**DEVELOPMENT OF PSYCHOSIS AND BIPOLAR DISORDER IN INDIVIDUALS WITH ADHD TREATED WITH STIMULANTS: SYSTEMATIC REVIEW AND META-ANALYSIS**

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**KEYPOINTS**

**Question:** What is the risk of developing psychosis or bipolar disorder (BD) in individuals with ADHD treated with stimulant medications?

**Findings:** A meta-analysis of 15 studies (encompassing 390,759 participants) found that 2.8%, 2.4%, and 3.7% of individuals with ADHD treated with stimulants developed psychotic symptoms, a psychotic disorder, and BD, respectively. Amphetamines were associated with a 57% higher risk of psychosis compared to methylphenidate (OR=1.57, 95%CI 1.140-2.161).

**Meaning:** While stimulants are effective for ADHD, they carry a non-negligible risk of psychosis and BD, warranting psychoeducation, monitoring, and appropriate management strategies.

**ABSTRACT**

**Importance:** Individuals withattention-deficit/hyperactivity disorder (ADHD) may present with psychosis or bipolar disorder (BD) following treatment with stimulants.

**Objective:** We meta-analytically estimated the risk of developing psychosis or BD after exposure to stimulants in individuals with ADHD and assessed moderating factors affecting this risk.

**Data Sources:** We systematically searched several databases from inception until 1/10/2024.

**Study Selection**: We included studies with DSM/ICD-defined ADHD populations exposed to stimulants, where psychosis or BD outcomes were evaluated.

**Data Extraction and Synthesis:** We followed PRISMA and MOOSE guidelines and used the Newcastle–Ottawa Scale for study appraisal. We conducted random-effects meta-analysis, between-study heterogeneity analysis, and sensitivity analyses.

**Main Outcomes and Measures:** For the proportion of individuals developing psychotic symptoms, psychotic disorders and BD, effect sizes were % with 95%CIs. For the comparison between amphetamines and methylphenidate in the development of psychotic symptoms, effect size was OR (95% CI).

**Results:** Fifteen studies (n=390,759, mean age=12.6 years, 26.3% females) were eligible. Among individuals with ADHD prescribed stimulants, 2.8% (95%CI 0.7-9.9%), 2.4% (95%CI=1.6-3.6%), and 3.7% (95%CI=0.8-15.3%) developed psychotic symptoms, a psychotic disorder, and BD, respectively. Psychosis risk was significantly higher for amphetamines than with methylphenidate (OR=1.57, 95%CI=1.140-2.161). Sub-analyses revealed higher prevalence of psychotic symptoms in studies from America and in those with longer follow-up periods. Increased psychosis risk was associated with a higher proportion of female participants and smaller sample sizes.

**Conclusions and relevance:** This meta-analysis highlights a non-negligible occurrence of psychotic symptoms, psychotic disorders or BD in ADHD patients treated with stimulants, with amphetamines associated with higher occurrence than methylphenidate. Notably, the studies included in this meta-analysis cannot establish a causal role for stimulants in leading to psychosis or BD, as ADHD per se can be associated with these outcomes. Firm conclusions are also unwarranted at present given the high heterogeneity from our meta-analysis, highlighting the need for further studies with standardized designs and comparing individuals exposed vs non-exposed to stimulants. Nonetheless, clinicians may consider informing patients about the increased occurrence of psychosis or BD when assessing the benefits and potential risks of stimulants. Additionally, clinicians should monitor patients with ADHD during treatment with stimulants.

**INTRODUCTION**

Attention-Deficit/Hyperactivity Disorder (ADHD)1 is a neurodevelopmental condition characterized by developmentally inappropriate, persistent, and impairing inattention and/or hyperactivity/impulsivity. Medications including stimulants (e.g., amphetamines, methylphenidate) and non-stimulants (e.g., atomoxetine, guanfacine) are recommended for the management of individuals with ADHD, with stimulants as first-line pharmacological treatment in many clinical guidelines2. As all treatments, stimulants, alongside possible benefits, are associated with potential side effects, even though most of them can be managed3.

Among other adverse events, psychotic symptoms and manic symptoms can occur during treatment with stimulants4. Psychotic symptoms are often short-lived and tend to resolve after discontinuation of the stimulant5. However, symptoms may persist and lead to the development of a new-onset psychotic disorder, for which antipsychotic medications may be required4. Some factors including the duration of exposure, and the type of ADHD medication prescribed may affect the risk of developing psychosis. For instance, some individual studies suggest that the percentage of patients who have an episode of psychosis seem to be higher in those exposed to amphetamines compared to those exposed to methylphenidate6,7.

