Comparative effects of pharmacological interventions for the acute and long-term management of insomnia disorder in adults: a systematic review and network meta-analysis

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Summary

Background Behavioural, cognitive, and pharmacological interventions can all be effective for insomnia. However, because of inadequate resources, medications are more frequently used worldwide. We aimed to estimate the comparative effectiveness of pharmacological treatments for the acute and long-term treatment of adults with insomnia disorder.

Methods In this systematic review and network meta-analysis, we searched the Cochrane Central Register of Controlled Trials, MEDLINE, PubMed, Embase, PsycINFO, WHO International Clinical Trials Registry Platform, ClinicalTrials.gov, and websites of regulatory agencies from database inception to Nov 25, 2021, to identify published and unpublished randomised controlled trials. We included studies comparing pharmacological treatments or placebo as monotherapy for the treatment of adults (≥18 year) with insomnia disorder. We assessed the certainty of evidence using the confidence in network meta-analysis (CINeMA) framework. Primary outcomes were efficacy (ie, quality of sleep measured by any self-rated scale), treatment discontinuation for any reason and due to side-effects specifically, and safety (ie, number of patients with at least one adverse event) both for acute and long-term treatment. We estimated summary standardised mean differences (SMDs) and odds ratios (ORs) using pairwise and network meta-analysis with random effects. This study is registered with Open Science Framework, https://doi.org/10.17605/OSF.IO/PU4QJ.

Findings We included 170 trials (36 interventions and 47 950 participants) in the systematic review and 154 double-blind, randomised controlled trials (30 interventions and 44 089 participants) were eligible for the network meta-analysis. In terms of acute treatment, benzodiazepines, doxylamine, eszopiclone, lemborexant, seltorexant, zolpidem, and zopiclone were more efficacious than placebo (SMD range: 0·36–0·83 [CINeMA estimates of certainty: high to moderate]). Benzodiazepines, eszopiclone, zolpidem, and zopiclone were more efficacious than melatonin, ramelteon, and zaleplon (SMD 0·27–0·71 [moderate to very low]). Intermediate-acting benzodiazepines, long-acting benzodiazepines, and eszopiclone had fewer discontinuations due to any cause than ramelteon (OR 0·72 [95% CI 0·52–0·99; moderate], 0·70 [0·51–0·95; moderate] and 0·71 [0·52–0·98; moderate], respectively). Zopiclone and zolpidem caused more dropouts due to adverse events than did placebo (zopiclone: OR 2·00 [95% CI 1·28–3·13; very low]; zolpidem: 1·79 [1·25–2·50; moderate]); and zopiclone caused more dropouts than did eszopiclone (OR 1·82 [95% CI 1·01–3·33; low]), daridorexant (3·45 [1·41–8·33; low), and suvorexant (3·13 [1·47–6·67; low]). For the number of individuals with side-effects at study endpoint, benzodiazepines, eszopiclone, zolpidem, and zopiclone were worse than placebo, doxepin, seltorexant, and zaleplon (OR range 1·27–2·78 [high to very low]). For long-term treatment, eszopiclone and lemborexant were more effective than placebo (eszopiclone: SMD 0·63 [95% CI 0·36–0·90; very low]; lemborexant: 0·41 [0·04–0·78; very low]) and eszopiclone was more effective than ramelteon (0.63 [0·16–1·10; very low]) and zolpidem (0·60 [0·00–1·20; very low]). Compared with ramelteon, eszopiclone and zolpidem had a lower rate of all-cause discontinuations (eszopiclone: OR 0·43 [95% CI 0·20–0·93; very low]; zolpidem: 0·43 [0·19–0·95; very low]); however, zolpidem was associated with a higher number of dropouts due to side-effects than placebo (OR 2·00 [95% CI 1·11–3·70; very low]).

Interpretation Overall, eszopiclone and lemborexant had a favorable profile, but eszopiclone might cause substantial adverse events and safety data on lemborexant were inconclusive. Doxepin, seltorexant, and zaleplon were well tolerated, but data on efficacy and other important outcomes were scarce and do not allow firm conclusions. Many licensed drugs (including benzodiazepines, daridorexant, suvorexant, and trazodone) can be effective in the acute treatment of insomnia but are associated with poor tolerability, or information about long-term effects is not available. Melatonin, ramelteon, and non-licensed drugs did not show overall material benefits. These results should serve evidence-based clinical practice.

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Research in context

Evidence before this study

Insomnia is a highly prevalent disorder in the general population, with a chronic course and heavy burden for patients and the health-care system. Although both non-pharmacological and pharmacological interventions are available, medications are often prescribed due to greater accessibility, despite being associated with substantial adverse events (ie, falls [especially in older adults]). Pharmacological treatments have been mostly investigated in placebo-controlled trials so little information is available about their comparative effectiveness. In the scientific literature, we found five network meta-analyses, but these focused only on very specific populations (eg, older adults or people with diagnosed autoimmune disease) or had important methodological limitations (eg, including only placebo-controlled studies or a small subset of pharmacological treatments). To fill this gap, we did a systematic review and network meta-analysis including licensed and non-licensed medications for the acute and long-term treatment of insomnia disorder.

Added value of this study

We retrieved 170 studies including adults with insomnia disorder randomly assigned to 36 active pharmacological treatments or placebo. Using 154 double-blind randomised trials, we investigated the effects of medications for acute and long-term treatment across the following clinically-relevant primary outcomes: quality of sleep (efficacy), discontinuation due to any cause (acceptability), discontinuation due to any adverse event (tolerability), and presence of at least one adverse event (safety). Considering all the outcomes at different timepoints (ie, acute and long-term treatment), lemborexant and eszopiclone had the best profile in terms of efficacy, acceptability, and tolerability; however, eszopiclone might cause substantial adverse events and safety data on lemborexant were inconclusive. There was insufficient evidence to support the prescription of benzodiazepines and zolpidem in long-term treatment.

Implications of all the available evidence

The findings from this network meta-analysis represent the best available evidence base to guide the choice about pharmacological treatment for insomnia disorder in adults and will assist in shared decision making between patients, carers, and their clinicians, as well as policy makers. All statements comparing the merits of one drug with another should be tempered by the potential limitations of the current analysis, the quality of the available evidence, the characteristics of the patient populations, and the uncertainties that might result from choice of dose or treatment setting.

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Introduction

Insomnia disorder is a predominant complaint of dissatisfaction with sleep quantity or quality, associated with at least 3 months of difficulty in initiating and maintaining sleep and characterised by frequent awakenings or problems returning to sleep after awakenings, which lead to daytime consequences such as sleepiness and hyperactivity.[1] The prevalence of insomnia in the general population ranges from 12% to 20%.[2] Insomnia disorder has a chronic course, with persisting symptoms in 86% of individuals after 1 year and 59% after 5 years of a formal diagnosis.[3] Functional consequences of insomnia include reduced productivity, increased absenteeism, increased use of health care, and increased accident risk, with costs exceeding US$100 billion per year in the USA alone.[4] Insomnia is also a risk factor for mental health disorders such as depression, anxiety, and alcohol dependence;[5,6] metabolic syndrome;[7] hypertension and coronary heart disease;[8] worsened quality of life;[9] and increased mortality.[10]

General management measures for insomnia include treating comorbid medical and psychiatric conditions, modifying sleep-interfering medications and substances, and optimising the sleep environment.[11] International guidelines recommend cognitive behavioural interventions and medications as effective specific treatments for insomnia disorder,[11–14] but the lack of training and availability of clinical staff limit the use of non-pharmacological strategies worldwide. Digital cognitive behavioural therapy has shown some promising results, but more research is needed because this approach is associated with high rates of early dropout or disengagement.[15] Regulatory agencies have historically approved medications for the treatment of insomnia on the basis of evidence from short-term and placebo-controlled trials,[16] and only recently have asked pharmaceutical companies to submit long-term data for licensing purposes.[17] As a result, pharmacological treatment is now recommended only for the acute management of insomnia disorder[11–14] and little evidence is available about the comparative effectiveness of active treatments.[18]

Therefore, in this study, we did a systematic review and network meta-analysis to inform clinical practice by comparing different pharmacological treatments for the acute and long-term treatment of adults with insomnia.

