Medicines Adverse Reactions Committee

Meeting date	12/03/2026	Agenda item	3.2.1
Title	**Melatonin safety profile in adults**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Melatonin	Circadin	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
Melatonin	Slenyto	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
Melatonin	Vigisom	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
Melatonin	APOHEALTH Melatonin Sleep Aid	Arrotex Pharmaceuticals (NZ) Limited
Melatonin	Melotin	Arrotex Pharmaceuticals (NZ) Limited
Melatonin	SomniCare Melatonin	AFT Pharmaceuticals Ltd
Melatonin	Melatonin Generic Partners	Generic Partners (NZ) Ltd

PHARMAC funding	The Vigisom brand of modified-release 2 mg melatonin is funded for patients aged ≤ 18 years (unapproved indication) who meet the Specialist Authority criteria.
Previous MARC meetings	None
Classification	**Prescription except** when supplied in medicines for oral use containing 3mg or less per immediate release dose unit, or 2mg or less per modified release dose unit, when sold in the manufacturers original pack that has received consent from the Minister of Health or the Director General for the treatment of primary insomnia for adults aged 55 years or older for up to 13 weeks by a registered pharmacist; except when specified elsewhere in this schedule. **Pharmacy only** when supplied in medicines for oral use in immediate release preparations containing 5mg or less per dose unit for the treatment of jet lag in adults aged 18 or over, containing not more than 10 days' supply, in the manufacturers original pack that has received consent from the Minister or Director-General for sale as a pharmacy only medicine; when supplied in medicines for oral use containing 3mg or less per immediate release dose unit, or 2mg or less per modified release dose unit, for the treatment of primary insomnia for adults aged 18 years or older, containing not more than 30 days' supply, in the manufacturers original pack that has received consent from the Minister or Director-General.
Usage data	Funded community dispensing in 2024 (see section 2.6, Usage): • Number of dispensings: 177,221 • Number of people: 27,882
Advice sought	**The Committee is asked to advise:** • Is the known safety profile adequately reflected in the current data sheet and package labelling?

	○ If the answer is no, what further actions do the Committee recommend?

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1 PURPOSE

On 10 October 2025, melatonin was reclassified, meaning that if there are approved medicines, adults aged 18 years and over can purchase from pharmacies:

- up to 10 days of melatonin in an immediate-release presentation (≤5 mg per dose unit) for the treatment of jet lag
- up to 30 days of melatonin for the treatment of primary insomnia either as:
    - immediate-release (≤3 mg dose unit)
    - modified-release (≤2mg dose unit)

Adults aged 55 years and older can still obtain up to 13 weeks of melatonin following a pharmacist consultation.

Several pharmacy-only 2 mg modified-release melatonin products are approved for the treatment of insomnia in adults aged 55 years and over in New Zealand. Currently, there are no mandatory warning label statements required for melatonin products in New Zealand.

In June 2025, *Prescrire* International (Vol. 34, Issue 271) published two articles on the use of melatonin. Both articles noted that melatonin acts as an inducer of Cytochrome P450 (CYP450) enzymes, which may reduce the effectiveness of hormonal contraceptives. Additionally, several other safety concerns were highlighted, pointing out the importance of considering alternative options before initiating melatonin therapy. [1, 2] Therefore, Medsafe considered it important to review the safety profile of melatonin when taken by adults.

2 BACKGROUND

Melatonin has been available in many countries for years, particularly in the United States after it was classified as a dietary supplement in 1994 [4]. Several other jurisdictions also permit melatonin to be sold as a dietary supplement, including Canada (with restrictions for certain populations) and France (< 2mg immediate release) [4, 5]. In contrast, countries such as New Zealand, Australia, the United Kingdom, Denmark, Japan, South Korea and Sweden classify melatonin as a medicine, while Singapore treats it as a health supplement but subject it to closer regulation [6-10].

2.1 Melatonin

2.1.1 Mechanism of Action

Melatonin is a naturally occurring hormone secreted primarily in response to the circadian rhythm with low levels during the day and elevated during the night [11, 12]. This association suggests that melatonin has a role in sleep regulation, through action on melatonin receptors MT1 and MT2 [11]. Activation of these receptors can shift the timing of the body's internal clock in a predictable manner [13]. Administration of exogenous melatonin during the day increases sleep propensity, while at night it reinforces physiological processes associated with darkness [14]. While levels vary between individuals, nighttime melatonin levels tend to decline with age, and reduced melatonin levels are also found in individuals with mood disorders, dementia, severe pain, cancer, type 2 diabetes mellitus, and autistic spectrum disorder [15, 16].

