IQR)[*]	1.00 (0.75–1.00)	0.7 (0.5–1.0)	1.00 (0.75–1.00)
All prescriptions	(n = 197 062)	(n = 3976)	(n = 193 086)
Practicing specialist	76 162 (38.6%)	569 (14.3%)	75 593 (39.1%)
General practitioner	73 701 (37.4%)	2379 (59.8%)	71 322 (36.9%)
Hospital doctor	35 285 (17.9%)	935 (23.5%)	34 350 (17.8%)
Unknown	11 914 (6.0%)	93 (2.3%)	11 821 (6.1%)

[*]IQR, interquartile range (Q25–Q75).
[†]For ATC codes see materials and methods.

behavior (Table 4). Compared to the main analysis, sensitivity analyses with more strict criteria identified deviant users that were older. Further, the group of deviant users had a slightly higher proportion of users initiating immediate-release methylphenidate, a higher proportion of hospital doctors as initial prescribers and a higher proportion of users with prior use of drugs related to the nervous system. Conversely, using less strict criteria, deviant users were younger, and the group of deviant users had a higher proportion of users initiating practicing specialists at the expense of general practitioners and hospital doctors. Further, a lower proportion of users had prior use of drugs related to the nervous system (data not shown in full). When doctor shopping was the only criterion, there was considerable resemblance between deviant and non-deviant users with respect to predictive profile (data shown in supplementary material, Tables S3 and S4).

DISCUSSION

Deviant users of methylphenidate were characterized by higher age, higher use of extended-release methylphenidate and more use of opioids and drugs used in addictive disorders as compared to non-deviant users. These characteristics were significant predictors of deviant use.

Our study has several strengths. First, the use of the Danish National Prescription Registry allowed us to identify all Danish residents with incident use of methylphenidate. We are thus confident that our study is not fraught with selection bias. The long history of accurate prescription records allowed us to apply a run-in period of at least 12 years, thus ensuring very little misclassification of new users. Finally, the Registry has been described to have a high coverage and provide high quality data.[25]

Our study has a number of limitations. First, registration of the prescriber practice code in the Danish National Prescription Registry may be subject to some misclassification. The magnitude of this problem has previously been estimated to affect 11% of non-electronic prescriptions.[35] This will result in a slight underestimation of the number of different prescribers, making individuals seem less deviant. Second, the Registry does not allow us to see if the quantity dispensed is actually consumed by the individuals themselves or if it is diverted to third parties, possibly

Table 3. Predictive factors of deviant patterns of methylphenidate use assessed using logistic regression

Baseline characteristics	Univariate analysis	Multivariate analysis
	OR1 [95 % confidence interval]	OR2 [95 % confidence interval]
Sex		
Male	(ref.)	(ref.)
Female	0.75 [0.47–1.17]	0.79 [0.49–1.26]
Age at first dispensing (years)		
18–24	(ref.)	(ref.)
25–49	3.04 [1.64–5.62]	2.49 [1.32–4.70]
50+	0.76 [0.21–2.69]	0.59 [0.16–2.19]
Formulation of first dispensing		
Immediate release	(ref.)	(ref.)
Extended release	5.10 [3.28–7.95]	4.35 [2.78–6.82]
Type of initial prescriber		
Practicing specialist	(ref.)	(ref.)
General practitioner	3.76 [1.94–7.30]	3.06 [1.56–6.02]
Hospital doctor	4.73 [2.61–8.55]	4.07 [2.23–7.43]
Prior use of[*]		
Benzodiazepines and benzodiazepine-related drugs	3.00 [1.91–4.69]	1.68 [1.00–2.82]
Opioids	2.36 [1.41–3.96]	1.75 [1.01–3.02]
Antipsychotics	3.03 [1.93–4.78]	1.61 [0.97–2.67]
Antiepileptics	2.77 [1.64–4.69]	1.37 [0.76–2.47]
Antidepressants	1.42 [0.92–2.19]	1.07 [0.66–1.71]
Drugs used in addictive disorders	4.18 [2.30–7.60]	2.08 [1.10–3.94]

[*]Reference: no consumption.

Table 4. Sensitivity analysis with altering criteria to define deviant patterns of use by doctor shopping and number of DDDs

	Number of users identified with deviant patterns of use			
	No threshold	≥730 DDD/ year	≥1095 **DDD/ year**	≥1416 DDD/ year
No threshold	20 829	814	192	61
≥3 prescribers/year	3716	403	123	48
≥4 prescribers/year	1372	230	**82**[*]	35
≥5 prescribers/year	491	105	47	25

[*]Main analysis.
The bold data indicate the data from the main analysis, i.e. the criteria of deviant use which have been used in the main analysis. It is not of great significance that these are bold.

leading to an overestimation of use. Last, the Registry does not provide reasons for individuals visiting multiple prescribers.