Methods

Search strategy and selection criteria

Full details about the methods of this systematic review and network meta-analysis are reported in the protocol (appendix pp 18–40), which is available on the Open Science Framework.

We searched the Cochrane Central Register of Controlled Trials, MEDLINE, PubMed, Embase, and PsycINFO from the date of database inception to Nov 25, 2021. We also searched WHO International Clinical Trials Registry Platform, ClinicalTrials.gov, and websites of regulatory agencies from inception to Nov 25, 2021. No

See **Online** for appendix

For the **full details about the methods** see https://osf.io/pu4qj/

language restrictions were applied. We contacted investigators and relevant trial authors to supplement incomplete reports or obtain information about unpublished trials. The full search strategy is reported in the appendix (pp 9–14).

In the systematic review, we included randomised controlled trials (RCTs) comparing pharmacological treatments for insomnia against placebo or another active agent as oral monotherapy for adults with a diagnosis of insomnia disorder according to specific diagnostic criteria, including Diagnostic and Statistical Manual of Mental Disorders (DSM)-3, DSM-3-R, DSM-4, DSM-4 TR, DSM-5, International Classification of Diseases (ICD)-10, International Classification of Sleep Disorders (ICSD), ICSD-2, ICSD-3, Chinese Classification of Mental Disorders (CCMD)-2R, CCMD-3, or other standardised criteria. For the network meta-analysis, we considered only double-blind RCTs. Some drug classes (eg, barbiturates) and individual drugs (eg, chloral, ethchlorvynol, and triclofos) were a priori excluded due to their toxic adverse effects or risk of misuse and dependence.[11] For medications with an indication for insomnia according to the British National Formulary, the US Food and Drug Administration (FDA), the European Medicines Agency, the Pharmaceuticals and Medical Devices Agency in Japan, or the Therapeutic Goods Administration in Australia, we considered only RCTs with participants given doses within the corresponding therapeutic range (appendix pp 22–28). Both fixed and flexible dose regimens were included in the meta-analysis. We excluded cluster-randomised or cross-over trials and trials recruiting patients with secondary insomnia (ie, insomnia due to psychiatric or physical comorbidity, or due to a medication or a substance such as alcohol). As prespecified in the protocol, we grouped benzodiazepines into three categories based on their elimination half-life: short-acting benzodiazepines (<6 h), intermediate-acting benzodiazepines (6–24 h), and long-acting benzodiazepines (>24 h).[19]

Pairs of researchers (AK, FF, GLD, MC, NW, and VDF) independently selected the studies, reviewed the main reports and supplementary materials, extracted the relevant information from the included trials, and assessed the risk of bias. Any discrepancies were double-checked and resolved by discussion with other members of the review team (AC, FDC, and EGO).

Outcomes

Our primary outcomes were efficacy (measured as patient-rated quality of sleep or satisfaction with sleep index), all-cause discontinuation (the proportion of patients who stopped treatment for any reason, which is used as a measure for the acceptability of treatments because it encompasses both efficacy and tolerability), tolerability (treatment discontinuation measured by the proportion of patients who withdrew due to any adverse event), and safety (total number of patients with at least one adverse event). When the quality of sleep was measured with more than one rating scale, we used a predefined hierarchy based on psychometric properties and consistency of use across included trials (appendix p 29).

As secondary outcomes, we analysed additional objective and subjective measures of efficacy (sleep onset latency, wake time after sleep onset, total sleep time, and number of awakenings, evaluated both by polysomnography and by sleep questionnaire or sleep diary), hangover (eg, sedation and reduced alertness during the day) or increased alertness, rebound or withdrawal phenomena, the total number of patients with one specific adverse event, and the total number of patients with serious adverse events as defined by the FDA (appendix pp 29–30). We categorised common adverse events using Medical Dictionary for Regulatory Activities (MedDRA) and serious adverse events were defined as described by the FDA.

We assessed efficacy, acceptability, and tolerability in terms of acute and long-term outcomes. For the analysis of acute outcomes, we used outcome data after 4 weeks of treatment. If the information at 4 weeks was not available, we used data ranging between 1 and 12 weeks (we gave preference to the timepoint closest to 4 weeks; if equidistant, we took the longer outcome). For the long-term analysis, the longest timepoint after 3 months of treatment was used. As far as safety was concerned, the included trials reported data only at study endpoint, so for this analysis, we considered the number of patients with at least one adverse event during the trial duration. Whenever possible, we compared published with unpublished data and gave preference to unpublished information in case of disagreement.[20]

Data analysis

We contacted study authors if there were missing or unclear data. If dichotomous outcome data were still missing, we assumed that patients who dropped out after being randomly assigned had a negative outcome. For continuous outcome data, we used the method used in the original study to account for missing data, usually mixed model repeated measures or the last observation carried forward. If neither mixed model repeated measures or last observation carried forward results were reported, we analysed data on patients who had completed the study. We calculated missing SD from p values, *t* values, and SE or imputed them with a validated method.[21] We estimated summary odds ratios (ORs) for dichotomous outcomes and standardised mean differences (SMD, Cohen's d) for continuous outcomes with their 95% CIs using pairwise and network meta-analysis.[22] We used the netmeta package in R (version 4.0.5) and Stata (version 16.1). We assessed statistical heterogeneity in each pairwise and network meta-analysis comparison with t^2 and I^2 statistics.[23] We did network meta-analyses using a random-effects model within a frequentist setting, assuming equal heterogeneity across all comparisons and accounting for correlations induced by multiarm studies. For rare events (ie, for studies with no events in some of the treatment

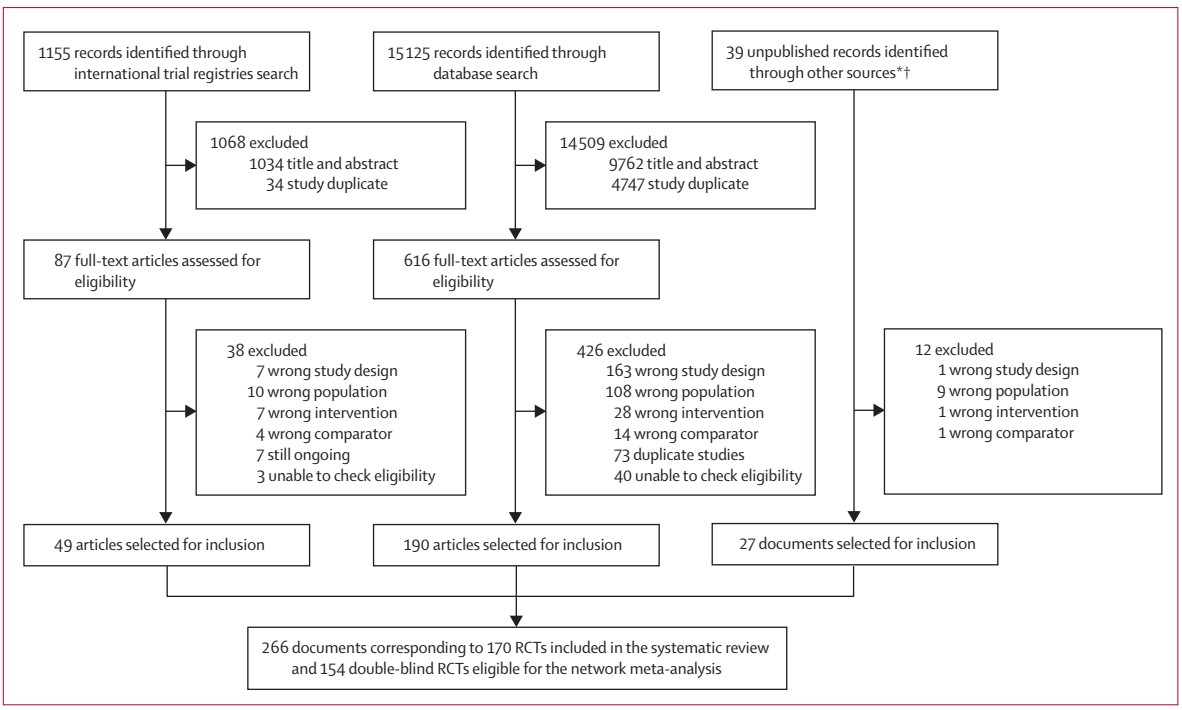


Figure 1: **Study selection process**
Overall, 154 double-blind, randomised controlled trials correspond to 30 interventions. For the acute treatment analysis, 86 trials (27 interventions) were included for efficacy, 100 trials (28 interventions) for acceptability, and 76 trials (25 interventions) for tolerability. For the long-term analysis, five trials (five interventions) were included for efficacy, eight trials (seven interventions) for acceptability, and eight trials (seven interventions) for tolerability. For safety, 86 trials (27 interventions) were included. RCT=randomised controlled trial. *Industry websites, websites of regulatory agencies, contact with authors, and hand-searched reviews. †The total number of unpublished records is the total number of results for each drug and on each unpublished database source.

