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Cardiovascular Effects and Safety of Lisdexamfetamine in Attention-Deficit/Hyperactivity Disorder and Healthy Volunteers: A Systematic Review

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Abstract

Background: *Lisdexamfetamine is a prodrug of dextroamphetamine used to treat attention-deficit/hyperactivity disorder. Its cardiovascular effects require interpretation across age groups, exposure durations and study designs.*

Objective: *To synthesize cardiovascular findings in people with attention-deficit/hyperactivity disorder and healthy volunteers, distinguishing physiological changes from clinical events.*

Methods: *Searches were conducted in PubMed, Embase, Cochrane Library, Google Scholar, and SciELO for publications from January 2000 to March 15, 2026. Cardiovascular results were extracted by population, exposure, comparator, and assessment time. Human appraisal of the evidence was performed by all four authors. Findings were synthesized narratively without meta-analysis.*

Results: *A total of 21 reports were included. Direct cardiovascular results from 15 primary reports across 15 protocols were synthesized, accounting for overlapping participants. In a four-week adult trial, least-squares mean pulse changes were +2.8, +4.2, and +5.2 beats/min with 30, 50, and 70 mg/day, versus 0.0 with placebo. Cardiovascular adverse events occurred in 35/358 lisdexamfetamine recipients and 0/62 placebo recipients. Two adolescent trials reported mean pulse changes of +4.7 and +6.7 beats/min, versus +0.3 and +2.0 with placebo. The exploratory preschool study reported −0.8 beats/min, whereas the preschool extension reported +4.67 beats/min. In a 104-week uncontrolled pediatric study, last-on-treatment changes were +7.0 beats/min, +3.4 mmHg systolic, and +3.2 mmHg diastolic. Mean Fridericia-corrected QT (QTcF) findings varied; individual abnormalities, arrhythmia, and syncope were reported.*

Conclusion: *Lisdexamfetamine commonly increases mean pulse and blood pressure in selected trial populations, although responses vary across studies and individuals. Short trials and uncontrolled extensions cannot exclude rare events or cumulative cardiovascular risk. Heterogeneity and limitations in search documentation constrain the interpretation of this review.*

Keywords: Attention Deficit Hyperactivity Disorder; Blood Pressure; Cardiovascular Safety; Electrocardiography; Heart Rate; Lisdexamfetamine; Systematic Review.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) can require pharmacological treatment across childhood, adolescence and adulthood. Lisdexamfetamine dimesylate is an amphetamine-based prodrug with demonstrated efficacy in selected ADHD populations. Treatment decisions nevertheless require consideration of adverse effects as well as symptom improvement, particularly when exposure may continue for years (Coghill et al., 2013; Coghill, Caballero, et al., 2014; Weisler et al., 2009).

Lisdexamfetamine consists of dextroamphetamine linked to L-lysine. After absorption, conversion in blood generates the active compound. This formulation changes the timing of exposure but does not eliminate sympathomimetic activity or demonstrate cardiovascular protection. A comparison in healthy volunteers found a later onset of some effects without establishing that the prodrug produces lower cardiovascular responses than an equimolar dose of immediate-release dextroamphetamine (Dolder et al., 2017; Pennick, 2010).

Cardiovascular evidence encompasses several different questions. Changes in pulse and blood pressure characterize physiological responses, whereas arrhythmia, myocardial infarction, stroke and cardiovascular death are clinical

outcomes. Trials designed for ADHD efficacy can describe common changes in vital signs but often have limited power and follow-up for rare events. Open-label extensions provide longer observation, although selective enrollment and discontinuation may influence apparent tolerability (Adler et al., 2009; Coghill et al., 2017).

This review examines pulse or heart rate, systolic and diastolic blood pressure, electrocardiographic (ECG) findings, corrected QT interval, cardiovascular adverse events, and cardiovascular treatment discontinuation during lisdexamfetamine exposure. QTcF and QTcB denote QT corrected by the Fridericia and Bazett formulas, respectively. The synthesis distinguishes therapeutic treatment from experimental dosing and separates direct cardiovascular data from companion publications and review context.

Materials and Methods

Review framework and registration

The cardiovascular effects of lisdexamfetamine in people with ADHD and healthy volunteers were examined. Reporting was organized using PRISMA 2020 (Page et al., 2021).

