Attention-deficit/hyperactivity disorder medication consumption in 64 countries and regions from 2015 to 2019: a longitudinal study

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Summary

Background Timely recognition and appropriate treatment of attention-deficit/hyperactivity disorder (ADHD) are essential to enhance long-term outcomes of individuals with ADHD. This study aimed to evaluate the multinational trends and patterns of ADHD medication consumption.

Methods In this longitudinal trend study, we used pharmaceutical sales data of ADHD medication from the IQVIA-Multinational Integrated Data Analysis System between 2015 and 2019, covering 64 countries across the world. Consumption rates of ADHD medication were expressed as defined daily dose per 1000 child and adolescent inhabitants (aged 5–19) per day (DDD/TID). Linear mixed models were used to estimate the multinational, regional, and income level trend changes.

Findings The results showed that multinational ADHD medication consumption increased by +9.72% (95% confidence interval [CI], +6.25%, +13.31%) per year, from 1.19 DDD/TID in 2015 to 1.43 DDD/TID in 2019 across the 64 countries with marked differences between geographical locations. When stratified by countries' income levels, increases in ADHD medication consumption were observed in high-income countries but not in middle-income countries. In 2019, the pooled consumption rates of ADHD medication were 6.39 DDD/TID (95% CI, 4.63, 8.84) in high-income countries, 0.37 DDD/TID (95% CI, 0.23, 0.58) in upper-middle-income countries and 0.02 DDD/TID (95% CI, 0.01, 0.05) in lower-middle-income countries.

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Interpretation Current ADHD prevalence estimates and rates of ADHD medication consumption in most middle-income countries are lower than the global epidemiological prevalence. It is therefore imperative to evaluate the potential barriers to diagnosis and treatment in these countries to minimise the risk of negative outcomes from undiagnosed and untreated ADHD.

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Keywords: Attention-deficit/hyperactivity disorder; Global health; Drug utilisation

Research in context

Evidence before this study

We searched PubMed for articles written in English and published between Jan 1, 2001 and May 1, 2022, using the following search terms: (((Multinational) OR (Global)) AND ((Treatment) OR (medication)) AND ((attention deficit hyperactivity disorder) OR (ADHD) OR (hyperkinetic disorder)) AND ((Consumption) OR (Use) OR (Utilisation)) AND (Trend)). We retrieved 62 records from the search and excluded articles that were deemed not relevant based on their titles. Four studies investigated multinational trends in ADHD medication use in eleven countries, five western countries, Nordic countries, and 14 countries/regions respectively, with different study years and designs.

Added value of this study

The current study assessed ADHD medication consumption in 64 countries, in particular, we covered data from middle-income countries where little is known on the ADHD medication consumption in the literature and data of newly approved ADHD medications. We identified an overall increase in ADHD medication consumption of +9.72% per year from 2015 to 2019 in 64 countries, but ADHD medication consumption is driven by high-income countries and not middle-income countries. Amphetamines and guanfacine were the two ADHD medications that had the greatest multinational increases over time.

Implications of all the available evidence

Given the debilitating aspects of ADHD and the importance of early-life interventions to prevent severe outcomes such as suicidality and trauma, the identified extreme imbalance in ADHD medication consumption by country income levels should be addressed in a timely manner. Further safety and tolerability studies are needed to respond to the rising trends of consumption of newer ADHD medications such as clonidine and guanfacine. Finally, there is little to no data on the consumption of ADHD medication in low-income countries and there is an urgent need to collect data in these countries.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder, with a worldwide population prevalence in epidemiological studies of around 7.2% in children and 2.5% in adults.[1,2] The diagnosis of ADHD is based on the presence of pervasive, developmentally inappropriate, and impairing levels of hyperactivity, inattentiveness, and impulsivity.[3] When untreated, individuals with ADHD are prone to a wide range of poor outcomes such as defiant, disruptive, and antisocial behaviours, emotional problems, self-harm, substance misuse, educational underachievement and exclusion from school, difficulties with employment and relationships, and criminality.[4] Therefore, timely recognition and appropriate treatment of ADHD are essential to enhance long-term well-beings of individuals with the condition. Current guidelines often recommend a combination of non-pharmacological (e.g. behavioural or cognitive therapy) and pharmacological treatment, depending on the patient's age, levels of impairment, and comorbidities.[5]

Stimulants (e.g., amphetamine-based and methylphenidate-based agents) and non-stimulants (e.g., atomoxetine, clonidine, and guanfacine) are licensed as pharmacological treatments for ADHD.[5] Stimulants are recommended as the first-line treatment due to their greater efficacy.[6] However, the recommendations from international clinical guidelines are inconsistent with respect to the order in which the stimulants should be offered,[5] with some guidelines advocating for methylphenidate over amphetamines in children while other guidelines make no distinction between the stimulants.[6–9] The non-stimulant atomoxetine is recommended by guidelines as second- or

third-line treatment.[7–9] As such, consumption patterns of different ADHD medications across geographical locations may differ but remain unclear.

We previously reported the prevalence of ADHD medication use in thirteen countries and one special administration region between 2001 and 2015 and found an increasing trend in all studied sites, with methylphenidate being the most commonly used ADHD medication in most countries.[10] However, existing literature on global ADHD medication use beyond 2015, in particular, that from middle-income countries as well as geographical regions such as Africa, Central and South America, Southern and Western Asia remained scarce. A recent study examined psychotropic medicine consumption in 65 countries and regions and found that geographical locations and income levels are explanatory factors for between-country/region consumption disparities.[11] Furthermore, guanfacine and clonidine were not licensed for ADHD in most countries and thus had relatively limited data at the time of the previous study. For instance, guanfacine was first licensed for ADHD in 2009 and 2015 by the United States (US) Food and Drug Administration (FDA) and European Medicines Agency (EMA) respectively. Clonidine was licensed by the US FDA in 2010 and not yet approved by the EMA.[12,13] The current study provides the most up-to-date data on the multinational trends and patterns of ADHD medication consumption according to country income level and geographical region with expanded coverage of countries and data for the more recently approved ADHD medications.

