



## Original article

# Age-related pharmacotherapy of attention deficit hyperactivity disorder in Slovenia in children and adolescents: A population-based study

M. Stuhec<sup>a,b,\*</sup>, I. Locatelli<sup>b</sup><sup>a</sup> Department for Clinical Pharmacy, Ormoz Psychiatric Hospital, Ptujška 33, 9242 2270, Ormoz, Slovenia, European Union<sup>b</sup> Faculty of Pharmacy, University of Ljubljana, Askerceva cesta 7, SI-1000 Ljubljana, Slovenia, European Union

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## ABSTRACT

**Background:** There are no data on age-related pharmacotherapy for Attention Deficit Hyperactivity Disorder (ADHD) medication in children and adolescents in the most European countries. The main aim of this paper was to obtain that data for children and adolescents in Slovenia.

**Method:** The number of ADHD drug prescriptions per patient was obtained from the health claims data on prescription drugs of the Health Insurance Institute of Slovenia for the study period (2003–2015). Three age groups were analyzed: 2–5 years, 6–12 years, and 13–17 years. Only immediate-release methylphenidate (IR-MPH), methylphenidate-osmotic release oral delivery system (OROS-MPH), and atomoxetine (ATX) were available and included in this study.

**Results:** Less than 50% of patients in Slovenia were treated with medication. The number of patients treated with MPH in the 6–12 age group remained approximately the same between 2007 and 2015 (604–729 patients). In the 13–17 age group, however that number increased 2-fold between 2003 and 2015, from 288 to 555. The number of patients treated with ATX in the 6–12 age group increased from 20 to 163 between 2007 and 2015. The number was similar in the 13–17 age group, increasing from 10 to 165 in the same period. In 2015, 21% of the patients from all age groups in this study were treated with ATX.

**Conclusions:** The number of patients treated for ADHD increased rapidly in all age groups. Patients under the age of six are prescribed medication in Slovenia, which should be avoided.

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## 1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common mental disorders in children and adolescents. The prevalence of ADHD is 3.4% worldwide (95% CI: 2.6–4.5), 5–7% in school-aged children, and between 2.5 and 5% in adults [1,2]. With the exception of Germany, there are almost no data on the epidemiology of ADHD in Eastern and Central Europe. Stuhec et al. (2015) estimate that the mean prevalence rate of child and adolescent ADHD patients in Slovenia in 2012 was 750 per 100,000 children and adolescents (0.75%). They conclude that ADHD is a common mental health disorder among Slovenian children and adolescents, and is still underdiagnosed in comparison to Western countries (e.g. Spain and Germany) [3,4]. While the

literature across Europe frequently comments on increased rates of ADHD diagnoses and questions whether ADHD is overdiagnosed and overtreated, data from reviews of clinical practice suggest the opposite may be true, with ADHD being both underrecognized and undertreated in many European countries [5,6]. ADHD has traditionally been conceptualized as a neurodevelopmental disorder that continues into adulthood in up to 50% of diagnosed cases [7].

ADHD is associated with significantly increased mortality rates in children, adolescents, and adults. A Danish study suggests, that the increased mortality is mainly driven by deaths from unnatural causes, especially accidents [8,9]. Even with medication, ADHD compromises the patients' social interactions and relationships as well as their educational and professional success [10]. Childhood mental disorders, especially ADHD, also indicate a risk for subsequent psychotic experiences and disorders during childhood. A study by Hennig et al. compared participants without a disorder to participants with a mental disorder including ADHD. ADHD

\* Corresponding author. Ptujška Cesta 33, Ormoz, Slovenia, European Union.

Tel.: +38641239414; fax: +386 2 74 15 147.

E-mail address: [matejstuhec@gmail.com](mailto:matejstuhec@gmail.com) (M. Stuhec).

patients had a higher risk of psychotic experiences at age 12 (OR: 1.70, 95% CI: 1.28–2.27) and of psychotic disorders at age 18 (OR: 2.31, 95% CI: 1.03–5.15). Especially the ADHD combined subtype at age 7 was strongly associated with psychotic experiences at age 12 (OR: 3.26, 95% CI: 1.74–6.10) [11].

ADHD is treated with pharmacotherapy and other interventions (e.g. cognitive behavioral therapy). Stimulants are the first line treatment for ADHD in children, adolescents, and adults, with medium to high effect sizes [12–15]. According to ADHD treatment guidelines, the nonstimulant atomoxetine (ATX) is often the second line treatment and has a medium effect size [16,17]. As such, ATX prescribing should be closely monitored to prevent inappropriate prescribing, which has additional costs [16,17]. Most medications have not been studied in children under six, so pharmacotherapy in these patients should be avoided [16]. In Slovenia, ATX consumption increased rapidly from 2001 to 2012, which did not happen in Germany, where prescribing of ATX is still stable [4,18]. It was suggested that European treatment guidelines should be adopted into clinical practice in Slovenia and a closer cooperation with the European Society for Child and Adolescent Psychiatry (ESCAP) is needed to avoid overprescribing ATX [19,20]. These results in Slovenia suggest that further research is needed to confirm or reject this practice in other European countries. Studies conducted in several countries have shown a significant increase in the use of ADHD drugs in the last years [21]. However, these data are not available for a number of countries, for example other ex-Yugoslavian countries and those in Eastern Europe [3]. Consequently, there are almost no data on age-related pharmacotherapy for ADHD medication in children and adolescents in many European countries including Slovenia, although ADHD medication has been used for more than 20 years.