groups), we did a network meta-analysis of double-blind RCTs using a fixed-effect Mantel-Haenszel approach and compared results with a fixed-effects inverse-variance model.[24]

We evaluated the transitivity assumption by comparing the distribution of key study characteristics across studies grouped by comparison. We assessed inconsistency between direct and indirect sources of evidence using global and local approaches. We assessed global inconsistency by using a design-by-treatment test.[25] We evaluated local inconsistency by using the back calculation and separate indirect from direct design evidence methods, comparing direct and indirect evidence for each pairwise treatment comparison.[24,26] A hierarchy of treatments was calculated for each outcome, acute and long-term outcomes, on the basis of the p-scores.[27] We assessed existence of small-study effects and publication bias for each treatment pair using a contour-enhanced funnel plot if at least ten studies studies that did the analysis were available.[28]

We assessed individual studies with the Cochrane risk of bias tool[23] and the certainty of evidence using the Confidence in Network Meta-Analysis framework (CINeMA).[29]

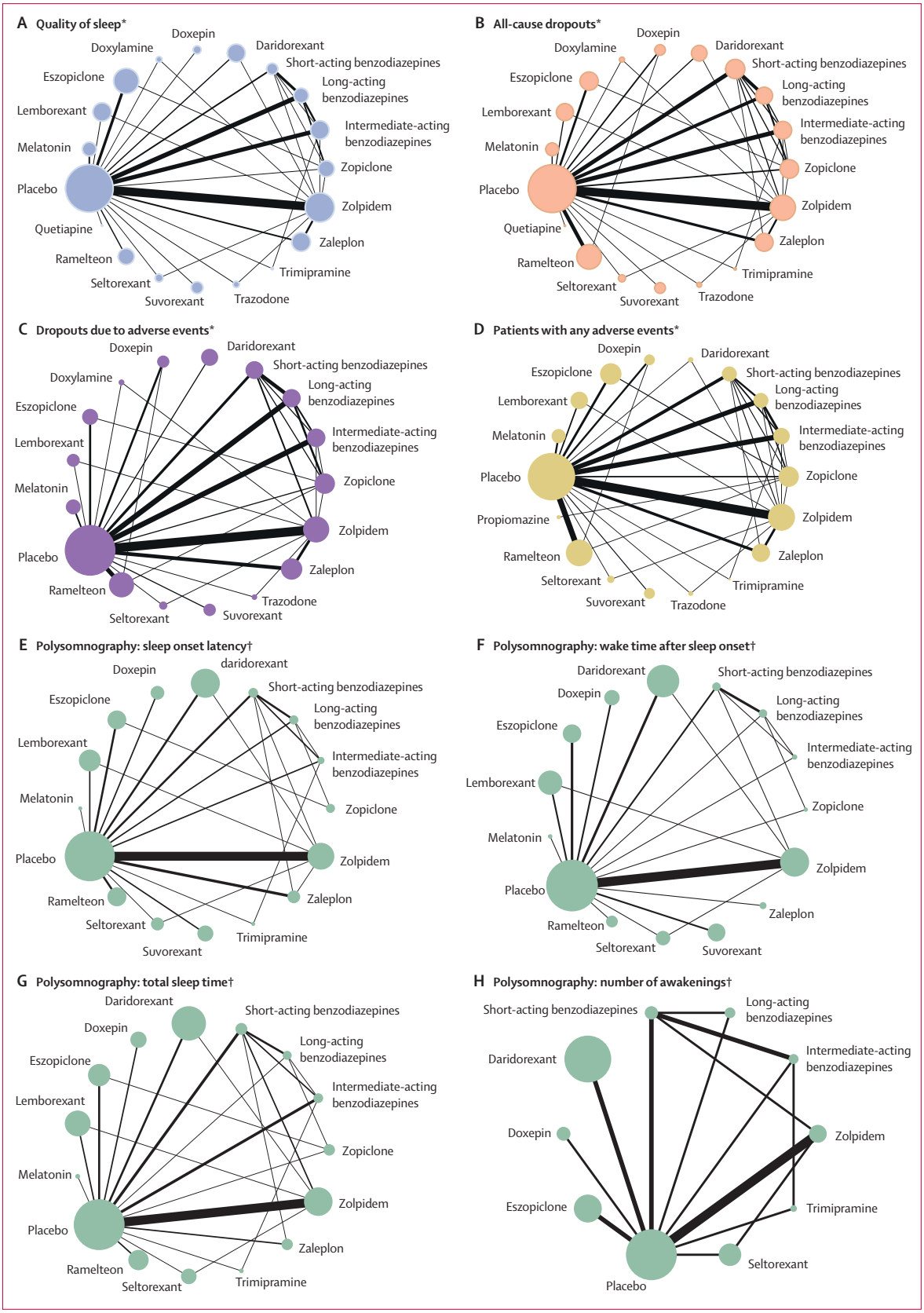
We evaluated possible heterogeneity of treatment effects and the robustness of our findings with subgroup network meta-analyses using age (>65 years and 18–65 years), severity of symptoms at baseline, and study sponsorship as covariates. We did sensitivity analyses including only trials at overall low risk of bias, trials employing standardised diagnostic criteria for insomnia, and trials with imputed SDs. We presented the findings from network meta-analysis using league tables and Vitruvian plots. Vitruvian plots use radial bar visualisation tools that synthesise the results of multiple outcomes (appendix pp 173–195).[30]

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit for publication.

Results

From 16 319 records initially retrieved from the search results, we included 170 RCTs published between May 1, 1977, and Nov 25, 2021, and compared 36 pharmacological treatments with each other or placebo; 154 double-blind RCTs were eligible for the network meta-analysis (figure 1). Overall, 12 670 participants were randomly assigned to placebo and 35 280 to one of the following medications: benzodiazepines (short half-life: alprazolam, brotizolam, midazolam, and triazolam; intermediate half-life: estazolam, loprazolam, lorazepam, lormetazepam, and temazepam; long half-life: flunitrazepam, flurazepam, nitrazepam, and quazepam),



(Figure 2 continues on next page)