With our simple method based on prescription data, it was only possible to identify individuals with a regular deviant use. Hence, users with a sporadic misuse or seasonality in their misuse (e.g. during examinations, stressful work etc.) were unlikely

identified as deviant users. In addition, individuals filling only one methylphenidate prescription were also not identified as deviant users, although early drop-out may also be a likely indicator of misuse. Further, our method does not capture individuals with a non-medical use of methylphenidate or individuals obtaining methylphenidate through prescription diversion, which has been reported a major source of non-prescribed methylphenidate e.g. among students.[36,37] The number of deviant users did not change during the study period, and overall we found that deviant use among Danish adults was rare. However, in light of the above mentioned limitations, we expect this number to be an underestimation of the true number of adult misusers in Denmark.

Our underlying assumption was that users characterized by high use and doctor shopping, might be individuals with a medical methylphenidate misuse. However, there is no method against which we can compare our results for validation. Based on our findings, it remains to be elucidated if deviant users represent medical misusers or if deviant users merely represent an outer end of a normal spectrum. In Denmark, methylphenidate is not licensed for the treatment for ADHD in adults. However, the U.S. Food and Drug Administration (FDA) and the U.K. National Institute for Health and Care Excellence (NICE) recommend maximum doses of 72 mg/day and 100 mg/day.[38,39] We estimated that deviant users had a median daily methylphenidate use of approximately 3.8 DDD corresponding to 114 mg. For comparison, non-deviant users had a median daily use of approximately 0.4 DDD corresponding to 12 mg. To our knowledge, no national or international guideline would recommend dosages as high as 114 mg daily.

The study population generally had a high use of drugs related to the nervous system, which is in accordance with previous findings.[1,3] We found that individuals with prior use of opioids or drugs for addictive disorders had an increased risk of deviant methylphenidate use. Prior use of opioids may thus be a marker of methylphenidate misuse. Similarly, drugs used to treat addictive disorders have previously been correlated with methylphenidate misuse and misuse in general.[16,20] Prior use of drugs used in addictive disorders was the strongest predictor of deviant use. This warrants further investigation as it is not recommended to initiate treatment with methylphenidate among individuals with a history of substance abuse. We identified a marked effect modification by sex, in that the increased risk of deviant use in relation to prior use of these drugs was only observed among women. Differences in stimulant misuse between men

and women have been observed in other studies.[12] Furthermore, a higher correlation between substance use disorders and female youths with ADHD compared to male youths has been observed in one Danish study.[40]

Contrary to our hypothesis, initiation of treatment with extended-release methylphenidate was a strong predictor of deviant use. Studies have previously reported more widespread medical misuse of immediate-release over extended-release methylphenidate among adults, although both formulations have been correlated with misuse.[12,13,41] There are several possible explanations for these findings. Possibly, deviant users simply do not represent medical misusers, as suggested above. Confounding by indication may be another possible explanation; if the prescriber anticipates abuse problems in a given patient, he may prefer to prescribe the oral formulation that allegedly has the lowest abuse potential.

Doctor shopping and dispensed quantities were used as proxy measures of medical misuse. However, there is no consensus of which threshold values should be used to define deviant use. The numbers of deviant users were highly dependent on our definition thresholds. Required amount of dispensed quantities was the criterion giving the largest relative change in results. When only considering doctor shopping as criterion of deviant use we saw more resemblance between deviant and non-deviant users. Thus, in users of methylphenidate, doctor shopping alone is not suffice as a criterion to differentiate between deviant and non-deviant users and hence predict potential medical misuse.

In Denmark, all residents have one designated general practitioner which in part complicates doctor shopping. Besides obtaining prescriptions from the general practitioner, different short cuts exist: contact with the on-call general practitioner, prescriptions from a practicing specialist or hospital doctor or finally, a switch in the regular general practitioner. During the study period there was no regulation on communication between different prescribers.

In conclusion, deviant users of methylphenidate were characterized by higher age, higher use of extended-release methylphenidate and more use of opioids and drugs used for addictive disorders as compared to non-deviant users. Our results do not allow us to confirm if doctor shopping and high dispensed quantity identify medical misusers.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS:

- We identified deviant users of methylphenidate in Denmark by using a proxy for deviant use defined by doctor shopping and large dispensed quantity.
- Deviant users were characterized by higher age, higher use of extended-release methylphenidate and more use of opioids and drugs used for addictive disorders as compared to non-deviant users.
- Doctor shopping alone does not seem suffice as a criterion to identify deviant users of methylphenidate.

