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Dose–response relationships of multiple drug-induced hypothermia: a meta-analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 September 2026 and was last updated on 19 September 2026.

INTRODUCTION

Review question / Objective To quantify and compare the hypothermic potency (dose–response slope β), efficacy (maximum observed cooling) and dose–response curve shape of drugs that lower body temperature, and to assess the consistency of dose-dependent cooling across pharmacological classes and species (rodents, non-rodent mammals and humans), including the testing of non-linearity with no-intercept restricted cubic splines and the comparison of rat and mouse study-level slopes.

Rationale Pharmacologically induced hypothermia — core cooling by drugs that suppress heat production or promote heat loss — offers a simple and inexpensive alternative to device-based cooling. However, existing studies are mostly single-drug or single-class reports, and systematic cross-drug, cross-species quantitative comparisons remain limited: potency and efficacy are rarely reported on a common metric, dose–response curve shape has seldom been examined, and animal and human dose–response data have rarely been linked. A quantitative basis for choosing among hypothermia-inducing drugs is therefore lacking. This review addresses these gaps by fitting unified no-intercept regressions across 49 studies covering 31 drugs, defining potency (slope β), efficacy (maximum observed cooling) and effective dose range for each drug, and pooling study-level slopes with random-effects meta-analysis.

Condition being studied The condition of interest is drug-induced hypothermia — the lowering of body temperature by drugs that suppress heat production or promote heat loss — and its therapeutic application as targeted temperature management for neuroprotection after cardiac arrest, neonatal hypoxic–ischaemic encephalopathy, ischaemic stroke and other acute brain injuries, as well as perioperative temperature management. This review characterises the dose–response properties of candidate hypothermia-

inducing drugs across pharmacological classes and species.

METHODS

Search strategy Six electronic databases were searched: PubMed, Embase, Web of Science, the Cochrane Library, Wanfang Data and CNKI (from database inception to 13 April 2026), using a combination of MeSH terms and free-text words. Condition and outcome terms: "Hypothermia, Induced" (MeSH), "Body Temperature" (MeSH), "therapeutic hypothermia", "targeted temperature management", "artificial hibernation", "hypothermia therapy" and "body cooling", together with their Chinese equivalents. Drug terms: dexmedetomidine, propofol, apomorphine, chlorpromazine, bromocriptine, tetrahydrocannabinol, sedatives and anesthetics. Term groups were combined with AND; terms within groups with OR. The reference lists of all included studies were additionally screened record by record (citation tracing). The complete search strategies for all six databases are provided in Supplemental Data S2.

Participant or population The review includes both animal experiments and human studies. Animal studies: rats, mice, gerbils, cats and monkeys (all sexes, strains and ages). Human studies: perioperative patients receiving dexmedetomidine or propofol, and healthy participants receiving melatonin. No restriction on sex, age or health status was applied; the population of interest is any participant or experimental animal in which drug-induced change in body temperature was measured at two or more non-zero dose levels with a zero-dose control.

Intervention Administration of any drug reported to lower body temperature, across pharmacological classes: antipsychotics, dopamine receptor agonists, cannabinoids, α_2-adrenoceptor agonists, GABAergic/anaesthetic-related agents, opioids, serotonergic compounds, cholinergic and neurotensin ligands, and peripherally acting compounds (31 drugs in total). All doses, routes of administration, timings and frequencies are eligible, provided that body-temperature change was reported at two or more non-zero dose levels in addition to a zero-dose control.

Comparator The comparator is the zero-dose control group of each included study, typically treated with physiological saline or the vehicle in which the drug was dissolved (saline, distilled water or the corresponding solvent). The temperature change of every dose group is referenced to this saline/vehicle control, so that $\Delta T = 0$ at dose 0.

Study designs to be included Animal experimental studies with a parallel-group design, a zero-dose control and at least two non-zero dose levels, and human clinical studies including randomised controlled trials (dexmedetomidine) and experimental volunteer studies (propofol, melatonin). Excluded: single-dose designs, reviews, conference abstracts, duplicate publications and studies without available full text.

Eligibility criteria Additional inclusion criteria: no publication-date restriction (database inception to the search date); no language restriction (English- and Chinese-language reports are both eligible); any publication type with usable quantitative dose–response temperature data. Additional exclusion criteria: reviews, systematic reviews, conference abstracts and duplicate publications; records with no full text available; and studies whose temperature data could not be converted to group means ± SE.

Information sources Electronic databases: PubMed, Embase, Web of Science, the Cochrane Library, Wanfang Data and CNKI (searched from database inception to 13 April 2026). Additional sources: the reference lists of all included studies, screened record by record (citation tracing). Trial registers and grey literature were not searched, and authors of included studies were not contacted.

