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Adverse events associated with oral administration of melatonin: A critical systematic review of clinical evidence

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ABSTRACT

While melatonin was once thought of simply as a sleep-inducing hormone, recent research has resulted in development of a deeper understanding of the complex physiological activity of melatonin in the human body. Along with this understanding has come widespread, increasing use of melatonin supplementation, extending beyond its traditional use as a sleep aid into novel fields of application. This increased use often involves off-label and self-prescription, escalating the importance of safety data. In order to examine the current knowledge relating to safety of the exogenous neurohormone, we conducted a comprehensive, critical systematic review of clinical evidence. We examined controlled studies of oral melatonin supplementation in humans when they presented any statistical analysis of adverse events. Of the fifty articles identified, twenty-six found no statistically significant adverse events, while twenty-four articles reported on at least one statistically significant adverse event. Adverse events were generally minor, short-lived and easily managed, with the most commonly reported adverse events relating to fatigue, mood, or psychomotor and neurocognitive performance. A few studies noted adverse events relating to endocrine (e.g. reproductive parameters, glucose metabolism) and cardiovascular (e.g. blood pressure, heart rate) function, which appear to be influenced by dosage, dose timing and potential interactions with antihypertensive drugs. Oral melatonin supplementation in humans has a generally favourable safety profile with some exceptions. Most adverse effects can likely be easily avoided or managed by dosing in accordance with natural circadian rhythms. Further research is required to explore the potential for melatonin to interact with endogenous hormones and pharmaceuticals.

1. Introduction

The physiological and clinical importance of melatonin has been recognised for decades, particularly relating to sleep.[1,2] While regulation of its prescription or over-the-counter (OTC) availability varies by country, it is widely used as a remedy for sleep disorders,[3,4] with global prevalence of use expected to continue increasing in coming years.[5] Compared to some other prescription and OTC sleep-aids, melatonin has demonstrated favourable efficacy and tolerability.[6,7] Due to its wide-spread, growing use, it is imperative to ensure thorough understanding of the safety of melatonin supplementation.

As research uncovers the complex scope of melatonin's physiological activity, its application is extending beyond sleep support into new fields such as oncology,[8] fertility,[9] gastroenterology,[10] cardiology,[11] and immunology.[12] Many of these novel applications do not yet have sufficient evidence of safety and efficacy. Use of melatonin for novel applications, combined with increases in off-label prescribing[13] and self-prescription resulting from OTC or online availability,[14,15] may leave consumers vulnerable to unknown risks.

While a brief narrative review was recently conducted,[16] there has been no comprehensive review of evidence for safety of melatonin to date. In response, we conducted a systematic review of available evidence relating to adverse effects of orally-administered melatonin.

2. Methods

The aim of this review was to explore available clinical evidence regarding the safety of oral melatonin supplementation in humans. A protocol was developed in adherence with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 checklist.[17]

2.1. Data sources

A search was conducted 7–9th August 2017, using AMED (EBSCOhost), CINAHL (EBSCOhost) and PubMed (NLM) databases.

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Four search-strings were combined to identify papers involving melatonin administration, safety assessment, relevant study designs, and human participants. The full search string was as follows: *S1: melatonin AND (S2:(safety OR adverse OR risk OR toxicology) OR S3:(trial OR RCT OR clinical OR epidemiolog* OR observation* OR random* OR placebo)) NOT (S4: animals NOT human)*. S4 was added to exclude studies limited to animals while including studies involving both animal and human participants.

2.2. Study selection

Citations were downloaded into EndNote X8 (Clarivate Analytics 2017) citation management program. Duplicates were removed and citations filtered according to eligibility criteria by title and abstract. Additional criteria limiting to controlled designs with statistical analyses of adverse events were then applied and citations were screened again by abstract. The resulting citations were then inspected by full-text and those adhering to eligibility criteria selected for review. Reference lists of selected studies were searched for additional eligible papers, as were reference lists of review articles noted during screening. Study selection was undertaken by one reviewer (HF) and a representative sample of citations was checked by a second reviewer (AS), with discrepancies resolved through discussion until reaching consensus.

Articles were considered for inclusion if they detailed oral administration of melatonin to human participants with statistical analyses of adverse events, in keeping with the CONSORT (Consolidated Standards of Reporting Trials) Extension for Harms.[18] This included articles where adverse events were identified during analyses of study outcomes. No restrictions were placed on date or language. Articles were excluded if melatonin was only given in combination with other interventions, whereby the independent effect of melatonin could not be assessed.

2.3. Data extraction and quality assessment

Data were extracted from selected papers into forms prepared with consideration to Cochrane Network guidelines,[19] including domains of study characteristics, population, details of melatonin administration, comparative interventions, participants' concomitant medications, and details of adverse event reporting and measures. Attention was paid to melatonin form, dosage, duration, and statistical findings of adverse events. The data extraction form was prepared by two reviewers (HF, AS). Data extraction was completed by one reviewer (HF) and periodically checked by a second reviewer (AS) with discrepancies resolved through discussion until reaching consensus.

Quality of evidence reporting in studies selected for review was appraised with the CONSORT 2010 Checklist[20] and Extension for Harms.[18]

2.4. Data synthesis

Two reviewers (HF, AS) assessed extracted data to identify findings relevant to the safety of melatonin and to synthesise a comprehensive review. Particular attention was given to statistical significance of adverse events, populations adverse events were reported in, nature and severity of adverse events, correlation of adverse events with form and dosage of melatonin, and the potential role of melatonin in drug interactions.

3. Results

Following citation screening (summarised in Fig. 1), fifty articles complied with eligibility criteria. During full-text appraisal, 456 were excluded either because melatonin was not administered orally, or the study did not statistically analyse adverse events.

3.1. Quality assessment findings

Few studies performed well under the CONSORT checklist and extension, particularly those conducted before development of such reporting guidelines. While participant eligibility criteria and intervention methods were generally well-described, other aspects of methodology were poorly reported. Outcomes were rarely explicitly defined, sample-size calculations infrequently employed, and randomisation and blinding rarely described in adequate detail to allow reproduction of methods. Reporting of outcomes frequently neglected inclusion of a comprehensive analysis of harms, often focussing on adverse events related to primary outcomes rather than assessing a broad scope of adverse events. Discussions generally acknowledged trial limitations and provided balanced interpretation of results, however, there was rarely any direction for readers to access trial protocols. Full details in Table 1.

3.2. Study characteristics

Included studies arose from an extensive timeline of 1976[21] to 2016,[22–25]and wide geographical spread covering all World Health Organisation regions with the exception of Africa. All included studies involved some method of control, whether by placebo,[21,23–60] comparator intervention,[61–63] both,[22,64–69] or un-medicated control group.[70] Five studies did not employ randomisation.[29,30,36,57,59] Sample sizes ranged from six[43,49] to 392[37] with a total of 3803 and an average of 76 participants.

Study populations were most frequently healthy individuals (n = 18),[23,29,31,38,39,43,46–48,52–5457,59,60,65,68,70] followed by individuals undergoing surgical procedures (n = 8).,[24,32,34,35,61–6366] Populations of individuals with neurological/mental health conditions (n = 5),[21,25,49,56,67] sleep disorders (n = 5),[28,36,37,41,69] or a combination of both (n = 4)[27,50,55,58] were also common. Other populations included those with endocrine abnormalities (n = 3),[30,33,42] cardiovascular conditions (n = 3),[40,44,45] asthma (n = 1),[26] fibromyalgia (n = 1)[64] and cancer (n = 1).[51] Within these populations, nine specifically focussed on women,[24,26,30,34,42,47,60,64,70] six on men,[38,39,43,48,54,57] seven on older adults,[36,37,44,45,56,65,67] and five on children.[27,55,58,61,62]

Almost half of the studies (n = 24) did not report the form of melatonin given, while fifteen used immediate-release formulas,[22–2428,33,40,43,44,47,53,55,58,60,62,69] seven used prolonged-release formulas,[25,36,37,41,54,56,65] three used a combination of immediate- and prolonged-release melatonin,[27,50,52] and one used a medium-fast release formula.[67] Dosages most commonly ranged from 2 mg to 10 mg daily, however, exceptions to this ranged from 0.3 mg[43] to 1600 mg daily.[21] Melatonin was typically given in the evening or before bed,[22,25,26,28,29,32–37,39–45,48,50–52,55,56,58,59,64,67,69,70] with a number of studies administering melatonin before a procedure or outcome measure test,[23,24,30,31,38,46,47,53,54,60–63,65,66,68] or at multiple time-points throughout the day.[21,49,57] Duration of study ranged from single administrations,[23,24,46,53,54,60–63,66,68] to 3.5 years daily dosing.[67] Full details of study characteristics in Table 2.

3.3. Adverse events

Of the fifty articles assessed, twenty-six reported no statistically significant difference in adverse events between intervention and control conditions.[22,25–28,32–37,41,42,45,48,50–52,55,56,58,61–64,69] The remaining twenty-four reported at least one statistically significant adverse event attributed to melatonin.[21,23,24,29–31,38–40,43,44,46,47,49,53,54,57,59,60,65–68,70] Adverse events are detailed below and summarised in Table 3.

