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The effect of Dual Orexin Receptor Antagonists on sleep: a systematic review and pairwise meta-analysis

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ABSTRACT

Evidence supporting pharmacological treatment of insomnia remains limited. Dual orexin receptor antagonists (DORAs), a novel drug class, show therapeutic promise. This systematic review and meta-analysis evaluates DORAs' efficacy, safety, and tolerability across all eligible populations, regardless of diagnosis.

We systematically searched MEDLINE, Embase, PsycINFO, Cochrane CENTRAL, WHO ICTRP, ClinicalTrials.gov through January 2026 for randomised controlled trials comparing DORAs with placebo. We included studies across all patient populations. Analyses employed random-effects models, calculating risk ratios (RR) for dichotomous outcomes, weighted mean differences (MD) for continuous outcomes, and standardised mean differences (SMD) when scales varied. Primary outcomes included subjective total sleep time, sleep quality, treatment-emergent somnolence and insomnia. Subgroup and sensitivity analyses explored heterogeneity and result robustness.

77 trials (16,416 participants) were included. DORAs improved subjective total sleep time (MD = 18.91 min , 95 % CI: 15.87 to 21.95). Sleep quality was not improved (SMD = 0.19, 95 % CI: 0.02 to 0.39). DORAs increased the risk of somnolence (RR = 2.91, 95 % CI: 2.31 to 3.67), while no difference was found for insomnia (RR = 0.97, 95 % CI: 0.60 to 1.57). Effects were consistent across treatment durations.

DORAs appear largely efficacious, safe and tolerable. Clinical interpretation should be done with caution, in conditions other than insomnia, as data for these diagnoses were scarce.

1. Introduction

Insomnia is a sleep-wake disorder affecting millions of people worldwide, with a prevalence of 30–35 % and a chronic course of illness in many cases [1]. As defined by the DSM-V, insomnia is characterised by reduced sleep quality or quantity, causing significant daytime impairment of functioning [2].

Insomnia has been associated with increased cardiovascular risk and diseases, such as diabetes, hypertension, metabolic syndrome, ischemic heart disease and stroke [3–8]. At the same time, insomnia and sleep disturbance are highly comorbid with several major psychiatric conditions, with bidirectional causality being implicated for Major Depressive Disorder and Neurodegenerative Disorders [9–12].

Thus, recent revisions of diagnostic criteria for insomnia disorder

Abbreviations: **CBTi**, cognitive behavioral therapy for insomnia; **CI**, confidence interval; **DORA**, dual orexin receptor antagonist; **DSM**, diagnostic and statistical manual of mental disorders; **FDA**, food and drug administration; **GRADE**, grading of recommendations assessment, development and evaluation; **LSEQ**, Leeds sleep evaluation questionnaire; **MDD**, major depressive disorder; **MD**, mean difference; **NAW**, number of awakenings; **OR1,2**, orexin receptors 1 and 2; **PRISMA**, preferred reporting items for systematic reviews and meta-analyses; **PSQI**, Pittsburgh sleep quality index; **RCT**, randomized controlled trial; **RR**, risk ratio; **RoB**, risk of bias; **SMD**, standardized mean difference; **SOL**, sleep onset latency; **sNAW**, subjective number of awakenings; **sSOL**, subjective sleep onset latency; **sTST**, subjective total sleep time; **sWASO**, subjective wake after sleep onset; **TST**, total sleep time; **WASO**, wake after sleep onset.

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have established that symptoms of insomnia, such as reduced total sleep time, increased sleep onset latency or wakefulness after sleep onset, as well as reduced sleep quality, transcend specific diagnoses. Accordingly, the previously used distinction between primary and secondary insomnia has been abandoned [2,13,14]. This reflects treatment approaches in daily clinical practice, where insomnia is typically treated using the same methods, irrespective of its cause or associated diagnosis [15].

Despite insomnia's effect on patients' health and quality of life, very few pharmacological treatment options have been found to be of adequate efficacy [16,17]. Benzodiazepines and z-drugs are commonly used, but they are associated with serious adverse effects such as addiction, cognitive impairment and driving underperformance, falls and hospitalization, particularly in the elderly [18–20]. As per current guidelines, Cognitive Behavioral Therapy for Insomnia (CBTi) is the treatment of choice, while all pharmacological options are supported by weak evidence, especially concerning long-term treatment [21–23]. However, there are practical constraints that need to be considered, such as the limited availability of CBTi amid growing demand, which often outstrips service capacity[24]. Additional challenges include patients' adherence and the appropriateness of CBTi for specific groups, such as individuals with Autism Spectrum Disorders [25–27]. Furthermore, the quality of evidence is affected by inherent limitations of psychotherapeutic trials, including issues with blinding and the common use of comparators such as waitlists or no treatment, which may lead to inflated effect sizes [28]. Lastly, evaluation of safety outcomes require more attention as drop-out rates may be considerably high [29]. Therefore, pharmacotherapy may be the only viable option for some individuals, particularly when CBTi fails to alleviate symptoms.

The Dual Orexin Receptor Antagonists (DORAs) is a class of drugs approved mainly for the treatment of difficulties with sleep onset and/or maintenance, with suvorexant being the first to be approved by the Food and Drug Administration (FDA) in 2014 [30]. Daridorexant is the only medication licensed in the UK and Europe for long-term treatment of chronic insomnia in adults, recommended when CBT-I is ineffective or unavailable European Medicines Agency [31]; National Institute for Health and Care Excellence [32]. Other hypnotics are limited to short-term use, and alternative DORAs like suvorexant and lemborexant are not yet approved in the UK or by EMA.

Orexins A and B are peptide neurotransmitters excreted by the lateral hypothalamic neurons, which are most active during the day [33]. Orexin's binding with orexin receptors 1 and 2 (OR1 and OR2) of the tuberomammillary nucleus is believed to stabilise wakefulness, among other actions.The DORAs are competitive antagonists of orexins for their binding positions at both the OR1 and OR2, which underpins their mechanism of action for the treatment of insomnia [34].

Currently, several pairwise and network meta-analyses have investigated the DORAs' efficacy, safety and tolerability, both as a drug class and for each DORA separately [18,35–41]. However, all aforementioned reviews and meta-analyses focus on insomnia as the primary diagnosis of the participants. To our knowledge, there is no meta-analytic evidence concerning the effect of DORAs on sleep in patients with any underlying condition.