While manic symptoms have also been reported by clinicians in association with stimulant treatment, a systematic review and meta-analysis evaluating the emergence of manic symptoms following stimulant treatment failed to find an increase in manic symptoms in those treated with stimulants compared to placebo8. However, that review only focused on individuals with established bipolar disorder (BD). As such, the risk of incident BD in individuals with ADHD without BD exposed to stimulants remains unclear.

Overall, to date, no meta-analysis has estimated the magnitude of the risk of developing psychosis or BD when exposed to stimulant medication, not the factors moderating possible risk. Our aim was to fill this gap by estimating the risk of psychosis or BD after exposure to stimulant medication for ADHD, and identify any moderating factors which can affect the risk of developing psychosis.

**METHODS**

The protocol for this study was pre-registered on PROSPERO (CRD42024616752). This study was reported in accordance with the PRISMA 2020 item checklist9 (eTable 1) and MOOSE checklist10 (eTable 2).

**Literature search**

A systematic search strategy was used, with no language restrictions, to identify relevant articles, and a two-step literature search from inception until 1st October 2024 was implemented by two independent authors (GSP, CA). Search strategy and databases searched can be found in eMethods 1.

Articles identified were screened at the title/abstract level, and after the exclusion of those which did not meet our inclusion criteria, the full texts of the remaining articles were assessed for eligibility, and decisions were made regarding their inclusion or not in this study. We completed our searches with manual backward and forward reference searching (looking at previously published articles and articles citing the included studies). Any discrepancies were resolved with the first author (GSP). Any missing information/data useful to assess eligibility were obtained by contacting the corresponding authors and/or first and last authors of the articles.

**Inclusion and Exclusion Criteria**

Inclusion criteria were: a) individual studies of any design (observational or interventional studies) b) conducted in individuals with DSM/ICD defined ADHD using clinical criteria or scores above clinical threshold on validated psychometric instruments, c) treated with stimulant medication – i.e., amphetamines – including lisdexamfetamine- and methylphenidate- and c) in which the % of individuals who developed psychotic symptoms, a psychotic disorder, or mania/BD was reported. Exclusion criteria: a) reviews, clinical cases, abstracts, study protocols, b) studies conducted in individuals with other disorders, c) studies without information on the development of psychosis or mania/BD, d) studies evaluating participants with pre-established BD or psychosis.

**Data extraction Strategy**

Three researchers (CA, JPC, JTC) independently extracted data from the included studies, into a database (a Microsoft Excel spreadsheet). Variables extracted can be found in eMethods 2.

**Strategy for Data Synthesis**

Our outcomes were the % of individuals (95% CI) exposed to stimulant medication who developed psychotic symptoms, a psychotic disorder, or BD. We also compared the development of psychotic symptoms in individuals exposed to amphetamines and those exposed to methylphenidate, using Odds Ratio (OR, 95% CI) as effect size.

Since high heterogeneity was found, random-effects meta-analyses were conducted11. The presence of publication bias was assessed by Egger’s test12, complemented by the “trim and fill” method to correct for the presence of missing studies when a risk of publication bias (i.e., small sample bias) was detected. Any correction was based on the assumption that the effect sizes of all the studies were normally distributed around the centre of a funnel plot. In the event of asymmetries, this method adjusts for the potential effect of unpublished studies. Heterogeneity among study point estimates was assessed using Q statistics. The proportion of the total variability in the effect size estimates was evaluated with the I2 index13 and considered statistically significant when p<0.05. I2>50% is typically considered an indication of high variability in the effect size estimates reflecting true heterogeneity as opposed to heterogeneity due to random variance.

We conducted sub-analyses for psychotic symptoms outcome to estimate the association between the evaluated outcomes and a) design of the studies (longitudinal cohorts vs clinical trials) b) diagnostic instrument used (DSM-any version vs ICD-any version, with or without additional validated measures) c) continent (Europe vs Asia vs America), d) registry data (yes vs no), e) explicitly reporting how outcome of interest being present was excluded at baseline and f) duration of follow-up (<1 year vs 1-5 years vs >5 years). Furthermore, we conducted meta-regression analyses for our primary outcome whenever ≥7 studies were available for each regressor providing this information14,15, to estimate the association between the development of psychotic symptoms and: a) % males, b) age, c) duration of follow-up, d) year of publication and e) sample size. Additional leave-one-out sensitivity analyses evaluated the stability of the meta-analytic findings when each study was removed at a time.