Fatigue, Sleep and Psychological Effects Seventeen studies which included fatigue, unwanted sleepiness or sleeplessness within their assessment of adverse events found no statistically significant difference between melatonin and placebo.[22,25,27,28,32–34,42,48,50–52,55,56,58,64,67] Ten studies reporting on psychological adverse events (e.g. depression,

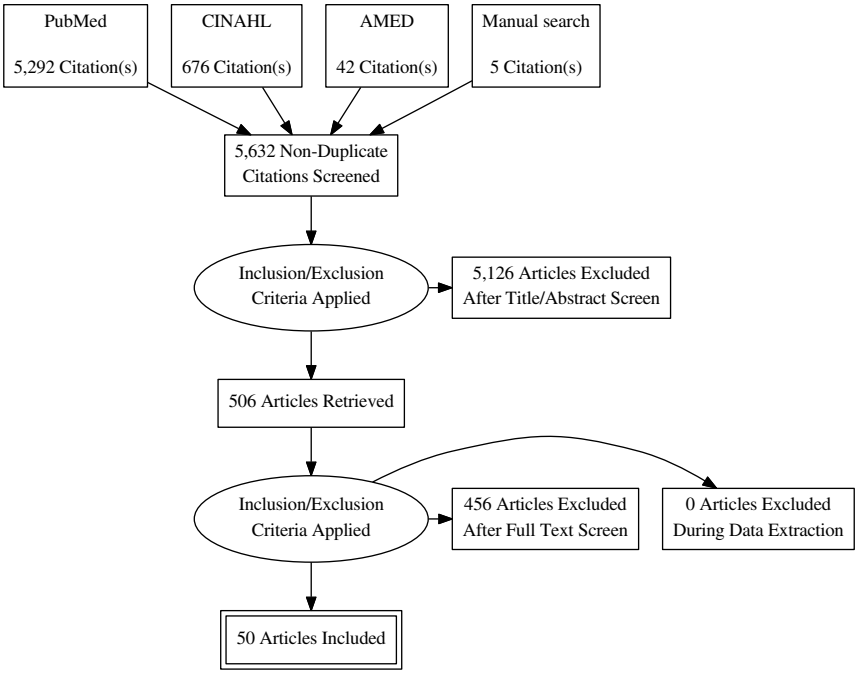

Fig. 1. Study selection flowchart for review of melatonin safety Workflow of literature search and study selection process.

anxiety, mood changes) found no statistically significant difference between melatonin and placebo.[25,27,32,37,38,43,48,55,58,61]

A significant increase in fatigue with melatonin administration, alongside decrease in vigour/energy, was reported in two studies which dosed melatonin during daylight hours.[38,49] One of these studies also noted a significant increase in confusion.[38] Similarly, other papers reported a significant increase in sleepiness,[68] or decrease in alertness[54] when melatonin was dosed during morning hours, and another reported morning drowsiness and weakness when melatonin was dosed late at night (22:30hrs).[40] One study assessing melatonin for post-operative pain found a significant incidence of drowsiness and somnolence alongside reduced incidence of fatigue, compared to placebo.[66]

Conversely, one study reported an increase in latency to sleep onset when 0.3 mg melatonin was given at 21:00hrs, however, sleep parameters improved when this dose was given at 18:00 or 20:00hrs and when a 1 mg dose was given at any of the three administration times.[43] Another study reported loss of sleep associated with melatonin, albeit at very high doses (150–1600 mg daily), in patients with severe depression or Huntington's chorea.[21] These high doses were divided throughout the day and were also associated with onset or exacerbation of psychological symptoms (depression, anger, psychosis), and weight loss.[21] Another study found a decrease in positive mood and increase in withdrawn behaviour in participants taking melatonin compared with those on placebo, however, these outcomes were measured by carer-observation rather than participant self-report, and were ameliorated by day-time exposure to bright light.[67]

Physical, Psychomotor and Neurocognitive Performance Of those studies including assessment of physical, psychomotor and neurocognitive performance, four found no significant difference between melatonin and placebo conditions.[43,48,56,65] Seven studies reported adverse effects on performance parameters; two in professional athletes,[23,31] four in healthy participants,[38,46,53,68] and one in participants with seasonal affective disorder.[49]

In one study of soccer players, adverse impacts were seen on select physical performance tests (hand-grip strength, squat jumps, counter-movement jumps), yet was only statistically significant for the higher dose of melatonin (8 mg) and not for the lower dose (5 mg).[31] No effect was seen on other parameters assessed in the study (five-jump test, medicine-ball throws, modified agility test).[31] A similar study of soccer players, using 5 mg melatonin administered in the morning (07:30hrs) reported an adverse impact on performance in hand-grip strength, medicine-ball throws and cognitive reaction time.[23] This impact was significant for a short time after administration (seen at 08:00 but not 12:00hrs) and did not extend to other physical performance parameters (five-jump test, modified agility test).[23]

When given before a driving test, 5 mg melatonin was found to significantly impact on selective attention, although parameters remained within normal range.[53] No other effects to driving performance metrics assessed in this study were reported under melatonin administration compared with placebo.[53]

Reaction time was adversely effected by melatonin in another study during a four-choice visual reaction time test, given two hours after day-time administration of 240 mg melatonin or placebo.[38] Notably, while reaction time decreased in this test, accuracy improved, and outcomes of four other tests assessing performance, visual sensitivity and memory were not affected by melatonin.[38] Visual tracking and reaction time were also adversely impacted following a 5 mg day-time dose of melatonin when compared to placebo.[46] This adverse effect on visual tracking and reaction time was demonstrated again in a similar study, alongside adverse impacts on spatial memory and vigilance tasks.[68] In another study using a lower day-time dose (2–2.4 mg), visual reaction time was once again reduced, while attention, vigilance and cognitive processing were unaffected.[49]

Reproductive Health Four studies reported adverse effects or potentially adverse changes to reproductive function.[39,57,59,70] One study found 7.5–300 mg melatonin administered daily to healthy women suppressed luteinising hormone and subsequent ovulation within one menstrual cycle, although this effect was intended as the study was exploring potential contraceptive effects of melatonin.[70] Alterations to normal cycles of the hormone prolactin were seen in both women and men after 2 mg melatonin was administered daily for four months,[59] and similarly, a significant increase in prolactin was seen acutely in men after single administrations of 2–4 mg.[57]

When 3 mg melatonin was given to men daily for three months, two of the eight participants experienced reduction in sperm concentration and motility, alongside reduction in oestrogens and an increase in androgen:oestrogen ratio.[39] This affected only a minority of participants, yet the change was significant in comparison to affected participants'

Table 1
Results of critical appraisal of melatonin safety review included literature, with CONSORT 2010 Checklist and CONSORT Extension for Reporting Harms.

