HHS Public Access

Author manuscript

Biol Psychiatry. Author manuscript; available in PMC 2020 September 01.

Published in final edited form as:

Biol Psychiatry. 2019 September 01; 86(5): 335–343. doi:10.1016/j.biopsych.2019.04.009.

Risks and benefits of ADHD medication on behavioral and neuropsychiatric outcomes: a qualitative review of pharmacoepidemiology studies using linked prescription databases

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Abstract

ADHD medication is one of the most commonly prescribed medication classes in child and adolescent psychiatry, and its use is increasing rapidly in adult psychiatry. However, major questions and concerns remain regarding the benefits and risks of ADHD medication, especially in real-world settings. We conducted a qualitative systematic review on studies that investigated the effects of ADHD medication on behavioral and neuropsychiatric outcomes using linked prescription databases from the last ten years, and identified 40 studies from Europe, North America, and Asia. Among them, 18 have used within-individual designs to account for confounding by indication. These studies suggested short-term beneficial effects of ADHD medication on several behavioral or neuropsychiatric outcomes (i.e., injuries, motor vehicle accidents, education, substance use disorder), with estimates suggesting relative risk reduction of 9–58% for these outcomes. The within-individuals studies found no evidence of increased risks for suicidality and seizures. Replications studies are needed for several other important outcomes (i.e., criminality, depression, mania, psychosis). The available evidence from pharmacoepidemiology studies on long-term effects of ADHD medication are less clear. We discussed time-varying confounding and other limitations which should be considered when interpreting results from

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pharmacoepidemiology studies. Further, we highlighted several knowledge gaps to be addressed in future research and implications for research on mechanisms of outcomes of ADHD medications.

Keywords

ADHD medication; short-term outcomes; long-term outcomes; pharmacoepidemiology; within-individual design; real-world evidence

BACKGROUND

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder of childhood that persists into adolescence and adulthood for many individuals (1–3). The prevalence of clinically diagnosed ADHD is increasing in most developed countries (4). For instance, the prevalence among children and adolescents in the US increased from 6.1% in 1997–1998 to 10.2% in 2015–2016 (5). Although these increases appear to reflect changes in diagnostic criteria and awareness of ADHD to a greater extent than they reflect true increases in the prevalence of the condition itself (6), more individuals are nevertheless now being identified worldwide as candidates for ADHD treatment.

Treating ADHD is a major public health issue, as the disorder is associated with high rates of comorbidity (7, 8) and serious outcomes (9–11). Numerous randomized controlled trials (RCTs) have established the efficacy of medications, particularly stimulants, for reducing the core symptoms of ADHD in children, adolescents, and adults, though for some there are side effects and difficulties in tolerating treatment (12). Clinical guidelines now generally recommend stimulants as the first-line pharmacological treatment for school-aged children, adolescents, and adults (13–16). The prevalence of ADHD medication use has increased dramatically in many developed countries during the last decades (17, 18).

Major questions and concerns remain, however, regarding the benefits and risks of ADHD medications (16, 19, 20). Many extant concerns stem from the limitations of the existing research and reflect the inherent constraints of RCTs (21, 22). With respect to ADHD medications, we want to highlight three limitations of RCTs (Table 1). First, the generalizability of findings from existing RCTs to populations with more comorbidity and greater severity is unclear. For example, research has found that individuals excluded from RCTs on ADHD medication show higher rates of comorbidity and lower functioning (23). Second, few RCTs include follow-up evaluations of long-term outcomes. In fact, a recent comprehensive meta-analysis of RCTs did not have sufficient data to inform on outcomes past 12 weeks (12). Third, there is increasing recognition of the need for treatment to address not only the symptoms of ADHD but also ADHD-associated functional impairments (24). And yet, existing RCTs can only provide limited evidence for the effects of pharmacotherapy on risk of rare-but-serious or longer-term outcomes, such as serious injury, suicidality, or other forms of psychopathology. These limitations are compounded by questions of whether ADHD medication may be particularly harmful or helpful for rare outcomes in potentially at-risk subgroups. For example, concerns remain about prescribing ADHD medications to individuals with substance use problems (25, 26) and preschool

children (27, 28). Thus, research needs “real-world data” to better provide “real-world evidence” regarding the broader risks and benefits of ADHD medication (29).