Methods

Data sources

We obtained the multinational ADHD medication sales data from the IQVIA-Multinational Integrated Data Analysis System (MIDAS) database. MIDAS captures multinational data on sales volume of specific pharmaceutical products from different distribution channels (manufacturers, wholesalers, hospitals, and retail pharmacies) with international standardisation to allow comparisons of national sales volume. The average national coverage of MIDAS data was reported as 88%.[11,14,15] For countries where the MIDAS database did not have 100% market coverage, adjustments were made by IQVIA to estimate the total sales volume based on knowledge of the market share of participating wholesalers and retail or hospital pharmacies.[16] The MIDAS database has been validated against external data sources[17] and used as a proxy to evaluate multinational consumption of medication.[14,18,19] Like previous studies, we adopted the sales data as a proxy for consumption of each country. The MIDAS database does not contain patient-level data; thus, no information on patient demographics was available and institutional review board approval was not required.

Data inclusion

Data on the sales of ADHD medication between 2015 and 2019 were collected from 64 countries and regions in the IQVIA-MIDAS database. ADHD medication in this study, namely, amphetamines, methylphenidate, atomoxetine, clonidine, and guanfacine, were identified by the European Pharmaceutical Market Research Association (EphMRA) Anatomical Therapeutic Chemical (ATC) classification codes (Table S1, Supplement pp2). Amphetamines included "amfetamine", "dexamfetamine", "metamfetamine," and "lisdexamfetamine". Methylphenidate included "methylphenidate", and "dexmethylphenidate". For amphetamines, guanfacine, and clonidine, only products with ATC codes that started with "N" for the nervous system were included due to their alternative indications for non-ADHD conditions. The included countries/regions were divided into the following areas: Northern America, Central and South America, Northern Europe, Eastern Europe, Southern Europe, Western Europe, Oceania, Eastern Asia, South-eastern Asia, Southern Asia, Western Asia, Northern Africa, and Southern Africa, based on their geographical regions according to United Nations (UN)' "*Standard Country or Area Codes for Statistical Use*".[20] Additional yearly country-level variables were obtained from other data sources: the mid-year population estimates of each country/region from the UN Population Division[21]; country income measured by Gross Domestic Product (GDP) per capita in US dollar, from the UN National Accounts Estimates of Main Aggregates[22]; age-standardised country-specific prevalence rates of ADHD were obtained from the Global Burden of Disease (GBD) data via the Global Health Data Exchange (GHDx).[23] As ADHD medications are mainly prescribed in children and adolescents, age-specific population estimates and age-standardised ADHD prevalence for age five to nineteen years were used.[10] The characteristics of included countries and availability of different ADHD medications sold were presented in Table S2, Supplement pp3.

Statistical analysis

The main outcome metric was the rate of ADHD medication consumption, expressed as the defined daily dose (DDD) per thousand child and adolescent inhabitants per day (DDD/TID). DDD is the assumed average maintenance dose per day for a drug used for its main indication and was only available for single-molecule products. As such, DDD for combination products was converted from a standard unit (defined as a single tablet, capsule, or ampoule/vial or 5 mL oral suspension), formulation, with their respective drug ingredients mapped to the ATC/DDD Index developed by the World Health Organisation (WHO) Collaborating Centre for Drug Statistics Methodology (Table S1, Supplement pp2).[24]

At the national level, consumption rates in DDD/TID were calculated with a 95% confidence interval (CI) estimated by the Poisson method.[10] The multinational and regional consumption levels were computed by pooling the estimates from individual countries using a random-effects model. The time trends of ADHD medication consumption were evaluated at multinational, regional, and national levels across the study period. At the national level, the average annual percentage change in DDD/TID with 95% CI was estimated using a linear regression model, with log-transformed consumption in DDD/TID as the dependent variable and year as the independent variable. Natural logarithm transformation was performed on consumption as it demonstrated a non-linear relationship with time. The worldwide and regional trend changes were estimated using linear mixed models, controlling for within-country correlations. We further stratified the sales data based on country income levels (i.e., lower-middle income, upper-middle income, and high income according to the 2019 World Bank income classification[21]) to investigate how consumption trends vary with country income levels. Additional analyses were conducted by including country-specific yearly GDP per capita, geographical region, and ADHD prevalence in the linear mixed model with random-effects to investigate their effects on ADHD medication consumption. Continuous factors (GDP per capita and ADHD prevalence) included in the models were log-transformed. The statistical significance level was set at $P < 0.05$. All analyses were conducted using Statistical Analysis System (SAS) v9.4 (SAS Institute, Cary, NC, USA) and R Foundation for Statistical Computing version 3.6.0 (Vienna, Austria).

Role of the funding source

The funding source had no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the article; and in the decision to submit it for publication. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Multinational trends of ADHD medication consumption 2015–2019

Among the 64 countries/regions, representing approximately 62.4% of the global population, there was an overall increase in ADHD medication consumption from 2015 to 2019 (Table 1, Fig. 1). The average annual percentage change of ADHD medication collectively was +9.72% (95% CI, +6.25% to +13.31%), from 1.19 DDD/TID (95% CI, 0.79 to 1.79) in 2015 to 1.43 DDD/TID (95% CI, 0.99 to 2.07) in 2019.

The trends of ADHD medication consumption varied between regions (Table 1; Fig. S1, Supplement pp10). Annual increases in consumption were observed in South-eastern Asia (+20.84%; 95% CI, +8.95% to +34.02%), Northern Europe (+18.08%; 95% CI, +13.39% to +22.96%), Eastern Asia (+18.09%; 95% CI, +13.81% to +22.53%), Western Asia (+15.27%; 95% CI, +10.51% to +20.23%), Oceania (+11.36%; 95% CI, +10.20% to +12.54%), Southern Europe (+10.79%; 95% CI, +7.21% to +14.48%), Northern America (+5.78%; 95% CI, +1.14% to +10.64%), Western Europe (+5.25%; 95% CI, +3.82% to +6.69%), Southern Africa (+4.31%; 95% CI, +2.95% to +5.67%). No significant changes were observed in Eastern Europe, Northern Africa, Southern Asia, Central and South America and the Caribbean.

