BMJ Mental Health

PHARMACOLOGICAL TREATMENTS

Risk of hospitalisation for first-onset psychosis or mania within a year of ADHD medication initiation in adults with ADHD

Ragna Kristin Gudbrandsdottir,[1,2] Engilbert Sigurdsson ,[1,2] Þorsteinn Ivar Albertsson ,[1] Halldora Jonsdottir,[1,2] Oddur Ingimarsson [1,2]

[1]Faculty of Medicine, School of Health Sciences, University of Iceland, Reykjavík, Iceland
[2]Mental Health Services, Landspitali National University Hospital of Iceland, Reykjavík, Iceland

Correspondence to
Dr Oddur Ingimarsson, Faculty of Medicine, School of Health Sciences, University of Iceland, Reykjavík, Iceland; odduri@landspitali.is

Received 18 December 2024
Accepted 2 April 2025

To cite: Gudbrandsdottir RK, Sigurdsson E, Albertsson Þ, *et al*. *BMJ Ment Health* 2025;**28**:1–7.

ABSTRACT

Background The prevalence of attention-deficit hyperactivity disorder (ADHD) drug treatment for youth and adults has been rising exponentially in Iceland over the past 15 years. The efficacy of ADHD drugs is not as strongly supported for adults as for children and adolescents, and adult use has been reported to increase the risk of psychosis or mania.

Objective To assess the absolute risk of hospitalisation for first-onset psychosis or mania in adults diagnosed with ADHD within 1 year of being prescribed ADHD drugs and to examine the proportional attributable risk.

Methods This study included all adults prescribed ADHD drugs in Iceland between 1 January 2010 and 31 December 2022. Records from the Icelandic Prescription Drug Register were linked to the Hospital Discharge Register to identify individuals who were admitted due to psychosis or mania. This risk was compared with the risk of all other first-onset hospitalisations for psychosis, mania or mixed episodes between 1 January 2018 and 31 December 2020.

Findings 16 125 individuals aged 18 or older initiated ADHD drug therapy during the study period. Of those, 61 were hospitalised due to first-onset psychosis or mania within a year. This corresponds to an absolute risk of 0.38% for such an admission. The general population risk for all other first-onset hospitalisations for psychosis or mania from 2018 through 2020 for Icelanders aged 18–67 was 0.048%. The estimated relative risk was 7.99 (95% CI 6.06, 10.54), the proportional attributable risk 87.5% and the number needed to harm 302 (95% CI 271, 340). Within 1 year of hospital discharge, 69% (42/61) had been represcribed their ADHD medication, and 26.2% (11/42) of these had to be readmitted for psychosis or mania

Conclusions The risk of hospitalisation for psychosis or mania with prescription ADHD drugs is small but real among adults, and represcription is strongly associated with readmission.

Clinical implications Clinicians and adults diagnosed with ADHD should be aware of the association between ADHD drugs and the risk of developing psychosis or mania requiring hospitalisation in adults with ADHD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is a growing concern that commencing attention-deficit hyperactivity disorder (ADHD) medications may increase the risk of first-onset psychosis or mania in adults with ADHD, including episodes severe enough to require hospitalisation. Of those admitted who are represcribed ADHD drugs following discharge, almost half develop psychotic or manic episodes again within a year.

WHAT THIS STUDY ADDS

⇒ For adults, for up to a year following the first treatment with methylphenidate, amphetamines or atomoxetine, there is a small but clinically relevant risk of developing a first-onset psychotic episode or mania severe enough to require admission. In eight to nine cases out of 10, the admission might have been avoided were it not for the use of ADHD medicines. In Iceland, around two-thirds of those admitted are represcribed ADHD drugs within a year, and of those, one in four is readmitted within a year.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Both prescribing clinicians and adults commencing ADHD drug treatment need to be aware of the small but real risk of first-onset psychosis or mania severe enough to require hospitalisation within a year. If ADHD drugs are represcribed in the wake of such episodes, regular follow-up must be provided for at least 1 year.

BACKGROUND

Attention-deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder among children, characterised by inattention, hyperactivity and impulsivity.[1] Although some core symptoms, particularly motor hyperactivity, become less prominent with age, over half of those diagnosed with childhood ADHD continue to experience persistent symptoms into adulthood.[2]

The prescription of ADHD drugs has increased sharply in Iceland in recent years, particularly for adults.[3 4] In 2010, 1.5% of women (786 of 53 105) and 1.6% of men (894 of 54 872) aged 18–44 were prescribed ADHD medication. In 2023, the percentages had risen to 11% for women (5972 of 54 503) and 9.4% for men (5373

of 57 074) in that age group. In 2023, 14.7% of youth aged 7–17 were dispensed a prescription for ADHD medication, as well as 10.2% of adults aged 18–44, the prevalence being though notably higher among certain age groups of youth and young adults.[4] This use of ADHD medications in Iceland is higher than the estimated prevalence of the disorder, which is in the range of 2.2%–7.2% among children and 2.5%–5.2% among adults.[5 6] In Iceland, only psychiatrists or paediatricians with experience in diagnosing neurodevelopmental disorders can initiate treatment with ADHD drugs following an ADHD diagnosis. The diagnostic workup is most commonly done by a psychologist or a psychiatrist or at least confirmed by a psychiatrist.

