The effect of prescription and over-the-counter medications on core temperature in adults during heat stress: a systematic review and meta-analysis

Lily Hospers,[a] Gabrielle A. Dillon,[b,c] Andrew J. McLachlan,[d] Lacy M. Alexander,[b] W Larry Kenney,[b] Anthony Capon,[e] Kristie L. Ebi,[f] Edward Ashworth,[a] Ollie Jay,[a,g,**] and Yorgi Mavros[a,g,*]

[a]Heat and Health Research Centre, Faculty of Medicine and Health, University of Sydney, Sydney, Australia
[b]Noll Laboratory, Department of Kinesiology, The Pennsylvania State University, University Park, State College, PA, USA
[c]Department of Health and Kinesiology, University of Illinois, Urbana, IL, USA
[d]Sydney Pharmacy School, Faculty of Medicine and Health, University of Sydney, Sydney, Australia
[e]Monash Sustainable Development Institute, Monash University, Melbourne, VIC, Australia
[f]Center for Health and the Global Environment, University of Washington, WA, USA

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Summary

Background Heat stress impacts are an escalating global health concern. Public health bodies such as the World Health Organization (WHO) warn that certain medications impair thermoregulation, with limited supporting evidence. Our aim was to investigate whether medications listed by the WHO increase core temperature responses during heat stress.

Methods For this systematic review and meta-analysis, MEDLINE, PubMed, Scopus, CINAHL, Web of Science, and EMBASE were searched up to Jan.30, 2024. Randomised studies exposing humans to exertional and/or passive heat stress that investigated a drug identified by WHO compared to no drug/placebo were eligible. The primary outcome was core temperature (e.g., rectal, oesophageal, aural, tympanic). We assessed risk of bias (Cochrane's Risk of Bias 2) and certainty of evidence (GRADE). The study was pre-registered on PROSPERO (CRD42020170684).

Findings Thirty-five studies were included enrolling 353 individuals (16 women; 4.5%). Twenty-seven unique medications were tested. The average age of participants across studies was <30 years, and only one study included a clinical population. Under heat stress, there was moderate quality evidence that drugs with high anticholinergic properties increased core temperature at air temperatures ≥30°C (+0.42°C; 95% CI 0.04, 0.79°C; p = 0.03) alongside reduced sweating, although evidence is limited to the drug atropine. Similarly, non-selective beta-blockers (+0.11°C; 95% CI 0.02, 0.19°C; p = 0.02), adrenaline (+0.41°C; 95% CI 0.21, 0.61°C) and anti-Parkinson's agents (+0.13°C; 95% CI 0.07, 0.19°C; p = 0.02) elevated core temperature. Antidepressants, diuretics, or drugs with weak anticholinergic effects did not alter core temperature responses.

Interpretation Current evidence supports strong anticholinergics, non-selective beta-blockers, adrenaline, and anti-Parkinson's agents impairing thermoregulation during heat stress. No evidence indicated thermoregulation is impacted by other WHO-listed medications. Evidence is predominantly limited to healthy young men, with short heat stress exposures. Studies over longer durations, in women, older adults and those with chronic diseases are required to better inform the pharmaceutical management of patients during hot weather.

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Keywords: Drugs; Heat illness; Medications; Thermoregulation

*Corresponding author. Heat and Health Research Centre, University of Sydney, Camperdown, NSW 2006, Australia.
**Corresponding author. Heat and Health Research Centre, University of Sydney, Camperdown, NSW 2006, Australia.
E-mail addresses: yorgi.mavros@sydney.edu.au (Y. Mavros), ollie.jay@sydney.edu.au (O. Jay).
[g]Co-senior authors.

Research in context

Evidence before this study

Guidance from public health agencies such as the World Health Organization (WHO) state that certain medications can increase the risk of heat-related illness during hot weather. However, no supporting evidence for this guidance is provided. We searched (1 April, 2020) PubMED using keywords of "medication" OR "drugs" AND "heat illness" OR "thermoregulation" OR "core temperature", and filtering for systematic reviews. We found one systematic review on non-steroidal anti-inflammatory drugs (NSAIDs) and thermoregulation during exercise, and narrative reviews focussing on biological pathways. However, no systematic reviews of the drugs commonly referred to by public health agencies as increasing the risk of heat-illness were found.

Added value of this study

This is the first systematic review to investigate whether drugs commonly identified by public health agencies as increasing the risk of heat-related illness cause an exacerbated core temperature response to heat stress. Thirty-five studies were found, with 10 of the 11 drug categories identified by the WHO studied. Our study shows that current evidence supports heightened hyperthermia risk with only some medications identified by the WHO as impairing thermoregulation during heat stress. Our study particularly highlights the paucity of studies examining the effects of antipsychotics and antidepressants with strong anticholinergic properties, as well as a scarcity of data in women and people with chronic diseases for all medications.

Implications of all the available evidence

While more research assessing women, and clinical populations is urgently needed, physicians should interpret with caution conventional public health messaging related to the thermoregulatory effects of some drugs (e.g., antidepressants) during hot weather.

Introduction

As hot weather becomes more common across the globe due to climate change, identifying and protecting those most vulnerable to heat-related illnesses has never been more important. Simultaneously, prescription medication use is increasing with 88.5% of U.S. adults aged 65 years or older taking at least one prescription medication daily.[1] Across most international (World Health Organization, WHO)[2,3] and national public health agencies (e.g., Centers for Disease Control and Prevention,[4] Public Health Agency of Canada,[5] United Kingdom Health Security Agency)[6] there is consistent messaging that "certain medications" increase the risk of hyperthermia by impairing the physiological capacity to regulate core temperature. The WHO explicitly state that General Practitioners should subsequently "*be aware of potential side-effects of the medicine prescribed and adjust dose, if necessary, during hot weather and heat-waves*".[7]

Epidemiological evidence[8–11] indicates taking medications to manage psychiatric illness or cardiovascular disease, or medications with high anticholinergic activity are associated with two-times the risk of heat-related morbidity and mortality. There is good biological plausibility that drugs identified by the WHO may increase heat stress risk through suppressed sweating (e.g., anticholinergics), reduced skin blood flow through depletions in blood volume (e.g., diuretics) or alterations to haemodynamics (e.g., beta-blockers), and/or elevated internal heat production (e.g., sympathomimetics).[12] To date though, no literature review exists that systematically assesses the evidence of medications impairing thermoregulation in the heat.

To inform clinical and pharmaceutical practice and the delivery of health services when preparing for, or coping with, periods of extreme heat, a comprehensive understanding of the evidence documenting the actual effects of common drugs on human core temperature regulation during heat stress is essential. Therefore, the aim of this study was to systematically review and investigate the quality of the evidence reporting the effects of prescription, or over-the-counter medications listed by the WHO as impairing physiological thermoregulation, on human core temperature responses during heat stress.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis were registered with PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020170684). Reporting is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement,[8,9] and extension for Reporting Literature Searches in Systematic Review (PRISMA-S).[10] Electronic databases MEDLINE, PubMed, Scopus, CINAHL, Web of Science, and EMBASE were searched from date of inception until the 30th of January 2024 using a mix of MeSH terms and keywords related to a) prescription or over-the-counter drug classes listed by the World Health Organization as impairing human thermoregulation during heat stress[11]; AND b) heat exposure, thermal strain, and physiological heat loss mechanisms. The full search strategy, including search terms and databases search can be found in the appendix (Supplementary Tables S1 and S2; pp 13–21). Preprints, trial registries and theses were not searched, and unpublished studies were not eligible. Hand searching for additional papers was conducted by LH

through forward and backward citation searching of eligible papers, reference lists of eligible papers and other relevant papers and reviews, as well as author searches of all first and last authors from eligible studies.

Eligibility criteria were as follows: All studies in humans were included, with no age, gender or disease restrictions. Studies were required to investigate a prescription or over-the-counter medications belonging to classes identified by the WHO as increasing the risk of heat-related illness. Only drugs approved for therapeutic use by a major agency, e.g., U.S. Food and Drug Administration were included. Illicit drugs and poisons were excluded. Drugs must have been administered using a therapeutic dose with a normal administration route. Systemic effects must have occurred if a different administration route (e.g., intravenous injection) was used. Studies with drugs only administered for local effects (e.g., microdialysis) were excluded. A placebo or comparison condition with the same heat stress was required, with the order of experimental and control conditions randomised. Studies with a control period immediately followed by drug administration were excluded. The primary outcome was change in core temperature (rectal, oesophageal, tympanic, aural canal, sublingual). Secondary outcomes included sweat rate and skin temperature. Potential heat stressors include exercise (increased metabolic heat), high ambient temperatures, or a combination, if comparisons across intervention and control conditions were possible. Experiments must have occurred in a controlled climate, with ambient air temperatures ≥25°C for passive heating studies and no minimum for exercise. A minimum exposure or exercise time of 30 min was required. In crossover design studies, exercise could be set as fixed workloads or percentages of aerobic capacity. We ensured exercise prescribed by percentage of maximal heart rate resulted in equivalent workloads between conditions. In parallel design studies, heat production from exercise had to be fixed relative to body mass. Time-to-exhaustion and time-trial studies were included if data could be extracted for a fixed workload period or common time. No other restrictions were placed on exercise modality, workload, or the ambient conditions so long as they were consistent between trials. Studies without standardised conditions and heat production, or using encapsulated heating like water immersion or water-perfused suit were excluded.