		Title and Abstract			Introduction			Methods															
Study	Year	1a	1b	*1c*	2a	2b	*2c*	3a	3b	4a	4b	5	6a	6b	*6c*	*6d*	7a	7b	8a	8b	9	10	11a	11b
Baandrup et al [25]	2016	514	514	x	514-5	151	x	515	516	515-6	515	516	516	x	x	x	519	519	516-7	517	517	517	517	516
Beigom Khezri et al [24]	2016	963	x	963	964	964	964	964	x	964	964	964	965	x	965	x	965	x	964	964	964	964	964	x
Ghattassi et al [23]	2016	x	94	94	94	94	94	96	x	95	x	96	96-7	x	x	x	x	x	x	x	x	x	x	x
Goncalves et al [22]	2016	1127	1127	x	1127	1127	x	1128	x	1127	x	1128	1128	x	1128	1128	1128	1129	1128	1128	x	x	1128	x
Garaulet et al [30]	2015	x	1650	x	1651	1651	x	x	x	x	x	1651	1651	x	x	x	x	x	x	x	x	x	x	x
Kirksey et al [35]	2015	2370	x	x	2370	2370-1	x	2371	x	2371	x	x	2371	x	x	2371	2371	x	2371	x	x	2371	2371	x
de Zanette et al [64]	2014	1	x	x	2	2	x	2	x	3	2	4	4-5	x	4	x	3	x	4	x	4	4	4	4
Fallah et al [62]	2014	741	741	741	741	741	741	742	x	742	742	742	742	x	742	x	742	x	742	742	742	742	742	742
Ghattassi et al [31]	2014	x	x	x	885-6	886	x	886	x	x	887	886-7	887-9	x	x	x	x	x	x	x	x	x	x	x
Goyal et al [33]	2014	1	1	1	1-2	2	x	2	x	2	2	2	2-3	x	x	x	3	x	2	2	x	2	2	x
Hansen et al [34]	2014	683	x	683	683-4	684	x	684	684	684	684	x	684-91	x	x	x	692	x	684	684	684	684	684	684
Parandavar et al [42]	2014	1405	1405	1405	1405-6	1406	x	1407	x	1407	1406	1407	1406	x	x	1406	x	x	1407	1407	1407	1407	1407	1407
Pokharel et al [63]	2014	1	x	x	1	2	x	2	x	2	x	2	x	x	x	x	2	x	x	x	x	x	x	2
Rubio-Sastre et al [47]	2014	x	1715	1715	1715	1715	1715	x	x	x	x	1715-6	x	x	x	x	x	x	x	x	x	x	x	1716
Sookprasert et al [51]	2014	7327	7327	7327	7327-8	7328	7328	7328	7328	7328	7328	7328	7328-9	x	x	7329	x	x	x	7328	x	x	x	7328
Wade et al [56]	2014	947	947	947	947-8	948	x	948	949	948-9	x	949	949	x	x	949	949	x	949	949	x	x	x	949
Wilhelmsen-Langeland et al [69]	2013	306	x	x	308	308	x	311	x	308-9	309	311-2	309-10	x	x	310-1	x	x	312	x	312	x	312	311-2
Lemoine et al [37]	2012	9	9	9	9-10	10	10	10	x	10	x	10	12	x	x	x	x	x	x	x	x	x	x	x
Rechcinski et al [45]	2012	x	24	24	24-5	25	x	x	x	25	x	x	25-6	x	x	x	x	x	x	25	x	x	26	x
Ucar et al [54]	2012	x	x	x	1113-4	1114	x	1114	x	1114	1114	1114	1115	x	x	x	x	x	x	1114	x	x	x	x
Lemoine et al [36]	2011	x	301	301	301-2	302	302	302	x	302	302	302	x	x	x	303	x	302	–	–	–	x	x	x
Wright et al [58]	2011	175	x	175	175-7	177	x	177	x	177	177	178	178	x	x	178-9	177	x	178	178	x	178	x	178
Ashrafi et al [61]	2010	x	x	x	235-6	236	x	x	x	236	236	x	x	x	x	x	x	x	x	x	x	x	x	x
Radwan et al [66]	2010	x	1	x	1-2	2	2	2	x	2	x	2	3	x	3	3	3	x	2	2	x	2	2	x
Rechcinski et al [44]	2010	x	x	56	56	56	56	x	x	56	x	57	57	x	x	x	x	x	x	56	x	x	x	x
Gogenur et al [32]	2009	1152	1152	x	1152	1152	x	1152	x	1152-3	1152	1153	1153	x	x	x	1153	x	X1152	1152	x	1152	1152	1153
Luthringer et al [41]	2009	x	x	239	239-40	240	x	240	x	240	240	241	241-2	x	x	242	x	x	x	241	x	x	x	240
Otmani et al [65]	2008	x	1	1	1-2	2	2	2-3	x	2-3	3	3	3-4	x	x	x	x	x	x	x	x	x	x	x
Riemersma-van der Lek et al [67]	2008	2642	2642	2642	2642	2642-3	x	2643	2644	2643	2643	2643	2646	x	2653	2646	2649	x	2643	2643	x	x	2643	x
Carr et al [27]	2007	x	x	351	351-2	352	352	352	x	352	x	352	352	x	x	352	x	x	x	x	x	x	x	x
Van der Heijden et al [55]	2007	x	233	233	233-4	234	x	234	x	234	234	234	234-6	x	x	236	236	x	x	236	x	236	236	234
Cavallo et al [28]	2005	x	172	x	172	172	x	173	x	173	x	173	173-4	x	173	173	174	x	173	x	x	x	x	173
Campos et al [26]	2004	947	x	947	947	947	x	947	x	947	x	947	947-8	x	x	x	x	x	x	x	x	x	947	947
Rogers et al [68]	2003	x	x	207	207-8	208	208	208	x	208	208	208	208-9	x	x	x	x	x	x	208	x	x	x	208
Singer et al [50]	2003	893	893	893	893	893	893	893	x	895	x	894	894-5	x	x	896	896	x	x	896	x	x	x	894
Luboshitzky et al [39]	2002	x	x	572	572	572	x	573	x	573	x	573	573	x	x	x	x	x	x	x	x	x	x	573
Cagnacci et al [60]	2001	x	339	339	339	339	x	340	x	340	340	340	340	x	x	x	x	x	x	x	x	x	x	340
Pires et al [43]	2001	x	x	x	326-7	327	x	327	x	327	x	327	327	x	x	x	x	x	327	x	x	x	x	327
Edwards et al [29]	2000	x	x	x	1502	1502-3	x	x	1503-4	x	1503	x	1504	x	x	x	x	x	x	x	x	x	1503	x
Lusardi et al [40]	2000	x	423	x	423	424	x	424	x	424	x	424	424	x	x	x	x	x	x	x	x	x	x	424
Seabra et al [48]	2000	193	x	193	193-4	194	194	x	x	194	x	x	195	x	x	195	x	x	x	x	x	x	x	194
Rogers et al [46]	1998	x	x	47	47	47	47	48	x	48	48	48	48-9	x	x	x	x	x	x	48	x	x	x	x
Suhner et al [52]	1998(a)	x	x	x	656	656-7	x	657	x	657	657	657	657-8	x	x	658	x	x	657	657	x	x	x	x
Suhner et al [53]	1998(b)	x	7	7	7	7-8	7-8	8	x	8	8	8	8-9	x	x	8-9	9	x	x	x	x	x	x	x
Voordouw et al [70]	1992	x	x	x	108-9	109	x	109	x	109	x	109	x	x	x	x	x	x	x	x	x	x	x	x
Webley et al [57]	1988	x	x	x	19-20	20	x	21	x	x	x	21	x	x	x	x	x	x	x	x	x	x	x	21
Wright et al [59]	1986	x	x	375	375-6	376	x	376	x	x	x	376	376-7	x	x	x	x	x	x	x	x	x	x	376
Lieberman et al [38]	1985	x	x	201	201	x	x	x	x	x	x	202	202-3	x	x	x	x	x	x	x	x	x	x	x

(*continued on next page*)

Table 1 (*continued*)

		Title and Abstract			Introduction			Methods																	
Sherer et al [49]	1985	x	x	x	277	x	277	x	x	277-8	x	278	278	x	x	x	x	x	x	x	x	x	278	278
Carman et al.[21]	1976	x	x	1181	1181	1181	x	x	x	x	1181	x	1181	x	x	x	x	x	x	x	x	x	1181	1181

		Statistical Methods			Results													Discussion				Other Information		
Study	Year	12a	12b	*12c*	13a	13b	*13c*	14a	14b	15	16a	*16b*	17a	1-7b	*17c*	18	19a	*19b*	20a	*20b*	21	22	23	24	25
Baandrup et al [25]	2016	517	x	x	517-8	517-8	518	517	x	519	519-22	522	518	x	x	x	520-2	x	521	521	521	521	514	515	523
Beigom Khezri et al [24]	2016	966	966	966	966	965-6	x	964	x	966	966	968	x	x	x	x	968	966-7	x	969	968-9	967-9	x	x	x
Ghattassi et al [23]	2016	97-8	97-8	x	x	x	x	x	x	x	x	x	98-101	x	x	x	x	x	103	101-3	x	101-3	x	x	x
Goncalves et al [22]	2016	1128-9	1129	x	1129	1129	x	x	x	1130	1130	1131	1130	1-1-3-0	x	1131	1129	1129	x	x	x	112-9-32	1128	1128	1132
Garaulet et al [30]	2015	1652	1652	x	x	x	x	1651	x	1652	x	x	x	x	1653	x	x	x	1656	165-4-6	1654	165-4-6	x	x	1656
Kirksey et al [35]	2015	2371	2371	x	2372	2372	2372	2371	x	2373	2372	Suppl 6	2372-4	x	x	x	2373	x	2374-5	237-3-5	2375	237-3-5	x	2371	2370
de Zanette et al [64]	2014	6	6	x	6	6	3 + 6	x	x	7	x	6	6-9	x	x	x	6	x	12	12	11-12	11-12	2	2	13
Fallah et al [62]	2014	742	x	x	x	742	742	742	x	742	x	x	742-3	x	x	743	743	743	744	744	744	744	744	x	744
Ghattassi et al [31]	2014	889	x	x	x	x	x	x	x	x	x	x	889-90	x	x	x	x	x	892	890-2	891	890-2	x	x	x
Goyal et al [33]	2014	3-4	4	4	4	3	3	2	x	4	4-8	7-8	x	x	x	8	7-8	7	9	8-9	9	8-9	1	1	9
Hansen et al [34]	2014	691-2	692	692	688, 92	688, 92	688, 92	692	692	689	692	693	692	6-9-0	x	x	691	x	693	693-4	694	693-4	684	684	694
Parandavar et al [42]	2014	1408	1408	1408	1408	1408	x	1406	x	1409	140-9-11	1411	1409-11	x	x	x	1411	x	1413	141-2-13	x	141-2-13	1408	x	1414
Pokharel et al [63]	2014	2	2	x	3	3	x	x	x	4	3-4	4	x	x	x	x	3-4	x	6	3-6	x	3-6	x	x	6
Rubio-Sastre et al [47]	2014	1716	x	x	x	x	x	1715	x	1719B	x	x	x	x	x	x	x	x	1718	171-6-8	171-6-8	171-6-8	x	x	1719
Sookprasert et al [51]	2014	7330	7330	x	7329-31	7331	x	x	x	7330	7329	7334	7333	x	x	x	7334	x	7335-6	733-4-6	733-4-5	733-4-6	7328	7328	7336
Wade et al [56]	2014	x	x	x	950	950	950	x	949	960	951-4	961	x	x	x	x	961	955	955-7	955-7	955-7	955-7	x	x	957
Wilhelmsen-Langeland et al [69]	2013	312	312	312	309	309	309	309	x	313	313-7	x	x	x	x	x	314-5	x	318-9	316-9	318	316-9	308	308	319
Lemoine et al [37]	2012	12	x	x	12-13	11	11	10	x	x	13	14	13-14	x	x	x	14-15	x	16	14-16	14-16	14-16	1	1	16
Rechcinski et al [45]	2012	26	26	x	x	x	x	x	x	25	26	26	x	x	x	x	x	x	28	27-8	27	27-8	x	x	28
Ucar et al [54]	2012	1115	1115	x	x	x	x	x	x	x	x	x	1115-6	x	x	x	x	x	1117	111-6-7	1117	111-6-7	x	x	1117
Lemoine et al [36]	2011	303	303	303	303	303	x	x	302	x	x	306-8	x	x	x	x	306-8	306-7	x	x	x	308-10	x	x	310
Wright et al [58]	2011	179	179	179	180	179	179	x	x	x	181	x	x	x	x	x	180-1	x	182-3	182-3	x	182-3	x	x	183
Ashrafi et al [61]	2010	236	x	x	236	x	x	236	x	x	x	x	x	x	x	237	237	x	x	x	x	237	x	x	238
Radwan et al [66]	2010	3	3	x	x	x	x	x	x	3	3	4	x	x	x	x	4	x	x	x	4-5	4-5	x	x	x
Rechcinski et al [44]	2010	57	x	x	57	x	x	x	x	57	57-8	x	x	x	x	59	58	58	60	58-60	58-9	58-60	x	x	60

