

Regional and national trends in attention-deficit/hyperactivity disorder (ADHD) medication use: a multinational study in North America, Europe, Asia and Australia

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Abstract

Background: The use of medications to treat attention deficit/hyperactivity disorder (ADHD) has increased but the prevalence of ADHD medication use across multiple world regions is not known. Our objective was to determine the regional and national prevalence of ADHD medication use in children and adults, with a specific focus on time trends in ADHD medication prevalence.

Methods: We conducted an observational study using population-based databases from 14 countries (four in Asia and Australia (AA), two in North America (NA), five in Northern Europe (NE), and three in Western/Southern Europe (W/SE)). Using a common protocol approach to define study populations and parameters similarly across countries we estimated annual prevalence of ADHD medication use (per 100) with 95% confidence intervals (CI) between 2001 and 2015 (dependent on data availability), by country and region and stratified by age and sex. We reported annual absolute and relative percentage changes to describe time trends.

Findings: Over 150 million individuals were included. ADHD medication prevalence in 2010 (per 100 children aged 3-18) varied between 0.27 and 6.69 (AA: 0.95, NA: 4.48, NE: 1.95, W/SE: 0.70). The prevalence of ADHD medication use among children increased over time in all countries and regions; the absolute increase per year ranged from 0.02 to 0.26 (per 100). Among adults over 18 years, prevalence of any ADHD medication use (per 100) in 2010 varied between 0.003 and 1.48 (AA: 0.05, NA: 1.42, NE: 0.47, W/SE: 0.03). The absolute increase in ADHD medication prevalence per year ranged from 0.0006 to 0.12 (per 100). Methylphenidate was the most commonly used ADHD medication in most countries.

Interpretation: Leveraging a common protocol and data from 14 countries, these results show increases over time but large variations in ADHD medication use in multiple regions. The recommendations of evidence-based guidelines need to be followed consistently in clinical practice. Further research is warranted to describe the safety and effectiveness of ADHD medication in the short and long term, and to inform evidence-based guidelines, particularly in adults.

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Research in context

Evidence before this study

We searched PubMed for English language studies published from January 1, 1966, to June 21, 2017, with the following terms: (treatment OR medication) AND (prevalence OR trend OR utilization) AND (attention deficit hyperactivity disorder or ADHD or hyperkinetic disorder).

The search yielded 3,832 articles.

We excluded articles that we deemed to be not relevant on the basis of their titles. We reviewed abstracts of the remaining articles to identify potentially relevant articles and scanned reference lists of relevant articles. The primary criterion was that the study reported ADHD medication prevalence. Most previous studies were from Europe and North America; with a few studies from Asia and Australia region in more recent years. However, only studies from Northern European countries, the US and the United Kingdom (UK) investigated the prevalence in adults. Two multi-national studies were identified (in children); one included the five Nordic countries and the other one included four Western and Southern Europe countries and the US.

Added value of this study

To date, this is the largest cross-national comparison of ADHD medication use, leveraging a common protocol and standard definitions, and data from 14 sources relating to over 150 million individuals to estimate the prevalence and trends of ADHD medication use. These results show marked differences between countries and multiple world regions, with large absolute and relative increases in the prevalence over time of ADHD medication use in both children and adults.

Implications of all the available evidence

Increasing ADHD medication use in both children and adults supports a need for monitoring medication safety and effectiveness in exposed populations, particularly in adults where knowledge about ADHD medication use is more limited.