Screening was performed using Covidence software (Veritas Health Innovation, Melbourne, Australia, www.covidence.org). Three authors screened papers (LH, GD, EA), with all stages of screening (title, abstract and full text) performed in duplicate. All conflicts were resolved by consensus with YM. Studies measuring any outcome related to human thermoregulation (e.g., sweating, blood flow or skin temperature) were progressed to full-text screening to maximise sensitivity.

Data extraction

LH and YM extracted and analysed the data. LH extracted summary-level data, including design, drug and dose investigated, heat-stress protocol (ambient conditions and exercise protocol), and participant characteristics such as age, sex and clinical status. The primary outcome was core temperature, measured with any valid method (rectal, oesophageal, sublingual, axillary, tympanic, aural).[12] Other outcomes extracted were skin temperature or measures of sweat rate. Baseline and last common time-point core temperatures, and last common time-point sweat rate and skin temperatures were extracted. For single studies with multiple citations, data were extracted from the most complete report, and supplemented with associated citations. Data presented in figures were extracted with WebPlotDigitizer (v4.5).[13] Numerical data were extracted as mean and standard deviation (SD). If not reported, SD was calculated from standard error, confidence intervals or p-values as per the Cochrane Handbook.[14]

Statistics

Effect sizes for core temperature are given as the difference in mean change from baseline to end-heat stress between conditions, reflecting differences in body heat storage.[15] For sweat rate, effect sizes are standardised mean differences (Cohen's *d*), calculated by dividing end-trial mean difference between conditions by pooled standard deviation. Skin temperature effect sizes are end-heat stress mean differences between conditions. All effect sizes include 95% confidence intervals (95% CIs) and are statistically significant if 95% CIs do not include 0. Drugs were categorised into classes identified by WHO as impairing thermoregulation during heat stress (e.g., beta-blockers, antidepressants).[2,3] Anticholinergic burden was scored using the Anticholinergic Burden (ACB) Score Calculator,[16–18] with Pralidoxime given an ACB score of 1. For drug combinations, ACB scores were summed. Drugs were classified as 1 (mild anticholinergic burden), 2 (moderate anticholinergic burden) or 3 (high anticholinergic burden). YM performed the meta-analysis using metafor (v4.4-0)[19] within R (v4.3.2). A random-effects meta-analysis with restricted maximum likelihood estimation was run. When there were multiple effect sizes from the same study, a multilevel random effects meta-analysis was performed with effect sizes clustered within studies. Pooled effect sizes are reported with 95% CIs and p-values. Heterogeneity is reported using the I^2 statistic.[14] Heterogeneity was explored by restricting meta-analyses to air temperatures ≥30°C, and where appropriate, categorising drugs into sub-classes (e.g., selective and non-selective beta-blockers, selective serotonin reuptake inhibitors). Meta-analyses were re-run by restricting analyses to studies using rectal or oesophageal temperature. Moderator analyses compared selective and non-selective beta-blockers. Because of an insufficient

number of effect sizes other moderator analyses were not performed. p-values ≤ 0.05 were considered statistically significant.

To assess for publication bias, funnel plots for analyses with ≥10 effect sizes were inspected for evidence of asymmetry, while hat values and standardised residuals also calculated and plotted. Effect sizes with a standardised residuals >±3 and hat values greater than twice the average were defined as potentially influential. Sensitivity analyses for random effects models were run by calculating Cook's distance at both the effect and study level. Effect sizes or studies with a Cook's distance ≥1 were removed and meta-analyses were re-run.

LH and YM assessed risk of bias using Risk of Bias 2 (RoB2)[20] and the quality of evidence using GRADE.[14,21] Risk of bias figures were created using the Robvis.[22]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Following duplicate removal, 31,330 articles were screened by title and abstract. Two-hundred and eighty-three studies underwent full-text screening, with 35 studies (39 citations)[23–61] and 57 effect sizes (k = 57) included (Fig. 1). Common reasons for exclusion were no heat stress (24%) and no randomisation (13%). Twenty-seven different drugs were tested across 10 of the 11 WHO drug classes identified as impairing thermoregulation during heat stress. The most tested drugs were anticholinergics, antidepressants (with a mild anticholinergic burden), and beta-blockers. Only one study of over-the-counter medication (fexofenadine) was retrieved.[62] Only two studies tested drug combinations.[28,35] Five studies (14%) used dosing regimens lasting four days or longer, with all other studies examining acute doses, or doses from the day/night before or morning of the experiment. No studies tested anticonvulsant, anti-vertigo, gastrointestinal or urinary incontinence drugs.

In total, 353 individuals were enrolled. Of the 35 studies, 33 (94%) recruited men only, one recruited women only, and one study recruited both men and women. In total, only 16 women (4.5%) but 337 men (95.5%) were recruited. Most studies (30/35; 86%) included fewer than 12 participants. Average age across all studies was less than 30 years. All participants were healthy (34/35 studies) except for one study that investigated untreated males with mild hypertension.[51] Most studies (29/35; 83%) included exercise (k = 49), mainly through cycling (22 studies; k = 40). Six studies (k = 8) involved passive heat exposure. Ambient temperatures ranged from 18°C to 52°C, with forty-one comparisons (k = 41) at air temperatures ≥30°C. Absolute humidity ranged from 5.7 g/m^3 to 52.3 g/m^3. Exposure duration ranged from 30 to 210 min. Rectal (23/35; 66%) and oesophageal (8/35; 23%) were the most common measures of core temperature. Detailed participant and study characteristics are given in the appendix (Supplementary Tables S3 and S4; pp 22–28). Two studies were excluded due to insufficient data to calculate standard deviations,[62,63] while one water immersion[64] and one water-perfused suit study[65] were excluded. These study results are summarised in the Appendix (pp 5–12).

Two drugs with ACB = 3 (k = 8), three (k = 5) with ACB = 2 and eleven (k = 23) with ACB = 1 were captured (Fig. 2). Drugs with ACB = 3 yielded greater rises in core temperature at ≥30°C (+0.42°C; 95% CI 0.04, 0.79°C; p = 0.03; I^2 = 93%; GRADE = Moderate), with large sweating reductions (d = –2.4; 95% CI –4.6, –0.2; p = 0.04, I^2 = 0%) and higher skin temperatures (+2.9°C; 95% CI 2.0, 3.7°C; p = 0.0003, I^2 = 80%). No effect on core temperature was observed for drugs with ACB = 2 (p = 0.52; GRADE = Low) or ACB = 1 (p = 0.27; GRADE = Moderate), including studies ≥30°C (p = 0.54 and p = 0.33 respectively). There were no differences in sweating or skin temperature for drugs with ACB≤2.

Ten randomised controlled trials investigated psychotropic medications (Fig. 3). Eight studies tested antidepressants, namely atypical antidepressant bupropion (k = 7), selective serotonin reuptake inhibitors (SSRI) citalopram (k = 2) and paroxetine (k = 1), and the noradrenaline reuptake inhibitor (NRI) reboxetine (k = 2). Compared to control, there was no effect of antidepressants on core temperature when pooled across all conditions (–0.01°C; 95% CI –0.14, 0.12°C; p = 0.88; I^2 = 61%; GRADE = Moderate), or at ≥30°C (–0.04°C; 95% CI –0.14, 0.06°C; p = 0.36; I^2 = 0%; GRADE = Moderate). No sweating data were reported for any antidepressants. Two studies of bupropion measured skin temperature, with no effect observed (0.06°C; 95% CI –0.39, 0.52°C; p = 0.68; I^2 = 0%). One antipsychotic, haloperidol, was examined (k = 2) with smaller rises in core temperature (–0.15°C; 95% CI –0.26, –0.03°C; p = 0.01; I^2 = 72%; GRADE = Low) compared to control, but sweating and skin temperature were not measured. Meprobamate was the only anxiolytic tested (k = 2) with no effect on core temperature (+0.06°C; 95% CI –0.05, 0.16°C; p = 0.09; I^2 = 0%; GRADE = Low). Sweating was not measured, while skin temperature was not altered (+0.04°C; 95% CI –0.14, 0.22°C; p = 0.66; I^2 = 42%).

Cardiovascular agents tested (beta-blockers, vasodilators, diuretics) are shown in Fig. 4. Beta-blockers were the most tested drug (k = 16), specifically propranolol (k = 9), atenolol (k = 5), metoprolol (k = 1) and pindolol (k = 1). When pooled together, beta-blockers did not alter the rise in core temperature (+0.08°C; 95% CI –0.01, 0.16°C; p = 0.07; I^2 = 84%; GRADE = Low).