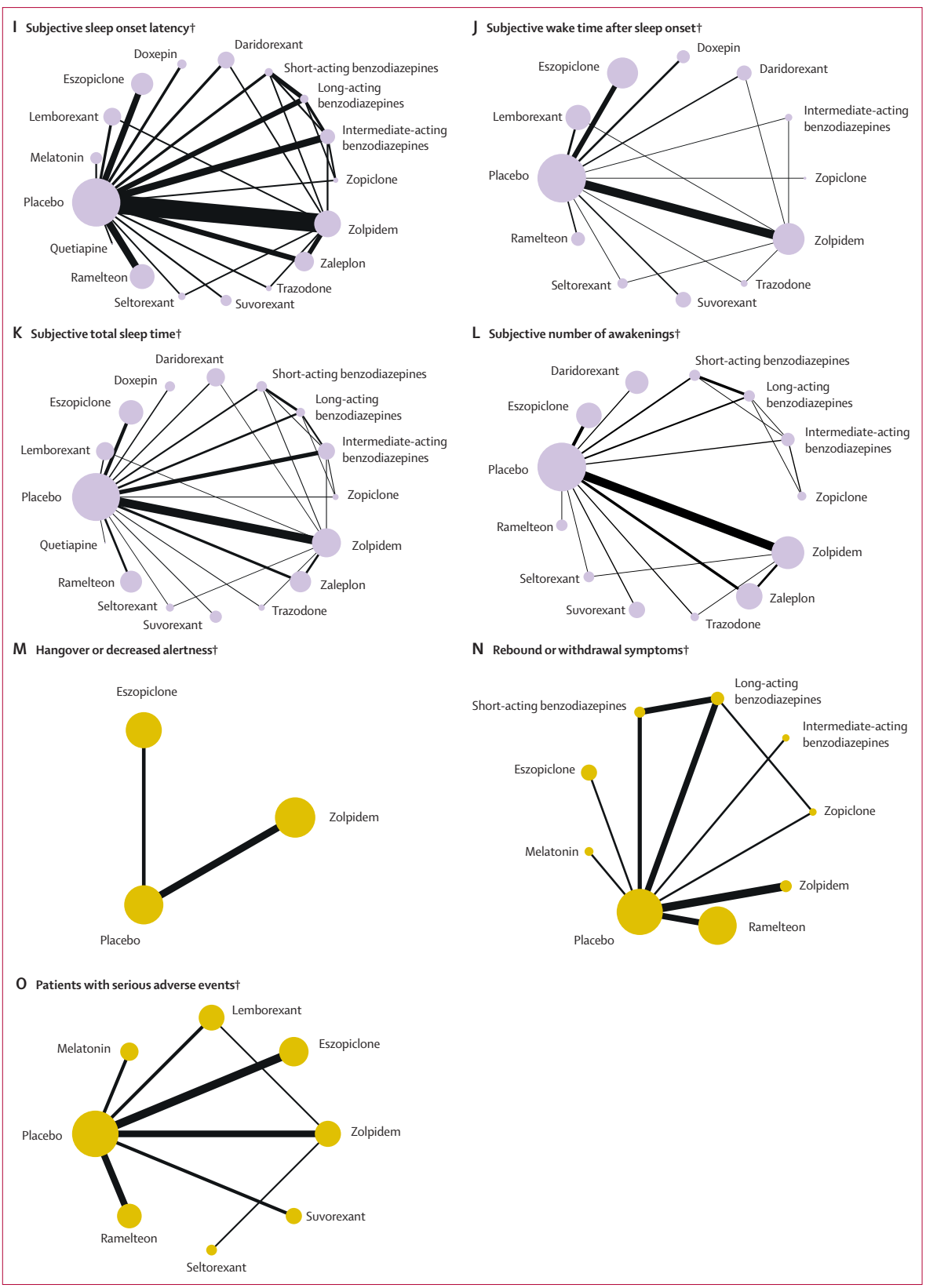


Figure 2: **Network of eligible comparisons for efficacy, acceptability, and tolerability at 4 weeks, and safety (primary and secondary outcomes) at study endpoint**

Network plots of eligible direct comparisons. Efficacy (quality of sleep: subjective quality of sleep, sleep onset latency, wake time after sleep onset, total sleep time, and number of awakenings), all-cause dropout rate, and dropouts due to adverse events were analysed at 4 (range 1–12) weeks. Patients experiencing any adverse events, harm outcomes, and specific adverse events were analysed at study endpoint. Network plots of long-term outcomes are reported in the appendix (pp 146–152). The width of the lines is proportional to the number of trials comparing each pair of treatments. The size of the nodes is proportional to the number of randomised participants. *Primary outcomes. †Secondary outcomes.

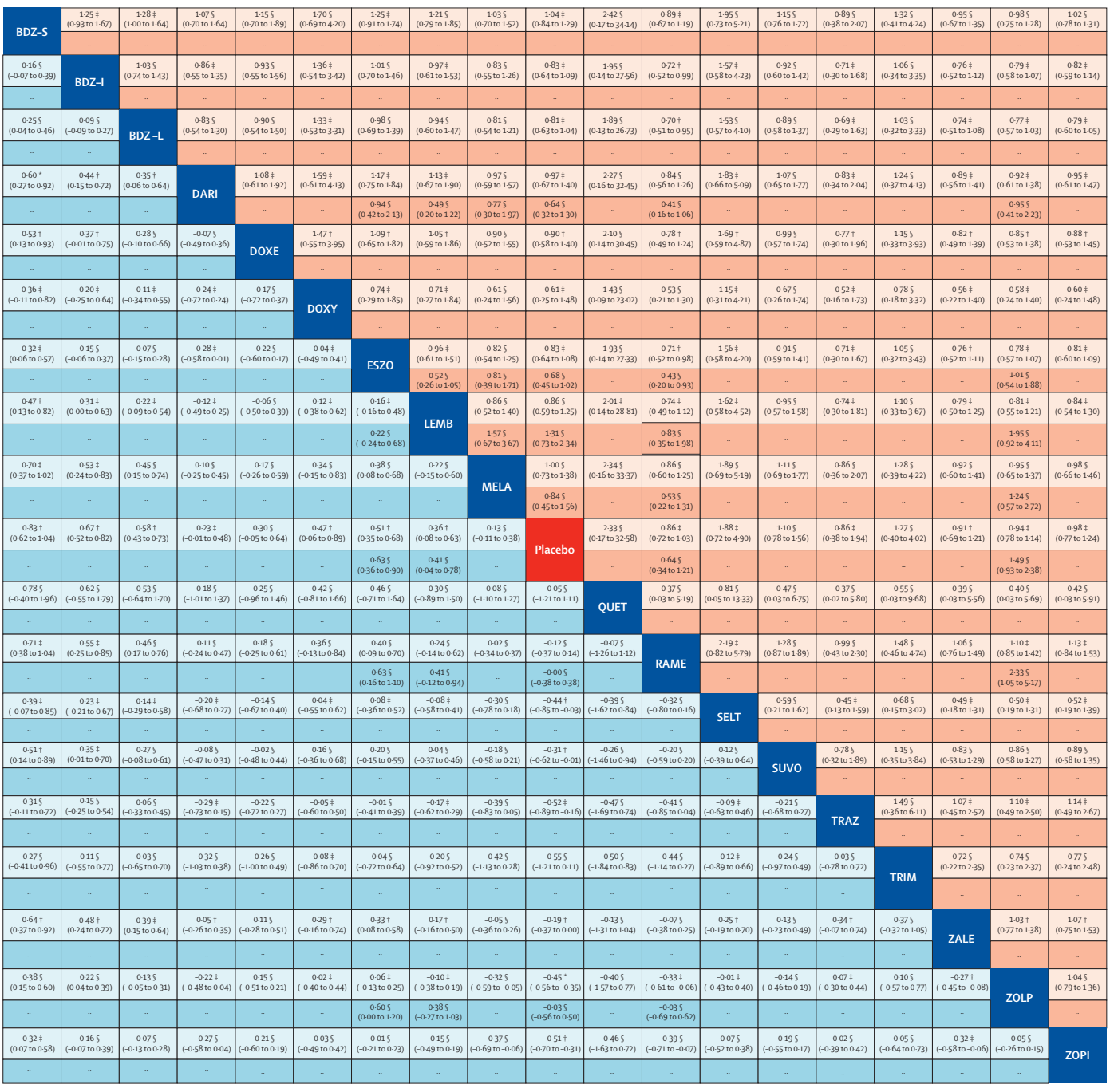


Figure 3: **Network meta-analysis for efficacy and acceptability at 4 weeks and after 3 months**

Comparisons should be read from left to right. Efficacy and acceptability estimates are located at the intersection between the column-defining treatment and the row-defining treatment. For efficacy, data are in standardised mean difference (95% CI), and data above 0 favour the column-defining treatment. For acceptability, data are odds ratio (95% CI), and data above 1 favour the column-defining treatment. Pharmacological treatments are reported in alphabetical order. The certainty of the evidence (according to confidence in network meta-analysis [CINeMA]) was incorporated in this figure as footnotes. BZD-I=intermediate-acting benzodiazepine. BZD-L=long-acting benzodiazepine. BZD-S=short-acting benzodiazepine. DARI=daridorexant. DOXE=doxepin. DOXY=doxylamine. ESZO=eszopiclone. LEMB=Lemborexant. MELA=melatonin. QUET=quetiapine. RAME=ramelteon. SELT=seltorexant. SUVO=suvorexant. TRAZ=trazodone. TRIM=trimipramine. ZALE=zaleplon. ZOLP=zolpidem. ZOPI=zopiclone. *High certainty of evidence, †Moderate certainty of evidence. ‡Low certainty of evidence. §Very low certainty of evidence.

daridorexant, diphenhydramine, doxepin, doxylamine, eszopiclone, lemborexant, melatonin, mirtazapine, ramelteon, propiomazine, quetiapine, seltorexant, suvorexant, trazodone, trimipramine, zaleplon, zolpidem, or zopiclone. The full description of study characteristics is in the appendix (pp 38–134).

