ADHD medication discontinuation and persistence across the lifespan: a multinational study

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Abstract

Background: Although often intended for long-term treatment, discontinuation of medication for attention deficit/hyperactivity disorder (ADHD) is common. However, cross-national estimates of discontinuation are missing due to a lack of standardized measures. The aim of this multinational study was to show ADHD treatment discontinuation across the lifespan and describe similarities and differences across countries to guide clinical practice.

Methods: Using a common analytical protocol and prescription data from nine countries/administrative regions, we identified new users of ADHD medication between 2010 and 2020. We examined treatment discontinuation and persistence over five-years, stratified by age-at-initiation (children, adolescents, young adults, and adults) and sex. Ethnicity data were not available.

Outcomes: We included 1,229,972 individuals (735,503 [60%] males, 494,469 females [40%]) initiating ADHD medication (median age range 8-21). Across countries, discontinuation was lowest in children and highest in young adults. Within one year of initiation, 65% of children, 47% of adolescents, 39% of young adults and 48% of adults remained on treatment. The percent discontinuing was highest at ages 18 to 19. Treatment persistence for up to five years was relatively higher across countries when accounting for medication re-initiation; at five-years follow-up, 50-60% of children and 30-40% of adolescents and adults were covered by treatment in most countries. Patterns were similar across sex.

Interpretation: Early medication discontinuation is prevalent in ADHD treatment, particularly among young adults. Although medication re-initiation is common, treatment persistence in adolescents and adults is lower than expected given data about the persistence of ADHD. We discuss possible reasons for these treatment patterns and avenues for reducing premature medication cessation.

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Research in context

Evidence before this study

A systematic search for observational studies examining medication discontinuation and persistence to ADHD medication treatment was conducted in PubMed up to March 10, 2023. The search with ("ADHD" OR "attention deficit hyperactivity disorder") AND ("medication" OR "treatment") AND ("medication adherence" OR "discontinuation" OR "pattern" OR "persistence") yielded 991 articles, including 202 reviews. We excluded articles that did not report the rate or proportion of adherence, persistence, or discontinuation of ADHD medications. In total, we identified four relevant reviews published between 2010 and 2014, and three multinational studies, including between 5 to 8 European countries. Most prior studies were from Europe and North America, focused on children and adolescents, and included small numbers of females. Reviews concluded that medication persistence is poor in ADHD, with average rates of non-adherence or discontinuation ranging from 13% to 87% across children, adolescents and adults. However, variations in the measures used limit the possibilities for cross-study comparisons or meta-analyses. Further, up-to-date evidence on the extent of treatment discontinuation across the lifespan in males and females is needed given the global increase in ADHD medication use and increasing treatment coverage in adults and females with ADHD.

Added value of this study

We extend to the existing literature by presenting the, to date, largest multinational study of ADHD medication (stimulant and non-stimulant) treatment discontinuation and persistence in children, adolescents and adults, in males and females. Our findings are based on dispensing data between 2010-2020 from nine countries/regions across North America, Europe, Asia and Australia. Using a common analytic protocol and outcome measures, we show strong similarities in ADHD medication treatment patterns across countries. Early discontinuation rates differed substantially by age, with higher rates in adolescents and adults compared to children across countries and time-points. We provide new knowledge on longer-term treatment persistence, showing that 30-60% patients still received medication for up to 5 years when allowing for re-initiation of treatment. Finally, we show that although more males than females received ADHD medication across countries, this difference decreased with age and patterns of discontinuation and persistence were similar across sex.

Implications of all the available evidence

Early medication discontinuation is common in ADHD across countries. This can represent a major barrier to positive treatment outcomes. Patterns of longer-term treatment persistence illustrate that many individuals come back to treatment after medication breaks. Yet, treatment persistence is lower than what is to be expected based on previously reported age-related remission in ADHD. Medication discontinuation and persistence rates vary substantially by age, with late adolescence and early adulthood emerging as a critical window for intervention aimed at reducing premature treatment cessation. Causes of treatment discontinuation are multifactorial, and they are likely to differ across the lifespan, requiring further cross-country systematic investigation.