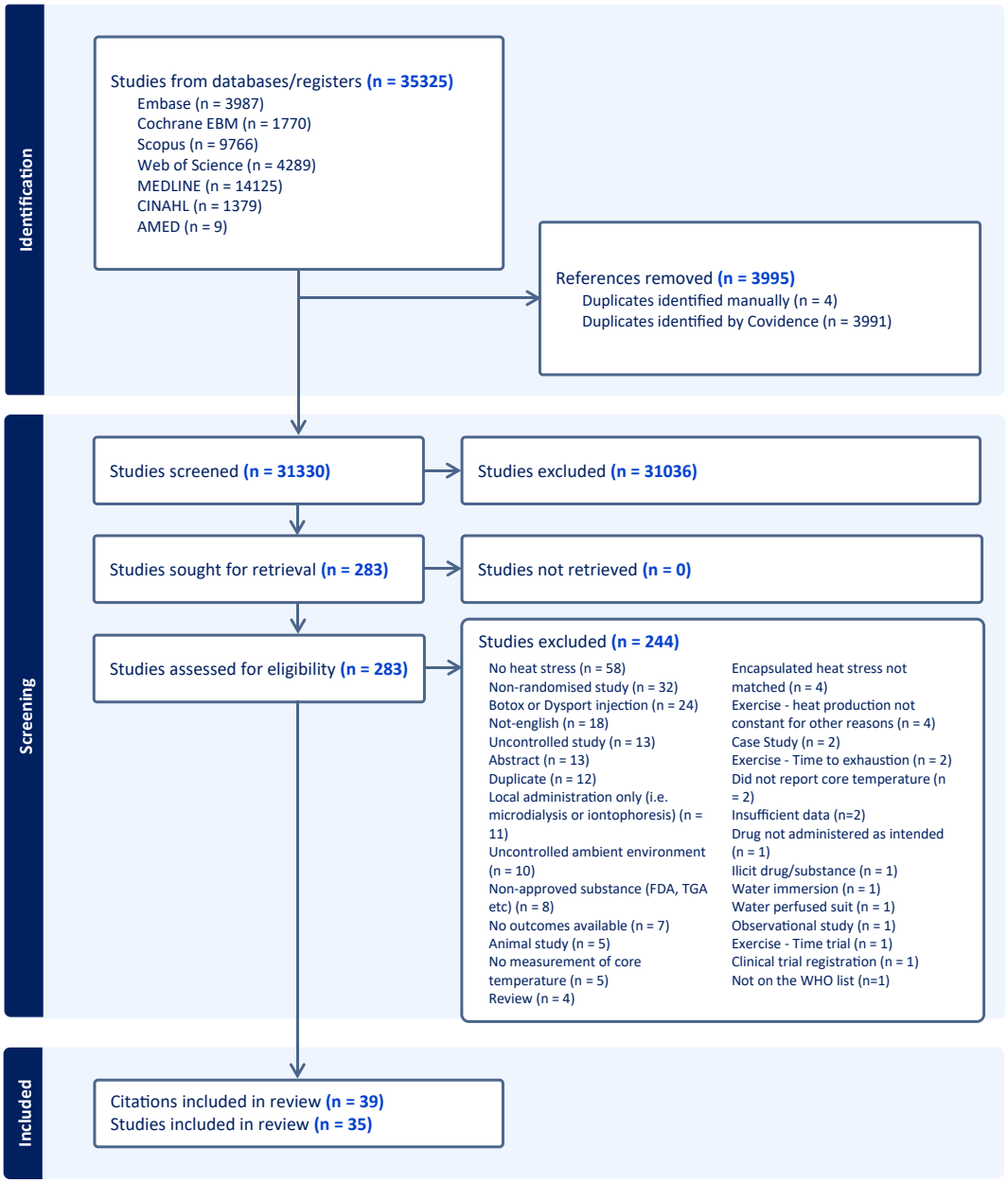

Fig. 1: **PRISMA flow diagram**.

There were no changes in sweating (d = 0.25; 95% CI –0.33, 0.85; p = 0.33; I^2 = 27%), but skin temperature was lower (–0.37°C; 95% CI –0.65, –0.09; p = 0.01; I^2 = 97%). Core temperature results are consistent with analyses restricted to air temperatures ≥30°C (+0.06°C; 95% CI –0.05, 0.18°C; p = 0.24; I^2 = 90%; GRADE = Low). There was a moderating effect of non-selective vs. selective beta blockers (p = 0.03) with greater core temperature rises for non-selective beta-blockers (+0.11°C; 95% CI 0.02, 0.19°C; p = 0.02; I^2 = 71%; GRADE = Moderate) but not selective beta-blockers (–0.02°C; 95% CI –0.15, 0.10°C; p = 0.64; I^2 = 62%; GRADE = Moderate). Lower skin temperatures were observed with non-selective beta-blockers (–0.46°C; 95% CI –0.81, –0.12; p = 0.01; I^2 = 96%), but sweating was unaffected (d = 0.33; 95% CI –0.30, 0.97; p = 0.22; I^2 = 97%). Sweating and skin temperature was not altered with selective beta-blockers (p = 0.32 and p = 0.22 respectively).

Four studies (k = 4) assessed vasodilators, all at ≥30°C: two assessed an alpha-1 blocker (prazosin), one an alpha-2 agonist (clonidine), and one a calcium-channel

Current WHO Health Messaging		GRADE Assessment; Outcome = Change in Core temperature (°C)		Systematic Review
Medication	Proposed Mechanism	Relative effect (95% CI)	Quality of the evidence	Summary of Evidence
Anticholinergics	"Can affect central thermoregulation… and prevent or reduce sweating."[1] "…anticholinergic medications, could results in a rise of body temperature that can culminate in life-threatening heatstroke."[2]	Anticholinergic burden score = 3 ≥30°C air temp: +0.42 [0.04, 0.79] All: +0.27 [-0.15, 0.70]	⊕⊕⊕◯[a] Moderate ⊕⊕◯◯[ab] Low	There is MODERATE quality evidence that drugs with an ACB score of 3 show a significant rise in core temperature, but only at air temperatures ≥ 30°C. The greater rise in core temperature was observed alongside large, significant reductions in sweating (d=-2.4; 95%CI -4.6, -0.2; p=0.04) and higher skin temperatures (+2.9°C; 95%CI 2.0, 3.7°C; p=0.0003). There was no evidence of an effect on core temperature for drugs with ACB score of 1 or 2. Similarly, there was no evidence for an effect on sweating or skin temperature for drugs with an ACB score of 1 or 2.
		Anticholinergic burden score = 2 ≥30°C air temp: -0.10 [-0.65, 0.45] All: -0.09 [-0.42, 0.25]	⊕⊕◯◯[ac] Low ⊕⊕◯◯[ac] Low	
		Anticholinergic burden score = 1 ≥30°C air temp: -0.03 [-0.03, 0.09] All: +0.03 [-0.03, 0.09]	⊕⊕⊕◯[a] Moderate ⊕⊕⊕◯[a] Moderate	