(*continued on next page*)

Table 1 (*continued*)

		Statistical Methods			Results														Discussion				Other Information		
Gogenur et al [32]	2009	1153-4	1154	x	1153	x	x	1154	x	1154	1154	1154	x	x	x	x	1154	x	1155	1155	x	115-4-5	x	x	x
Luthringer et al [41]	2009	242	242	242	243	x	x	x	x	243	242-6	x	x	x	x	x	246	x	x	246-8	247	246-8	x	x	248
Otmani et al [65]	2008	4	4	x	x	x	x	x	x	x	x	x	x	x	x	x	4-8	x	10	8-11	9-10	8-11	x	x	11
Riemersma-van der Lek et al [67]	2008	2648	2648	x	2645	2645	x	2644	x	2644	2645	x	2650-1	2-6-4-9-5-1	2653	2652	264-9-53	x	2653	265-2-4	2653	265-2-4	2642	2642	2654
Carr et al [27]	2007	x	x	x	352	353	353	353	x	352	352	352	x	x	x	x	353	x	354	354	354	354	x	x	355
Van der Heijden et al [55]	2007	236	x	236	235	236	x	234	x	236	x	238	x	x	x	x	238-9	x	240	239-40	240	239-40	234	234	233
Cavallo et al [28]	2005	174	174	174	174-5	x	x	x	x	x	174-5	175	174-5	x	x	x	175	x	175-6	175-6	175	175-6	x	x	176
Campos et al [26]	2004	948	948	948	948	948	x	X	x	949	949	x	x	x	x	x	948	x	x	x	x	948-50	x	x	947
Rogers et al [68]	2003	209	x	x	x	x	x	x	x	x	x	x	210	x	x	x	x	x	x	x	x	211	x	x	212
Singer et al [50]	2003	896	896	896	896	x	x	x	x	897	894	x	x	x	x	x	x	896-7	899	898-9	899	898-9	x	x	900
Luboshitzky et al [39]	2002	574	x	x	573-4	x	x	x	x	574	574	574	x	x	x	574	x	x	x	x	x	574-7	x	x	572
Cagnacci et al [60]	2001	341	341	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	344	343-4	343	343-4	x	x	x
Pires et al [43]	2001	327-8	328	x	x	x	x	x	x	x	x	x	328-9	x	x	x	x	x	330	330-1	330-1	330-1	x	x	331
Edwards et al [29]	2000	1505	1505	x	1503	1503	1503	x	x	1503	150-3-4	x	x	x	x	1509	1509	x	1510-1	151-0-1	151-0-1	151-0-1	x	x	x
Lusardi et al [40]	2000	425	x	x	425	425	425	x	x	x	x	x	425	x	x	x	425	x	x	426	426	426	x	x	x
Seabra et al [48]	2000	195	x	x	196	x	x	x	x	x	196-9	198	196-7	x	x	x	199	196-9	198-9	196-9	198-9	196-9	x	x	199
Rogers et al [46]	1998	48	x	x	x	x	x	x	x	x	x	x	49-50	x	x	x	x	x	52	50-2	52	50-2	x	x	52
Suhner et al [52]	1998(a)	658	658	x	658-9	658-9	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	662-4	x	x	x
Suhner et al [53]	1998(b)	9	x	9	x	9	x	x	x	x	x	x	x	x	x	x	x	x	11	11-12	11	11-12	x	x	x
Voordouw et al [70]	1992	110-1	111	x	x	x	111	x	x	x	x	x	x	x	x	x	x	x	x	x	x	115-6	x	x	x
Webley et al [57]	1988	22	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	27-30	x	x	x
Wright et al [59]	1986	x	x	x	x	x	x	376	x	x	377-9	x	x	x	x	x	x	x	x	x	x	379-81	x	x	381
Lieberman et al [38]	1985	x	x	x	x	x	x	x	x	x	x	x	204-5	x	x	x	x	x	x	x	205-6	205-6	x	x	206
Sherer et al [49]	1985	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	281	280-1	x	280-1	x	x	x
Carman et al.[21]	1976	x	x	x	1182	x	118-2-4	x	1182-4	x	118-2-4	1182-4	x	x	x	x	118-2-4	x	1185	118-4-5	1185	118-4-5	x	x	x

Italicised letters denote domains from extension for reporting harms; Numbers indicate page of manuscript where criteria have been reported; x indicates criteria were not reported.

Table 2
Characteristics of studies included in systematic review of melatonin safety.

Study	Year	Country	Design	Sample	Population	Comparison	Details of Melatonin Dose				
							Dosage	Form*	Frequency	Timing	Duration
Baandrup et al [25]	2016	Denmark	Randomised placebo-controlled blinded trial	86 38 F, 48 M	Benzodiazepine withdrawal in schizophrenia and bipolar	Placebo	2 mg	PR	Once daily	2 hours before bed	24 weeks
Beigom Khezri et al [24]	2016	Iran	Randomised placebo-controlled double-blind trial	120 F	Pregnant women undergoing C-section with spinal anaesthesia	Placebo	3 mg 6 mg	IR	Single dose	20 mins before procedure	Single administration
Ghattassi et al [23]	2016	Tunisia	Randomised placebo-controlled double-blind crossover trial	12 F	Soccer players who were without injury, non-smokers and did not consume alcohol or caffeine	Placebo	5 mg	IR	Single dose	07:30 hours, 30 min. before exercise testing	Single administration
Goncalves et al [22]	2016	Brazil	Randomised placebo-controlled double-blind study	178 133 F, 45 M	Patients aged 18-65 with migraine at least 1 year since onset and at least 3 episodes or 4 days per month.	Placebo and Amitriptyline 25 mg	3 mg	IR	Once daily	At bed time	12 weeks
Garaulet et al [30]	2015	Spain	Placebo-controlled crossover clinical trial	17 F	Non-diabetic, non-obese young women of European descent, with and without T2DM risk-associated SNP of melatonin receptors	Placebo	5 mg	NR	Twice daily	09:00 and 21:00 hours, before oral glucose tolerance test	2 non-consecutive days
Kirksey et al [35]	2015	USA	Randomised placebo-controlled double-blind pilot study	37 20 F, 17 M	Patients undergoing total knee arthroplasty under regional anaesthesia with sedation	Placebo	5 mg	NR	Once daily	Shortly before bed	6 days from 72 hrs pre-operatively.
De Zanette et al [64]	2014	Brazil	Randomised double-dummy double-blind three arm parallel clinical trial	63 F	Women aged 18-65 with fibromyalgia refractory to current treatment	Amitriptyline (25 mg) with placebo, Amitriptyline with melatonin.	10 mg (combined with placebo)	NR	Once daily	At bed time	42 days
Fallah et al [62]	2014	Iran	Randomised single-blind clinical trial	60 19 F, 41 M	Children aged 1-8 undergoing EEG who didn't naturally sleep/ immobilise, who were normally healthy or with mild systemic disease	Midazolam (0.75 mg/kg given orally in water)	0.3 mg/kg dissolved in water	IR	Single dose	Before procedure	Single administration
Ghattassi et al [31]	2014	Tunisia	Randomised placebo-controlled double-blind crossover trial	12	Healthy professional soccer players	Placebo and alternative dose of melatonin	5 mg and 8 mg	NR	Single doses on two occasions	21:00 hours, 30 min. before exercise testing	Not defined
Goyal et al [33]	2014	USA	Randomised placebo-controlled double-blind crossover trial	39 22 F, 17 M	Patients meeting three or more of the five criteria for metabolic syndrome	Placebo	8 mg	IR	Once daily	1 hour before bed	10 weeks
Hansen et al [34]	2014	Denmark	Randomised placebo-controlled double-blind trial	54 F	Women aged 30-75 undergoing breast cancer surgery, without signs of major depression	Placebo	6 mg	NR	Once daily	1 hour before bed	13 weeks from 1 week pre-operatively
Parandavar et al [42]	2014	Iran	Randomised placebo-controlled double-blind clinical trial	240 F	Menopausal women aged 40-60 referring to gynaecological clinics	Placebo	3 mg	NR	Once daily	18:00-21:00 hours	3 months
Pokharel et al [63]	2014	India	Randomised controlled factorial trial	80 61 F, 19 M	Adults aged 18-65 undergoing laparoscopic cholecystectomy with an anxiety score of 3 or more on VAS	0.5 mg Oral Alprazolam alone and in combination with melatonin	3 mg	NR	Single dose	90 min. before surgery	Single administration
	2014	Spain		21 F	Healthy young women	Placebo	5 mg	IR	Two doses		