REFERENCES

1. 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; **69**: 589–598. doi:10.1007/s00228-012-1344-0.
2. Scheffler RM, Hinshaw SP, Modrek S, Levine P. The global market for ADHD medications. *Health Aff (Millwood)* 2007; **26**: 450–457. doi:10.1377/hlthaff.26.2.450.
3. 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.
4. Kaye S, Darke S. The diversion and misuse of pharmaceutical stimulants: what do we know and why should we care?: Pharmaceutical stimulant diversion and misuse. *Addiction* 2012; **107**: 467–477. doi:10.1111/j.1360-0443.2011.03720.x.
5. Geirs DP, Pottegård A, Halldórsson M, Zoëga H. A nationwide study of attention-deficit/hyperactivity disorder drug use among adults in Iceland 2003–2012. *Basic Clin Pharmacol Toxicol* 2014; n/a–n/a. doi:10.1111/bcpt.12243.
6. Hugtenburg JG, Heerdink ER, Egberts ACG. Increased psychotropic drug consumption by children in the Netherlands during 1995–2001 is caused by increased use of methylphenidate by boys. *Eur J Clin Pharmacol* 2004; **60**. doi:10.1007/s00228-004-0765-9.
7. 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**: 1443–1450. doi:10.1007/s00228-012-1265-y.
8. The Danish Health and Medicines Authority. [Evaluation of the safety in the use of methylphenidate]. Available at: http://laegemiddelstyrelsen.dk/~/media/853DB0D8B52942CDA24484E8DF9E1DAB.ashx.
9. Parasrampuria DA, Schoedel KA, Schuller R, *et al.* Assessment of pharmacokinetics and pharmacodynamic effects related to abuse potential of a unique oral osmotic-controlled extended-release methylphenidate formulation in humans. *J Clin Pharmacol* 2007; **47**: 1476–1488. doi:10.1177/0091270007308615.
10. Kollins SH, MacDonald EK, Rush CR. Assessing the abuse potential of methylphenidate in nonhuman and human subjects: a review. *Pharmacol Biochem Behav* 2001; **68**: 611–627.
11. Kollins SH. Abuse liability of medications used to treat attention-deficit/hyperactivity disorder (ADHD). *Am J Addict* 2007; **16**: 35–44. doi:10.1080/10550490601082775.
12. Wilens TE, Adler LA, Adams J, *et al.* Misuse and diversion of stimulants prescribed for ADHD: a systematic review of the literature. *J Am Acad Child Adolesc Psychiatry* 2008; **47**: 21–31. doi:10.1097/chi.0b013e31815a56f1.

13. Wilens TE, Gignac M, Swezey A, Monuteaux MC, Biederman J. Characteristics of adolescents and young adults with ADHD who divert or misuse their prescribed medications. *J Am Acad Child Adolesc Psychiatry* 2006; **45**: 408–414. doi:10.1097/01.chi.0000199027.68828.b3.

14. Frauger E, Pauly V, Thirion X, *et al.* Estimation of clonazepam abuse liability: a new method using a reimbursed drug database. *Int Clin Psychopharmacol* 2009; **24**: 318–324. doi:10.1097/YIC.0b013e328330ae4b.

15. Pauly V, Frauger E, Pradel V, *et al.* Which indicators can public health authorities use to monitor prescription drug abuse and evaluate the impact of regulatory measures? Controlling High Dosage Buprenorphine abuse. *Drug Alcohol Depend* 2011; **113**: 29–36. doi:10.1016/j.drugalcdep.2010.06.016.

16. Frauger E, Pauly V, Natali F, *et al.* Patterns of methylphenidate use and assessment of its abuse and diversion in two french administrative areas using a proxy of deviant behaviour determined from a reimbursement database. *CNS Drugs* 2011; **25**: 415–424.

17. Wainstein L, Victorri-Vigneau C, Sébille V, *et al.* Pharmacoepidemiological characterization of psychotropic drugs consumption using a latent class analysis. *Int Clin Psychopharmacol* 2011; **26**: 54–62. doi:10.1097/YIC.0b013e3283400cb2.

18. Rouby F, Pradel V, Frauger E, *et al.* Assessment of abuse of tianeptine from a reimbursement database using "doctor-shopping" as an indicator: assessment of abuse liability of tianeptine. *Fundam Clin Pharmacol* 2012; **26**: 286–294. doi:10.1111/j.1472-8206.2010.00906.x.

19. Pradel V, Delga C, Rouby F, Micallef J, Lapeyre-Mestre M. Assessment of abuse potential of benzodiazepines from a prescription database using "doctor shopping"as an indicator. *CNS Drugs* 2010; **24**: 611–620.

