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REVIEW

Optimizing the Time and Dose of Melatonin as a Sleep-Promoting Drug: A Systematic Review of Randomized Controlled Trials and Dose–Response Meta-Analysis

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ABSTRACT

Previous studies have reported inconsistent results about exogenous melatonin's sleep-promoting effects. A possible explanation relies on the heterogeneity in administration schedule and dose, which might be accountable for differences in treatment efficacy. In this paper, we undertook a systematic review and meta-analysis of double-blind, randomized controlled trials performed on patients with insomnia and healthy volunteers, evaluating the effect of melatonin administration on sleep-related parameters. The standardized mean difference between treatment and placebo groups in terms of sleep onset latency and total sleep time were used as outcomes. Dose–response and meta-regression models were estimated to explore how time of administration, dose, and other treatment-related parameters might affect exogenous melatonin's efficacy. We included 26 randomized controlled trials published between 1987 and 2020, for a total of 1689 observations. Dose–response meta-analysis showed that melatonin gradually reduces sleep onset latency and increases total sleep time, peaking at 4 mg/day. Meta-regression models showed that insomnia status ($\beta = 0.50$, $p < 0.001$) and time between treatment administration and the sleep episode ($\beta = -0.16$, $p = 0.023$) were significant predictors of sleep onset latency, while the time of day ($\beta = -0.086$, $p < 0.01$) was the only significant predictor of total sleep time. Our results suggest that advancing the timing of administration (3 h before the desired bedtime) and increasing the administered dose (4 mg/day), as compared to the exogenous melatonin schedule most used in clinical practice (2 mg 30 min before the desired bedtime), might optimize the efficacy of exogenous melatonin in promoting sleep.

1 | Background

Sleep complaints are reported in about one-third of the adult population. Disturbances related to trouble falling asleep and staying asleep (insomnia-related symptoms) are the most frequent [1, 2]. Indeed, among the sleep disturbances recognized by the *International Classification of Sleep Disorders* (ICSD) [3], insomnia is the most common [2], and it is associated with different health outcomes, such as cardiovascular and metabolic diseases, changes in immune function,

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impairment in cognitive processes and mental health disturbances [4]. Close to 60% of adults seeking treatment for insomnia-related symptoms are prescribed sedative and/or hypnotic medications [5]. In the previous decade, sleeplessness complaints and insomnia diagnoses significantly increased over time. Such increase was paralleled, and even outpaced, by the volume of prescriptions for sedative-hypnotics (i.e., benzodiazepines [BZ] and nonbenzodiazepine [z-drugs and Ramelteon] drugs) [6]. Due to side effects and risk profiles associated with sleep medications [7–9], interventions to reduce the prescription of hypnotics by healthcare providers have been promoted [10–12]. Although the updated study of the sleeplessness-related outcomes registered during 2008–2015 showed a decrease in the trend of prescription of sedative-hypnotics FDA-approved for insomnia [13], insomnia-related symptoms remain a significant public health issue [1, 14], highlighting the need to optimize the treatments for sleep disturbances.

Available substances to treat insomnia include BZ and benzodiazepine receptor agonists, antidepressants, antipsychotics, antihistamines, phytotherapeutic substances, and melatonin [15]. Among these, exogenous melatonin (exo-MEL) is a promising option to treat insomnia-related symptoms [16]. Several studies have reported its efficacy in improving sleep [17] and its safety profile [18], even at very high doses [19]. Exo-MEL is largely recognized as a chronobiotic drug acting as a circadian rhythm synchronizer; [20] conversely, its use as a sleep-promoting drug has been under debate due to the inconsistency of its described effects [21, 22]. Many possible sources of heterogeneity in experimental designs (e.g., dose, timing of administration, treatment duration, fast or slow-release formulations, patients with sleep disorders vs. healthy volunteers, people with different chronotypes) might be accountable for these conflicting results. The systematic investigation of these treatment parameters is an important step toward understanding the role of exo-MEL in sleep promotion and insomnia treatment.

Several meta-analyses have been performed to assess the efficacy of exo-MEL in treating primary sleep disorders [18, 23–25]. These studies have demonstrated that exo-MEL decreases sleep onset latency (SOL) and increases sleep efficiency (SE) and total sleep time (TST) in several clinical conditions such as insomnia, schizophrenia, Alzheimer's disease, as well as in healthy volunteers [23]. Likewise, exo-MEL was found to be effective in reducing SOL in primary insomnia and Delayed Sleep-Wake Phase Disorder (DSWPD) and in regulating the sleep-wake patterns in blind patients compared with placebo [24]. Other meta-analyses, however, showed that the reduction in SOL was less significant for primary sleep disorders associated with insomnia as compared to patients with DSWPD [18], suggesting that the efficacy of exo-MEL may be different based on the diagnosis or according to participants' circadian phase when administered. Furthermore, none of these studies have established conclusions about the optimal treatment parameters. Only one meta-analysis has explored the dose−response effects of exo-MEL [25]. The authors demonstrated that exo-MEL significantly reduced SOL, increased TST, and improved overall sleep quality compared to placebo and that longer treatments (in a range from 7 to 126 days) and higher doses (in a range from 0.5 to 5 mg) were associated with greater effects on SOL and TST. Ferracioli-Oda et al.'s study represents an important step toward the identification of the posology that maximizes exo-MEL efficacy in clinical contexts; still, their results need to be replicated on a less heterogeneous sample in terms of age (i.e., pediatric vs. adult populations) and disease status (i.e., sleep disorders vs. circadian rhythm disorders). Moreover, the influence of important exo-MEL effect modifiers was not evaluated. For example, even if it is known that exo-MEL sleep-promoting action is highly influenced by the phase of the endogenous melatonin production (i.e., the most reliable marker of the phase of the circadian oscillator located in the suprachiasmatic nuclei) [26], the authors did not assess how the time of the day and the individual's biological time in which the treatment was administered might have influenced sleep-related outcomes.

The present study aimed at exploring how the administration schedule might influence exo-MEL efficacy, with the objective of optimizing its sleep-promoting effect. SOL and TST were considered as the main outcomes. Timing of administration, sample characteristics (i.e., healthy volunteers vs. insomnia patients), treatment duration, dose, and formulation (i.e., immediate release vs. prolonged release) were considered as possible treatment effect modifiers.

2 | Methods

2.1 | Eligibility Criteria

We included all fixed-dose, double-blind, RCTs in which placebo was compared to an exo-MEL treatment in healthy participants or in patients with primary insomnia. Further inclusion criteria were the following: English language; human samples; adult population (>18 years); >5 study participants and studies using EEG, actigraphy, self-report, video recording, or muscle relaxation as a sleep assessment method. Exclusion criteria were the following: pediatric population; use of melatonin agonists; combination of exo-MEL with another sleep disorder treatment; exo-MEL dose >10 mg/day; exo-MEL used as a chronobiotic drug; medical comorbidities; primary or secondary circadian or sleep disorders other than insomnia; shift work; case reports, case series, open-label studies, editorials, reviews, and research articles not published in peer-reviewed journals; and inadequate reporting of study outcomes. The meta-analysis was conducted in accordance with the PRISMA statement [27].

2.2 | Search Strategy and Selection Process

All articles published until March 2021 were searched in MEDLINE database. The search terms used were: (((melatonin) OR (“exogenous melatonin”)) AND ((((“healthy volunteers”) OR (“healthy subjects”)) OR (“healthy adults”)) OR (insomnia))) AND ((hypnotic) OR (sleep-inducing)) OR (“sleep-promoting”)) OR (soporific))). Filters: Humans, English, Adult: 19+ years.

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In addition, the full texts of all included RCTs and recent meta-analyses were obtained, and snowball searches of reference lists were conducted. The titles and abstracts were independently screened by two reviewers (F. C. S. and S. B.). They also independently extracted data from the studies finally included in the current work. All concerns during study selection and data extraction were resolved by a common full text read of the source and by further discussion until consensus was achieved.