The levels of ADHD medication consumption varied greatly by region throughout the study period. In 2019, pooled ADHD medication consumption rates were highest in North America (111.93 DDD/TID; 95% CI, 108.72 to 115.24), followed by Oceania (34.52 DDD/TID; 95% CI, 19.25 to 61.88), Western Europe (17.37 DDD/TID; 95% CI, 9.05 to 33.35), and Northern Europe (11.72 DDD/TID; 95% CI, 6.17 to 22.25). ADHD medication consumption rates in all other regions were much lower, at less than 10 DDD/TID, despite some having upward trends between 2015 and 2019 (Fig. 2).

ADHD medication consumption and prevalence of ADHD, geographical region and income level

In the multivariable analysis, adjusting for yearly GDP per capita, ADHD prevalence, and geographical region, the worldwide trend for an increase in ADHD medication consumption was smaller but remained statistically significant (average annual percentage change: +4.58%; 95% CI, +1.33 to +7.93). When adjusting for these factors, ADHD prevalence ($P = 0.22$) and geographical region ($P = 0.37$) were not associated with the trends, while GDP per capita ($P < 0.001$) was positively associated with the trend in ADHD medication consumption (Table S3, Supplement pp5).

We also investigated ADHD medication consumption in countries by income levels. The annual average increase of ADHD medication consumption was only significant for high-income countries (n = 39; +11.28%; 95% CI, +9.48% to +13.12%). No significant changes in ADHD consumption rates were observed for upper-middle (n = 17; +3.23%; 95% CI, −1.88% to 8.61%) nor lower-middle-income countries (n = 8; +16.60%; 95% CI, −7.15% to +46.43%; Table 2). In 2019, the pooled consumption rates of ADHD medication were 6.39 DDD/TID (95% CI, 4.63 to 8.84) in high-income countries, 0.37 DDD/TID (95% CI, 0.23 to 0.58) in upper-middle-income countries and 0.02 DDD/TID (95% CI, 0.01 to 0.05) in lower-middle-income countries (Table 2).

	DDD/TID in 2015 (95%CI)[a]	DDD/TID in 2019 (95%CI)[a]	Average annual percentage change (%, 95%CI)[b]	P-value
Worldwide	**1.19 (0.79, 1.79)**	**1.43 (0.99, 2.07)**	**9.72 (6.25, 13.31)**	**<0.001**
America (North)	**89.19 (62.25, 127.79)**	**111.93 (108.72, 115.24)**	**5.78 (1.14, 10.64)**	**0.021**
Canada	74.24 (74.23, 74.25)	113.60 (113.59, 113.62)	11.22 (10.34, 12.10)	<0.001
United States	107.15 (107.15, 107.16)	110.28 (110.28, 110.28)	0.61 (0.13, 1.10)	0.028
America (Central and South) and the Caribbean	**0.79 (0.43, 1.46)**	**0.61 (0.37, 1.02)**	**−6.32 (-12.77, 0.61)**	**0.072**
Argentina	0.71 (0.71, 0.71)	0.80 (0.80, 0.80)	2.25 (−0.76, 5.36)	0.099
Brazil	2.55 (2.55, 2.55)	4.60 (4.60, 4.60)	15.89 (14.37, 17.42)	<0.001
Chile	1.03 (1.03, 1.04)	0.82 (0.82, 0.82)	−5.7 (−7.82, −3.52)	0.004
Colombia	0.03 (0.03, 0.03)	0.02 (0.02, 0.02)	−12.62 (−23.51, −0.18)	0.048
Ecuador	0.28 (0.28, 0.28)	0.30 (0.30, 0.30)	−0.16 (−8.89, 9.40)	0.959
Mexico	2.26 (2.26, 2.26)	3.15 (3.14, 3.15)	10.37 (3.33, 17.89)	0.018
Peru	0.23 (0.23, 0.23)	0.11 (0.11, 0.12)	−15.20 (−28.77, 0.94)	0.057
Puerto Rico	24.50 (24.48, 24.52)	26.54 (26.52, 26.56)	1.70 (−2.5, 6.07)	0.294
Uruguay	1.82 (1.82, 1.83)	2.18 (2.17, 2.18)	4.60 (−5.37, 15.61)	0.248
Venezuela	0.27 (0.27, 0.27)	0.02 (0.02, 0.02)	−46.35 (−61.87, −24.51)	0.010
Europe (West)	**14.10 (7.16, 27.74)**	**17.37 (9.05, 33.35)**	**5.25 (3.82, 6.69)**	**<0.001**
Austria	4.87 (4.86, 4.87)	6.83 (6.83, 6.84)	8.88 (6.73, 11.06)	<0.001
Belgium	16.57 (16.56, 16.58)	21.46 (21.45, 21.47)	6.16 (3.87, 8.49)	0.003
France	3.18 (3.18, 3.18)	4.56 (4.56, 4.56)	9.50 (8.92, 10.08)	<0.001
Germany	17.49 (17.48, 17.49)	21.28 (21.27, 21.28)	5.02 (2.87, 7.22)	0.005
Luxembourg	15.57 (15.53, 15.61)	14.43 (14.39, 14.47)	−1.78 (−2.63, −0.91)	0.007
Netherlands	49.40 (49.38, 49.41)	58.94 (58.92, 58.95)	3.87 (1.29, 6.52)	0.017
Switzerland	32.08 (32.07, 32.10)	39.49 (39.48, 39.51)	5.48 (4.50, 6.46)	<0.001
Europe (North)	**6.05 (3.18, 11.49)**	**11.72 (6.17, 22.25)**	**18.08 (13.39, 22.96)**	**<0.001**
Denmark	49.90 (49.88, 49.92)	72.71 (72.68, 72.74)	9.80 (7.65, 11.99)	<0.001
Estonia	1.92 (1.91, 1.93)	4.57 (4.56, 4.59)	23.73 (8.54, 41.04)	0.014
Finland	15.95 (15.93, 15.96)	33.24 (33.22, 33.26)	20.25 (18.80, 21.72)	<0.001
Ireland	5.47 (5.46, 5.48)	7.77 (7.76, 7.78)	9.03 (7.41, 10.68)	<0.001
Latvia	0.32 (0.31, 0.32)	0.73 (0.73, 0.74)	28.09 (6.29, 54.35)	0.024
Lithuania	0.10 (0.10, 0.10)	0.57 (0.56, 0.57)	51.95 (34.03, 72.28)	0.002
Norway	49.59 (49.57, 49.62)	74.75 (74.73, 74.78)	10.47 (7.29, 13.76)	0.002
Sweden	71.72 (71.69, 71.74)	99.27 (99.25, 99.30)	8.18 (6.51, 9.88)	<0.001
United Kingdom	11.56 (11.56, 11.57)	15.70 (15.70, 15.71)	7.71 (6.49, 8.94)	<0.001
Europe (South)	**1.06 (0.47, 2.39)**	**1.61 (0.65, 3.97)**	**10.79 (7.21, 14.48)**	**<0.001**
Croatia	0.09 (0.09, 0.09)	0.22 (0.22, 0.23)	24.27 (16.03, 33.09)	0.002
Greece	0.40 (0.40, 0.40)	0.71 (0.71, 0.71)	16.12 (11.39, 21.06)	0.001
Italy	0.23 (0.23, 0.23)	0.54 (0.53, 0.54)	23.26 (20.17, 26.43)	<0.001
Portugal	15.49 (15.48, 15.50)	17.79 (17.78, 17.80)	3.16 (−0.08, 6.51)	0.053