To classify the evidence and make recommendations, we applied GRADE16 (which sets four categories for rating quality of evidence- high, moderate, low and very low- based on study design, risk of bias, inconsistency, indirectness and imprecision) and US Preventive Services Task Force (USPSTF) grading system17(eMethods 3 in the Supplement).

All p values reported in the meta-analyses were two-sided, with alpha=0.05. Comprehensive Meta-analysis (CMA) V318 was used to perform the analyses.

**Risk of bias (quality) assessment**

For study appraisal, we used the Newcastle–Ottawa Scale (NOS)19. This scale has three domains: selection, comparability, and outcome (for details see eMethods 4).

**RESULTS**

The literature search yielded 1,414 non-duplicated citations, which were screened for eligibility. 15 studies were finally included (see Figure 1 for PRISMA Flowchart and Table 1 for characteristics of the included studies), encompassing in total 390,759 individuals. The mean age of the sample was 12.6 years ranging from 8.5 to 31.1 years. The proportion of females was 26.3%, ranging from 11.9 to 60.2%. In those studies providing this data, 76.8% individuals with ADHD met criteria for the combined presentation, 16.4% for predominantly inattentive presentation and 8.5% for predominantly hyperactive-impulsive presentation.

**Meta-analytical results**

Overall, 2.8% (95%CI= 0.7-9.9%), 2.4% (95%CI= 1.6-3.6%) and 3.7% (95%CI= 0.8-15.3%) of individuals with ADHD who had been prescribed stimulant medication developed psychotic symptoms (k=10, n=237,035), a psychotic disorder (k=3, n=91,396) and BD (k=4, n=92,945), respectively. The development of psychotic symptoms in individuals exposed to amphetamines was higher than in those exposed to methylphenidate (OR=1.57, 95%CI 1.140-2.161, k=3, n=231,325). Leave one study out analyses for the development of psychotic symptoms can be found in eFigure 1, ranging from 1.8% (95%CI=0.4-6.8%) to 4.4% (95%CI=2.4-7.9%).

Heterogeneity across the included studies was statistically significant for psychotic symptoms (Q=2813.497, I2=99.6, p<0.001), psychotic disorders (Q=80.269, I2=97.508, p<0.001), and BD (Q=70.043, I2=95.717, p<0.001), indicating high variability in the effect size estimates.

**Sensitivity analyses and publication bias**

Differences were found between the studies according to the continent in which the study was carried out (Q=145.42, p<0.001): 6.3% (95%CI=0.8-35.0%), 1.6% (95%CI= 1.2-2.1%) and 0.3% (95%CI= 0.2-0.8%) of individuals with ADHD who had been prescribed stimulant medication developed psychotic symptoms in America (k=5, n=226,969), Asia (k=2, n=4,108), and Europe (k=2, n=1,737), respectively. Differences were found between the studies according to the duration of follow up (Q=16.07, p<0.001): 7.2% (95%CI=2.9-16.9%), 0.7% (95%CI=0.2-2.4%), and 0.2% (95%CI= 0.1-0.6%) of individuals with ADHD who had been prescribed stimulant medication developed psychotic symptoms in studies with a follow up of >5 years (k=3, n=4,625), 1-5 years (k=3, n=5,248), and of <1 year (k=2, n=221,924), respectively. The diagnostic instrument used, the design of the study, whether the results came from registry data or explicitly excluded psychosis at baseline did not have an influence on the results (all p>0.05). Full sub-analyses results are provided in eTable 5.

An increasing proportion of females increased the development of psychotic symptoms (β=0.012; 95%CI from 0.002 to 0.023; Z=2.30; p=0.021) (eFigure 2). A decreasing sample size increased the development of psychotic symptoms (β=-0.0001; 95%CI from -0.0001 to -0.0001 Z=-3.84; p<0.001). There was no association between mean age of the participants (p=0.977) or year of publication (p=0.232) and the development of psychotic symptoms. There was a trend of an association between duration of follow up and the development of psychotic symptoms (β=0.454; 95%CI from -0.0008 to 0.909; Z=1.96; p=0.0503). Details on the meta-regression analyses are provided in eTable 6**.** No indication of publication bias was found for any of the outcomes (see Egger’s test in eTable 7 and funnel plot for the primary outcome in eFigure 3).

**Quality Assessment**

The quality of the included studies was good in 11 studies (73.3%), and moderate in 4 studies (26.7%), indicating overall good quality. GRADE and USPSTF recommendations are reported in Table 2.

