Efficacy of micronised progesterone for sleep: a systematic review and meta-analysis of randomised controlled trial data

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Abbreviations: GABA-A, γ-aminobutyric acid type A; MPA, medroxyprogesterone acetate; PSQI, Pittsburgh Sleep Quality Index; WHI, Women's Health Initiative

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Abstract

Context: Pre-clinical data has shown progesterone metabolites improve sleep parameters through positive allosteric modulation of the GABA-A receptor. We undertook a systematic review and meta-analysis of randomised controlled trials to assess micronised progesterone treatment on sleep outcomes.

Evidence Acquisition: Using PRISMA guidelines, we searched MEDLINE, Embase, PsycInfo and the Cochrane Central Register of Controlled Trials for randomised controlled trials of micronised progesterone treatment on sleep outcomes up to March 31, 2020. This study is registered with the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42020165981. A random-effects model was used for quantitative analysis.

Evidence Synthesis: Our search strategy retrieved 9 randomised controlled trials comprising 388 participants. One additional unpublished trial was found. Eight trials enrolled post-menopausal women. Compared with placebo, micronised progesterone improved various sleep parameters as measured by polysomnography, including total sleep time and sleep onset latency, though studies were inconsistent. Meta-analysis of 4 trials favoured micronised progesterone for sleep onset latency (effect size, 7.10; C.I. 1.30, 12.91) but not total sleep time (effect size, 20.72; C.I -0.16, 41.59) or sleep efficiency (effect size, 1.31; C.I. -2.09, 4.70). Self-reported sleep outcomes improved in most trials. Concomitant estradiol administration and improvement in vasomotor symptoms limit conclusions in some studies.

Conclusions: Micronised progesterone improves various sleep outcomes in randomised controlled trials, predominantly in studies enrolling post-menopausal women. Further research could evaluate the efficacy of micronised progesterone monotherapy using polysomnography or validated questionnaires in larger cohorts.

Keywords: Progesterone, sleep, menopause

Introduction

Progesterone is a sex steroid with biological roles including preparation of the uterus for implantation. However, accumulating pre-clinical data has demonstrated additional non-reproductive effects in the central nervous system in both sexes (1). Progesterone metabolites, including allopregnanolone, are positive allosteric modulators of the γ-aminobutyric acid type A (GABA-A) receptor (2,3) and have been shown to produce similar changes to sleep architecture as benzodiazepines (4).

Micronised progesterone or progestin treatment is often prescribed with estradiol as menopausal hormone therapy for women with an intact uterus. Impaired sleep is commonly reported at the menopausal transition (5-7) and has been shown to improve with combination estrogen/progesterone therapy (8). Given pre-clinical data demonstrating modulation of the GABA-A receptor with progesterone monotherapy, we undertook a systematic review of randomised controlled trials that reported the effects of micronised progesterone treatment compared with placebo or an active comparator on sleep outcomes in adult women and men.

Methods

Preferred reporting items for systematic review and meta-analysis (PRISMA) reporting guidelines were used in the development of this systematic review (9). This study is registered with the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42020165981.

Eligibility Criteria

Randomised controlled trials that evaluated micronised progesterone treatment compared with placebo or an active comparator were included in this review. Trials were eligible for inclusion provided they were published in peer-reviewed journals and in the English language.

Information Sources and Search Strategy

A literature search was conducted on relevant databases, including Medline, Embase, PsycInfo and the Cochrane Central Register of Controlled Trials (CENTRAL). We developed a search strategy from Medical Subject Headings (MeSH) and text words related to sleep and progesterone up to 31st March 2020. The Cochrane Highly Sensitive Search Strategy was used to restrict the search to randomised controlled trials only. Reference lists from relevant systematic reviews and studies were assessed. Two review authors (BN and BL) screened titles and abstracts identified through the search strategy for relevant studies. Duplicates were excluded and remaining studies were assessed for eligibility by pre-determined selection criteria. This was defined as: (1) randomised and quasi-randomised controlled trials, (2) published in a peer-reviewed journal, (3) participants aged ≥ 18 years, (4) administration of micronised progesterone, (5) report of at least one sleep outcome and (6) published in English. Additional search was also undertaken for completed unpublished trials. No studies were excluded based on year. Final eligibility was determined by the agreement of both reviewers. Details of the search strategy are shown in Table 1 (10).