(Table 1 continues on next page)

	DDD/TID in 2015 (95%CI)[a]	DDD/TID in 2019 (95%CI)[a]	Average annual percentage change (%, 95%CI)[b]	P-value
(Continued from previous page)				
Serbia	0.18 (0.18, 0.19)	0.21 (0.21, 0.21)	3.42 (−1.63, 8.73)	0.122
Slovenia	3.22 (3.21, 3.23)	3.98 (3.96, 3.99)	4.96 (3.07, 6.88)	0.003
Spain	19.70 (19.69, 19.70)	22.18 (22.17, 22.19)	2.86 (1.67, 4.07)	0.005
Europe (East)	**0.39 (0.19, 0.82)**	**0.24 (0.11, 0.48)**	**22.39 (-1.87, 52.63)**	**0.072**
Bulgaria	0.05 (0.04, 0.05)	0.06 (0.06, 0.06)	7.17 (2.17, 12.42)	0.019
Czech Republic	3.94 (3.94, 3.95)	5.41 (5.41, 5.42)	7.74 (5.34, 10.19)	0.002
Hungary	0.62 (0.62, 0.62)	1.35 (1.34, 1.35)	21.84 (16.95, 26.93)	<0.001
Poland	1.13 (1.13, 1.13)	2.12 (2.12, 2.12)	17.81 (13.24, 22.55)	<0.001
Romania	0.91 (0.91, 0.91)	1.01 (1.00, 1.01)	2.24 (−4.14, 9.05)	0.353
Russia	0.01 (0.01, 0.01)	0.02 (0.02, 0.02)	18.11 (2.00, 36.76)	0.036
Slovakia	1.56 (1.55, 1.56)	1.18 (1.18, 1.19)	−8.58 (−21.05, 5.86)	0.147
Ukraine	$8.4*10^{-7}$ ($-3.2*10^{-7}$, $2.0*10^{-6}$)	$5.2*10^{-4}$ ($4.9*10^{-4}$, $5.5*10^{-4}$)	175.11 (−80.59, 3799.21)	0.311
Oceania	**22.32 (13.21, 37.71)**	**34.52 (19.25, 61.88)**	**11.36 (10.20, 12.54)**	**<0.001**
Australia	29.17 (29.16, 29.18)	46.49 (46.48, 46.50)	12.24 (9.93, 14.61)	<0.001
New Zealand	17.08 (17.07, 17.09)	25.63 (25.61, 25.64)	10.49 (9.52, 11.46)	<0.001
Asia (East)	**1.26 (0.24, 6.53)**	**2.44 (0.35, 16.87)**	**18.09 (13.81, 22.53)**	**<0.001**
China	0.04 (0.04, 0.04)	0.10 (0.10, 0.10)	24.59 (17.87, 31.7)	0.001
Japan	5.04 (5.03, 5.04)	12.20 (12.20, 12.20)	25.40 (20.79, 30.18)	<0.001
Korea	3.42 (3.42, 3.42)	5.53 (5.52, 5.53)	12.98 (4.75, 21.86)	0.014
Taiwan	3.74 (3.73, 3.74)	5.53 (5.52, 5.53)	10.16 (2.03, 18.95)	0.028
Asia (West)	**0.30 (0.10, 0.93)**	**0.51 (0.17, 1.58)**	**15.27 (10.51, 20.23)**	**<0.001**
Jordan	0.06 (0.06, 0.06)	0.10 (0.10, 0.10)	18.33 (2.82, 36.17)	0.032
Kuwait	0.02 (0.02, 0.02)	0.06 (0.06, 0.06)	24.07 (3.27, 49.05)	0.033
Lebanon	1.31 (1.30, 1.31)	1.72 (1.72, 1.72)	7.68 (2.52, 13.09)	0.017
Saudi Arabia	0.15 (0.15, 0.15)	0.20 (0.20, 0.20)	10.08 (−11.83, 37.43)	0.262
Turkey	3.38 (3.38, 3.38)	5.11 (5.11, 5.11)	10.57 (7.80, 13.41)	0.001
United Arab Emirates	0.81 (0.81, 0.81)	1.66 (1.66, 1.66)	21.93 (3.21, 44.05)	0.032
Asia (South-east)	**0.14 (0.004, 4.94)**	**0.29 (0.004, 22.66)**	**20.84 (8.95, 34.02)**	**0.004**
Philippines	0.02 (0.02, 0.02)	0.03 (0.03, 0.03)	8.16 (2.68, 13.94)	0.017
Thailand	0.85 (0.85, 0.85)	2.66 (2.66, 2.66)	35.01 (25.82, 44.86)	<0.001
Asia (South)	**0.03 (0.02, 0.03)**	**0.03 (0.02, 0.04)**	**−1.26 (-10.89, 9.40)**	**0.778**
India	0.03 (0.03, 0.03)	0.03 (0.03, 0.03)	7.27 (4.70, 9.90)	0.003
Pakistan	0.03 (0.03, 0.03)	0.02 (0.02, 0.02)	−9.12 (−27.89, 14.53)	0.280
Africa (North)	**0.03 (0.01, 0.08)**	**0.03 (0.01, 0.11)**	**4.18 (-5.74, 15.14)**	**0.397**
Algeria	0.02 (0.02, 0.02)	0.01 (0.01, 0.01)	−2.03 (−4.76, 0.78)	0.104
Egypt	0.12 (0.12, 0.12)	0.33 (0.33, 0.33)	27.06 (15.21, 40.14)	0.004
Morocco	0.003 (0.003, 0.003)	0.001 (0.001, 0.001)	−19.78 (−25.86, −13.19)	0.003
Tunisia	0.09 (0.09, 0.09)	0.18 (0.18, 0.18)	17.95 (13.47, 22.61)	<0.001
Africa (South)	**4.69 (4.69, 4.69)**	**5.55 (5.55, 5.55)**	**4.31 (2.95, 5.67)**	**0.002**
South Africa	4.69 (4.69, 4.69)	5.55 (5.55, 5.55)	4.31 (2.95, 5.67)	0.002

