



Brief report

Abuse of methylphenidate in Germany: Data from spontaneous reports of adverse drug reactions



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ABSTRACT

To retrieve insights into abuse/dependence of methylphenidate (MPH) in Germany, a query of a pharmacovigilance database was performed (observation interval: 1993 until 2012). From 1190 reports of any ADR related to MPH, $n=23$ (2%) cases of MPH abuse were identified (mean age 29 years; male sex 78%; mean daily MPH-dosage 111 ± 126.6 mg). As oral application was predominant (70%), the majority of reported cases of MPH abuse might be due to pharmacologic neuroenhancement.

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1. Introduction

Methylphenidate (MPH) is an amphetamine-like agent that is approved for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy with or without cataplexy. Probably due to increasing incidence of ADHD-diagnoses, a rise of annual MPH-prescriptions could be observed in last few years (Schubert et al., 2010). However, the relative increase in WHO estimates of consumption of MPH (268.9%), from 4.66 to 17.9 defined daily doses per 1000 population, during 1995 and 2006 far exceeded the relative increase in number of prescriptions per year, from 15,044,359 to 30,137,136 (100.3%) (Swanson and Volkow, 2008), leaving room for different interpretations such as possible increase of MPH abuse for the purpose of recreational use (Frauger et al., 2012) or pharmacologic neuroenhancement (Teter et al., 2005; Boyd et al., 2006; Franke et al., 2011; Dietz et al., 2013). The hypothesis of increasing MPH abuse necessitates to be proven. In this context, data derived from pharmacovigilance institutions might be helpful. Pharmacovigilance databases that record spontaneous reports of adverse drug reactions (ADR) may provide valuable insights into aspects of the abuse of prescription drugs such as MPH. Naturally, data retrieved using spontaneous ADR reports do less allow drawing definite conclusions about epidemiologic aspects

of ADR, but rather to evaluate the physicians' reporting behaviour concerning the particular ADR and characteristics of patients that have developed an ADR. In the present paper we intended to:

- identify the number of cases of MPH abuse that were reported to the database of a German medical regulatory body,
- analyse the clinical and demographical characteristics of associated patients, and
- search for possible changes of the reporting frequency over the observation interval in order to retrieve insights into the reporting behaviour of physicians in Germany regarding MPH abuse.

2. Methods

To investigate the aspects as listed above we analysed all reported cases of MPH abuse and dependence that had been submitted to the responsible federal authority, the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM], Germany). The BfArM is a Federal Institute within the portfolio of the Federal Ministry of Health. It is responsible for the surveillance of risks due to medical products in Germany. Among other functions, BfArM records spontaneous reports about ADR of pharmaceuticals. Sources of reports are clinicians, pharmaceutical companies, the Drug Commission of the German Medical Association, systematic clinical trials, and the literature. It gains information in pharmacovigilance through systematic studies of published reports from Germany. Each BfArM report is documented in a separate standard form filled out by the reporting person. Electronic documentation of reported ADR is performed at the BfArM since the year 1993 (approval of MPH in Germany in the year 1954).

On October 19th, 2012 (index-date) a query of the entire BfArM database of ADR was performed using the standardised Medical Dictionary for Regulatory

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Activities (MeDRA) query (SMQ). The applied SMQ-term was “drug abuse” that also implicated the terms “drug abuse”, “drug abuser”, “drug dependence”, “intentional drug misuse”, “intentional overdose”, “maternal use of illicit drugs”, “multiple drug overdose intentional”, “polysubstance dependence” and “substance abuse”. The reports that were retrieved by using this SMQ-term and their narratives, respectively, were searched by hand and assessed for the presence of MPH abuse independently by two examiners (MG and CSL). The retrieved cases were analysed systematically, regardless of whether they occurred with MPH monotherapy or under a regime of MPH plus co-medication. Inclusion criterion was the description of MPH abuse or dependence. Due to heterogeneous presentation of the data, it was neither possible to verify the plausibility of the reported MPH abuse nor to identify the individual motivation to abuse MPH (e.g. pharmacologic neuroenhancement, recreational use, inducing an instant “high” etc.). Thus, the attribution of MPH abuse/dependence was derived directly from the case narratives of the BfArM reports (phrases such as “...the patient had abused methylphenidate...”). This implicates that no causality assessment of the suggested relation between MPH use and the development of the reported addictive behaviours was performed. Data was extracted using the following parameters: year of report, age and sex of patient, indication for prescription of MPH, presence of any other psychiatric diagnosis other than substance-related disorders, duration of MPH abuse or dependence until report to BfArM, mean daily taken MPH dosage, way of MPH application, and previous and/or current abuse of or dependence on psychotropic substances other than MPH. Polytoxicomania was used according to ICD-10 F19.1 or F19.2 criteria of “polytoxicomania” (multiple substance dependence or abuse) and was also derived directly from the original BfArM reports without the performance of a separate plausibility check. The term “psychotropic substance” was defined as any applicable agent with psychotropic properties including nicotine, alcohol, any