Introduction

Attention deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in children with worldwide prevalence rates in school-aged children estimated at 5-7%.^{1,2} Although ADHD is often perceived as a disorder of childhood and adolescence, there is increasing evidence that symptoms and impairment may persist into adulthood for up to 65% of children with ADHD and that ADHD is present in approximately 2.5% in adults.^{3,4} ADHD is associated with a diverse range of adverse health, academic and psychosocial outcomes⁵ and is associated with other mental health disorders such as depression, anxiety and substance misuse.⁶ Whilst the epidemiological evidence suggests that the prevalence of ADHD is similar across the world there is considerable variation in the rate of diagnosis between different countries.^{1,7}

Behavioural intervention and drug treatments are frequently used to manage ADHD symptoms and impairments. Guidelines for children from North America, the United Kingdom (UK) and Europe recommend the use of stimulants such as methylphenidate (MPH), and amphetamines, and non-stimulants such as atomoxetine when pharmacologic intervention is considered appropriate for the management of ADHD.⁸⁻¹² Compared to children, there are fewer clinical treatment guidelines and fewer medications specifically licensed for the treatment of ADHD in adults.¹⁰⁻¹² However, available guidelines do recommend pharmacological treatment as the first-line therapy for ADHD in adults.¹⁰⁻¹²

In the past few decades, an increased prevalence of ADHD and increased use of ADHD medications has been observed in several countries,¹³⁻¹⁵ increasing concerns about possible over-diagnosis and inappropriate prescribing of ADHD medications. In this context, in July 2013 the UK National Institute for Health and Care Excellence (NICE) issued a Guidance to avoid

methylphenidate use in children and young people with mild and moderate ADHD amid concerns about stimulant safety and effectiveness.¹⁶

Estimates of the trends of ADHD medication use over time and across countries are needed to give us insight about the population-level distribution of medication use. In addition, since most previous studies have focused on children and adolescents, little is known about the use of ADHD medication in adults. Moreover, some studies have focused on medication use only among individuals diagnosed with ADHD,¹⁷ which may underestimate exposure to ADHD medication because it is not uncommon for ADHD medications to be prescribed to control hyperactivity symptoms among patients with other disorders such as autism spectrum disorder. Therefore, we aimed to describe the prevalence and trends in prevalence over time of ADHD medication use in children, adolescents and adults, focusing on different age groups, sex and type of ADHD medications across countries in four regions; Asia and Australia, North America, Northern Europe and Western/Southern Europe.

Methods

Common protocol approach

We used a common protocol to study the prevalence of ADHD medication use in 15 participating sites from 14 different countries from four regions: Asia and Australia (Australia, Hong Kong, Japan, Taiwan); North America (Canada and two sites in the United States (US)); Northern Europe (Denmark, Finland, Iceland, Norway, Sweden); Western/Southern Europe (France, United Kingdom, Spain). The sites were chosen based on the availability of national administrative data, and where this was not possible (US, Canada, UK), we prioritized data sources that had a defined population to serve as the denominator, with data in which we could measure the study parameters (medication prescription, dispensation). As countries within the

research networks of the Nordic Pharmacoepidemiological Network (NorPEN) have a common data and research structure, similar underlying health systems and have jointly published in this area previously,¹⁸ we decided to maintain the NorPEN countries as one of two European regions. Each country contributed data from administrative databases for a time period between 1st January 2001 and 31st December 2015.

All of the data sources were generated from the automated capture of patient-level electronic data from either administrative clinical records or administrative claims records in a defined population or portion thereof.

Additional details about the databases, source population, health care system, method of medication information capture, coding system used, and other aspects of data collection are detailed in Tables 1 and A1 to A3.

Data collection

In each site, the study population consisted of all individuals who were three years of age or older during the study period (1st January 2001 to 31st December 2015, subject to data availability in each site). Individuals were grouped by age as follows: 3-5 years old (kindergarten/preschool), 6-11 years (primary school), 12-16 years (secondary school), 17-18 years (older adolescent) and 19 or above (adults). As data from Canada only included individuals up to 11 years old, Canada was excluded from age-specific analyses for individuals age 12 or above.

Where possible, the total number of persons in each calendar year served as the denominator to calculate prevalence. Otherwise, for databases with universal coverage, census or population data were used to determine denominator data, defined as the total number of the population of the

target age group in the middle (July) or end (December) of that particular year in the individual database. The numerator (ADHD medication use) was ascertained by examining the medication records of all individuals who were available in that year (Table 1 and A1).