CI, confidence interval; DDD/TID, Defined Daily Dose per 1000 child and adolescent inhabitants per day. [a]Worldwide and regional estimates with 95% CI were calculated by pooling the estimates using meta-analysis (random-effects model). [b]The average annual change is calculated using a linear regression model, with log-transformed consumption in DDD/TID as the dependent variable and year as the independent variable. The average annual change was expressed as average annual percentage change, calculated by [exp (the coefficient of the year variable)−1] × 100%.

Table 1: **Worldwide, regional, and national levels of ADHD medication consumption in 2015 and 2019 and average annual percentage change in consumption.**

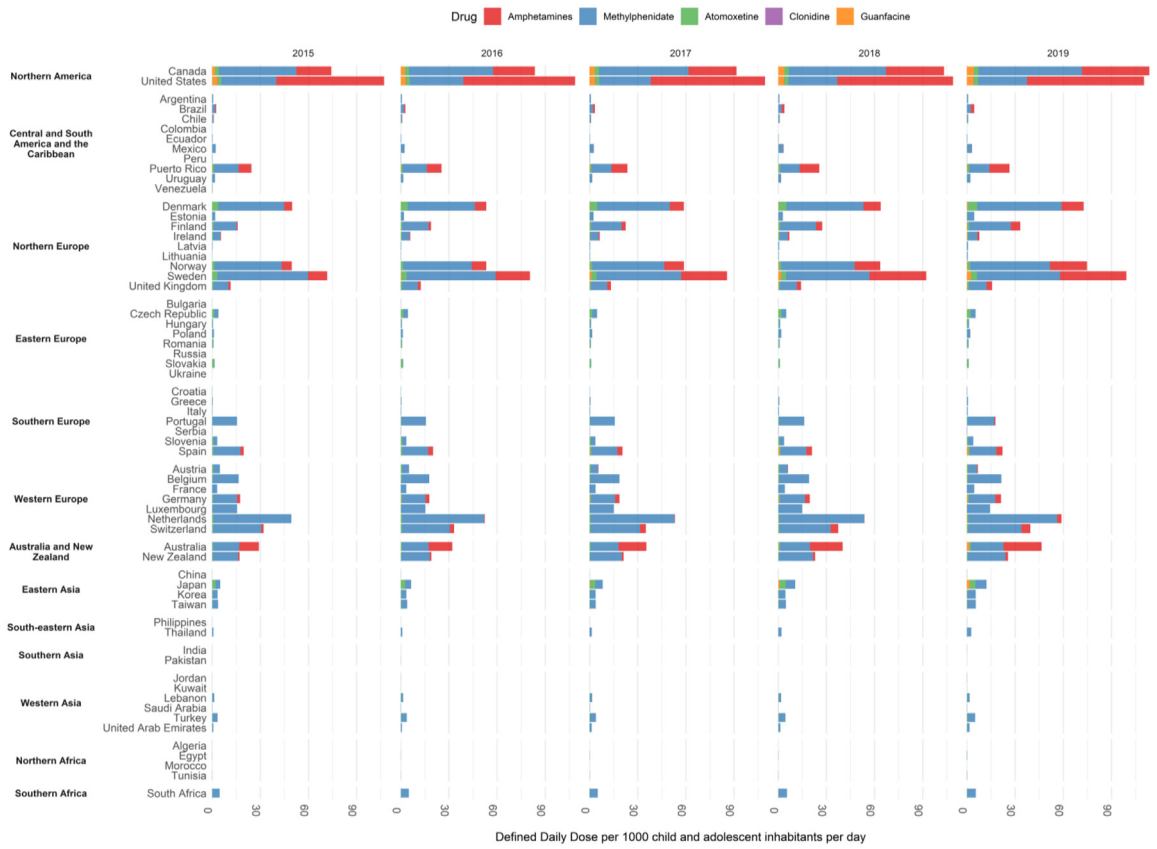


Fig. 1: **Worldwide ADHD medication consumption from 2015 to 2019.**

Consumption of individual ADHD medications

Overall, most countries had both stimulant and non-stimulant medication, with methylphenidate and atomoxetine having the highest country coverage for the two classes (Fig. 3). Amphetamines, clonidine, and guanfacine were not sold in lower-middle-income countries of this study (Table S2, Supplement pp3). The average annual changes for individual ADHD medications from 2015 to 2019 worldwide, by region, and by country are available in Table S4, Supplement pp6. The greatest multinational increases in DDD/TID during the study period were for amphetamines and guanfacine, with average annual increases of +30.32% (95% CI, +21.66% to +39.59%) and +79.77% (95% CI, +53.62% to +110.36%) respectively. In 2019, Canada was the country with the highest consumption of methylphenidate and guanfacine; the US had the highest consumption of amphetamines and clonidine; and Denmark had the highest consumption of atomoxetine (Fig. 3).

Discussion

This study examined ADHD medication consumption in 64 countries from 2015 to 2019 and found that overall ADHD medication consumption has been rising consistently. However, there were marked geographical differences in ADHD medication consumption and trends over time. Furthermore, the increases in ADHD medication consumption were only observed in high-income countries. Middle-income countries in the study, despite having much lower baseline ADHD consumption levels than ADHD prevalence, did not show any increases in ADHD medication consumption over time. Patterns of consumption of individual ADHD medications varied from country to country. Notably, increases in clonidine and guanfacine consumption in Europe (North, South, and West) and Eastern Asia were observed, suggesting the need for further safety monitoring for these relatively new ADHD pharmacological treatment options.