2.3 | Study Outcomes and Control Variables

We considered SOL and TST differences in treatment (i.e., exo-MEL) and placebo groups as study outcomes. We also extracted data on the time of administration, time between melatonin administration and bedtime sleep episode, administered dose, the type of formulation (prolonged release vs. fast release), treatment duration, and insomnia status of the sample. When a nocturnal sleep episode was evaluated and the time of administration was not reported [28–34], we estimated it by averaging time intervals provided by the authors for bedtime; or else based it on the average bedtime in the country where the study was conducted for the same age range of the sample, and based it on the time between exo-MEL administration and bedtime, which was reported in each study (see Supporting Information S1: Table 1). The time window between exo-MEL administration and the sleep episode was considered both as a quantitative and as a categorical variable. As a categorical variable, it assumed the following values: 0 (exo-MEL taken 0−0.5 h before bedtime), 1 (0.5−1.5 h before bedtime), 2 (1.5−2.5 h before bedtime), 3 (2.5−3.5 h before bedtime). In two studies [35, 36], the non-oral exo-MEL formulation was administered. Those studies have been excluded from dose −response and meta-regression analyses since exo-MEL effective doses were not directly comparable with those of oral formulations. We further excluded two studies from meta-regression [37, 38], since the multiple attempts at falling asleep included in the study protocols prevented us from identifying a precise time between melatonin administration and the sleep episode.

2.4 | Study Risk of Bias Assessment

The risk of bias for the primary outcomes was independently evaluated by two authors (F. C. S. and S. B.) using the Cochrane Collaboration's risk of bias tool [39]. The randomization strategy, allocation concealment, blinding, missing outcomes, selective reporting, and other possible sources of bias (e.g., risk of including participants with morbid conditions potentially affecting sleep; wash-out periods of sufficient length between the administration of different melatonin doses; authors' conflicts of interests) were assessed for each trial that satisfied the eligibility criteria. For each domain, the risk of bias could be rated as “Low,” “Unclear,” or “High.” Study quality was considered “High” if the risk of bias was “Low” in at least four out of seven domains; “Not high” otherwise. All concerns during the risk of bias assessment were resolved by consensus. The results of our risk of bias assessment are displayed in the Supporting Information S1: Table 2.

2.5 | Statistical Analysis

The standardized mean difference (SMD) between exo-MEL and placebo groups in terms of posttreatment SOL and TST (outcome variables) expressed the effect size. Pooled SMDs analysis was performed using a random-effects model. Results were re-expressed in minutes by multiplying SMD for the weighted average of the standard deviation across the intervention groups, as recommended by Cochrane guidelines [40]. For TST, the average standard deviation was computed, including only studies in which sleep duration was assessed during an overnight sleep opportunity.

Heterogeneity was determined by means of I^2 statistics [41]. The metric describes the percentage of the total variation for which heterogeneity between studies is accountable, rather than sampling error. I^2 values of 25%, 50%, and 75% define low, moderate, and high heterogeneity, respectively. Funnel plots were tested for potential asymmetries using Egger's test [42].

Dose−response models from the SMDs in exo-MEL and placebo groups for the outcome variables were estimated according to the two-stage approach by Crippa and Orsini [43]. In the first stage, a dose−response model was fitted for each study. The association between exo-MEL dose and study outcomes were modeled using a restricted cubic spline with three knots located at 0.1, 0.5, and 0.9 percentiles of the dosage distribution. In the second stage, a multivariate random-effects model was estimated to create a pooled dose−response curve combining all study-specific curves. The predicted values for exo-MEL dose ranging from 0 to 5 mg/day were then tested using a Wald test considering the predicted effect size at 2 mg/day (SMD melatonin—placebo) as the reference for comparisons. A natural cubic spline with three knots (0.1, 0.5, 0.9 percentiles of the distribution) was used to model the relationship between SOL reduction and exo-MEL time of administration with respect to bedtime.

Meta-regression models were estimated to explore how possible effect modifiers (clock time of administration, time between exo-MEL administration and sleep episode, treatment duration, type of exo-MEL formulation, dose, and insomnia status) might modulate exo-MEL efficacy. To exclude that our results might be negatively affected by the quality of the studies, significant predictors of exo-MEL efficacy were then included in a further meta-regression model adjusted for study quality as measured using the Cochrane Collaboration's risk of bias tool. A further metaregression model was fitted considering the timing of administration with the respect to the sleep episode as the independent variable and the SOL reduction as the dependent variable. The timing of administration was included in this last model as a categorical variable, and bedtime (i.e., 0 h) was considered the reference for comparisons.

All analyses were carried out using R software version 4.1.0 and the dosresmeta and meta packages [44, 45]. The level of significance was set at 0.05.

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3 | Results

Figure 1 details the flow for the selection of studies. The 26 studies eventually included (Table 1) were published between 1987 and 2020 and included 1689 observations. Studies excluded after full-text revision are described in Supporting Information S1: Table 3.

3.1 | SOL

The analyses considering SOL as the outcome have been performed on 25 out of the 26 studies included in the quantitative synthesis, evaluating 55 subsamples: some studies included different experimental groups to which exo-MEL was administered at different times of the day and/or doses. Sixteen studies (35 subsamples) reported information on time of administration. For the remaining nine studies (20 subsamples), the time of administration was estimated as described in Section 2. Fourteen studies were conducted on healthy volunteers, 10 on insomnia patients, and two included samples of both healthy volunteers and insomnia patients (36 subsamples of healthy volunteers, 19 of insomnia patients). Sleep parameters were assessed using EEG in 20 studies (44 subsamples), actigraphy in two studies (four subsamples), self-reported measures in two studies (three subsamples), and indirectly through muscle relaxation monitoring in one study (four subsamples). In seven studies (eight subsamples), a prolonged-release formulation of melatonin has been used, while in two studies (three subsamples), a non-oral formulation has been administered. Time of administration ranged from 08:00 to 02:00 h, which corresponded to a range of 0−3.5 h before the sleep episode. Exo-MEL daily administered dose ranged from 0.1 to 10 mg. Treatment duration ranged from 1 to 28 days. According to the rating criteria defined in Section 2, 14 studies were considered of high quality (37 subsamples), and 11 were not (18 subsamples).

Quantitative synthesis of the eligible studies showed a significant reduction in SOL following exo-MEL administration as compared to placebo (SMD = −0.46 [9.31 min], 95% CI = −0.61 to −0.30 [12.43−6.19 min], $p < 0.001$) (Figure 2).

Moderate heterogeneity among the studies was present ($I^2 = 49.9\%$). Egger's test result supported the presence of an asymmetry in the funnel plot ($p = 0.015$) (Figure 3).

Dose−response metanalysis showed that the daily dose of exo-MEL significantly predicted the mean difference between