**DISCUSSION**

To the best of our knowledge, this is the first meta-analysis to estimate the risk of developing psychotic symptoms, a psychotic disorder, and BD in individuals with ADHD treated with stimulants. We found that 2.8%, 2.4%, and 3.7% of individuals with ADHD who had been prescribed stimulants developed psychotic symptoms, a psychotic disorder, and BD, respectively. Amphetamines were associated with a 57% higher risk of developing psychotic symptoms compared to methylphenidate.

Although not high, a 2.8% development of psychotic symptoms as found in our study represents a non-negligible risk and lends further meta-analytic support to the 2007 Food and Drug Administration (FDA) change in the drug label for stimulants, alerting on the possible risk of new onset of psychosis20. This figure should be to considered alongside the fact that a childhood diagnosis of ADHD per se increases the risk of a subsequent psychotic disorder later on in life, with a relative risk of 4.7421, and that the global incidence of psychosis in the general population is 26.6 per 100 000 person-years22,23. Furthermore, development of psychosis is 8% after 0.5 years to 25% after three years in individuals at Clinical High Risk24. Offspring of affected parents have also an increase wisk strongly elevated RR and lifetime risk of developing any mental disorder as well as the same mental disorder diagnosed in the parent25. Importantly, we found low level evidence of a cause-effect relationship between stimulants and the development of psychosis in individuals with ADHD according to *GRADE* rating. Indeed, two within-individual design studies, in which the risk of psychosis was evaluated in individual with ADHD during periods with and without methylphenidate treatment, failed to find an association between stimulant use and increased risk of psychosis26,27. To our knowledge, analogous studies on amphetamines are currently lacking.

Overall, the possible mechanisms underlying the development of psychosis in individuals treated with stimulants require further elucidation. It is thought that the mechanism of stimulant related psychosis may be mediated by dopaminergic excess28. It would appear that some individuals may rarely develop psychosis after exposure to stimulants and some may be sensitive(i.e., highly likely to develop psychosis) even after taking low doses of stimulants or without exposure to stimulants4,20. There are also other specific factors to be taken into consideration. Stimulants seem to cause psychosis more often at high doses and with parenteral use29. Frequency of stimulant use and severity of dependence to stimulant medication have been associated with psychosis, while sociodemographic factors have not30. Interestingly, and contrary to meta-analytical evidence for the development of psychosis from clinical high risk populations where a lower proportion of female individuals was associated with an increased risk of psychosis24, in our meta-regressions, female sex increased the risk for development of psychosis. Furthermore, sleep deprivation seems to play an important role in the development of psychotic symptoms too31. The risk of developing psychotic symptoms may be higher if stimulants are prescribed in people without an ADHD diagnosis. For instance, it was found that stimulant initiation was associated with an increased risk of hospitalization for psychosis or mania in the subsequent 60 days (OR=1.86)32, which contrast with our findings suggesting that the risk increases in the long-term. This study was not limited to individuals with an ADHD diagnosis. Notably, a study found that earlier onset methamphetamine use and being male were more specifically related to transient psychotic symptoms, while a family history of a primary psychotic disorder and comorbid major depression were specifically related to persistent psychotic symptoms33.

Overall, considering the established benefits of stimulants for ADHD, the magnitude of the risk of psychosis, and the uncertainty regarding cause-effects mechanisms, we deem that our results should not discourage clinical guidelines from recommending stimulant medications as first line treatments for ADHD. Selective use of stimulant medications is recommended, with shared decision-making and monitoring for adverse outcomes (*USPSTF* Grade C recommendation). In any case, it isimportant for prescribers to inform patients and their families about the possibility of developing this side effect34, carefully monitor for the risk of psychosis once stimulants are started, and slowly titrate stimulant medications. Once stimulant-induced psychosis is developed, individuals who develop it should be considered to be at risk for future development of an enduring psychotic illness, and prioritized or at least considered for early intervention of integrated care across substance use and mental health services35.

While several clinical guidelines for ADHD do not address the management of psychosis occurring during stimulant treatment, the National Institute of Health and Clinical Excellence (NICE, 2008) guidelines suggest that, if psychosis occurs due to stimulant use, the stimulant should be discontinued21. Notably, data from the FDA show thatsigns and symptoms of psychosis usually disappear on stopping the stimulants in about 90% of cases, without the need to introduce using an antipychotic36. Based on our meta-analytic data, among stimulants, methylphenidate should be preferred to minimize the risk of psychosis. Second line pharmacological treatments such as atomoxetine, that do not seem to increase the risk of psychosis37, would be another option.

