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Title: Attention-Deficit/Hyperactivity Disorder medication consumption in 64 countries and regions from 2015 to 2019: a longitudinal study

Authors: Adrienne Y.L. Chan,[1-4] MPH; Tian-Tian Ma,[2,3] PhD; Kenneth K.C. Man,*[2-5] PhD; Ian C.K. Wong,*[2-5] PhD

*Principal investigators

Authors' affiliation:

[1] Groningen Research Institute of Pharmacy, Unit of Pharmacotherapy Epidemiology and Economics, University of Groningen, Groningen, The Netherlands

[2] Laboratory of Data Discovery for Health ($D^2$4H), Hong Kong Science Park, Hong Kong SAR, China

[3] Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

[4] Research Department of Practice and Policy, School of Pharmacy, University College London, London, United Kingdom

[5] Centre for Medicines Optimisation Research and Education, University College London Hospitals NHS Foundation Trust, London, UK

Background

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] 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.[3] We previously reported the prevalence of ADHD medication use in thirteen countries and one special administration region between 2001 to 2015 and found an increasing trend in all studied sites, with methylphenidate being the most commonly used ADHD medication in most countries.[4] 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. 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.[6,7]

Aims and objectives

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.

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 MIDAS database has been validated against external data sources[8] and used as a proxy to evaluate multinational consumption of medication.[9-11] 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, will be identified by the European Pharmaceutical Market Research Association (EphMRA) Anatomical Therapeutic Chemical (ATC) classification codes (**Table 1**). Amphetamines included "amfetamine", "dexamfetamine," "metamfetamine," and "lisdexamfetamine". Methylphenidate includes "methylphenidate," and "dexmethylphenidate". For amphetamines, guanfacine, and clonidine, only products with ATC codes that started with "N" for the nervous system will be included due to their alternative indications for non-ADHD conditions. The included countries/regions will be 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*".[12] 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;[13] country income measured by Gross Domestic Product (GDP) per capita in US dollar, from the UN National Accounts Estimates of Main Aggregates;[14] age-standardised country-specific prevalence rates of ADHD will be obtained from the Global Burden of Disease (GBD) data via the Global Health Data Exchange (GHDx).[15] 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 will be used.[4]

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**).[16] For products without drug strength and DDD, we will impute the strength based on the most sold product for that ingredient.

At the national level, consumption rates in DDD/TID will be calculated with a 95% confidence interval (CI) estimated by the Poisson method.[4] The multinational and regional consumption levels will be computed by pooling the estimates from individual countries using a random-effects model. The time trends of ADHD medication consumption will be 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 will be 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[13]) to investigate how consumption trends vary with country income levels. Additional analyses will be 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 will be log-transformed. The statistical significance level was set at $p<0{\cdot}05$. All analyses will be 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) will be used for data analysis.

Table 1. Defined daily dose of different ADHD medication according to the World Health Organisation Anatomical Therapeutic Chemical Classification System

ATC code	Name	Defined daily dose	Unit
N06BA01	amfetamine	15	mg
N06BA02	dexamfetamine	15	mg
N06BA03	metamfetamine	15	mg
N06BA04	methylphenidate	30	mg
N06BA09	atomoxetine	80	mg
N06BA11	dexmethylphenidate	15	mg
N06BA12	lisdexamfetamine	30	mg
C02AC01	clonidine	0·45	mg
C02AC02	guanfacine	3	mg

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