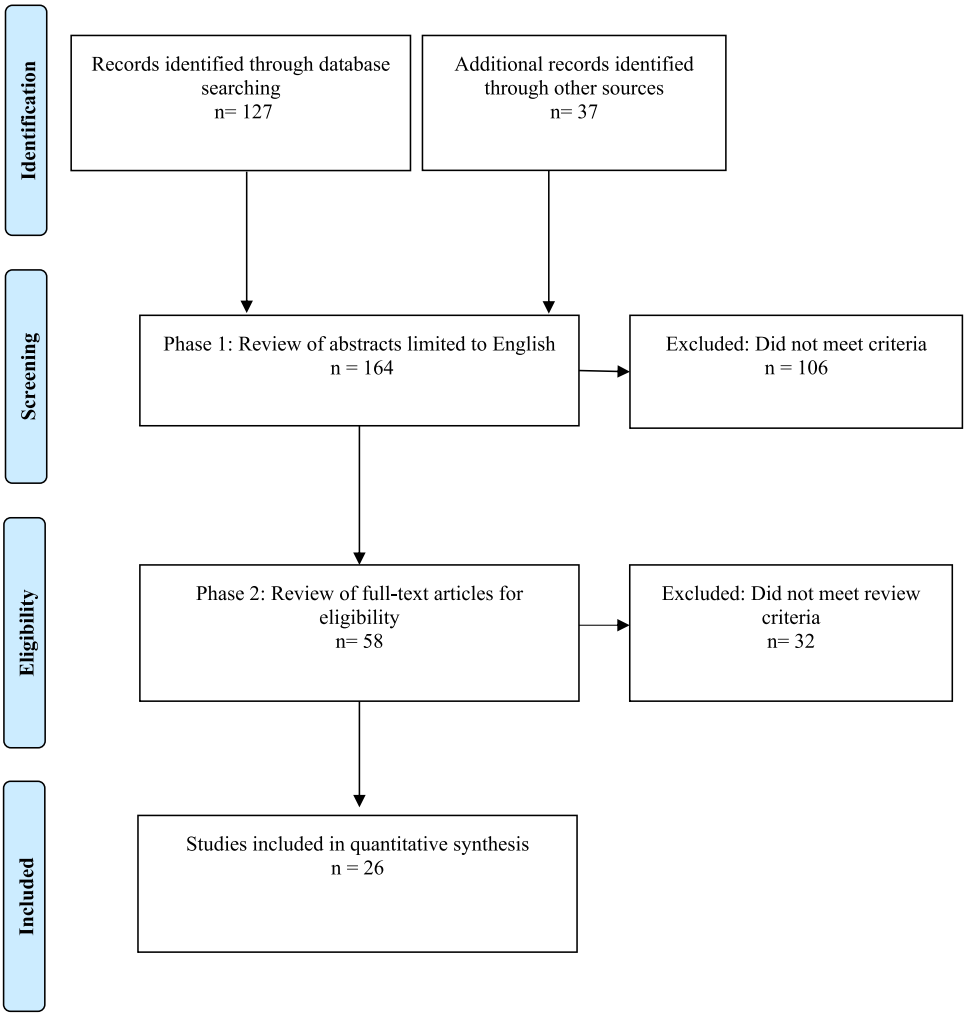


FIGURE 1 | Flowchart of the study selection process.

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TABLE 1 | Studies evaluating the sleep-promoting effect of exogenous melatonin.

Study	Insomnia status	Sex (males %)	Age (mean ± SD)	Sample size (melatonin)	Sample size (placebo)	Dose (mg/day)	Time of administration	Hours before sleep episode	Treatment duration	Melatonin formulation	Outcome	Technique
Aeschbach et al., 2009 [35]	Healthy	0.5	27.8 ± 3.6	7	7		8:00	1:00	1	Transdermal	SOL, TST	EEG
Almeida Montes et al., 2003 [32]	Insomnia	0.6	50 ± 12.7	10	10	0.3	23:30	1:00	7	PR	SOL, TST	Self-reported
				10	10	1	23:30	1:00	7	PR		
Arbon et al., 2015 [46]	Healthy	0.75	58.8 ± 2.9	16	16	2	21:00	2:00	1	PR	SOL, TST	EEG
Attenburrow et al., 1996 [29]	Healthy	0.27	53.9[a]	15	15	0.3	20:30	2:00	1	FR	SOL, TST	EEG
				15	15	1	20:30	2:00	1	FR		
Baskett et al., 2003 [31]	Healthy	0.2	73[a]	19	19	5	23:30	0:00	28	FR	SOL, TST	Actigraphy
	Insomnia	0.5	72[a]	15	15	5	23:30	0:00	28	FR		
Cajochen et al., 1998 [47]	Healthy	1	27 ± 5	10	10	5	20:45	3:15	1	FR	SOL, TST	EEG
Dawson et al., 1998 [36]	Insomnia		65.67 ± 15.55	12	12		19:00	3:30	3	Transbuccal	SOL, TST	EEG
				12	12		19:00	3:30	4	Transbuccal		
Dollins et al., 1994 [48]	Healthy	1	23.05 ± 4.22	20	20	0.1	11:45	1:45	1	FR	SOL, TST	Button pressure
				20	20	0.3	11:45	1:45	1	FR		
				20	20	1	11:45	1:45	1	FR		
				20	20	10	11:45	1:45	1	FR		
Ellis et al., 1996 [49]	Insomnia	0.6	46 ± 11	15	15	5	20:00	3:00	7	FR	TST	Self-reported
Haimov et al., 1995 [28]	Insomnia	0.5	73.1 ± 3.9	8	8	2	20:45	2:00	7	PR	SOL	Actigraphy
				8	8	2	20:45	2:00	7	FR		
Hughes and Badia., 1997 [50]	Healthy	1	18–30[b]	8	8	1	10:00	2:00	1	FR	SOL, TST	EEG
				8	8	10	10:00	2:00	1	FR		

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TABLE 1 | (Continued)

Study	Insomnia status	Sex (males %)	Age (mean ± SD)	Sample size (melatonin)	Sample size (placebo)	Dose (mg/day)	Time of administration	Hours before sleep episode	Treatment duration	Melatonin formulation	Outcome	Technique
Hughes et al., 1998 [51]	Insomnia	0.36	70.29 ± 7	14	14	0.5	21:30	0:30	14	FR	SOL	EEG
				14	14	0.5	21:30	0:30	14	PR		
				14	14	0.5	2:00	0:15	14	FR		
James et al., 1987 [52]	Healthy	0.7	29.9[a]	10	10	1	22:45	0:15	1	FR	SOL, TST	EEG
				10	10	5	22:45	0:15	1	FR		
James et al., 1990 [53]	Insomnia	0.4	33.4[a]	10	10	1	22:45	0:15	1	FR	SOL, TST	EEG
				10	10	5	22:45	0:15	1	FR		
Lushington et al., 1997 [37]	Insomnia	0	65.4 ± 7.4	22	22	5	14:00		1	FR	SOL	EEG
Luthringer et al., 2009 [54]	Insomnia	0.65	59.6 ± 2.9	20	20	2	22:00	2:00	21	PR	SOL, TST	EEG
Nave et al., 1995 [55]	Healthy	1	24.6 ± 2.7	12	12	3	16:00	2:00	1	FR	SOL, TST	EEG
				12	12	6	16:00	2:00	1	FR		
				12	12	3	17:30	0:30	1	FR		
				12	12	6	17:30	0:30	1	FR		
Nave et al., 1996 [38]	Healthy	1	24.5 ± 0.9	6	6	3	12:00		1	FR	SOL, TST	EEG
Pires et al., 2001 [56]	Healthy	1	22–24[b]	6	6	0.3	18:00	0:00	1	FR	SOL, TST	EEG
				6	6	1	18:00	0:00	1	FR		
				6	6	0.3	20:00	0:00	1	FR		
				6	6	1	20:00	0:00	1	FR		
				6	6	0.3	21:00	0:00	1	FR		
				6	6	1	21:00	0:00	1	FR		
Rajaratnam et al., 2004 [57]	Healthy	1	24.4 ± 4.4	8	8	1.5	16:00	0:00	8	PR	SOL, TST	EEG
Ribeiro Pinto et al., 2004 [58]	Healthy	1	28 ± 4	30	10	10	22:00	1:00	14	FR	SOL	EEG

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TABLE 1 | (Continued)

Study	Insomnia status	Sex (males %)	Age (mean ± SD)	Sample size (melatonin)	Sample size (placebo)	Dose (mg/day)	Time of administration	Hours before sleep episode	Treatment duration	Melatonin formulation	Outcome	Technique
Wade et al., 2007 [33]	Insomnia	0.4	66.1 ± 6.4	169	165	2	21:30	2:00	21	PR	SOL	Self-reported
Xu et al., 2020 [34]		0.41	57.24 ± 5.59	29	32	3	21:30	1:00	28	FR	SOL, TST	EEG
Zhdanova et al., 1995 [59]	Healthy	1	26.5 ± 3.18	6	6	0.3	20:00	2:00	1	FR	SOL	EEG
				5	6	1	20:00	2:00	1	FR		
				6	6	0.3	21:00	1:00	1	FR		
				5	6	1	21:00	1:00	1	FR		
Zhdanova et al., 1996 [60]	Healthy	1	28.5 ± 6.24	12	12	0.3	21:00	3:00	3	FR	SOL	EEG
				12	12	1	21:00	3:00	3	FR		
Zhdanova et al., 2001 [30]	Healthy		>50[b]	15	15	0.1	22:00	0:30	7	FR	SOL, TST	EEG
				15	15	0.3	22:00	0:30	7	FR		
				15	15	3	22:00	0:30	7	FR		
	Insomnia			15	15	0.1	22:00	0:30	7	FR		
				15	15	0.3	22:00	0:30	7	FR		
				15	15	3	22:00	0:30	7	FR		

Abbreviations: EEG, electroencephalography; FR, fast release; PR, prolonged release; SD, standard deviation; SOL, sleep onset latency; TST, total sleep time.
[a]Standard deviation of the age not reported.
[b]Age is reported as a range.