Main outcome(s) Primary outcome: drug-induced change in body or core temperature (ΔT, °C), a continuous measure extracted for each dose group as mean ± SE (SD converted to SE as $SD/\sqrt{n}$). Effect measures derived from these data: (1) potency — the no-intercept regression slope β (°C per mg/kg; °C per μg/kg for human dexmedetomidine and °C per μg/mL for propofol); and (2) efficacy — the maximum observed cooling (°C). All dose-group values are referenced to the study's own zero-dose control, so that $\Delta T = 0$ at dose 0.

Additional outcome(s) Secondary outcomes: (1) non-linearity of the dose–response relationship, assessed by comparing no-intercept linear and restricted cubic spline (RCS) models with ANOVA and reported as P values with model R^2; (2) between-species consistency — the difference between rat and mouse study-level slopes (subgroup difference P) and the direction of effects in cat, monkey and human studies; and (3)

between-study heterogeneity of pooled slopes, reported as τ^2, I^2 and the Cochran Q test P value.

Data management Database records were managed in EndNote, where automated deduplication was performed (159 duplicates removed) and automated tools flagged ineligible records. Data extracted from the included studies were managed in spreadsheets (Microsoft Excel), with dose-group rows keyed by study ID. All statistical analyses were conducted in R 4.6.0 using the meta, rms and splines packages. The complete raw dataset (all dose groups) and the full search strategies are provided as Supplemental Data S1 and S2.

Quality assessment / Risk of bias analysis Two investigators will independently assess the methodological quality of all included animal studies with the SYRCLE risk-of-bias tool, covering sequence generation, baseline characteristics, allocation concealment, random housing, blinding of caregivers, random outcome assessment, blinding of assessors, incomplete outcome data, selective reporting and other sources of bias; each item will be rated "low risk", "unclear" or "high risk". Human studies will be assessed with the corresponding items where applicable. Disagreements will be resolved by discussion with a third investigator. Results will be presented as a risk-of-bias summary.

Strategy of data synthesis Dose–response relationships will be fitted by no-intercept linear regression ($\Delta T = \beta \times \text{Dose}$), with the regression slope β as the effect measure. Two complementary strategies will be used: one-stage pooled ordinary-least-squares regressions for dose–response curve display, and a two-stage meta-analysis in which study-level slopes are pooled with inverse-variance random-effects models (REML). Between-study heterogeneity will be quantified with τ^2 and I^2 and the Cochran Q test; sources of heterogeneity will be explored with Baujat decomposition and species subgroup analyses (rat versus mouse). Non-linearity will be tested by comparing no-intercept linear and restricted cubic spline (RCS, three knots) models with ANOVA. Sensitivity analyses will include leave-one-out analyses and exclusion of studies with extreme dose ranges (Davies 1980; Asanami 2000) and of McMahon (2007; 0–100 mg/kg). No overall cross-drug pooling will be performed; results will be interpreted per drug. Analyses will be conducted in R 4.6.0 (meta, rms and splines packages).

Subgroup analysis Planned subgroup analyses will compare study-level slopes between rat and mouse studies for drugs with two or more studies in each species (THC: rat k = 8 versus mouse k = 3; apomorphine: rat k = 2 versus mouse k = 4), with subgroup difference P values obtained from random-effects pooling. Species-stratified non-linearity testing (rat-only and mouse-only restricted cubic spline tests) will also be performed for THC and apomorphine. No other subgroup analyses are planned; the non-rodent (cat, monkey) and human data will be examined descriptively as cross-species validation.

Sensitivity analysis For the pooled slopes of THC, apomorphine and γ-hydroxybutyrate, leave-one-out analyses will be performed (excluding each study in turn) to assess the influence of individual studies, and Baujat decomposition will identify the studies contributing most to heterogeneity. A pre-specified sensitivity analysis will additionally exclude McMahon (2007; 0–100 mg/kg, a dose range matching Davies 1980) from the THC analyses. Studies with extreme dose ranges (Davies 1980, THC, 0–100 mg/kg; Asanami 2000, chlorpromazine, 0–250 mg/kg) will be excluded from all pooled analyses. For the THC non-linearity tests, species-stratified and species-adjusted models will serve as sensitivity checks.

Language restriction No language restriction; English- and Chinese-language reports are eligible.

Country(ies) involved China.

Other relevant information This registration is retrospective: the review has been completed and is being submitted for publication (registered during the submission process). The review follows the PRISMA 2020 statement; completed PRISMA 2020 checklists (main and abstract) accompany the manuscript. The full raw dataset (all dose groups) is provided as Supplemental Data S1, the complete search strategies for all six databases as Supplemental Data S2, and source data accompany every figure. The review received no specific funding.

Keywords therapeutic hypothermia; drug-induced hypothermia; dose–response; thermoregulation.

Dissemination plans The results will be disseminated through publication in a peer-reviewed journal. The full raw dataset (all dose groups), the complete search strategies for all six databases and the source data for every figure will be made publicly available alongside the publication as Supplemental Data S1 and S2.

Contributions of each author

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