approved drug with psychoactive properties, and any illicit drug. The particular durations of MPH abuse and dependence until the time of their reporting to BfArM were also derived directly from the respective case narratives (e. g. phrases such as “...the patient had abused methylphenidate for 6 months...”). Extracted data were analysed by descriptive values (mean and median values, and mean standard deviation).

3. Results

On the index date $n=1190$ reports of any ADR related to MPH were reported to BfArM. One hundred and ten (9%) reports were related to the SMQ term “drug abuse”. According to our analysis we could identify $n=23$ (2%) cases of MPH abuse, with the first report dating back to 1999 and the last to 2012. There was a preponderance of male persons (78%; $n=18$) and the mean age of the study population was 29 years. ADHD was the most common indication for the prescription of MPH ($n=10/43.5\%$), whereas $n=5$ (22%) subjects received MPH without any medical indication. Finally, we could identify a relatively constant low number of reports of MPH abuse per year ranging between 1 and 5 cases between the years 2004 and 2010 (see Fig. 1). However, the annual absolute numbers of reports of MPH abuse/dependence were

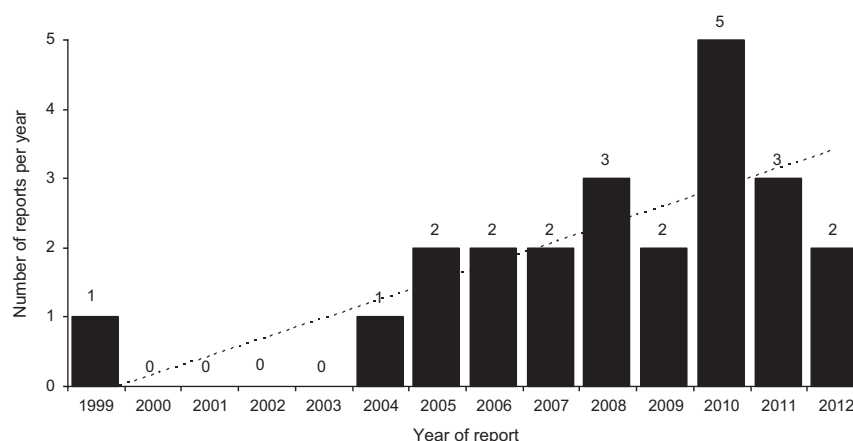


Fig. 1. Number of annual reports of methylphenidate abuse/dependence in Germany between 1999 and October 2012 (total number of report $n=23$).

Table 1

Characteristics of detected cases, indication for prescription of MPH, psychiatric diagnoses other than substance-related disorders, frequency of MPH-abuse and -dependence, frequency of withdrawal syndrome after discontinuation of MPH ($n=23$ cases).

Mean age (years) (missing data on $n=6/26\%$)	29 ± 13.2 SD (median 25, range 10–60)
Sex (missing data on $n=1/4\%$)	F: $n=4/17\%$; M: $n=18/78\%$
Original indication for prescription of MPH (missing data on $n=7/30\%$)	
ADHD	10/43.5%
Narcolepsy	1/4.5%
Without medical indication	5/22%
Way of application (missing data on $n=1/4\%$)	
Oral	16/70%
Nasal inhalation	4/17%
Intravenous	2/9%
Mean daily MPH dosage (mg) (missing data on $n=6/26\%$)	111 ± 126.6 SD (54, range 10–432)
Psychiatric diagnoses (missing data on $n=18/7\%$)	
MDD	1/4%
Personality disorder	3/13%
MDD plus personality disorder	1/4%
Current abuse of other PS (missing data on $n=19/83\%$)	4/17%
Previous abuse of other PS (missing data on $n=20/87\%$)	3/13%
Duration of MPH abuse (months) (missing data on $n=14/61\%$)	7.7 ± 11.4 SD (median 3, range 1–36)