The overall increase of +9.72% per year in the multinational ADHD medication consumption from 2015 to 2019 in our study, consistent with previous findings,[10] showed that multinational ADHD medication consumption has been increasing since at least 2001. Similar to previous reports, ADHD medication consumption remained considerably higher in North America than the rest of the world, with the 2019 pooled estimate for North America being three times higher than that for Oceania, the region with the second

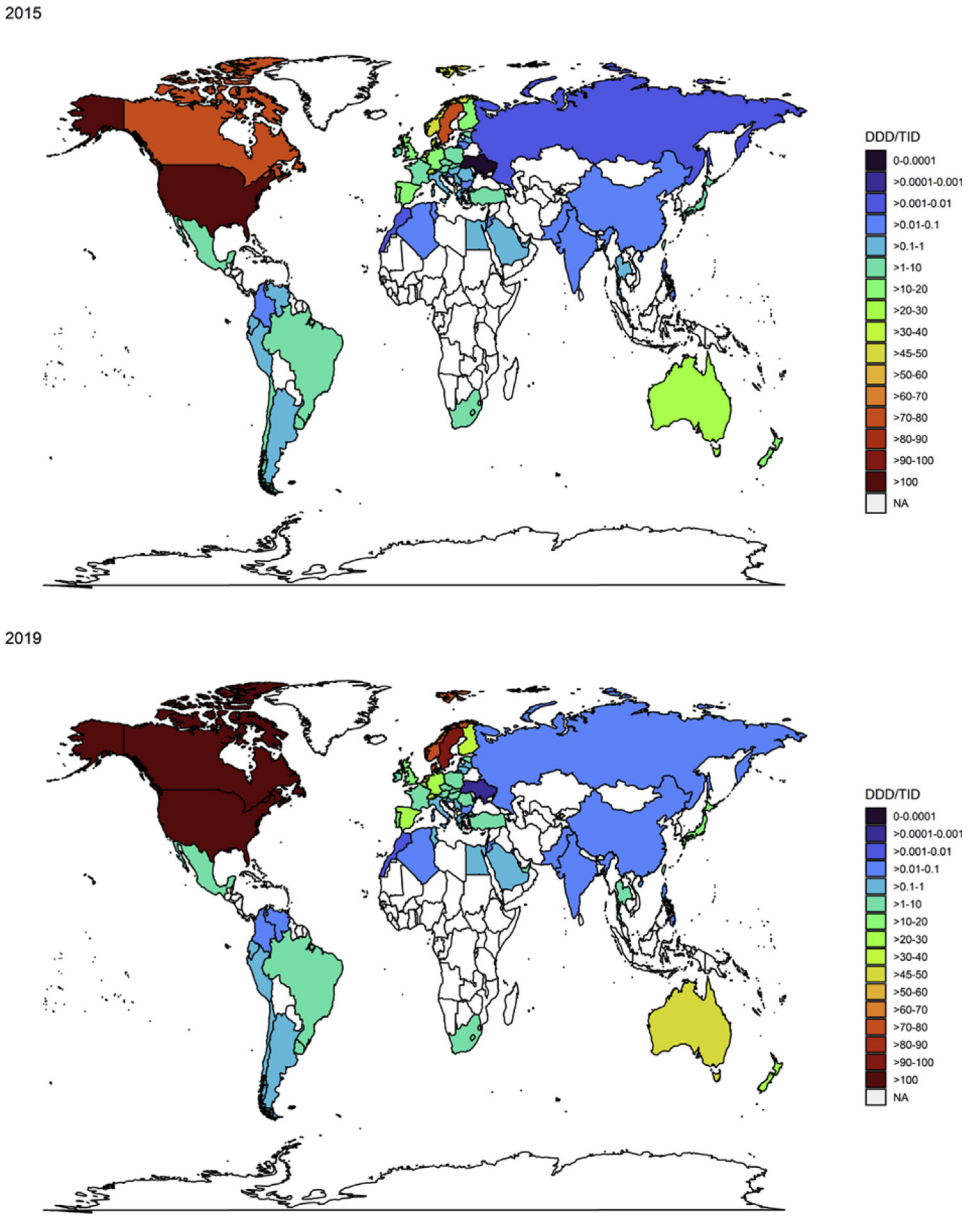


***Fig. 2:* ADHD medication consumption in DDD/TID in 2015 and 2019**. DDD/TID, defined daily dose per 1000 child and adolescent inhabitants per day; NA, data not available.

highest ADHD medication consumption rate. Overall, four regions, namely North America, Oceania, Western Europe, and Northern Europe, made up 85% of multinational ADHD medication consumption. Even so, some of the fastest-growing regions in our study period, including South-eastern Asia, Eastern Asia, and Western Asia, were those with low consumption rates in 2015, indicating that these regions might be catching up to the multinational norms of ADHD medication use. Contrary to the previously reported trend between 2001 and 2015, the average annual increase in ADHD medication consumption in the US between 2015 and 2019 was relatively small (+0.61%).[10] We further conducted a post-hoc analysis (Table S5, Supplement pp10) to test the effect of consumption level in 2015 on the trends of ADHD medication consumption and found no meaningful effects. This suggests that the prescription of ADHD medication in the US, having a much higher level than the second ranking country, may have hit a ceiling that is higher than the population prevalence for ADHD. Other potential reasons may include a more cautionary approach taken by clinicians and regulators

Income level	Consumption (defined daily dose per 1000 child and adolescent inhabitants per day)					Average annual change[a] (%, 95% CI)	P-value
	2015	2016	2017	2018	2019		
Lower-middle (n = 8)	0.03 (0.01, 0.05)	0.01 (0.01, 0.02)	0.01 (0.01, 0.02)	0.03 (0.01, 0.07)	0.02 (0.01, 0.05)	16.60 (−7.15, 46.43)	0.179
Upper-middle (n = 17)	0.33 (0.20, 0.52)	0.32 (0.20, 0.51)	0.32 (0.20, 0.50)	0.35 (0.22, 0.55)	0.37 (0.23, 0.58)	3.23 (−1.88, 8.61)	0.216
High (n = 39)	4.16 (2.87, 6.02)	4.51 (3.15, 6.46)	5.09 (3.59, 7.22)	5.57 (3.98, 7.79)	6.39 (4.63, 8.84)	11.28 (9.48, 13.12)	<0.001

