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BEYOND SYMPTOM CONTROL: ADHD PHARMACOTHERAPY AND REAL-WORLD RISK REDUCTION – A NARRATIVE REVIEW

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ABSTRACT

Background: ADHD is associated with substantial impairment and elevated risks of severe real-world adverse events across the lifespan (e.g., suicidal behavior, motor vehicle crashes, substance misuse, criminality, and premature mortality). While randomized trials establish short-term efficacy for symptom control, evaluating long-term real-world risk reduction requires synthesizing evidence from diverse observational and causal-inference designs.

Aim: This narrative review synthesizes current evidence on the association between ADHD pharmacotherapy and major real-world functional outcomes, balancing behavioral risk reduction against potential long-term cardiovascular safety concerns.

Methodology: We searched PubMed, Web of Science, Embase, and PsycINFO for studies on stimulant and non-stimulant treatments. Evidence from randomized trials, register-based studies, within-individual comparisons, and target-trial emulations was synthesized narratively, focusing on how study design affects causal inference.

Results: ADHD pharmacotherapy is associated with lower rates of suicidal behavior, substance-related problems, transport accidents, criminal convictions, psychiatric hospitalizations, and premature mortality. Conversely, long-term cumulative exposure—particularly to stimulants—is linked to increasing cardiovascular risk, especially hypertension, with stronger associations at longer durations and higher doses.

Conclusions: ADHD pharmacotherapy contributes to critical real-world risk reduction beyond core symptom control. Clinical decisions should balance these behavioral and survival benefits against potential long-term cardiovascular risks through ongoing safety monitoring and individualized benefit-risk assessments.

KEYWORDS

Attention-Deficit/Hyperactivity Disorder, ADHD Pharmacotherapy, Real-World Outcomes, Risk Reduction, Cardiovascular Safety, Mortality

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Introduction

ADHD beyond core symptoms

Attention-deficit/hyperactivity disorder (ADHD) is defined by persistent symptoms of inattention and/or hyperactivity-impulsivity, but its clinical burden extends beyond symptom severity alone. ADHD is associated with functional impairment across social relationships, education, employment, and economic stability, as well as with reduced health-related quality of life (HRQoL); such impairments are among the reasons patients seek treatment [1, 2]. Symptoms and functioning are related but distinct constructs, and improvement in one does not necessarily correspond to an equivalent improvement in the other. This distinction is particularly relevant in adults, in whom executive-function difficulties involving organization, planning, time management, and completion of goal-directed tasks may interfere with independent functioning and occupational demands [2].

Randomized trials demonstrate that pharmacological treatment can reduce core ADHD symptoms over the short term, whereas treatment effects on functional and quality-of-life outcomes are generally smaller than those observed on symptom measures [1, 3]. Evidence from adult trials is further limited by the short duration of most studies, sparse long-term data, and low or very low certainty for several patient-important outcomes [4]. Accordingly, symptom-focused efficacy measures address an important but incomplete aspect of treatment effectiveness. On their own, they do not establish whether pharmacotherapy is associated with changes in clinically consequential outcomes that are not adequately captured by symptom-rating scales.

Large databases and registries have broadened the range of outcomes studied under routine-care conditions, including mood disorders, substance use disorders, suicidal behavior, criminality, traumatic brain injury, motor vehicle crashes, other accidents and injuries, and educational outcomes [5]. These outcomes complement symptom-based measures by capturing clinically meaningful events and functional consequences in broader patient populations. However, observational evidence introduces distinct methodological challenges. Exposure definitions may vary across studies, and associations between medication use and outcomes may remain vulnerable to confounding; consequently, such findings require cautious causal interpretation.

Rationale and objective of the review

Recent real-world evidence encompasses complementary observational designs, including target-trial emulations and longitudinal self-controlled analyses examining associations as prescribing patterns change over time [6, 7, 8]. Together, these approaches allow the assessment of first and recurrent events, cause-specific mortality, differences between medicated and nonmedicated periods, and outcomes in populations drawn from routine clinical practice. Findings vary across outcomes. In the target-trial emulation, ADHD pharmacotherapy was associated with lower rates of first suicidal behaviors, substance misuse, transport accidents, and criminality, whereas the association with first accidental injuries was not statistically significant; for recurrent events, lower rates were observed across all five outcomes [8]. The magnitude of associations with some real-world outcomes also appeared to attenuate over time as prescribing increased, a pattern that may reflect expansion of treatment to broader populations with fewer symptoms or impairments, although this interpretation remains inferential [7].

A balanced interpretation should neither equate observational associations with proof of causal prevention nor disregard potentially clinically meaningful population-level findings solely because they arise from observational data. Potential harms also require consideration. Long-term cardiovascular data further support incorporating somatic safety into benefit-risk assessment, particularly during prolonged treatment [9]. This narrative review therefore synthesizes and critically interprets evidence on ADHD pharmacotherapy and

major real-world outcomes beyond core symptom control. Particular attention is given to suicidal behavior, substance-related outcomes, accidental injuries, transport accidents, criminality, occupational and mental-health outcomes, mortality, cardiovascular safety, and the methodological designs that shape causal interpretation.

