



Original article

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

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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

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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

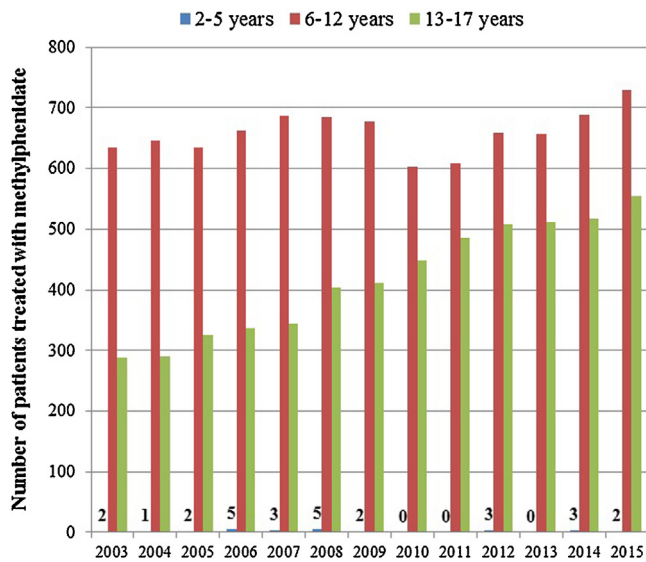


Fig. 1. Number of patients, treated with methylphenidate, from 2003 to 2015. Annual absolute numbers are given for the 2–5 age group treated with methylphenidate.

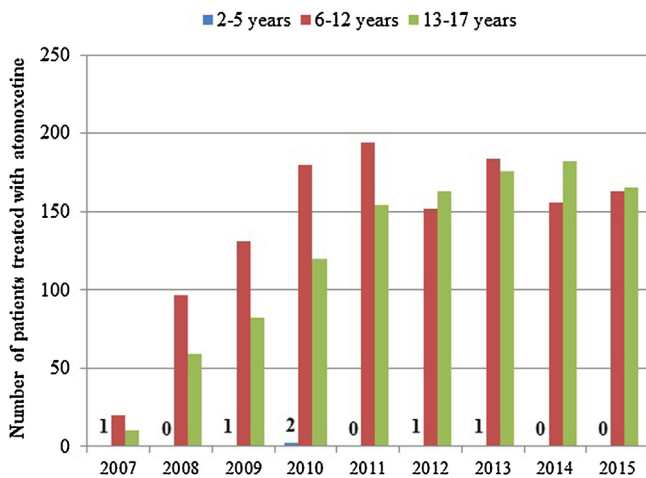


Fig. 2. Number of patients, treated with atomoxetine, from 2007 (market launch) to 2015. Annual absolute numbers are given for the 2–5 age group treated with atomoxetine.

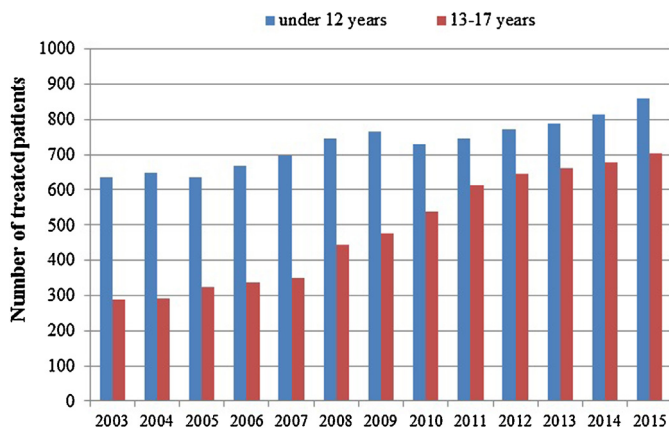


Fig. 3. Number of patients treated with methylphenidate or atomoxetine from 2003 to 2015, divided into 2 age groups.

2015, the ratio of patients treated with MPH to patients treated with ATX was 5:1 (21% of treated patients were treated with ATX). In 2012 1416 patients under the age of 18 were treated with ADHD medication, while the estimated number of patients under 18, diagnosed with ADHD was 2950 [3], meaning that 48% of diagnosed patients was treated with ADHD medication.

4. Discussion

This study is the first in Central Europe and one of the first in Europe to examine age-related pharmacotherapy in children and adolescents with ADHD. The results could be applicable to many Eastern and Central European countries. According to our results, the number of treated children and adolescents with ADHD in 2012 in Slovenia was 1416 [3], which means that 48% of ADHD patients were treated with pharmacotherapy. The number points to a positive trend and is comparable that of Germany, where 52.0% of ADHD patients received ADHD pharmacotherapy during follow-up in a 2012 study. The majority (91.6%) started on MPH, with IR-MPH being the initial treatment choice in 75.3% [25]. According to Garbe et. al. prescription rates of ADHD medication increased dramatically in the past two decades in many countries including the UK. MPH remained the most commonly prescribed drug during the 20-year study period, making up 88.9% of all prescriptions in the 6–24 age group [26]. This trend has not been seen in our research, because 19% of the treated patients were treated with ATX in Slovenia in 2015. This research confirms the results of a previous pharmacoepidemiological study in Slovenia [18]. Stuhec et al. report that in 2012, the consumption of OROS-MPH was 3.65 times greater than that of ATX and 5.24 times greater than that of IR-MPH. IR-MPH only contributed 13.0% to the total ADHD drug consumption, ATX 18.7%, and OROS-MPH 68.3%. These results show a strong similarity between the percentages calculated from defined daily dose (DDD)/1000 inhabitants/day (total national consumption) and prescription/patient and individual database, which means that this database could be widely applicable. According to our results, the prescription rate of ATX in patients undergoing ADHD pharmacotherapy in the 6–17 age group was 21% in 2015, which is higher than the European average of 13.5% in the same age group [27]. The largest increase in patients treated with MPH was in the 13–17 age group. In the 6–12 age group however, the number of treated patients remained approximately constant during the study period. While the number of patients using ATX increased 8-fold between 2007 and 2015, the number of patients using MPH over the same period increased by only 15%, which means that ATX was used much more often in this part of the study period, although ADHD treatment guidelines suggest ATX as a second line treatment [16,17]. These data suggest that national insurance companies (who pay for the treatments) should consider imposing restrictions on ATX prescribing, which could also reduce the price of ATX. As of 2016, there are no treatment guidelines for ADHD treatment and diagnosis in Slovenia [16].