The review was registered in PROSPERO (CRD420261343822), published on March 18, 2026. The cardiovascular question and publication period specified in this manuscript were retained. Supplementary Material, Section S6, describes the registration and scope.

Eligibility and evidence categories

People with ADHD and healthy volunteers of any age exposed to acute or repeated oral lisdexamfetamine were eligible. Comparators comprised placebo, another medication, baseline measurements, or no concurrent control. Outcomes comprised pulse or heart rate, blood pressure, ECG measurements, QTc, arrhythmia, hypertension, cardiovascular adverse events, and withdrawal attributed to cardiovascular intolerance.

Eligible designs included randomized and nonrandomized trials, open-label studies and extensions, human pharmacokinetic or pharmacodynamic studies, observational studies, and case reports. Publications were classified as contributing direct cardiovascular evidence when blood-pressure, pulse, ECG, or cardiovascular adverse-event results were reported. Companion publications without extractable cardiovascular results and reviews were used for context.

Studies without separately interpretable lisdexamfetamine results, studies of dextroamphetamine alone, recreational exposure, and substance-use populations outside the review question were excluded. Combination studies required separately interpretable lisdexamfetamine data. Experimental supratherapeutic dosing was distinguished from therapeutic regimens, and narrative pharmacological reviews were considered separately from primary clinical outcomes.

Information sources and reported searches

Searches were conducted in PubMed, Embase, Cochrane Library, Google Scholar, and SciELO for publications from January 1, 2000, to March 15, 2026. In PubMed, lisdexamfetamine or broader stimulant terms were combined with cardiovascular and safety terms; clinical-trial and review filters and an English-language restriction were applied. In Embase, lisdexamfetamine was combined with cardiovascular and safety terms. Google Scholar included drug-name variants and cardiovascular terms; SciELO used the drug name. The source strategies are presented in Supplementary Material, Section S1.

The database searches differed in language and publication-type filters. The PubMed English-language restriction and the unrestricted-language SciELO search were retained. During manuscript preparation, the identities and numerical findings of the cited publications were checked against their source reports.

Selection and data handling

Records were managed in Rayyan and screened by two independent reviewers, with discussion or third-reviewer adjudication. Human review of the study-level appraisals was completed by all four authors.

Data extraction covered publication identity, design, population, sample definition, dose, duration, comparator, cardiovascular outcomes, and adverse events. Each source assessment time was retained, and randomized, treated, safety, and outcome-specific populations were distinguished. Unspecified denominators and unreported events were kept separate from numerical observations. Supplementary Material, Section S3, provides the quantitative source locations.

Publications were linked by protocol and participant flow. Two trials reported in one publication were treated separately, and secondary analyses were linked to their parent trial. Unique participants were not summed across rollover cohorts (Supplementary Material, Section S2).

Appraisal and synthesis

Human appraisal of the evidence was performed by all four authors. The appropriate RoB 2 versions were applied to randomized parallel and crossover trials, and JBI criteria were applied to uncontrolled follow-up. Outcome-specific judgments, responses, reasons, and source locations are presented in Supplementary Material, Section S4. These instruments were used to assess pulse and blood pressure, while ECG/QTc findings and cardiovascular adverse events were interpreted separately. JBI item responses were reported without deriving a numerical quality score.

Results were organized by population, comparator, exposure duration, and outcome. Narrative synthesis was performed without meta-analysis. Within-group change was distinguished from a between-group treatment effect, and standard deviations were distinguished from confidence intervals. Acute pharmacodynamic measurements, treatment-endpoint changes, and event-rate estimates were presented separately. Design limitations were considered narratively. GRADE and a formal analysis of bias from missing results were not

performed. The observational studies discussed below were used as contextual evidence.

Results

Selection record and report inventory

A total of 727 records were identified: PubMed 170, Embase 327, Cochrane Library 181, Google Scholar 38, and SciELO 11. After removal of 99 duplicates, 628 records were screened and 557 were excluded by title or abstract. Of 71 reports sought, 47 were retrieved and 24 were not retrieved. Following eligibility assessment, 26 reports were excluded and 21 were included in the review (Figure 1).