For the acute treatment analysis, 86 trials (27 interventions; 21213 participants) were included for efficacy, 100 trials (28 interventions; 27991 participants) for acceptability, and 76 trials (25 interventions; 22811 participants) for tolerability. For the long-term analysis, five trials (five interventions; 2560 participants) were included for efficacy, and eight trials (seven interventions; 5152 participants) for acceptability and tolerability. For safety, 86 trials (27 interventions; 26543 participants) were included.

The mean study sample size was 265 (SD 311) participants, mean age was 51·7 (12·2) years, and 30113 (62·8%) of the patients were women. Of 160 studies reporting the information, 84 (52·5%) included adults aged 18–65 years, 15 (9·4%) included only older adults (>65 years), and 61 (38·1%) included adults without an age limit. The median duration of acute treatment was 2 (IQR 2–4) weeks and for the long-term studies was 25 (19–26) weeks. Of 170 trials included in the systematic review, 151 (88·8%) recruited outpatients only, 121 (71·2%) were placebo controlled, 71 (41·8%) enrolled patients only from North America, and 65 (38·2%) had three or more treatment groups. For the diagnosis of insomnia, 81 (47·6%) of studies used DSM standardised criteria; 90 (52·4%) of the 170 trials were funded by pharmaceutical companies, 43 (25·3%) were funded by non-profit entities, and sponsorship was unclear for 37 (21·8%). We retrieved unpublished information for 37 (24·0%) of 154 included trials. In terms of risk of bias, 82 (48·3%) trials were rated low risk, 33 (19·4%) unclear risk, and 55 (32·4%) high risk (appendix pp 135–40). We found no clear evidence of violations of the transitivity assumption when comparing characteristics of studies across comparisons; however, in most outcomes, the number of studies per comparison was small (appendix p 252).

Figure 2 shows the network of eligible comparisons for primary and secondary outcomes at 4 weeks (for long-term outcomes, see appendix pp 146–52). All pharmaceutical treatments had at least one placebo-controlled trial in one or more outcomes, except mirtazapine (figure 2). In terms of geometry of the networks, only the acute treatment outcomes had head-to-head trials between drugs and the corresponding network plots were well connected, whereas long-term data relied exclusively on placebo-controlled studies and the network plots were star shaped (appendix pp 147–51). The appendix (p 144) provides detailed results of all pairwise meta-analyses.

Figure 3 and figure 4 show the results of the network meta-analysis for the acute and long-term treatment outcomes (additional information is also reported in the appendix (pp 154–72). Benzodiazepines (short-acting, intermediate-acting, and long-acting), doxylamine, eszopiclone, lemborexant, zolpidem, and zopiclone were more efficacious than placebo in the acute treatment of insomnia disorder, with SMD ranging from 0·36 and 0·83 (moderate to high certainty of evidence). For long-term treatment, eszopiclone and lemborexant were more efficacious than placebo (eszopiclone: SMD 0·63 [95% CI 0·36–0·90; very low]; lemborexant: 0.41 [0·04–0·78; very low]) and no data were available for benzodiazepines, daridorexant, doxepin, doxylamine, melatonin, propiomazine, seltorexant, suvorexant, quetiapine, trazodone, trimipramine, zaleplon, and zopiclone. In terms of head-to-head comparisons, after 4 weeks of treatment, short-acting benzodiazepines were more effective than daridorexant, lemborexant, and zaleplon (SMDs 0·47–0·64 [high to moderate]), eszopiclone and zolpidem were more effective than zaleplon (eszopiclone: 0·33 [0·08–0·58; moderate]; zolpidem: 0·27 [0·08–0·45; moderate]; figure 3).

Intermediate-acting benzodiazepines, long-acting benzodiazepines, and eszopiclone had fewer discontinuations due to any cause than did ramelteon (intermediate-acting benzodiazepines: OR 0·72 [95% CI 0·52–0·99; moderate]; long-acting benzodiazepines: 0·70 [0·51–0·95; moderate]; and eszopiclone: 0·71 [0·52–0·98; moderate]) in acute treatment (figure 3). In the long term, eszopiclone and zolpidem caused fewer discontinuations than ramelteon (eszopiclone: OR 0·43 [95% CI 0·20–0·93; very low]; zolpidem: 0·43 [0·19·0·95; very low]; figure 3). Zopiclone and zolpidem caused more dropouts due to adverse events than did placebo after 4 weeks of treatment (zopiclone: 2·00 [1·28–3·13; very low]; zolpidem: 1·79 [1·25–2·50; moderate]). Zopiclone also caused more dropouts due to adverse events than did eszopiclone (1·82 [1·01–3·33]; low), daridorexant (3·45 [1·41–8·33; low), and suvorexant (3·13 [1·47–6·67; low]); figure 4). In terms of the number of patients reporting a side-effect at study endpoint, benzodiazepines, eszopiclone, zolpidem, and zopiclone had more side-effects reported than did placebo, doxepin, seltorexant, and zaleplon (OR range 1·27–2·78 [high to very low]), with zopiclone also having more than lemborexant, melatonin, ramelteon, and suvorexant (figure 4). Figure 5 shows a visual summary of the Vitruvian plots comparing all the drugs included in the network meta-analysis with placebo across all the primary outcomes, both acute and long term (see also appendix pp 173–195).

Secondary efficacy outcomes accorded with the results of the primary outcomes (https://github.com/andcipriani/NMA-on-insomnia/tree/main/3.%20Secondary%20Outcomes). In terms of specific adverse events, eszopiclone and zolpidem were associated with increased incidence of dizziness and nausea, and ramelteon caused more fatigue, lemborexant caused more headache, and a large group of drugs (including benzodiazepines, doxylamine,