The precise mechanism by which methylphenidate exerts its therapeutic effect remains unknown but is generally believed to be associated with inhibition of dopamine reuptake, thus correcting the presumed dopamine deficit in the synapse and thereby improving reinforcement responses.[7] In addition to dopamine reuptake inhibition, amphetamine stimulates dopamine release, resulting in up to four times more dopamine release.[8] Since stimulants like methylphenidate and amphetamine raise the level of dopamine in key monoaminergic synapses, their use can result in psychosis or mania in predisposed individuals.[8 9] Atomoxetine is a non-stimulant and has been a second- or third-line drug for ADHD in adults. Among adults in Iceland, its use has especially been aimed at those who have a recent history of active addiction. It is a potent inhibitor of the presynaptic norepinephrine transporter but, in contrast to the stimulants, has no direct pharmacological effects on dopaminergic receptors.[10] Treatment with atomoxetine can also result in psychotic or manic symptoms.[11 12] A study from the USA that assessed the risk of psychosis in youths aged 13–25 who received treatment with stimulants for ADHD found that the risk of psychosis was 0.10% for methylphenidate and 0.21% for amphetamines.[8] Furthermore, it has recently been reported that the risk of psychosis and mania is increased on amphetamines with a dose–response relationship, the OR being over five for psychosis or mania for those on high doses compared with controls.[13] A Canadian case-crossover study found that stimulant initiation in adults aged under 25 with ADHD was associated with an increased risk of hospitalisation due to psychosis or mania within 60 days of prescription.[14] One-third of those individuals were represcribed stimulants after discharge, and of these, 45% were readmitted at a median of 18 days in due course.[14] A large nationwide population-based study in Taiwan found that methylphenidate use increased the risk of developing any psychotic disorder among individuals with ADHD.[15] Not all studies have, though, found such an effect on the risk of psychosis among young people with ADHD.[16] It must also be noted in this context that longitudinal studies have indicated that a childhood diagnosis of ADHD is a risk factor for a diagnosis of psychosis in adult life.[17]

Objective

To investigate the risk of hospitalisation for first-onset psychosis or mania within a year of ADHD medication initiation among all adults in Iceland. This is important in view of the rapid expansion of ADHD drug prescriptions for adults in Iceland and data indicating that the use of ADHD medications for adults is not as strongly supported by research as for youth with ADHD,[15] while psychosis and mania appear to develop more commonly among adults than children and adolescents.[18]

METHODS

This nationwide population-based retrospective cohort study included all adults prescribed ADHD drugs in Iceland between 1 January 2010 and 31 December 2022.

Data sources

Data were retrieved from two administrative databases with nationwide coverage: the Icelandic Prescription Medicines Register (IPMR) and the Icelandic Hospital Discharge Register (IHDR). We received data from the IPMR on all dispensed ADHD drugs from 1 January 2010 to 31 December 2022. The IPMR is a centralised database containing national-level data on all dispensed prescription drugs to the outpatient population since 1 January 2003. The IHDR holds information on all hospital admissions in Iceland since 1999. Admission date, the number of inpatient days and diagnoses coded using the International Classification of Diseases 10th edition (ICD-10) are among the information stored in the database. The data warehouse of Landspitali-The National University Hospital was used to examine the general population risk of all first-onset admissions for psychosis, mania or mixed episodes from 1 January 2018 to 31 December 2020, including all such admissions directly associated with the use of psychoactive substances (F1X.5).

Definitions of ADHD drug use, psychosis and mania

We defined ADHD drugs according to the WHO Anatomic Therapeutic Chemical classification group of centrally acting sympathomimetics (N06BA): amphetamine (N06BA01), dexamphetamine (N06BA02) and lisdexamphetamine (N06BA12) constituted the class of amphetamines, and methylphenidate (N06BA04) was classified in a drug class of its own, as was atomoxetine (N06BA09).

Patients who did not fill any prescription for any of the three ADHD drug classes since the establishment of the IPMR database on 1 January 2003 through 2009 were considered naive to that drug class. Initiation of therapy or new use of a certain ADHD drug class was defined, among naive patients, as filling a prescription for one of the specified ADHD drug classes listed above for the first time during the study period. Drug use was defined as one or more filled prescriptions of an ADHD drug in a year, and in Iceland, these are prescribed to last for 30 days. Therefore, new use not only applies to those who started treatment with ADHD drugs for the first time but also to those who switched ADHD drug classes during the study period. The reason for this definition was mainly that in Iceland, methylphenidate or atomoxetine must be prescribed and tried first before switching to lisdexamphetamine or dexamphetamine. Therefore, the inclusion of those who switched ADHD classes was the only way to assess the risk for those prescribed lisdexamphetamine or dexamphetamine. Different formulations of medicines within the same ADHD drug class were merged in the analysis.

Diagnoses of mania or psychosis in the IHDR were used to identify individuals admitted to a psychiatric ward within a year of initiating treatment with a specific ADHD drug class. First-onset psychosis or mania was defined as the occurrence of psychosis or mania in admitted individuals with no recorded history of such symptoms, no diagnosis and no previous hospitalisations for psychosis or mania. This definition was based on electronic health records, which included the hospital and the primary care medical notes from all general practitioners in Iceland.