Pharmacoepidemiology research using population-based prescription databases is an increasingly recognized approach for this purpose. These databases are usually linked with other health records or registers and provide individual-level data on diagnosis, prescription, and demographic information (30). As an alternative to RCTs, they have several strengths (Table 1), including data on patients from real-world practice, longer follow-up time, and larger samples. However, unlike RCTs that use randomized treatment assignment to help balance potential confounding factors, whether measured, unmeasured, or unknown, pharmacoepidemiology studies are prone to bias if confounding is not properly addressed (31, 32). A particularly important type of confounding in pharmacoepidemiology studies is “confounding by indication,” which occurs when factors involved in selecting patients into a particular treatment also affect the outcome (33). Within-individual designs, or self-controlled designs, present one approach to account for confounding by indication (34, 35). Instead of comparing medication users and nonusers, within-individual designs compare the risk of outcomes during medicated time periods to that of non-medicated time periods within the same individual. Because the comparison is within the same individual, all confounding from factors that are stable throughout the observed time at risk is eliminated, even if they are unmeasured or unknown.

In the current paper, we reviewed population-based pharmacoepidemiology studies of ADHD medication and behavioral and neuropsychiatric outcomes. These studies address two type of research questions. One question is whether ADHD medications protect against the risk of an outcome, usually a functional or behavioral impairment associated with ADHD (e.g., injuries and accidents, criminality). The second is whether ADHD medications increase the risk of adverse outcomes (e.g., mania, seizures, substance abuse), given concerns from clinical or preclinical studies (36). We highlight the key findings and limitations of these studies. Finally, we discuss remaining knowledge gaps for future studies and investigations of mechanisms of medication effects on ADHD-associated outcomes.

EVIDENCE FROM PHARMACOEPIDEMIOLOGY STUDIES ON ADHD MEDICATIONS

We performed a systematic search in PubMed and Embase for studies that investigated the association between ADHD medications and behavioral or neuropsychiatric outcomes using population-based prescription databases between January 01, 2008 and February 01, 2019, with no language restrictions. We used terms related to ADHD (“Attention-deficit/hyperactivity disorder”, “ADHD”) and medication (“medication”, “stimulant*”, “treatment”) and type of data (“regist*”, “claim*”, “record*”, “population*”) in combination. We followed the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (37) and identified 40 eligible studies (Supplementary Figure 1), encompassing ten different outcomes (Supplementary Table 1). We classified the effects of medication as short-term (e.g., concurrent effects) or long-term (e.g., any extended or accumulated effects). In addition, we distinguished three

main types of design/analytical approaches to account for confounding: regression adjustment, propensity-score methods, and within-individual comparisons, and summarized the results separately for those using within-individual comparisons (Figure 1) as they are less biased by unmeasured confounding.

Injuries and traumas

We identified eleven studies on injuries and traumas from Europe, North America, and Asia (38–48). Six studies examined short-term effects, of which four used within-individual designs (39, 41, 43, 44). Four studies, including three within-individual studies, found ADHD medication was significantly associated with 9–32% reduced risk of injury (39–41, 44), with some evidence that results may differ depending on sex (41, 44). No substantial differences were found between studies focusing on stimulants (41, 44, 45) and those considering any ADHD medication (39, 40, 43), while no studies have analyzed the effect of non-stimulant medications separately.

Six studies examined long-term effects, and five of them found a statistically significant negative association between ADHD medication and injuries risk (38, 40, 46–48). Only one study reported a non-statistically significant negative association for medium or high vs low treatment adherence (42). None used a within-individual design.

Motor vehicle accidents

We identified two studies on motor vehicle accidents, one from Sweden and one from the US, and both used within-individual designs (49, 50). When evaluating short-term effects, they reported 38–58% reduced risk of motor vehicle accidents associated with ADHD medication in males (49, 50). However, only one study found a similar result in females (50), while the other found a non-statistically significant positive association in females (49).

One study using a within-individual design also found that ADHD medications were associated long-term reduction in the risk of motor vehicle accidents (50).