Introduction

Attention deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder, with a prevalence of ~5% in children and ~2.5% in adults.[1] Pharmacological treatment coupled with non-pharmacological therapy is an integral part of evidence-based ADHD care.[2] The use of ADHD medication has increased markedly across age groups over the past two decades, particularly in high-income countires.[3,4] Central nervous systems stimulants (e.g. methylphenidate) are recommended as first-line pharmacological treatment and non-stimulants (e.g. atomoxetine) as second line.[2] Longitudinal studies show that two-thirds of youth with ADHD continue to have impairing symptoms in adulthood,[5] highlighting that a considerable proportion of individuals with ADHD may require long-term treatment and support.

Numerous randomized controlled trials (RCTs) have shown short-term beneficial effects of medications for reducing core symptoms of ADHD.[1,6] Observational studies also show positive effects of ADHD pharmacological treatment on important behavioral and functional outcomes (e.g., reducing the risk of injuries, accidents, substance use disorders, criminal convictions, and improving educational outcomes).[7,8] Less is known about longer-term ADHD treatment, but recent data suggest that use of ADHD medication for up to two years is generally safe.[9] One RCT found methylphenidate effective in managing ADHD symptoms even after two years of treatment, although efficacy varied by age and beneficial effects of continued treatment were not found in all participants.[10]

Prior research suggests that 50-80% of individuals with ADHD initiating medication treatment stop within 1-2 years.[11-16] These rates exceed expected age-related decreases in symptoms during a similar time-frame,[5] suggesting that treatment is prematurely discontinued in some individuals with ADHD for whom symptoms persist,[17] which can present a major barrier to effective treatment in

ADHD. A review of 91 studies[16] found that discontinuation rates were high, with medication side-effects, poor response, dosing inconvenience, stigma and patient attitudes as the main reasons.[16] Further, this and other reviews,[13,18] concluded that the large variation in methods and measures used to assess discontinuation of ADHD medication makes it difficult to compare results across studies and countries. We identified three prior multinational studies on discontinuation,[19-21] but all were conducted in Europe, used varied methodologies, and were limited to treatment in adults[19] or children/adolescent[21] only, or lisdexamfetamine medication.[20] Another pertinent issue largely ignored in prior research is re-initiation of medications following discontinuation (i.e., planned or non-planned treatment breaks). A recent Australian study used a novel method[22] to analyze medication persistence, taking re-initiation into account.[23] About half of individuals with ADHD remained on medication at five years, suggesting that such measures of medication persistence provide important insights complementing traditional approaches studying time to first medication discontinuation.[23] In addition, increasing use of ADHD medications,[3] newly available therapeutic options (e.g., lisdexamfetamine, guanfacine),[3] and growing number of adults, in particular females, being considered for treatment,[2,24,25] may have affected patterns of medication discontinuation and persistence in ADHD. Despite this, population-based studies from multiple geographical regions considering differences across ages and sex are currently lacking.

To address these issues, we present the largest-to-date, multinational study of ADHD medication treatment discontinuation and persistence among children, adolescents and adults, in males and females. We describe differences and similarities across countries, age groups, sex, and medication classes using prescription records of 1.2 million individuals who initiated ADHD medications from nine different countries/regions.

Methods

Data sources

We used dispensing data, referring to prescriptions dispensed from pharmacies in each included country except in the UK, where only prescription records were available. For simplicity, these will from now also be referred to as dispensations. Dispensing data were used to estimate discontinuation and persistence of ADHD medication in nine countries/regions. Australia contributed patient-level dispensing data from a national administrative medication database[26] covering a random 10% sample of the national population. Denmark, Iceland, Hong Kong Special Administrative Region (Hong Kong SAR), the Netherlands, Norway and Sweden contributed patient-level dispensing data from national prescription registers or electronic health records with national coverage; the UK provided patient-level primary care data covering 6% of the UK population[27] and the US contributed electronic health records from the TriNetX Research Network database which currently includes a total of ~1.2 million individuals with ADHD. Most countries provided data on dispensation of ADHD medication from 1 January 2009 until 31 December 2020; the exceptions were Australia (data from 1 July 2012), and Denmark and Norway (data until 31 December 2018 and 31 December 2019, respectively).