2.1.2 Endogenous melatonin synthesis

Endogenous melatonin is synthesised from the amino acid tryptophan, mainly in the pineal gland. First, tryptophan is hydroxylated by tryptophan hydroxylase to 5-hydroxytryptophan (5-HTP), which is then decarboxylated by L-amino acid decarboxylase (AADC) to produce serotonin. Serotonin is subsequently acetylated by arylalkylamine N-acetyltransferase (AANAT), the rate-limiting and circadian-regulated step, forming N-acetylserotonin (NAS). Finally, NAS is methylated by acetylserotonin O-methyltransferase (ASMT), to produce melatonin which is released into the blood. Melatonin production depends on the availability of

serotonin and noradrenaline. Both β-adrenergic antagonists and pineal gland denervation, can stop melatonin's normal nightly release and interfere with light-dark regulation. [17]

Figure 1: Melatonin biosynthesis pathways including the chemical reactions [17]

AANAT is the primary rate-limiting enzyme in melatonin synthesis. However, other N-acetyltransferases, including NAT1 and NAT2, have also been shown to contribute to serotonin acetylation in extra-pineal tissues such as the gastrointestinal (GI) tract and retina, where AANAT expression is minimal. [17]

In skin cells, melatonin is synthesised from L-tryptophan via serotonin and NAS and is subsequently metabolised through indolic and kynuric pathways. CYP450 enzymes, including CYP1A1, CYP1A2, and CYP1B1, contribute to its oxidative metabolism and formation of biologically active metabolites. The indolic pathway generates metabolites with antioxidant and potential neuroprotective properties, while the kynuric pathway is associated with antioxidant, anti-inflammatory, and cytoprotective effects. [17]

In peripheral tissues capable of synthesising melatonin (e.g., retina, GI tract, bone marrow, skin, cerebellum, ovary, lymphocytes, testis), melatonin appears to act locally, modulating immune responses, oxidative stress, and cellular metabolism, with minimal release into the systemic circulation. In the GI tract, melatonin contributes to the regulation of gut mobility and mucosal protection, while in the bone marrow it plays a role in the regulation of haematopoiesis and immune function. [17]

Melatonin is thought to be an immune modulator, both pro-inflammatory and anti-inflammatory [17].

Figure 2: Melatonin's dual role in antioxidant and pro-oxidant pathways [17]

Comments:

Melatonin is primarily produced in the pineal gland but is also found in extra-pineal sites.

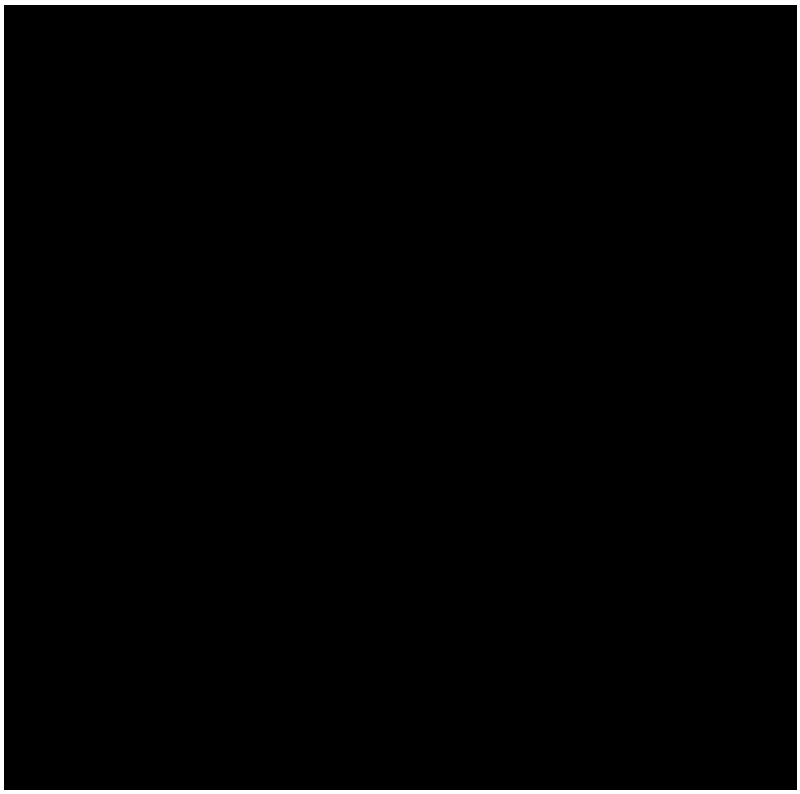
When endogenous melatonin synthesis is decreased, it can result in metabolic circadian disruptions, insulin resistance, and sleep disturbances [35].