Aligning with recent updates on classification, diagnosis and treatment of insomnia, as well as with daily clinical practice, this systematic review and pairwise meta-analysis examines the efficacy, safety and tolerability of all DORAs, both as a category and for each drug separately, on sleep-related parameters, irrespective of primary diagnosis.

2. Methods

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Table S1) [42].

2.1. Protocol

An a priori written study protocol was published in Open Science Framework in March 2025 and is provided in detail at the Supplementary Material, Section 2 (Registration DOI: 10.17605/OSF.IO/DE2U9).

2.2. Population, intervention, and types of included studies

Patients with any type of health problems were included, irrespective of any psychiatric or medical diagnosis, not excluding healthy individuals. No restrictions in terms of age, sex, ethnicity, comorbidities, chronicity of illness, dose range, or system of diagnostic classification were applied. The intervention of interest was DORAs, either as monotherapy or adjunctive therapy, administered in any form or preparation, at or above therapeutic levels – subtherapeutic doses were excluded. The comparator was placebo. The study eligibility criteria included: (a) inclusion of only RCTs (excluding cluster RCTs); (b) no restrictions on blinding methods, accepting open-label, single-blind, or double-blind designs; and (c) reporting of any sleep-related efficacy, safety, or tolerability outcomes. No minimum trial duration was set as inclusion criterion. In cases of crossover-design of the RCTs, results were extracted only for the first trial period. If this was not possible due to reporting of only overall results, studies were included only if the washout period between treatment phases was at least five times the drug's half-life time, in order to mitigate the risk of carryover effects [43,44].

2.3. Search strategy and selection criteria

A systematic literature search was undertaken using Medline (via Ovid – see Table S2 for search string), EMBASE, APA (American Psychological Association, via PsycINFO), Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) up to January 2026. No limitations were applied in terms of language, year, and status of publication. We also searched and screened the references of previously published relevant reviews and all included studies if applicable.

At least two reviewers (AS, PL, PP, IB) independently screened all abstracts and subsequently the relevant full texts from the searches performed, as well as additional records identified through other sources. This process was conducted using Rayyan [45]. Any conflicts that arose during the selection process were resolved through extensive discussions among the reviewers and, when necessary, with the senior authors (MS and ASL).

2.4. Outcome measures and data extraction

2.4.1. Primary outcomes

The primary outcomes of our study were (i) subjective total sleep time (sTST - continuous) measured in minutes, as reported by the participants; (ii) sleep quality (continuous) as measured by any validated sleep quality measure/questionnaire, such as Pittsburgh sleep quality index (PSQI) or Leeds sleep evaluation questionnaire (LSEQ) [46,47]; (iii) number of participants with somnolence (dichotomous) as a treatment emergent side effect and (iv) number of participants with insomnia (dichotomous) as a treatment emergent side effect. If available, study data for these outcomes were categorised based on time points of assessment: all time points (using the last reported endpoint), short-term (last endpoint within 6 weeks of baseline), and long-term (last endpoint more than 6 weeks from baseline).

2.4.2. Secondary outcomes

Secondary outcomes included (i) polysomnographic or actigraphic recordings of total sleep time (TST - continuous), enabling the exploration of potential differences between patient-rated subjective and objective evaluations of insomnia; (ii) sleep onset latency (continuous), both subjective (sSOL) and objective (SOL), i.e. the time needed to fall

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asleep, which serves as an indicator of sleep onset insomnia; (iii) the number of nocturnal awakenings (continuous), representing disturbances in sleep continuity; (iv) nocturnal time spent awake after sleep onset (wakefulness after sleep onset) (continuous), both subjective (sWASO) and objective (WASO), a quantitative measure of sleep maintenance; (v) daytime impairment (DI) (continuous), assessed through performance tasks and self-reported scales like the Epworth Sleepiness Scale or the Stanford Sleepiness Scale [48,49]; (vi) patients' subjective well-being/quality of life (e.g., SF-36, EURO-Qol) (continuous), an outcome that integrates aspects of both efficacy and tolerability; (vii) therapeutic effect on parasomnias, specifically nightmares, vivid dreams and parasomnia behaviours; (viii) number of dropouts due to adverse effects (dichotomous); (ix) number of dropouts due to sleep-related adverse effects (dichotomous); (x) number of participants with adverse effects as a global measure of tolerability (dichotomous); (xi) number of participants with sleep-related adverse effects (dichotomous); (xii) number of participants reporting parasomnias (dichotomous) as treatment-emergent adverse effects; (xiii) the number of participants who required hypnotic rescue treatment for insomnia using a hypnotic drug other than the DORAs, as required during the trial (dichotomous) and (xiv) any other relevant outcomes, such as behaviour integrity, as a perceived impact of sleep on cognitive and psychomotor functioning upon waking.

Data extraction was performed by at least two reviewers (AS, PL, PP, IB) independently. The first and/or corresponding authors from all included studies were contacted for missing information and possible corrections. In case of missing data concerning standard deviation (SD), respective values were calculated through standard errors, confidence intervals (CIs) and p-values or, in some cases, medians and interquartile ranges. Finally, any conflict between the reviewers was resolved through discussion with the senior authors (ASL and MS).

2.5. Statistical analysis

This meta-analysis was conducted with the use of R Studio version 4.4.1 [50]. We employed the random-effects model of meta-analysis. The model is typically more conservative in assessing statistical significance. However, a potential disadvantage is that it more weight is assigned to smaller studies, as compared to the fixed effect model, with a possible impact on the effect size [51]. To test the robustness of our findings, we performed a sensitivity analysis for the primary outcomes, examining the impact of using a fixed-effect model.

For dichotomous outcomes risk ratio (RR) was calculated, while weighted mean difference (MD) was used for continuous variables. When an outcome had different units of measurement, the effect size was calculated as Hedge's adjusted g (standardised mean difference, SMD). Effect sizes are presented along with their 95 % CIs.

Change-from-baseline data were considered preferable to post-intervention (endpoint) values, owning to its reduced between-person variability [52]. In case change data were not available, endpoint values were extracted.

Heterogeneity was assessed via inspection of the forest plots, and calculating the I^2-value and its 95 % CI. Reasons for heterogeneity were explored with the following subgroup and sensitivity analyses.