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Table 2 (*continued*)

Study	Year	Country	Design	Sample	Population	Comparison	Details of Melatonin Dose				
							Dosage	Form*	Frequency	Timing	Duration
Rubio-Sastre et al [47]			Randomised placebo-controlled single-blind crossover trial							08:45 and 20:45, before testing	Two administrations on non-consecutive days
Sookprasert et al [51]	2014	Thailand	Randomised placebo-controlled double-blind trial	151 47 F, 104 M	Patients with advanced non-small cell lung cancer, aged 18-70 years, receiving chemotherapy.	Placebo and alternative dose of melatonin	10 mg and 20 mg	NR	Once daily	After 21:00 hours	Six months
Wade et al [56]	2014	UK and USA	Randomised placebo-controlled double-blind multicentre trial	73 36 F, 37 M	Outpatients aged 50-85 with diagnosed mild to moderate Alzheimer's disease	Placebo	2 mg	PR	Once daily	1-2 hours before bed	24 weeks
Wilhelmsen-Langeland et al [69]	2013	Norway	Randomised placebo-controlled double-blind trial and open-label follow-up	40 28 F, 12 M	Generally healthy adolescents and adults aged 16-25 with chronic sleep problems	Placebo capsule, dim light, bright light.	3 mg	IR	Once daily	After 20:00 hours	2 weeks for trial, 3 months for follow-up.
Lemoine et al [37]	2012	France and Israel	Combined analysis of four randomised placebo-controlled double blind trials and three single-blind open-label studies	392	Middle-aged and elderly patients with both insomnia and hypertension	Placebo	2 mg	PR	Once daily	2 hours before bed	3-28 weeks for controlled trials, up to 1 year for open-label studies
Rechcinski et al [45]	2012	Poland	Randomised placebo-controlled	60 16 F, 44 M	Adult patients aged 48-80 with coronary artery disease who were non-dippers in ambulatory blood pressure	Placebo	5 mg	NR	Once daily	21:00-23:00 hours	30 days
Ucar et al [54]	2012	Denmark	Randomised placebo-controlled double-blind crossover trial	21 M	Healthy male subjects aged 18-30	Placebo (folic acid)	4 mg	PR	Single dose	08:30 hours, before testing	Single administration
Lemoine et al [36]	2011	France and Israel	Prospective open-label study after single-blind placebo run-in and double-blind placebo-controlled dose-ranging study	208	Community-dwelling adults with primary insomnia	Placebo run-in	2 mg	PR	Once daily	1-2 hours before bed	6-12 months
Wright et al [58]	2011	UK	Randomised placebo-controlled double-blind crossover trial	20 4 F, 16 M	Children aged 3-16 with diagnosed autism spectrum disorder and serious sleep problems	Placebo	2 mg titrated up to 10 mg (if required)	IR	Once daily	30-40 mins before bed	3 months
Ashrafi et al [61]	2010	Iran	Randomised controlled trial	348 151 F, 197 M	Uncooperative children undergoing EEG	Chloral hydrate 5%, 1 mL/kg	2-6 mg	NR	Single dose	30-60 mins before procedure	Single administration
Rechcinski et al [44]	2010	Poland	Randomised placebo-controlled	60 16 F, 44 M	Ambulatory patients aged 48-80 years with coronary artery disease who showed a < 10% change in mean systolic blood pressure during sleep compared with daytime.	Placebo	5 mg	IR	Once daily	21:00-23:00 hours	90 days

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Table 2 (*continued*)

Study	Year	Country	Design	Sample	Population	Comparison	Details of Melatonin Dose				
							Dosage	Form*	Frequency	Timing	Duration
Gogenur et al [32]	2009	Denmark	Randomised placebo-controlled double-blind trial	121 86 F, 35 M	Patients aged 18-80 undergoing ambulatory laparoscopic cholecystectomy	Placebo	5 mg	NR	Once daily	Approx 30 min. before bed	3 nights post-operatively
Luthringer et al [41]	2009	France	Randomised placebo-controlled double-blind phase 2 study	40 16 F, 24 M	Adult out-patients aged ≥55 who met DSM-IV criteria for primary insomnia	Placebo	2 mg	PR	Once daily	2 hours before bed	3 weeks
Radwan et al [66]	2009	Egypt	Randomised placebo-controlled double-blind study	75 39 F, 36 M	Adults aged 30-55 years scheduled for elective abdominal surgery under general anaesthesia	Placebo and Gabapentin	6 mg	NR	Single dose	1 hour before surgery	Single administration
Otmani et al [65]	2008	France	Randomised placebo-controlled double-blind crossover trial	16 4 F, 12 M	Middle-aged and elderly healthy adults with a valid driving licence	Placebo, Zolpidem, combined Zolpidem + melatonin	2 mg	PR	Once daily	20:00 hours, before testing	2 days per treatment
Riemersma-van der Lek et al [67]	2008	Netherlands	Randomised placebo-controlled, double-blind	189	Elderly residents of group care facilities, with dementia (predominantly female)	Placebo, light, and in combination with light.	2.5 mg	MFR	1 hour before bed	Approx. 1 hour before bed	Up to 3.5 years (15 ± 12 months)
Carr et al [27]	2007	Canada	Follow-up of a randomised placebo-controlled double-blind cross-over trial with additional open label trial	41 13 F, 28 M	Children with neurodevelopmental disabilities and treatment-resistant circadian rhythm sleep disorders	Placebo	5 mg	PR and IR	Not reported	Not reported	10 day trial and 3 month open-label.
Van der Heijden et al [55]	2007	Netherlands	Randomised placebo-controlled double-blind trial	105 27 F, 78 M	Children with diagnosed ADHD and chronic sleep onset insomnia, aged 6-12, unmedicated	Placebo	3-6 mg (dependent on body weight)	IR	Once daily	19:00 hours	4 weeks
Cavallo et al [28]	2005	USA	Randomised placebo-controlled double-blind crossover trial	28	Paediatric residents adapting to night shift	Placebo	3 mg	IR	Once daily	Morning of night-shift (before bed)	2 weeks
Campos et al [26]	2004	Brazil	Randomised placebo-controlled double-blind study	22 F	Women with asthma	Placebo	3 mg	NR	Once daily	2 hours before bed	28 days
Rogers et al [68]	2003	Australia	Randomised placebo-controlled double-blind crossover trial	16 10 F, 6 M	Healthy young subjects	Temazepam 10 mg and placebo.	5 mg	NR	Single dose	12:00 hours, before testing	Single administration
Singer et al [50]	2003	USA	Randomised placebo-controlled double-blind trial	157 88 F, 69 M	Subjects with Alzheimer's disease and a night-time disturbance	Placebo and alternative dose of melatonin	10 mg IR* and 2.5 mg PR*	IR and PR	Once daily	1 hour before bed	2 months
Luboshitzky et al [39]	2002	Israel	Randomised placebo-controlled double-blind crossover trial	8 M	Healthy men aged 23.4 ± 1.2 years	Placebo	3 mg	NR	Once daily	17:00-18:00 hours	3 months
Cagnacci et al [60]	2001	Italy	Randomised placebo-controlled double-blind cross-over trial	22 F	Post-menopausal women with or without hormone replacement therapy	Placebo	1 mg	IR	Single dose	08:30 hours, 45 min. before oral and intravenous glucose tolerance testing	Single administration

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Table 2 (*continued*)

Study	Year	Country	Design	Sample	Population	Comparison	Details of Melatonin Dose				
							Dosage	Form*	Frequency	Timing	Duration
Pires et al [43]	2001	Brazil	Randomised placebo-controlled double-blind crossover trial	6 M	Healthy men aged 22-24 years	Placebo	0.3 mg and 1 mg	IR	Three separate doses spaced min 4-7 days apart	18:00, 20:00 and 21:00 hours	2-3 weeks
Edwards et al [29]	2000	UK	Placebo-controlled double-blind study	31 28 M, 3 F	Sports officials and sports scientists travelling from UK to Eastern Australia	Placebo	5 mg	NR	5 doses (before flight + once daily)	22:00-23:00 hours Eastern Australia time	4-5 days
Lusardi et al [40]	2000	Italy	Randomised placebo-controlled double-blind crossover trial	47 20 F, 27 M	Adult men and post-menopausal women with mild to moderate hypertension well controlled with nifedipine GITS 30 or 60 mg monotherapy	Placebo	5 mg	IR	Once daily	22:30 hours	4 weeks
Seabra et al [48]	2000	Brazil	Randomised placebo-controlled double-blind trial	40 M	Men aged 25-55 with normal sleep pattern and normal baseline clinical parameters	Placebo	10 mg	NR	Once daily	Approx. 1 hour before bed	28 days
Rogers et al [46]	1998	Australia	Randomised placebo-controlled double-blind crossover trial	16 6 F, 10M	Healthy young subjects	Placebo	5 mg	NR	Single dose	12:30 hours, before testing	Single administration
Suhner et al [52]	1998(a)	Switzerland	Randomised placebo-controlled double-blind study	320 148 F, 172 M	Volunteers undertaking intercontinental flights through 6-8 time zones (to assess effect on jet lag).	Placebo and alternative dose of melatonin	0.5 mg IR*, 5 mg IR*, 2 mg PR*	IR and PR	Once daily	At bed time	4 days
Suhner et al [53]	1998(b)	Switzerland	Randomised placebo-controlled double-blind crossover study	20 8 F, 12 M	Healthy volunteers aged 21-57	Placebo	5 mg	IR	Single dose	16:30 hours, 90 min. before testing	Single administration
Voordouw et al [70]	1992	Netherlands	Randomised controlled trial	40 F	Women aged 18-37, unmedicated, with regular, healthy menstrual cycle.	Control group and melatonin combined with progestin	7.5-300 mg	NR	Once daily during various parts of menstrual cycle	At night	4 months
Webley et al [57]	1988	Germany	Placebo-controlled double-blind crossover trial	11 M	Healthy young males aged 20-27.	Placebo	2 mg and 4 mg	NR	Once daily	Between 08:00-12:00 or 20:00-24:00	2 administrations, 2 weeks apart
Wright et al [59]	1986	UK	Placebo-controlled crossover trial	12 2 F, 10 M	Healthy, unmedicated adults aged 22-46 years	Placebo	2 mg	NR	Once daily	17:00 hours	4 weeks
Lieberman et al [38]	1985	USA	Randomised placebo-controlled double-blind crossover trial	14 M	Men aged 18-45	Placebo	240 mg in divided doses of 80 mg	NR	Hourly	12:00, 13:00 and 14:00 hours, before testing	Single 2 hour testing period
Sherer et al [49]	1985	USA	Randomised placebo-controlled double-blind crossover trial	6	Patients with diagnosed SAD (Seasonal Affective Disorder)	Placebo	2-2.4 mg, in divided doses of 200ug	NR	Not clearly reported	30 min prior to + every hour of light treatment	1 week
Carman et al [21]	1976	USA	Randomised placebo-controlled double-blind cross-over case series	8 6 F, 2 M	6 patients with major primary depression, 2 patients with Huntington's	Placebo	150-1600 mg (divided doses)	Varied	One to four times daily	Varied	Varied (stopped with onset of AE)