ADHD=attention deficit hyperactivity disorder; F=female; max=maximum value; min=minimum value; MDD=major depressive disorder; SD=mean standard deviation; M=male; MPH=methylphenidate; PS=psychotropic substance (defined as any applicable agent with psychotropic properties including nicotine, alcohol, any approved drug with psychotropic properties, and any illicit drug).

increasing between the years 2004 and 2010. Further details are given in Table 1.

4. Discussion

Our analysis of spontaneous reports submitted to the German Federal Institute for Drugs and Medical Devices (BfArM) resulted in the detection of 23 cases of MPH abuse between 1993 and 2012, which represented only 2% of all reports of any ADR related to MPH. Although underreporting, defined as non-reporting of ADR (although the respective ADR has occurred and was observed by a physician) resulting in a discrepancy between the frequency of reported and truly occurring ADR (LePendou et al., 2013), is a common problem regarding the monitoring and assessment of ADR in pharmacovigilance datasets (Jacob et al., 2013) that likely has contributed to the relatively low number of identified reports of MPH abuse/dependence, it should be considered that reporting of ADR is legally required. Generally, the conclusions that can be drawn on the basis of our analysis are principally limited by the small sample size. In spite of suboptimal quality of the data, our analysis revealed a constantly low number of annual reports of MPH abuse in Germany between 1993 and 2012 with increasing annual absolute frequencies between the years 2004 and 2010.

The abuse potential of MPH was emphasized in the literature shortly after its introduction to the market (Jorgensen and Kodahl, 1961; Hahn et al., 1969; Willey, 1971) and is still subject of ongoing research (Volkow and Swanson, 2003; Forrester, 2006). Thus, low number of reports of MPH abuse to a Germany medical regulatory detected in this analysis was surprisingly low and could reflect either low willingness of physicians to report such observations (underreporting) or low vigilance towards MPH abuse in general. However, the frequency of these reports increased between 2004 and 2010 and first reports of MPH abuse were reported to BfArM not before 1999. This partly corresponds with a remarkable increase of the annual prescription volume of MPH in the year 2007 (45.7 million daily doses of MPH) compared to 1997 in Germany (nearly tenfold increase) (Lohse et al., 2008) – a possible indirect reference to MPH abuse, independently of markedly increased prevalence rates of ADHD in Germany (Schubert et al., 2010). A further connection, not necessarily contrary to the latter, may be seen in the observation that the phenomenon of pharmacologic neuroenhancement emerged as widespread phenomenon around the year 2000 (Babcock and Byrne, 2000; McCabe et al., 2004). In this regard, the physicians' sensibility regarding MPH abuse in the context of pharmacologic neuroenhancement and the physicians' reporting behaviour might have changed.

Intranasal and intravenous application of MPH cause effects similar to the effects of cocaine (getting “high”), rendering this application pattern as typical for recreational use of MPH (Morton and Stockton, 2000; Klein-Schwartz, 2002; McCabe et al., 2004), while oral application is usually performed for the purpose of pharmacologic neuroenhancement (Morton and Stockton, 2000). Considering that oral application of MPH was most frequent (~70%) in the studied cases, it is possible that the intended effect of MPH use within this cohort was pharmacologic neuroenhancement, although no information regarding the individual reasons for a non-medical use of MPH were available.

Considering that annual MPH-consumption far exceeds MPH-prescriptions (Swanson and Volkow, 2008), the low number of

reports of MPH abuse in Germany might be due to a low vigilance of physicians concerning MPH abuse or willingness to report suspicious cases (underreporting) (Jacob et al., 2013). Taking into account the emerging evidence of increasing abuse of prescription stimulants (Babcock and Byrne, 2000; McCabe et al., 2004; Boyd et al., 2006; McCabe, 2008; Franke et al., 2011; Dietz et al., 2013) we would like to encourage physicians to report cases suspicious of MPH abuse to the responsible pharmacovigilance institutions in order to facilitate a naturalistic monitoring of an otherwise possibly unperceived problematic development. The low number of reported cases of abuse identified in this analysis may also give rise to the conclusion that the abuse potential of MPH may be lower than generally suggested.