Subgroup analyses were performed for all the primary outcomes, including (i) total nocturnal sleep time, (ii) sleep quality (as measured by any validated sleep quality measure/questionnaire), (iii) insomnia as a treatment emergent side effect, and (iv) somnolence as a treatment emergent side effect. The following subgroups were considered a priori, as per our published protocol (depending on data availability): (a) per primary diagnosis, (b) per specific DORA (suvorexant, lemborexant, daridorexant etc.), (c) monotherapy vs. add-on DORA treatment, (d) participants older than 65 vs. not., (e) comorbid substance misuse vs. not, (f) presence of an organic mental disorder vs. not and (g) inclusion of supratherapeutic doses or not.

Sensitivity analyses on the primary outcomes were also planned a priori; (a) exclusion of non-double–blind studies (open and single-blind studies), (b) exclusion of studies that presented only completer analyses, (c) exclusion of studies with high risk of bias, (d) fixed effect instead of random effects model, (e) exclusion of studies with imputed data, (f) exclusion of sponsored studies, (g) exclusion of studies that allowed the use of hypnotics other than DORA which were prescribed as required during the study, (h) exclusion of studies whose duration was 5 days or less. A post hoc sensitivity analysis was conducted with the exclusion of studies whose inclusion criteria required more than one diagnosis.

2.6. Risk of bias

Two independent reviewers (AS and PL) assessed the risk of bias using the Cochrane risk of bias tool (study based) for randomised trials (RoB) [53]. The overall risk of bias for each study was classified as as 'high', 'moderate' or 'low' based on the assessment of individual risk of bias components according to Furukawa et al. (Table S4) [54].

2.7. Publication bias

To address potential publication bias, our search strategy included grey literature databases, such as clinical trial registries and major conferences' abstract lists (see paragraph 2.3). For the primary outcomes, contour-enhanced funnel plots with a minimum of ten studies were generated and evaluated for symmetry, using the 'trim and fill' method and the Egger's g test [55–57].

2.8. Certainty of evidence

We used Cochrane's GRADE approach to assess the certainty of the evidence. A Summary of Findings table was generated for all primary outcomes and for (TST) [58].

3. Results

3.1. Search results and characteristics of included studies

We identified 1998 records, of which 318 were sought for a full-text screening. We included 77 relevant RCTs with a total of 16,416 randomised participants. The studies were published between 2012 and 2025. The search and screening results are summarised in the PRISMA flow diagram and table of included studies, as presented in the Supplementary material (Fig. S1 and Table S3, respectively) [42]. The mean number of patients per study was 181.67 and the median was 48, while the range of study participants was 10–1021. Most studies (53.84 %) used a parallel design. The majority of the RCTs were conducted in USA (41 studies, 52.56 % of all included studies) [59–63,63,64,64–76,77–95]. Almost all studies compared DORAs with placebo as monotherapy, except for one [71]. The majority of the studies included adults; mean age was 51.24 years (range 18–89), while 14 of them included only elderly people (18.18 %). Females comprised a larger proportion of the population (53.29 %). The majority of the included RCTs were sponsored, with the exception of 6 studies [59,81,82,84,96,97]. Average trial duration was 28.42 days and median duration was 9 days, with a range from 1 to 365 days. Finally, Several studies required that patients fulfill the criteria of DSM-V for Insomnia Disorder, while also diagnosed with other conditions, such as multiple sclerosis [59], Parkinson's disease [60], bipolar disorder [98], Alzheimer's disease [99], nocturia [73], post-traumatic stress disorder [100], early menopause [83], fibromyalgia [84], diabetes mellitus [92].

The 77 relevant RCTs involved with participants with a wide spectrum of diagnoses, including: (i) Insomnia Disorder (or Primary Insomnia or Chronic Insomnia, 25 RCTs) [66–68,70,72,73,75,76,77,78,83,85,94,100–109], (ii) Major Depressive Disorder (MDD, five RCTs) [65,110,86,88,111], (iii) Bipolar Disorder (one RCT) [98], (iv) Substance Use Disorder (three RCTs) [71,74,112], (v) Obstructive Sleep

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Apnea (four RCTs) [63,64,113,114], (vi) Chronic Obstructive Pulmonary Disease (three RCTs) [63,87,115], (vii) Alzheimer's Disease (two RCTs) [79,99], (viii) ICU admission diagnoses (most: Infection) (one RCT) or (ix) Severe Acute Disease (one RCT) [96,116], (x) Fibromyalgia (one RCT) [84], (xi) Painful Diabetic Neuropathy (one RCT) [69], (xii) Migraine (one RCT) [61], (xiii) Multiple Sclerosis (one RCT) [59], (xiv) Diabetes (one RCT) [92], (xv) Restless Leg Syndrome (two RCTs) [91,117], (xvi) Parkinson's Disease (one RCT)[60] and (xvii) history of heart surgery (one RCT)[82]. 24 studies involved only healthy participants (32.83 %) [64,80,81,89,90,93,95,97,107,118–130]. All psychiatric diagnoses were operational, with the use of DSM-IV or DSM-V.

32 ongoing studies without published results were identified (Table S5).

3.2. Risk of bias assessment

56 studies (72.73 %) were judged as having overall low risk bias, while 20 studies (25.97 %) were judged as having an overall moderate risk of bias; only one study (1.30 %) was at overall high risk of bias. The risk of bias summary plot and assessment per individual study are presented in the Supplementary material (Figs. S2 and S3, respectively).

3.3. Primary outcomes

3.3.1. Subjective Total Sleep Time (sTST)

27 studies provided sTST data measured in minutes, using sleep diaries [61,66,67,69,71–73,76,77,78,83,85,91,92,94–96,98,101,103,