Study Selection

Our search strategy is outlined in Figure 1.

Data Collection

The data from included studies were extracted independently by two authors using a predetermined form. Results were compared for accuracy and any differences were resolved through discussion. The following data were extracted: inclusion and exclusion criteria of the study, sample size, duration of study, dosage of micronised progesterone, route of administration of micronised progesterone, comparator group and relevant sleep outcomes.

The Cochrane risk-of-bias tool for randomised trials was used to assess the design, conduct and reporting of the included studies (11). Judgement of bias is based on five domains: randomisation process, deviations from intended interventions, missing outcome data, measurement of outcome and selection of reported result. The final judgement is classified as low, high or unclear risk. Two reviewers independently conducted the assessment and compared results across the five domains for each study.

Data Items

Population: Adult women and men aged ≥ 18 years

Intervention: Micronised progesterone

Comparator: Placebo, progestin

Outcome: Sleep parameters, including sleep polysomnography and self-reported sleep questionnaires

Study type: Randomised controlled trials

Role of the funding source

There was no funding source for this study.

Meta-analysis

We undertook a random-effects meta-analysis using Review Manager™ 5.4 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). The primary outcome was the mean difference of polysomnography parameters (total sleep time, sleep efficiency, sleep onset latency) following micronised progesterone compared with placebo. Total sleep time is defined as the total amount of sleep during total recording time; sleep onset latency is the time in minutes from 'lights out' until falling asleep; and sleep efficiency is the percentage of time in bed actually spent in sleep (12). We quantified the extent to which variability observed corresponded to between-study differences using the I^2 statistic (13).

Results

There were 325 studies identified using MEDLINE, Embase and PsycINFO. After duplicates were removed, 259 studies remained. Review of title and abstract excluded a further 201 studies. Of the remaining 58 articles assessed for eligibility, 31 were excluded as they did not assess the effect of micronised progesterone, 9 reported no sleep outcomes and 9 were review articles. The remaining 9 studies met the inclusion criteria. One additional completed but unpublished randomised controlled trial was included. A summary of these studies is included in Table 2.

A total of 577 participants were enrolled in the ten studies. Eight of the ten studies enrolled post-menopausal women with one study enrolling peri-menopausal women and the other enrolling men (Table 2). Micronised progesterone was administered orally in nine studies at doses ranging from 100-300mg daily.

Four studies undertook a randomised double-blind placebo-controlled cross-over design. Of the remaining studies, three were placebo controlled. Progestins (medroxyprogesterone acetate (MPA) (14,15) and dydrogesterone (16)) were used as active comparator in three studies. Zolpidem was an active comparator in another (17). Concomitant estradiol was administered in four studies (14-16,18).

Polysomnography was the most commonly used measure of sleep assessment (15,17,19-21). Various sleep parameters were found to improve following micronised progesterone administration. In placebo-controlled trials, 300mg oral micronised progesterone improved total sleep time (21), sleep onset latency (20,21), wake after sleep onset (19), stage 2 sleep (20) and slow wave sleep (19). There was no difference in sleep efficiency (19-21) except in one study in the night when blood sampling was undertaken (19). 9mg intranasal progesterone improved total sleep time, sleep efficiency, wake after sleep onset and stage 2 sleep, whereas 4.5mg intranasal progesterone only increased stage 2 sleep (17).