Education

We identified seven studies from Europe and the US that examined different aspects of medication use, including timing of medication use, on educational outcomes including changes in test scores, grades, or grade point average (GPA). In terms of short-term effects, two studies used within-individual design and found a statistically significant association between ADHD medication and increased test scores (51) and grade improvement (52), while another study found a non-significant mean difference between current and past users of stimulants (53).

In terms of long-term effects, one study found that late stimulant medication starters (individuals starting stimulants within 12 months from the tests) had higher scores than early starters (individuals starting stimulants earlier than 12 months before the tests) (53), while another study found that late start of stimulant medication was associated with higher risk of academic decline in mathematics, but not in language arts, compared with early start (54).

Two studies found consistent treatment with ADHD medication was associated with higher GPA compared with inconsistent treatment (55, 56).

Criminality

We identified two studies on criminality. One study was performed in Sweden using a within-individual design. The study reported 32% and 41% reduced risk of criminality associated with ADHD medication in males and females, respectively, and no significant difference between stimulants and atomoxetine (57). The study also reported a non-statistically significant long-term protective effect (57). The other study was performed in Denmark and reported ADHD medication was associated with significant reduction in both risk of conviction and risk of incarceration (58).

Suicidality

We identified five studies from Europe and Asia that investigated completed suicide or suicide attempts or self-harm (59–63). Three studies investigated short-term effects (59, 62, 63) and two of them adopted within-individual designs (59, 63). None of these studies found evidence for an increased risk of suicidal events, regardless of sex or type of medication (stimulant or non-stimulant).

Three studies investigated long-term effects and found no evidence for an increased risk of suicidal events (60–62). None of them used a within-individual design.

Substance use disorder

We identified three studies on substance use disorder, two from Europe (64, 65) and one from the US (66). Two studies investigating short-term effects using within-individual designs reported that ADHD medication was associated with 27–35% reduced risk of substance use disorder (64, 66).

All three studies investigated long-term effects (64–66). One study adopted a within-individual design and found statistically significant negative associations for previous treatment and treatment duration (66). The other two studies also reported negative associations when comparing treatment to no treatment, although one was not statistically significant (65).

Depression

We identified two studies on risk of depression, one from Sweden and one from Taiwan (67, 68). One study investigating short-term effects using a within-individual design, found ADHD medication was associated with 20% reduced rate of unplanned hospital visits due to depression (67).

Both studies investigated the long-term effect of ADHD medication on depression and found a negative association, but neither used a within-individual design (67, 68).

Bipolar disorder and mania

We identified two studies on bipolar disorder/mania, one from Sweden and one from Taiwan (69, 70). Only the study from Sweden investigated short-term effects and, using a within-individual design, examined the risk of mania associated with treatment with stimulants among patients with bipolar disorder (69). The study found patients on methylphenidate monotherapy had an increased rate of manic episodes within 3 months of medication initiation. By contrast, for patients taking mood stabilizers, the rate of mania was lower after starting methylphenidate.

Both studies investigated the long-term effect of ADHD medication on bipolar disorder (70) and mania (69). The Swedish study found similar results within 3–6 months as results from 0–3 months (69). The Taiwanese study found patients with long-term use of methylphenidate (>365 days) were less likely to be diagnosed with bipolar disorder compared to ADHD patients never taken methylphenidate. The associations for short-term treatment (<= 365 days) or atomoxetine were not statistically significant (70).

Psychosis

We identified two studies on risk of psychotic events (71, 72). One study, from Hong Kong, investigated short-term effects using a within-individual design and did not find evidence for an association between stimulant use and psychotic events among individuals who had a history of psychotic events (71).

The other study, from Taiwan, investigated long-term effects and found a positive association between stimulant use and risk of any psychotic disorders in individuals diagnosed with ADHD, although the association was not statistically significant when considering schizophrenia as the main outcome (72).

Seizures

We identified five studies on seizures, four from the US and one from Sweden, and two of them used a within-individual design (73–77). For short-term effects, none of the five studies found evidence for an increased risk of seizures, regardless of the type of medication (stimulant or non-stimulant) (73–77). Results from the studies that used a within-individual design suggest a possible protective short-term effect of ADHD medication in individuals both with and without a history of seizures (76, 77).