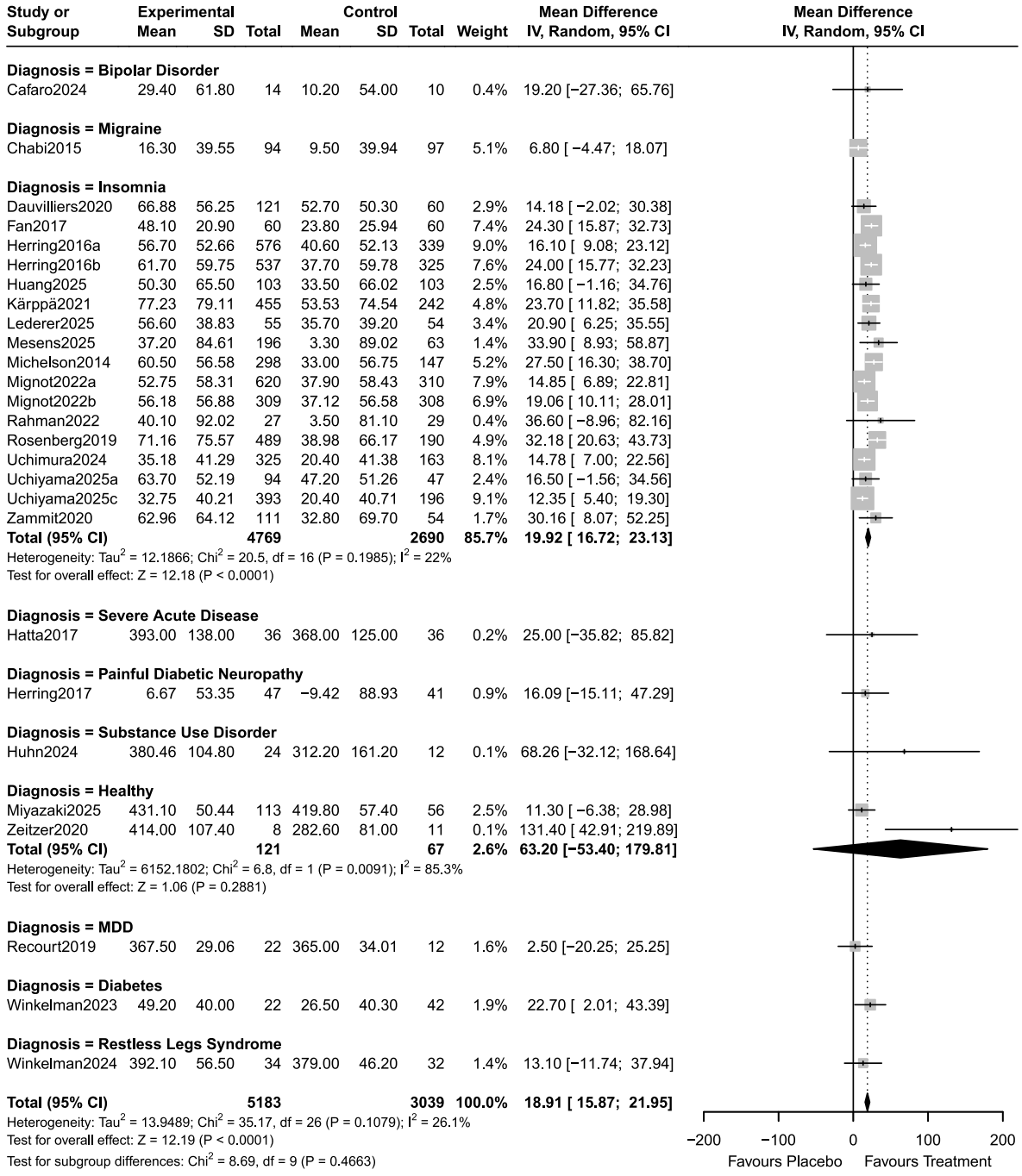

Fig. 1. Forest plot – subjective TST measured in minutes, pooled result and subgroup analysis by Diagnosis. Note. MD = Weighted Mean difference with 95 % CI (Confidence Intervals). "Favours treatment" indicates higher sTST.

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106–108,111,123]. DORAs were found to improve sTST compared to placebo (MD = 18.91 min , 95 % CI: 15.87; 21.95, p-value<0.01, 27 RCTs, N = 8,222, I^2 = 26.1 %, Fig. 1). This effect was consistent following both short- and long-term treatment with DORAs. (Figures S4.2 and S4.3). The certainty of evidence is high for this outcome (Table S6).

3.3.2. Quality of Sleep

17 studies reported data on Sleep Quality, using scales such as PSQI, Patient-Reported Outcomes Measurement Information System - Sleep Disturbance (PROMIS-SD), a visual analogue scale or a Likert scale [59,66,67,72,73,76,82,88,92,95,96,99,101,106,112]. The analysis showed no difference between DORAs and placebo, although substantial heterogeneity was found (SMD = 0.19, 95 % CI: 0.02; 0.39, p-value = 0.07, 17 RCTs, N = 5,222, I^2 = 70.4 %, Fig. 2). Trials with longer duration (more than 6 weeks) reached statistical significance, although the improvement in sleep quality with DORAs versus placebo was clinically small (Figures S5.2 and 5.3). The certainty of evidence is moderate for this outcome (Table S6).

3.3.3. Somnolence as a treatment emergent side effect

60 RCTs reported somnolence as a treatment emergent side effect [60–66,68–73,75,76,77–79,81–87,89,90,92–94,96,98,109,114,116,124,129,130]. The results showed that more participants on DORAs experienced somnolence compared to placebo (RR = 2.91, 95 % CI: 2.31; 3.67, p-value<0.01, 60 RCTs, N = 14,454, I^2 = 31.6 %, Fig. 3). This effect was consistent following both short- and long-term treatment with DORAs. (Figures S6.2 and S6.3). The certainty of evidence is high for this outcome (Table S6).

3.3.4. Insomnia as treatment emergent side effect

Ten studies reported insomnia as treatment emergent side effect [67,71,84,86,92,93,111,114,116,130]. The analysis showed that there was no difference between DORAs and placebo concerning this outcome and no heterogeneity was found (RR = 0.97, 95 % CI: 0.60; 1.57, p-value = 0.95, 10 RCTs, N = 1001, I^2 = 0 %, Fig. 4). All studies reported assessments after short term treatment with DORAs (less than 6 weeks). The certainty of evidence is moderate for this outcome (Table S6).

3.4. Secondary outcomes

3.4.1. Objective Total Sleep Time (TST)

27 studies reported on objective TST measured in minutes, using either polysomnography or actigraphy [63,63,67,71,76,79,84,85,89,91,94–100,104,107,111–115,117,127,128,130]. DORAs significantly increased TST compared to placebo, although substantial heterogeneity was observed. (MD = 31.42 min, 95 % CI: 24.91; 38.93, p-value<0.01, 28 RCTs, N = 2,906, I^2 = 60.2 %, Fig. S8). All studies only reported on