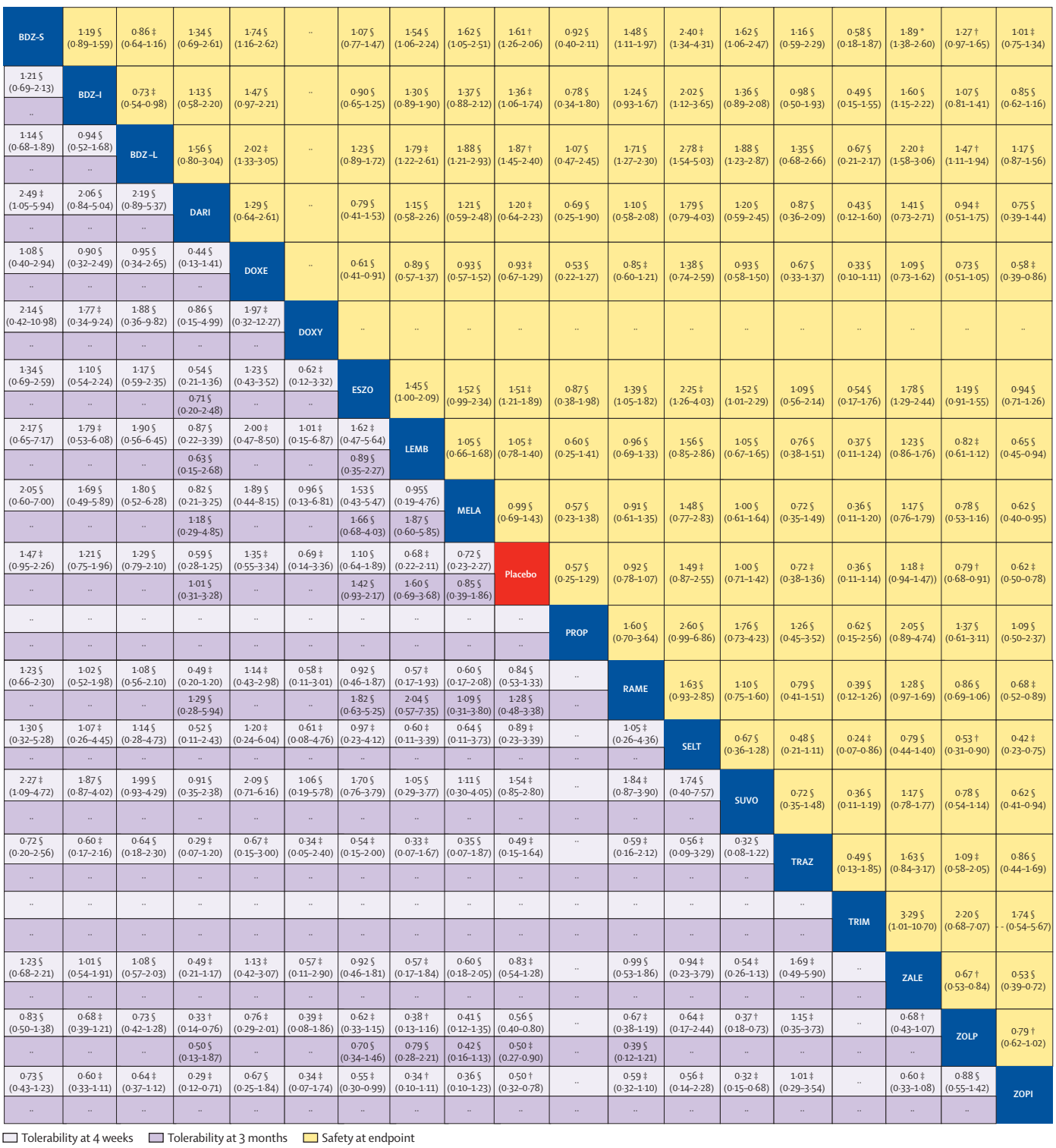
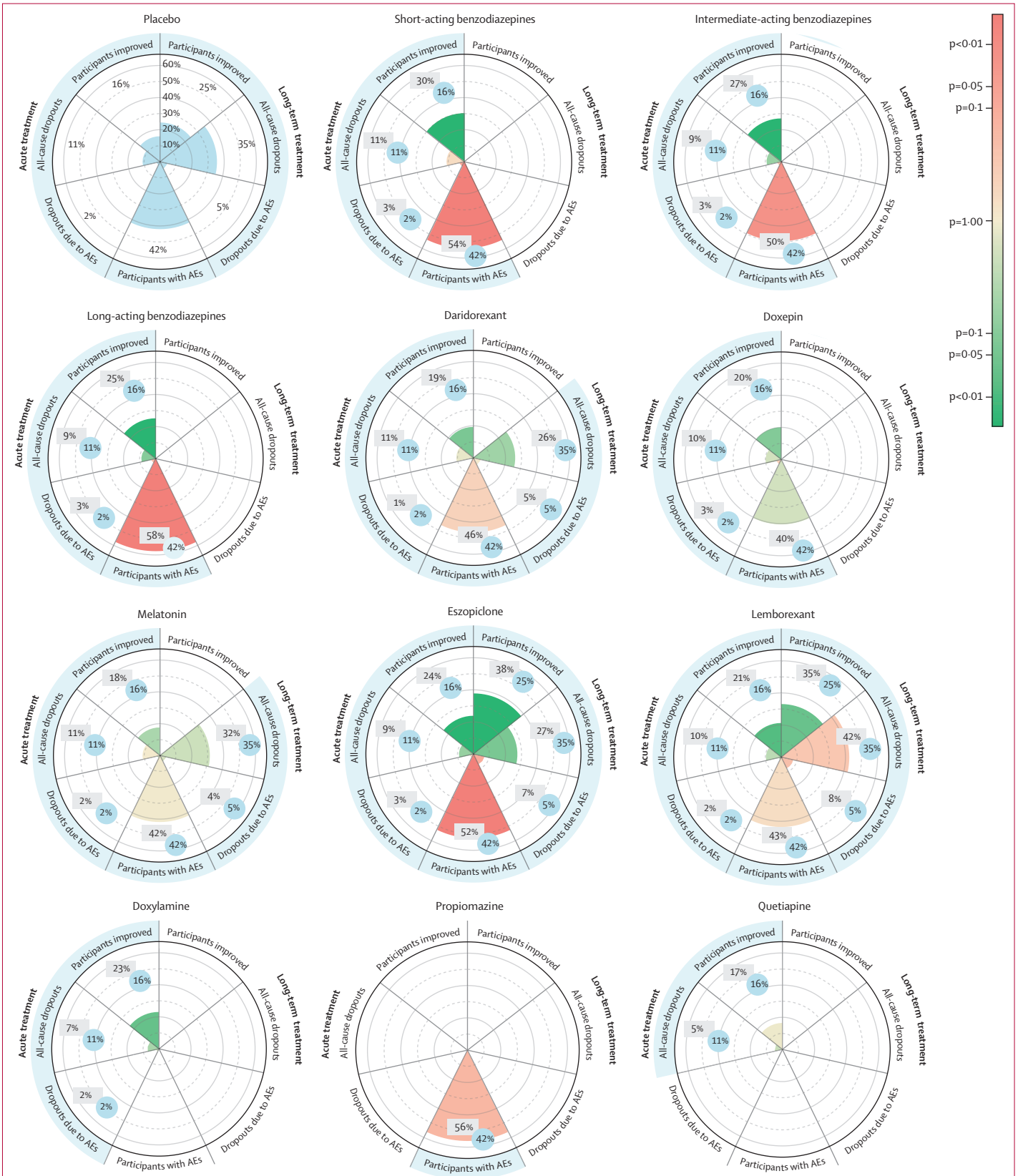


Figure 4: **Network meta-analysis for tolerability at 4 weeks and after 3 months, and safety at endpoint**
Comparisons should be read from left to right. Tolerability and safety estimates are located at the intersection between the column-defining treatment and the row-defining treatment. Data are in OR (95% CIs). For tolerability, ORs below 1 favour the column-defining treatment. For safety, ORs above 1 favour the column-defining treatment. Pharmacological treatments are reported in alphabetical order. The certainty of the evidence (according to confidence in network meta-analysis [CINeMA]) was incorporated in this figure as footnotes. BZD-I=intermediate-acting benzodiazepine. BZD-L=long-acting benzodiazepine. BZD-S=short-acting benzodiazepine. DARI=daridorexant. DOXE=doxepin. DOXY=doxylamine. ESZO=eszopiclone. LEMB=Lemborexant. MELA=melatonin. OR=odds ratio. PROP=propiomazine. RAME=ramelteon. SELT=seltorexant. SUVO=suvorexant. TRAZ=trazodone. TRIM=trimipramine. ZALE=zaleplon. ZOLP=zolpidem. ZOPI=zopiclone. *High certainty of evidence, †Moderate certainty of evidence. ‡Low certainty of evidence. §Very low certainty of evidence.