Ethical review of or approval for the use of each data source was obtained by the respective contributing authors in each of the participating countries (Table A2). Additional references for the data sources used in this study are listed in Table A3.

Medication definition

To identify ADHD medication, we examined WHO Anatomical Therapeutic Chemical (ATC) classification codes¹⁹ within records for prescribed medication, dispensed medication or insurance claims for dispensed medication. If medications were not coded using the ATC system in a particular database, drug ingredients were mapped to ATC terminology (Table A1). Data about medications that were available and licensed for the treatment of ADHD in the specific country were compiled, with a focus on the most common medications used for ADHD (as listed in Table A4). Exposure was defined as a medication record for an ADHD medication (either prescribed or dispensed) at least once in the relevant study year. We examined ADHD medication use regardless of a confirmed diagnosis of ADHD.

Data analysis

Only the country level researchers had access to individual level data. All countries provided aggregate data to the primary authors (SRR/KKCM), who then evaluated the patterns of medication use across the study period, comparing trends over time between the 14 countries. The annual prevalence of each medication was expressed per 100 persons. Overall annual prevalence, and prevalence by region and country were calculated with a 95% confidence

interval (CI) estimated by Poisson method.²⁰ Regional pooled prevalences with 95% CI were estimated using DerSimonian and Laird's random-effects model²¹ to account for heterogeneity across different sites. A linear regression model, assuming a linear trend, was used to test for time trends in the annual prevalence and the absolute changes in prevalence for each year throughout the study period. We fitted one model per region, with 'year' as the only predictor variable in the model. Relative change in the prevalence per year were evaluated as percentage change for each site by the following formula:

$$\frac{\textit{Prevalence of the current year} - \textit{Prevalence of previous year}}{\textit{Prevalence of the previous year}} \times 100\%$$

Age specific and sex specific analyses were conducted. Cross-sectional comparisons of the prevalence, type of medications used and sex ratio (annual ratio of males to females of all ages) by country were made for the year 2010. The statistical significance level was set at $p < 0.05$. Statistical Analysis System (SAS) v9.4 (SAS Inc., USA), Review Manager 5.3 (Copenhagen: The Cochrane Collaboration) and Stata SE version 11 (StataCorp, College Station, TX, USA) were used for data manipulation and analysis.

Results

Data available across all sites covered a total of 154.5 million individuals over the study period (Table 1). The overall pooled prevalence of ADHD medication use in children and adolescents across all regions was 1.95 per 100 (95% CI 0.76 to 3.13) (Figure A1). For children ages three to 18 years, considerable national variation was evident in the prevalence of any ADHD medication use over the study period ranging from a low of 0.27 per 100 in year 2010 (France) to a high of 6.69 per 100 in 2010 (US Medicaid) (Figure 1). Regional prevalence was highest in North America with a pooled prevalence of 4.48 (95% CI 2.86 to 6.10), followed by Northern

Europe (1.95; 95% CI 1.47 to 2.44). A lower prevalence was observed in Asia and Australia and Western/Southern Europe with a prevalence of 0.95 (95% CI 0.35 to 1.56) and 0.70 (95% CI 0.31 to 1.10) respectively.