The variable and sometimes opposing immunomodulatory effects of melatonin complicate prediction of its overall effect when taken as a supplement or medicine.

2.1.3 Pharmacokinetic Interactions

According to the New Zealand Data Sheets (NZDS) for approved melatonin products, melatonin has been shown to act as a CYP3A inducer *in vitro* at supra-therapeutic concentrations [12, 18]. An interaction between melatonin and other substances that affect CYP1A enzymes is also considered possible [12, 18]. The major enzymes known to be involved in melatonin catabolism include CYP1A2, CYP1A1, CYP1B1, and potentially CYP2C19 [11, 12]. **Error! Reference source not found.** illustrates the metabolic interconversions of melatonin in detail.

Figure 3: Formation of melatonin and interconversions [19]



Comments:

While the NZDS classifies melatonin as a CYP3A inducer based on *in vitro* findings at supra-therapeutic concentrations, there is currently insufficient clinical evidence to support a clinically relevant induction effect *in vivo*.

2.1.4 Indication

Melatonin modified-release 2 mg tablets are approved and available in New Zealand as monotherapy for the short-term treatment of primary insomnia in patients aged 55 years and over, including pharmacy-only packs of up to 30 tablets [12, 20].

Slenyto modified-release tablets (1 mg and 5 mg) were approved for use in New Zealand in August 2021 for the treatment of insomnia in children and adolescents aged 2 to 18 years with autism spectrum disorder (ASD) and/or Smith-Magenis syndrome (SMS) when sleep-hygiene measures are insufficient.

There are currently no approved products indicated for jet lag, or insomnia in adults under the age of 55 years.

2.2 Sleep disorder

There is growing evidence that melatonin secretion declines with ageing, although a causal link has not been proven with the increased prevalence of insomnia in older individuals [22]. Melatonin has demonstrated some efficacy in adults with insomnia and circadian rhythm sleep disorders [22]. The majority of clinical trials for melatonin were thus conducted in populations aged 55 years and above.

Insomnia is one of the most common sleep disorders. It not only affects daytime cognitive function but is also associated with reduced quality of life and an increased risk of various comorbid conditions, including depression, anxiety disorders, dementia, cardiovascular disease, diabetes mellitus, and infections [24].

Risk factors for insomnia include female sex, older age, and a personal or family history of the condition. Psychological factors (e.g., anxiety and poor stress coping) and biological factors (e.g., hyperarousal and hypothalamic-pituitary-adrenal axis activity) have also been associated with increased risk, although the role of hyperarousal remains unclear. [25]

2.3 Jet lag

Jet lag is a temporary circadian rhythm sleep disorder that occurs when a person travels rapidly across multiple time zones, causing a mismatch between the body's internal clock and the local time at the destination [26].

It commonly presents with symptoms such as insomnia, daytime sleepiness, fatigue, headaches, mood changes, and GI upset [26].

Jet lag can affect people of all ages, sexes, and ethnic backgrounds; however, travellers aged 60 years and older may cope less well than younger individuals. Key risk factors for jet lag include crossing multiple time zones, travelling eastward, inadequate or mistimed light exposure after arrival, individual factors such as genetic variability or pre-existing sleep disorders, and frequent long-haul travel that leads to cumulative circadian disruption. [26]

2.4 Data sheets

Drowsiness, sleepiness, dizziness, headache, and nausea are the most frequently reported adverse effects noted [27]. Table 1 summarises the safety information reported in data sheets for melatonin containing products across countries, including New Zealand.

Table 1: Information listed under Indications, Special warnings and precaution for use and/or Undesirable effects [27-30]

Information	Vigisom 2 mg prolonged release tablet (NZ)	Voquily 2 mg immediate release capsule (Australia)	Melatonin 2 mg immediate release capsule (UK)	Slenyto 1 mg, 5 mg extended-release tablet (Canada)
Age for use (years)	55 and above	18 and above	18 and above	2 to <18
Indications	Insomnia	Jet lag	Jet lag	Insomnia
Sedation with alcohol	Reduced effectiveness of melatonin on sleep	Potential to enhance drowsiness	Impaired sleep and increased symptoms of jet lag	Increased sedation
Drowsiness	Included	Included	Included	Included
Autoimmune disorder	Included	Included	Included	Included
Liver impairment	Included	Included	Included	Included
Renal impairment	Included	Included	Included	Included
Use in elderly	Included	Included	Included	Not included
Use in pregnancy	Included	Included	Included	Included
Use in lactation	Included	Included	Included	Included
Interaction with hypnotics	Included	Included	Included	Included
Seizure	Not included	Included	Included	Included
Suicide attempt/ideation	Not included	Included	Not included	Not included
Confusion	Not included	Included	Not included	Not included
Decreased appetite	Not included	Included	Not included	Included
Tachycardia	Not included	Included	Not included	Included
Hyperhidrosis	Not included	Included	Not included	Not included

Hyperglycaemia	Not included	Not included	Listed	Not included

2.5 Product label

Pharmacy-only medicines are not required to have data sheets, therefore the only source of safety information is the package labeling. According to the Label Statements Database, which determins the mandatory package labelling, there are currently no statements required for products containing melatonin [57]. Nevertheless, pharmacy-only melatonin products in New Zealand typically include warning statements.