Study population

Using unique personal identification numbers, we linked records from the IPMR to the IHDR to identify individuals who had been admitted to a psychiatric ward due to psychosis or mania within a year of new use of a specific ADHD drug. We limited our analysis to 365 days after treatment initiation, anticipating that the susceptibility to being hospitalised for psychosis or mania on medicines from one of the three drug classes should generally have become apparent within that time frame. Data from the nationwide hospital and primary care electronic health records were collected on prior psychiatric diagnoses. All medical notes from each such admission were reviewed to internally validate the outcome and evaluate the temporal association between the use of prescribed ADHD drugs and the development of first-onset psychosis or mania. We looked specifically for comments on the use of ADHD drugs as well as ADHD drug abuse in the medical notes. ADHD drug abuse was defined as inappropriate use of the ADHD medication in the week leading up to the admission, for example, taking more than the prescribed dosage or using non-oral administration routes such as nasal or intravenous use. Substance abuse was defined as an ICD-10 diagnostic code of harmful substance use or dependence in the medical records during the admission or during or following any previous contacts or admissions to a psychiatric unit in Iceland. For those hospitalised, data from the IPMR were used to evaluate represcriptions of ADHD drugs after discharge. Hospital records of those who were represcribed ADHD drugs were analysed to estimate whether a subsequent hospitalisation for psychosis or mania took place within a year.

Outcomes

The primary outcome was hospitalisation for first-onset psychosis or mania <1 year of initiation of therapy with an ADHD drug from any of the three classes of ADHD medicines as defined. The absolute risk associated with the three ADHD drug classes in use in Iceland during the study period was calculated for each drug class.

Statistical analysis

The incidence of new adult ADHD drug use was calculated annually from 2010 to 2022 and defined as the number of individuals with new ADHD drug use each year during the study period per 1000 Icelandic inhabitants aged 18 or older at the end of each year, stratified by age. Additionally, the incidence was stratified by the type of ADHD drug class prescribed, estimated using only the first-ever prescription from any of the three ADHD drug classes during the study period, that is, methylphenidate, atomoxetine or amphetamines.

The number of individuals hospitalised for psychosis or mania during the study period was stratified by year and is presented as count and proportion. Electronic health records were reviewed to ensure that the admission was indeed one of first-onset psychosis or mania.

A Kaplan-Meier survival analysis was performed to assess the time from initiation of treatment with a medicine from a particular ADHD drug class to hospitalisation for psychosis or mania, with a follow-up period of 365 days.

The absolute risk in the study period was estimated by dividing the number of individuals hospitalised for first-onset psychosis or mania within a year of initiating treatment with a new ADHD drug by the number of individuals who had initiated therapy with those ADHD drugs. Furthermore, the absolute risk was stratified by years and type of ADHD drug class. As per the definition of the study population, individuals hospitalised following new ADHD drug class treatment were excluded from subsequent re-exposure to new use of a different ADHD medication. In contrast, those not hospitalised within a year following new ADHD drug class use could continue to be at risk following re-exposure if they switched ADHD drugs during the study period, for example, from methylphenidate to lisdexamphetamine or atomoxetine. Consequently, when stratifying risk by years, the denominator signified the total number of exposures to an ADHD drug of a particular class during any given year. Similarly, when stratifying risk by ADHD drugs, the denominator indicated the total number of exposures within each drug class: methylphenidate, amphetamines (mainly lisdexamphetamine) or atomoxetine. We calculated an estimate of the relative risk (RR) for a first-onset admission for psychosis or mania from 2010 to 2022 among those prescribed ADHD medication within a year by comparing that risk with the risk for all other first-onset admissions for psychosis, mania or mixed episodes for adults aged 18–67 in 2018, 2019 and 2020. Based on these figures, we also calculated an estimate of the proportional attributable risk and the number needed to harm (NNH).

Statistical analyses were done using R V.4.1.2.

FINDINGS

The study population's flow chart is illustrated in figure 1. A total of 16 125 adults initiated new use of an ADHD drug during the 13-year-long study period; 8284 (51.4%) were women, and the median age was 33 (IQR 25–43) years. The majority (11 289/16 125=70%) of new users received ADHD medication from one drug class during the study period, a quarter (4033/16,125=25.1%) from two drug classes, and under 5% (785/16 125=4.9%) received a prescription for three or more ADHD drug classes. Following new use, 112 were admitted for psychosis or mania within a year. Of these, 61 (54.5%) were hospitalised for first-onset psychosis or mania, and, importantly, none of these were receiving more than one ADHD medication upon admission.

The mean incidence of new ADHD drug use was 5.8 per 1000 inhabitants during the study period, rising from 2.5 in 2010 to 11.3 in 2022 per 1000 inhabitants. A nearly sixfold increase in the absolute number of new adult users per year was observed over the study period, from 591 in 2010 to 3309 in 2022. Overall, the incidence of such treatment was three times higher in the 18–39 years age group (9.5 per 1000) compared with those aged 40 or older (3.1 per 1000). The drug most frequently dispensed for the first time during the first half of the study period was methylphenidate. However, there has been a massive surge in the use of lisdexamphetamine since 2017, resulting in it being the most commonly prescribed new ADHD medication for adults in Iceland since 2021. The number of new adult prescriptions per year for lisdexamphetamine (mainly), dexamphetamine or amphetamine for adults, for example, increased from 54 in 2017 to 2233 in 2022. During the same period, the number of new adult prescriptions per year for methylphenidate only rose from 1204 to 1321.