Systematic Review and Meta-Analysis Findings										
Author (Year)	Drug	Dose	Administration	Air Temp (°C)	Heating Protocol	Core Temp Method	Δ Skin Temp (°C)	Δ Sweating (Cohen's d)	Δ Core Temp(°C)	Estimate (°C) [95% CI]
Anticholinergics Anticholinergic burden score = *3*										
Above 30°C										
Kolka 1984a,b	Atropine	2 mg	Intramuscular	48.4	Exercise	Rectal	2.8 [2.2, 3.4]*	-2.4 [-3.6, -1.1]		0.50 [0.24, 0.76]
Cadarette 1986	Atropine	2 mg	Intramuscular	42.3	Exercise	Rectal	3.9 [3.2, 4.6]†	-		0.59 [0.41, 0.77]
Cadarette 1986	Atropine	2 mg	Intramuscular	33.9	Exercise	Rectal	3.7 [3.0, 4.4]†	-		0.51 [0.31, 0.71]
Strachan 2004	Paroxetine	20 mg	Oral	31.5	Exercise	Rectal	-	-		-0.05 [-0.22, 0.12]
Cadarette 1986	Atropine	2 mg	Intramuscular	30.4	Exercise	Rectal	3.0 [2.6, 3.4]†	-		0.89 [0.76, 1.02]
Kolka 1987a,b	Atropine	2 mg	Intramuscular	30.3	Exercise	Oesophageal	2.1 [1.6, 2.6]‡	-2.8 [-4.7, -0.8]		0.32 [0.19, 0.45]
Kolka 1987a,b	Atropine + Pralidoxime	2 + 600 mg	Intramuscular	30.3	Exercise	Oesophageal	2.8 [2.2, 3.3]‡	-2.4 [-4.1, -0.7]		0.59 [0.37, 0.81]
Below 30°C										
Kolka 1989	Atropine	2 mg	Intramuscular	22.0	Exercise	Oesophageal	2.0 [1.2, 2.8]‡	-1.8 [-3.4, -0.2]		-0.27 [-0.40, -0.14]
Random effects model for ACB = 3 at air temperatures ≥30°C (Q = 135, df = 6, p < 0.01, I² = 93%), p-value of model = 0.03										***0.42 [0.04, 0.79]***
Random effects model for ACB =3 (Q =228, df = 7, p < 0.01; I² = 96%), p-value for model = 0.17										***0.27 [-0.15, 0.70]***
Anticholinergics Anticholinergic burden score = *2*										
Above 30°C										
Rammsayer 1997 + Hennig 1995	Haloperidol	3 mg	Oral	52.0	Passive	Tympanic	-	-		-0.09 [-0.17, -0.01]
Gordon 1987	Atenolol + Nifedipine	50 + 20 mg	Oral	45.0	Exercise	Rectal	-0.6 [-1.0, -0.3]§	-0.5 [-0.3, 1.4]		0.09 [-0.06, 0.24]
Roelands 2008b	Reboxetine	8 mg	Oral	30.0	Exercise	Rectal	-	-		-0.43 [-0.78, -0.08]
Below 30°C										
Rammsayer 1997 + Hennig 1995	Haloperidol	3 mg	Oral	28.0	Passive	Tympanic	-	-		-0.21 [-0.31, -0.11]
Roelands 2008b	Reboxetine	8 mg	Oral	18.0	Exercise	Rectal	-	-		0.21 [-0.18, 0.60]
Random effects model for ACB=2 at air temperatures ≥30°C (Q = 8, df=2, p = 0.02, I² =86), p-value of model = 0.54										***-0.10 [-0.70, 0.49]***
Random effects model for ACB=2 (Q =36, df = 4, p < 0.01; I² = 92%), p-value for model = 0.52										***-0.09 [-0.42, 0.25]***
Anticholinergics Anticholinergic burden score = *1*										
Above 30°C										
Gordon 1987	Nifedipine	20 mg	Oral	45.0	Exercise	Rectal	-0.1 [-0.4, 0.3]§	0.7 [-0.2, 1.6]		0.04 [-0.09, 0.17]
Gordon 1987	Atenolol	50 mg	Oral	45.0	Exercise	Rectal	-0.4, [-0.7, -0.1]§	0.3 [-0.6, 1.1]		0.03 [-0.09, 0.15]
Gordon 1987	Propranolol + Nifedipine	80 + 20 mg	Oral	45.0	Exercise	Rectal	-0.4 [-0.7, -0.1]§	1.0 [0.0, 1.9]		0.20 [0.05, 0.35]
Cramer 2017	Furosemide	40 to 80 mg	Oral	41.0	Passive	Oesophageal	-0.2, [-0.6, 0.2]¶	0.0, [-0.7, 0.8]		0.05 [-0.16, 0.26]
Kaufman 1988	Bromocriptine	2.5 mg	Oral	39.0	Exercise	Rectal	0.6 [-1.1, -0.2]§	0.5 [-0.3, 1.2]		0.14 [-0.08, 0.36]
McCord 2008	Fexofenadine	540mg	Oral	35.0	Exercise	Gastrointestinal	-	-		-0.07 [-0.32, 0.18]
Gordon 1985a,b	Atenolol	100 mg	Oral	33.2	Exercise	Rectal	-0.1, [-0.4, 0.1]§	0.1 [-0.8, 0.9]		-0.09 [-0.21, 0.03]
Freund 1987	Atenolol	100 mg	Oral	31.7	Exercise	Rectal	0.1, [0.0, 0.1]§	-		-0.02 [-0.05, 0.01]
Kolka 1987a,b	Pralidoxime	600 mg	Intramuscular	30.3	Exercise	Oesophageal	0.3 [-0.3, 1.0]‡	-2.0 [-3.7, -0.3]		0.15 [-0.02, 0.32]
Cordery 2017	Bupropion	300 mg	Oral	30.2	Exercise	Rectal	0.2 [-0.2, 0.6]§	-		-0.09 [-0.27, 0.09]
Cordery 2016	L-DOPA + Carbidopa	100 + 25 mg	Oral	30.2	Exercise	Rectal	0.7 [0.3, 1.0]§	-		0.13 [-0.02, 0.28]
Goekint 2011	Citalopram	10 mg	Oral	30.0	Exercise	Rectal	-	-		0.19 [-0.09, 0.47]
Roelands 2009	Bupropion	150 mg	Oral	30.0	Exercise	Rectal	-	-		0.28 [-0.07, 0.63]
Roelands 2012	Bupropion	150 mg	Oral	30.0	Exercise	Rectal	-0.1 [-0.5, 0.3]§	-		0.07 [-0.22, 0.36]
Roelands 2012	Bupropion	225 mg	Oral	30.0	Exercise	Rectal	0.0 [-0.4, 0.5]§	-		-0.05 [-0.32, 0.22]
Roelands 2012	Bupropion	300 mg	Oral	30.0	Exercise	Rectal	0.1 [-0.4, 0.6]§	-		0.06 [-0.24, 0.36]
Watson 2005	Bupropion	300 mg	Oral	30.0	Exercise	Rectal	-	-		-0.08 [-0.24, 0.08]
Below 30°C										
Trinity 2010	Atenolol	0.2 mg·kg⁻¹	Oral	23.0	Exercise	Rectal	-0.4, [-0.8, 0.0]‖	-		-0.13 [-0.37, 0.11]
Trinity 2010	Atenolol	0.2 mg·kg⁻¹	Oral	23.0	Exercise	Rectal	-0.1, [-0.5, 0.2]‖	-		0.14 [-0.10, 0.38]
Roy 2000	Triamterene + Hydrochlorothiazide	100 + 50 mg	Oral	23.0	Exercise	Rectal	-	-0.9, [-1.9, 0.0]		0.21 [0.01, 0.41]
Pescatello 1990	Metoprolol	50 mg	Oral	22.0	Exercise	Oesophageal	-0.3 [-1.3, 0.6]**	-		-0.10 [-0.53, 0.33]
Goekint 2011	Citalopram	10 mg	Oral	18.0	Exercise	Rectal	-	-		-0.06 [-0.21, 0.09]
Watson 2005	Bupropion	300 mg	Oral	18.0	Exercise	Rectal	-	-		0.03 [-0.15, 0.21]
Random effects model for ACB=1 at air temperatures ≥30°C (Q = 30, df = 16, p = 0.02, I² =46%), p-value of model = 0.33										***0.03 [-0.03, 0.09]***
Random effects model for ACB=1 (Q =51, df = 22, p < 0.01; I² = 56%), p-value for model = 0.27										***0.03 [-0.03, 0.09]***

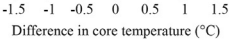

Fig. 2: **Effect of anticholinergic medications on core temperature.** Temp = temperature. [1]World Health Organization. Regional Office for E. Public health advice on preventing health effects of heat: new and updated information for different audiences. Copenhagen: WHO Regional Office for Europe; 2011. [2]World Health Organization. Regional Office for E, European C. Improving public health responses to extreme weather/ heat-waves: EuroHEAT: technical summary. Copenhagen: WHO Regional Office for Europe; 2009. [a]The population sampled does not reflect the population that would usually take this medication. The effects of this medication may be different in the target population. [b]While the point estimate reflects the potential for harm (greater rise in core temperature), the 95% CIs indicate a range of values that include the potential for significant harm through to benefit. [c]While the point estimate indicates the potential for benefit (a lower rise in core temperature), the 95% CIs

blocker (nifedipine). No studies examined Angiotensin Converting Enzyme Inhibitors (ACE-inhibitors), angiotensin-2 receptor blockers or nitrates (Fig. 4). There was no effect of vasodilators on core temperature (+0.11°C; 95% CI –0.13, 0.36°C; p = 0.23; I^2 = 77%; GRADE = Low). One study (nifedipine, calcium channel blocker) measured sweating, with no difference observed. Three studies measured skin temperature, with no difference compared to control (–0.09°C; 95% CI –0.30, 0.11; p = 0.19; I^2 = 0%).

Three studies investigated diuretics (k = 3): acetazolamide, hydrochlorothiazide and furosemide (Fig. 4), with no effect on core temperature (+0.16°C; 95% CI –0.24, 0.56°C; p = 0.23; I^2 = 15%; GRADE = Very low). Two studies measured sweating, with no differences compared to control (d = –0.42; 95% CI –1.34, 0.49; p = 0.37; I^2 = 57%). One study measured skin temperature, reporting no difference (Fig. 4).

One study tested nifedipine combined with either atenolol or propranolol at 45°C (k = 2), with a greater core temperature rise (+0.15°C; 95% CI 0.04, 0.25°C; p < 0.01; I^2 = 0%; GRADE = Moderate) observed compared to control (Fig. 4). Higher sweating was reported with nifedipine combined with propranolol, but not atenolol, while both drug combinations yielded lower skin temperatures (Fig. 4).

Two studies examined anti-Parkinson's disease agents bromocriptine and the combination of levodopa and carbidopa (k = 2), with greater core temperature increases compared to control (+0.13°C; 95% CI 0.07, 0.19°C; p = 0.02; I^2 = 0%; GRADE = Moderate) (Fig. 5). Sweating was measured with bromocriptine (k = 1) with no difference reported. Both studies measured skin temperature, reporting equivocal results.

Two studies investigated sympathomimetics (intravenous adrenaline; k = 1) and CNS stimulants (methylphenidate; k = 2) (Fig. 5). Core temperature increases were greater with adrenaline (+0.41°C; 95% CI 0.21, 0.61°C; GRADE = Moderate), but not methylphenidate (+0.11°C, 95% CI –0.07, 0.30; p = 0.24; I^2 = 0%; GRADE = Moderate). Sweating and skin temperature was measured with adrenaline, with no difference compared to control.