20. Pradel V, Thirion X, Ronfle E, Masut A, Micallef J, Bégaud B. Assessment of doctor-shopping for high dosage buprenorphine maintenance treatment in a French region: development of a new method for prescription database. *Pharmacoepidemiol Drug Saf* 2004; **13**: 473–481. doi:10.1002/pds.892.

21. Bramness JG, Furu K, Engeland A, Skurtveit S. Carisoprodol use and abuse in Norway. A pharmacoepidemiological study. *Br J Clin Pharmacol* 2007; **64**: 210–218. doi:10.1111/j.1365-2125.2007.02847.x.

22. Chen C-Y, Yeh H-H, Fang S-Y, Wu EC-H, Chang I-S, Lin K-M. Overlapping prescriptions of stimulants for children and adolescents with attention-deficit hyperactivity disorder. *Psychiatr Serv* 2012; **63**: 1011–1018.

23. Hallas J, Støvring H. Templates for analysis of individual-level prescription data. *Basic Clin Pharmacol Toxicol* 2006; **98**: 260–265.

24. Nordmann S, Pradel V, Lapeyre-Mestre M, *et al.* Doctor shopping reveals geographical variations in opioid abuse. *Pain Physician* 2013; **16**: 89–100.

25. Wallach Kildemoes H, Toft Sorensen H, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011; **39**: 38–41. doi:10.1177/1403494810394717.

26. Pedersen CB, Gøtzsche H, Møller JØ, Mortensen PB. The Danish civil registration system. *Dan Med Bull* 2006; **53**: 441–449.

27. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2014. 2013.

28. The Danish Health and Medicines Authority. [Guide to medicamental treatment of children and adolescents with psychiatric disorder]. Available at: https://www.retsinformation.dk/forms/R0710.aspx?id = 146409. Accessed March 16, 2015.

29. Danish Health and Medicines Authority. [Ritalin—Summary of Product Characteristics]. Available at: www.produktresume.dk.

30. Institute of Rational Pharmacotherapy. [Strattera (atomoxetin)]. Available at: http://www.irf.dk/dk/anmeldelser/praeparatanmeldelser/arkiv/strattera_.htm. Accessed March 18, 2015.

31. WHOCC—ATC/DDD Index. Available at: http://www.whocc.no/atc_ddd_index/?code=N06BA04&showdescription=yes. Accessed May 19, 2014.

32. Pottegård A, Hallas J. Physicians' and pharmacies' overview of patients' medication. An analysis of fidelity coefficients. *Eur J Clin Pharmacol* 2011; **67**: 919–924. doi:10.1007/s00228-011-1026-3.

33. Pottegård A, Bjerregaard BK, Kortegaard LS, Zoëga H. Early discontinuation of ADHD drug treatment: a Danish Nationwide Drug Utilization Study. *Basic Clin Pharmacol Toxicol* 2014. doi:10.1111/bcpt.12325.

34. Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health* 2011; **39**: 12–16.

35. Statistics Denmark. [Handbook for data in the National Prescription Registry] (in Danish). Available at: http://www.dst.dk/~/media/Kontorer/13-Forskning-og-Metode/LMDB%20H%C3%A5ndbog%202014.pdf. Accessed September 24, 2014.

36. Barrett SP, Darredeau C, Bordy LE, Pihl RO. Characteristics of methylphenidate misuse in a university student sample. *Can J Psychiatry Rev Can Psychiatr* 2005; **50**: 457–461.

37. Darredeau C, Barrett SP, Jardin B, Pihl RO. Patterns and predictors of medication compliance, diversion, and misuse in adult prescribed methylphenidate users. *Hum Psychopharmacol Clin Exp* 2007; **22**: 529–536. doi:10.1002/hup.883.

38. FDA. Highlights of prescribing information on Concerta. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021121s015s017lbl.pdf. Accessed October 7, 2014.

39. Treatment for attention deficit hyperactivity disorder in adults—NICE pathways. Available at: http://pathways.nice.org.uk/pathways/attention-deficit-hyperactivity-disorder#path=view%3A/pathways/attention-deficit-hyperactivity-disorder/treatment-for-attention-deficit-hyperactivity-disorder-in-adults.xml&content=view-node%3Anodes-how-to-use-drug-treatment. Accessed October 7, 2014.

40. Dalsgaard S, Mortensen PB, Frydenberg M, Thomsen PH. ADHD, stimulant treatment in childhood and subsequent substance abuse in adulthood—a naturalistic long-term follow-up study. *Addict Behav* 2014; **39**: 325–328. doi:10.1016/j.addbeh.2013.09.002.

41. Bright GM, Delphia B, Wildberger B. Survey evaluation of the abuse potential of short-acting versus long-acting stimulants in ADHD. Presented at the 160th Annual Meeting of the American Psychiatric Association; San Diego. 2007.

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