Of the 61 patients hospitalised during the study period, 48 were admitted for first-onset psychosis and 13 for first-onset mania (p<0.001). The majority were males, 40 (65.6%), and 7 out of 10 were in the age category 18–39 years at the time of hospitalisation (table 1). The majority, 43 (70.5%), of hospitalisations were observed in patients who had been exposed to only one ADHD drug class during the study period, while 14 (23.9%) had initiated medicines from two ADHD drug classes,

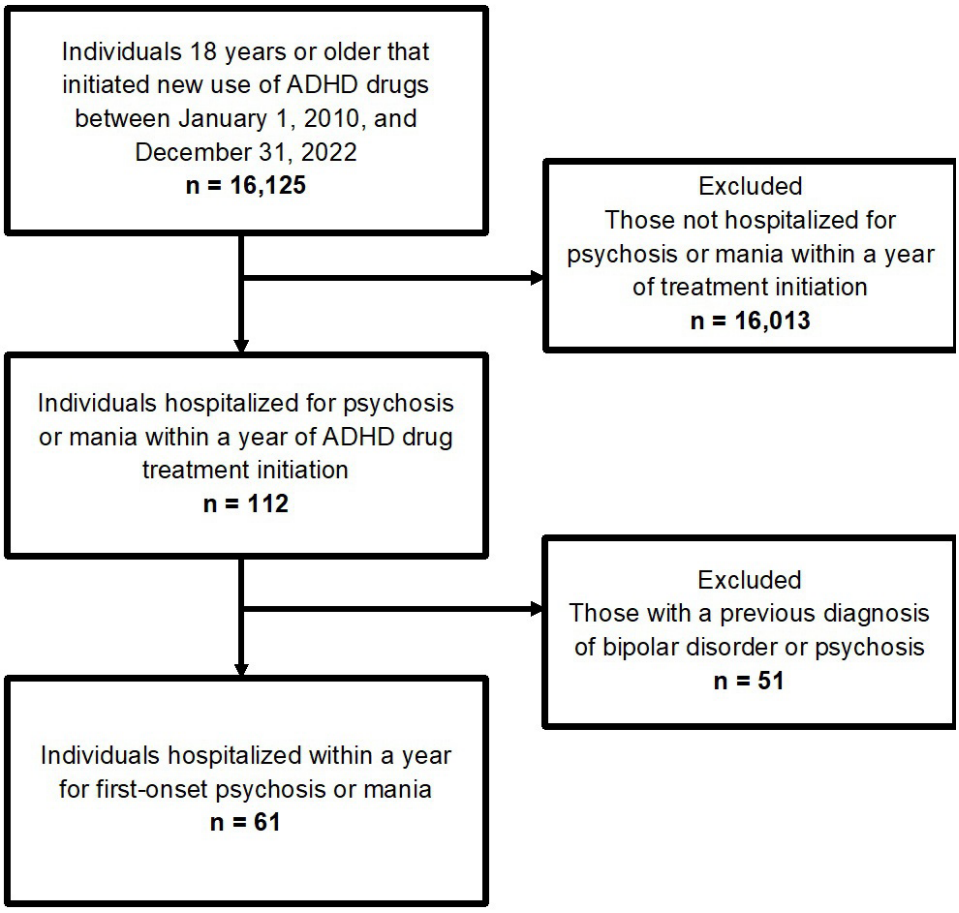

Figure 1 Flow chart of the study population. ADHD, attention deficit hyperactivity disorder.

Table 1 Patient characteristics and clinical factors associated with first-onset psychosis or mania

Variable	Patients (n=61)
Males (n (%))	40 (65.6)
Age, median mean age (IQR)	33 (25–43)
Age category, years, n (%)	
18–29	25 (41)
30–39	18 (29.5)
40–49	14 (22.9)
50–67	4 (6.6)
ADHD drug class, n (%)	
Methylphenidate	25 (41)
Amphetamines	21 (34.4)
Atomoxetine	15 (24.6)
Days on ADHD drug class before admission* (median, mean, min, max, IQR)	172, 174.4, 1, 363, 90–250
Number of ADHD drugs initiated, n (%)	
One	43 (70.5)
Two	14 (23.9)
Three	4 (6.6)
ADHD drug abuse reported, n (%)	7 (11.5)
Lifetime history of substance abuse, n (%)	31 (50.8)
Days in admission, median (IQR)	8 (4–17)
ADHD drug dispensed in the year following discharge, n (%)	42 (68.9)

*Value of 1 refers to a patient who had been on methylphenidate admitted 1 day after changing over to lisdexamphetamine.
ADHD, attention-deficit hyperactivity disorder.

for example, first trying methylphenidate and later lisdexamphetamine, and four (6.6%) from three ADHD drug classes. The median length of admission was 8 days (IQR 4–17).