Regarding development of BD, a previous study found that mania/hypomania was frequently observed in patients with BD (up to 40%) in the 2 months after starting stimulants for the treatment of ADHD or bipolar depression38. One in thirteen adults with ADHD is diagnosed with BD while nearly one in six adults with BD has ADHD39. Our results suggest a much lower risk in individuals with ADHD following prescription of stimulants, and lower than the risk of developing BD in at-risk populations40. Furthermore, there is very low evidence of a cause-effect relationship between stimulants and the development of BD in individuals with ADHD according to *GRADE rating*. Notably, in comparison with other medications, treatment-emergent mania seems to be twice as often with antidepressants as with stimulants (44% vs. 18%)41.

Again, monitoring and psychoeducation measures would be recommended, but stimulants seem to be overall safe when prescribed within indications. The underlying mechanisms for stimulant-induced mania remain poorly understood but are hypothesized to involve dysregulation of dopaminergic and noradrenergic pathways. Stimulants enhance dopaminergic and noradrenergic neurotransmission by inhibiting reuptake and increasing the release of these neurotransmitters42. NICE guidelines2 emphasize the importance of carefully evaluating comorbidities, including BD, before initiating stimulant treatment for ADHD, which we agree with. Specifically, NICE (2023)2 guidelines recommend a thorough psychiatric assessment, particularly in individuals with a family history of BD. Stimulants should only be prescribed for ADHD when a comprehensive risk-benefit analysis has been conducted, and patients should be regularly monitored for the emergence of manic or hypomanic symptoms2. Although a growing body of evidence has been generated over the last decade about the contexts in which even individuals with established BD may benefit from stimulants43, more research is needed given methodological issues of available (e.g., heterogeneous samples, dependent measures, type/dose of agent)44.

Our study has some limitations. First and importantly, it is not possible to differentiate the effect of the medication from that of ADHD itself. Future Second, it was not possible to analyse the development of manic symptoms with stimulant medication as we only found one study providing this data. Third, even though we explored heterogeneity with meta-regressions, we could not address this comprehensively due to the paucity of relevant data, such as information on severity of ADHD, comorbid mental health conditions, or medication usage. Again, given the nature of available data, we could not assess the effect of different doses, different formulations, combination of different medications, or the effect of non-stimulant medications. Fourth, studies included in the meta-analysis included a mixture of children, adolescents and young adults. We thus could not confirm our hypothesis of children having a lower risk of psychosis. Finally, some studies used electronic health record data, which may be less accurate than those obtained through direct clinical assessments or standardized diagnostic interviews.

Despite these limitations, this study provides the first comprehensive estimate of the risk of developing psychosis or BD in individuals with ADHD exposed to stimulant medication. This meta-analysis highlights a non-negligible risk of psychosis and BD in patients with ADHD treated with stimulants, with amphetamines posing a higher risk than methylphenidate. Even though there is no evidence to support a causal role of stimulant in leading to psychosis, our findings underscore the need for comprehensive psychoeducation, careful monitoring, and discussion with patients and their carers about management strategies, including potential stimulant rechallenge, following stimulant-associated psychosis. Future research exploring additional predictorsand preventive interventions is warranted.

**Declaration of interest:** Dr Salazar de Pablo has received honoraria from Janssen Cilag, Lundbeck, Angelini and Menarini. Dr Aymerich has received honoraria from Neuraxpharm and Janssen. Dr Catalan has received personal fees from Janssen. Dr Solmi received honoraria/has been a consultant for Angelini, AbbVie, Boehringer Ingelheim, Lundbeck, Otsuka. Dr Corbeil is currently receiving a fellowship award from the Canadian Institutes of Health Research (#202210MFE-491926-64860). Prof Fusar-Poli reports research fees from Lundbeck and honoraria from Lundbeck, Angelini, Menarini, and Boehringer. Prof Cortese, NIHR Research Professor (NIHR303122) is funded by the NIHR for this research project. Samuele Cortese is also supported by NIHR grants NIHR203684, NIHR203035, NIHR130077, NIHR128472, RP-PG-0618-20003 and by grant 101095568-HORIZONHLTH- 2022-DISEASE-07-03 from the European Research Executive Agency. Prof. Cortese has declared reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH) in relation to lectures delivered for ACAMH, the Canadian AADHD Alliance Resource, the British Association of Psychopharmacology, Healthcare Convention and CCM Group team for educational activity on ADHD, and has received honoraria from Medice. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR, NHS or the UK Department of Health and Social Care.