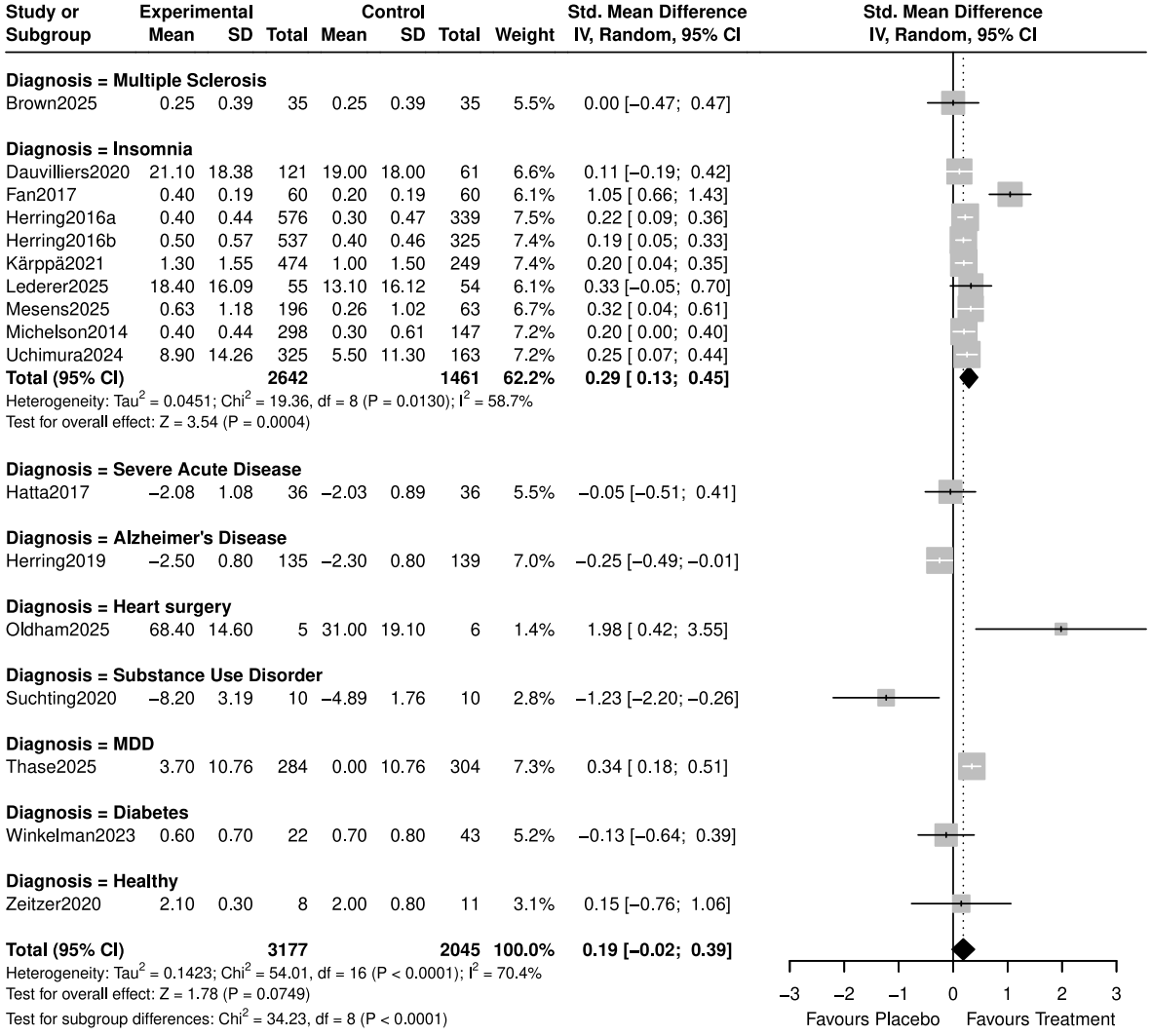

Fig. 2. Forest plot – Sleep Quality measured by PSQI, PROMIS-SD, visual analog or likert scales, pooled result and subgroup analysis by diagnosis. Note. SMD = Standardised Mean difference with 95 % CI (Confidence Intervals). "Favours treatment" indicates improved sleep quality.

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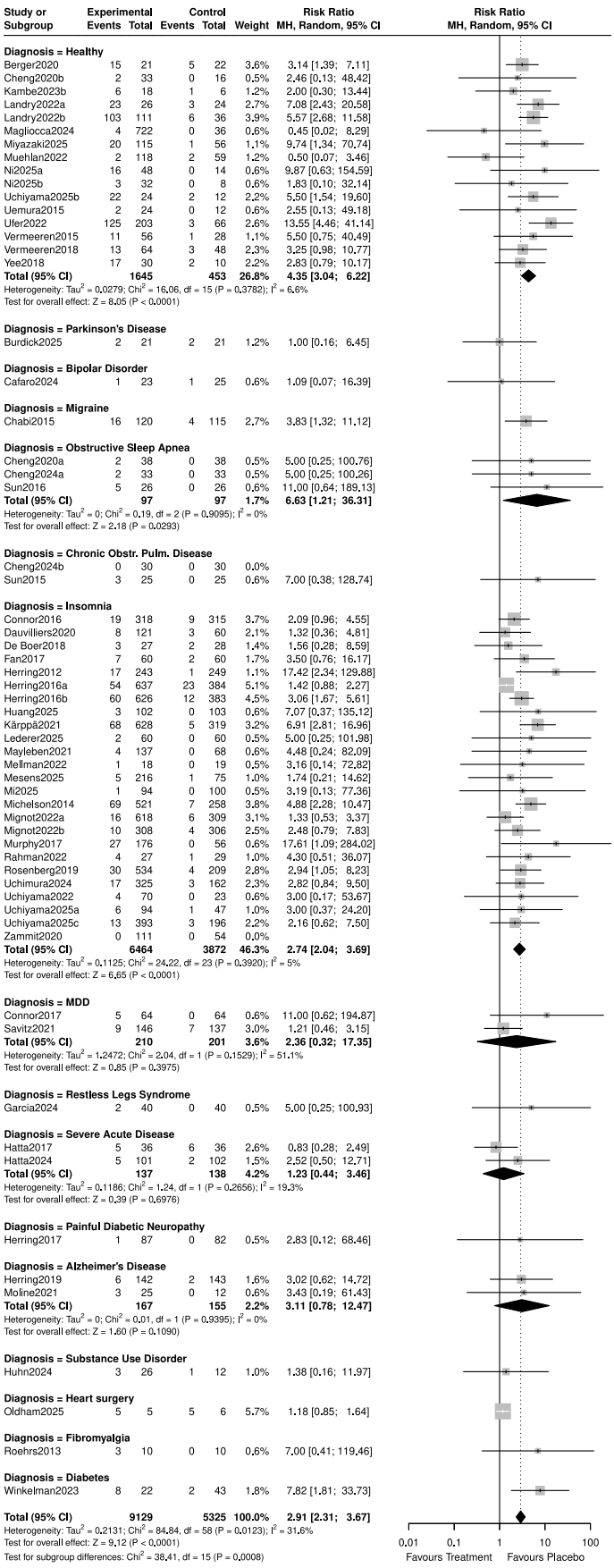

Fig. 3. Forest plot – Number of participants with Somnolence as treatment emergent adverse effect, pooled result and subgroup analysis by diagnosis. Note. RR = Risk Ratio with 95 % CI (Confidence Intervals). "Favours treatment" indicates fewer participants with somnolence.