(Figure 5 continues on next page)

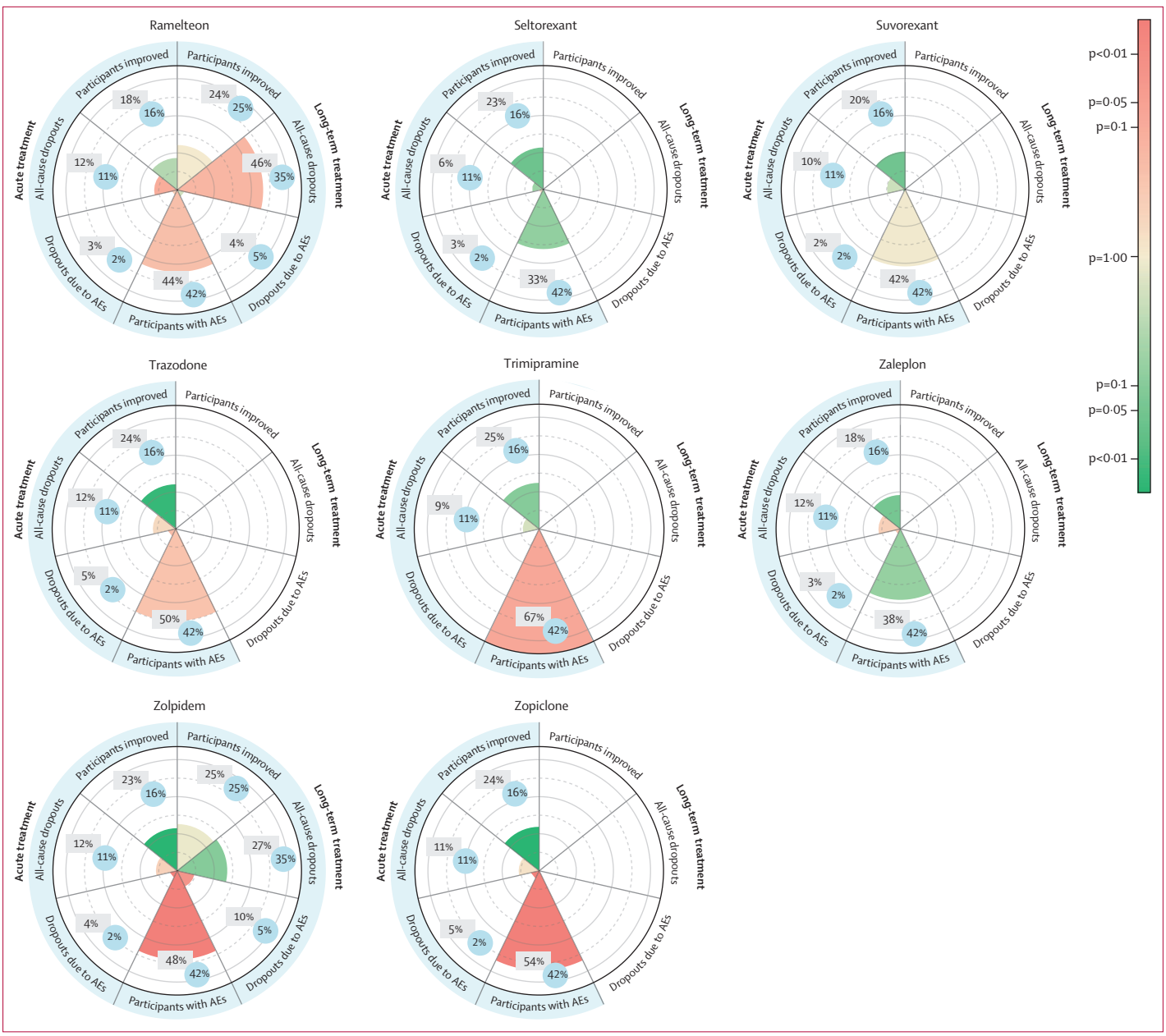


Figure 5: **Summary of Vitruvian plots for the overall profile of each active treatment and placebo across the seven primary outcomes**
Efficacy (participants improved), acceptability (all-cause dropouts), and tolerability (dropouts due to adverse events) are reported both as acute treatment (left) and long-term treatment (right). Safety (participants with adverse events) is reported in the bottom wedge and refers to the outcome at end of treatment. Colour indicates the relative performance of the intervention of interest and the precision of the estimate in comparison with placebo, from green (the intervention is better than placebo), to yellow (unclear whether the drug performs better or worse than placebo), and to red (the intervention is worse than placebo). Estimated event rates are expressed as absolute percentages for active treatments (grey rectangles) and placebo (light blue circles). Coloured wedge titles indicate availability of data for the analyses (see the Results section and the appendix [pp 173–195] for more details). AEs=adverse events.

eszopiclone, lemborexant, ramelteon, suvorexant, trazodone, zolpidem, and zopiclone) had a higher risk of sedation and somnolence than placebo or other active treatments (https://github.com/andcipriani/NMA-on-insomnia/tree/main/3.%20Secondary%20Outcomes/27.%20List%20of%20specific%20adverse%20events%20(number%20of%20patients)). We found only few data about hangover, withdrawal symptoms, and serious adverse events, so our analyses did not produce any meaningful results (https://github.com/andcipriani/NMA-on-insomnia/tree/main/3.%20Secondary%20Outcomes).

We found evidence of inconsistency in one (3%) comparison of 34 for acceptability (short term), one (5%) comparison of 21 for tolerability (short term), and three (9%) of 34 for safety (appendix p 170). We checked the data for errors, potential transitivity violations, or other

sources of inconsistency, but data extraction and data entry were found to be correct and no important variables were identified that differed across comparisons. We report the evaluation of local inconsistency for each primary outcome in the appendix (p 171) and report the evaluations of inconsistency for subgroup and sensitivity analyses in the appendix (pp 206–11). The appendix (p 172) shows the ranking of treatments based on the P-scores for each outcome.

We did subgroup analyses to study the effect of age (preplanned analysis), severity at baseline, and sponsorship (post-hoc analyses). These findings did not substantially differ from those of the primary analyses for most of the comparisons (appendix pp 196–202). In accordance with the review protocol, we also did sensitivity analyses including only trials at overall low risk of bias, only trials using standardised diagnostic criteria for insomnia, and only trials not imputed for continuous outcomes, and the results did not change significantly (appendix pp 203–05).

The certainty of the evidence for the primary outcomes as measured with CINeMA varied from high to very low (overall; 39 comparisons scored high or moderate). The majority of the comparisons involving benzodiazepines, doxepin, eszopiclone, lemborexant, ramelteon, zaleplon, zolpidem, and zopiclone were rated as moderate or low, and comparisons involving melatonin and suvorexant were rated as very low. Full information on CINeMA is described in the appendix (pp 212–268).

Discussion

To our knowledge, this systematic review and network meta-analysis is the most comprehensive data synthesis on pharmacological treatments for adults with a diagnosis of insomnia disorder. Considering all the outcomes at different timepoints (ie, acute and long-term treatment), lemborexant and eszopiclone had the best profile in terms of efficacy, acceptability, and tolerability; however, eszopiclone might cause substantial adverse events and safety data on lemborexant were inconclusive. Benzodiazepines (short-acting, intermediate-acting, and long-acting) were very effective in the acute treatment but their tolerability and safety profiles were not favourable; most importantly, there were no data available from long-term trials, so a proper evaluation of the clinical effects of these medications was not possible. The liability of benzodiazepines to produce tolerance, dependence, and withdrawal effects is well recognised. The FDA have drawn particular attention to the risks of CNS toxicity when benzodiazepines are coadministered with opiates.[31] Benzodiazepines are often prescribed not only for insomnia, but also for multiple indications, including generalised anxiety disorder, panic disorder, social phobia, and seizures.[29] Before starting patients on benzodiazepines, clinicians should always assess the potential benefit and risks for the individual patient, use caution when prescribing additional medications, aim for the lowest effective dose for the shortest treatment duration possible, and taper patients off benzodiazepines slowly, with regular and frequent follow up.[32] For the short-term treatment of insomnia, our findings suggest that benzodiazepines with intermediate half-lives, such as temazepam and lormetazepam, have better acceptability than short-acting or long-acting compounds.

Although structurally dissimilar to benzodiazepines, Z-drugs (ie, zopiclone, eszopiclone, zaleplon, and zolpidem) produce their hypnotic effects via benzodiazepine receptors, thereby enhancing the action of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). Among the Z-drugs included in our analyses, eszopiclone appears to have the best profile in term of short-term and long-term efficacy and acceptability. Eszopiclone is the active isomer of zopiclone but binds preferentially to the α-3 benzodiazepine GABA receptor subtype, which might underpin its particular therapeutic profile.[33]

Enhancing the activity of GABA has been the most common mechanism employed by licensed hypnotic drugs, but there is long tradition of using centrally acting histamine-1-receptor (H_1-receptor) antagonists, such as diphenhydramine and doxylamine, to facilitate sleep. Such compounds are often present in over-the-counter treatments for insomnia, and H_1 receptor antagonism is also the basis of the hypnotic action of the tricyclic antidepressants doxepin and trimipramine, as well as mirtazapine and quetiapine.[34] The antidepressant drug trazodone is used widely as a hypnotic, and its sedative effects are probably attributable to a combination of antihistaminic and noradrenergic α-1 receptor blockade.[35] With the exception of quetiapine, all the other H_1 receptor antagonists mentioned showed some efficacy in terms of quality of sleep in the short-term, but, among them, only doxepin had evidence to suggest its benefits in terms of number of dropouts and adverse events.