The publication inventory characterizes 18 empirical reports and two reviews. Fifteen empirical reports contributed direct cardiovascular results across 15 protocols: Mattingly et al. (2012) and Weisler et al. (2009) describe the same adult-extension protocol, whereas Newcorn et al. (2017) reports two trials. Three other-outcome companions and two reviews were used for context (Coghill, Caballero, et al., 2014; Mattos, 2014). Table 1 and Supplementary Material, Section S2, describe these evidence families and their participant overlap.

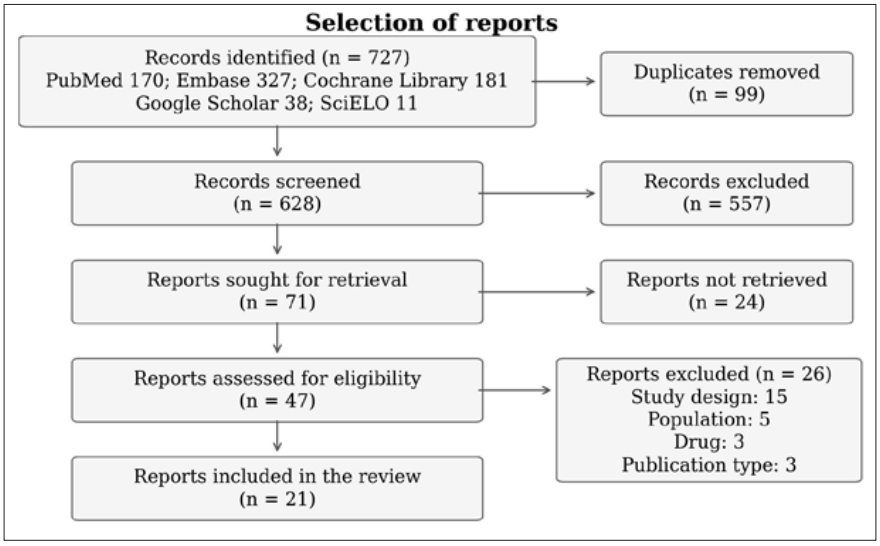


Figure 1: Selection of reports for the systematic review.

Preschool children

The exploratory preschool study included 24 children aged four to five years and used 5–30 mg/day for eight weeks. At week 8 or early termination, mean (standard deviation [SD]) changes were −0.8 (12.75) beats/min in pulse, −1.1 (7.31) mmHg in systolic pressure, and +1.5 (6.93) mmHg in diastolic pressure. Two blood-pressure adverse events were reported without cardiovascular withdrawal. These small-sample findings illustrate variability rather than cardiovascular protection (Childress et al., 2020).

The six-week preschool trial randomized 199 children. Safety analyses included 146 lisdexamfetamine recipients and 45 placebo recipients; the vital-sign summaries included 131 and 41, respectively. All active doses (5, 10, 20, and 30 mg/day) contributed to the pooled cardiovascular results. At week 6 or early termination, mean (SD) pulse changes were +2.7 (10.79) versus +1.2 (9.90) beats/min, systolic changes +1.0 (7.51) versus +0.3 (6.06) mmHg, and diastolic changes +1.7 (5.90) versus 0.0 (6.88) mmHg (Childress, Lloyd, Jacobsen, et al., 2022).

The 52-week preschool study included 113 treated children, with 101 contributing endpoint vital signs and 69 completing follow-up. Mean (SD) pulse, systolic, and diastolic changes were +4.67 (11.000) beats/min, +1.92 (7.729) mmHg, and +3.10 (7.581) mmHg. For 86 rollover children, baseline preceded the antecedent study; 27 entered directly. These populations cannot be summed as independent samples (Childress, Lloyd, Johnson, et al., 2022).

Children and adolescents

The seven-week European trial randomized 336 children and adolescents and included 332 in the safety set. Its safety results report mean (SD) pulse changes of +5.5 (13.2) beats/min with lisdexamfetamine, −0.6 (10.6) with placebo, and +3.4 (13.2) with osmotic-release oral system methylphenidate. Blood-pressure changes were smaller and no formal safety comparisons were performed. The subsequent randomized-withdrawal study addresses maintenance after open-label exposure and selection for response or tolerability, rather than treatment-initiation risk (Coghill et al., 2013; Coghill, Banaschewski, et al., 2014).