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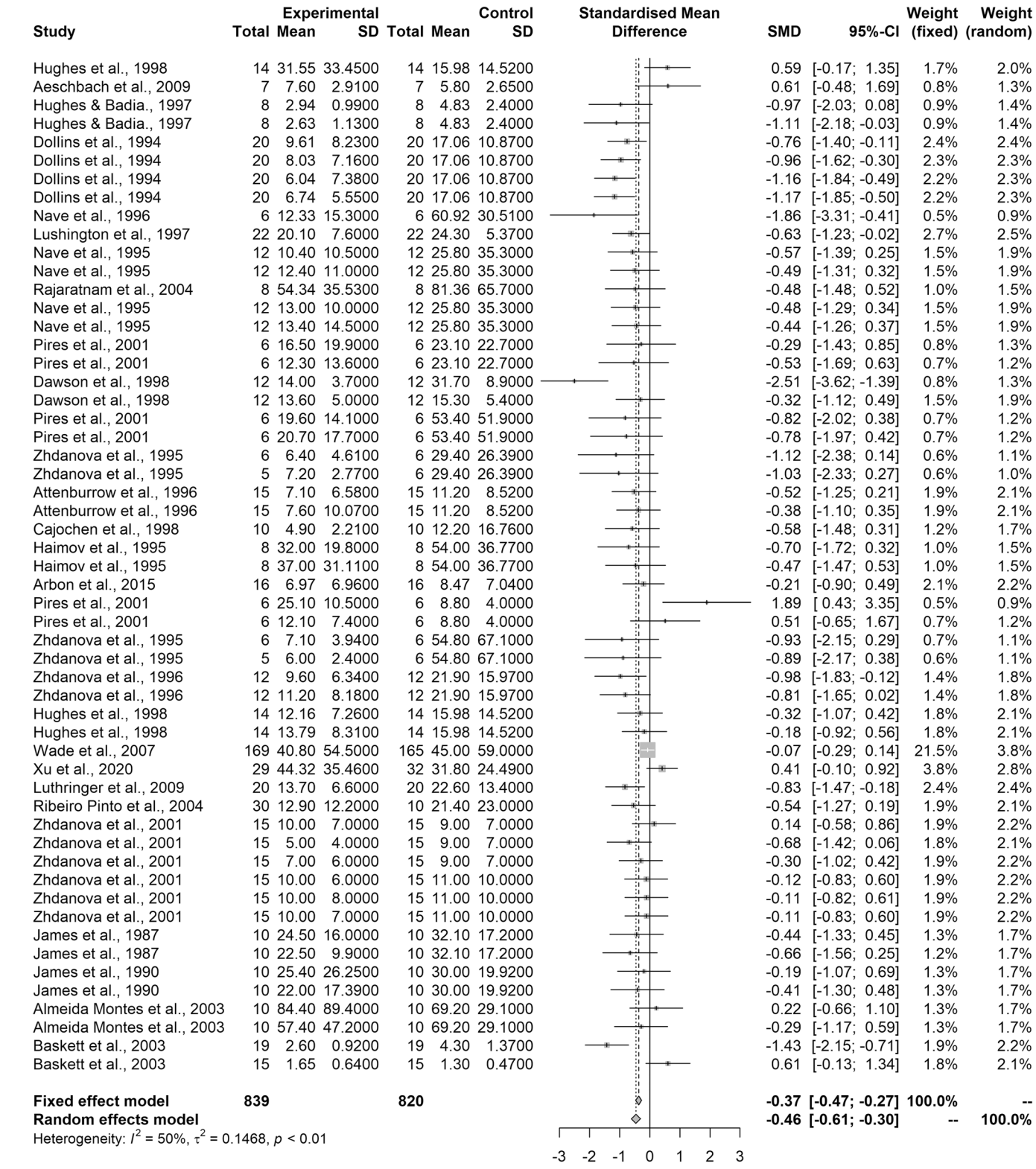


FIGURE 2 | The effect of exo-MEL administration on sleep onset latency as compared to placebo, expressed as standardized mean difference (SMD). Horizontal lines represent a 95% confidence interval for each study. The diamond at the bottom of the figure indicates the pooled mean effect and the relative confidence interval. Melatonin administration significantly reduced sleep onset latency.

treatment and placebo groups in SOL ($p < 0.001$) and that the relationship between dose and SOL reduction significantly differed from linearity ($p < 0.001$). Figure 4 displays the fitted dose–response curve. Melatonin efficacy in reducing SOL gradually increases along with the dose, peaking at 4 mg/day. A further increase in the administered dose provides no additional benefit.

As a post hoc analysis, we then tested for significance the SMD predicted by the dose–response model for doses ranging from 0

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(placebo) to 5 mg against 2 mg, that is the melatonin dose currently recommended for insomnia treatment [61]. Results showed that a dose of 2 mg is significantly more effective than a placebo and 1 mg and significantly less effective than 3 and 4 mg (Table 2).

Results from the meta-regression models showed that insomnia status ($\beta = 0.51$, $p < 0.001$) and time between exo-MEL administration and the sleep episode ($\beta = -0.16$, $p = 0.023$) were significant predictors of SOL. In particular, exo-MEL's sleep-promoting effect is reduced in insomnia patients compared to healthy volunteers, while its effect increases by advancing the time of administration with respect to the sleep episode. In Model 3, we tested whether study quality might have affected our results by running a meta-regression model considering insomnia status, hours before sleep episode, and study quality as regressors; and SMD (melatonin—placebo) in SOL as the dependent variable. Insomnia status and hours before the sleep episode held their predictivity on the outcome variable, while study quality was not significantly associated with SOL ($\beta = 0.077$, $p = 0.66$). Table 3 displays the results of the fitted models.

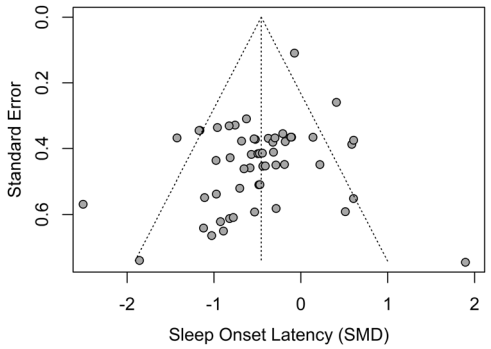


FIGURE 3 | The effect size of each study was plotted against the relative standard error (funnel plot). Egger's test result supports the presence of an asymmetry in the funnel plot ($p = 0.015$).

Visual inspection of the curve modeling the relationship between exo-MEL time of administration and SOL reduction suggests that advancing the time of administration with respect to the sleep episode (i.e., administering it earlier, increasing the phase-angle) enhances exo-MEL sleep-promoting properties. Particularly, exo-MEL is maximally effective in promoting sleep when taken 1−3 h before the sleep episode (Figure 5). Outside this time window, exo-MEL efficacy seems to be less dependent on administration timing. The metaregression model fitted including the time of administration as an independent, categorical variable, confirmed that administering exo-MEL 1 h before the sleep episode does not significantly differ from administering exo-MEL at the timing of the sleep episode (i.e., 0 h before sleep episode onset), while SOL significantly decreased at both 2 and 3 h before the sleep episode (Table 4). The predicted values of SOL reduction at different times of administration are in line with the proposed interpretation, as shown in Table 5. Indeed, a steeper decline in SOL can be observed 1−3 h before the sleep episode as compared to 0−1 h before the sleep episode. Conversely, the predicted value of SOL reduction at 3.5 h before the sleep episode is comparable to the value predicted at 3 h before the sleep episode. This result could be explained by the presence of a plateau in the time−response curve after reaching the peak of efficacy at 3 h (Table 5).