References

- Babcock, Q., Byrne, T., 2000. Student perceptions of methylphenidate abuse at a public liberal arts college. *Journal of American College Health* 49, 143–145.
- Boyd, C., McCabe, S., Cranford, J., Young, A., 2006. Adolescents' motivations to abuse prescription medications. *Pediatrics* 118, 2472–2480.
- Dietz, P., Striegel, H., Franke, A., Lieb, K., Simon, P., Ulrich, R., 2013. Randomized response estimates for the 12-month prevalence of cognitive-enhancing drug use in university students. *Pharmacotherapy* 33, 44–50.
- Forrester, M., 2006. Methylphenidate abuse in Texas, 1998–2004. *Journal of Toxicology and Environmental Health* 69, 1145–1153.
- Franke, A., Bonertz, C., Christmann, M., Huss, M., Fellgiebel, A., Hildt, E., Lieb, K., 2011. Non-medical use of prescription stimulants and illicit use of stimulants for cognitive enhancement in pupils and students in Germany. *Pharmacopsychiatry* 44, 60–66.
- Frauger, E., Nordmann, S., Orleans, V., Pradel, V., Pauly, V., Thirion, X., Micallef, J., réseau des CEIPs, 2012. Which psychoactive prescription drugs are illegally obtained and through which ways of acquisition? About OPPIUM survey. *Fundamental and Clinical Pharmacology* 26, 549–556.
- Hahn, H., Schweid, A., Beaty, H., 1969. Complications of injecting dissolved methylphenidate tablets. *Archives of Internal Medicine* 123, 656–659.
- Jacob, D., Marrón, B., Ehrlich, J., Rutherford, P., 2013. Pharmacovigilance as a tool for safety and monitoring: a review of general issues and the specific challenges with end-stage renal failure patients. *Drug, Healthcare and Patient Safety* 5, 105–112.
- Jorgensen, F., Kodahl, T., 1961. On the abuse of Ritalin. *Ugeskrift for Laeger* 123, 1275–1279.
- Klein-Schwartz, W., 2002. Abuse and toxicity of methylphenidate. *Current Opinion in Pediatrics* 14, 219–223.
- LePendou, P., Iyer, S., Bauer-Mehren, A., Harpaz, R., Mortensen, J., Podchyska, T., Ferris, T., Shah, N., 2013. Pharmacovigilance using clinical notes. *Clinical Pharmacology and Therapeutics* 93, 547–555.
- Lohse, M., Lorenzen, A., Müller-Oerlinghausen, B., 2008. *Arzneiverordnungs-Report*. Springer, Berlin, Heidelberg, New York p. 2008.
- McCabe, S., 2008. Screening for drug abuse among medical and nonmedical users of prescription drugs in a probability sample of college students. *Archives of Pediatrics & Adolescent Medicine* 162, 225–231.
- McCabe, S., Teter, C., Boyd, C., Guthrie, S., 2004. Prevalence and correlates of illicit methylphenidate use among 8th, 10th, and 12th grade students in the United States, 2001. *Journal of Adolescent Health* 35, 501–504.
- Morton, W., Stockton, G., 2000. Methylphenidate abuse and psychiatric side effects. *Journal of Clinical Psychiatry* 2, 159–164.
- Schubert, I., Köster, I., Lehmkuhl, G., 2010. The changing prevalence of attention-deficit/hyperactivity disorder and methylphenidate prescriptions: a study of data from a random sample of insureds of the AOK health insurance company in the German State of Hessen, 2000–2007. *Deutsches Ärzteblatt International* 107, 615–621.
- Swanson, J., Volkow, N., 2008. Increasing use of stimulants warns of potential abuse. *Nature* 453, 586.
- Teter, C., McCabe, S., Cranford, J., Boyd, C., Guthrie, S., 2005. Prevalence and motives for illicit use of prescription stimulants in an undergraduate student sample. *Journal of American College Health* 53, 253–262.
- Volkow, N., Swanson, J., 2003. Variables that affect the clinical use and abuse of methylphenidate in the treatment of ADHD. *American Journal of Psychiatry* 160, 1901–1909.
- Willey, R., 1971. Abuse of methylphenidate (Ritalin). *New England Journal of Medicine* 19, 464.