The prevalence of ADHD medication use among children increased over time in all countries and regions; the absolute increase per year ranged from 0.02 to 0.26 (0.06 to 0.17 in Asia and Australia, 0.13 to 0.24 in North America, 0.08 to 0.26 in Northern Europe, 0.02 to 0.14 in Western/Southern Europe) (Table 2). The magnitude of the annual relative increase also varied (Table A5). The average relative percentage change per year in Northern Europe was highest (15.07% [95%CI 7.15 to 23.00] per year between years 2001 to 2013) followed by Asia and Australia (11.35% [95%CI 2.39 to 20.32] per year between years 2001 to 2015), North America (10.34% [95%CI 9.46 to 11.23] per year between years 2001 to 2014) and Western/Southern Europe (8.96% [95%CI 4.96 to 12.95] per year between years 2001 to 2014). The average relative percentage increase across all countries was 14.55% (95%CI 12.69 to 16.41) per year between years 2001 to 2015. By country, Canada had the highest yearly increase with average percentage increases of 45.11% (95% CI 43.50% to 46.71%) per year (2001 to 2009) Hong Kong, Taiwan, Finland, Denmark, and Sweden ranked second to sixth respectively, with increases in prevalence ranging from 24.18% (95%CI 23.94 to 24.42) (Hong Kong) to 20.15% (95%CI 19.91 to 20.39) (Sweden). The lowest average increase per year among all countries was observed in the two US data sources with average increase of 3.16% (95%CI 3.14 to 3.18) in US Medicaid (2001 to 2010) and 2.83% (95%CI 2.80 to 2.86) (2001 to 2014) in US MarketScan (Table A5).

The age group with the highest annual prevalence of ADHD medication use was age 6-11 in Asia-Pacific region, US Medicaid and Finland, and age 12-16 in the rest of the sites. The time

trend in the age group-specific prevalence of ADHD medication use was similar to the overall time trend in children (Figure 2 to 5).

The overall pooled prevalence of ADHD medication use in adults was 0.39 per 100 (95% CI 0.31 to 0.47) (Figure A2). The national prevalence of any ADHD medication use for adults over the study period shows the prevalence ranging from as low as 0.003 per 100 in year 2010 (Japan) to a high of 1.48 per 100 in 2010 (US MarketScan) (Figure 6). Regional prevalence was highest in North America with a prevalence of 1.42 (95% CI 1.29 to 1.54), followed by Northern Europe (0.47; 95% CI 0.31 to 0.62). A lower prevalence was observed in Asia and Australia and Western/Southern Europe with a prevalence of 0.05 (95% CI 0.004 to 0.10) and 0.03 (95% CI 0.01 to 0.04) respectively. The prevalence of ADHD medication use in adults increased in all countries over time; the absolute increase per year ranged from 0.0006 to 0.12 (0.0006 to 0.02 in Asia and Australia, 0.09 to 0.12 in North America, 0.01 to 0.10 in Northern Europe and 0.002 to 0.007 in Western/Southern Europe) (Table 3). The average yearly percentage increase across all countries was 18.87% (95% CI 16.25 to 21.49) with the highest average yearly percentage increase in ADHD medication use being observed in the Asia and Australia region (25.06% [95% CI 17.65 to 32.46] per year from 2001 to 2015) followed by Northern Europe (18.81% [95% CI 10.74 to 26.87] per year from 2001 to 2013) and Western/Southern Europe (17.01% [95% CI 11.83 to 22.19] per year from 2001 to 2014). Both the US data sources had a relatively low average yearly increase with a rate of 12.98% (95% CI 10.39 to 15.57) per year (11.66% [95% CI 11.62 to 11.69] and 14.30% [95% CI 14.22 to 14.38] per year in US MarketScan from 2001 to 2014 and US Medicaid from 2001 to 2010 respectively). In contrast to the low absolute prevalence of ADHD medication use in Japan, the annual rate of increase was highest in Japan, with an average increase of 75.88% (95% CI 70.55 to 81.21) per year (2010 to 2015). Denmark

and Sweden followed with an average relative annual prevalence increase of 28.84% (95% CI 28.61 to 29.06) (2001 to 2013) and 27.37% (95% CI 27.10 to 27.63) per year respectively (2006 to 2013) (Table A6).

The overall male to female ratio among those with medication use was 2.0 to 1 across all countries. The lowest male to female ratios were in US MarketScan (1.3 to 1) and Iceland (1.8 to 1). The male to female ratio was highest in Hong Kong (6.4 to 1), followed by Japan (4.6 to 1) and Finland (4.0 to 1).