* IR = Immediate release, PR = Prolonged release, MFR = Medium-fast release, NR = Not reported.

baseline measurements.

Glucose Metabolism When 5 mg melatonin was given before an oral glucose-tolerance test, it was found to significantly reduce pancreatic insulin release if given in the morning, and to impair insulin sensitivity if given in the evening.[47] Another study found glucose tolerance was decreased following the same dosing approach, yet this decrease was only seen after morning administration and only in participants carrying the MTNR1B genetic polymorphism, which has been identified as a risk factor for type 2 diabetes.[30] Similarly, when 1 mg melatonin was given in the morning, it appeared to reduce glucose tolerance and insulin sensitivity in postmenopausal women, in both those with and without hormone replacement therapy.[60] One other study reported on increased blood glucose as an adverse event, but found no statistical significance between melatonin and placebo conditions.[56]

Potential Drug Interactions Drug interactions were rarely purposefully investigated but rather reported based on notification by participants. Seventeen reviewed papers co-administered melatonin to participants taking various medications without reporting any occurrence of apparent drug interactions. These co-administered medications were taken either as part of the study protocol (e.g. patients undergoing surgical procedures) or as pre-existing prescriptions and included anxiolytics,[25,67] anti-psychotics,[25,67] anti-depressants,[25,67] mood stabilisers,[25] anticholinergics,[25,63] surgical anaesthesia,[24,32,34,35,63,66] anti-emetics,[32,51,66] analgesics,[22,24,32,35,36,63,64,66] non-steroidal anti-inflammatories,[32,36,63,66] muscle relaxants,[32,63] asthma medications (steroids, bronchodilators),[26] antibiotics,[32,36,51] oncological treatment (chemotherapy, radiation, anti-hormone therapy),[34,51] statins,[36,45] thyroid hormones,[36] anti-diabetic agents (glibenclamide, metformin, insulin),[36,45] sex hormones (oestradiol),[36] antacids,[36] anti-coagulants,[45] Alzheimer's treatment (anti-cholinesterase inhibitors, memantine),[56] and other unspecified medications.[27,50]

When potential drug interactions were identified, they were most commonly reported in populations medicated for cardiovascular conditions. When given alongside existing therapy of antihypertensive calcium-channel blocker nifedipine, melatonin (5 mg nightly over four weeks) was found to significantly increase participants' otherwise well-controlled blood pressure and heart rate, appearing to inhibit or counteract the effects of nifedipine.[40] These findings were consistent with another study whereby melatonin (5 mg nightly over twelve weeks) was seen to promote an excessive difference between diurnal and nocturnal blood pressure values (day:night ratio), an increase in day-time systolic and diastolic blood pressure, and acceleration of mean heart rate when given to participants with coronary artery disease who were medicated with cardiovascular drugs.[44] From these studies alone, it is not possible to determine whether these effects were caused by melatonin or by its interaction with medications.

One paper conducted an analysis of the incidence of adverse events between participants with and without co-administration of melatonin and antihypertensives, finding no significant difference in vital signs between groups.[37] Seven other papers reported on cardiovascular-related adverse events during the study period (dysrhythmia, stroke, atrial fibrillation, myocardial infarction, aortic stenosis, palpitations, angina pectoris), however, no significant differences were seen between groups and none were attributed to melatonin.[25,33,34,36,52,56,61]

Another study compared effects of melatonin with sedative zolpidem, and with the combination of both drugs, on psychomotor function, memory recall and driving skills.[65] The results demonstrated that while melatonin alone did not adversely affect these functions, it potentiated the sedative action of zolpidem, resulting in additive effects whereby performance was significantly reduced.[65]

Other Adverse Events Twenty-six papers reported on a wide range of adverse events which did not demonstrate a significant difference between groups (see Table 3).[22,25–28,32–37,41,42,45,48,50–52,55,56,58,61–64,69]

One study assessing the potential of 4 mg melatonin to increase a neurological sensory gating mechanism (P50 suppression) found melatonin to have the opposite of the intended effect in certain participants.[54] While the study was conducted on healthy participants, melatonin was seen to lessen P50 suppression in participants with high baseline suppression.[54]

One paper reported that constipation, as a side-effect, reached statistical significance after daily administration of 2.5 mg melatonin for up to 3.5 years (15 ± 12 months average).[67] Increased incidence of headache was seen in women undergoing spinal anaesthesia before caesarean section when they were administered 6 mg melatonin before the procedure, however this increased incidence was not seen in participants taking a lower 3 mg dose.[24] Another study assessing the potential of melatonin to alleviate jet-lag reported a "rocking" sensation as the only significant event in the melatonin group compared with placebo.[29]

4. Discussion

This is the first systematic review to provide a comprehensive overview of evidence for the safety of oral melatonin supplementation. Of the fifty studies reviewed, twenty-four reported statistically significant adverse events attributed to melatonin. Consistent with other literature,[16] reported adverse events were generally short-lived and associated with day-time dosing. While the perceived severity of adverse events relies largely on subjective and relative factors, the more serious adverse events reported were seen at excessively high doses or in specific populations.

The most frequently reported adverse events related to reductions in psychomotor and neurocognitive function or fatigue and excessive sleepiness, which are all consistent with melatonin's long-observed sedative and hypnotic properties.[71] Largely, these events were reported in studies involving administration of melatonin directly before testing psychomotor and neurocognitive function, or administration during daylight hours when endogenous melatonin activity is low.[72] This suggests that in order to avoid such adverse effects, melatonin should not be taken directly prior to activities requiring high levels of alertness, but rather should be administered at night when possible, in keeping with human biological circadian rhythms and with other published literature on melatonin for sleep disorders.[73] Additionally, the sedative action of melatonin was found to have an additive effect when administered with zolpidem,[65] so caution should be exercised in regards to combining melatonin with other sedatives.

One notable finding of this review relates to observed adverse effects of melatonin on blood pressure and heart rate in populations with cardiovascular conditions and concurrent antihypertensive medications. It is unclear whether these adverse effects are attributable to melatonin itself or to melatonin-drug interactions. A rise in blood pressure and heart rate was seen in two studies, as well as an increase in the difference between diurnal and nocturnal blood pressure, while in another study no adverse effect could be seen in these vital signs, nor any difference between participants with and without concurrent use of antihypertensives. A substantial body of literature has demonstrated potential for melatonin to reduce blood pressure,[11,74–80] and possibly also to reduce heart rate[81] and variability between diurnal and nocturnal blood pressure.[82] There is, however, some evidence from *in vitro* and animal studies of modulatory effects by melatonin on calcium-channel activity,[83–85] suggesting possible interactions with antihypertensives of the calcium-channel blocker class. Nonetheless, it is possible that melatonin's antihypertensive activity may offset the clinical significance of any interactions with other antihypertensive medications.[86] Certainly, there is a need for further research investigating use of melatonin in medicated hypertensive patients and caution should be practiced with this population.

This review has identified a number of findings regarding the potential for melatonin to impact on endocrine parameters, particularly reproductive factors and glucose metabolism. These findings include alterations to sex hormones in both men and women, suppression of ovulation and sperm count, and reductions in insulin activity. Animal

Table 3
Adverse events reported in literature included in review of melatonin safety.