Three out of five studies investigated long-term effects, including one study that used within-individual design (76), and none found evidence for an increased risk of seizures (73, 74, 76).

KEY FINDINGS AND LIMITATIONS

An increasing number of pharmacoepidemiology studies on short-term benefits and risk (18 of 26 studies) have applied within-individual designs to account for confounding factors. The overall pattern of results suggests several short-term benefits and few short-term risks on behavioral and neuropsychiatric outcomes (Figure 1). The available evidence for several important outcomes (e.g. criminality, depression, mania, psychosis) is, however, still scarce,

and replications are needed. Consequently, systematic reviews with sufficient data for meta-analyses of short-term effects of ADHD medication have only been applied to injuries as an outcome, finding reduced risk of injuries associated with ADHD medication among individuals with ADHD (78, 79). Quality assessment of the included within-individual studies using the Newcastle-Ottawa Scale suggested high quality (78).

Future within-individual studies of short-term benefits and risks need to consider limitations related to time-varying confounding. Specifically, time-varying factors (e.g., life events, episodes of disease) that motivate individuals to start/stop treatment may simultaneously change their risk of outcomes (e.g., suicidal behavior, substance abuse) and therefore confound the within-individual associations. Several statistical methods have been suggested for appropriate adjustment for time-varying confounding, such as inverse probability of treatment weighting and G estimation, although they also rely on the measurement of time-varying confounders (80). An alternative approach is to use negative controls to detect confounding bias (both time-invariant and time-varying) (81). A drug with similar prescription patterns as the studied medication and with no or negligible causal effects on the studied outcome could be used as a negative control. For example, previous studies have used SSRIs as a negative control in studies of ADHD medications and motor vehicle accidents (49, 50), but they would be unsuitable for studies on suicidality because of the effects of SSRIs on the outcome.

The available evidence from pharmacoepidemiology studies of long-term effects is less clear. There are three main limitations to consider. First, an important problem is that the research question or hypothesis was not clearly defined in many studies. This makes it difficult to disentangle whether a study is addressing *the long-term effect of being treated with ADHD medication for a period* (e.g., is ADHD medication status at baseline associated with risk of an outcome several years later), or *the cumulative effect of being treated for longer periods of time* (e.g., is longer duration of ADHD medication treatment associated with higher risk of an outcome). In many available studies, it is also unclear whether these effects are independent from concurrent effect of ADHD medication (e.g., whether the observed long-term effect is explained by exposure to ADHD medication at the time of outcome measure).

Second, some previous studies have used survival analyses on time-to-event outcomes (e.g., injuries, suicide attempts) with duration of treatment defined as time-fixed variables (38, 61). However, duration of treatment depends on length of follow-up time, and time-dependent bias can occur if such variables are analyzed as time-fixed variables (82). To eliminate such bias, duration of treatment should be considered as a time-varying variable, or measured in an equal time window for all participants (66, 67, 72).

Third, few studies of long-term effects have used within-individual designs (3 out of 21 studies), which means that unmeasured confounding factors may explain observed findings. One explanation to why these designs have been less frequently used is that they only allow explorations of certain long-term effects. The few available studies used a lagged approach (50, 66, 76) to test whether medication status at a given time predicted the risk of outcome a few years later. Both concurrent and lagged medication status were included as predictors.

There are several additional, more general, limitations that needs to be considered when interpreting results from both short-term and long-term studies of ADHD medication. First, the use of ADHD medication was measured by filled prescriptions, so the results may only apply to patients who choose to fill prescriptions (83). Further, if patients did not take the medication as indicated, it would introduce misclassification of exposure and bias the results towards the null. Second, unlike double-blinded RCTs, treatment assignment is not masked for either patients or clinicians. It is possible that the same clinician who prescribed ADHD medication also made the outcome assessment, particularly for psychiatric outcomes, which might lead to biased results (32). Third, most of the studies used data from one country/state/region, which may not be generalizable to other settings. For example, there are important cross-national differences in diagnostic and treatment practices of ADHD (17), as well as variation in the validity of ADHD diagnosis from different data sources (32). For studies using insurance claims data, patients with private insurance may be different from those publicly insured or uninsured in terms of access to health care and risks of adverse outcomes. Validation with other samples is necessary.