Methodology

This article was designed as a narrative review focused on real-world clinical and functional outcomes associated with attention-deficit/hyperactivity disorder (ADHD) pharmacotherapy. The literature was identified using a targeted narrative search strategy defined by the scope and objectives of the review. Searches were conducted in PubMed, Web of Science, Embase, and PsycINFO from database inception through July 2026 and were supplemented by Google Scholar searches and manual screening of reference lists. Search terms combined ADHD-related concepts with pharmacotherapy terms and outcome terms covering premature mortality, suicidal behavior and self-harm, accidental injuries, transport accidents, criminality, substance-related problems, psychiatric hospitalization, work disability, and health-related quality of life (HRQoL). Selection emphasized peer-reviewed studies directly addressing clinically relevant functional or real-world outcomes associated with stimulant or non-stimulant pharmacotherapy. The narrative approach was used to integrate evidence generated by heterogeneous study designs, including randomized controlled trials, systematic reviews, nationwide register studies, retrospective and prospective cohorts, self-controlled case series, within-person analyses, and target-trial emulations. Because these approaches estimate different treatment contrasts and address different sources of bias, their findings were synthesized qualitatively rather than pooled into a single quantitative estimate. The included literature comprised randomized controlled trials, systematic reviews and meta-analyses, observational cohort and register-based studies, and longitudinal analyses. Publications were considered relevant when they addressed at least one of the predefined outcome domains: suicidal behavior and self-harm; substance-related outcomes; accidental injuries; transport accidents; criminality; occupational functioning and broader mental-health outcomes; premature mortality; and treatment-related cardiovascular safety. Studies involving children, adolescents, or adults with ADHD and examining stimulant or non-stimulant pharmacotherapy in relation to these functional or real-world outcomes were considered within scope. Publications were not emphasized when ADHD pharmacotherapy was peripheral to the main research question or when the study population, exposure, or outcomes fell outside the predefined clinical and functional scope of the review. Because the purpose of the review was to provide a clinically oriented narrative synthesis rather than a pooled estimate of treatment efficacy or effectiveness, no formal meta-analysis or quantitative pooling was performed. No formal risk-of-bias instrument was applied; instead, methodological strengths and limitations relevant to interpretation were considered narratively for each study design. Findings were synthesized according to their clinical and methodological context. The synthesis considered reported relative and absolute risk estimates, temporal patterns of events, treatment duration, and relevant comorbidity where these data were available. Particular attention was paid to the implications of study design for causal interpretation. Between-individual observational comparisons were interpreted cautiously because of their vulnerability to treatment-selection effects and confounding by indication. Within-individual Methodology were considered in relation to their ability to control for characteristics that remain stable within individuals over time, while recognizing their continued susceptibility to time-varying confounding. Target-trial emulations [10] were evaluated according to whether key design components, including eligibility criteria, treatment strategies, follow-up, and time zero, were explicitly aligned, thereby helping to avoid important design biases. Findings from observational studies were therefore described primarily as associations, with causal terminology calibrated to the design and assumptions underlying each estimate. To structure the synthesis, findings were organized by outcome domain and interpreted according to the design used to generate each estimate. First events, recurrent events, and comparisons between medicated and unmedicated periods were considered separately when these contrasts were reported. Estimates from randomized trials, conventional cohorts, within-individual analyses, and target-trial emulations were not treated as directly interchangeable because they address different clinical questions and sources of bias. Greater interpretive emphasis was placed on convergence of findings across methodologically distinct designs than on any single estimate. Within each design, results were interpreted in relation to both the biases addressed by the analytic approach and those that could remain, including time-varying confounding, treatment selection, exposure misclassification, and changes in concurrent care. Outcome-specific differences were retained rather than combined into a single overall treatment estimate, and differences according to prior event history, medication class, age, treatment duration, or prescribing era were preserved when they were relevant to clinical interpretation.

Results

Characteristics of the evidence base

The evidence base spans short-term randomized evidence on symptom efficacy and functioning, large observational databases, national registries, and more recent target-trial emulations. Trial syntheses confirm the short-term efficacy of several ADHD medications and show improvements in functional or HRQoL measures, although these effects are generally smaller than those observed for core symptoms and long-term randomized data remain sparse [1, 3, 4]. Registry-based evidence extends the scope beyond outcomes typically assessed in conventional trials to include serious injuries, motor vehicle crashes, substance-related outcomes, suicidality, criminality, and educational or other functional outcomes [5].

Within-individual designs compare periods of medication use and non-use within the same individual, thereby controlling for characteristics that remain stable over time while remaining susceptible to time-varying confounding and carryover effects. More recent target-trial emulations use population-based data to compare treatment initiation with non-initiation while explicitly aligning eligibility criteria, treatment strategies, and the start of follow-up [6, 8]. Across these study designs, reported associations varied by outcome and analytic approach, underscoring the importance of considering estimates within the methodological context in which they were generated.