Study population

Our study base consisted of individuals aged three years or older initiating ADHD medication between 2010 and 2020 (the study period varied depending on the data available in each country, see above). Similar to prior pharmaco-epidemiological ADHD studies,[28-30] we used a 12-month wash-out period without any ADHD medication dispensations to define new users and excluded individuals with missing data on sex, birthdate, dispensing date, or using ADHD medication for other indications. Exclusions depended on the data available in each country (Supplementary

tables 1 and 2, supplementary figure 1). Based on age of the time of the first dispensed ADHD medication, the study population was divided into children[4-11 years], adolescents[12-17 years], young adults[18-24 years], and adults[≥ 25 years)].

Measures

ADHD medication dispensations were identified using World Health Organisation Anatomical Therapeutic Chemical (ATC) classification codes or data source-specific drug codes mapped to ATC codes. We included six of the most commonly used medications licensed for ADHD treatment; the stimulants methylphenidate [N06BA04], amphetamine [N06BA01], dexamphetamine [N06BA02], and lisdexamfetamine [N06BA12], and the non-stimulants atomoxetine [N06BA09] and guanfacine [C02AC02]. The date of initiation was defined as the date of the first recorded dispensation of any of the considered ADHD medications, after a 12-month period without any dispensation. We defined discontinuation of ADHD medication as a gap of ≥180 days between two dispensations. In the UK, this was defined using prescription dates. Switches between medications were not considered discontinuation if dispensations occurred less than 180 days apart. The maximum length of a single prescription according to country-specific regulations was 90 days in five (i.e., Iceland, Netherlands, Norway Sweden, and US) out of the nine contributing countries/regions. Therefore, we selected a cut-off of ≥180 days without a dispensing to ensure we captured clinically meaningful medication breaks rather than shorter treatment breaks.

Statistical analysis

We used a distributed network approach and a common analytic protocol to perform comparable analyses in each country. The study protocol and analysis plan were published on the OSF Preregistration platform (https://osf.io/py4s7). For each country, we described the characteristics

of the study population and the number of new medication users by specific medications during the study period (2010-2020).

To describe the time to first ADHD medication discontinuation, we report estimates of country-specific Kaplan-Meier curves (KM-curves) showing the proportions of individuals remaining on treatment at 1-year, 2-year, 3-year, 4-year, and 5-years following initiation. We then combined point estimates and standard errors of the proportion of ADHD individuals remaining on treatment for each country, stratified by age group and follow-up point by using the generic inverse variance method of restricted maximum likelihood.[31] We used a random-effect meta-analysis model and Hartung-Knapp-Sidik-Jonkman confidence interval (CI) for the pooled estimates and assessed cross-country heterogeneity using the Cochran's Q test and the I^2 statistic, with an I^2>75% representing significant heterogeneity. We also examined the likelihood of individuals discontinuing their ADHD medication for the first time across ages. This was done by calculating the proportion of individuals who had their first medication discontinuation at each age among those who remained on treatment at each age.