**Table 1: Characteristics of the included studies.**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First author and year of publication** | **Country** | **Study design** | **ADHD criteria (subtypes)** | **Sample size** | **Age: mean**±**SD (range)** | **% of females** | **Medication** | **Race/ ethnicity** | **Outcome** | **Duration of follow up** | **NOS:**  **score,**  **rate** |
| Baweja 201645 | USA | Naturalistic non-randomized clinical trial | DSM-IV, DSM-V (n.a.) | 38 | 9.4±1.7 (children) | 28% | Stimulants | 26.3% “racial/ ethnic minority” | Mania (symptoms) Bipolar Disorder | 6 weeks | 5, moderate quality |
| Björkenstam 202046 | Sweeden | Longitudinal cohort | ICD-9, ICD-10 (n.a.) | 13,237 | N.a (ADOL) | 60.2% | MPH, INN, AMP | N.a. | Psychosis (disorder) | Up to 14 years | 8, high quality |
| Cherland 198947 | Canada | Longitudinal cohort | DSM-III, DSM-IV (n.a.) | 98 | N.a. (4-18) | 24.0% | MPH, pemoline | N.a. | Psychosis (symptoms) Bipolar Disorder | 7 years | 9, high quality |
| Coghill 201748 | Multicountry | Longitudinal cohort | DSM-IV-TR2 (79.9% combined, 17.8% PRED inattentive, 2.2% PRED hyperactive-impulsive | 314 | 11.4±2.9 (6-19) | 20.4% | LDX | 98.7% white | Psychosis (symptoms) | 2 years | 9, high quality |
| Cortese 201549 | Italy | Longitudinal cohort | DSM-IV (84,7% combined, 11.7% PRED innatentive  3,6% PRED hiperactive-impulsive | 1,426 | 10.7±2.8 (6-18) | 11.9% | MPH | N.a. | Psychosis (symptoms) | 5 years | 8, high quality |
| Dalsgaard 201550 | Denmark | Longitudinal cohort | DSM-IV, ICD10 (65.9% combined, 19.7% PRED hyperactive-impulsive, 14.4% inattentive) | 208 | 31.1±6.6 at follow-up (children & ADOL at baseline) | 12.0% | Stimulants | N.a. | Psychosis (disorder) | Until they were adults (31.1±6.6 years) | 6, moderate quality |
| Elmaghraby 202451 | USA | Longitudinal cohort | ICD-9, ICD-10 (n.a.) | 4,358 | 10.2±3.6 (6-18)1 | 31.4%1 | MPH, AMP | 83.5% white, 5.0% black or African-American, 1.7% Asian, 7.4% other, 2.5% n.a. | Psychosis (symptoms) | 7.7 years (mean duration) | 6, moderate quality |
| Golubchik 201852 | Israel | Open-label randomized clinical trial | DSM-IV-TR3 (n.a.) | 60 | 12.5±2.5 (8-18) | 41.7 | MPH | N.a. | Psychosis (symptoms) | 12 weeks | 7, high quality |
| Hamard 20247 | Multicountry | Longitudinal cohort | ICD (n.a.) | 5,221 | 17.2±3.6 (13-25) | 38.8% | MPH, AMP | N.a. | Psychosis (symptoms) | N.a. | 9, high quality |
| MacKenzie 201653 | Canada | Longitudinal cohort | DSM-IV (n.a.) | 17 | 11.8±4.0 (6-21) | 50.0% | MPH, LDX, INN | N.a. | Psychosis (symptoms) | N.a. | 8, high quality |
| Moran 20196 | USA | Longitudinal cohort | ICD-9 (n.a.) | 221,846 | N.a. (13-25) | 37.3% | MPH, AMP | N.a. | Psychosis (symptoms) | 155- 162 days median duration | 7, high quality |
| Park 202254 | South Korea | Longitudinal cohort | ICD-10 (n.a.) | 3,508 | 8.9±2.7 (children & ADOL) | 16.6% | MPH | N.a. | Psychosis (symptoms) | 1.5 | 9, high quality |
| Shyu 201555 | Taiwan | Longitudinal cohort | ICD-9 (n.a.) | 53,600 | 9.4±3.3 (children) | 20.2% | MPH | N.a. | Psychosis (disorder) | ADHD diagnosis to 2012 (max 12 years) | 9, high quality |
| Tillman 200656 | USA | Longitudinal cohort | DSM-IV4 (n.a.) | 81 | 9.7±2.0 (7-16) | 17.0% | N.a./ any | N.a. | Bipolar Disorder | 6 years | 5, quality moderate |
| Wang 201657 | Taiwan | Longitudinal cohort | ICD-9 (n.a.) | 86,747 | 8.5±3.1 (children) | 18,9% | N.a../ any | N.a. | Bipolar Disorder | 5.1±3.1 years. ​ | 9, high quality |
| ADHD-RS-IV: ADHD Rating Scale IV; ADOL: adolescents; AMP: amphetamine; DSM: Diagnostic and Statistical Manual of Mental Disorders; ICD: International Classification of Diseases; INN: Dexamphetamine; K-SADS-PL: Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version; LDX: lisdexamfetamine; MPH: methylphenidate; WASH-U-K-SADS: Washington University Kiddie Schedule for Affective Disorders and Schizophrenia.  1Data from the full sample at diagnosis; 2Complemented with ADHD-RS-IV; 3Complemented with K-SADS-PL and ADHD-RS-IV;4Complemented with WASH-U-K-SADS | | | | | | | | | | | |