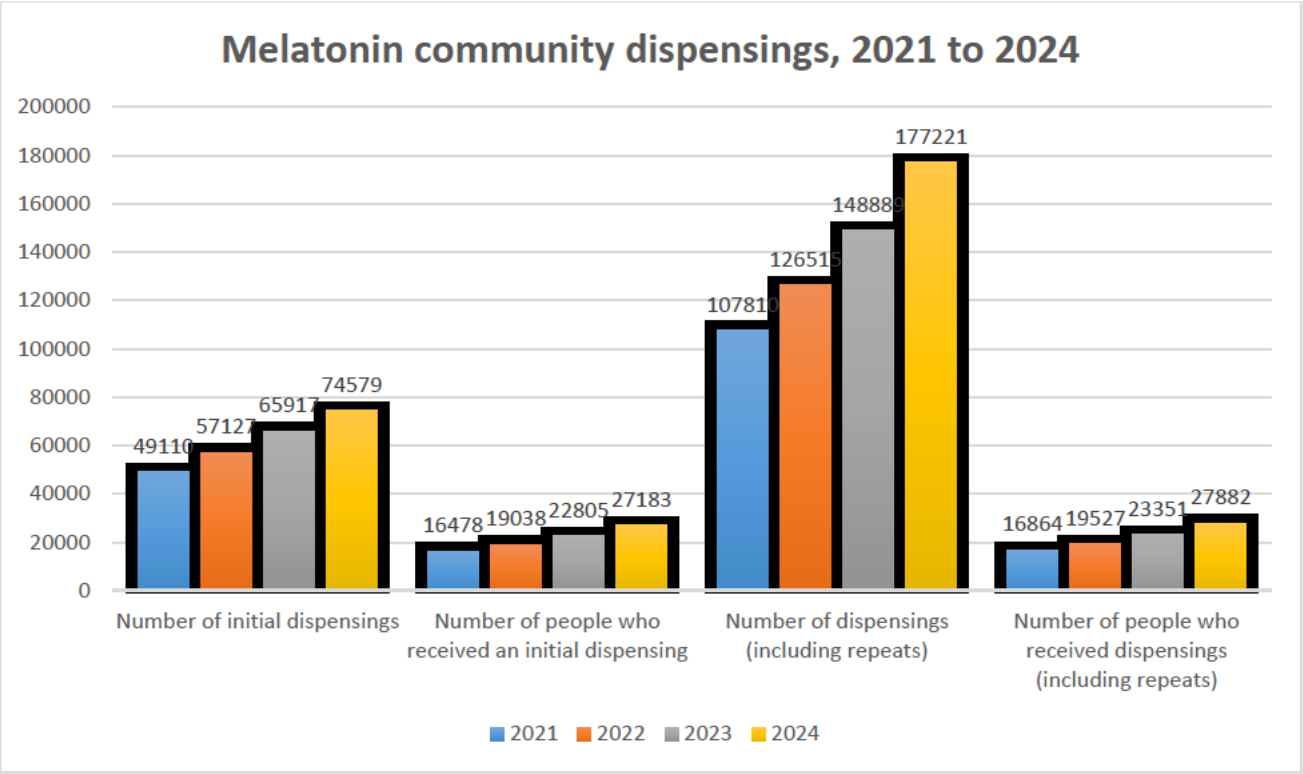
Figure 4: Packaging of the pharmacy-only Vigisom 2 mg prolonged-release tablets

Figure 5: Packaging of the pharmacy-only Melotin 2 mg prolonged-release tablets

2.6 Usage

Usage data for melatonin dispensed in the community shown in Figure 1Figure 6. This data does not capture prescriptions dispensed without public funding, such as those who did not meet the Special Authority criteria.

Figure 6: Melatonin community dispensings, 2021 to 2024



Source: Health New Zealand Pharmaceutical Data Web Tool (accessed 19 February 2026)

3 SCIENTIFIC INFORMATION

3.1 Published literature

A literature search was conducted via Ovid MEDLINE(R) and Epub Ahead of Print on 12 December 2025, covering publications from 1946 to 12 December 2025, and limited to the past 10 years. The search identified 74 articles and of these 16 articles were considered relevant.