3.2 | TST

We included 19 studies, which evaluated 42 subsamples. Twelve studies (28 subsamples) reported information on time of administration, and 11 studies were conducted on healthy participants, six on insomnia patients, and two on both

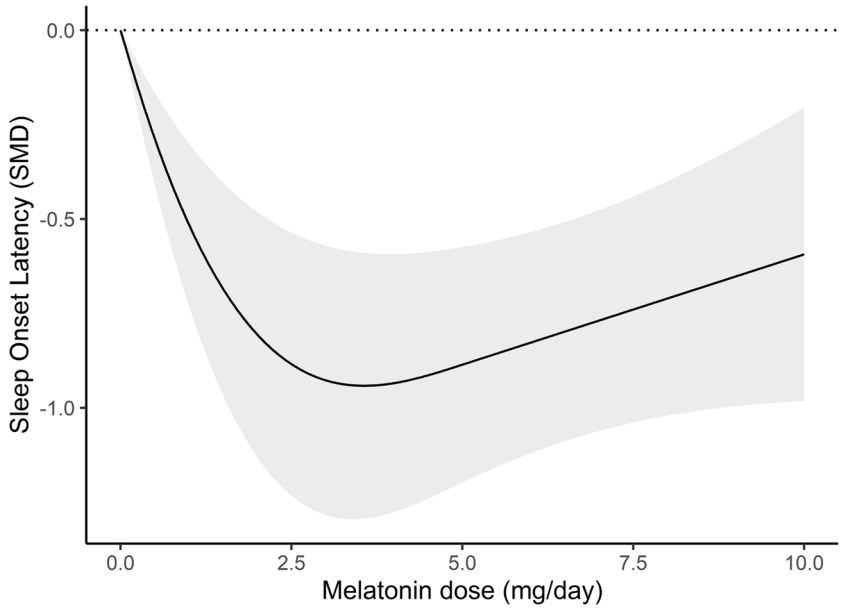


FIGURE 4 | Pooled dose−response curve of sleep onset latency (standardized mean difference between melatonin and placebo groups; SMD) as a function of melatonin daily dose. Melatonin administration significantly reduced sleep onset latency, reaching the highest efficacy at a dose ranging from 3 to 5 mg/day.

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TABLE 2 | The predicted efficacy of melatonin in reducing sleep onset latency at different doses was tested considering 2 mg/day as the reference for comparisons.

Dose mg/day	Predicted SMD (min)	Predicted lower bound SMD (min)	Predicted upper bound SMD (min)	*p*
0	0.51 (10.45)	0.28 (5.61)	0.75 (15.28)	<0.001*
1	0.19 (3.84)	0.11 (2.18)	0.27 (5.50)	<0.001*
3	−0.085 (−1.73)	−0.12 (−2.48)	−0.049 (−0.99)	<0.001*
4	−0.10 (−2.06)	−0.17 (−3.46)	−0.032 (−0.66)	0.004*
5	−0.082 (−1.68)	−0.20 (−4.07)	0.035 (0.71)	0.17

Note: A dose of 2 mg/day is significantly more effective than a placebo (0 mg/day) and 1 mg/day, whereas 3 and 4 mg/day are significantly more effective compared to 2 mg/day. Predicted values are expressed in standardized mean difference (SMD) and in minutes (min).
*$p < 0.05$.

insomnia patients and healthy participants (29 subsamples healthy, 13 insomnia). Sleep parameters were assessed using EEG in 15 studies (33 subsamples), actigraphy in one study (two subsamples), indirectly through muscle relaxation monitoring in one study (four subsamples), and through self-reported measures in two studies (three subsamples). In four studies (five subsamples), a prolonged-release formulation of melatonin has been used, while in two studies (three subsamples), a non-oral formulation has been administered. The timing of administration ranged between 8:00 and 23.30 h, which corresponded to a range of 0−3.5 h before the sleep episode. Treatment duration ranged from 1 to 28 days. The administered dose ranged from 0.1 to 10 mg/day. Thirteen studies were considered of high quality (30 subsamples), and seven were not (12 subsamples).

Results showed a significant increase in TST following exo-MEL administration as compared to placebo (SMD = −0.43 [19.67 min], 95% CI = 0.27−0.60 [12.35−27.00 min], $p < 0.001$) (Figure 6).

Moderate heterogeneity among the studies was present ($I^2 = 38.1\%$). Egger's test result suggested the absence of asymmetries in the funnel plot ($p = 0.24$) (Figure 7).

Results of the dose−response meta-analysis showed that exo-MEL daily dose significantly predicted the difference between treatment and placebo groups in TST ($p = 0.005$) and that the relationship between dose and effect size significantly differed from linearity ($p = 0.02$). Figure 8 displays the fitted dose −response curve. Melatonin efficacy in increasing TST gradually increases along with the dose until reaching a peak between 3 and 5 mg/day. A further increase in the administered dose provides no additional benefit, in agreement with what emerged from the SOL dose−response curve fitting.

As for SOL, we tested whether the efficacy of diverse doses (0−5 mg/day) might be significantly different from the efficacy of 2 mg/day. As 2 mg/day is significantly more effective than placebo and 1 mg/day, a daily dose of 3 mg significantly increased TST compared to 2 mg (Table 6).

Results from meta-regression models showed that time of administration ($\beta = -0.086$, $p < 0.01$) was the only significant predictor of TST. In particular, a later exo-MEL administration, closer to bedtime, is associated with a reduced increase in TST.

To test whether study quality might have affected our results, we also ran a meta-regression model considering the time of administration and study quality as regressors and SMD (melatonin—placebo) in TST as the dependent variable. The time of administration held its predictivity on the outcome variable, while study quality was not significantly associated with TST ($\beta = 0.19$, $p = 0.23$). Table 7 displays the results of the fitted models.

4 | Discussion

In the present study, we aimed at identifying possible exo-MEL effect modifiers with the objective of maximizing its efficacy as a sleep-promoting drug. The results suggest that advancing the time of administration (i.e., administering it earlier, increasing the phase angle between the time of administration and sleep episode) and increasing the dose of exo-MEL may improve its efficacy in reducing SOL, compared to the most commonly advised clinical practice of prescribing 2 mg 30 min before bedtime [46]. Moreover, we showed that exo-MEL is more effective in reducing SOL in healthy volunteers compared to insomnia patients and that later administration is associated with lower effectiveness in increasing TST. These findings suggest that melatonin efficacy might be increased by optimizing the treatment schedule and might lead to reconsideration of its role in insomnia treatment.

Several meta-analyses have demonstrated that exo-MEL administration might be beneficial for sleep. Brzezinski et al. [23] found that melatonin reduced sleep latency by 4 min and increased sleep duration by 12.8 min as compared to placebo. Exo-MEL shortened sleep latency by 5.05 min in insomnia patients according to Auld et al. [24], by 7.2 min according to Buscemi et al. [18], and by 7.06 min according to Ferracioli-Oda et al. [25] In line with those studies, our results showed that exo-MEL administration reduced SOL (9.31 min) and increased TST (19.67 min) compared to a placebo.

While exo-MEL efficacy as a sleep-promoting agent has been proven by several studies, to the best of our knowledge, this is the first systematic attempt to identify the optimal treatment schedule (time of administration and dose) for adults. Out of the four aforementioned meta-analyses, only Ferracioli-Oda et al. [25] demonstrated that the efficacy increases along with

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TABLE 3 | Meta-regression models were estimated considering the standardized mean difference in sleep onset latency (melatonin—placebo) as the dependent variable.

	Model 1			Model 2			Model 3		
	Estimate	Standard error	*p* value	Estimate	Standard error	*p* value	Estimate	Standard error	*p* value
Intercept	−0.47	0.30	0.12	−0.33	0.14	0.017*	−0.31	0.12	0.011*
Hours before bedtime	−0.16	0.068	0.022*	−0.23	0.073	0.002*	−0.25	0.086	0.003*
Dose (mg)	−0.021	0.024	0.39						
Insomnia	0.51	0.13	<0.001*	0.35	0.17	0.042*	0.41	0.14	0.003*
Time of the day	0.0051	0.014	0.71						
Treatment duration (days)				0.0032	0.0099	0.74			
Prolonged release				0.072	0.19	0.71			
Study quality (not high)							0.077	0.17	0.66

Note: In model 1, the number of hours between melatonin administration and the sleep episode, dose, time of administration (clock time), and insomnia status were included as regressors. In model 2, the number of hours between melatonin administration and the sleep episode, insomnia status, treatment duration, and the use of a prolonged release formulation were considered as independent variables. Results show that insomnia status and the time between melatonin administration and the sleep episode significantly predict melatonin efficacy. In particular, melatonin is less effective in insomnia patients compared to healthy controls and melatonin efficacy gradually increases when the time of administration is advanced (earlier) with respect to the sleep episode. Model 3 shows that these results are not affected by study quality.