Suicidal behavior and self-harm

Several large-scale studies have associated ADHD medication with lower rates of suicide attempts or suicidal behavior, although temporal patterns around treatment initiation and the choice of reference period materially affect interpretation. In U.S. claims data, medication use was associated with lower odds of suicide attempts in both population-level and within-individual analyses, with the favorable association observed primarily for stimulant treatment [11]. A target-trial emulation in newly diagnosed patients likewise reported a lower rate of first suicidal behavior after treatment initiation and reduced rates of recurrent events; associations were more pronounced among individuals with a prior history of the outcome [8]. An important temporal pattern was identified in a self-controlled analysis of methylphenidate: suicide-attempt risk was markedly elevated during the 90 days preceding the first prescription, remained elevated during the first 90 days after initiation, and subsequently returned toward baseline during continued treatment [12]. Direct comparison of the pretreatment and early-treatment periods did not indicate an increase after treatment initiation. A similar concentration of suicide-attempt events around the treatment transition was observed in U.S. claims data [11]. These temporal patterns are compatible with confounding by indication or other time-varying factors, because worsening psychiatric status may contribute both to treatment initiation and to suicidal behavior.

Retrospective cohort evidence further illustrates the importance of comparator selection. When patients receiving methylphenidate were compared with individuals without recorded psychiatric treatment or methylphenidate exposure, subsequent suicide-attempt risk estimates were higher in the methylphenidate group across all exposure-duration categories, although the hazard ratios attenuated with longer cumulative exposure [13]. Because psychiatric morbidity was more prevalent among methylphenidate-treated individuals, these between-group estimates remain susceptible to residual differences in clinical severity. Medication-class analyses provide additional evidence that the pretreatment period is clinically important. In a within-individual study, suicidal-behavior odds were particularly elevated during the two months before initiation of atomoxetine and alpha-2 agonists [14]. After this pretreatment period was separated from other off-treatment time, modestly elevated odds were also observed during treatment with stimulants, atomoxetine, and alpha-2 agonists relative to the remaining off-treatment periods. However, direct comparisons between treatment and pretreatment periods showed lower odds during treatment for all three medication classes [14]. These findings indicate that the estimated direction and magnitude of associations can depend substantially on how high-risk pretreatment time is handled analytically.

Taken together, the reviewed evidence does not support a simple interpretation that initiation of ADHD pharmacotherapy causes an acute increase in suicidal behavior. Risk appears to be elevated before treatment initiation in several analyses, and some studies show attenuation after treatment begins or with continued exposure. However, on-treatment associations are not uniform across designs or comparator definitions. Earlier large-scale analyses reported favorable associations, particularly for stimulant treatment, whereas more recent within-individual evidence found modestly elevated on-treatment odds when the high-risk pretreatment

period was excluded from the off-treatment reference category [8, 11, 14]. Residual time-varying confounding and treatment-selection effects therefore remain important considerations.

The magnitude of the main estimates illustrates both potential clinical relevance and methodological variation. In the U.S. claims analysis, medication exposure was associated with lower odds of suicide attempts in the within-individual model [11]. In the Swedish target-trial emulation, weighted first-event rates were 14.5 versus 16.9 per 1000 person-years for treatment initiation versus non-initiation, with an adjusted incidence rate ratio of 0.83 [8]. Recurrent suicidal behaviors were also less frequent in the target-trial analysis. These estimates should not be treated as interchangeable because one design compares medicated with unmedicated periods within individuals, whereas the other compares treatment strategies beginning after diagnosis. Their findings are broadly concordant with respect to the absence of evidence for an acute increase following treatment initiation, while the newer medication-class analysis demonstrates that estimates relative to later off-treatment periods may differ.

Substance-related outcomes

The included population-level evidence does not indicate that therapeutic stimulant treatment is associated with an increased risk of subsequent substance-related problems. In Swedish register data, stimulant treatment was associated with a lower subsequent rate of substance-related outcomes, and longer cumulative treatment was associated with progressively lower subsequent risk [15]. Large U.S. within-individual analyses similarly found lower odds of concurrent substance-related events during medicated months in both males and females. Lower odds of events were also observed two years after medicated periods, although the long-term findings were less consistent in sensitivity analyses among females [16].

Target-trial emulation provides complementary evidence. Treatment initiation was associated with a lower rate of first substance misuse events and with a larger reduction in recurrent events over two years [8]. Earlier pooled observational evidence was less conclusive. Although the qualitative evidence predominantly showed lower substance-related risk during treatment, the pooled hazard ratio for substance use disorder outcomes did not reach statistical significance and between-study heterogeneity was moderate [5]. Differences in outcome definitions and analytic approaches should therefore be considered when comparing estimates across studies.

Evidence from a highly selected high-risk population is also informative but should not be generalized without caution. In a randomized placebo-controlled study of incarcerated men with ADHD and amphetamine dependence, high-dose methylphenidate administered within a structured treatment program reduced ADHD symptoms, increased the proportion of drug-negative and amphetamine-negative urine samples, delayed relapse, and improved treatment retention [17]. Median treatment retention was longer in the methylphenidate group than in the placebo group. Improvement in ADHD symptoms was therefore accompanied by more favorable substance-use and retention outcomes, although the study did not establish that symptom improvement itself mediated the better treatment retention. The selected population, methylphenidate dose, and intensity of concurrent treatment differ substantially from routine outpatient care.

