INPLASY

The effect of blood pressure lowering drugs and blood pressure lowering on headache: a systematic review and network meta-analysis of randomized, double-blind clinical trials

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ADMINISTRATIVE INFORMATION

Support - Program grant from the National Health and Medical Research Council, Australia.

Review Stage at time of this submission - Data analysis.

Conflicts of interest - George Health Enterprises, the social enterprise arm of The George Institute for Global Health, has received investment to develop fixed-dose combination products containing aspirin, statin and blood pressure lowering drugs. George Health Enterprises has submitted patents for low-dose blood pressure combinations, on which Professor Rodgers is listed as one of the inventors. Professor Rodgers is seconded part-time to George Medicines Pty Ltd (GM). All staff employed by TGI have an institutional interest to declare with respect to George Health Enterprises. None of the TGI staff have a direct financial interest in these investments.

INPLASY registration number: INPLASY202520027

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 6 February 2025 and was last updated on 6 February 2025.

INTRODUCTION

Review question / Objective To compare, among adults, the effect of major classes of blood pressure (BP) lowering drugs and their combinations on headache, and also to evaluate the association between BP lowering and headache.

Rationale Headache is ranked among the 15 leading causes of the global burden of disease and all-age disability adjusted life years. Headache can occur after an acute increase in blood pressure (BP). However, the association between chronic high BP or reduction in BP with headache is not clear. Two previous meta-analyses (Law et al. 2005 and Webb et al. 2012) showed a protective effect of BP-lowering drugs on headache (1, 2). The latest of the two was conducted in 2012, and both meta-analyses did not assess the effect of combinations of BP-lowering drugs on headache. There is a need to update evidence on the effects of BP-lowering drugs and BP-lowering on headache, including studying effect of combination therapy.

1. Law M, Morris JK, Jordan R, Wald N. Headaches and the treatment of blood pressure: results from a meta-analysis of 94 randomized placebo-controlled trials with 24,000 participants. Circulation. 2005;112(15):2301-6.
2. Webb AJ, Rothwell PM. The effect of antihypertensive treatment on headache and blood

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pressure variability in randomized controlled trials: a systematic review. J Neurol. 2012;259(9):1781-7.

Condition being studied Headache.
In this review headache in general will be evaluated.

METHODS

Search strategy Search Strategy for RCTs: EBM Reviews - Cochrane Central Register of Controlled Trials 1. exp Angiotensin-Converting Enzyme Inhibitors/ 2. (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril$ or perindopril$ or pivopril or quinapril$ or ramipril$ or rentiapril or saralasin or s nitrosocaptopril or spirapril$ or temocapril$ or teprotide or trandolapril$ or utibapril$ or zabicipril$ or zofenopril$ or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril or Enalaprilat).tw. 3. exp Angiotensin Receptor Antagonists/ 4. (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or KT3-671 or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan).tw. 5. exp calcium channel blockers/ 6. (amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM or azelnidipine or clevidipine).tw. 7. (aliskiren or ciprokiren or ditekiren or enalkiren or remikiren or rasilez or tekturna or terlakiren or zankiren or ketanserin).tw. 8. (methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or methylpropionic acid or dopergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa or methyldihydroxyphenylalanine or methyl dopa or mulfasin or presinol or presolisin or sedometil or sembrina or taquinil or dihydroxyphenylalanine or methylphenylalanine or methylalanine or alpha methyl dopa or guanfacine or guanabenz or guanadrel or guanethidine or debrisoquine or betanidine or guanoxan or guanoclor or guanazodine or guanoxabenz).tw. 9. (reserpine or serpentina or rauwolfia or serpasil).tw. 10. (clonidine or adesipress or arkamin or caprysin or catapres$ or catasan or chlofazolin or chlophazolin or clinidine or clofelin$ or clofenil or clomidine or clondine or clonistada or clonnirit or clophelin$ or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or moxonidine or rilmenidine or rescinnamine or deserpidine or methoserpidine or bietaserpine or azamethonium or mecamylamine).tw. 11. exp hydralazine/ 12. (dihydralazine or hydralazin$ or hydrallazin$ or hydralizine or hydrazinophtalazine or hydrazinophthalazine or hydrazinophtalizine or dralzine or hydralacin or hydrolazine or hypophthalin or hypoftalin or hydrazinophthalazine or idralazina or 1-hydrazinophthalazine or apressin or nepresol or apressoline or apresoline or apresolin or alphapress or alazine or idralazina or lopress or plethorit or praeparat hydralazine or diazoxide or minoxidil or nitroprusside sodium or todralazine or tolazoline or endralazine or cadralazine or pinacidil).tw. 13. exp adrenergic beta-antagonists/ 14. (acebutolol or adimolol or afurolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or flestolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropranolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol

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or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol or
esatenolol).tw. 15. exp adrenergic alpha
antagonists/ 16. (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin or Indoramin or phenoxybenzamine or phentolamine or tolazoline or
urapidil).tw. 17. exp
thiazides/ 18. exp sodium potassium chloride symporter
inhibitors/ 19. (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or
thiazide?).tw. 20. (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamideor altizide or bemetizide or benzthiazide or benzylhydrochlorothiazide or butizide or clopamide or epitizide or hydrochlorothiazide or hydroflumethiazide or mefruside or meticrane or metipamide or teclothiazide or tripamide or xipamide or
quinethazone).tw. 21. (azosemide or furosemide or frusemide or fursemide indacrinone or ozolinone or phenoxybenzoic acid or muzolimine or bumetanide or burinex or cicletanine or etozolonie or torsemide or ethacrynic acid or veratide or piretanide or ticrynafen or tienilic acid or
tizolemid).tw. 22. exp Mineralocorticoid Receptor
Antagonists/ 23. (amiloride or triamterene or canrenoate potassium or canrenone$ or spironolactone$ or aldosterone antagonist$ or aldactone$ or practon$ or sc-9420$ or spiractin$ or sc-14266$ or soldactone$ or soludactone$ or aldadiene$ or phanurane$ or sc-9376 or
eplerenone$).tw. 24. exp BP-lowering
agents/ 25.
or/1-24 26. randomized controlled
trial.pt. 27.
random$.tw. 28. (placebo or ?blind or parallel or cross?over or
trial).tw. 29.
or/26-28.
30.(abstract or conference or meeting or proceedings or protocol or cluster or letter or comment or editorial or opinion or commentary or process evaluation or non-comparative or single-group or cochrane).ti.
31.(abstract or conference or letter or comment or editorial or commentary).pt.
32.(conference or abstract or meeting or scientific).vo.
33.(mice or rabbit$ or rats or dogs).ti.
34. or/30-33
35. 25 and 29
36. 35 not 34
37. limit 36 to english language

Participant or population Inclusion: Adults (age ≥18 years or as defined by the study).
Exclusion: 1. Acute/unstable cardiovascular conditions: hypertensive crisis/urgency, acute myocardial infarction (MI), recent MI (within <1 month), acute coronary syndrome, unstable angina, acute stroke, acute heart failure. 2. Renal diseases: nephrotic syndrome, dialysis dependent renal failure, IgA-Nephropathy, acute renal failure. 3. Severe liver disease. 4. Mental illnesses/ neurological disorders: acute schizophrenia, acute mania etc., epilepsy, seizers, tremor, and Parkinson's disease. 5. Recent major surgeries/ transplants. 6. Endocrine disorders (e.g., hyperthyroidism and gigantism) except diabetes. 7. Pregnancy, pre-eclampsia. 8. Portal hypertension, pulmonary hypertension. 9. Benign prostatic hyperplasia. 10. Raynaud's disease.

Intervention Placebo or drug(s) from the same five major classes or their combinations taken orally at fixed doses for 2 to 26 weeks.

Comparator Placebo or drug(s) from the same five major classes or their combinations taken orally at fixed doses for 2 to 26 weeks.

Study designs to be included Randomised, double-blind trials.

Eligibility criteria Trials should satisfy the following criteria:
1. Randomised, double-blind trials.
2. Enrolled adult participants (age ≥18 years or as defined by the study)
3. Evaluated BP-lowering drug(s) from five major classes (Angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics)
4. Evaluated BP-lowering drugs taken orally at fixed doses for 2 to 26 weeks
5. Compared BP-lowering drug(s) from five major classes with Placebo or drug(s) from the same five major classes or their combinations
6. Reported data on headache
7. Non-differentially concomitant therapy between the comparison groups
8. Included participants free from a health condition that could alter, or interfere with the assessment of the effects of BP-lowering drugs

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9. Be published in English language.

Information sources Cochrane Central Register of Controlled Trials (until December 2022) for trials of BP-lowering drugs; MEDLINE (from 1946 to December 2022), and Epistemonikos (inception to 21-Sep-2017) for systematic reviews of randomized trial of BP-lowering drugs from the references of which relevant randomised trials were identified.