Finally, we assessed medication treatment persistence up to five years following initiation using the Proportion of Patients Covered (PPC) method,[22,23] which allows a person to re-enter analyses after a break in treatment. The PPC is calculated as:

$$PPC = \frac{patients\ currently\ covered\ by\ their\ latest\ medication\ dispensation}{all\ individuals\ who\ initiated\ medication\ treatment\ and\ remained\ in\ follow-up}$$

Because most countries did not have information on the exact number of days covered by each dispensation, we defined a treatment period by dispensations occurring no longer than 180 days apart. The start of a treatment period was the date of the first dispensation and the end was the

date of the last dispensation plus the estimated length of a dispensation. For each country, the approximate length of each dispensation was calculated based on the number of days in which 75% of people in the same age and sex group received a subsequent dispensation (occurring less than 180 days apart).[23]

Subgroup and sensitivity analyses

We also calculated country-specific Kaplan-Meier and PPC curves stratified by sex and medication class (i.e., stimulants and non-stimulants). In a sensitivity analysis, we explored country-specific patterns of treatment discontinuation in countries where the maximum specific prescription length differed from 90 days (supplemental methods).

Data management and data analyses were performed with R (R Foundation for Statistical Computing) and Stata (Stata Corp LP, College Station, TX).

Ethics and consent

Ethical review of or approval for the use of each data source was obtained by the contributing authors and ethics organisations in participating countries. Informed consent was not required for the included data sources (Supplemental Note 1).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Our final study population included 1,229,972 individuals (735,503 [60%] males and 494,469 females [40%]; sex-distribution by country is presented in Table 1) who initiated ADHD medications aged 3 years or older across the nine countries/regions between 2010 and 2020. The median age at first dispensed ADHD medication ranged from 16 to 21 years in most countries,

except for Australia (11 years), Hong Kong (8 years) and the UK (11 years). Australia, Hong Kong and the UK also had the highest proportion of males, ranging from 68-77%, compared to around 60% in other countries (Table 1). We did not have access to information on ethnicity. Methylphenidate was the medication of choice for treatment initiation in all countries. This was followed by atomoxetine (the main non-stimulant ADHD medication) in most countries and by dexamphetamine in Australia and the US. We observed little variation in the ADHD medications of initiation over time across countries, although there was increased uptake of lisdexamfetamine since its introduction for ADHD treatment particularly in Australia, Sweden and the US (Supplementary Figures 2 and 3).

Treatment discontinuation

The median time to first discontinuation was lowest in the US (142 days) and highest in Sweden, Norway and the UK, ranging from 411-432 days (Table 1). Pooled estimates of the proportion of individuals remaining on ADHD medication treatment without discontinuation up to five years after initiation are presented with 95% confidence intervals in Figure 1. Within one year of treatment initiation, 65% (95%CI 60-70) of children, 47% (95%CI 43-51) of adolescents, 39% (95%CI 36-42) of young adults and 48% (95%CI 44-52) of adults remained on treatment. At 5-year follow-up, 24% (95%CI 18-30) of children and 9% (95%CI 6-12) of adolescents, 10% (95%CI 7-12) of young adults and 15% (95%CI 11-19) of adults remained on treatment. The cross-country heterogeneity measured by the inconsistency index (I^2) was significant (p-value from Cochran Q test<0.05) and high (I^2 >75) in all age-groups and follow-up points. Country-specific KM-curves (Figure 2) showed a similar pattern across age-groups and countries as the pooled estimates with some exceptions; the proportion of children remaining on treatment was considerably higher in Denmark (e.g., 82% at 1-year, 47% at 5-years) than in other countries. Age-differences were less evident in the US, Hong Kong and Australia, where the proportion

remaining on treatment was low overall and more similar across age groups. The proportion of discontinuation was highest at ages 18 to 19 as evident in all countries with sufficient number of observations among adults (Figure 3).

Treatment persistence

The proportion of patients persisting to ADHD medication up to five years after initiation in the PPC analysis was higher than the KM estimate, as the former accounted for re-initiation (Figure 4). For example, 50-60% of children and 30-40% of adolescents and adults were covered by treatment at 5-year follow-up across all countries, except the US, where the PPC curves in children were more similar to adolescents and adults.