In the 104-week European open-label study, 314 participants received treatment and 191 completed follow-up. At the last on-treatment assessment, mean pulse increased by 7.0 beats/min (95% confidence interval [CI], 5.7–8.2), systolic pressure by 3.4 mmHg (95% CI, 2.2–4.5) and diastolic pressure by 3.2 mmHg (95% CI, 2.2–4.2). Mean QTcF changed by −0.6 ms (95% CI, −2.3 to 1.2). These are uncontrolled changes, and the last assessment is not necessarily the 104-week visit (Coghill et al., 2017).

Growth and cognitive publications from that European study describe the same cohort. They provide additional outcome information, rather than two new cardiovascular samples. Some participants had entered from antecedent trials, adding

another source of overlap across publications (Banaschewski et al., 2018; Coghill et al., 2018).

Newcorn et al. (2017) reported two distinct adolescent trials: an eight-week flexible-dose study with 464 randomized participants and a six-week forced-dose study with 549. Mean pulse changes with lisdexamfetamine were +4.7 and +6.7 beats/min, respectively, compared with +0.3 and +2.0 with placebo. Table 2 preserves the outcome-specific denominators and dispersion reported in the publication.

A nine-week comparison in children and adolescents with an inadequate prior methylphenidate response found mean (SD) pulse changes of +3.6 (10.49) beats/min with lisdexamfetamine and +3.7 (10.75) with atomoxetine. Safety populations were 128 and 134, respectively; ECG changes used smaller, visit-specific samples. No participant withdrew because of a clinically significant blood-pressure, pulse, or ECG measurement in that trial (Dittmann et al., 2013).

The school-age extension treated 272 children and reported endpoint mean (SD) pulse +1.4 (13.7) beats/min, systolic pressure +0.7 (10.0) mmHg, and diastolic pressure +0.6 (8.3) mmHg. The adolescent extension included 265 in its safety set and reported +6.3 (12.74) beats/min, +2.3 (10.53) mmHg, and +2.5 (8.37) mmHg, respectively. Both used antecedent-study measurements for baseline in at least some participants; the adolescent changes were explicitly calculated from the antecedent-trial baseline. These are not uniformly new-treatment contrasts. The emotional-control companion supplied no separate cardiovascular dataset (Findling et al., 2008, 2013; Katic et al., 2013).

Table 1: Clinical protocols contributing cardiovascular results

Publication	Population and sample	Lisdexamfetamine exposure	Comparison and interpretation
Childress et al. (2020; preschool)	24; open-label	5–30 mg/day; 8 weeks	No concurrent control; early preschool study
Childress, Lloyd, Jacobsen, et al. (2022)	199 randomized; preschool	5/10/20/30 mg/day; 6 weeks	Placebo; safety denominators differ from efficacy pooling
Childress, Lloyd, Johnson, et al. (2022)	113 safety; preschool	5–30 mg/day; 52 weeks	No control; 86 rollover participants
Coghill et al. (2013)	336 randomized; ages 6–17	30/50/70 mg/day; 7 weeks	Placebo and OROS-MPH reference arm
Coghill, Banaschewski, et al. (2014)	276 open label; 157 randomized	30/50/70 mg/day; 26 weeks then 6-week withdrawal	Continued lisdexamfetamine versus placebo after selection
Coghill et al. (2017); companion reports 2018	314 safety; 191 completers	30/50/70 mg/day; 104 weeks	No control; one cohort, with antecedent-trial participants
Findling et al. (2008)	272 treated; 147 completers; ages 6–12	30/50/70 mg/day; 12 months	No concurrent control; long-term extension
Findling et al. (2013)	265 safety; 269 enrolled; adolescents	30/50/70 mg/day; 52 weeks	No concurrent control; antecedent-trial participants
Newcorn et al. (2017), flexible	464 randomized; 459 safety	30–70 mg/day; 8 weeks	Placebo and OROS-MPH; ages 13–17
Newcorn et al. (2017), forced	549 randomized; 547 safety	Titration to 70 mg/day; 6 weeks	Placebo and OROS-MPH; distinct trial
Dittmann et al. (2013)	267 randomized; 262 safety; ages 6–17	30/50/70 mg/day; 9 weeks	Atomoxetine; inadequate prior methylphenidate response
Adler et al. (2009)	358 lisdexamfetamine + 62 placebo; ages 18–55	30/50/70 mg/day; 4 weeks	Placebo; total includes all arms
Weisler et al. (2009); Mattingly et al. (2012)	349 safety; adult extension	30/50/70 mg/day; 12 months	No control; same cohort in both publications
Dolder et al. (2017)	24 healthy volunteers	Single 100 mg dose; crossover	Equimolar dextroamphetamine and placebo; experimental dose
Ermer et al. (2016)	30 healthy volunteers	Single 70 mg dose per period; crossover	Same capsule intact or mixed in orange juice or yogurt