Overall, the reviewed studies do not indicate a generalized increase in substance-related events associated with ADHD pharmacotherapy and more commonly report lower rates during or after treatment. However, these findings concern substance-related clinical and functional outcomes and should not be interpreted as excluding the distinct risks of misuse or diversion of prescribed stimulant medication.

Accidental injuries

ADHD is associated with an elevated risk of accidental injury in children, adolescents, and adults, although direct evidence characterizing changes in risk across the entire lifespan remains limited. In children and adolescents, a meta-analysis found higher odds and hazards of unintentional injury compared with individuals without ADHD, while a broader systematic review suggested that accident and injury patterns may vary with age and context [18, 19]. Evidence regarding medication is generally favorable in observational designs, although estimates vary across study designs and outcome definitions.

Meta-analytic observational evidence in children and adolescents associated ADHD medication with a lower risk of unintentional injury, with a pooled effect estimate of approximately 0.88 in analyses designed to reduce confounding by indication [19]. A self-controlled case-series analysis similarly found lower rates of trauma-related emergency-department admissions during methylphenidate-exposed periods than during nonexposed periods, including when only the first trauma episode was considered [20]. Swedish within-

individual register data also associated medicated periods with lower rates of unintentional injuries among children and adolescents with ADHD, together with a substantially lower rate of traumatic brain injury [21].

The target-trial evidence was more modest for accidental injuries. In newly diagnosed patients, treatment initiation was not associated with a statistically significant reduction in the first accidental injury, whereas recurrent accidental injuries occurred at a slightly lower rate under the treatment-initiation strategy; among individuals with a previous accidental injury, the estimate also favored treatment [8]. These findings differed in magnitude from earlier observational estimates. The pediatric meta-analysis reported a pooled effect estimate of 0.879, whereas the self-controlled case-series study reported an incidence rate ratio of 0.91 for trauma-related emergency-department admissions and 0.89 when only the first episode was considered [19, 20]. Overall, observational within-individual studies generally associated medication exposure with lower injury rates, whereas the target-trial emulation showed little evidence of a reduction in first accidental injuries and a smaller association for recurrent injuries. Effect estimates should therefore be interpreted according to the specific injury definition, event structure, population, and analytic design.

Transport accidents

Transport outcomes show a relatively consistent pattern across several real-world study designs, although estimates vary by population and analytic approach. In continuously monitored driving data, drivers with ADHD experienced higher rates of crashes and near-crashes than comparison drivers, and crash risk increased with ADHD symptom severity [22]. The same study found similarly elevated driving risk among drivers with depression, suggesting that some risk may extend across psychiatric conditions characterized by attention or concentration difficulties. Exploratory analyses did not show attenuation of crash risk according to usual ADHD medication treatment, although medication exposure could not be linked temporally to individual crash events [22]. In a U.S. cohort of more than two million people with ADHD, within-individual analyses associated medicated months with 38% lower odds of motor vehicle crashes in males and 42% lower odds in females; favorable associations were also observed in within-individual analyses of crash risk two years later [23].

A Taiwanese cohort also associated methylphenidate exposure with lower transport-accident risk in between-individual analyses, with lower estimates at higher cumulative exposure [24]. However, the corresponding self-controlled case-series analyses showed favorable but statistically non-significant estimates during the examined post-exposure periods, indicating greater uncertainty in the within-individual comparison [24]. Higher transport-accident risk was observed in specific comorbidity-defined subgroups, particularly males with epilepsy, oppositional defiant disorder/conduct disorder, or intellectual disability and females with autism-spectrum disorder or intellectual disability [24]. These findings emphasize substantial heterogeneity in baseline transport risk across clinical subgroups.

Target-trial emulation associated treatment initiation with a lower rate of first transport accidents and with a somewhat larger reduction in recurrent transport accidents [8]. The adjusted incidence rate ratio was 0.88 for first events and 0.84 for recurrent events; favorable associations were also observed in analyses stratified by previous event history [8]. Longitudinal Swedish analyses similarly found lower traffic-crash rates during medicated than nonmedicated periods across successive prescribing eras, but the magnitude of the association attenuated as medication prescribing increased [7]. Changes in the age and sex distribution of treated individuals did not fully account for this attenuation. Expansion of treatment to a broader population with fewer symptoms or impairments was proposed as one possible explanation, but this mechanism was not directly established [7]. Overall, the available studies predominantly associate ADHD medication exposure or treatment initiation with lower rates of real-world transport accidents, while the magnitude and statistical certainty of these associations vary according to study design, population characteristics, and exposure definition.

Criminality

Within-individual register analyses generally associate ADHD medication use with lower concurrent rates of criminal convictions. In a nationwide Swedish cohort, conviction rates were lower during medicated than nonmedicated periods in both men and women, with favorable associations in sensitivity analyses of stimulant and non-stimulant treatment and of violent, drug-related, and less severe crimes [25]. Analyses of treatment transitions likewise showed higher conviction risk during nonmedicated periods regardless of the direction of the treatment-status transition. A sensitivity analysis using SSRI treatment did not show a comparable association with criminal convictions. However, the same study did not identify a statistically

significant long-term association between medication status at the beginning of follow-up and criminality several years later after accounting for concurrent medication use [25].