Subgroup and sensitivity analyses

Sex-stratified analyses showed similar treatment patterns across males and females for both KM- and PPC curves across countries and ages (Supplementary figures 4-7). In absolute numbers, more males than females received medications for ADHD in all countries, yet this difference decreased with age, as evidenced by the different age-distributions of ADHD medication received in males and females. Nevertheless, the proportion who discontinued at each age was similar by sex (Supplementary figures 8 and 9). Analyses for stimulants (Supplementary figures 10 and 12) were similar to the main analyses, as these are the most used ADHD medications. Individuals initiating non-stimulants had higher rates of discontinuation (Supplementary figure 11) and lower rates of treatment persistence (Supplementary figure 13) over time, and less clear age differences compared to people initiating stimulant treatment. KM-curves estimated using the country-specific maximum length of prescription to define discontinuation showed smaller differences between age-groups in Australia and the UK, compared to the main analyses, whereas results from Hong Kong indicated that majority discontinued medications after the first dispensation.

PPC-curves showed more similar treatment patterns as the main analyses in all three countries/regions (Supplementary figure 14).

Discussion

In this large multinational investigation of ADHD medication discontinuation and persistence across the lifespan, including data from nine different countries/regions, we found that early medication discontinuation in ADHD is common across countries. Further, we contribute knowledge on the long-term treatment persistence in ADHD, showing that the proportion of patients covered by medication in the five years following initiation is comparatively higher when accounting for re-initiation.

Our results show considerably higher rates of early discontinuation in adolescents and adults than children, across countries. Within one year of medication initiation, 65% of children and 40-50% of adolescents and adults remained on treatment and by two years this had dropped to 20-30% of adolescents and adults. Young adults (18-24 years) had the highest rates of early discontinuation across countries, closely followed by adolescents (12-17 years). Discontinuation rates in the first years following treatment initiation far exceed reported age-related remission rates in youth with ADHD in a similar time-frame.[5] Higher discontinuation rates in adults may partly be explained by meta-analytic evidence from 133 RCTs[6] showing that in the short-term, ADHD medications are generally less effective and less well tolerated in adults than in children and adolescents. Similar comparisons for children vs. adolescents were not possible due to a paucity of data.[6] We found that the proportion who discontinue peaked at age 18 to 19 years. This coincides with the transition from pediatric to adult mental health services, which is often poorly experienced and reported to be one reason for ADHD treatment discontinuation in prior research.[16,32] Other reasons reported by young people in qualitative research include lack of parental support in

managing medications, perceiving ADHD as a childhood or education-related disorder, side-effects, low effectiveness and concerns of dependence. Further, changing life circumstances (e.g. leaving school, starting a new job) meant that some young individuals felt they no longer needed medications.[32] Nevertheless, late adolescence and early adulthood appear to be an important window for targeted interventions aimed at reducing premature medication cessation in individuals where treatment is still warranted and effective. This may include improved provision of care, providing treatment options with fewer adverse effects, and patient education to increase awareness of the often persistent nature of ADHD[5] and reduce misconceptions about ADHD and its treatments.[16,32] Further, simple text messaging (SMS)-based interventions have shown promising results in pilot studies in children[28] and adults with ADHD,[33] suggesting this may be a cost-effective method to support continued treatment when needed. Across countries, the steepest treatment drop-off occurred in the first year of initiation. Such high discontinuation rates shortly after initiation are unlikely to be explained by symptom remission, but may instead reflect challenges of finding the right type, dose and formulation of ADHD medication, since tolerability and effect are highly variable across individuals with ADHD.[1,6] Further, our analyses included individuals who only redeemed a single prescription. Prior studies have reported low rates of initial prescription renewal in ADHD,[11,12] and suggested that this may in part be explained by symptoms of ADHD itself, such as forgetfulness and poor organizational skills, and the need for frequent contact with care-providers to obtain renewed prescriptions.[11,12]