ADHD, attention-deficit/hyperactivity disorder; OROS-MPH, osmotic-release oral system methylphenidate. Counts refer to the stated randomized or safety population, not a common analysis denominator. Companion reports and rollover participants are not additional independent samples. The complete report inventory is in Supplementary Material, Section S2.

Table 2: Vital-sign changes in two adolescent trials reported by Newcorn et al. (2017)

Trial and treatment	n for vital-sign summaries	Pulse change, beats/min	Systolic pressure change, mmHg	Diastolic pressure change, mmHg
Flexible, lisdexamfetamine	179	+4.7 ± 11.82	+2.4 ± 9.46	+2.8 ± 8.41
Flexible, placebo	89	+0.3 ± 11.32	−0.8 ± 8.97	−1.2 ± 8.11
Flexible, OROS-MPH	184	+6.0 ± 10.52	+0.4 ± 9.90	+2.2 ± 8.64
Forced, lisdexamfetamine	210	+6.7 ± 12.78	+1.6 ± 9.65	+3.3 ± 8.11
Forced, placebo	106	+2.0 ± 10.99	−1.5 ± 9.75	−0.4 ± 8.17
Forced, OROS-MPH	216	+7.6 ± 12.47	+2.6 ± 10.15	+3.3 ± 9.13

Values are mean change from baseline ± standard deviation at the last on-treatment assessment, transcribed from the publication's Table 4. The flexible-dose trial lasted eight weeks and the forced-dose trial six weeks. Denominators reproduce that table and differ from the total safety populations used for adverse-event reporting. They are not confidence intervals or placebo-adjusted estimates. OROS-MPH, osmotic-release oral system methylphenidate.

Adults with attention deficit hyperactivity disorder

In the four-week adult trial, the safety set comprised 358 lisdexamfetamine recipients and 62 placebo recipients. Least-squares mean pulse changes were 0.0 with placebo and +2.8, +4.2, and +5.2 beats/min with 30, 50, and 70 mg/day. Mean blood-pressure differences versus placebo were not statistically significant. Cardiovascular adverse events occurred in 35 lisdexamfetamine recipients and no placebo recipients; seven lisdexamfetamine recipients withdrew for cardiovascular complaints. Using treatment-specific denominators, these proportions are 35/358 (9.8%) and 7/358 (2.0%), calculated from the published counts. The article abstract uses the full 420-person population to report 8.3% and 1.7%; these are not active-treatment risks (Adler et al., 2009).

The adult extension included 349 treated participants and 191 completers. Endpoint mean (SD) changes were +3.2 (11.6) beats/min in pulse, +3.1 (10.7) mmHg systolic, +1.3 (7.6) mmHg diastolic, and +6.2 (18.1) ms in QTcF. Safety baseline was the final antecedent-trial visit for those entering within seven days, or a new screening assessment after a longer interval; it was not uniformly a pretreatment baseline. Mattingly et al. (2012) reanalyzed this same cohort (Weisler et al., 2009).

Healthy volunteers and experimental exposure

Dolder et al. (2017) compared a single 100 mg dose of lisdexamfetamine dimesylate with equimolar dextroamphetamine and placebo in 24 healthy participants. Mean (standard error) absolute maximum heart rates were 94 (3.1), 94 (3.4), and 76 (1.5) beats/min, respectively; corresponding maximum systolic pressures were 157 (3.1), 158 (2.8), and 131 (2.7) mmHg. These are peak absolute measurements, not baseline changes. The experimental lisdexamfetamine dose exceeded usual therapeutic dosing, and a delayed onset did not establish lower peak cardiovascular responses or superior safety.