Fexofenadine was the only antihistamine studied (k = 1), with no effect on core temperature (–0.07°C; 95% CI –0.32, 0.18°C; GRADE = Low). Sweating and skin temperature were not measured (Fig. 5).

Two antiemetic medications, ondansetron and granisetron were tested (two studies, k = 2) (Fig. 5) with core temperature not affected (–0.01°C, 95% CI –0.07, 0.06; p = 0.47; I^2 = 0%; GRADE = Low), and no effects on sweating or skin temperature.

No study was rated as "low risk" of bias, while twenty-six studies had "some concerns," and nine were "high-risk" (appendix Supplementary Figs. S1–S20; pp 45–64). GRADE ratings were low-to-moderate, with none considered high quality (appendix Supplementary Tables S6–S18; pp 30–44). Common reasons for downgrading evidence were high uncertainty in the estimate and participants not being representative of the target population.

Most analyses show substantial to considerable heterogeneity. Restricting analyses to medication subtypes reduced heterogeneity with atypical antidepressants (bupropion), and air temperatures ≥30°C reduced heterogeneity for all antidepressants and selective beta blockers. For all other analyses where I^2 was ≥50%, heterogeneity sources remain unresolved. Funnel plots showed no evidence for publication bias (appendix Supplementary Figs. S21–S25; pp 65–69), and no outliers were detected (appendix Supplementary Figs. S26–S43; pp 70–87). Meta-analyses findings were robust to sensitivity analyses. Restricting analyses to measures of rectal or oesophageal temperatures, did not alter any results (appendix Supplementary Table S5; p 29). One study of propranolol[52] was likely influential. Removal of effect sizes for this study did not alter the outcomes for beta-blockers, but reduced heterogeneity to negligible for non-selective beta-blockers at air temperatures ≥30°C, with a statistically significant effect on core temperature (+0.03°C; 95% CI 0.02, 0.05; p < 0.01; I^2 = 0%).

Discussion

Warnings that common medications interfere with thermoregulation and may increase the dangers of heatwaves are ubiquitous in public health guidelines globally.[66,67] These warnings are subsequently propagated in the academic literature[68,69] and mainstream media.[70] The WHO report the adverse effects of 11 different drugs categories on the ability to physiologically keep cool during heat stress.[2,3] Our analysis of the thermoregulatory literature addresses each medication category, and examines the evidence for i) greater rises in core temperature during a heat-stress exposure – the primary driver of heat-related illness,[71] and ii) the associated mechanism of thermoregulatory impairment, i.e., reduced sweating. Greater core temperature rises were found for 4 drug categories: anticholinergics with an anticholinergic burden (ACB) score of 3 at air

ranges from a significant benefit through to significant harm. Skin temperature measured using; * 3-site average of arm, calf and chest; † 3-site average of calf, chest and forearm; ‡ 8-site average of back, calf, chest, forearm, hand, head, thigh and arm; § 4-site average of calf, chest, shoulder and thigh; ¶ 6-site average of abdomen, calf, chest, lower back, shoulder and thigh; || 6-site average of arm, back, calf, chest, forearm and thigh; ** 8-site average of chest, posterior flank, forehead, anterior flank, upper arm, forearm, thigh and calf.

Current WHO Health Messaging		GRADE Assessment, Outcome = Change in Core temperature (°C)		Systematic Review
Medication	**Proposed Mechanism**	**Relative effect (95% CI)**	**Quality of the evidence**	**Summary of Evidence**
Antipsychotics	"Can inhibit the sweating mechanism…, central thermoregulation…, and vasodilation."[1] "…in addition to their peripheral effects…, interfere with the thermoregulatory centre and afferent pathways to the hypothalamus, slowing efferent responses, namely cutaneous vasodilatation, thereby reducing heat elimination."[2]	*All: -0.15 [-0.26, -0.03]*	⊕⊕◯◯[ab] Low	Haloperidol was the only antipsychotic tested. There was a significantly *smaller* rise in core temperature for haloperidol compared to control during heat stress. Sweating and skin temperature was not measured.
Anxiolytics and muscle relaxants	"Reduce sweating…, decrease cardiac output and therefore reduce cooling by vasodilation…"[1]	*All: +0.06 [-0.05, 0.16]*	⊕⊕◯◯[acd] Low	Meprobamate was the only anxiolytic tested. There was no evidence for an effect of meprobamate on core temperature during heat stress. Sweating was not measured. Skin temperature was not different between conditions for meprobamate.
Antidepressants	"Reduce sweating; some can reduce centrally induced thermoregulation…"[1]	*≥30 °C air temp: -0.04 [-0.14, 0.06]* *All: -0.01 [-0.14, 0.12]*	⊕⊕⊕◯[a] Moderate ⊕⊕⊕◯[a] Moderate	Four different antidepressants were tested. There was no evidence for an effect of antidepressants on core temperature during heat stress. None of the included studies reported sweating. Skin temperature was only measured in trials of bupropion, with no effect compared to control.

Systematic Review and Meta-Analysis Findings										
Author (Year)	**Drug**	**Dose**	**Administration**	**Air Temp (°C)**	**Heating Protocol**	**Core Temp Method**	**Δ Skin Temp (°C)**	**Δ Sweating (Cohen's d)**	**Δ Core Temp (°C)**	**Estimate (°C) [95% CI]**
Antipsychotics										
Above 30 °C										
Rammsayer 1997 + Hennig 1995	Haloperidol	3 mg	Oral	52.0	Passive	Tympanic	-	-		-0.09 [-0.17, -0.01]
Below 30 °C										
Rammsayer 1997 + Hennig 1995	Haloperidol	3 mg	Oral	28.0	Passive	Tympanic	-	-		-0.21 [-0.31, -0.11]
Random effects model for antipsychotics (Q = 4, df = 1, p = 0.06; I² = 72%), p-value for model = 0.01										***-0.15 [-0.26, -0.03]***
Anxiolytics and muscle relaxants										
Above 30 °C										
Iampietro 1965	Meprobamate	800 mg	Oral	43.3	Passive	Rectal	-0.2 [-0.6, 0.2]*	-		0.06 [0.02, 0.10]
Below 30 °C										
Iampietro 1965	Meprobamate	800 mg	Oral	26.7	Passive	Rectal	0.1 [-0.1, 0.3]*	-		0.04 [-0.04, 0.12]
Random effects model for anxiolytics (Q = 0, df = 1, p = 0.65; I² = 0.0%), p-value for model = 0.09										***0.06 [-0.05, 0.16]***
Antidepressants										
Norepinephrine reuptake inhibitors (NRIs)										
Above 30 °C										
Roelands 2008b	Reboxetine	8 mg	Oral	30.0	Exercise	Rectal	-	-		-0.43 [-0.78, -0.08]
Below 30 °C										
Roelands 2008b	Reboxetine	8 mg	Oral	18.0	Exercise	Rectal	-	-		0.21 [-0.18, 0.60]
Random effects model for NRIs (Q = 6, df = 1, p = 0.02; I² = 82%), p-value for model = 0.72										***-0.12 [-0.74, 0.51]***
Selective serotonin reuptake inhibitors (SSRIs)										
Above 30 °C										
Strachan 2004	Paroxetine	20 mg	Oral	31.5	Exercise	Rectal	-	-		-0.05 [-0.22, 0.12]
Goekint 2011	Citalopram	10 mg	Oral	30.0	Exercise	Rectal	-	-		0.19 [-0.09, 0.47]
Below 30 °C										
Goekint 2011	Citalopram	10 mg	Oral	18.0	Exercise	Rectal	-	-		-0.06 [-0.21, 0.09]
Random effects model for SSRIs (Q = 6, df = 2, p = 0.05; I² = 55%), p-value for model = 0.88										***-0.01 [-0.40, 0.37]***
Atypical antidepressant										
Above 30 °C										
Cordery 2017	Bupropion	300 mg	Oral	30.2	Exercise	Rectal	0.2 [-0.2, 0.6]†	-		-0.09 [-0.27, 0.09]
Roelands 2012	Bupropion	300 mg	Oral	30.0	Exercise	Rectal	0.1 [-0.4, 0.6]†	-		0.06 [-0.24, 0.36]
Watson 2005	Bupropion	300 mg	Oral	30.0	Exercise	Rectal	-	-		-0.08 [-0.24, 0.08]
Roelands 2012	Bupropion	225 mg	Oral	30.0	Exercise	Rectal	0.0 [-0.4, 0.5]†	-		-0.05 [-0.32, 0.22]
Roelands 2012	Bupropion	150 mg	Oral	30.0	Exercise	Rectal	-0.1 [-0.5, 0.3]†	-		0.07 [-0.22, 0.36]
Roelands 2009	Bupropion	150 mg	Oral	30.0	Exercise	Rectal	-	-		0.28 [-0.07, 0.63]
Below 30 °C										
Watson 2005	Bupropion	300 mg	Oral	18.0	Exercise	Rectal	-	-		0.03 [-0.15, 0.21]
Random effects model for atypical antidepressants (Q = 7, df = 6, p = 0.28; I² = 12%), p-value for model = 0.80										***-0.01 [-0.15, 0.12]***
Random effects model for all antidepressants at air temperature ≥ 30 °C (Q = 13, df = 8, p = 0.13, I² = 0%), p-value of model = 0.36										***-0.04 [-0.14, 0.06]***
Random effects model for all antidepressants (Q = 34, df = 11, p < 0.01; I² = 61%), p-value for model = 0.88										***-0.01 [-0.14, 0.12]***