Whilst country-specific analyses of treatment discontinuation showed largely similar patterns, meta-analytic estimates showed high cross-country heterogeneity and we observed some important country-specific findings. Whilst children had the lowest discontinuation rates across countries, estimates from Denmark stood out, with nearly 90% of children remaining in treatment

within 1-year of initiation, 75% at 2-year and >50% at 5-year. These rates exceed the other countries included and most prior reports from other countries/data sources.[12,16,34,35] Among the Nordic countries, the prevalence of prescription in Denmark is lower than in its neighboring countries (i.e. Sweden, Norway),[3] which might suggest that treatment is mainly offered to those with more severe ADHD symptoms and greater need for treatment. However, the relationship between discontinuation rate and prevalence of prescription is more complicated when comparing other countries with more substantial variation in the prevalence of ADHD medication use. Further, discontinuation rates were higher, and age-differences were less pronounced in the US, Hong Kong and Australia, as compared to the European countries. These findings may in part reflect underlying differences in regulation, clinical practice, the organization of care and educational systems, and cultural differences in attitudes towards ADHD diagnosis and medication.[3,16,36,37] Differential prescription patterns in the US, where methylphenidate is not the most commonly used medication in contrast to the rest of the world,[3] may also have contributed to cross-country heterogeneity. Future research aimed at identifying country-specific modifiers of discontinuation, as well as how the prevalence of prescribing may influence discontinuation patterns, could inform clinical practice.

Analyses of treatment persistence showed relatively higher proportion of individuals covered by ADHD medication up to five years after initiation when accounting for treatment re-initiation (e.g., 50-60% of children and 30-40% of adolescents and adults), compared to analyses of the first discontinuation only. Our findings illustrate that many individuals with ADHD return to treatment after medication breaks and receive long-term medication treatment. This pattern of on-and-off treatment may partly map onto the dynamic nature of ADHD. Recent longitudinal studies show that many individuals with ADHD experience a waxing and waning of symptoms across

development, including periods of remission and recurrence, which suggests that the need for medication treatment also varies over time.[3,38] One RCT [10] showed beneficial effects of continued treatment compared to discontinuation and switch to placebo in individuals treated with methylphenidate for an average of 4.5 years.[10] However, effect sizes were smaller than those reported in short-term RCTs of methylphenidate treatment and only significant in children. Further, around 60% of participants receiving placebo did not experience worsening of symptoms during the 7-week trial.[10] This, together with our findings of relatively high persistence across five years highlights that regular re-assessment of the need for continued ADHD treatment is good clinical practice, and that more research is needed on the safety, efficacy and outcomes of long-term ADHD medication treatment.

Our study population included 40% females, allowing us to perform well-powered sex-stratified analyses and address some important knowledge gaps as treatment of ADHD in females remains understudied.[25,39] Across countries, although more boys than girls received ADHD medication, we found limited evidence for sex differences in discontinuation and treatment persistence over the five-year follow-up. Similarly, recent reviews[25,39] found that current evidence does not support major sex differences in effectiveness or tolerance of pharmacologic ADHD treatment, although small samples of females in most prior research precluded strong conclusions.[25,39] Further, the increasing rates of medication treatment for ADHD among females of reproductive-age [24] emphasizes the need for more research on sex-differences in ADHD treatment, including on the causes underlying discontinuation (e.g., differential symptom presentation, comorbidities, compliance rates, pregnancy, adverse drug reactions).[32,39] Individuals initiating non-stimulant ADHD medications had higher rates of discontinuation and lower treatment persistence over time, across countries and age-groups, compared with people initiating stimulant medications.

This likely reflects the lower efficacy of non-stimulants[6] and differential indications for initiating treatment with a non-stimulant medication, e.g. contra-indications, failing or experiencing intolerable side-effects of stimulant treatment.[2] Finally, the median age at first dispensation was relatively high, reflecting that an increasing number of individuals are being diagnosed and initiating treatment as adults.[4] Indeed, this study is the largest description of ADHD treatment patterns among middle-aged and older adults to date, with individuals aged ≥50 years representing around 5% of the total included study population. With a growing number of adults being diagnosed with ADHD, treatment in this age-group will likely increase, meaning greater knowledge about treatment patterns, effectiveness, tolerance and the impact of ADHD medications on adult-onset somatic diseases linked to ADHD[40] are needed.