**Table 2: GRADE and USPSTF Grading**

|  |  |
| --- | --- |
| **GRADE Approach** | **USPSTF Grading** |
| **Quality of Evidence**   * **Study Design:** Studies were primarily observational, which starts at a "low" GRADE rating for observational studies. * **Risk of Bias:** 73.3% of studies were rated as "good" quality and 26.7% as "moderate". This indicates a low risk of bias overall. * **Inconsistency:** Significant heterogeneity (I² > 95%) was observed in most outcomes. * **Indirectness:** Direct evidence exists for the population of interest (patients with DSM/ICD-defined ADHD on stimulant medications). * **Imprecision:** Confidence intervals are wide, particularly for sensitivity analyses, indicating potential imprecision. * **Publication Bias:** No evidence of publication bias was found (Egger’s test and funnel plots). | **Certainty of Evidence**   * **High Certainty:** N/A due to observational study design and high heterogeneity. * **Moderate Certainty:** Psychosis development in ADHD patients prescribed stimulants is supported by meta-analytic evidence but limited by heterogeneity and imprecision. |
| **GRADE Evidence Rating:**   * **Psychosis and Bipolar Disorder Development:** Low. * **Subgroup Analyses (Duration of Follow-Up, Continent):** Very Low | **Magnitude of Net Benefit**   * **Potential Harms:** Development of psychosis or bipolar disorder, particularly with amphetamine use. * **Potential Benefits:** Effective management of ADHD symptoms and functional improvements.   **USPSTF Grade:** C Selective use of stimulant medications is recommended, being methylphenidate preferred than amphetamines, with shared decision-making and monitoring for adverse outcomes. |
| **2. Strength of Recommendation**   * Psychotic symptoms occur in approximately 2.8% of individuals with ADHD on stimulant medication (higher with amphetamines). * Psychotic disorders occur in 2.4% and bipolar disorder 3.7% of individuals with ADHD on stimulant medication. * Caution is warranted when prescribing stimulants, especially for those at higher risk (e.g., those exposed to amphetamines, at clinical high risk or with a family history of psychosis).   **Recommendation:**  -Recommendation for close monitoring of ADHD patients prescribed stimulants, particularly amphetamines. | **Summary Recommendations**   1. **Monitoring Practices:** Clinicians should monitor ADHD patients closely for psychotic symptoms, especially those prescribed amphetamines (>5 years). 2. **Shared Decision-Making:** Engage patients and caregivers in discussions about risks versus benefits, considering individual factors such as age, sex, and ADHD subtype. 3. **Research Needs:** High heterogeneity and imprecision highlight the need for further studies with standardized designs and longer follow-up periods to refine risk estimates. |

**Figure 1 PRISMA flowchart 2021**

**Identification of studies via other methods**

**Identification of studies via databases and registers**

Records identified from:

Websites (n = 0 )

Organisations (n = 0)

Citation searching (n = 240)

etc.