Meta-analysis of polysomnography studies showed improvement in sleep onset latency (effect size, 7.10; C.I. 1.30, 12.91) but not total sleep time (effect size, 20.72; C.I -0.16, 41.59) or sleep efficiency (effect size, 1.31; C.I. -2.09, 4.70). Subgroup analysis for those treated with oral micronised progesterone showed reduced sleep onset latency (effect size, 6.89; C.I. 0.69, 13.08) but no

improvement in total sleep time (effect size, 14.65; C.I. -14.10, 43.39) or sleep efficiency (effect size, 0.47; C.I. -3.34, 4.29) (Figure 2). There was no heterogeneity between studies evaluating sleep onset latency and sleep efficiency but moderate heterogeneity (54%) between studies evaluating total sleep time.

Sleep quality also improved in the study that utilised the Pittsburgh Sleep Quality Index (PSQI) though there was no difference between the micronised progesterone and MPA groups (16). Self-reported sleep measures improved (14,18,22,23) but did not differ from the estradiol monotherapy comparator group in one study (18).

Among the nine published randomised controlled trials included in this review, missing outcome data resulted in a high risk of bias for two trials and unclear blinding resulted in high risk of bias for another. Information about random sequence generation was unclear in two trials. A summary of trials that were at low, unclear, and high risk of bias for each domain is shown in Table S1 (10).

Discussion

We performed a systematic review and meta-analysis to summarise the effect of micronised progesterone on sleep outcomes. The pooled results showed improved sleep onset latency with oral micronised progesterone. Studies utilising self-reported sleep questionnaires demonstrated improvements following micronised progesterone administration but these were not consistently superior to an active comparator.

Progestogens and sleep physiology

Progestogens, including micronised progesterone and progestins, are commonly prescribed as menopausal hormone therapy. Oral micronised progesterone is bioidentical to human progesterone whereas the progestins are synthetic progestogen derivatives (24). MPA is a derivative of 17α-hydroxyprogesterone with agonistic activity at the progesterone, androgen and glucocorticoid receptors, whereas dydrogesterone is a retroprogesterone with almost exclusive progestogenic activity (24).

Progesterone is known to produce sedative and hypnotic effects (25). Progesterone metabolites, including allopregnanolone, are positive allosteric modulators of the γ-aminobutyric acid type A (GABA-A) receptor (2,3,26) and have been shown to produce similar changes to sleep architecture as benzodiazepines (4).

Pre-clinical studies have demonstrated that both MPA (27) and dydrogesterone (28) also increase central nervous system allopregnanolone concentrations, providing a plausible basis for improvement in sleep parameters. However, the focus of this review remains on micronised progesterone given long-term safety concerns with progestins. MPA, together with conjugated equine estrogen, was associated with an increased risk of breast cancer and coronary heart disease in the Women's Health Initiative (WHI) trial (29). Estrogen plus micronised progesterone, compared to estrogen plus progestin therapy, is associated with a lower risk of breast cancer (30) and does not impair endothelial function (31) or other cardiovascular safety parameters (32).

Polysomnography

Polysomnography is considered the gold-standard investigation for assessing sleep quality (33). Improvements in sleep parameters were seen at various stages of the sleep cycle following micronised progesterone therapy compared with placebo (15,17,19-21), including one study in men (20) and another enrolling post-menopausal women without vasomotor symptoms (19). The physiological basis underlying these changes has been demonstrated in pre-clinical studies where progesterone metabolites have been shown to act as positive allosteric modulators of the GABA-A receptor (4).

Self-reported sleep questionnaires

Subjective improvements in sleep were assessed using a variety of questionnaires. Self-reported sleep quality using a -5 to +5 scale improved significantly after 12 weeks treatment with 300mg micronised progesterone compared to placebo in a trial enrolling post-menopausal women with vasomotor symptoms, though the frequency and intensity of night hot flushes also improved (22). Similarly, there was a significant reduction in sleep disturbance measured by visuoanalogic scale, compared to both MPA and a control group (14). Although vasomotor symptoms also improved, there was no correlation between the improvement in vasomotor symptoms and sleep scores in this study.