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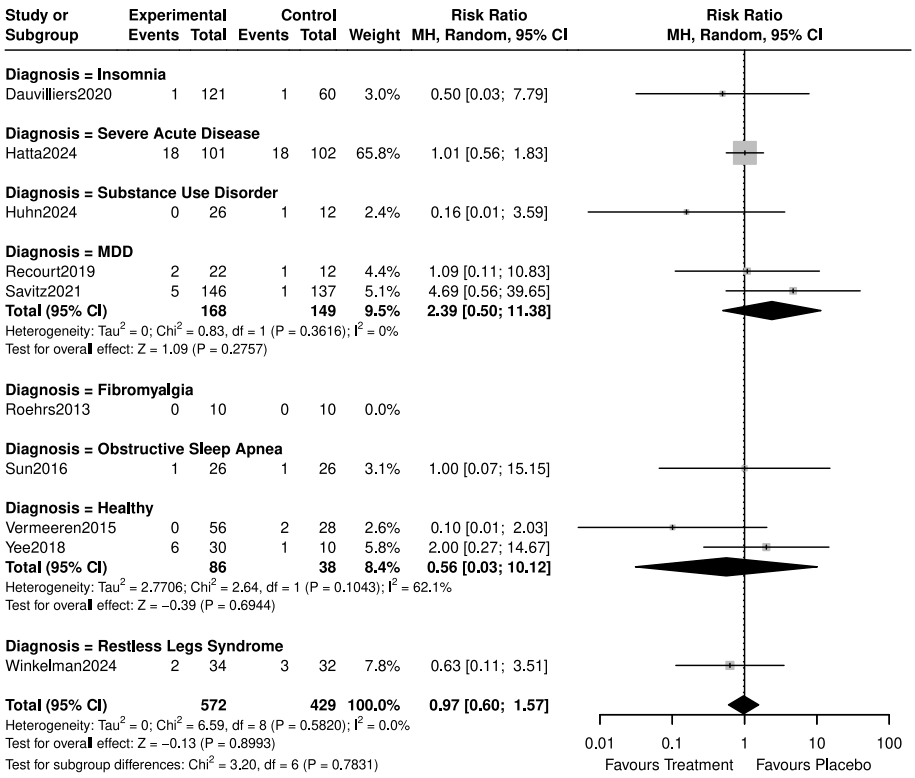

Fig. 4. Forest plot – Number of participants with Insomnia as treatment emergent adverse effect, pooled result and subgroup analysis. Note. RR = Risk Ratio with 95 % CI (Confidence Intervals). "Favours treatment" indicates fewer participants with insomnia as treatment-emergent adverse effect.

assessments after short term treatment with DORAs (less than 6 weeks). The certainty of evidence is moderate for this outcome (Table S6).

3.4.2. Sleep onset latency

3.4.2.1. Subjective sleep onset latency (sSOL). 25 RCTs reported sSOL measured in minutes, using sleep diaries [59,61,64,66,67,69,71,72,76, 77,83,85,91,92,94–96,101,103,104,106–108,111,123,131]. This analysis showed that DORAs significantly decreased sSOL compared to placebo, with data presenting substantial heterogeneity (MD = −8.07 min, 95 % CI: 10.20; −5.94; p-value <0.01, 25 RCTs, N = 6,861, I^2 = 61.4 %, Figure S9.1).

3.4.2.2. Objective sleep onset latency (SOL). 31 studies reported SOL measured in minutes, using either Polysomnography or Actigraphy [62, 63,63,66,66,67,71,76,78,84,85,89,94,97,99,100,103–105,107,109, 111,113–115,117,127,128,130]. This analysis showed that DORAs significantly decreased SOL compared to placebo, with data presenting high heterogeneity. (MD = −9.95 min , 95 % CI: 13.15; −6.75; p-value<0.01, 31 RCTs, N = 6,585, I^2 = 77.5 %, Figure S9.2).

3.4.3. Number of nocturnal awakenings

3.4.3.1. Self-reported number of nocturnal awakenings (sNAW). Nine RCTs reported on sNAW [61,66,69,76,77,96,111,123]. The meta-analysis showed that there is no difference between DORAs and placebo concerning this outcome (MD = −0.001 awakenings, 95 % CI: −0.08; 0.08, p-value = 0.98, 9 RCTs, N = 3,624, I^2 = 39.9 %, Figure S10.1).

3.4.3.2. Objective number of nocturnal awakenings (NAW). Seven RCTs reported on NAW using either Polysomnography or Actigraphy [63,76, 79,84,111–113]. The results showed that there is no difference between DORAs and placebo (MD = −0.02 awakenings, 95 % CI: −1.42; 1.39, p-value = 0.98, 7 RCTs, N = 638, I^2 = 44.7 %, Figure S10.2).

3.4.4. Nocturnal time spent awake after sleep onset

3.4.4.1. Self-reported nocturnal time spent awake after sleep onset (sWASO). 21 RCTs reported on sWASO measured in minutes [61,66,67, 69,71,72,76,77,83,85,91,92,94], [103,104,106–108,111,123]. This analysis showed that DORAs significantly decreased sWASO compared to placebo (MD = −7.3 min, 95 % CI: 10.47; −4.58, p-value<0.01, 21 RCTs, N = 6517, I^2 = 46.6 %, Figure S11.1).

3.4.4.2. Objective nocturnal time spent awake after sleep onset (WASO). 31 studies reported on objective WASO using either Polysomnography or Actigraphy [60,62,63,66,66,67,71,76,78,84,85,89,91, 94,97,99], [100,103–105,107,111,113–115,117,127,128,130]. The results showed that DORAs significantly decreased WASO, though a high heterogeneity was found. (MD = −18.88 min, 95 % CI: −23.63; −15.13, p-value=<0.01, 31 RCTs, N = 6,693, I^2 = 76.7 %, Figure S11.2).