More recently developed hypnotics have targeted novel pharmacological mechanisms, with melatonin and ramelteon facilitating the activity of the pineal hormone (melatonin), whereas daridorexant, lemborexant, seltorexant, and suvorexant antagonise orexin receptors in the CNS.[34] Melatonergic interventions had poor efficacy, with no data in the long-term. In our analysis, lemborexant was the most efficacious orexin antagonist for improving sleep in both the short-term and long-term, whereas seltorexant and suvorexant had a better tolerability profile. Daridorexant, approved by the FDA in January, 2022,[36] did not show an overall material benefit in the treatment of insomnia disorder.

Current treatment guidelines have conflicting recommendations,[11–14] and the findings from our study differ from those of a systematic review and network meta-analysis about hypnotics for insomnia in older adults,[37] which included 24 studies (5917 patients) and listed doxepin, zaleplon, and suvorexant among the best options. Age can be a moderator of treatment effect, but it is not clear why older adults would respond better to

specific medications than the entire population of adults.[38] The analysis of separate outcomes for acute and long-term treatment, the higher number of studies, the larger total sample, and the inclusion of unpublished data in our review might explain why we found different results.

Quality of sleep was evaluated by various subjective scales and questionnaires. Older studies, particularly those investigating benzodiazepines, used mainly Likert scales, whereas most recent studies used more specific and standardised scales. Most recent trials tended also to report objective measures to assess sleep more consistently. However, the majority of the included studies were old (the median publication year for benzodiazepines was 1990) and they did not report such data. In evaluating efficacy as primary outcome, we considered subjective quality of sleep because it is considered the most clinically informative measurement.[12] It is worth noting that we also analysed polysomnography or actigraphy data whenever available, with results being in line with the primary findings.

Insomnia disorder is often persistent and is essential to consider the long-term effects.[2] We found only very few studies evaluating long-term treatment for insomnia. Clinicians and patients should be aware that most of the pharmacological agents used long term for insomnia have only indications for acute treatment from regulatory agencies. Observational studies evaluating hypnotics in the long term found associations with several safety concerns, including dementia,[39] fractures,[40] and infections.[16] However, evidence from observational studies should be interpreted with caution as these studies might be biased by residual confounding.[13]

Our literature search was as comprehensive as possible. We contacted study authors for supplemental material and the funnel plots were not suggestive of small study effects or publication bias. However, we cannot rule out the possibility that some unpublished studies remain missing and that published reports overestimated the efficacy of treatments.[41] There are online archives where trials are prospectively registered; however, these archives collect reliable information only about the most recent studies.[20] By making the dataset fully and freely available, we welcome any information that might help to clarify any mistakes or omissions in our dataset.

Our study has some limitations. According to CINeMA, we rated many comparisons as low or very low quality, especially for the long-term timepoints, and many trials did not report adequate information about randomisation and allocation concealment, which restricts the interpretation of these results.[42] To increase the methodological rigour of the contributing evidence, we included only double-blind trials, which were very similar in design and conduct. The poor information in terms of risk of bias assessment might be a matter of reporting; however, we presented full details about the risk of bias of all included studies and CINeMA in the appendix (pp 135–40, 252–316). At visual inspection, the network for the acute timepoints is well connected, but the geometry of the networks for the long-term timepoints showed single-standing nodes, almost always connected only to placebo. Comparisons between many active treatments relied on indirect evidence and were based on the untestable consistency assumption, which might have limited the reliability of the results.[25]

We excluded patients with physical comorbidities and treatment-resistant insomnia, which might limit the applicability of the results to these clinical subgroups, but it was intended as a methodological strength to assure transitivity in the network. Some of the trials combined sleep hygiene education with pharmacological treatments, a potential confounding factor that could affect transitivity; however, we did not find strong evidence of inconsistency across the network. We analysed only average treatment effects and were not able to investigate potentially important clinical and demographic modifiers of treatment response at the individual patient level (eg, gender, severity of symptoms, and duration of illness). We did not do a formal cost-effectiveness analysis and data about specific adverse events were reported inconsistently across the individual studies. This absence is an important limitation because patients and clinicians make their own judgement, not only considering efficacy and acceptability of treatment but also the incidence and severity of side-effects.[43] Many, but not all, the drugs included in our analysis are off-patent and available in generic form, which might have important implications in terms of public health policy and recommendations from health technology assessment bodies. Of 30 drugs included in our network, only lorazepam is included in the WHO list of essential medicines,[44] which makes it available worldwide and also ready to use in low-income and middle-income countries.

In conclusion, the findings from this network meta-analysis represent the best evidence base that is currently available to guide the choice of pharmacological treatment for insomnia in adults. All statements comparing the merits of one drug with another should be tempered by the potential limitations of the available evidence, the characteristics of the patient populations, and the uncertainties that might result from choice of dose or treatment setting. From a clinical point of view, it is important to also consider non-pharmacological treatments for insomnia disorder, as they are supported by high-quality evidence and recommended as first-line treatment by guidelines.[12] We hope that these results will inform shared decision making for patients, carers, clinicians, guideline developers, and policy makers. Future studies should focus on the specific characteristics of patients to provide personalised estimates of comparative effectiveness and individualised predictions regarding the probability of response to treatment and of side-effects.[45]

Contributors

FDC and AC conceived and designed the study. CDG, EGO, CB, and LA contributed to the methods of the study. AK, FF, GLD, MC, NW, and VDF selected the articles and extracted the data. FDC, EGO, CDG, OE,

and AC analysed the data. AC, FDC, EGO, GLD, and OE accessed and verified the data. FDC and AC wrote the first draft of the manuscript. GLD, MC, EGO, VDF, NW, AK, AT, ZM, FF, CDG, DJQ, PC, CB, and LA interpreted the data and contributed to the writing of the final version of the manuscript. All authors agreed with the results and conclusions of this Article. AC, EGO, OE, and FDC had full access to all the data, and AC was responsible for the decision to submit for publication.

Declaration of interests

FDC is supported by the UK National Institute for Health Research (NIHR) professorship to AC (grant RP-2017–08-ST2–006) and by the NIHR Oxford Health Biomedical Research Centre (BRC-1215-20005), and is a DPhil candidate at the University of Oxford and an employee of Boehringer Ingelheim International. EGO is supported by NIHR Applied Research Collaboration Oxford and Thames Valley at Oxford Health National Health Service Foundation Trust, by the NIHR Oxford Cognitive Health Clinical Research Facility, and by the NIHR Oxford Health Biomedical Research Centre (BRC-1215-20005), and has also received research and consultancy fees from Angelini Pharma. AT has received research and consultancy fees from INCiPiT (Italian Network for Paediatric Trials) and Angelini Pharma. DJQ has received funding for a randomised controlled trial of melatonin in acute mania (MIAMI-UK), funded by the UK National Institute for Health (RCPG 0407-10155-RISC); Lundbeck supplied the active modified release medication and placebo but were otherwise independent of the study. DJQ has also received a consultancy fee from Guidepoint (Boston, MA, USA). AC is supported by the NIHR Oxford Cognitive Health Clinical Research Facility, by an NIHR Research professorship (RP-2017-08-ST2–006), by the NIHR Oxford and Thames Valley Applied Research Collaboration, and by the NIHR Oxford Health Biomedical Research Centre (BRC-1215–20005). AC has also received research and consultancy fees from INCiPiT (Italian Network for Paediatric Trials), CARIPLO Foundation, and Angelini Pharma, and is the chief and principal investigator of two trials about seltorexant in depression, sponsored by Janssen. OE was supported by the Swiss National Science Foundation (80083). All other authors declare no competing interests.

Data sharing

The full dataset and information for the Vitruvian plots are freely available online GitHub (https://github.com/andcipriani/NMA-on-insomnia).

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