The male to female ratio in medication use was greater in children than in adults; the range in children was 2.0 to 6.3 as compared to 0.9 to 2.7 in adults. The lowest male to female ratios in children were in Australia (2.0 to 1) and US MarketScan (2.2 to 1) whereas the highest were in Finland (6.3 to 1), followed by Hong Kong (5.8 to 1) and the UK (5.4 to 1). In adults, the ratio was lowest in US MarketScan (0.9 to 1) and France (1.2 to 1). The highest male to female ratio in adults was in Finland (2.7 to 1), the UK (2.3 to 1) and Hong Kong (2.0 to 1). (Figure A3-A4)

In 2010, methylphenidate was the most commonly used medication in all of the participating sites except one (US MarketScan). Of individuals who used ADHD medication, over 90% used methylphenidate in Hong Kong, Taiwan, Canada, Finland, and Spain (Table A7). In Japan, Denmark, Iceland, Norway, Sweden, and UK, approximately 75% to 90% patients received methylphenidate. In terms of the type of ADHD medication, 59% of individual patients in Australia and 45% of patients in US Medicaid used methylphenidate (Table A7). In US MarketScan, amphetamine was the most commonly used medication (41%) followed by methylphenidate (34%) and lisdexamfetamine (21%). Atomoxetine was the second most commonly used ADHD medication in 10 countries (Hong Kong, Japan, Taiwan, Denmark, Finland, Iceland, Norway, Sweden, Spain, and UK) (Table A7). Table A8 includes ADHD

diagnosis prevalence estimates from studies included in the Thomas et al.² and the 2010 prevalence estimates for ADHD medication use in children 3-18 found in our study. The variation in medication prevalence is much greater than the prevalence of ADHD diagnosis. All other additional results are contained in the Appendix. (Figure A5)

Discussion

In this large, population-based study of 14 countries, both the sharp increases in prescribing of ADHD medication and the marked geographical disparities in use were noteworthy. We found wide variation by country and region in the prevalence of ADHD medication use, with the 2010 cross-sectional estimates in North America markedly higher than other participating countries. Across regions, the prevalence of ADHD medication use has increased strikingly since 2000. This consistent rise in prevalence was notable in children as well as adults in all four regions. The high variation across regions as well as within regions, suggests variation in clinical approach to the treatment of ADHD.

The prevalence of ADHD medication use and the increase over time varied widely across regions. Within Europe, the contrast between patterns in Northern versus Western/Southern Europe was striking, as well as the disparities between nations within a given region, with Iceland having the highest prevalence of all European countries (over 4·19 per 100 for children, 1·06 per 100 for adults). The average relative percentage increase per year was also higher among children and adults in the Northern Europe region than in the Western/Southern Europe region, leading to further increases in the regional disparity in medication use patterns over time.

The prevalence in Asia and Australia in 2010 approximated or surpassed the prevalence in Western/Southern Europe. The average percentage increase per year between the regions for

both children and adults ranged within twelve percentage points (8.96% to 16.61% for children, 17.01% to 25.06% for adults). The average yearly increase in the US (2.83% children/11.66% adults in MarketScan, 3.16% children/14.30% adults in Medicaid) was lowest among all countries in both children and adults; however, given the high absolute prevalence within the US, this consistent increase is notable.

Some of the disparities may reflect geographical differences in the epidemiological prevalence of ADHD. Whilst previous studies suggested the epidemiological prevalence of an ADHD diagnosis may be higher in North America than in other regions,^{1, 2} with reported estimates around 8.8% in the US²² and 3.5% to 5.6% in France,²³ and 3% to 5% in the UK,²⁴ the analysis of Polanczyk et al. suggests that these differences can be largely accounted for by methodological differences between the different studies.²⁵ Notwithstanding the fact that ADHD may be over diagnosed and treated in the US, while under-diagnosed in some countries in Asia,²⁶ a consistent increase in the use of ADHD medication in all countries is observed in this study.