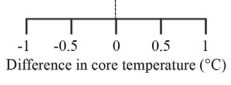

***Fig. 3:* Effect of antipsychotic, anxiolytics and antidepressants on core temperature.** Temp = temperature. [1]World Health Organization. Regional Office for E. Public health advice on preventing health effects of heat: new and updated information for different audiences. Copenhagen: WHO Regional Office for Europe; 2011. [2]World Health Organization. Regional Office for E, European C. Improving public health responses to extreme weather/heat-waves: EuroHEAT: technical summary. Copenhagen: WHO Regional Office for Europe; 2009. [a]The population sampled does not reflect all groups that could potentially take this medication. The effects of this medication may be different in older individuals for example, or those with other chronic illnesses. [b]Only one study has been conducted with antipsychotic medication. While a significant benefit (lower rise in core temperature) was observed, we cannot say with confidence that this result is reflective of all other antipsychotic medications. [c]While the point estimate indicates the potential for harm (a greater rise in core temperature), the 95% CIs ranges from a significant benefit through to significant harm. [d]Only one study has been conducted with anxiolytic medications. We cannot say with confidence that this result is reflective of all other anxiolytics. Skin temperature measured using; * 17-site average (sites not reported); † 4-site average of calf, chest, shoulder and thigh.

Current Public Health Messaging		GRADE Assessment, Outcome = Change in Core temperature (°C)		Systematic Review
Medication	**Proposed Mechanism**	**Absolute effect (95% CI)**	**Quality of the evidence**	**Summary of Evidence**
Beta-blockers	"Can prevent dilation of the blood vessels, reducing the capacity to dissipate heat by convection."[1]	*≥30 °C air temp: +0.06 [-0.05, 0.18]* *All: +0.08 [-0.01, 0.16]*	⊕⊕◯◯[ab] Low ⊕⊕◯◯[ab] Low	Only non-selective beta-blockers resulted in greater rises in core temperature, accompanied by lower skin temperatures (-0.46°C; 95%CI -0.81, -0.12; p=0.01) potentially reducing skin surface heat dissipation by convection/radiation.
Non-selective beta-blockers		*≥30 °C air temp: 0.09 [-0.01, 0.19]* *All: 0.11 [0.02, 0.19]*	⊕⊕◯◯[ab] Low ⊕⊕⊕◯[a] Moderate	
Selective beta-blockers		*≥30 °C air temp: -0.02 [-0.08, 0.04]* *All: -0.02 [-0.15, 0.10]*	⊕⊕⊕◯[a] Moderate ⊕⊕⊕◯[a] Moderate	
Vasodilators	"…worsen hypotension in vulnerable patients."[1] "…precipitate hypotension in people who tend to be dehydrated during excessive heat exposure."[2]	*All: +0.11 [-0.13, 0.36]*	⊕⊕◯◯[ac] Low	There was no evidence of an effect on core temperature. There was no evidence for an effect on sweating (one study of nifedipine) or skin temperature (three studies) (-0.09°C; 95%CI -0.30, 0.11; p=0.19).
Diuretics	Can lead to dehydration and reduce blood pressure."[1] "…dehydration, peripheral vasodilatation and decreased venous return resulting in reduced cardiac output" and hent syncope.[1]	*All: +0.16 [-0.24, 0.56]*	⊕◯◯◯[acd] Very Low	Three diuretics were studied, with no evidence for an effect on core temperature. Similarly, there was no evidence of an effect on sweating in two studies (d=-0.42; 95%CI -1.34, 0.49; p=0.37) or on skin temperature.

Systematic Review and Meta-Analysis Findings

Author (Year)	Drug	Dose	Administration	Air Temp (°C)	Heating Protocol	Core Temp Method	Δ Skin Temp (°C)	Δ Sweating (Cohen's d)	Δ Core Temp (°C)	Estimate (°C) [95% CI]
Antihypertensives										
Non-selective beta-blockers										
Above 30°C										
Apte 1992	Propranolol	120 mg	Oral	49.1	Passive	Aural	-0.1 [-0.2, 0.1][a]	-0.2 [-1.2, 0.9]		0.15 [-0.22, 0.52]
Braudenberger 1980	Propranolol	160 mg	Oral	46.0	Passive	Rectal	0.0 [-0.5, 0.5][a]	0.0 [-1.1, 1.1]		0.03 [-0.30, 0.36]
Gordon 1987	Propranolol	80 mg	Oral	45.0	Exercise	Rectal	-0.7 [-1.0, 0.4][a]	1.1 [0.2, 2.0]		0.05 [-0.08, 0.18]
Gordon 1985a,b	Propranolol	160 mg	Oral	33.2	Exercise	Rectal	-0.2 [-0.5, 0.0][a]	0.5 [-0.3, 1.4]		0.03 [-0.09, 0.15]
Pescatello 1987	Propranolol	80 mg	Oral	32.0	Exercise	Oesophageal	-0.9 [-0.9, -0.8][f]	-		0.24 [0.16, 0.32]
Freund 1987	Propranolol	160 mg	Oral	31.7	Exercise	Rectal	-0.5 [-0.6, -0.4][g]	-		0.03 [0.0, 0.06]
Below 30°C										
Mack 1986	Propranolol	80 mg	Oral	22.0	Exercise	Oesophageal	-0.4 [-0.7, -0.1][h]	0.1 [-1.0, 1.3]		0.21 [0.09, 0.33]
Pescatello 1987	Propranolol	80 mg	Oral	22.0	Exercise	Oesophageal	-1.4 [-1.5, -1.2][h]	-		0.19 [0.12, 0.26]
Pescatello 1990	Propranolol	80 mg	Oral	22.0	Exercise	Oesophageal	-0.5 [-1.3, 0.4][h]	-		0.13 [-0.26, 0.52]
Pescatello 1990	Pindolol	5 mg	Oral	22.0	Exercise	Oesophageal	-0.1 [-0.9, 0.7][h]	-		0.13 [-0.22, 0.48]
Random effects model for non-selective beta-blockers at air temperature ≥30 °C (Q = 25, df = 5 , p < 0.01, I² = 76%), p-value of model = 0.07										0.09 [-0.01, 0.19]
Random effects model for all non-selective beta-blockers (Q = 31, df = 9 , p < 0.01, I² = 71%), p-value of model = 0.02										0.11 [0.02, 0.19]
Selective beta-blockers										
Above 30°C										
Gordon 1987	Atenolol	50 mg	Oral	45.0	Exercise	Rectal	-0.4 [-0.7, -0.1][a]	0.3 [-0.6, 1.1]		0.03 [-0.09, 0.15]
Gordon 1985a,b	Atenolol	100 mg	Oral	33.2	Exercise	Rectal	-0.1 [-0.4, 0.1][a]	0.1 [-0.8, 0.9]		-0.09 [-0.21, 0.03]
Freund 1987	Atenolol	100 mg	Oral	31.7	Exercise	Rectal	0.1 [0.0, 0.1][g]	-		-0.02 [-0.05, 0.01]
Below 30°C										
Trinity 2010	Atenolol	0.2 mg·kg^{-1}	Oral	23.0	Exercise	Rectal	-0.4 [-0.8, 0.0][i]	-		-0.13 [-0.37, 0.11]
Trinity 2010	Atenolol	0.2 mg·kg^{-1}	Oral	23.0	Exercise	Rectal	-0.1 [-0.5, 0.2][i]	-		0.14 [-0.10, 0.38]
Pescatello 1990	Metoprolol	50 mg	Oral	22.0	Exercise	Oesophageal	-0.3 [-1.3, 0.6][h]	-		-0.10 [-0.53, 0.33]
Random effects model for selective beta-blockers at air temperature ≥30 °C (Q = 2, df = 2, p = 0.37, I² = 0%), p-value of model = 0.28										-0.02 [-0.08, 0.04]
Random effects model for all selective beta-blockers (Q = 11, df = 5, p = 0.06, I² =62%), p-value of model = 0.64										-0.02 [-0.15, 0.10]
Random effects model for beta-blockers at air temperature ≥30 °C (Q = 57, df = 8, p < 0.01, I² = 90%), p-value of model = 0.24										***0.06 [-0.05, 0.18]***
Random effects model for all beta-blockers (Q = 78, df = 15, p < 0.01; I² = 84%), p-value for model = 0.07										***0.08 [-0.01, 0.16]***
Vasodilators										
Above 30°C										
Gordon 1987	Nifedipine	20 mg	Oral	45.0	Exercise	Rectal	-0.1 [-0.4, 0.3][a]	0.7 [-0.2, 1.6]		0.04 [-0.09, 0.17]
Arya 1997	Clonidine	1.5 mcg·kg^{-1}	Intravenous	40.0	Passive	Sublingual	-	-		0.00 [-0.14, 0.14]
Kenney 1991	Prazosin	3 mg	Oral	36.0	Exercise	Oesophageal	0.0, [-0.4, 0.4][a]	-		0.32 [0.20, 0.44]
Franke 1993	Prazosin	5 mg	Oral	35.0	Exercise	Rectal	-0.1, [-0.2, 0.0][a]	-		0.07 [-0.19, 0.33]
Random effects model for vasodilators (Q = 15, df = 3, p < 0.01; I² = 77%), p-value for model = 0.23										***0.11 [-0.13, 0.36]***
Diuretics										
Above 30°C										
Cramer 2017	Furosemide	40 to 80 mg	Oral	41.0	Passive	Oesophageal	-0.2, [-0.6, 0.2][a]	0.0, [-0.7, 0.8]		0.05 [-0.16, 0.26]
Below 30°C										
Brechue 1990	Acetazolamide	250 mg	Oral	25.0	Exercise	Rectal	-	-		0.61 [-0.07, 1.29]
Roy 2000	Triamterene + Hydrochlorothiazide	100 + 50 mg	Oral	23.0	Exercise	Rectal	-	-0.9, [-1.9, 0.0]		0.21 [0.01, 0.41]
Random effects model for diuretics (Q = 3, df = 2, p = 0.22; I² = 15%), p-value for model = 0.23										***0.16 [-0.24, 0.56]***
Combined antihypertensive treatment										
Above 30°C										
Gordon 1987	Atenolol + Nifedipine	50 + 20 mg	Oral	45.0	Exercise	Rectal	-0.6 [-1.0, -0.3][a]	-0.5 [-0.3, 1.4]		0.09 [-0.06, 0.24]
Gordon 1987	Propranolol + Nifedipine	80 + 20 mg	Oral	45.0	Exercise	Rectal	-0.4 [-0.7, -0.1][a]	1.0 [0.0, 1.0]		0.20 [0.05, 0.35]
Random effects model for combined anti-hypertensives (Q = 1, df = 1, p = 0.32; I² = 0.0%), p-value for model = 0.01										***0.15 [0.04, 0.25]***