The risk of hospitalisation remained relatively similar for those 61 individuals who were admitted throughout the year following initiation of treatment (figure 2). The median time from ADHD drug exposure to hospitalisation for first-onset psychosis or mania was 172 days, and the mean time was 174.4 days. Thus, almost half of the hospitalisations occurred more than half a year after the onset of treatment.

Methylphenidate was the most common ADHD drug used by those admitted (25/61=41%), in line with being the most prescribed stimulant overall during the study period. It was followed by amphetamines (21/61=34.4%) and finally atomoxetine (15/61=24.6%). Prior to 2017, no cases of psychosis or mania were identified that were directly linked to prescribed lisdexamphetamine, dexamphetamine or other amphetamines for ADHD. The pattern changed as of 2017–2018, after dexamphetamine and subsequently lisdexamphetamine were registered in Iceland. The majority of admitted cases (65.6%) during the remainder of the study period followed the use of prescribed lisdexamphetamine (figure 3).

Upon admission, only 11% of patients reported or admitted to some form of abuse of the ADHD drug they had been prescribed. Around one in two, or 50.8%, of those hospitalised had ever received a diagnosis of a substance abuse disorder according to their electronic medical records at the time of the admission. Not unexpectedly, this was most common in the atomoxetine group, where it applied to two out of three (10/15=66.7%), while recorded for just under half in the

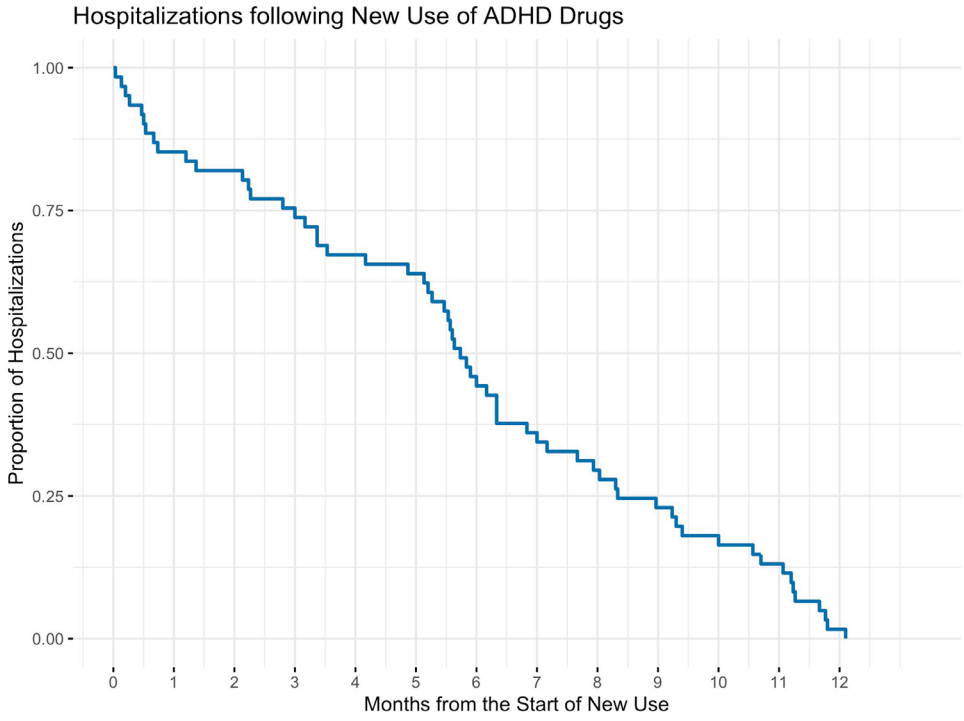

Figure 2 A Kaplan-Meier survival curve illustrating the time to hospitalisation for new-onset psychosis or mania within 1 year following the initiation of new ADHD medication use. ADHD, attention deficit hyperactivity disorder.

amphetamines group (10/21=47.6%) and in the methylphenidate group (11/25=44.0%). Within 1 year of discharge, 42 of the 61 patients (68.9%) had been represcribed an ADHD drug. One in four (11/42=26.2%) of those who were represcribed an ADHD drug after discharge were readmitted for psychosis or mania within a year.

The estimated absolute risk of admission for first-onset psychosis or mania within a year of commencing ADHD medication was 0.38%. The calculated estimate of the risk in the general population of all other such first-onset admissions for adults aged 18–67 years in 2018–2020 was 0.048% per year. Around 25% of that risk (0.012%) stemmed from admissions linked to the use of psychoactive substances (F1X.5) and 28% (0.013%) from manic or mixed episodes. The estimated RR within a year of ADHD drug initiation for first-onset admissions due to first-onset psychosis or mania was thus 7.99 (95% CI