Given the evidence that the underlying epidemiological prevalence of ADHD is similar across the world when diagnosed using consistent criteria and methods,¹ much of the absolute variation in ADHD medication use, may be explained by differences in how diagnostic criteria are applied in practice by clinicians, the thresholds required by clinicians to initiate treatment for individuals with an ADHD diagnosis; and the persistence of ADHD medication treatment over time. The structure and funding of the health care system, such as direct access to specialists and other prescribers, availability and cost of medicines, availability of non-pharmacological treatments for ADHD, may all influence the prescribing patterns of medication.²⁷ Additionally, a portion of the differences may be due to the proportion of off-label use of ADHD medications.²⁸ Differences in regional clinical guidelines in ADHD treatment recommendations may also contribute to the

difference in the prescribing prevalence across the world. Non-pharmacological treatment is recommended as first line treatment for children and young people aged 6 years or above with ADHD in the NICE guideline,¹² whereas medications are recommended as first line treatment in the American Academy of Pediatrics (AAP)⁸ and American Academy of Child and Adolescent Psychiatry (AACAP) guidelines.⁹ Cultural variations in the perception of ADHD and ADHD treatment both within and between countries may also contribute to variation in the use of ADHD medication,²⁹ for example, perceived stigma may influence a parent or patient's willingness to use medication.²⁹ Public attitudes towards psychotropic medication became more positive between 1998 and 2006 in the US³⁰ and in a Swedish community between 1976 and 2003.³¹ On the other hand, countries like Hong Kong and Taiwan where Chinese culture is dominant, conservative attitudes and resistance toward ADHD medications are common.¹⁵ Lastly, ADHD medication use may increase as clinicians and guidelines incorporate emerging evidence about the effectiveness or safety of ADHD medications, for example that behavioral therapy in combination with medication is more effective than behavioral therapy alone.³²

The three previous multi-national studies that compared prevalence of ADHD medications did so across four European countries and the US,¹³ or across Northern European countries.^{14, 33} When compared to our estimates, the estimates for two Western European countries that could not be included in our study (Germany and the Netherlands) were higher than our Western/Southern European estimates, but our results were similar to the previous Northern European estimates, which may be expected as estimates were derived from the same data sources. Despite these differences, we confirm the between-country variation found in previous studies and add the comparison of an additional two regions for a total of four world regions.

The two US data sources for the most part represent distinct populations, those who were privately insured through employers (MarketScan) and those who were covered by Medicaid, a federal and state government social health care program for individuals with low incomes. The differences in estimates, with higher estimates in Medicaid for both children and adults, are likely to be due to a combination of factors, including the nature of insurance type, in terms of the cost and availability of medications and non-pharmacological treatments, as well as differences in the demographic characteristics of the populations. Factors affecting the Medicaid population, such as limited financial resources, poor health of children and their parents, and limited resources of the public educational system may affect the treatment decision-making of both providers and families.³⁴ For instance, family of higher socioeconomic status may have more resources for non-pharmacological treatment and thus may be less likely to use ADHD medications. Though the two data sources are only two components of the US population, this evidence of within-country variation is noteworthy and can be used to examine more closely the determinants of within-country variation.

Results of the study have significant implications for clinical practice, health systems and policies. The wide variation in the prescribing prevalence of ADHD medications likely reflect different clinical approaches in treating ADHD across nations, resulting from a multitude of factors. For individuals with ADHD, these results suggest that the nature of pharmacological treatment may depend largely on where individuals live. Although there is no clear evidence as to what optimal rates of prescribing may be, it seems likely that many patients may be undertreated (especially in low-use areas) and/or that some may be over-treated with medication. For most countries, despite considerable increases in the prescribing of ADHD medications, these rates continue to fall short of the expected prevalence of ADHD (e.g. Japan).² It would