Suggestions for future studies

First, future studies should clearly state whether the analyses are exploratory or driven by *a priori* hypotheses about either potential benefit (i.e. a hypothesis about the effectiveness of ADHD medication) or potential risk (a hypothesis about the safety of ADHD medication). Clarity around the type of research question and hypothesis may guide the data analyses and interpretation of the results.

Second, future studies may benefit from greater standardization of analyses and reporting (31, 32). The STROBE statement provides a useful guideline for strengthening the reporting of observational studies in epidemiology, including pharmacoepidemiology studies (84). For studies using within-individual designs, it would be helpful to report the overall number of patients in the study sample, as well as the number that contributes to the within-individual comparison. Improved clarity in reporting is of critical importance for replication studies and meta-analyses.

Third, it would be informative if future studies could, when possible, translate estimates of relative risk into absolute risk for a meaningful period. In many situations, absolute risk gives more relevant information to both patients and clinicians.

Fourth, future studies need to address issues related to selective reporting of findings. A pre-specified study protocol, as it is obligated for RCTs, would be particularly valuable to improve the transparency and interpretation of pharmacoepidemiology studies (31, 32).

REMAINING KNOWLEDGE GAPS

We see four main knowledge gaps that need to be addressed in future research. First, as highlighted above, more well-conducted pharmacoepidemiology studies are needed to resolve knowledge gaps around the long-term consequences of ADHD medication. This is an important limitation given that many patients may receive medications for years, and some studies suggest that the beneficial effect of ADHD medications may decline two to

three years after treatment initiation and that long-term use may be associated with adverse outcomes (85, 86). To address these knowledge gaps, long-term follow-up data (e.g., from childhood to early adulthood) is needed. Data with such time span is increasingly available from administrative healthcare databases, and it should be combined with analytic approaches that handle complex effects of duration, timing, and intensity of medication exposures on outcomes (e.g. time-weighted cumulative exposure models) (87).

One particular important question regarding the long-term effects is whether early exposure to ADHD medication change the developmental trajectories of patients, for example development of substance use problem. Animal studies suggest that repeated exposure to stimulants during the sensitive adolescent period was associated with long-term risk of substance abuse (88). Clinical follow-up studies suggest that ADHD medication neither protects nor increases the risk of later substance use disorders (89, 90), whereas pharmacoepidemiology studies based on prescription databases have found that ADHD medication was associated with lower risk of substance-related events up to three years later (64, 66). These results might be explained by the differences in the research questions and methods of animal, clinical, and pharmacoepidemiology studies. Therefore, more translational research is required to provide practitioners, patients, and their families with this critical information.

Second, although existing studies suggest that ADHD medication, on average in the whole patient population, is associated with short-term benefits and few short-term risks, less is known about benefits and risks in specific sub-groups. For example, older adults are overall underrepresented in existing studies (91, 92). With aging, a series of changes occur that modify the pharmacokinetics and pharmacodynamics of ADHD medication. This may influence the efficacy, tolerability, and safety of ADHD medication treatment (93). Further, many individuals with ADHD present with comorbidities, such as anxiety, personality, and substance use disorders (25, 26). The profile of benefits and risks in individuals with comorbidities may look like the profile in those without, but there are some indications that it may differ. For example, ADHD medication may be less effective among individuals with ADHD and autism spectrum disorders (94). These knowledge gaps need to be addressed.

Third, the high rate of comorbidity and multi-morbidity in individuals with ADHD means that many individuals with ADHD will use medications for other mental/physical health conditions, in addition to ADHD medication. Individuals with ADHD may face problems related to polypharmacy and drug-drug interactions, particularly among older adults with ADHD. Studies on the safety of ADHD medication in combination with other medications are therefore needed (95).

Fourth, in addition to neuropsychiatric outcomes, there are concerns about the safety of ADHD medications for somatic outcomes (e.g., cardiovascular disease, growth delay) (36). However, most of the existing studies are based on clinical samples, and evidence from population-based studies are yet limited (96–98). Future pharmacoepidemiology studies are warranted to investigate both short-term and long-term risks of somatic outcomes associated with ADHD medications and to identify potential at-risk groups.