3.4.5. Daytime impairment (Sleep awakening score)

18 RCTs reported data on daytime impairment [60,67,72,73,76,78, 81,85,94,97], [104,106,108,114,121,123,130]. This outcome was measured by the Insomnia Severity Index, the Insomnia Daytime Symptoms and Impacts Questionnaire, visual analog or likert scales [132,133]. The meta-analysis showed no difference between DORAs and placebo concerning this outcome although a very high heterogeneity was found (SMD = 0.04, 95 % CI: −0.27; 0.35; p = 0.80, 18 RCTs, N = 5, 498, I^2 = 86.8 %, Fig. S12).

3.4.6. Quality of life

Only one RCT reported data on Quality of Life, using the European Quality-of-Life five-Dimensions scale [73,134]. Meta-analysis was not performed for this outcome (Fig. S13).

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3.4.7. Number of dropouts due to adverse effects

34 RCTs reported on the number of dropouts due to any adverse effect [61,63–66,66,67,69,70,72,76,77,78,81,83,85,86,88], [91–94, 100,101,103–108,116,123]. The results showed that there is no difference between DORAs and placebo (RR = 1.07, 95 % CI: 0.80; 1.42; p-value = 0.65, 34 RCTs, N = 11,859, I^2 = 0.0 %, Fig. S14).

3.4.8. Number of participants with adverse effects

72 RCTs reported on the number of participants with adverse effects as a global measure of tolerability [59–63,63,64–66, [66–76], [77–86], [88–96,98], [100,101,103,104,106–109,111,114–117], [119–123,125, 126,128,130]. The risk of adverse effects was higher in participants receiving DORAs compared to placebo, while a moderate heterogeneity was found (RR = 1.22, 95 % CI: 1.12; 1.33, p-value <0.01, 72 RCTs, N = 14,941, I^2 = 49.6 %, Fig. S15).

3.4.9. Number of participants with sleep - related adverse effects

23 RCTs reported on the number of participants with sleep related adverse effects [59,60,62,69,72,73,75,76,83,85,89,94,98,100], [101, 103,107,108,114,120,122,123,130]. The analysis showed that participants receiving a DORA were more likely to experience a sleep-related adverse effect than those on placebo (RR = 4.10, 95 % CI: 2.83; 5.95, p-value <0.01, 23 RCTs, N = 4370, I^2 = 0 %, I^2 = 0 %, Fig. S16).

3.4.10. Number of participants with parasomnia symptoms as treatment emergent adverse effects

19 RCTs reported on the number of participants with parasomnias as treatment emergent adverse effects [61,66,70,74,78,79,84,86,90,92,99, 104,106,107,109,117,121]. The analysis showed that participants receiving DORAs were more likely to experience parasomnia symptoms (vivid or abnormal dreams, nightmares or sleep paralysis) than those on placebo (RR = 2.60, 95 % CI: 1.42; 4.78, p-value<0.01, 19 RCTs, N = 5091, I^2 = 0 %, Fig. S17).

3.5. Publication bias

Both p-values for Egger's test and the respective regression plots indicate lack of asymmetry for all outcomes. However, careful inspection of funnel plots and trim-and-fill funnel plots shows a mild small-study effect for the outcomes of Sleep Quality and Somnolence as treatment emergent adverse effect (Supplementary Material Section 10).

3.6. Subgroup analyses

Subgroup analysis per diagnosis or per DORA did not show any change of the pooled results. All subgroup analyses' forest plots are presented in the Supplementary Material (Section 9).

3.7. Sensitivity analyses

The majority of pooled estimates remained stable following the exclusion of studies based on pre-specified sensitivity criteria. It is noted that almost all analyses of primary outcomes included studies sponsored by pharmaceutical companies. However, for objectively measured TST, the sensitivity analysis suggests that DORAs may still be effective compared to placebo even when sponsored studies are excluded (MD = 21.83 min, 95 % CI: 2.72; 40.94, p-value = 0.03, 3 RCTs, N = 112, I^2 = 0 %, Figure S8.10). All sensitivity analyses' forest plots are presented in the Supplementary Material (Section 9).

4. Discussion

To our knowledge, this is the largest meta-analysis to date examining DORAs, based on 77 studies including more than 16,000 participants randomised and evaluating a wide range of outcomes. Our diagnosis-blind approach allowed us to investigate the effect of DORAs on sleep in populations with any underlying condition.

Based on our findings, participants who received DORAs experienced significant improvements in TST, WASO and SOL (both self-reported and objective), compared to those who received placebo, but not in sleep quality. Regarding safety and tolerability outcomes, DORAs were associated with more sleep-related adverse effects. However, dropout rates due to adverse effects were comparable between the two groups, indicating good overall acceptability and tolerability, despite the inclusion of very high doses. The evidence for primary outcomes and objective TST is of moderate to high certainty, reinforcing confidence in our findings.

We observed substantial heterogeneity for most efficacy outcomes. In contrast, safety and tolerability data were homogeneous across studies. Notably, even among outcomes with high heterogeneity, the direction of effect was concordant in nearly all studies, indicating variability in effect magnitude rather than inconsistent therapeutic benefits.

One potential source of heterogeneity could be unmeasured psychiatric comorbidities, such as subthreshold depression or anxiety [135, 136]. Nevertheless, our analysis could not confirm this as a key source; a sensitivity analysis excluding relevant trials did not reduce the I^2 value (Figure S5.1.13). This limitation is due in part to the broad diagnostic classifications of psychiatric comorbidities (especially mood disorders), which lack information on severity or treatment resistance, limiting interpretation and potentially obscuring subgroup effects.

The results of studies with participants diagnosed with Alzheimer's Disease or Substance Use Disorder showed substantial differences from other studies, concerning Sleep Quality and TST (Fig. 2 and S8) [79,99, 112], This may reflect mechanistic differences, as neurodegenerative disease and substance-related circadian disruption may limit responsiveness to sleep interventions[137–139].

This meta-analysis is novel for its inclusion of supratherapeutic doses. these higher doses do not change the core findings, a formal dose-response relationship has yet to be established in the literature. Determining this relationship is an essential direction for future research to fully understand the clinical profile of DORAs.