Evidence from Denmark suggests that early ADHD pharmacotherapy may also be associated with later criminality-related outcomes. The analyses examined police interactions during early adolescence and criminal charges at older ages, using hospital-level variation in prescribing propensity as an instrumental variable and conducting additional analyses addressing observed background characteristics and proxies of ADHD severity [26]. The overall findings suggested fewer police interactions and a lower probability of criminal charges among children on the margin of receiving pharmacological treatment, although individual age-specific estimates were not uniformly precise.

A Swedish target-trial emulation found lower rates of both first and recurrent criminal events after treatment initiation, with an adjusted incidence rate ratio of 0.87 for first criminality events and 0.75 for recurrent events [8]. Earlier Swedish within-individual analyses similarly found lower concurrent conviction rates during medicated periods in both sexes [25]. More recent longitudinal analyses found lower crime rates during medicated than nonmedicated periods across successive prescribing eras, while the magnitude of the association attenuated in the main analysis as prescribing increased. However, the temporal trend for crime was no longer statistically significant after age and sex matching. Expansion of treatment to broader populations with fewer impairments or risky behaviors was proposed as one possible explanation for attenuation over time, but this mechanism was not directly established [7]. Overall, the available studies show broadly concordant associations between ADHD medication and lower concurrent, first-event, or recurrent criminality rates, while evidence for a persistent long-term association independent of current treatment is less clear.

Occupational functioning and broader mental-health outcomes

Functional impairment in adults with ADHD extends to employment and economic outcomes, including lower job stability, reduced work performance, interpersonal difficulties in the workplace, sickness absence, lower income, and financial stress [2]. Trial-based reviews indicate that pharmacotherapy can improve functional and HRQoL outcomes, although treatment effects on these measures are generally smaller than those observed for core ADHD symptoms [1]. Symptom improvement and occupational functioning should therefore be considered as related but distinct treatment outcomes.

A large Swedish register study examined work disability and hospitalization outcomes in relation to the use of individual ADHD medications. In the principal within-individual analysis, atomoxetine was associated with a modestly lower risk of work disability, defined as sickness absence or disability pension, with an adjusted hazard ratio of 0.89 [27]. In age-stratified analyses, atomoxetine and methylphenidate were associated with lower work-disability risk among adolescents and young adults aged 16–29 years, whereas these associations were not observed among adults aged 30 years or older. Associations with psychiatric hospitalization also differed across medications: lower risks were observed during use of amphetamine, lisdexamphetamine, ADHD polytherapy, dexamphetamine, and methylphenidate, whereas the overall estimates for atomoxetine, modafinil, clonidine, and guanfacine were not statistically significant. These findings demonstrate substantial medication- and outcome-specific variation in the observed associations.

Earlier synthesis of registry evidence similarly reported predominantly favorable associations for several functional and mood-related outcomes, although results were not uniform across domains [5]. Mood-related findings were generally favorable but included an adverse association in one study, while educational outcomes included favorable, neutral, and unfavorable findings. Occupational and broader mental-health outcomes should therefore be reported separately rather than summarized as a single generalized functional effect of pharmacotherapy.

Premature mortality

Premature mortality represents one of the most consequential outcomes considered in this review. Population-based and longitudinal evidence indicates that individuals with ADHD have an elevated risk of premature mortality compared with those without ADHD. Swedish register data showed substantially higher all-cause premature mortality among individuals with ADHD, with the association becoming progressively stronger as the number of psychiatric comorbidities increased [28]. A UK longitudinal cohort similarly associated childhood ADHD problems with higher premature mortality by later middle age. In path analyses, smoking and midlife waist-hip ratio mediated this association in the better-fitting model; when BMI-defined

obesity was used instead of waist–hip ratio, smoking, obesity, and systolic blood pressure were identified as mediators [29].

A target-trial emulation of newly diagnosed patients directly examined ADHD pharmacotherapy initiation in relation to mortality. Initiating treatment was associated with lower two-year all-cause mortality than non-initiation, with weighted risks of 39.1 versus 48.1 deaths per 10,000 individuals and an adjusted hazard ratio of 0.79 [6]. The association was more pronounced for unnatural-cause mortality, with an adjusted hazard ratio of 0.75, whereas natural-cause mortality was not significantly lower. Among specific unnatural causes, treatment initiation was associated with a substantially lower rate of death from accidental poisoning, while the association with death by suicide was not statistically significant. A case-crossover sensitivity analysis likewise associated medication use with lower all-cause and unnatural-cause mortality, but not with natural-cause mortality. Absolute two-year mortality risks were low despite the clinical severity of the outcome.