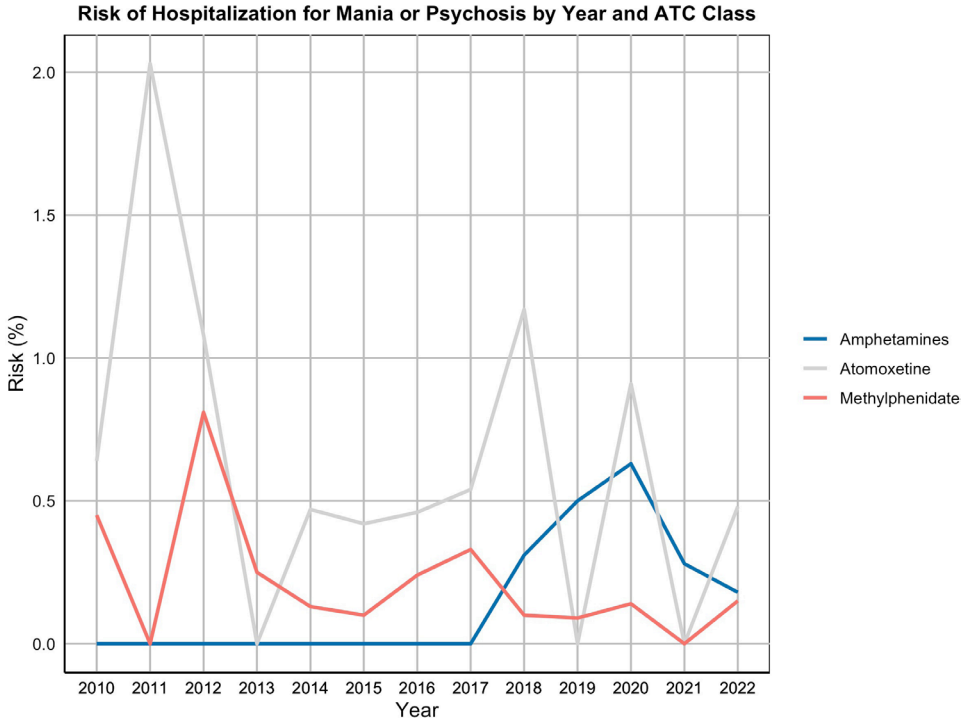

Figure 3 The risk of hospitalisation for first-onset psychosis and mania. ATC, anatomic therapeutic chemical

6.06, 10.54), the proportional attributable risk 87.5% and the NNH 302 (95% CI 271, 340). The absolute risk of first-onset psychosis or mania was highest among individuals who started therapy with atomoxetine (0.60%), followed by amphetamines (0.33%) and finally methylphenidate (0.19%).

DISCUSSION

In this nationwide cohort study involving 16 125 adults prescribed methylphenidate, amphetamine derivatives or atomoxetine to treat ADHD, 61 individuals (0.38%) were hospitalised due to first-onset psychosis or mania within a year of commencing treatment. Approximately 1 in 264 adults who had been prescribed stimulants or atomoxetine were hospitalised within a year for first-onset psychosis or mania, but 1 in 330 for first-onset psychosis. Moran *et al* reported that approximately 1 in 660 developed first-onset psychosis in a younger population of adolescents and young adults prescribed methylphenidate or amphetamine for ADHD in the USA.[8] They defined first-onset psychosis as a new diagnostic code for psychosis and a subsequent prescription for antipsychotic medication, whereas we focused on a more stringently defined outcome, namely those hospitalised. It is reasonable to assume that more patients developed milder psychotic or manic symptoms but did not require or seek admission to the hospital and thus were not admitted nor counted. The age difference may also matter in this context because the study of Moran *et al* included only adolescents and young adults up to 25 years of age, whereas our study included adults of any age.[8] We observed that 59% were older than 30 years, the median age being 33 years (IQR 25–43), when admitted. In this context, it is worth noting that the mean age of admission to the early intervention first psychosis programme in Reykjavik was 23.4 years from 2010 to 2020.[19] It is also important to note that the risk of an admission for first-onset psychosis or mania within a year of starting on ADHD drugs as an adult in Iceland appears in 8–9 cases out of 10 to be most probably attributed to the ADHD drug treatment, as the estimated proportional attributable risk is 87.5%.

Few studies have assessed the risk of hospitalisation for first-onset psychosis or mania following initiation of ADHD drug therapy. Our study approach compares best with the study of Cressman *et al* in Canada, who reported a risk of 0.13% for hospitalisation for psychosis or mania among young people never on antipsychotics aged 25 and younger in the much shorter period of 60 days following ADHD stimulant initiation.[14] However, in our study, around 75% of those hospitalised had been on their ADHD medication for more than 60 days when admitted.

The risk of first-onset psychosis or mania was highest in our study among those prescribed atomoxetine, which has historically, in line with clinical guidelines in Iceland, been the first ADHD drug of choice for individuals with a recently active substance use disorder. However, it is worth noting that the number of new users of atomoxetine during the research period was very small, around 1%, compared with new users of stimulants and has not been growing in stark contrast to the exponentially growing prescriptions of lisdexamphetamine in Iceland since 2017.[3] Therefore, each case of psychosis or mania had a comparatively much greater effect on the absolute risk in the atomoxetine group, as well as being more likely to have been affected to some extent by some form of non-disclosed substance use. The risk of first-onset psychosis or mania that we observed was almost twofold among those prescribed lisdexamphetamine or dexamphetamine compared with methylphenidate, which is in line with previous research.[8 20]