*$p < 0.05$.

the dose (range 0.5−5 mg) without proposing a specific dose range for clinical contexts. Regarding the dose, our dose−response model predicted that exo-MEL reaches its highest efficacy in reducing SOL and increasing TST at 4 mg/day. With regard to sleep latency reduction, 3 and 4 mg/day are significantly more effective than 2 mg/day, while 3 mg/day is significantly more effective than 2 mg/day in increasing TST. These results might have several clinical and regulatory implications. The American Academy for Sleep Medicine (AASM) currently recommends the use of exo-MEL at a dosage of 2 mg/day for the treatment of chronic insomnia [61].

It is very likely that the time of administration, and not only the dose, plays a crucial role in determining exo-MEL efficacy. Our meta-regression analysis showed that advancing the time of administration of exo-MEL with respect to the sleep episode increased its efficacy in sleep promotion. Although exo-MEL taken just before trying to fall asleep or 1 h before the sleep episode is effective in reducing SOL compared to placebo, the efficacy was further increased by widening the time interval (phase angle) between exo-MEL administration and the sleep episode. The time−response curve was steepest between 1 and 3 h before the sleep episode, while outside this interval, the time−response relationship seemed to weaken. A meta-regression model demonstrated that administering exo-MEL 1 h before the sleep episode does not lead to an increase in treatment efficacy compared to the administration at the sleep episode onset, whereas administering exo-MEL both 2 and 3 h before the sleep episode predicted a significant decrease in SOL. The predicted SOL reduction values at different administration timepoints also showed that advancing the administration timing beyond 3 h might not lead to clinically relevant improvement, as if the time−response curve reached a plateau after peaking at 3 h. Nevertheless, only in two of the studies included in the present metanalysis exo-MEL was administered earlier than 3 h before the sleep episode (i.e., 3.5 h), so that any conclusion on the time−response curve shape beyond 3 h should be confirmed by further investigations.

Individual's circadian phase could be a relevant effect modifier, as described in studies evaluating the chronobiotic effect of exo-MEL, which showed how the effect of exo-MEL depends on the interaction between clock time of administration and biological time [20, 62] Unfortunately, we could not include a circadian phase measure in our analyses (i.e., chronotype, Dim Light Melatonin Onset [DLMO]) because this was not investigated in most of the studies included in the present quantitative synthesis. Only three studies reported the individual circadian phase as measured through the endogenous melatonin profiles before exo-MEL administration [30, 51, 60]. In these studies, endogenous melatonin concentration peaked one to 2 h before the sleep episode, exo-MEL was administered at a timing close to the average DLMO [60], or even after the average DLMO [30, 51], and a significant decrease in SOL was observed in two of them [51, 60]. These results are not conclusive and reflect the heterogeneity of the effect of melatonin when administered in the evening, as previously reported [17]. In the present study, we found that the time window between administration and sleep significantly predicted SOL reduction in models adjusted

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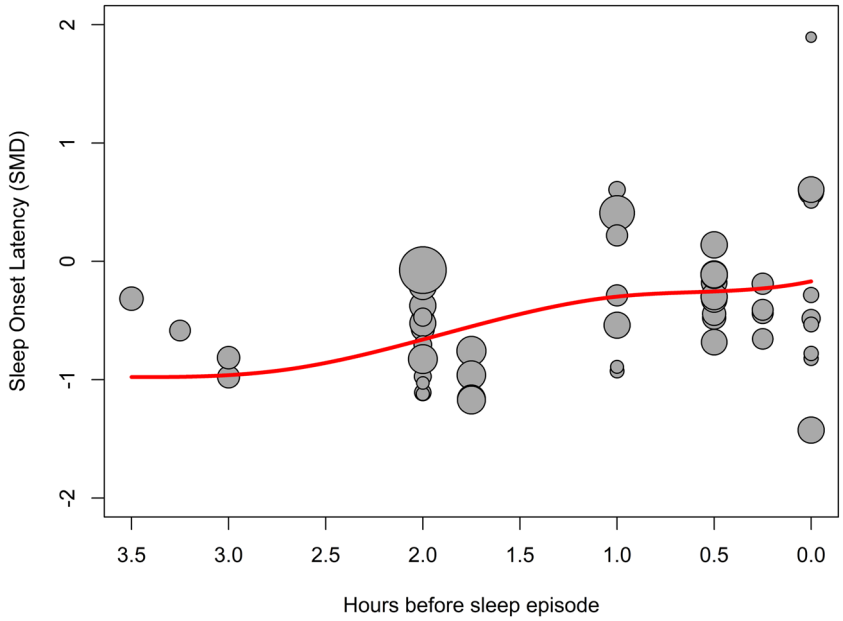


FIGURE 5 | Pooled time−response curve of sleep onset latency (standardized mean difference between melatonin and placebo groups, SMD) as a function of time of administration of melatonin with respect to the sleep episode. The sleep-promoting effect of advancing the time of melatonin administration is more apparent when exo-MEL is taken between 1 and 3 h before the sleep episode. Outside this time window, the relationship between timing and efficacy seems weaker.

TABLE 4 | Meta-regression model was estimated considering the standardized mean difference in sleep onset latency (melatonin—placebo) as the dependent variable and the time window between exo-MEL administration and the sleep episode as a predictor.

	Estimate	Standard error	*p* value
Intercept	−0.24	0.12	0.04*
0			
1	−0.14	0.25	0.57
2	−0.44	0.17	0.01*
3	−0.60	0.28	0.01*

Note: Administration time was included in the model as a categorical variable expressing the number of hours at which exo-MEL was taken with respect to the sleep episode. For the categorization procedure, please refer to the Section 2. Bedtime (i.e., 0 h before the sleep episode) was considered as the reference for comparison and represented in the Table by a blank row. Administering exo-MEL 1 h before the sleep episode did not significantly improve its efficacy as compared to the administration right before the sleep episode, whereas both 2 and 3 h before the sleep episode were associated with a significant reduction in sleep onset latency. Of note, the effect size is higher for 3 h before the sleep episode as compared to 2 h ($\beta = -0.60$ vs. $\beta = -0.46$, respectively).
Significance code: *$p < 0.05$.

TABLE 5 | The predicted efficacy of exo-MEL in reducing sleep onset latency (SOL) at different times of administration with respect to bedtime are shown.

Timing of administration (hours before bedtime)	SOL mel-pla (SMD)	SOL mel-pla (min)
0	−0.17	−3.45
0.5	−0.25	−5.19
1	−0.30	−6.08
1.5	−0.45	−9.10
2	−0.66	−13.48
2.5	−0.86	−17.51
3	−0.96	−19.62
3.5	−0.98	−19.95

Note: As suggested by the fitted time−response curve, advancing the time of administration is paralleled by the greatest reduction in sleep onset latency between 1 and 3 h before the sleep episode. Results are reported as the standardized mean difference (SMD) in melatonin and placebo groups and as the relative conversion in minutes.

for the clock time of administration. This result suggests that advancing exo-MEL time of administration might favor sleep onset independently from its chronobiotic properties.