The observed mortality pattern was therefore concentrated primarily in deaths from unnatural causes rather than natural causes. In a head-to-head sensitivity analysis, initiation of stimulant versus non-stimulant medication did not show a statistically significant difference in all-cause mortality [6]. Although the target-trial emulation and case-crossover analyses yielded broadly concordant findings, the evidence remains observational and does not establish that medication itself caused the lower mortality rates. Mortality findings should therefore be interpreted as associations, particularly for individual causes of death for which the number of events was limited.

Long-term cardiovascular outcomes and safety

Potential benefits observed in other real-world outcome domains do not exclude adverse safety associations. Long-term cardiovascular safety is particularly relevant because ADHD pharmacotherapy may continue for several years. In a Swedish nested case-control study, longer cumulative exposure to ADHD medication was associated with an increased risk of incident cardiovascular disease, with associations most apparent for hypertension and arterial disease [9]. The overall association increased most rapidly during the first three years of cumulative exposure and subsequently stabilized. Dose-stratified analyses also showed stronger duration-related associations at higher average doses, with statistically significant estimates observed among individuals with an average dose of at least 1.5 defined daily doses [9].

The cardiovascular findings differ from the predominantly favorable associations reported for several behavioral and external outcomes. In the long-term study, adjusted odds ratios for overall cardiovascular disease increased across the initial exposure categories, reaching 1.27 for three to five years of cumulative use and 1.23 after more than five years compared with nonuse [9]. Hypertension showed the clearest condition-specific association, with adjusted odds ratios of 1.72 after three to five years and 1.80 after more than five years. Arterial disease was also associated with cumulative exposure, although the estimate after more than five years was less precise and its confidence interval included the null. No statistically significant increases were identified for arrhythmias, heart failure, ischemic heart disease, thromboembolic disease, or cerebrovascular disease in the condition-specific analyses [9].

Short-term randomized evidence provides a different perspective on cardiovascular safety. Trial syntheses identified small increases in systolic or diastolic blood pressure with some ADHD medications, with patterns varying by medication and age group [3]. However, randomized evidence beyond the short term was sparse: insufficient data were available for the 26- and 52-week timepoints, and long-duration adverse cardiovascular events were inadequately reported [3, 4]. Thus, short-term trials primarily characterize changes in cardiovascular parameters, whereas the longer-term observational evidence addresses associations with clinically diagnosed cardiovascular disease. The latter remains susceptible to residual and time-varying confounding and should not be interpreted as establishing a causal effect of prolonged ADHD medication exposure on cardiovascular disease [9].

Discussion

Beyond symptom control

The central conclusion of this review is that ADHD pharmacotherapy evaluation must extend beyond symptom scales. Across large observational settings, pharmacotherapy is associated with lower rates of suicide- and substance-related events, transport accidents, criminal convictions, psychiatric hospitalizations, and premature mortality, though consistency and magnitude vary by outcome and study design [5, 6, 8, 27]. These findings extend, rather than replace, randomized evidence showing short-term improvements in core ADHD symptoms, functioning, and HRQoL [1, 3].

A plausible explanatory model is that reduced inattention and impulsivity, alongside better daily functioning, decreases exposure to high-risk circumstances. While compatible with this pathway, the evidence does not establish mediation or a single causal mechanism. Furthermore, real-world associations vary across populations and prescribing eras. For example, as medication use expanded in Sweden, risk reductions for self-harm, injury, traffic crashes, and crime persisted across successive periods, though associations with injuries and traffic crashes attenuated over time, and self-harm showed no significant temporal trend [7]. This suggests that the magnitude of real-world benefits may partly reflect the changing composition of the treated population and is not constant across clinical settings or prescribing eras.

Not all real-world outcomes are equivalent

The term “real-world outcomes” should not obscure clinically important differences between endpoints. Suicidal behavior, substance misuse, accidental injury, transport accidents, criminality, and mortality differ in clinical meaning, frequency, and ascertainment. They also show distinct patterns of association with treatment. Target-trial evidence found lower rates of first suicidal behaviors, substance misuse, transport accidents, and criminality after treatment initiation, whereas the estimate for first accidental injury was not statistically significant; recurrent accidental injuries, however, were associated with a modestly lower rate [8]. More broadly, the magnitude of associations differed across the five outcomes and between first and recurrent events. Likewise, the mortality association was more pronounced for unnatural causes, whereas natural-cause mortality was not significantly lower [6].

This outcome specificity is important for clinical interpretation. An association observed for one endpoint should not be assumed to apply with the same magnitude to another, and estimates for first events should not be treated as interchangeable with those for recurrent events. Medication-class differences also require cautious interpretation: stimulants were associated with lower rates of the five outcomes than non-stimulants in a head-to-head analysis, but most treatment initiators received methylphenidate [8]. The evidence therefore supports domain-specific conclusions rather than a single composite statement that ADHD pharmacotherapy “reduces risk” across all real-world outcomes.

From association to causality

The central methodological challenge is determining whether observed differences between treated and untreated patients reflect true treatment effects or systematic differences between groups. Conventional observational comparisons are vulnerable to confounding by indication, as medicated patients often differ systematically from untreated individuals in characteristics related to both treatment selection and outcome risk [5], potentially exaggerating either harm or benefit.