PSQI is a validated tool for assessment of self-reported sleep quality (34). Sleep quality measured by PSQI improved significantly in a study of post-menopausal women but there was no significant difference compared to a comparator group treated with MPA (16). Self-reported sleep outcomes using other questionnaires did not reveal significant improvements following micronised

progesterone therapy (17,18,21). These studies had small sample sizes and were not powered to detect a difference in these outcome measures.

Study population

Eight of the ten studies included in this systematic review were performed in post-menopausal women, with one study performed in peri-menopausal women, and another in men with no history of sleep disturbance to avoid interference from endogenous progesterone secretion. Several of these studies enrolled women with vasomotor symptoms (15,22), while this was listed as an exclusion criteria in another (19) . The improvement in self-reported sleep outcomes cannot be fully dissected from the reduction in night-time vasomotor symptoms. Similarly, studies involving concomitant administration of estradiol (16) to post-menopausal women with vasomotor symptoms cannot discern the magnitude of effect directly attributable to progesterone (8).

Micronised progesterone dose

Doses of 100-300mg oral micronised progesterone were used in the included studies. All studies that utilised polysomnography showed improvement in sleep parameters with doses of 200-300mg. Treatment with 100mg micronised progesterone resulted in improvements in improvements in sleep quality (14,16,18) but did not differ from comparator or control groups in two studies (16,18). There is significant inter-individual variability following oral micronised progesterone (35), and the dose that results in maximal effect while minimising potential side effects such as drowsiness has not been studied.

Clinical implications

Micronised progesterone could be considered for improvement of sleep in post-menopausal women treated with menopausal hormone therapy, with placebo-controlled trials utilising polysomnography prescribing 300mg at night. Given its mechanism of action, drowsiness is a documented adverse

effect so night-time administration is recommended and does not impair morning cognitive function (21).

Limitations

There are several limitations of this systematic review and meta-analysis. Firstly, several included studies had a small sample size and were not powered to detect changes in self-reported sleep outcomes. Secondly, some of the evidence from this review cannot discern the magnitude of effect on sleep quality through an indirect reduction in vasomotor symptoms which can also improve sleep quality. Similarly, concomitant estradiol administration may also improve sleep parameters in post-menopausal women with vasomotor symptoms. Several studies were at risk of selection and/or attrition bias. Despite this, we undertook a comprehensive search of the literature aided by an expert librarian and a prospectively registered protocol. This is, to our knowledge, the first systematic review specifically designed at assessment of sleep parameters with micronised progesterone therapy.

Conclusions

Randomised controlled data demonstrates that micronised progesterone improves various aspects of the sleep cycle and self-reported sleep outcomes, predominantly in studies involving post-menopausal women. However, results are inconsistent between studies. Further research should utilise polysomnography or validated sleep questionnaires such as PSQI in larger cohorts.

Data availability

Some or all data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

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Figure Legends

Figure 1. Selection of studies for inclusion

Figure 2. Random-effects meta-analysis of micronised progesterone on polysomnography parameters: (a) total sleep time; (b) sleep onset latency; (c) sleep efficiency. Vertical line represents no treatment effect. Squares and horizontal lines represent the point estimates and associated confidence interval for each study. The diamonds represent the random-effects pooled mean difference and its width the associated confidence interval. Studies are separated by progesterone administration route. CI, confidence interval; IV, inverse variance; SD, standard deviation

Table 1. MEDLINE search strategy

Search strategy for MEDLINE
1. exp Progesterone/ or (progesterone).tw. 2. exp Sleep/or exp Sleep Latency/or exp Sleep, Slow-Wave/or exp Sleep, REM/or exp Sleep Stages/ or sleep.tw. 3. 1 and 2 4. limit 3 to "all adult (19 plus years)" 5. randomised controlled trial.pt. 6. controlled clinical trial.pt. 7. (randomized or randomised).ab. 8. placebo.ab. 9. clinical trials as topic.sh. 10. randomly.ab. 11. trial.ti. 12. groups.ab. 13. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 14. exp animals/not humans.sh. 15. 13 not 14