The significance of the variable "Hours before the sleep episode" in predicting SOL reduction irrespective of exo-MEL clock time of administration might be explained by possible mechanisms of action of both exogenous and endogenous melatonin. For instance, the drop in core body temperature induced by exo-MEL, which is likely to contribute to its acute soporific action [63], was shown to peak 2.5 h after administration in a study in which a fast-release formulation at the dose of 5 mg at 17:00 h was used [64]. Moreover, a similar time frame elapses, under physiological conditions, between the onset of the endogenous melatonin synthesis (i.e., the DLMO) and sleep onset, which typically occurs around 2 h before the habitual onset of nocturnal sleep [65, 66]. It is possible that a similar temporal gradient may be required to activate somnogenic mechanisms via exo-MEL [17]. A comparable time lag between exo-MEL administration and the subsequent drop in core body temperature, as well as between DLMO and sleep onset, may explain our results. In this light, exo-MEL appears to be most effective at promoting sleep onset when its administration mirrors the pattern of endogenous melatonin synthesis, reaching the highest blood concentration when endogenous

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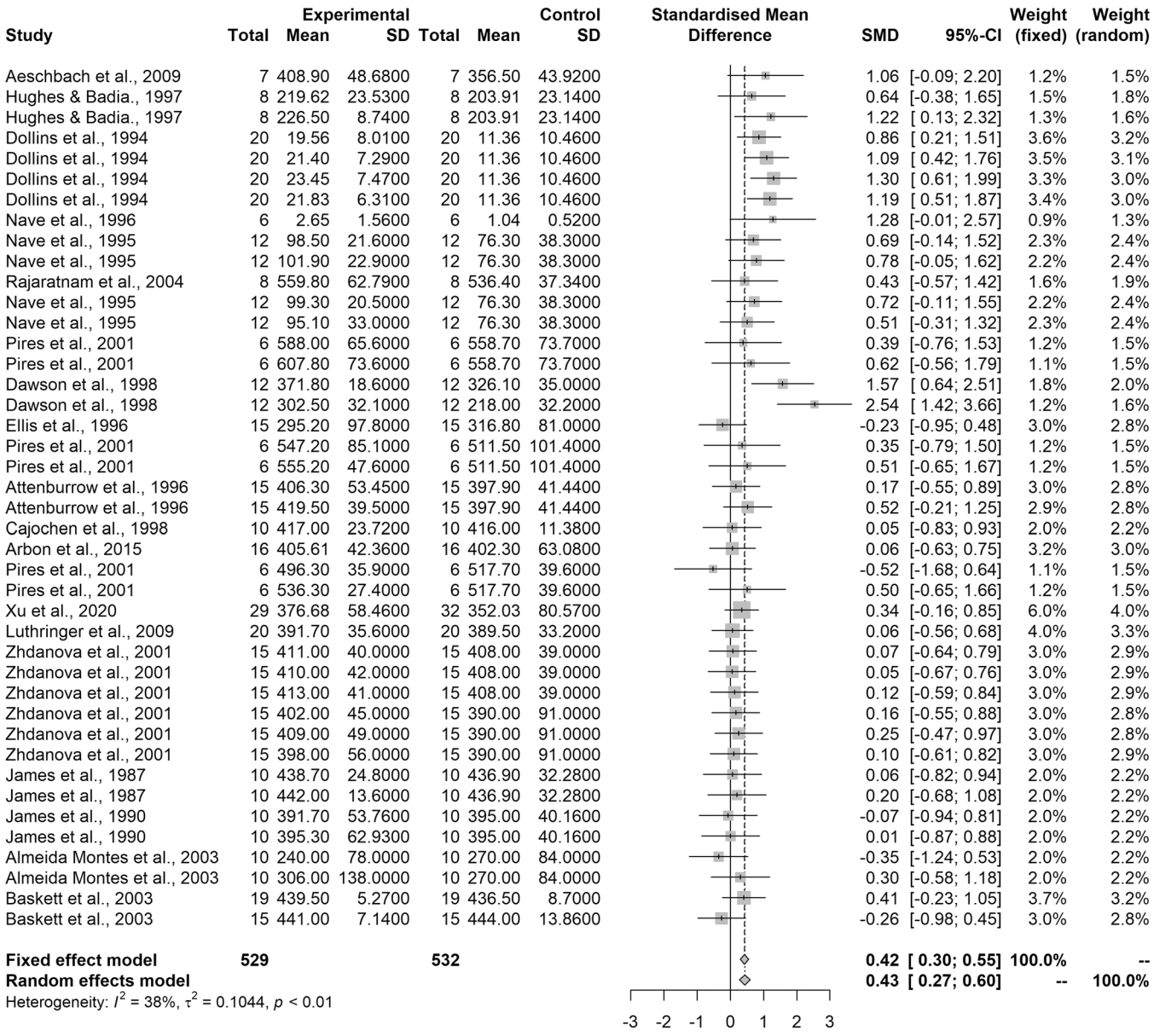


FIGURE 6 | The effect of melatonin administration on total sleep time as compared to placebo, expressed as standardized mean difference SMD). Horizontal lines represent a 95% confidence interval for each study. The diamond at the bottom of the figure indicates the pooled mean effect and the relative confidence interval. Melatonin administration significantly increased total sleep time.

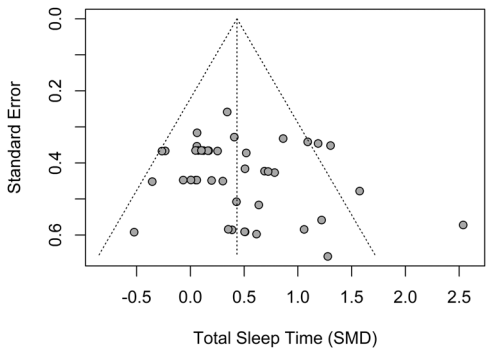


FIGURE 7 | The effect size of each study was plotted against the relative standard error (funnel plot). No asymmetry in the plot suggests the presence of a publication bias in the studies included to explore melatonin's effect on total sleep time (Egger's test, $p = 0.24$).

melatonin would. Taking into account the time required by exo-MEL to reach the peak in blood concentration after oral administration (highly variable, but around 50 min on average for fast-release exo-MEL; around 167 min for prolonged release exo-MEL) [67], as well as our time−response curve, we might conclude that administering exo-MEL 3 h before the desired bedtime would maximize its sleep-promoting action.

Our findings indicate that the exo-MEL schedule most commonly advised in clinical practice might not be the most effective when the proposed models are translated into simulated clinical cases. Indeed, our model predicts that a patient taking 2 mg of exo-MEL 30 min before a desired bedtime of 22:30 h would have a treatment efficacy close to zero (SMD = 0.021). Instead, if exo-MEL is administered to the same patient 3 h before the sleep episode at the dose of 4 mg (the best schedule according to our study), Model 1 predicts a clinically

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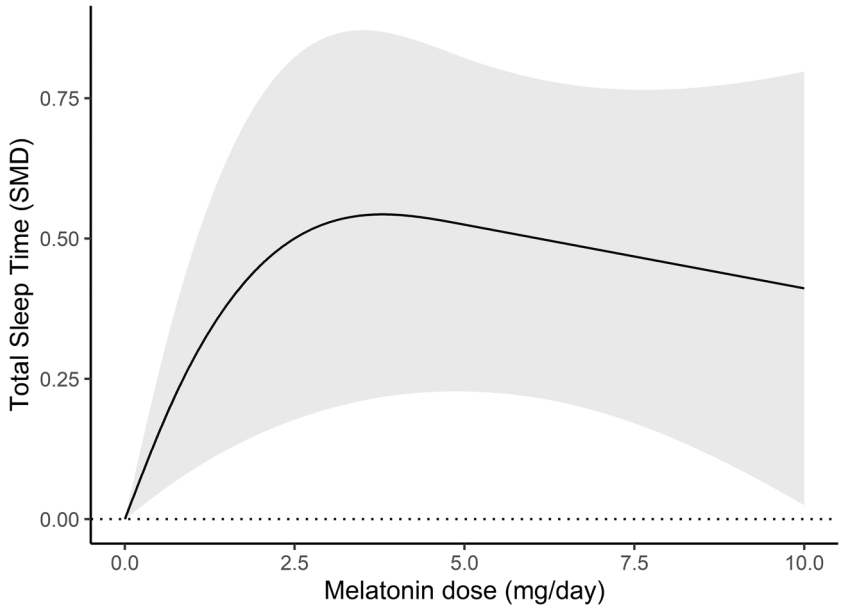


FIGURE 8 | Pooled dose−response curve of total sleep time (standardized mean difference between melatonin and placebo groups, SMD) as a function of melatonin daily dose. Melatonin administration significantly increases total sleep time, reaching the highest efficacy when administered at a dose ranging from 3 to 5 mg/day.