seem most likely that the increase represent increased recognition of ADHD and the importance of effective treatment to avoid long-term problems. In contrast, in the US, where rates of prescribing are, in many states, already higher than the generally accepted epidemiological prevalence rates,³⁵ the continued increase in prescribing rate should be considered as a cautionary note for clinicians and regulators who should ensure that they are not over diagnosing and medicating children and young people with ADHD. Given the adverse developmental and functional implications of under-treatment, as well as the negative individual and societal impact of overtreatment (including diversion of stimulant drugs), it is important that clinical practice reflect the available evidence and are based on careful monitoring of children. To ensure that individuals with ADHD receive optimal treatment across nations, efforts are needed to assure that structured approaches are applied to the diagnosis and treatment of ADHD and to develop consensus on the best practices in the light of available evidence. International organizations such as the World Health Organization may have a role to play in convening and supporting policy initiatives to improve the consistent identification and treatment of ADHD across the international community.

In contrast to the number of pharmacoepidemiological studies on the use of ADHD medications in children and adolescents, far fewer data are available for adults. We observed an increase in the prevalence of ADHD medication use among adults in all participating sites. With a prevalence of 1.42 per 100 persons in 2010, the US has the highest prevalence in adults among all countries (1.48 and 1.35 in MarketScan and Medicaid respectively); 3-fold that of Northern Europe, 27-fold that of Asia and Australia, and as high as 56-fold estimates of Western/Southern Europe. Our results are similar to a previous meta-analysis where the prevalence of adult ADHD was reported as 2.5 per 100 with estimates in the US ranging from 2.9 to 4.7 per 100.³ Though

diagnosis and treatment guidelines for adult ADHD are emerging, research continues into the course of ADHD from childhood and presentation of ADHD in adulthood³⁶. Overall, when considered in terms of epidemiological prevalence of ADHD in adults and the recommendations from guidelines that medication is a first-line treatment for adults with ADHD, the data suggests that ADHD medication are not likely being overprescribed in adults. The large differences across different countries with respect to the use of ADHD medications in adults raises questions about how well guidelines are being followed. In order to increase the confidence of clinicians treating adults, further research is also required to demonstrate the longer term of the safety and effectiveness of ADHD medications in adult populations.

The results of this study must be taken in context of the following limitations. Though the common protocol enabled us to standardize the measurement of the population and medications under study, some variables in each country's database had been previously defined. For example, the medication data may reflect prescribed, dispensed, administrative or clinical records. Though most of the countries had data sources with essentially complete population coverage, the denominator estimates may have differences in accuracy and generalizability as the data came from different sources (government census or administrative databases). The trends observed in the US private insurance data may be influenced by shifts in the population who contributed to the data source. Several medications used for ADHD also have other indications, or are used off label or in the context of differential diagnosis. Since the study was not able to include the diagnoses and indications for the study groups, we cannot investigate the clinical characteristics of those who used ADHD medications. We examined the number of individuals exposed at least once to ADHD medication, but we did not measure exposure over time, which would reflect adherence to ADHD medication. Additionally, for each country, as discussed

above, the data may reflect differences in ADHD diagnosis and treatment practice. For example, most data sources only captured ambulatory or outpatient medication, however the extent of the capture (inclusion of specialist prescriptions or out-of-pocket medications) may have an influence on the comparability of the estimates. These differences in the measurement of ADHD medication may have influenced the absolute estimates and may be a limitation for comparisons between countries. However, the trends in ADHD medication use over time are compelling and are similar to previously published research.^{13, 15} Linear regression models, that assumed linear trends, were used to estimate the overall trends in ADHD medication use. However, our assumptions were supported by post hoc spline-based models that resulted in very similar estimates. In addition, we estimated the prescribing prevalence with the Poisson method, which may have resulted in conservative (wide) confidence intervals, however, the resulting confidence intervals are sufficiently narrow for the purposes of this study. Lastly, due to the nature of the collected data via the common protocol, we could not present several relevant analyses: 1) medication use and trends among young adults (age 18-25), 2) age and gender stratified estimates in three sites, Japan, Taiwan and Canada, and 3) age-specific estimates of medication use by medication type.