Table 2. Characteristics of included trials

Reference	Study type	Individuals	Intervention	Comparison group(s)	Outcome	Results
Caufriez, 2011 (19)	Randomised double-blind placebo-controlled cross-over trial	Post-menopausal women (n=8), mean age 57.4 years	Micronised progesterone 300mg	Placebo	Polysomnography	Progesterone vs. placebo (during night with blood sampling): total sleep time 20% higher, sleep efficiency 15% higher, mean duration of wake after sleep onset 53% lower, slow-wave sleep duration 50% higher, and total slow-wave activity 45% higher under progesterone than under placebo ($p \leq 0.05$). No difference in sleep parameters on night without blood sampling.
Friess, 1997 (20)	Randomised double-blind placebo-controlled cross-over trial	Men (n=9), mean age 24.7 ± 4.3 years	Micronised progesterone 300mg	Placebo	Polysomnography	Progesterone vs. placebo: Slow wave sleep latency (minutes) (15.12 ± 6.2 vs. 21.7 ± 3.2, $p<0.05$) Stage 2 sleep (minutes) (283.6 ± 24.1 vs. 251.6 ± 34.1, $p<0.05$) No difference in total sleep time, sleep efficiency or sleep latency.
Gambacciani, 2005 (14)	Randomised controlled trial	Post-menopausal women (n=60), mean age 53 years	CEE + micronised progesterone 100mg (n=20)	CEE + MPA 2.5mg (n=20) Calcium 1000mg (n=20)	Visuoanalogic score (VAS) for sleep disturbance (0-10)	CEE + oral micronised progesterone: Significant reduction in VAS vs. both CEE + MPA 2.5mg and control groups ($p<0.05$) *No correlation seen between reduction in vasomotor and sleep scores

Heinrich, 2005 (18)	Randomised double-blind placebo-controlled trial	Post-menopausal women (n=35), mean age 64.1 ± 0.6 years	Estradiol valerate 2mg + micronised progesterone 100mg (n=10)	Estradiol valerate 2mg (n=12) Placebo (n=13)	One item from depression questionnaire and one from menopausal index combined to new scale (0-7)	Improvements in sleep quality seen in all groups but not different between groups, F=0.49 (p=0.62)
Hitchcock, 2012 (22)	Randomised double-blind placebo-controlled trial	Post-menopausal women (n=133), mean age 55 years, 91% Caucasian	Micronised progesterone 300mg (n=75)	Placebo (n=58)	Rating of change from baseline on -5 to +5 scale	Progesterone vs. placebo: improvement in sleep with progesterone, z-score 2.36 (p=0.019)
Leeangkoonsathian, 2017 (16)	Randomised controlled trial	Post-menopausal women (n=100), mean age 52.1 ± 4.1 years, Thai	Estradiol 1mg + micronised progesterone 100mg (n=50)	Estradiol 1mg + dydrogesterone 10mg (n=50)	Pittsburgh sleep quality index (PSQI)	PQSI improved in both groups but no difference between groups: 10.52 ± 4.27 to 4.91 ± 3.15 in the dydrogesterone group vs. 10.16 ± 3.60 to 6.27 ± 3.04 in the micronised progesterone group (p=0.08)
Montplaisir, 2001 (15)	Randomised controlled trial	Post-menopausal women (n=21), mean age 55 years	CEE 0.625mg + micronised progesterone 200mg (n=10)	CEE 0.625mg + MPA 5mg (n=11)	Polysomnography	Micronised progesterone vs. MPA: sleep efficiency (p=0.04), time spent awake after sleep onset (p=0.02) Sleep efficiency: micronised progesterone baseline 80.9% vs. 6-month 89.4% (p=0.014) Time spent awake after sleep onset: micronised progesterone baseline 86.4 min vs. 6-month 47.5 min (p=0.007)
Schussler, 2008 (21)	Randomised double-blind placebo-controlled cross-over trial	Post-menopausal women (n=10), mean age 60.3 ± 5.7 years	Micronised progesterone 300mg	Placebo	Polysomnography	Total sleep time: progesterone vs. placebo (p<0.05), progesterone vs. baseline (p<0.05) Sleep onset latency: progesterone vs. placebo (p<0.05) Awake (sleep period time): progesterone vs. placebo (p<0.05), progesterone vs. baseline (p<0.05) Subjective sleep quality questionnaire (p=ns)