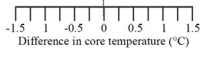

Fig. 4: **Effect of betablockers, vasodilators and diuretics on core temperature.** Temp = temperature. [1]World Health Organization. Regional Office for E. Public health advice on preventing health effects of heat: new and updated information for different audiences. Copenhagen: WHO Regional Office for Europe; 2011. [2]World Health Organization. Regional Office for E, European C. Improving public health responses to extreme weather/heat-waves: EuroHEAT: technical summary. Copenhagen: WHO Regional Office for Europe; 2009. [a]The population sampled does not reflect the population that would usually take this medication. The effects of this medication may be different in the target population. [b]While the point estimate reflects the potential for harm (greater rise in core temperature), the 95% CIs include the null. [c]While the point estimate

temperatures ≥30°C, the sympathomimetic adrenaline, anti-Parkinson agents, and beta-blockers (non-selective only). We did not find evidence supporting the adverse effects of the remaining 7 drug categories on human thermoregulation during heat stress, including antidepressants, antihistamines, anxiolytics, antipsychotics, and diuretics, while no studies on antiepileptics were retrieved. Across all drug categories, quality of evidence ranged from moderate to very low.

The negative effects of strong anticholinergics (ACB = 3) are evidenced by higher core temperatures, reduced sweating, and higher skin temperatures, but findings are limited to intramuscular administration of atropine. Atropine is a first-line treatment for symptomatic bradycardia with no reversible cause,[72] an anti-sialagogue in surgical settings, an antidote to organophosphate/muscarinic poisons,[73] or as eye drops for myopia.[74] These findings may therefore have limited relevance in a broad public health setting. Other medications with strong anticholinergic properties such as amitriptyline (antidepressant) and scopolamine (motion sickness) need to be researched. Mild anticholinergics (ACB = 1), some of which are also classed as beta-blockers (e.g., atenolol) and antidepressants (e.g., bupropion), have been extensively assessed with no effects on core temperature or sweating (Fig. 2).

Despite epidemiological studies showing psychotropic medications are associated with increased risk of morbidity and mortality during hot weather,[75–77] no evidence was found that antidepressants, anxiolytics or antipsychotics alter physiological thermoregulation during heat stress (Fig. 3). These drugs are often reported to reduce sweating, but no study investigating psychotropic medication measured this variable. Epidemiological studies cannot untangle medication effects on heat stress risk from the disease being treated. Behavioural deficits in thermoregulation due to medication or underlying conditions may increase morbidity and mortality risks. Similarly, behaviours associated with mental illness, such as substance use (nicotine[78] or recreational drugs[79]), can exacerbate heat stress[65,80] and contribute to increased heat morbidity/mortality risk. Future research is required to understand increasing morbidity risk in those with mental illness for better public health guidance. This includes testing more psychotropic medications and examining how perceptions of heat, behavioural adaptations and substance use contribute.

Among antihypertensives (Fig. 4), higher core temperatures were only observed with non-selective beta-blockers (e.g., propranolol), with lower skin temperatures but no sweating differences. Peripheral effects of non-selective beta-blockers on adrenoreceptors result in vasoconstriction,[81,82] reducing heat dissipation capacity via convection/radiation or impaired core-to-shell heat distribution. Current recommendations for beta-blockers are therefore partially supported. Third-generation beta-blockers have not been tested. Carvedilol, for example, is a non-selective beta-blocker that can cause peripheral vasodilation through alpha-blockade and may therefore not impose a thermoregulatory disadvantage. Indeed, the four studies of vasodilators captured, including two assessing the alpha-blocker prazosin, did not demonstrate any core or skin temperature effects. The limited evidence assessing the thermoregulatory impacts of diuretics did not show any altered core temperature response. Diuretics can deplete blood volume by ~20% and blunt increases in skin blood flow.[30] However, blood osmolality is maintained minimising sweating impacts via osmoreceptors,[83] which is how sweating is impaired with dehydration from inadequate sweat loss replenishment.

Two studies assessing anti-Parkinson agents showed higher core temperatures (Fig. 5). However, there were no effects on sweating or skin temperature, so the mechanism of action is unclear. Finally, sympathomimetics and CNS stimulants raise metabolic rate and thus internal heat production.[84] The effects of adrenaline were examined in one study with higher core temperatures reported.

Overall, the quality of evidence obtained was broadly low-to-moderate. Most common reasons for downgrading evidence were uncertainty in the estimate and participants not being representative of the target population. To date, evidence is mostly limited to healthy young men inducing hyperthermia through exercise in warm-to-hot conditions over relatively short durations exposed to a single drug. How our findings translate to women, older people, particularly with chronic diseases and/or taking multiple medications, is unknown. Due to reduced sweating and cardiac output, older adults are at greater risk in hot weather and may be more vulnerable to further medication-induced declines in these functions, thus increasing their risk of hospitalisation during heatwaves.[85] Multimorbidity also often results in older adults taking multiple medications. In the U.S. 12.5% of people use ≥5 prescription drugs, rising to 42% in people 65 years or older,[1] while in Canada the proportion is potentially 60%.[86] With only two effect sizes for drug combinations and no studies in older adults, the

reflects the potential for harm (greater rise in core temperature), the 95% CIs indicate a range of values that include the potential for significant harm through to benefit. [d]The proportion of information from studies at high risk of bias is sufficient to affect interpretation of results. Skin temperature measured using; *4-site average of calf, chest, shoulder and thigh; †8-site average of chest, posterior flank, forehead, anterior flank, upper arm, forearm, thigh and calf; ‡6-site average of arm, back, calf, chest, forearm and thigh; § 8-site average of chest, posterior flank, forehead, anterior flank, upper arm, forearm, thigh and calf; ¶ 6-site average of abdomen, calf, chest, lower back, shoulder and thigh.