Ermer et al. (2016) compared a single 70 mg capsule given intact or mixed in orange juice or yogurt in 30 healthy adults. With the intact capsule, mean (SD) pulse change at 12 hours was +14.2 (12.75) beats/min; systolic change at four hours was +20.4 (10.71) mmHg and diastolic change at two hours +10.2 (9.58) mmHg. Similar responses occurred with the mixtures. These results were retained as time-specific acute changes. There was no placebo arm; dextroamphetamine was a measured analyte, not an administered comparator.

Electrocardiography and clinical adverse events

Mean QTcF changes varied across reports and do not establish an absence of individual abnormalities. In the adult extension, one participant had a QTcF increase of at least 60 ms; a reported tracing showed QTcB 511 ms with QTcF 473 ms and normalized on repeat measurement (Weisler et al., 2009). The adolescent extension reported a QTcF of 464 ms, an increase of 71 ms, at an unscheduled visit seven days after termination. That participant had elevated QTcB before extension treatment, and investigators judged the event unrelated. The study also reported five syncope events in four participants, three episodes considered treatment-related; syncope required serious-adverse-event reporting by protocol (Findling et al., 2013).

The European pediatric extension reported one severe, serious arrhythmia considered related to lisdexamfetamine and a previously unrecognized patent foramen ovale, leading to discontinuation. Seven syncope events occurred in six participants; three events were considered treatment-related, and syncope was classified as serious by protocol (Coghill et al., 2017). These counts are presented separately by trial and observation period.

Two lisdexamfetamine recipients in the forced-dose adolescent trial discontinued because of palpitations (Newcorn et al., 2017). Event definitions and observation periods differed across studies, and no unified denominator for rare cardiovascular outcomes could be established. Consequently, this review does not estimate a pooled incidence of arrhythmia, myocardial infarction, stroke, or cardiovascular death. Table 3 summarizes the principal design limitations; the study-level appraisal is in Supplementary Material, Section S4.

Table 3: Design limitations relevant to cardiovascular interpretation

Evidence type	Examples	Limitation	Consequence
Randomized parallel trials	Adler 2009; Coghill 2013; Newcorn 2017	Selected populations, limited duration, safety often secondary	Supports measured short-term changes; limited inference for rare events
Randomized withdrawal	Coghill, Banaschewski, et al., 2014	Randomization after open-label treatment and response/tolerability selection	Maintenance and withdrawal effects do not equal initiation risk
Open-label extensions	Childress long term; Coghill 2017; Findling 2008/2013; Weisler 2009	No concurrent control, attrition, rollover enrollment	Observed changes cannot be assigned a placebo-adjusted causal effect
Experimental crossover	Dolder 2017; Ermer 2016	Healthy volunteers, single-dose regimens, short observation	Acute pharmacology does not establish chronic clinical-event risk
Companion and contextual reports	Banaschewski 2018; Coghill 2018; Mattingly 2012; Katic 2013; reviews	Shared participants, different primary outcomes, secondary synthesis	No additional independent cohort or formal certainty rating

Design limitations are summarized in Table 3, and the outcome-specific appraisal and its source evidence are presented in Supplementary Material, Section S4.

Discussion

Physiological effects and their interpretation

The most reproducible finding is an average increase in pulse and, in several studies, blood pressure during lisdexamfetamine exposure. Magnitude depends on dose, population, comparison and assessment time. An uncontrolled change over an extension cannot be interpreted as the same effect as a placebo-adjusted difference in a randomized trial. Similarly, a small group mean does not describe every participant or exclude clinically important outliers.

Prodrug activation explains part of the exposure profile but cannot serve as a cardiovascular safety endpoint. Pharmacokinetic bioequivalence, delay in peak exposure and symptom efficacy address different questions from arrhythmia or vascular outcomes. The acute healthy-volunteer studies are useful for pharmacology, but their screening, single-dose conditions and experimental regimens limit translation to routine long-term care (Dolder et al., 2017; Ermer et al., 2016).

Clinical events and contextual epidemiology

Larger observational studies provide context for endpoints that small trials cannot resolve. In Denmark and Sweden, Forns et al. (2022) compared lisdexamfetamine initiators with people who had previously used other ADHD medications. The pooled adjusted incidence-rate ratio for major cardiovascular and cerebrovascular events was 1.10 (95% CI, 0.77–1.58). The comparator was not concurrent active treatment or lifelong nonuse. The interval remains compatible with both lower and higher rates, and residual confounding limits causal interpretation.