Main outcome(s) Primary outcome: Participants with at least one headache post-randomisation to the latest follow-up available in each included trial.

Additional outcome(s) Association between BP-lowering and headache.

Data management The database is hosted by The George Institute for Global Health. All stages of the study (search, screening and data extraction) were performed by two reviewers independently in duplicate. Conflicts were solved by discussion between the reviewers or by adjudication by a third senior reviewer. Data from each included trial was collected in electronic forms using Distiller SR.

Quality assessment / Risk of bias analysis Given the inclusion of more than 400 studies and the inadequate data reporting in many older trials, conducting a standard risk of bias assessment would be inefficient and unreliable. Risk of bias assessment in the included studies was not performed because of the following reasons:
1- Risk of bias arising from selection bias: In all most all studies, all that is reported is the study is "randomised" or participants were "randomly" allocated and there is no information reported about random sequence generation or allocation concealment. Consequently, this domain will be marked as "no information" for most studies.
2- Bias due to deviations from intended interventions: In most studies, all that is reported is the study was "double-blind" and there is no information reported on who all were blinded, consequently this domain will be marked as "no information" for most studies.
3- Bias due to missing outcome data: we will report the number of participants randomised and analysed.
4- Bias in measurement of the outcome: All included studies were "double-blind".
5- Bias in selection of the reported results: We considered outcome reporting bias as not relevant to this meta-analysis because objectives of almost all trials included were not to assess the effect of BP-lowering drugs on headache. Also, in most trials, headache is reported as an adverse event and was not assessed and reported as an outcome.

Strategy of data synthesis Network meta-analysis will be performed using the "arm-based approach", and effect estimates will be calculated using Mantel-Haenszel random effects meta-analysis using a frequentist approach. The risk of headache will be defined as reported number of participants with at least one headache event in a group divided by the number of participants analysed for events in that group. If the total number analysed for the group is not available, it will be replaced with the number of participants randomized to that group. Network estimates will be expressed as odds ratios and their 95% CI. Separate network analysis will be done by drug-class versus placebo and drug versus placebo. Results will be presented as a network diagram with the number of available comparisons between nodes (drug-classes, their combinations or placbo). Effect estimates will be summarized as forest plots by drug-class. Direct and indirect risk estimates will be shown in a network league table to allow comparison. Relative effectiveness of drug-class in reducing headache risk will be presented as a table of P-scores or a network treatment rank plot. Forest plots will also be presented for all available drug comparisons with headache events from NMA.
For each drug class, meta-regression will be performed with variance ratio, pulse pressure difference and difference in mean change in SBP / DBPfrom baseline between intervention and comparator (treatment effect) at final follow-up as the primary independent variables and headache risk as the outcome. Regression coefficients will be interpreted as change in risk for every 1 mmHg increase in treatment effect. P-values will be considered significant at 5% level.
Variance ratio, pulse pressure difference , and treatment efficacy will be estimates at the class level using meta-analysis and plotted against the corresponding class-specific headache risk estimate with 95% confidence intervals.
When there are more than 10 trials in the meta-analysis and the funnel plot is symmetrical, heterogeneity, will be expressed using 95% prediction intervals (PI) for the summary effects. We will also evaluate the I2 statistic. I2 values will be interpreted as unimportant (0% to 40%), moderate (30% to 60%), substantial (50% to 90%), and considerable (75% to 100%) heterogeneity.

Subgroup analysis In addition to comparing the five classes of BP-lowering drugs with placebo and their combinations or drug(s) from the same five

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major classes (active vs. active) , the following sub-group analyses will be performed for the primary outcome, if feasible:
1- By Study duration (≤10 weeks and > 11 weeks)
2- By standard dose.

Sensitivity analysis The following sensitivity analyses will be performed for the primary outcome to assess the robustness of the findings:
1. Excluding studies with >10% participants of the randomised participants not analysed
2. Excluding crossover trials.

Language restriction Only studies published in English language were included.

Country(ies) involved India, Australia.

Keywords Headache, blood pressure, hypertension, blood pressure lowering medication, prevention.

Dissemination plans Findings of this study will be published in journal and presented at academic conferences.

Contributions of each author
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Author 2 - Abdul Salam.
Author 3 - Rashmi Pant.
Author 4 - Vidyasagar Kota.
Author 5 - Rupasvi Dhurjati.
Author 6 - Anthony Rodgers.

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