IMPLICATIONS FOR RESEARCH ON PREDICTORS AND MECHANISMS OF OUTCOMES OF ADHD MEDICATIONS

Experimental trials of pharmacological interventions provide a powerful approach to identify markers of treatment or risk responses and to investigate treatment mechanisms (99). The application of such approaches to pharmacoepidemiological studies is more challenging than experimental trials, because of the need to control for the various confounders discussed above, but can address questions relating to longer term outcomes. One example is the effect of methylphenidate on risk of mania in patients with comorbid and ADHD and bipolar disorder, which is moderated by concomitant use of mood stabilisers (69). This finding has immediate implications for current clinical practice, illustrating the potential for incorporation of predictors into pharmacoepidemiological studies to inform personalised medicine.

Another set of questions relate to the neural and cognitive processes that underpin ADHD itself, and the treatment response to drug treatments. Multiple functional deficits of neural circuitry are associated with ADHD and proposed to mediate causal effects of genes (and environment), as well as treatment effects of medications (100). One approach is to manipulate neural biomarkers with treatments, such as stimulants, and evaluate their role as mediators of the clinical response (101). Such studies are best suited to short-term experimental study designs that can incorporate functional neuroimaging to capture neural/cognitive changes resulting from drug treatments, and link these to changes in clinical symptoms of ADHD.

Although challenging it may also be possible to incorporate such approaches into pharmacoepidemiological studies. Databases may be interrogated for results of neuropsychological and medical test results, and digital health technologies might enable large-scale evaluation of neurocognitive functions, particularly if these became widely used as part of the assessment of patients with neurodevelopmental disorders. It may then be able to infer direct relationships between changes in neurocognitive processes and longer-term ADHD related health outcomes. Overall, these approaches could potentially be used to target causal processes earlier in development and open new avenues for developing novel treatment targeting mediating mechanisms and optimising treatment outcomes.

CONCLUSION

Available pharmacoepidemiology studies suggests short-term beneficial effects of ADHD medications on several behavioral and neuropsychiatric outcomes (e.g., injuries, motor vehicle accidents, education, substance use disorder) and no increased risk for suicidality and seizures. An increasing number of studies have applied within-individual designs, or self-controlled designs, to account for confounding by indication. Replications are needed for several other important outcomes (e.g. criminality, depression, mania, psychosis). The available evidence from pharmacoepidemiology studies of long-term effects are less clear. Time-varying confounding and other limitations have to be considered when interpreting results from pharmacoepidemiology studies. Potential beneficial effects of ADHD

medications will have to be carefully weighed against potential harms, including side effects and societal problems (e.g., stimulant misuse and diversion) (102, 103).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding/Support:

This work was supported by grants from the Swedish Research Council (2013–2280) and the National Institute of Mental Health (R01MH102221). LG is supported by the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 643051. This report reflects only the authors' views and the European Union is not responsible for any use that may be made of the information it contains. ZC is supported by the Swedish Research Council (2018–02213). PQ is supported by the National Institute on Drug Abuse (R00DA040727). PA is supported by NIHR Biomedical Research Centre for Mental Health, NIHR/MRC (14/23/17) and NIHR senior investigator award (NF-SI-0616–10040).

Conflict of Interest Disclosures:

PA has received funds for consultancy on behalf of KCL to Shire, Eli-Lilly, and Novartis, regarding the diagnosis and treatment of ADHD; educational/research awards from Shire, Eli-Lilly, Novartis, Vifor Pharma, GW Pharma, and QbTech; speaker at sponsored events for Shire, Eli-Lilly, and Novartis. HL reported serving as a speaker for Eli Lilly and Shire and reported receiving a research grant from Shire, all outside of the submitted work. All other authors report no biomedical financial interests or potential conflicts of interest.