Study	Year	Adverse events reported or assessed during trial	Measures of adverse events	Phase of day given*	Adverse events†
Baandrup et al [25]	2016	Exacerbation of psychosis and anxiety, mood changes, suicidal ideation, somnolence, alcohol abuse, cardiovascular events, digestive symptoms, urogenital symptoms, musculoskeletal symptoms, influenza, hyponatraemia.	Not defined.	Before bed	None.
Goncalves et al [22]	2016	Sleepiness, pruritis, dizziness, epigastric pain, weight gain, dry mouth, insomnia, constipation, worsening headache.	Not defined.	Before bed	None.
Kirksey et al [35]	2015	Post-operative nausea and vomiting, dizziness, pruritis, other side effects.	Recorded by nurses using VAS (visual analogue scale).	Before bed	None.
De Zanette et al [64]	2014	Nausea, dizziness, weight gain, dry mouth, headache, vivid nightmares, drowsiness, behavioural changes, worsening of pain.	Self-report questionnaire.	Before bed	None.
Goyal et al [33]	2014	Stroke, nausea, dizziness, fatigue, drowsiness, early-morning waking, sleep disturbance.	Not defined.	Before bed	None.
Hansen et al [34]	2014	Headache, dizziness, sleepiness, tiredness, difficulty falling asleep, more awakenings at night, paraesthesia (mouth, limbs), memory problems, breathing difficulties, cough, pneumonia, atrial fibrillation, nausea, vomiting, reflux, abdominal pain, dry mouth, obstipation, diarrhoea, urinary urgency, lower back pain, flushing sweating, itching	Not defined.	Before bed	None.
Wade et al [56]	2014	Angina pectoris, abdominal discomfort, diarrhoea, nausea, vomiting, fatigue, increased blood creatinine, increased blood glucose, decreased appetite, back pain, abnormal dreams, agitation, cognitive disorder, insomnia, urinary tract infection, cough, nasopharyngitis, upper respiratory tract infection, fall, thyroid neoplasm, burning feet syndrome, headache, somnolence, delusion, restlessness.	Spontaneous reporting by participants or carers, assessment of vital signs, physical examination and laboratory tests. All assessed at 3, 12 and 24 weeks.	Before bed	None.
Lemoine et al [37]	2012	Blood and lymphatic system disorders, cardiac disorders, congenital, familial and genetic disorders, ear and labyrinth disorders, gastrointestinal disorders, hepatobiliary disorders, immune system disorders, infections and infestations, injury, poisoning and procedural complications, metabolic and nutrition disorders, musculoskeletal and connective tissue disorders, neoplasms, nervous system disorders, psychiatric disorders, renal and urinary disorders, reproductive system and breast disorders, respiratory, thoracic and mediastinal disorders, skin and subcutaneous disorders, vascular disorders.	Clinical measures of vital signs taken. Other measures not defined.	Before bed	None.
Lemoine et al [36]	2011	Serious: fractures, duodenal sphincterectomy, dilation of the bile duct, worsening of venous insufficiency, fall from ladder, myocardial infarction, syncope from aortic stenosis, cholecystitis from gallstones. Non-serious: pharyngitis, back pain, asthenia, respiratory tract infection, bronchitis, arthralgia, sinusitis, rhinitis, headache, gastroenteritis, dizziness, headache.	Not defined.	Before bed	None.
Wright et al [58]	2011	Daytime drowsiness, dizziness, headaches, vomiting, tummy aches, reduced appetite, low mood, anxiety, irritability, reduced alertness, confusion, tearfulness, diarrhoea, constipation, rashes, sore throat, ear aches, asthma, seizures, mild tremor, bed wetting, other.	Side effects questionnaire and a 24-hour phone number available for parents to report other AE spontaneously.	Before bed	None.
Gogenur et al [32]	2009	Sleepiness, tired, headache, confusion, depression, nausea, dizziness, other unexpected symptoms.	Not defined.	Before bed	None.

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Table 3 (*continued*)

Study	Year	Adverse events reported or assessed during trial	Measures of adverse events	Phase of day given*	Adverse events†
Luthringer et al [41]	2009	Effects on vital signs, headache, others (not defined).	Clinical examination of blood pressure, pulse rate, ECG, blood, urine and adverse event self-reporting by participants.	Before bed	None.
Riemersma-van der Lek et al [67]	2008	Lowering of mood, withdrawn behaviour, dizziness, drowsiness, eye complaints, feebleness, headache, hunger, hyperactivity, inability to sleep, irritability, nausea, constipation, pins and needles, stomach ache, sweating, trembling hands, other complaints.	Caregiver ratings on Likert scale.	Before bed	Constipation, lowering of mood, increase in withdrawn mood.
Campos et al [26]	2004	Mild headache, epigastric pain.	Self-report by participants.	Before bed	None.
Singer et al [50]	2003	Abnormal behaviour, aches, pain, falls, fatigue, gastrointestinal distress, infection, respiratory symptoms, skin tissue symptoms, urinary symptoms.	Standard clinical trial adverse event questionnaire administered twice per week.	Before bed	None.
Seabra et al [48]	2000	Somnolence, headache, fatigue, tremor, cognitive alteration, depression irritability, illness, torpor, tinnitus.	Questionnaire administered weekly and also one week after end of trial.	Before bed	None.
Suhner et al [52]	1998(a)	Daytime sleepiness, headache, dizziness, confusion, loss of appetite, nausea, vomiting, diarrhoea, constipation, pruritus, abdominal cramps, heartburn, flatulence, swelling of arms/legs, sweating, hot flushes, palpitations, exanthema.	Administration of questionnaire listing adverse events normally association with jet lag, alongside open response for other symptoms.	Before bed	None.
Ghattassi et al [31]	2014	Reduced performance in hand-grip strength, squat jump and countermovement jump tests.	Hand-grip test, squat jump test, countermovement jump test, 5-jump test, medicine ball throw test, modified agility test.	Night	Reduced performance in hand-grip strength, squat jump and countermovement jump tests with higher dose of melatonin (8 mg) but not lower dose (5 mg).
Sookprasert et al [51]	2014	Fatigue, anorexia, neuropathy, anaemia, nausea, liver dysfunction, mucositis, lowering of glomerula filtration rate, febrile neutrapaenia, thrombocytopaenia.	CTCAE version 3, ECOG PS, and standard haemotology, chemistry, electrolytes, urinalysis, physical examination.	Night	None.
Wilhelmsen-Langeland et al [69]	2013	Headache, nausea, discomfort in the eyes, skin irritation.	Retrospectively recorded at the end of each period (2 weeks and 3 months) using a form developed for the study.	Night	None.
Rechcinski et al [45]	2012	Changes to estimated apnoea/hypopnoea index.	24 hour ECG holter monitoring.	Night	None.
Rechcinski et al [44]	2010	Excessive increase between diurnal and nocturnal blood pressure values (day/night ratio), acceleration of mean heart rate/pulse frequency, increase in daytime systolic and diastolic blood pressure.	Ambulatory blood pressure and heart rate monitor.	Night	Excessive increase between diurnal and nocturnal blood pressure values (day/night ratio), acceleration of mean heart rate/pulse frequency, increase in daytime systolic and diastolic blood pressure.
Otmani et al [65]	2008	Reduced cognitive performance, Reduced psychomotor performance, Reduced memory recall, Reduced dexterity, Increased sedation.	Selection of cognitive, psychomotor, dexterity and memory recall tasks. Simulated driving task, PCAG sedation scale, HPLC and radio-immunoassay.	Night	While melatonin alone did not adversely affect scores, it worsened the adverse effects of zolpidem.
Van der Heijden et al [55]	2007	Headache, hyperactivity, dizziness, abdominal pain, nose bleeding, itching or painful lumps on skin, diarrhoea, decreased mood, maintenance insomnia.	Unstructured interview at 3 weeks. Structured questionnaire at 2 year follow-up.	Night	None.
Edwards et al [29]	2000	Headaches, Dizziness, Disorientating 'rocking' sensation.	Self-report by participants.	Night	'Rocking' sensation higher in melatonin group. No other differences between groups.
Lusardi et al [40]	2000	Increase in systolic and diastolic blood pressure, increase in heart rate, morning drowsiness, weakness.	Ambulatory blood pressure monitoring, spontaneous self-report of other adverse events.	Night	Increase in blood pressure and heart rate. Morning drowsiness, weakness.
Voordouw et al [70]	1992	Suppression of luteinising hormone (LH) and ovulation.	Serum testing of hormone levels throughout menstrual cycle for 1 month prior to treatment and during 4 months of treatment.	Night	Suppression of luteinising hormone (LH) and ovulation.
Parandavar et al [42]	2014	Headache, vertigo, nausea, vomiting, sleepiness, vaginal bleeding and spotting, heartburn, tingling of extremities, feeling of fullness, constipation, diarrhoea, flatulence.	Not defined.	Evening and Night	None.
Pires et al [43]	2001	Increased sleep latency, morning sleepiness, effects on mood, effects on visual reaction time.	Actigraphy, polysomnography, SSS (Stanford Sleepiness Scale), POMS (Profile of Mood States), visual reaction time test.	Evening and Night	Increased latency to sleep onset seen at lowest dose (0.3 mg), when given at latest time point (21:00 hours).
Luboshitzky et al [39]	2002	Reductions in sperm concentrations and motility. Reductions in oestrogens and increase in androgen:oestrogen ratio.	Semen analysis by microscopy and hormone measurement by immunoassay.	Evening	Reductions in sperm concentrations and motility. Reductions in oestrogens and increase in androgen:oestrogen ratio.
Wright et al [59]	1986	Significant alterations in the timing of rising and falling of prolactin levels.	Serum testing of prolactin hormones after melatonin and after placebo treatment.	Evening	Alterations in the timing of rising and falling of prolactin levels.