Temporal confounding is prominent in suicidality studies. A marked increase in suicide-attempt risk during the 90 days before methylphenidate initiation suggests that treatment often starts during periods of escalating psychiatric crisis rather than at random [12]. Although risk remains elevated during the first 90 days post-initiation, it does not exceed the immediate pre-treatment level and declines during continued therapy. Failing to account for this pre-treatment pattern risks misattributing early post-initiation events directly to medication exposure.

Within-individual designs address time-invariant confounding by comparing medicated and unmedicated periods in the same person. While generating key evidence for criminality, substance-related outcomes, motor vehicle crashes, and suicidal behavior [11, 15, 16, 23, 25], these designs remain vulnerable to time-varying confounders, such as acute life events or depressive episodes that influence both treatment adherence and event risk.

Target-trial emulation addresses additional design biases by explicitly specifying clinical protocols, including eligibility, treatment strategies, follow-up, and time-zero alignment [10]. Recent mortality and multi-outcome studies used this framework to compare treatment initiation with non-initiation while accounting for treatment changes during follow-up [6, 8]. While strengthening causal interpretation, these emulations do not replicate randomization; validity still depends on accurate confounding adjustment and exposure ascertainment. Moreover, dispensing records do not guarantee adherence, and residual confounding may persist.

Causal language must therefore remain calibrated. While concordant associations across diverse populations and designs suggest that ADHD pharmacotherapy reduces several adverse outcomes, they do not exclude alternative explanations. Population-level estimates are not deterministic for individual patients, and observed associations vary by baseline risk, medication class, adherence, and clinical context.

Medication class, exposure, and heterogeneity

Class-specific associations with real-world outcomes are not uniform across medications or studies. For suicidal behavior, an earlier large claims analysis found lower risk primarily during stimulant treatment, whereas more recent within-individual evidence showed substantial increases in risk before treatment initiation and less consistent on-treatment associations across stimulant and non-stimulant classes. These findings also suggest that differences in clinical selection may complicate direct comparisons between medication classes [11, 14]. For work disability, atomoxetine was associated with lower risk in the overall analysis, while both atomoxetine and methylphenidate were associated with lower risk among adolescents and young adults but not among adults aged 30 years or older [27]. For mortality, the Swedish target-trial analysis did not detect a statistically significant difference between stimulant and non-stimulant initiation [6].

Treatment duration and continuity require similarly outcome-specific interpretation. Longer or cumulative exposure was associated with lower substance-related risk, whereas medication use was associated with lower concurrent and longer-term motor vehicle crash risk [15, 16, 23]. Within-individual analyses generally classified follow-up periods as medicated or unmedicated on the basis of dispensing records, which should not be equated with confirmed adherence. By contrast, cumulative exposure is particularly relevant to cardiovascular safety, where longer duration of ADHD medication use was associated with higher risk of cardiovascular disease, especially hypertension and arterial disease [9]. Accordingly, associations with treatment duration differ across outcome domains, making the relevant time horizon an important component of benefit–risk interpretation.

Heterogeneity also extends to demographic and clinical characteristics. Age, psychiatric and neurodevelopmental comorbidities, substance-related disorders, and prior adverse events are associated with substantial differences in baseline event risk. A history of the outcome may also identify subgroups with higher event burden and, for some outcomes, more pronounced treatment-associated rate reductions [8, 24, 28]. Future evaluations should therefore complement average population estimates with risk-stratified analyses that account for medication class, treatment exposure, baseline clinical characteristics, and prior event history.

Clinical, social, and public-health significance

The reviewed evidence supports a broader definition of treatment success. Symptom reduction remains crucial, but should be considered alongside functional outcomes and real-world adverse events [1, 2]. For individual patients, improvements in safety, occupational functioning, or psychiatric hospitalization carry clinical meaning that symptom scales alone cannot capture.

These broader implications are evident in transport safety, criminality, occupational outcomes, and healthcare utilization. While ADHD is linked to elevated crash risks, medication-related findings vary by study design: large database analyses report lower crash rates during treatment, whereas one naturalistic study found no significant reduction. Conversely, criminality studies consistently associate medication with lower conviction and recidivism rates [8, 22, 23, 25]. Furthermore, methylphenidate within structured programs has been shown to improve both ADHD and substance-use outcomes in severe amphetamine dependence [17]. Regarding employment, some medications were associated with reduced work-disability risk, particularly in younger adults [27]. While these endpoints better reflect daily social contexts, lower event rates cannot be automatically translated into reduced societal costs or improved productivity due to inconsistent estimations across studies. Thus, the significance of these findings lies in safety, service use, and justice-system contact rather than quantified economic returns.

Finally, mortality highlights the importance of non-symptom outcomes. ADHD is associated with excess premature mortality, particularly alongside psychiatric and substance-use comorbidities, while

initiating medication is linked to lower all-cause and unnatural-cause mortality over two years [6, 28]. These findings do not prove that medication alone prevents death, but support its role as a key component of a comprehensive risk-reduction strategy for vulnerable patients.