TABLE 6 | The predicted efficacy of melatonin in increasing total sleep time at different doses was tested considering 2 mg/day as the reference for comparisons.

Dose mg/day	Predicted SMD (min)	Predicted lower bound SMD (min)	Predicted upper bound SMD (min)	*p*
0	−0.32 (−14.57)	−0.53 (−23.85)	−0.12 (−5.29)	0.002*
1	−0.12 (−5.33)	−0.19 (−5.33)	−0.048 (−2.18)	0.001*
3	0.051 (2.33)	0.016 (0.71)	0.087 (3.96)	0.005*
4	0.059 (2.67)	−0.017 (−0.79)	0.14 (6.14)	0.131
5	0.044 (2.02)	−0.088 (−4.01)	0.18 (8.04)	0.512

Note: A dose of 2 mg/day is significantly more effective than a placebo (0 mg/day) and 1 mg/day, whereas 3 mg/day is significantly more effective than 2 mg/day. Predicted values are expressed as standardized mean difference (SMD) and minutes (min).
*$p < 0.05$.

significant lowering of SOL compared to placebo (SMD = −0.42 to 8.63 min), close to the pooled exo-MEL effect size (SMD = −0.46 to 9.31 min). Nonetheless, we acknowledge that the lowest effective dose of exo-MEL is recommended to minimize other side effects [21, 68]. Therefore, we also estimated the SOL reduction when exo-MEL is administered at 2 mg 3 h before the sleep episode. As compared to the placebo, Model 1 predicts an SOL reduction of 7.79 min (SMD = −0.38), suggesting that time of administration plays a more important role than dose in enhancing exo-MEL's sleep-promoting properties. Given a high variability in an individual's melatonin receptor sensitivity and in the threshold for receptor saturation [21], higher doses (up to 4 mg) might still further contribute to sleep promotion and could be considered as a treatment option after careful cost −benefit analysis, when lower doses fail to alleviate insomnia-related symptoms. Conversely, our pooled dose−response curve data suggest that reducing the dose below 2 mg might not provide the maximal decrease in SOL.

Optimizing an exo-MEL treatment schedule might lead to reconsideration of its role in primary insomnia treatment. Indeed, the current European guidelines do not recommend the use of exo-MEL [15], whereas the evidence in support of exo-MEL administration to patients with primary insomnia is weak, according to AASM [61]. Despite the fact that we found that exo-MEL efficacy in reducing SOL was lower in insomnia patients compared to healthy volunteers, its efficacy could be improved by optimizing the administration schedule. Our results, however, also suggest that even after optimizing the administration schedule, the degree of melatonin efficacy in insomnia treatment is limited compared to other therapeutic approaches, such as cognitive behavioral therapy (CBT). CBT has been shown to reduce SOL in insomnia patients by 19.03 min with respect to inactive comparators [69], more than twice the highest effect size predicted by our models. Nevertheless, exo-MEL might find a clinical application as an add-on treatment for severe cases or to manage CBT low adherence, which may critically undermine its efficacy [70]. Moreover, it is relevant to highlight that the increase in plasma melatonin levels in the late evening is not an imperative signal for sleep; rather, it has been defined as "a gentle promoter of general relaxation and sedation that, in favorable conditions,

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TABLE 7 | Meta-regression models were estimated considering the standardized mean difference in total sleep time (melatonin—placebo) as dependent variables.

	Model 4			Model 5			Model 6		
	Estimate	Standard error	*p* value	Estimate	Standard error	*p* value	Estimate	Standard error	*p* value
Intercept	2.13	0.43	<0.001*	2.12	0.32	<0.001*	1.94	0.32	<0.001*
Hours before bedtime	−0.068	0.083	0.41						
Dose (mg)	0.013	0.026	0.62						
Insomnia	−0.082	0.16	0.61	0.090	0.16	0.58			
Time of the day	−0.088	0.020	<0.001*	−0.090	0.018	<0.001*	−0.081	0.016	<0.001*
Treatment duration (days)				0.0010	0.0083	0.90			
Prolonged release				−0.18	0.20	0.35			
Study quality (not high)							0.019	0.16	0.23

Note: In model 4, the number of hours between exo-MEL administration and the sleep episode, dose, time of administration, and insomnia status were included as regressors. In model 5, insomnia status, time of the day, treatment duration, and the use of a prolonged release formulation were considered as independent variables. Results show that melatonin clock time of administration is the only significant predictor of melatonin efficacy in increasing total sleep time. In particular, melatonin gradually reduces its efficacy when administered later in the day, closer to bedtime. Model 6 shows that this result is not affected by study quality.

*$p < 0.05$.

significantly facilitates sleep onset" [60]. Factors such as light exposure and activities that promote states of alertness can interfere with the sleep-promoting effect of exo-MEL in the same way they interfere with natural sleep onset [22]. Also, the aroused state of insomnia [71] could interfere with its effects. Therefore, both sleep hygiene and CBT interventions could further enhance exo-MEL efficacy.

Our findings indicate that the efficacy of exo-MEL in increasing TST is predicted by the time of day at which it is administered. Specifically, we found that its ability to increase sleep duration decreases when administered close to bedtime while gradually increasing when administered earlier during the day. This is consistent with several studies demonstrating that melatonin possesses an acute sleep-promoting effect when administered during the day [20, 72], that is, when endogenous circulating melatonin levels are low. Indeed, exo-MEL's sleep-promoting action is highly influenced by the phase of the endogenous melatonin rhythm [26], such that in the absence of circulating endogenous melatonin, MEL receptors may be more sensitive to exo-MEL. Interestingly, Wyatt et al. [26] failed to demonstrate a time of day-related effect of exo-MEL in reducing SOL. Instead, the authors demonstrated its ability to increase SE when administered during the biological day (i.e., out of phase with endogenous melatonin) in a forced desynchrony study. An increase in SE might contribute to explain the increase in TST reported in the present study (exo-MEL vs. placebo) for daily sleep episodes.

Our study is the first systematic attempt to identify the optimal dose and time of administration of exo-MEL to enhance its sleep-promoting effect. Moreover, our results are based on randomized placebo-controlled trials (i.e., the most accurate experimental design in medical research), granting a highly controlled value to the conclusion. There are limitations, however, that should be addressed. In our work, we only included studies performed either in healthy participants or in insomnia patients, and therefore our findings in terms of dose and time of administration are not automatically generalizable to the treatment of other sleep disorders. Our results are based on studies in which exo-MEL was administered in a range of 0−3.5 h before the sleep episode; therefore, even if the fitted time−response curve suggested the presence of a plateau after 3 h before administration, we cannot fully rule out that a further advance in the timing of administration (more than 3 h before the sleep episode) would lead to a further increase in efficacy. The Egger test detected the presence of an asymmetry in the funnel plot of the studies exploring exo-MEL efficacy in reducing SOL, suggesting the possible presence of a publication bias in the body of research articles included in our work. Finally, our results are based on predicted data, and their replication in clinical trials is essential before drawing any definitive conclusion on exo-MEL optimal posology.

In conclusion, advancing the time of administration to 3 h before bedtime, using doses ranging between 2 and 4 mg, will enhance exo-MEL's sleep-promoting action. This study represents a first step toward the definition of the optimal exo-MEL treatment schedule, which may lead to reconsideration of its role in primary insomnia treatment.

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Author Contributions

Francy Cruz-Sanabria, Simone Bruno, and Ugo Faraguna conceived and designed the study. Francy Cruz-Sanabria and Simone Bruno selected the articles, extracted the data, and wrote the first draft of the manuscript. Simone Bruno, Francy Cruz-Sanabria, Alessio Crippa, and Paolo Frumento carried out the statistical analysis. Francy Cruz-Sanabria, Simone Bruno, Alessio Crippa, Paolo Frumento, Debra J. Skene, and Ugo Faraguna interpreted the data. Alessio Crippa, Paolo Frumento, Marco Scarselli, Debra J. Skene, and Ugo Faraguna critically revised the final version of the manuscript. All authors agreed with the results and conclusions of this article.

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Conflicts of Interest

U. F. is cofounder and president of Sleepacta S.r.l., a spin-off company of the University of Pisa operating in the field of sleep medicine. The remaining authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data sets were generated during the current study.

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