(*continued on next page*)

Table 3 (*continued*)

Study	Year	Adverse events reported or assessed during trial	Measures of adverse events	Phase of day given*	Adverse events†
Rogers et al [68]	2003	Sleepiness, adverse effects on neurobehavioural performance (sensory-motor co-ordination, logical reasoning, visual tracking, spatial memory, vigilance).	Sleepiness visual analogue scale. Computer-based performance tasks (Worksafe battery: unpredictable tracking task, special memory task, vigilance task, logical reasoning task).	Afternoon	Sleepiness. Melatonin adversely affected performance compared to placebo, but significantly less than temazepam.
Suhner et al [53]	1998(b)	Impact on driving performance, sleepiness.	Body sway movement test. 16-variable driving performance test. SSS (Stanford Sleepiness Scale).	Afternoon	Reduction in "selective attention" in melatonin group.
Rogers et al [46]	1986	Adverse effects on neurobehavioural performance (sensory-motor co-ordination, visual and auditory response and reaction time, visual tracking).	Computer-based performance tasks (Worksafe battery: two-choice visual response and reaction time task, simple auditory response and reaction time task, unpredictable tracking task).	Afternoon	Adverse effects on neurobehavioural performance (sensory-motor co-ordination, visual and auditory response and reaction time, visual tracking).
Lieberman et al [38]	1985	Adverse effect on profile of mood (vigour, fatigue, confusion, tension, depression, anger). Performance effects regarding auditory and visual reaction time, psychomotor performance, cognition and memory.	POMS (Profile of Mood States), SSS (Stanford Sleepiness Scale), simple auditory reaction time test, four-choice visual reaction time test, grooved pegboard test, digit symbol substitution test, critical flicker fusion test, recall and recognition memory test.	Afternoon	Adverse effect on profile of mood regarding vigour, fatigue and confusion. Reduced performance regarding visual reaction time but improved accuracy.
Garaulet et al [30]	2015	Decreased glucose tolerance.	OGTT (oral glucose tolerance test) after each dose.	Morning and night	Decreased glucose tolerance, seen only in carriers of MTNR1B genetic variant rs10830963, only after morning dose.
Rubio-Sastre et al [47]	2014	Impaired glucose tolerance.	OGTT (oral glucose tolerance test).	Morning and night	Reduced insulin release after morning dose. Impaired insulin sensitivity after evening dose.
Webley et al [57]	1988	Significant increase in prolactin levels.	Serum testing of prolactin hormones after melatonin and after placebo administration.	Morning and Night	Increase in prolactin levels. Greater significance after evening dose than after morning dose.
Ghattassi et al [23]	2016	Reduced reaction in cognitive performance, Reduced vigilance, Reduced physical performance.	Cognitive reaction and vigilance test, medicine ball throw, five jump test (5 J T), handgrip strength test, modified agility test.	Morning	Negative impact on performance seen in all but 5 J T and agility, but only seen at first (morning) time-point after MEL intervention.
Ucar et al [54]	2012	Reduced suppression of P50 response (reduced inhibitory gating in response to repeated auditory stimulus), reduced alertness, increased anxiety.	EEG (electroencephalograph)	Morning	Reduction of P50 suppression in those with high baseline suppression. Reduction of alertness.
Cavallo et al [28]	2005	Headache, abdominal pain, nausea, vomiting, diarrhoea, dizziness, excessive sleepiness.	Self-report daily with pre-coded adverse event list and additional open-ended question.	Morning	None.
Cagnacci et al [60]	2001	Reduced glucose tolerance and insulin sensitivity.	Oral glucose tolerance test (OGTT) and frequently sampled intravenous glucose tolerance test (FSIGT).	Morning	Reduced glucose tolerance and insulin sensitivity.
Beigom Khezri et al [24]	2016	Headache, pruritis, nausea, vomiting, vertigo, respiratory depression.	Not defined.	Not specified	Increased occurrence of headache with higher dose of melatonin (6 mg) but not lower dose (3 mg). No other differences between groups.
Fallah et al [62]	2014	Transient agitation.	Not defined.	Not specified	None.
Pokharel et al [63]	2014	Nausea, vomiting, headache, dizziness.	Not defined.	Not specified	None.
Ashrafi et al [61]	2010	Diarrhoea, agitation, dizziness, ataxia, dysrhythmia.	Not defined.	Not specified	None.
Radwan et al [66]	2010	Drowsiness, dizziness, somnolence, fatigue, nystagmus, headache, blurred vision, nausea, vomiting, urinary retention, constipation, pruritis.	Recorded during post-operative care.	Not specified	Increased occurrence of drowsiness, dizziness and somnolence compared to both placebo and gabapentin.
Carr et al [27]	2007	Nausea, vomiting, diarrhoea, impaired appetite, weight loss, excessive morning sedation, depression, irritability, hyperactivity, deterioration of behaviour, increase in seizures, nasal allergy, rash, deterioration of asthma, worsening of balance, new tremor, headache, visual disturbance.	Parental or caretaker report.	Not specified	None.
Sherer et al [49]	1985	Impacts on mood, attention, vigilance, reaction time and cognitive processes.	Hamilton Rating Scale. Continuous performance task, simple visual-tactile reaction time test, recall probability tests.	Not specified	Reduced visual/tactile reaction time, fatigue, reduced energy.
Carman et al [21]	1976	Exacerbation of dysphoric and psychotic symptoms, Onset of new psychotic symptoms, Loss of sleep, Loss of weight.	Observation by nurses, modified Nunney-Hamburg Mood and Behaviour Rating Scale.	Not specified	Exacerbation or onset of depression, anger or psychotic symptoms, loss of sleep, weight loss.

* Phase of Day describes the time of day the melatonin was given as it relates to daylight hours: Morning – 07:30-12:00hrs; Afternoon – 12:00-16:30hrs; Evening – 17:00hrs-18:00hrs; Night – 18:00hrs-24:00hrs; Not specified – No time of day was described in the manuscript; Before bed – Did not specify phase of day but indicated a time before retiring to bed.

† Significant difference between melatonin and placebo/control group/phase.

and *in vitro* studies reflect the findings of this review regarding melatonin's potential to interact with reproductive hormone[87–89] and insulin secretion cycles.[90] However, another study has shown the potential for melatonin to restore menstrual cycling to women with polycystic ovarian syndrome without affecting insulin activity in either adverse or beneficial ways.[91] Additionally, despite reductions in sperm parameters seen in a sub-group of men in one reviewed study, melatonin appears to offer protective effects on sperm parameters in other literature.[92–94] It is possible these endocrine effects are dependent on population or individual characteristics, or dosage timing and form of melatonin. For example, effects noted on glucose tolerance and insulin sensitivity were stronger after day-time dosing while mimicking normal night-time patterns of reduced glucose metabolism and insulin activity.[95] Melatonin is known to have phase-shifting effects on circadian rhythms of sleep,[96] so it is possible this phase-shifting applies to circadian rhythms of other physiological functions. Further research is necessary in order to better understand the role of melatonin in endocrine function and to determine optimal dosing protocols to avoid disrupting healthy endocrine cycles.

There are limitations present in this review. Primarily, during study selection, a number of papers reported no adverse events yet were excluded because they did not conduct statistical analyses of adverse events, which may have led to underestimation of the safety of melatonin when synthesising results. The heterogeneity of methods used in reviewed studies prohibited direct comparisons or meta-analyses and the broad range of medical conditions involved complicates classification of adverse events. Additionally, many reviewed studies did not assess a full scope of potential adverse events, focussing only on those relating to study outcomes or spontaneously reported by participants, which may have led to underestimation of the occurrence of adverse events in individual studies. This was reflected in section 6 of critical appraisal with the CONSORT tool. We recommend use of measures encompassing the full spectrum of adverse events listed in this review for future research in order to enable comprehensive analysis of melatonin's safety.

While this review reveals a high degree of safety for melatonin with few adverse events that cannot be easily avoided or managed in most populations, it also reveals lack of clarity regarding melatonin's relationship to endocrine processes, and its effect on hypertensive patients and potential drug interactions in this population. In addition, no clinical trials of melatonin in pregnant or lactating women were identified in our search, precluding assessment of its use in this vital population. As understandings of the physiological activity of melatonin expand, clinical research of melatonin has extended beyond treatment of sleep disorders into various other potential applications. These applications include adjuvant treatment of cancer,[8,97] its symptoms,[98] and side-effects of conventional cancer treatments,[99] treatment of liver diseases and injuries,[100,101] fertility support,[9,102] post-surgical recovery,[103,104] gastrointestinal disorders[10,105] cardiovascular function,[11,106] multiple sclerosis[12,107] and numerous others. The complexity of melatonin's interplay with the full scope of human physiological systems needs to be further clarified in order to avoid adverse events and optimise potential benefits in future clinical applications.

5. Conclusions

Oral melatonin supplementation in humans appears to be relatively safe, with some notable exceptions in particular populations. Adverse events are generally minor, short-lived, easily managed and likely avoidable if dosing is applied in accordance with the circadian rhythm of endogenous melatonin. However, further research into the physiological activity of melatonin and into a comprehensive scope of potential adverse events is required, and becomes more pressing as the application of melatonin extends beyond its traditional use as a sleep aid.

Conflicts of interest

The authors declare no conflicts of interest.

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