Benefit-risk balance

A clinically useful synthesis should consider potential benefits and harms simultaneously. The reviewed evidence includes favorable associations over two years for mortality and several behavioral and external-event outcomes, alongside a potential long-term cardiovascular safety signal associated with cumulative medication exposure [6, 8, 9]. These outcomes were evaluated over different time horizons: favorable associations for several real-world outcomes were estimated over two years, whereas cardiovascular risk was examined in relation to cumulative exposure extending over several years. Accordingly, evidence of lower real-world event rates should not be used to minimize safety monitoring. The cardiovascular findings support regular and consistent monitoring of cardiovascular signs and symptoms throughout treatment, with particular vigilance during higher-dose and prolonged therapy [9]. Because the long-term cardiovascular evidence is observational, these associations should be interpreted cautiously and should not be regarded as proof of causation. The clinically relevant question is therefore not whether medication is uniformly beneficial or harmful, but whether the potential benefits for clinically important real-world outcomes outweigh potential treatment-related harms for a particular patient over a defined time horizon.

Limitations of the current evidence and of this review

Several limitations constrain interpretation. First, most evidence for serious real-world outcomes is observational. Even advanced observational designs remain vulnerable to residual confounding from unmeasured or time-varying factors and to exposure misclassification when prescription or dispensing records do not correspond to medication actually taken [5, 6, 8, 10]. Changes in treatment, including discontinuation and switching, also require explicit consideration when exposure varies over time. Second, definitions and ascertainment of accidents and injuries vary across studies, as do the populations, settings, and types of events examined. This heterogeneity complicates direct comparison of injury-related estimates across studies [18, 19].

Third, study populations differ substantially in age, sex, comorbidity, and clinical context. Findings from pediatric populations should not be assumed to apply unchanged to adults, and results from highly selected groups, such as incarcerated men with ADHD and amphetamine dependence, require particular caution when extrapolated to broader ADHD populations [17]. Comorbidity is also associated with substantial variation in baseline event risk, as shown for transport accidents and premature mortality [24, 28].

This narrative review has additional limitations. It synthesizes a targeted body of literature and does not provide a quantitative meta-analysis, a formal risk-of-bias assessment across all included studies, or a preregistered systematic-review protocol. The included studies differ substantially in design, population, exposure definition, follow-up, and outcome ascertainment; consequently, the synthesis necessarily relies on qualitative appraisal of methodological strength and concordance across studies. The review was also not designed to systematically evaluate economic outcomes or broader measures of social participation and therefore cannot determine whether the observed event-rate associations translate into lower costs, greater productivity, or wider societal benefits. These limitations mean that the review is best understood as a clinically oriented narrative synthesis rather than a substitute for a fully systematic review and meta-analysis.

Future research directions

Future research should continue to strengthen causal inference through target-trial emulation and related designs that explicitly align eligibility, treatment initiation, time zero, and follow-up, together with appropriate adjustment for time-varying confounding and replication across populations and settings [6, 8, 10]. Further direct comparative studies of stimulant and non-stimulant strategies are warranted for patient-important and real-world outcomes. Such studies should account carefully for clinical factors that influence medication selection, including previous treatment response, adverse effects, risk of misuse or diversion, and medical or psychiatric comorbidity [3, 4, 14].

Long-term studies should clarify cardiovascular risk across cumulative exposure, medication classes, and prolonged treatment durations, with sufficient follow-up to characterize outcomes among patients receiving ADHD pharmacotherapy for many years [9]. Future research should also examine heterogeneity across age, sex, and broader patient subgroups and consider modifiable cardiovascular risk factors when characterizing long-term benefit-risk profiles [7, 29].

Conclusions

ADHD has consequences that extend beyond inattention, hyperactivity, and impulsivity to clinically important impairments and events affecting health, safety, and functioning. Across the included evidence, pharmacotherapy has been associated with lower rates of several clinically important real-world outcomes [5, 6, 8, 27]. These include suicidal behavior, substance-related events, transport accidents, criminality, psychiatric hospitalization, and premature mortality, although the consistency and magnitude of the associations differ across outcomes and medications. Findings for accidental injuries are more heterogeneous and appear more favorable for recurrent than for first events [8].

These findings broaden the concept of treatment success but do not justify unqualified causal claims. Most evidence for serious real-world outcomes is observational, and within-individual analyses and target-trial emulations remain vulnerable to residual confounding and limitations inherent in observational exposure and outcome ascertainment [8, 10]. The magnitude and interpretation of these associations also vary across outcomes, patient subgroups, treatment strategies, and analytic designs.

Clinical evaluation should therefore consider symptom response together with functional and real-world outcomes and balance favorable associations with behavioral and mortality outcomes against potential long-term safety concerns. In particular, the association between cumulative medication exposure and cardiovascular disease supports continued benefit-risk assessment during long-term therapy [9]. Overall, the evidence supports a multidimensional approach in which ADHD pharmacotherapy is assessed not only in terms of symptom improvement but also in relation to functioning, safety, and clinically important events in everyday life. Further research should clarify the long-term comparative benefit-risk profiles of different treatment strategies across clinically relevant patient groups.

Conflict of Interest: No conflicts of interest to declare.

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