Records removed *before screening*:

Duplicate records removed (n = 220 )

Records marked as ineligible by automation tools (n =0)

Records removed for other reasons (n = 0)

Records identified from\*:

Databases (n = 1633 )

Registers (n = 1)

**Identification**

Records screened

(n = 1414)

Records excluded

(n = 1363)

Reports not retrieved

(n =0)

Reports sought for retrieval

(n = 35)

Reports sought for retrieval

(n = 51)

Reports not retrieved

(n = 0)

**Screening**

Reports assessed for eligibility

(n = 35)

Reports excluded (n = 35)

Not meeting inclusion criteria (n =26)

Being included in electronic search (n=9)

Reports excluded:

(n=36)

Outcome not psychosis/ bipolar disorder (n=13)

Population not ADHD (n=11)

Other reason (n=9)

Design (n=4)

Reports assessed for eligibility

(n = 51)

Studies included in review

(n = 15)

Reports of included studies

(n = 15)

**Included**

**Figure 2: Forest plot outcome in individuals with ADHD exposed to stimulant medication**

**A/ Bipolar disorder in individuals with ADHD exposed to stimulant medication**



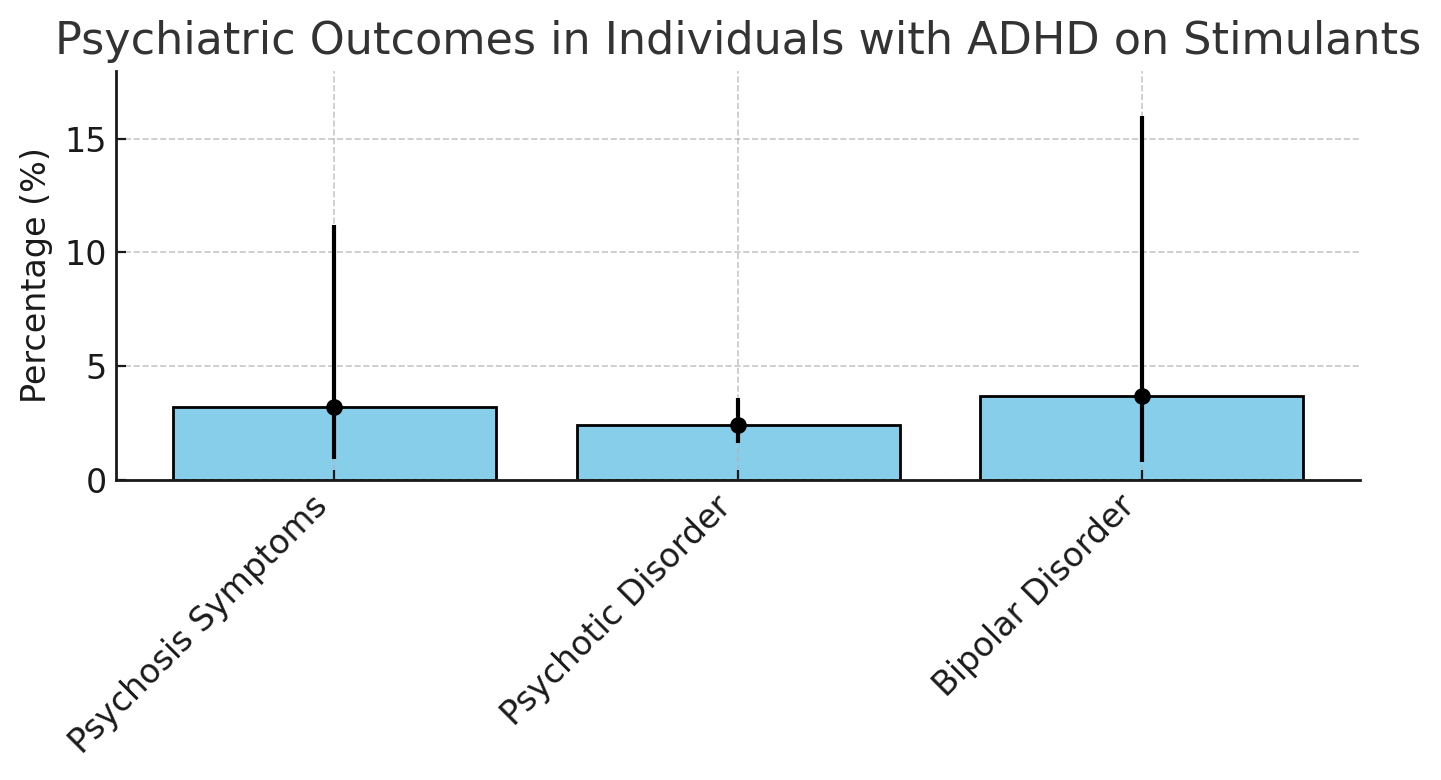
B/ **Psychotic disorder in individuals with ADHD exposed to stimulant medication**



C/ **Psychotic symptoms in individuals with ADHD exposed to stimulant medication**



**Figure 3: Development of psychosis and BD in individuals with ADHD exposed to stimulant medication**

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