Schussler, 2018 (17)	Randomised double-blind placebo-controlled cross-over trial	Post-menopausal women (n=12), mean age 59.6 ± 1.3 years	Intranasal progesterone 4.5mg Intranasal progesterone 9mg	Zolpidem 10mg Placebo	Polysomnography	9.0mg progesterone vs. placebo: Improved total sleep time, sleep efficiency index, wake after sleep onset, stage 2 sleep, non-rapid eye movement sleep (all p<0.05) 4.5mg progesterone vs. placebo: Improved stage 2 sleep (p<0.05)
Unpublished trial (23)	Randomised double-blind placebo-controlled trial	Peri-menopausal women (n=189), mean age 49.9 ± 4.6 years	Micronised progesterone 300mg	Placebo	Rating of change from baseline on -5 to +5 scale	Progesterone vs. placebo (mean(range)): 2 (0-4) vs. 0 (0-3)

CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate; PSQI, Pittsburgh Sleep Quality Index; VAS, visuoanalogic scale

Figure -1

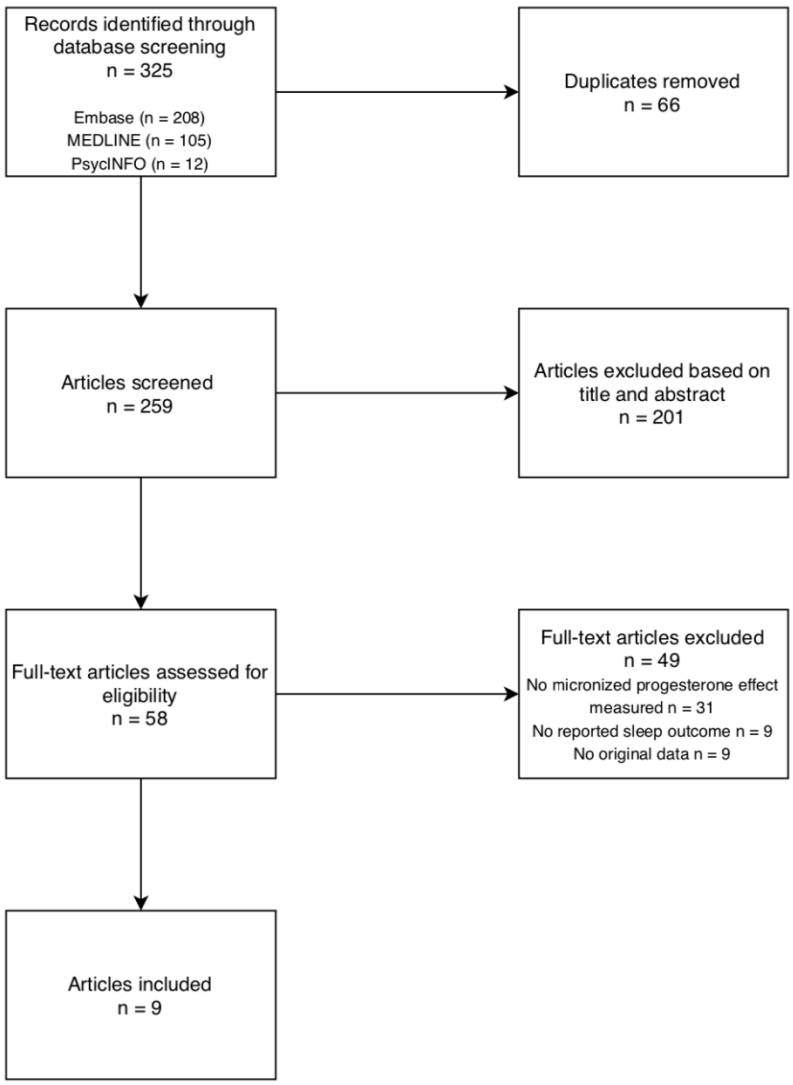
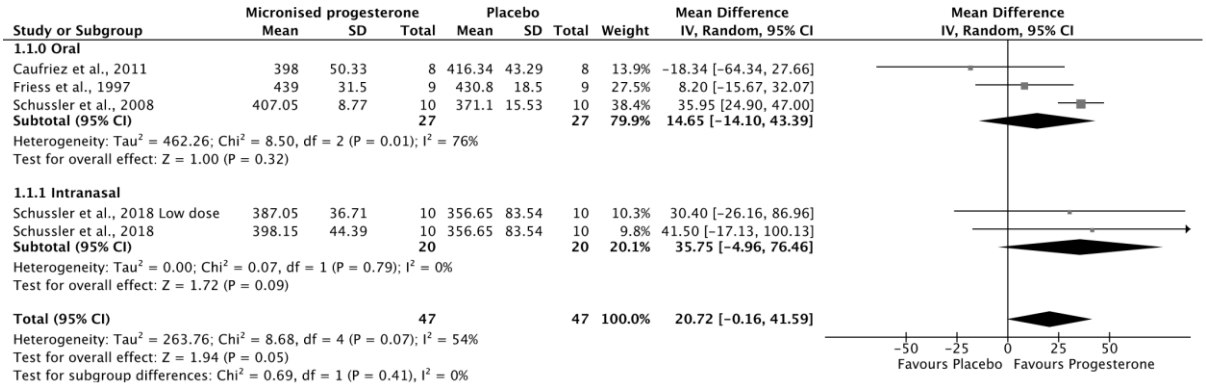
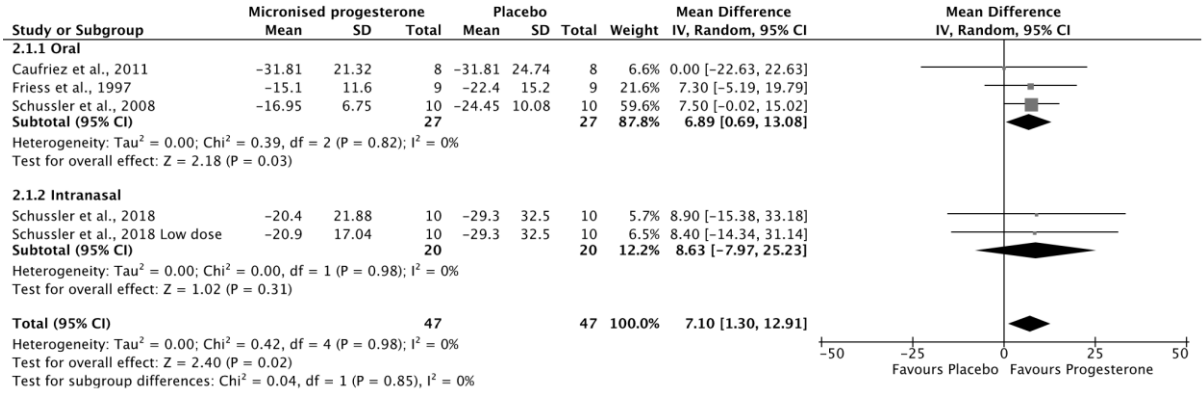


Figure -2

a. Total sleep time



b. Sleep onset latency



c. Sleep efficiency