It is concerning that most patients (68.9%) in our study resumed ADHD drug treatment within a year of hospital discharge. Few other studies have examined this matter. Cressman *et al* reported that 34% of the young adults admitted due to psychosis or mania in their study received a stimulant prescription within 100 days of discharge.[14] Of those, 45% were readmitted for psychosis or mania at a median of 18 days after the subsequent stimulant represcription.[14] In general, the use of stimulants to treat ADHD among individuals with a previous diagnosis of psychosis or bipolar disorder must be considered controversial, particularly when done in the wake of a recent admission for psychosis or mania owing to the potential risk of psychotic or manic symptoms developing again.[21 22] However, some studies have reported that the use of psychostimulants or atomoxetine to treat ADHD in individuals with psychotic disorders did not increase the risk of hospitalisation for psychosis if used concurrently with antipsychotic medication[23] or that such use might even reduce this risk.[23] In individuals diagnosed with bipolar disorder, the use of methylphenidate monotherapy was associated with a sixfold risk of manic episodes within 3 months of medication initiation in a recent Swedish study on 2307 adults with bipolar disorder.[24] Even so, that study found that if used concomitantly with mood-stabilising medication, the risk of mania became even lower than before once methylphenidate had been prescribed.[24] This indicates that the represcription of ADHD drugs after psychosis or mania should be done with caution and only be considered if patients are on antipsychotics or mood stabilisers and are able and willing to attend regular follow-ups to reduce the risk of re-emergence of psychotic or manic symptoms. The high proportion of patients who were represcribed ADHD drugs in our study and in the Canadian study of Cressman *et al*[14] suggests a lack of knowledge or professional awareness among physicians on the potential causative role of recently prescribed ADHD drugs in the development of psychosis or mania among adults. In our experience, most individuals request that their prescribing clinicians recommence their ADHD medication as soon as possible following inpatient episodes of psychosis or mania, not to mention milder episodes. In Iceland, at present, this only requires contacting their primary care physician via an app and that physician may be even less aware of the risk of psychotic or manic symptoms resurfacing than the psychiatrist who initiated the ADHD treatment.

To our knowledge, this is the first nationwide observational study on psychosis or mania requiring hospitalisation following stimulant or atomoxetine initiation among adults of any age. It includes all adult patients prescribed ADHD medications in Iceland and therefore has high generalisability for clinicians prescribing these medications. It provides valuable new insights on absolute and RR and NNH that should be considered by physicians prescribing ADHD medications to adults. Most previous studies on the potential adverse effects of treatment with ADHD drugs have focused only on children, adolescents or young adults. This is important because the prescribing of these drugs continues to increase fast among adults, for instance, in Iceland and the USA.[4 13] Another important strength is that all medical notes of those 61 admitted were examined by the authors to check whether those hospitalised acknowledged having used higher doses of their ADHD medication than prescribed, which only 11% reported, or possibly had used non-oral routes, which no one admitted to having done.

There are several limitations to our study that must be acknowledged. We only estimated the prevalence and risk of first-onset psychosis and mania based on those requiring admission to the hospital and are therefore bound to underestimate

the true risk of all episodes of psychosis or (hypo)mania or mixed mood episodes developing following the initiation of new ADHD drug treatment. Confounders of real-life clinical settings, such as non-disclosed ADHD drug abuse or misuse or some degree of substance abuse, may have influenced our findings. Nevertheless, importantly, those who had a previous history of psychotic or manic episodes were excluded from our analyses, which increases the validity of the presumed association between the onset of treatment with ADHD medications and the incident risk of the first episode of psychosis or mania within a year. While we cannot exclude the possibility that a subgroup of those admitted for first-onset psychosis or mania might have developed such symptoms eventually without initiating ADHD drug treatment, the fact that the estimated RR was 7.99, and the proportional attributable risk 87.5% indicates that this subgroup is probably small and probably does not account for more than 1–2 of every 10 cases.

Clinical implications

In conclusion, the risk of hospitalisation for first-onset psychosis or mania was approximately 1 in 264 among adults of any age prescribed methylphenidate, amphetamines or atomoxetine to treat ADHD during the study period. Adjusting for the general population risk of hospitalisation for first-onset psychosis or mania, the NNH was 302. The risk of such first-onset admissions taking place within a year of ADHD treatment commencing was eight times higher than that of all other first-onset admissions for psychosis or mania combined in 2018–2020. The majority of patients hospitalised were represcribed ADHD drugs within a year following discharge, and one in four was readmitted within a year. This raises concerns about whether the prescribing clinicians as well as the admitted individuals are sufficiently aware of the potential causal role of ADHD drugs in the development of first-onset psychosis or mania.

Contributors The study was planned by RKG, ES and OI. RKG collected the data and received help with statistics from ÞIA, ES and OI. All authors reviewed the findings, the interpretation of the findings and the discussion. RKG is a PhD student, supervised by OI and ES. RKG wrote the first draft of the manuscript, but all the authors reviewed and amended it in due course. OI is the guarantor of the work.

Funding This study was supported by a grant from Minningargjafasjóður Landspítala Íslands.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Icelandic national bioethics committee, study reference number of approval VSN-21-142. The study was a nationwide population-based retrospective cohort study that included all adults prescribed ADHD drugs in Iceland between 1 January 2010 and 31 December 2022. It is not feasible to do such nationwide population studies with informed consent from every patient involved.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data used in this study may be obtained from the following sources: the authors, Landspitali-The National University Hospital and The Directorate of Health in Iceland.