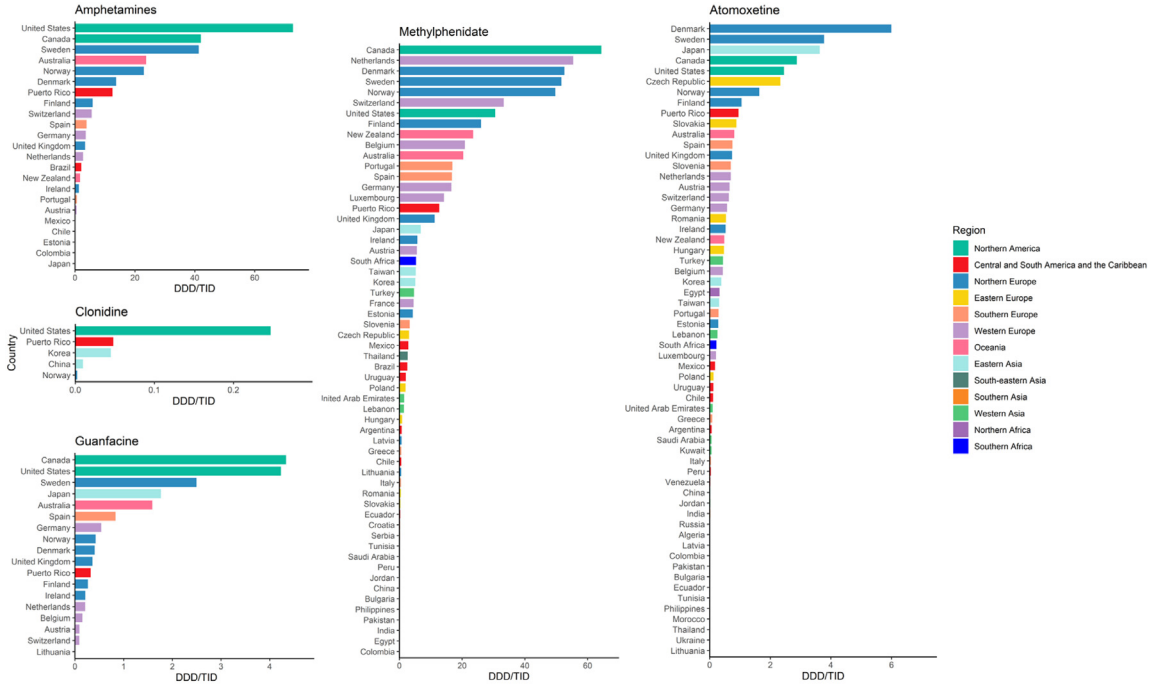
CI, confidence interval. [a]The average annual change is calculated using a linear regression model, with log-transformed consumption in DDD/TID as the dependent variable and year as the independent variable. The average annual change was expressed as average annual percentage change, calculated by [exp (the coefficient of the year variable)−1] × 100%.

Table 2: **. Annual ADHD medication consumption and average annual percentage change in consumption from 2015 to 2019 by country income level.**

when diagnosing and medicating children and young people and shifting preferences towards non-pharmacological options.

When investigating factors that could potentially explain the current patterns of ADHD medication consumption, we found that local ADHD prevalence estimates and geographical regions were not significantly associated with ADHD medication consumption. Findings by Polanczyk et al. suggested that when methodological differences were taken into account, the true prevalence of ADHD in contrast to the reported estimates from individual studies, did not increase over a 27-year time span, and was similar across geographical locations.[25] Thus, the rise in ADHD medication consumption is unlikely to be associated with increased ADHD prevalence. It may however be due to increased recognition of the important role of pharmacological treatment of ADHD. The lack of regional effect on trends of ADHD medication consumption is consistent with previous findings on ADHD medication use.[10] In addition, even within the same region, national guidelines and practices may differ substantially in their recommendations on the roles and balance between pharmacological and non-pharmacological treatment.[26] Non-pharmacological therapy is recommended as the first-line therapy or preferred in combination with pharmacotherapy for children with ADHD in some age groups in some countries.[5] However, this only partially explains the enormous differences in national ADHD medication consumption rates. Other factors may include physician-level differences in diagnostic and treatment practices, health budget allocation, cost structure and reimbursement status of ADHD medications, education policies, and cultural perceptions on medication use.

GDP per capita was a determinant factor for ADHD medication consumption. Although most regions noted a significant increase in ADHD medication consumption over time, no significant increase was observed when analyses were restricted to upper-middle and lower-middle income countries respectively. As such, the multinational increase in ADHD medication consumption seems to be driven by high-income countries. This observation is in contrast to the consumption of pharmacological treatment for cardiovascular diseases, where previous studies using MIDAS data found that the growth in consumption of cardiovascular medicines is higher in middle income countries than high income countries from 2008 to 2018.[27,28] While the reasons behind this observation were unclear and likely to be multifaceted, it is possible that in high-income countries, ADHD medications are more affordable, have more concerns about educational achievement, and possibly a larger market size generating greater interest from pharmaceutical companies. However, consumption rates of ADHD medication were strikingly higher in high-income countries than in middle-income



DDD/TID – defined daily dose per 1,000 child and adolescent inhabitants per day

Fig. 3: **Rankings of individual countries by ADHD medication consumption in 2019**. DDD/TID, defined daily dose per 1000 child and adolescent inhabitants per day.