Current Public Health Messaging		GRADE Assessment, Outcome = Change in Core temperature (°C)		Systematic Review
Medication	Proposed Mechanism	Relative effect (95% CI)	Quality of the evidence	Summary of Evidence
Antihistamines	"Can inhibit the sweating mechanism…"[1]	*-0.07 [-0.32, 0.18]*	⊕⊕◯◯[abc] Low	Only one antihistamine, fexofenadine, was studied, with no effect on core temperature. Sweating and skin temperature were not measured.
Anti-Parkinson's disease agents	"Can inhibit the sweating mechanism…"[1]	*+0.13 [0.07, 0.19]*	⊕⊕⊕◯[d] Moderate	There was a significant rise in core temperature with anti-Parkinson's disease agents compared to control. One study measured sweating with no evidence of an effect observed. Both studies measure skin temperature, however results were equivocal.
Sympathomimetics and CNS stimulants	"… increase heat production by increasing motor activity while reducing heat dissipation via peripheral vasoconstriction and decrease of cutaneous blood flow."[2]	*Adrenaline:+0.41 [0.21, 0.61]* *CNS Stimulants +0.11 [-0.07, 0.30]*	⊕⊕⊕◯[d] Moderate ⊕⊕⊕◯[e] Moderate	Intravenous adrenaline was examined in one study showing a significant increase in core temperature, with no changes in sweating or skin temperature. Oral methylphenidate was examined in another study. There was no evidence of an effect on core temperature. Skin temperature and sweating was not measured.
Other drug classes such as antiemetics, anti-vertigo drugs, gastrointestinal drugs, urinary incontinence drugs	"Also have anticholinergic effects."[1]	Antiemetic: *-0.01 [-0.07, 0.06]*	⊕⊕◯◯[af] Low	Two antiemetic medications were examined. There was no evidence of an effect on core temperature. Similarly, there was no effect on skin temperature (or sweating)

Systematic Review and Meta-Analysis Findings

Author (Year)	Drug	Dose	Administration	Air Temp (°C)	Heating Protocol	Core Temp Method	Δ Skin Temp (°C)	Δ Sweating (Cohen's d)	Δ Core Temp (°C)	Estimate [95% CI]
Antihistamines										
Above 30°C										
McCord 2008	Fexodenadine	540mg	Oral	35.0	Exercise	Gastrointestinal	-	-		-0.07 [-0.32, 0.18]
Anti-Parkinson agents										
Above 30°C										
Kaufman 1988	Bromocriptine	2.5 mg	Oral	39.0	Exercise	Rectal	-0.6 [-1.1, -0.2]*	0.5 [-0.3, 1.2]		0.14 [-0.08, 0.36]
Cordery 2016	L-DOPA + Carbidopa	100 + 25 mg	Oral	30.2	Exercise	Rectal	0.7 [0.3, 1.0]*	-		0.13 [-0.02, 0.28]
Random effects model for anti-Parkinson agents (Q = 0, df = 1, p = 0.94; I² = 0%), p-value for model = 0.02										***0.13 [0.07, 0.19]***
Sympathomimetics and CNS stimulants										
Sympathomimetics										
Above 30°C										
Mora-Rodriguez 1996	Adrenaline	0.1 mcg·kg⁻¹·min⁻¹	Intravenous	33.1	Exercise	Oesophageal	0.3 [-0.6, 1.3]†	0.1 [-0.9, 1.1]		0.41 [0.21, 0.61]
CNS stimulants										
Above 30°C										
Roelands 2008a	Methlyphenidate	20 mg	Oral	30.0	Exercise	Rectal	-	-		0.08 [-0.19, 0.35]
Below 30°C										
Roelands 2008a	Methlyphenidate	20 mg	Oral	18.0	Exercise	Rectal	-	-		0.14 [-0.12, 0.40]
Random effects model for CNS stimulants (Q = 0, df = 1, p = 0.75; I² = 0%), p-value for model = 0.24										***0.11 [-0.07, 0.30]***
Other Drugs										
Antiemetic										
Above 30°C										
McLellan 1996	Granistron	2 mg	Oral	40.0	Exercise	Rectal	0.1 [-0.2, 0.3]‡	0.1 [-0.8, 1.0]		-0.01 [-0.23, 0.21]
McLellan 1994	Ondansetron	8 mg	Oral	40.0	Exercise	Rectal	0.0 [-0.4, 0.4]‡	-		0.00 [-0.24, 0.24]
Random effects model for antiemetics (Q = 0, df = 1, p = 0.95; I² = 0.0%), p-value for model = 0.47										***-0.01 [-0.07, 0.06]***

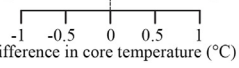

***Fig. 5:* Effect of anti Parkinson's agents, sympathomimetics, CNS stimulants and antiemetics on core temperature.** Temp = temperature. [1]World Health Organization. Regional Office for E. Public health advice on preventing health effects of heat: new and updated information for different audiences. Copenhagen: WHO Regional Office for Europe; 2011. [2]World Health Organization. Regional Office for E, European C. Improving public health responses to extreme weather/heat-waves: EuroHEAT: technical summary. Copenhagen: WHO Regional Office for Europe; 2009. [a]The population sampled does not reflect all groups that could potentially take this medication. The effects of this medication may be different in older individuals for example, or those with other chronic illnesses. [b]While the point estimate indicates the potential for benefit (a lower rise in core temperature), the 95% CIs ranges from a significant benefit through to significant harm. [c]Only one study has been conducted with antihistamine medication. We cannot say with confidence that this result is reflective of all other antihistamine medications. [d]The population sampled does not reflect the population that would usually take this medication. The effects of this medication may be different in the target population. [e]While the point estimate indicates the potential for harm (a greater rise in core temperature), the 95% CIs ranges from a small benefit through to significant harm. [f]While the point estimate does not suggest any effect of anti-emetic medication, the confidence intervals range from significantly lower to significantly greater core temperatures. [g]While the point estimate suggests harm (greater rise in core temperature), the 95% confidence intervals include a negligible effect. Skin temperature measured using; *4-site average of calf, chest, shoulder and thigh; † 5-site average of calf, chest, forearm, shoulder and thigh; ‡ 12-site average of abdomen, calf, chest, forehead, anterior thigh, foot, forearm, lower back, posterior thigh, shin, upper back and wrist.

risk for those taking multiple medications is unknown. Furthermore, data on women are also very limited. The prevalence of chronic diseases and thus medication usage is likely to be different between men and women. For example, women are more likely to seek treatment for depression and anxiety,[87] while sex differences in cardiovascular medication use are also observed.[88,89] The generalisability of our findings is also limited by the

modes and duration of heat stress. Only 8 of 48 studies induced hyperthermia passively, while the others used exercise in short exposures. Current guidelines do not differentiate between passive and active heat exposure, but these factors may alter the observed effect of certain drugs, especially those acting on skin blood flow. More research is needed assessing medication effects during prolonged passive heat exposure, particularly in older adults with chronic diseases who are less active during hot weather. Many of the meta-analyses show considerable heterogeneity with I^2 values ≥50%. Although some heterogeneity was reduced (e.g., by restricting antidepressant analyses to ≥30°C), much remains unexplained. Potential sources include the heat stress methods (passive vs. exercise), ambient conditions, exposure duration, and drug type and dosage. Due to limited data (e.g., only 8 passive heating studies), many factors could not be tested in our pre-planned moderator analyses. Potential sources of heterogeneity could be assessed in future randomised controlled trials, or meta-analyses with more data.

We only assessed direct disruptions to physiological thermoregulation, so deficits in behavioural thermoregulation or secondary exacerbations of cardiovascular or renal strain due to medications during heat exposure were not considered. Future research should examine these factors and their contribution to the risk of heat-related illness.

In conclusion, experimental evidence to date assessing the impacts of medications listed by public health organisations as increasing heat stress risk during hot weather show that drugs with strong anticholinergic properties (ACB = 3), non-selective beta-blockers, the sympathomimetic adrenaline, and the anti-Parkinson's agents bromocriptine and combined levodopa and carbidopa may alter core temperature responses during heat stress. Medications with weaker anticholinergic properties including several antidepressants (ACB ≤ 2), selective beta-blockers, and vasodilators, have been studied with no alterations to core temperature observed. No thermoregulatory effects of diuretics, antipsychotics, anxiolytics, antihistamines, sympathomimetics (other than adrenaline) and CNS stimulants were found, but evidence was limited to 1 study at ≥30°C per category. Most studies involve healthy young men under short heat stress exposures. Studies over longer durations, in women, older adults and those with chronic disease are urgently required to better inform the pharmaceutical management of patients during hot weather.

Contributors

YM, OJ and LH conceived the research question and designed the study. LH did the literature search. LH, GD and EA screened articles. LH, GD and EA read the full texts for eligibility. LH extracted data from the original trials. LH and YM evaluated the risk of bias. YM and LH verified the underlying data. YM did the analyses. LH and YM evaluated the quality of evidence. LH, YM, LK, LA, TC, KLE and OJ contributed to the interpretation of the results. LH and YM wrote the first draft of the manuscript. OJ critically revised the manuscript. All authors acknowledge full responsibility for the analyses and interpretation of the report. All authors have read and approved the final manuscript. YM is the guarantor. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data sharing statement

Raw data, and final data used for analysis are available upon reasonable request by emailing yorgi.mavros@sydney.edu.au.

Declaration of interests

KLB reports grants from the NIH, Wellcome Trust, honoraria for keynote talks and travel support from the World Health Organization to attend meetings, conferences and give keynote talks. KLB is also the Chair of the US National Academy of Sciences Board on Environmental Change and Society. All of KLBs declarations are outside the scope of the submitted work. LK acknowledges funding from the National Institutes of Health (NIH; AG067471) outside of the submitted work. OJ acknowledges funding from the National Health and Medical Research Council (NHMRC 2021/GNT2009507) for the submitted work. OJ also reports grants from the Wellcome Trust and Resilience NSW, consulting fees from a National Institutes of Health grant, expert testimony for the National Rugby League, support for attending meetings and travel from the Global Heat and Health Information Network and Minderoo Foundation – all of which are outside the scope of the submitted work.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102886.

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