ORCID iDs
Engilbert Sigurdsson http://orcid.org/0000-0001-9404-7982
Þorsteinn Ivar Albertsson http://orcid.org/0000-0002-3347-7636
Oddur Ingimarsson http://orcid.org/0000-0003-0534-362X

REFERENCES

1 Thapar A, Cooper M. Attention deficit hyperactivity disorder. *Lancet* 2016;387:1240–50.
2 Sonuga-Barke EJS, Becker SP, Bölte S, *et al*. Annual Research Review: Perspectives on progress in ADHD science - from characterization to cause. *J Child Psychol Psychiatry* 2023;64:506–32.
3 Eiríksdóttir VH. Notkun ADHD lyfja hjá fullorðnum og börnum 2013-2022. *Talnabrunnur-Fréttabréf Landlæknis Um Heilbrigðisupplýsingar* 2023;17:1–5.
4 Ingimarsson O, Gudbrandsdottir RK, Lauth BAM, *et al*. High prevalence of treatment with ADHD medicines indicates overdiagnosis of ADHD in Iceland. *Laeknabladid* 2024;110:402–10.
5 Sayal K, Prasad V, Daley D, *et al*. ADHD in children and young people: prevalence, care pathways, and service provision. *Lancet Psychiatry* 2018;5:175–86.
6 Simon V, Czobor P, Bálint S, *et al*. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *Br J Psychiatry* 2009;194:204–11.
7 Tripp G, Wickens JR. Neurobiology of ADHD. *Neuropharmacology* 2009;57:579–89.
8 Moran LV, Ongur D, Hsu J, *et al*. Psychosis with Methylphenidate or Amphetamine in Patients with ADHD. *N Engl J Med* 2019;380:1128–38.
9 Bloomfield MA, Howes OD. Dopaminergic mechanisms underlying psychosis. In: *Psychotic Disorders: Comprehensive Conceptualization and Treatments*. 2020: 277.
10 Michelson D, Adler L, Spencer T, *et al*. Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. *Biol Psychiatry* 2003;53:112–20.
11 Mosholder AD, Gelperin K, Hammad TA, *et al*. Hallucinations and other psychotic symptoms associated with the use of attention-deficit/hyperactivity disorder drugs in children. *Pediatrics* 2009;123:611–6.
12 Reed VA, Buitelaar JK, Anand E, *et al*. The Safety of Atomoxetine for the Treatment of Children and Adolescents with Attention-Deficit/Hyperactivity Disorder: A Comprehensive Review of Over a Decade of Research. *CNS Drugs* 2016;30:603–28.
13 Moran LV, Skinner JP, Shinn AK, *et al*. Risk of Incident Psychosis and Mania With Prescription Amphetamines. *Am J Psychiatry* 2024;181:901–9.
14 Cressman AM, Macdonald EM, Huang A, *et al*. Prescription Stimulant Use and Hospitalization for Psychosis or Mania: A Population-Based Study. *J Clin Psychopharmacol* 2015;35:667–71.
15 Shyu Y-C, Yuan S-S, Lee S-Y, *et al*. Attention-deficit/hyperactivity disorder, methylphenidate use and the risk of developing schizophrenia spectrum disorders: A nationwide population-based study in Taiwan. *Schizophr Res* 2015;168:161–7.
16 Hollis C, Chen Q, Chang Z, *et al*. Methylphenidate and the risk of psychosis in adolescents and young adults: a population-based cohort study. *Lancet Psychiatry* 2019;6:651–8.
17 Dalsgaard S, Mortensen PB, Frydenberg M, *et al*. Association between Attention-Deficit Hyperactivity Disorder in childhood and schizophrenia later in adulthood. *Eur Psychiatry* 2014;29:259–63.
18 Cunill R, Castells X, Tobias A, *et al*. Efficacy, safety and variability in pharmacotherapy for adults with attention deficit hyperactivity disorder: a meta-analysis and meta-regression in over 9000 patients. *Psychopharmacology (Berl)* 2016;233:187–97.
19 Gudbrandsdottir RK, Ingimarsson O. Functional recovery after first episode psychosis rehabilitation in an early intervention psychosis center in Iceland. *Laeknabladid* 2022;108:288–97.
20 Hamard J, Rousseau V, Durrieu G, *et al*. Psychosis with use of amphetamine drugs, methylphenidate and atomoxetine in adolescent and adults. *BMJ Ment Health* 2024;27:e300876.
21 O'Donoghue B, Lyne J, Madigan K, *et al*. Environmental factors and the age at onset in first episode psychosis. *Schizophr Res* 2015;168:106–12.
22 Curran C, Byrappa N, McBride A. Stimulant psychosis: systematic review. *Br J Psychiatry* 2004;185:196–204.
23 Corbeil O, Brodeur S, Courteau J, *et al*. Treatment with psychostimulants and atomoxetine in people with psychotic disorders: reassessing the risk of clinical deterioration in a real-world setting. *Br J Psychiatry* 2024;224:98–105.
24 Viktorin A, Rydén E, Thase ME, *et al*. The Risk of Treatment-Emergent Mania With Methylphenidate in Bipolar Disorder. *Am J Psychiatry* 2017;174:341–8.