countries—more than ten-fold greater than that in upper-middle-income countries and more than hundred-fold greater than in lower-middle-income countries (LMIC). Consumption rates of ADHD medication in middle-income countries were also considerably lower than the epidemiological prevalence of ADHD. Recently, the WHO reported huge geographical differences in resources for child and adolescent psychiatry, in particular, these resources were scarce in many middle-income countries and virtually non-existent in low-income countries.[29] Meanwhile, the application to include methylphenidate as an essential medicine for children, adolescents, and adults with ADHD was rejected twice by the WHO due to "uncertainties in the estimates of benefit of the medication".[30] This has a cyclical impact as the WHO essential medicines lists (EMLs) guide medication procurement and availability in many LMIC. As none of the ADHD medications was listed on EMLs, their usage will not be high. Cost and supply also act as barriers in LMIC, where medication use, including ADHD medications, often being reliant on non-government sources, as well as the lack of resources for child and adolescent psychiatry, and poor recognition to diagnose ADHD among doctors. These factors point to a potential treatment gap contravening the Sustainable Development Goal 3.8 which highlighted the importance of "access to safe, effective, quality and affordable essential medicines and vaccines for all," that needs to be addressed at a global level, in particular for those with moderate-to-severe ADHD where all guidelines agree on the central role of medication.[5,31]

Guanfacine, an alpha-2 adrenergic receptor agonist, was the fastest-growing ADHD medication during the study period. An extended-release formulation of guanfacine was first approved as a treatment for ADHD in the US in 2009. It has since been approved in several other countries.[32] In contrast, clonidine, another alpha-2 adrenergic receptor agonist, licensed for ADHD as the extended-release formulation, is only available in five countries. Although immediate-release clonidine is used off-label in some countries, our study did not capture this data.[33] There have been far fewer studies examining the safety and tolerability of clonidine and guanfacine than stimulants and atomoxetine. A recent network meta-analysis reported less precise estimates with wide CIs when evaluating the efficacy and tolerability of these medications, leading to uncertainty when interpreting the results.[5] This highlights the need for larger and longer-term studies that monitor the safety of these recently approved medications. Despite its fast growth, consumption rates of guanfacine remained low compared with stimulants. Following guanfacine, amphetamines had the second-highest annual increase in

consumption. Northern and Western Europe had the highest regional annual increase in amphetamines consumption during the study period. In non-US countries, this was likely due to the recent approval of lisdexamfetamine, an amphetamine prodrug, where previously only dexamfetamine's immediate release was available.[34] In children and adolescents, amphetamines may have moderately greater efficacy than methylphenidate in ADHD, whereas methylphenidate may have higher tolerability.[6] However, there is no conclusive clinical evidence to date to support a prospective choice for amphetamines over methylphenidate or vice versa or how individual differences may contribute to differential treatment responses. In addition, a recent study reported that amphetamine use was associated with a greater risk of psychosis than methylphenidate.[35] More studies of direct comparisons between stimulant medications, particularly those that look at differential responses at an individual level are required to inform current guidelines.[5,26]

This study is the first and largest multinational study to report recent data on ADHD medication consumption with several strengths. Firstly, the international standardisation of data used in this study allows comparisons of national-level medication consumption rates. Secondly, our study covered over half of the world's population, including lower-middle-income countries where ADHD medication consumption patterns received little to no attention in current literature. Thirdly, we explored the relationship between ADHD medication consumption and several country-level factors. Our study has some limitations. Firstly, although we investigated the effects of factors including GDP per capita and ADHD prevalence on ADHD medication consumption at the country-level, we did not investigate other qualitative factors, such as healthcare system differences with diagnosis and treatment, differences in national guidelines and cultural attitudes towards ADHD medication, which may have significant effects on ADHD medication use. Secondly, individual-level information was not available, as such, we were not able to evaluate the appropriateness of medication use, nor were we able to ascertain if the low ADHD medication consumption was due to the use of non-pharmacological treatment. We also could not ascertain whether the medication was used in children. In particular, increase in adult ADHD medication use was reported in some countries.[10,36] Thirdly, ADHD medication consumption could be underestimated in countries without 100% market coverage despite adjustments made to project the total consumption, especially in the 15 out of 64 countries that did not have hospital coverage.[19] However, total pharmaceutical market coverage in most countries was greater than 80%. Furthermore, this is unlikely to affect the estimation of trends as country-level differences were accounted for while the consumption levels between countries are too large for the underestimation to affect our conclusion. Lastly, as each country presents very different patterns and trends of ADHD medication consumption in our study, the current results are only applicable to the countries included. Specifically, data from low-income countries is urgently needed to complete the picture on global ADHD medication consumption.

Results from this study have significant implications for clinical practice and global health policies. In countries where ADHD medication consumption rates started low, rising consumption trends may represent increased awareness of treating ADHD. In countries where consumption rates were high (e.g., Canada and US), sustained efforts should be made to monitor the accuracy of diagnosis and appropriate use of ADHD medication to gain timely insights on diagnosis and prescribing patterns for ADHD. Furthermore, it is imperative to evaluate the barriers and access to ADHD treatment in middle-income countries. There is very little data on the consumption of ADHD medication in low-income countries and there is an urgent need to collect data in these countries.

The overall consumption of ADHD medication increased worldwide between 2015 and 2019. However, this change was mainly driven by high-income countries. As the epidemiological prevalence of ADHD is likely to be consistent across geographical regions, efforts should be made to understand the current barriers to the identification of ADHD and ADHD medication access in middle-income regions. Further safety and tolerability studies with head-to-head comparisons of various ADHD medications are needed in response to the rising trends of alpha-2-agonist ADHD medication consumption.

Contributors

AYLC, TTM, KKCM, and ICKW had full access to the aggregate analysis data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ICKW, and KKCM were responsible for the study concept, and ICKW, KKCM, and AYLC were responsible for the study design. AYLC, KKCM and TTM did the statistical analysis. AYLC, KKCM, ICKW, WCYL, DC, LG, YHJ, YH, LW, TYL, PI, KT, ES, and DT were involved in the acquisition or interpretation of data. AYLC, KKCM, and ICKW drafted the manuscript. AYLC, KKCM, ICKW, WCYL, DC, LG, YHJ, YH, LW, TYL, PI, KT, ES, and DT critically revised the manuscript for important intellectual content. TYL, PI, and ICKW were responsible for resource acquisition.

Data sharing statement

The underlying MIDAS data were provided by IQVIA under license. The terms of our agreement do not permit disclosure, sublicensing, or sharing of IQVIA MIDAS data. IQVIA will honour legitimate requests for MIDAS data from qualified researchers. Please contact IQVIA to seek approval for data access; a license fee may be applied.

Editor note

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Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2022.101780.

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