To our knowledge, this study presents the most comprehensive update of cross-sectional comparisons and longitudinal trends of ADHD medication use in children and adults with representation from many global regions. All the participating data sources used large databases that have been used extensively in pharmacoepidemiologic research and were representative of the corresponding populations. This study attempted to standardize the methodology that has been the source of much of the variation in previous estimates of ADHD medication prevalence complementing the existing global ADHD diagnosis prevalence estimates,³⁷ and ensuring an

accurate representation of the dynamics of ADHD medication use in adults and children globally. Cross national comparisons, such as those in our study, are needed to support our understanding of the factors that influence ADHD medication use.

Conclusion

In conclusion, the prevalence of ADHD medication use varies between countries and regions and has increased dramatically in the past decade. The average annual increase in the use of ADHD medication is as high in adults as it is in children. The highest rates of prescribing (and lowest rates of increase) were found for the US. In all countries, recommendations of evidence-based guidelines need to be followed consistently in clinical practice. Further research is warranted to describe the safety and effectiveness of ADHD medication in the short and long term, and to inform evidence-based guidelines, particularly in adults. These results can also serve as a foundation for further insight into the potential effects of health care access, the management of ADHD and the use of ADHD medications.

Authors contribution statement:

SRR/KKCM/PI/ICKW had full access to the aggregate analysis data in the study and take responsibility for the integrity of the analysis data and the accuracy of the data analysis. Study concept ICKW, KKCM, PI and study design: ICKW, SRR, KKCM, MCJMS. Acquisition, statistical analysis, or interpretation of data: all authors. Drafting of the manuscript: SRR, KKCM, ICKW. Critical revision of the manuscript for important intellectual content: All authors.

Conflict of interest statement:

Dr. Raman reports grants from GSK, outside the submitted work; Mr. Man reports personal fees from IQVIA Holdings, Inc. (Previously known as QuintilesIMS Holdings, Inc.), outside the submitted work; Dr. Bushnell reports grants from National Institute of Mental Health (F31MH107085), during the conduct of the study; other from graduate research assistantship with GlaxoSmithKline (ending 12/2015), outside the submitted work; Prof. Coghill reports grants and personal fees from Shire, personal fees from Eli Lilly, grants from Vifor, personal fees from Novartis, personal fees from Oxford University Press, outside the submitted work; Dr. Kieler reports other from Abbvie, Astellas, Astra-Zeneca, Bayer, Janssen Biotech, Novartis, Pfizer, Reckitt Benckiser, outside the submitted work; Dr. Nakamura reports grants from European Union FP7 programme, during the conduct of the study; personal fees from Janssen Pharmaceutical K.K., outside the submitted work; Dr. Pratt and Dr. Roughead report that they are members of the Australian Government Drug Utilisation Subcommittee of the Pharmaceutical Benefits Advisory Committee. Prof. Stürmer reports other relationships with GlaxoSmithKline, Merck, UCB BioSciences, and Shire, grants from AstraZeneca, grants from NovoNordisk, outside the submitted work; and that he owns stock in Novartis, Roche, BASF, AstraZeneca, and Novo Nordisk. None of these companies has any role in the research project; Prof. Wong reports grants from Research Grant Council, Hong Kong, grants from Innovative Medicines Initiative, grants from Shire, grants from Janssen-Cilag, grants from Eli-Lily, grants from Pfizer, grants from European Union FP7 programme, outside the submitted work; and Prof. Wong was a member of the National Institute of Health and Clinical Excellence (NICE) ADHD Guideline group and the British Association for Psychopharmacology ADHD guideline group and acted as an advisor to Shire. All other authors have nothing to declare.

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