Strength and weaknesses

By using real-world data from prescription databases across Europe, Asia, Australia and North America, most of which have near complete national coverage of dispensed medications, our findings have high generalizability to individuals with ADHD treated in routine clinical practice in several countries. Nevertheless, there are also limitations. First, our data sources predominantly cover Europe and the US. Thus, patterns of discontinuation and persistence in Africa, South America, and large parts of Asia, remain an important area of investigation. The lack of systematically collected prescription records from large parts of the world presents a limitation for the field in general, and we further highlight the need for research and infrastructure investment in order to gain a full picture of ADHD treatment globally. Second, although we include the main types of medications licensed for treatment of ADHD, it is possible that some patients defined as having discontinued their medication switched to a medication outside our study, but which is used in some countries (such as dexmethylphenidate and clonidine). Third, we used a one-year wash-out period to define initiation. As such, some

individuals classified as 'new users' could indeed have been reinitiating medications. Fourth, in most countries, we did not have information on the indication for each prescription. Although the included medications are, with some exceptions (e.g., certain stimulants are licensed for narcolepsy, guanfacine for hypertension in the US), only licensed for treating ADHD, off-label use can occur. This may be of particular concern at older ages (>50 years), with one Danish study suggesting that medications for ADHD among older adults often reflect off-label use.[41] Finally, a key limitation of all studies of treatment discontinuation and persistence, is the difficulty of defining such outcomes.[18] In pharmaco-epidemiological studies, the issue is further compounded by the use of administrative databases and medical records which often lack detailed information on e.g., treatment length and the reason for discontinuation. As such, we were not able to classify when discontinuation might have been warranted, e.g. due to significant symptoms remission or medication ineffectiveness. Further, the data do not indicate whether the dispensed medication was actually consumed and therefore, do not necessarily reflect medication adherence. We used a conservative definition of treatment discontinuation (i.e., allowing a long gap between dispensations) to increase the probability that we captured a real treatment gap and to enable cross-country comparison. Nevertheless, we may still have misclassified discontinuation, for example in individuals with shorter, but potentially clinically meaningful treatment breaks and among those who take medication infrequently and therefore do not need to refill within 180 days.

Conclusion

This population-based, up-to-date cross-country study of ADHD medication treatment patterns, based on consistent definitions, clarifies the scope of treatment discontinuation and persistence. Our findings can inform the allocation of resources in health-care settings to reduce premature

treatment cessation in ADHD, and they highlight adolescence and early adulthood as a key period for intervention. We identify directions for future research, most pertinently the need to identify modifiers of early medication treatment discontinuation, and to generate knowledge about the psychosocial and health-related outcomes of long-term medication treatment in ADHD, including among women and older adults.

Data Sharing

Country-specific regulations and laws prohibits us from sharing or making individual-level data publicly available. Access to these data is not possible without the permission of the relevant approving human research ethics committees and / or the data custodians. Details and country-specific data sharing statements are provided in Supplementary Note 1.

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Declarations of interest

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Contributor Statement

Zheng Chang, Honghui Yao, Lin Li, Aske Astrup, Le Gao, Kenneth KC Man, Malcolm B. Gillies, Tian Xie, and Yanli Zhang-James directly accessed and verified the country/region-specific data, and performed data curation and formal analysis of the country/region-specific data underlying the meta-data analyses reported in the manuscript.

Honghui Yao and Lin Li performed all meta-analyses and visualization of results presented in the manuscript under the supervison of Zheng Chang and Isabell Brikell.

Isabell Brikell, Honghui Yao, Lin Li, Zheng Chang and Kari Klungsøyr wrote the original draft.

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All authors contributed to the conceptualization of the study and writing – review & editing. All authors confirm that they had full access to all the data in the study and accept responsibility to submit the article for publication.

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