Zhang et al. (2024) examined a broader composite of incident cardiovascular disease in Swedish records. In the lisdexamfetamine-specific analysis, adjusted odds ratios were 1.23 (95% CI, 1.05–1.44) for more than two and up to three years of cumulative exposure and 1.17 (95% CI, 0.98–1.40) beyond three years. These categories do not establish a decline in risk within the same people. Class-level estimates for all ADHD medications cannot be relabeled as lisdexamfetamine-specific.

These studies evaluate different endpoints and exposure definitions. A broad disease composite that includes hypertension is not interchangeable with hospitalization for myocardial infarction or stroke and out-of-hospital vascular death. Observational estimates were not pooled with physiological changes, and these studies were used as contextual evidence rather than added retrospectively to the selection flow.

Applicability and clinical monitoring

Many trials enrolled participants without major cardiovascular disease and excluded relevant electrocardiographic abnormalities or uncontrolled hypertension. Their findings are consequently most applicable to selected, monitored populations. Extension studies can further enrich for people who tolerate treatment, while loss to follow-up may obscure later outcomes. Evidence from screened healthy volunteers is particularly indirect for older patients with ADHD and comorbidity.

Clinical guidance supports baseline cardiovascular assessment and monitoring matched to symptoms and risk. NICE recommends checking pulse and blood pressure before and after dose changes and every six months, with electrocardiography guided by clinical indications rather than routine use for every patient. These are external clinical recommendations, not outcomes demonstrated by this review (National Institute for Health and Care Excellence [NICE], 2018).

Clinical interpretation integrates pulse, blood pressure, and symptoms with treatment benefit, dose, concomitant medications, and baseline cardiovascular risk.

Limitations of the evidence and review process

The underlying evidence is heterogeneous in age, dose, design, exposure duration and measurement. Most trials were not powered for rare cardiovascular events, and selected populations limit applicability. Open-label studies lack a concurrent counterfactual, while companion publications and rollover participants preclude an unqualified total sample size. Mean QTc results do not exclude individual abnormalities or clinical arrhythmia.

The search used different language and publication-type filters across databases. These restrictions may have reduced retrieval of observational evidence. Twenty-four reports could not be retrieved. The source strategies retained for the review are presented in Supplementary Material, Section S1, and the 20 identifiable publications are characterized in Section S2.

The structured appraisal focused on pulse and blood-pressure outcomes. ECG/QTc findings and clinical adverse events were interpreted separately. A formal certainty assessment and an analysis of bias from missing results were not performed. These choices, along with clinical and methodological heterogeneity, inform the scope of the conclusions.

Research priorities include measurement of sustained hypertension, rhythm outcomes, major vascular events, and treatment discontinuation as distinct outcomes, using explicit definitions and longer follow-up in patients with clinically relevant baseline risk.

Conclusion

Lisdexamfetamine commonly increases average pulse and blood pressure in selected clinical populations, with substantial individual and between-study variation. QTcF findings are not uniformly increased, but individual ECG abnormalities, arrhythmia, syncope, and cardiovascular withdrawals require acknowledgment. Short trials and uncontrolled extensions cannot establish the absence of rare cardiovascular events or cumulative risk.

Therapeutic and experimental exposures, adults and children, and physiological and clinical outcomes require separate interpretation. Baseline cardiovascular assessment and ongoing monitoring remain relevant to treatment decisions, particularly when patients differ from the selected populations studied.

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Declarations

Ethics approval and consent

This review analyzes previously published aggregate findings and involved no new recruitment or access to identifiable individual participant data. Research ethics approval and individual participant consent were not applicable to this secondary review.

Data availability

The evidence sources, publication inventory, search strategies, result extraction, and study-level appraisal are identified in the manuscript and Supplementary Material. No new participant-level dataset was generated. The retained material does not include a complete original screening export or report-level exclusion file.

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Competing interests

The authors declare no competing interests.

Author review

Review of the study-level appraisals was completed by the four-author team, and the selection counts and manuscript were finalized.

Use of artificial intelligence

ChatGPT (OpenAI) was used to support English-language revision only.

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