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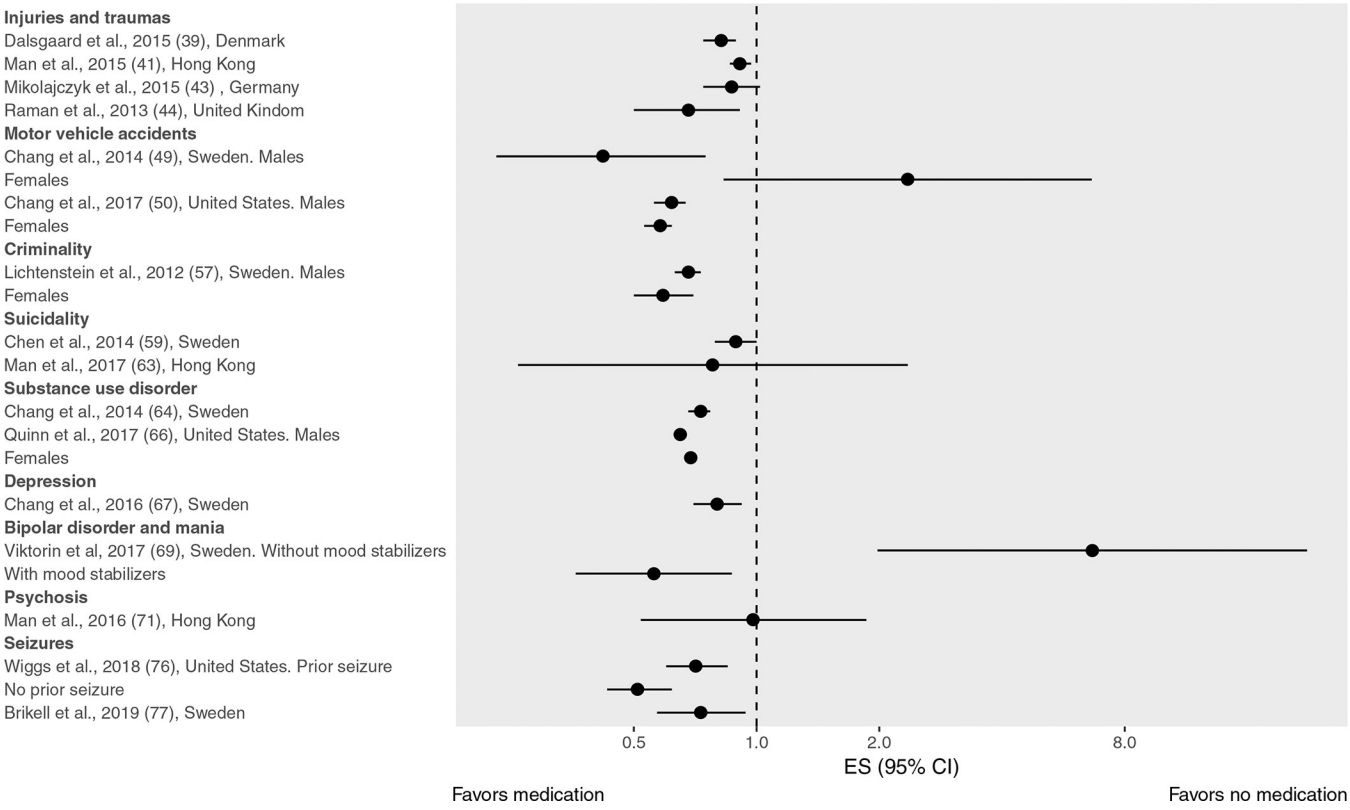

Figure 1. Forest plot of within-individual studies for short-term effects of ADHD medications.
Note: Studies on educational outcomes were not included because they used continuous measures of outcome.

Table 1.

Major advantages and disadvantages of randomized clinical trials and pharmacoepidemiology studies.

	Advantages	**Disadvantages**
Randomized clinical trials	• Randomized treatment assignment to balance all potential confounding factors • Both patients and researchers could be blinded from the treatment information	• Samples may not representative of the real world • Typically short-term • Usually not large enough to study rare outcomes
Pharmacoepidemiology studies using population-based prescription databases	• Representative of patients in real-world practice • Long follow-up time • Large sample size	• Confounding by indication • Misclassification of exposure • Lack of standardized analyses and reporting