In our research, some patients were treated with MPH and ATX in the 2–5 age group, which is not supported by the treatment guidelines of the British Association for Psychopharmacology [16]. Psychotherapy should be the first line treatment in these patients and there is clear evidence against pharmacotherapy in this age group until the effects are researched further. Even though this age group is small, it is clear that a change in prescribing trends is needed to properly treat patients in this age group [16]. So far, MPH and ATX have been tested a few times in double randomized double blind trials (RCTs) and did not show clear results in this population [28,29]. In a RCT by Abikoff et al., 114 preschoolers with ADHD, which improved with acute MPH treatment, were

randomized to their best MPH dose ($M = 14.22$ mg/day; $n = 63$) or a placebo (PL; $n = 51$) for 4 weeks. The patients improved in some aspects, however parent measures and teacher scores did not differentially improve with MPH. Authors suggest that additional improvements might require longer treatment, higher doses, and/or intensive behavioral treatment in combination with medication [28]. Another paper reports that ATX could alleviate ADHD symptoms in 5-year-old ADHD patients, but to a lesser extent than in older children, with some adverse events occurring at a higher rate in 5-year-old patients. Blood pressure and pulse also increased in 4- to 5-year-old patients, increasing the risk of cardiovascular problems [29,30]. Because our study is a population study, we could not extract more details about these patients. We suggest a further research regarding the reasons the patients in this age group were treated with medication. Non-stimulant medication (e.g. ATX) may still be a first-line treatment for individuals with some comorbidities, but further research is still needed [31].

The number of treated patients increased both in the under-12 and in the 13–17 age group, which is a positive trend, comparable to those in other developed countries [4,21,23,32]. However, the stable number of patients treated with MPH in the 6–12 age group means that few newly diagnosed patients are treated with MPH. The increase in MPH use in the 13–17 age group is probably also due to the cumulative effect of patients who were started on MPH and aged over the study period. However, new medication for ADHD in adults should be made available. In most countries in Central Europe, including Slovenia, ATX was the only new drug approved for adult ADHD in the period between 2007 and 2015. The most effective treatment strategies (e.g. stimulants with medium to high effect sizes) have not been approved as of 2016 [19]. Adult ADHD is highly comorbid with substance abuse, affective, and anxiety disorders, as well as with antisocial personality disorder. Appropriate pharmacotherapy should be chosen to protect patients from severely harmful comorbidities [33,34].

There are also some limitations in this study. A significant limitation is the NHI database. It only provides the number of patients treated with ADHD in Slovenia, but not the exact number of patients diagnosed with ADHD. It also has preset age categories that cannot be customized. There is also no information that would give insight into the patients' comorbidities (i.e. indications for medication use). Information on the dosages used in these patients is also not provided, preventing any conclusions about the appropriateness of prescribing in Slovenia, neither is there data on treatment efficacy, which is very important in clinical practice. Though not very significant, drug consumption rates in hospitals are also not provided. Another important limitation is the lack of data on possible combination treatment of ATX and MPH, although this is not supported by ADHD treatment guidelines and should be strictly avoided. In addition, a small proportion of patients could have a short trial treatment with concomitant medications (e.g. switchers with ATX + MPH) if switching was done with overlap, although guidelines recommend the immediate discontinuation of ATX when switching and only a short trial concomitant treatment when ATX is introduced. Guanfacine ER (GRX) could be an additional treatment strategy in combination treatment, but was unavailable in Slovenia.

This study also does not reveal the waiting time for an appointment with an ADHD specialist or the time to diagnosis for ADHD. We also did not measure medication adherence, which is often low in patients with mood disorders. Garbe et al. report that approximately 20% of patients treated for ADHD discontinued drug treatment within the first 6 months ($n = 6210$). After 6, 12, and 24 months of treatment initiation, 22.4%, 43.4%, and 66.3% of treated girls respectively, and 17.8%, 36.1%, and 54.1% of treated boys had discontinued ADHD treatment [25]. This issue should be considered in future research.

Despite these limitations, our findings have several clinical and practical implications. The increase in the number and percentage of patients treated for ADHD is a positive trend. Our data also suggests that national insurance companies (who pay for the treatments) should consider imposing restrictions on ATX prescribing, which could also reduce the price of ATX, and that national ADHD treatment guidelines should be established to improve stimulant use, control high ATX use, and avoid prescribing to preschool children until further research is available.

This research also revealed a need for a national study to provide more detailed data about the patients' characteristics, which are currently not in the database (e.g. family history, comorbidities, adverse events).

5. Conclusion

The number of patients treated for ADHD increased in all the studies age groups in Slovenia, which is a positive trend, although the use of ATX is still higher and the percentage of diagnosed patients undergoing treatment is lower than in other developed countries. Our results also point to a need for restrictions on ATX prescribing. This paper is also the first to investigate national age-related ADHD pharmacotherapy trends in this part of Europe and the results could be widely applicable to the management of ADHD treatment in this region.

Disclosure of interest

The authors declare that they have no competing interest.

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