The main aim of this research was to obtain the data on age-related ADHD pharmacotherapy in Slovenia in children and adolescents, including children under 6, for the study period between 2003 and 2015. The second aim was to investigate ADHD treatment patterns in individual patient groups. These data have not yet been published in the literature. We also wish to encourage other European countries in Central and Eastern Europe to invest more resources into treating ADHD in children and adolescents.

## 2. Methods

The health claims database of the Health Insurance Institute of Slovenia (NHI) was used to collect the number of patients who were prescribed ADHD drugs. The database contains information on the national and regional consumption and on the cost of medication dispensed in Slovenian outpatient pharmacy, if the medication is covered by the NHI insurance. It includes 10 regional Slovenian centers and is so representative of the entire Slovenian population (of around 2 millions). These data are mainly used for administrative purposes and serves to monitor the drug consumption in primary health system services (e.g. control of ambulatory prescribing). The database also includes anonymized patient metadata (age on prescription, sex, etc.) as well as any special features of the prescribing physician or the dispensing pharmacy. The NHI database is known for its reliability and accuracy and was already used in many published studies [18,22].

The study subjects were limited to those younger than 18 years. The number of children and adolescents who were prescribed ADHD drugs at least once each year during the study period (2003–2015) was obtained and analyzed for drug consumption trends during the study period. Patients were divided into 3 age groups (2–5 years, 6–12 years, and 13–17 years) for each year between 2003 and 2015 (e.g. a patient born in 1997 with ADHD drug prescription in 2009 was assigned to the 6–12 age group for 2009,

and to the 13–17 age group for 2010, if they were still prescribed ADHD drugs in 2010). The number of patients was retrieved separately for methylphenidate (MPH) and atomoxetine (ATX) prescriptions. All results are absolute numbers of treated patients in Slovenia. The relative number of patients was also calculated (number of patients per 1000 people in a specific age group). The population data during the study period was obtained from the Statistical Office of Slovenia.

In Slovenia, the pricing of medicinal products is regulated by the Slovenian Agency for Medicinal Products and Medical Devices. The products are paid through publicly funded insurances at the NHI. Everyone under the age of 18 has a mandatory health insurance at the NHI, which is state-controlled. Physicians usually prescribe prescription for 3 months (one prescription/Rx) in the maintenance phase and for one month after discontinuation/initiation. Drugs prescribed but not dispensed by a community pharmacist, are not included in the database. Once a prescription is dispensed at a community pharmacy, it is immediately added to the database. This database does not include hospital prescription (on chart) but only ambulatory prescription. Immediately when the patient is discharged from the hospital (and ambulatory prescription) prescription is necessary. This prescription is coded in this database after drug is dispensed by community pharmacist.

This study only includes ADHD medication available in Slovenia during the study period; that is immediate-release methylphenidate (IR-MPH), methylphenidate-osmotic release oral delivery system (OROS-MPH; market launch in 2006), and ATX (market launch in 2007). Both MPH forms were joined under the MPH category. Amphetamine, lisdexamfetamine dimesylate, and guanfacine were not available in Slovenia and were excluded from this research [18,20]. In Slovenia, only psychiatrists specialized in child and adolescent psychiatry can diagnose and begin the treatment of ADHD in children and adolescents. According to the consumption data for Slovenian hospitals [18], less than 1% of the total ADHD medication was prescribed in hospitals in the last study years [24].

The percentage of treated patients in 2012 was calculated from the total of diagnosed ADHD patients in Slovenia in 2012 (obtained from an article by Stuhec et al.) and from the number of treated patients calculated in this research [3]. Statistical analysis was done in Microsoft Excel 2010.

## 3. Results

In the 6–12 age group, the number of patients treated with MPH remained almost unchanged over the study period (app. 600 to 700 patients or 4.5 to 5.1 patients per 1000 children aged 6–12). However, in the 13–17 age group, the number of patients treated with MPH increased from 288 (2.4 per 1000 children aged 13–17) in 2003 to 555 (6.0 per 1000 children aged 13–17) in 2015, which is more than 2-fold increase (Fig. 1). During the study period, there were also 28 MPH prescriptions to 25 children under the age of 6.

The number of patients treated with ATX in the 6–12 age group increased from 20 (0.15 per 1000 children aged 6–12) in 2007 to 194 (1.5 per 1000 children) in 2011 and decreased to 163 (1.2 per 1000 children) in 2015. In the 2–5 age group, 6 patients were treated with ATX during the study period. In the 13–17 age group, the number of patients treated with ATX increased from 10 (0.11 per 1000 children aged 13–17) in 2007 to 120 (1.2 per 1000 children) in 2010 and to 165 (1.8 per 1000 children) in 2015 (Fig. 2).

The number of patients in the 13–17 age group treated with either ATX or MPH increased between 2003 and 2015, from 288 (2.4 per 1000 children aged 13–17) to 705 (7.7 per 1000 children). Between 2003 and 2015, the number of patients treated with ATX or MPH in the 6–12 age group increased from 636 (4.5 per 1000 children aged 6–12) to 858 or 6.2 per 1000 children (Fig. 3). In

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