The present meta-analysis demonstrates a strong efficacy of DORAs on increasing duration and improving continuity and quality of sleep. Although the analysis was conducted using a diagnosis-blind approach, the majority of included data, especially on sTST and sleep quality (Figs. 1 and 2), were derived from studies on insomnia disorder. As a result, pooled estimates are likely most representative of these populations, which may limit generalisability to other conditions.

Regarding sleep quality, the pooled analysis of all studies did not show a statistically significant improvement with DORAs (SMD = 0.34, 95 % CI: 0.03; 0.65, N = 3065, Figure S5.3). A subgroup analysis by diagnosis, however, revealed a clear, small benefit exclusively for participants with primary insomnia (SMD = 0.29, 95 % CI: 0.13 to 0.45, Fig. 1); for all other conditions, data were limited to single trials. Furthermore, an analysis restricted to longer-duration trials (>6 weeks) also demonstrated a clear, small benefit (SMD = 0.34, 95 % CI: 0.03 to 0.65, N = 3065; Figure S5.3). The latter finding suggests that perceived sleep quality may improve over a longer treatment period compared to sleep quantity or continuity, which showed significant gains even in short-term analyses (e.g., sTST MD = 19.07 min, 95 % CI: 16.56 to 21.58, N = 8610; Figure S4.2).

Our findings on efficacy seem to be in accordance with most relevant meta-analyses [35,36,39,40]. Only a meta-analysis in patients with obstructive sleep apnoea reported no reduction of WASO although TST was increased [140]; however, this synthesis included only four studies (N = 126) and may have been underpowered, as the cumulative number of participants included was less than 1000 [141]. Several observational studies also confirm our results of sleep-related efficacy, both in patients with insomnia and in those with mood disorders and substance use disorder [142,143], based on self-reported and objective measures [144–148].

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DORAs' pharmacodynamic actions as non-GABAergic hypnotics, acting through a reversible and competitive binding to orexin receptors may indicate a lower risk of tolerance and/or dependence of patients [34]. Many studies have investigated the use of DORAs for discontinuation of other hypnotics, such as benzodiazepines or benzodiazepine-receptor agonists (Z-drugs), with results showing successful dose reduction of these drugs or full transition to DORAs [143,149–154] with no reduction in effect when comparing studies of less than and more than six weeks. This suggests an absence of pharmacological tolerance and, by extension, a potentially lower risk of dependence. A separate review of data from trials longer than 6 months in duration further confirmed the sustained improvement in sTST (3 RCTs, N = 1262) [72,77,101]. Therfore, our findings support the current NICE guidance for the long-term use of daridorexant to treat chronic insomnia (TA922), which recommends discontinuation only in individuals who do not respond adequately within three months and regular reassessment for those who continue treatment National Institute for Health and Care Excellence [32].

Aside of sustained efficacy, no rebound insomnia or withdrawal phenomena have been reported in run-out periods of some RCTs [72,78,106]. However, this can only be confirmed by discontinuation trials, specifically designed to measure sleep parameters upon stopping DORAs in patients receiving long-term treatment.

Regarding safety, concerns remain about daytime somnolence, sleep-related events and parasomnias, all of which were found to increase with DORAs as compared to placebo. This adverse effect profile of DORAs has also been identified in most previous meta-analyses, with particular concerns associating DORAs with narcolepsy-like symptoms [37,39,40,109]. Pharmacovigilance studies also indicate a strong association of DORAs with sleep-related adverse effects, such as sleep paralysis, parasomnias and somnolence [155,156]. Thus, although generally well tolerated, treatment with DORAs warrants caution from both service users and physicians.

4.1. Limitations

To our knowledge, this systematic review and meta-analysis is the first to synthesise evidence using a diagnosis-blind approach. While this method aligns with recent changes in insomnia classification and treatment—moving away from the distinction between primary and secondary insomnia—it is not without limitations. The broad scope of evidence synthesis may contribute to the moderate to high heterogeneity observed in many efficacy outcomes. However, this heterogeneity cannot be solely attributed to the diagnosis-blind approach, as substantial variability was also observed within individual diagnostic categories. Heterogeneity may also be increased by effect modifiers such as trial duration and doses included, though this was not confirmed by relevant subgroup and sensitivity analyses. Finally, a broad scope of measurement tools included for outcomes such as sleep quality may account for increased between-study variability. Finally, our choice to include also super-therapeutic doses may expand the boundaries of acceptable doses, but may have also introduced additional heterogeneity or complicate the conclusions on the safety profile of DORAs.

4.2. Conclusion

This meta-analysis confirms the robust efficacy of DORAs—a recently approved insomnia treatment—for improving sleep across diagnoses. Their overall safety and tolerability profile is favorable, though the risk of sleep-related adverse effects and the lack of extended follow up data suggest a need for caution and monitoring. Clinical interpretation for conditions other than insomnia should be cautious, as these were underrepresented in the available trials.

CRediT authorship contribution statement

Anastasios Stefanou: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Investigation, Formal analysis, Data curation. **Paraskevi Lampropoulou:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Investigation, Formal analysis, Data curation. **Paraskevi Papageorgiou:** Data curation. **Ioanna Boskou:** Data curation. **Andreas S. Lappas:** Writing – review & editing, Project administration, Methodology, Investigation. **Nikolaos Christodoulou:** Writing – review & editing, Visualization, Validation. **Vasilios Panteleimon Bozikas:** Writing – review & editing, Visualization, Validation. **Myrto T. Samara:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

Data availability statement

The R code and associated data files used in this study are available as supplementary materials.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Myrto T. Samara reports a relationship with Lundbeck that includes: consulting or advisory and speaking and lecture fees. Myrto T. Samara reports a relationship with Viatris that includes: consulting or advisory and speaking and lecture fees. Myrto T. Samara reports a relationship with Recordati that includes: consulting or advisory and speaking and lecture fees. Vasilios Panteleimon Bozikas reports a relationship with Viatris that includes: consulting or advisory and speaking and lecture fees. Vasilios Panteleimon Bozikas reports a relationship with Vian Vianex that includes: consulting or advisory and speaking and lecture fees. Vasilios Panteleimon Bozikas reports a relationship with Teva that includes: consulting or advisory and speaking and lecture fees. Vasilios Panteleimon Bozikas reports a relationship with Innovis that includes: consulting or advisory and speaking and lecture fees. Vasilios Panteleimon Bozikas reports a relationship with Lundbeck that includes: consulting or advisory and speaking and lecture fees. Vasilios Panteleimon Bozikas reports a relationship with Johnson and Johnson that includes: consulting or advisory and speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2026.108792.

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