Search details used:

1. Melatonin/
2. Melatonin.m_titl.
3. 1 or 2
4. Melatonin/ae, to [Adverse Effects, Toxicity]
5. (adverse* or harm* or safety*).m_titl.
6. 3 and 5
7. (Melatonin adj3 (safety or harm* or adverse)).mp.
8. 4 or 6 or 7
9. limit 8 to (english language and last 10 years)
10. limit 8 to (english language and last 10 years)

The relevant articles are presented below in the order umbrella review, systemic reviews and meta-analysis, prospective and retrospective studies and narrative review. No information was found on whether exogenous melatonin reduces the effectiveness of hormonal contraception.

3.1.1 Umbrella review

3.1.1.1 Melatonin and health: An umbrella review of health outcomes and biological mechanisms of action - Posadzki, P. P., et al., 2018 [31]

Purpose: To evaluate the evidence from published systematic and narrative reviews on the health effects of melatonin, including potential mechanisms of action and health outcomes associated with its endogenous production and/or supplementation.

Study type: Umbrella review.

Method: A search was conducted for entries from January 1996 until July 2017, using Medline, Embase, Web of Science, Central, PsycInfo, and Cinahl. Findings from studies that did not pool data quantitatively (N = 164) were summarised narratively. Systematic reviews with quantitatively pooled data (N = 31) were incorporated into the subgroup analyses.

Results: 195 review articles met the inclusion criteria. Seven meta-analyses showed statistically significant results (P values < 0.001) under the random-effects model. These involved sleep latency, pre-operative anxiety, prevention of agitation and risk of breast cancer. Adverse events were reported only in 5.6% of the included reviews and were described as typically mild such as worsening of symptoms (seizures, asthma or headaches), transient headaches and dizziness, abdominal pain, fatigue and hypothermia.

Conclusions: Overall, the authors concluded that the risk-benefit ratio favours melatonin, given its substantial therapeutic benefits and the presence of only a few, generally mild adverse effects. However, they advised caution for individuals with autoimmune conditions, such as rheumatoid arthritis, asthma, or those with organ transplants, because melatonin has been reported to stimulate immune function.

Comments:

Although the authors advised exercising caution in individuals with autoimmune conditions, no supportive clinical data were provided for this recommendation beyond a theoretical mechanism whereby melatonin may stimulate components of the immune system, including interleukins, interferon-γ, T-helper cells, cytotoxic T cells, and B- and T-cell precursors. A warning for use in patients with autoimmune diseases is already included in Section 4.4 of the NZDS for Circadin.

Overall, the quality of this umbrella review is uncertain due to limitations in the underlying data. In 154 reviews (78.9), the quality of the primary studies was not assessed, and in the remaining reviews, quality ratings ranged widely from poor to high. The methodological quality of many included systematic reviews was also frequently poor. Potential duplication of patient data across reviews cannot be determined. Interpretation is further limited by the pooling of heterogeneous study designs and melatonin sources, and by difficulties distinguishing narrative from systematic reviews. These inconsistences, combined with missing or variably assessed data, reduce the strength and reliability of the overall conclusions.

3.1.2 Systematic review and meta-analysis

3.1.2.1 Safety of higher doses of melatonin in adults: A systematic review and meta-analysis - Menczel Schrire, Z., et al., 2022 [32]

Purpose: To investigate the general safety of higher doses of melatonin (≥10 mg) in adults.

Study Type: Systematic review and meta-analysis.

Method: Medline, Scopus, Embase and PsycINFO databases from inception until December 2019 with convenience searches until October 2020. Randomised controlled trials (RCT) investigating high-dose melatonin (≥10 mg) with any comparator in human adults over 30 years of age were included. Two investigators independently abstracted articles using PRISMA guidelines. Risk of bias was assessed by a committee of three investigators.

Results: Although 79 relevant RCTs comparing melatonin with control were identified, many did not provide any information on adverse effects, others were assessed as having a high risk of bias, and one study could not be assessed for risk of bias. Of the 79 articles, fourteen involved healthy participants, while the remaining studies included populations with a range of physical, mental, acute, and chronic medical conditions, such as cancer, dementia, and depression. Participants with more serious underlying conditions (e.g., Huntington's disease, cancer, fibromyalgia) tended to report a broader spectrum of adverse events. Commonly expected adverse events, such as tiredness and headache, were also more frequently reported in groups with severe illnesses such as acute respiratory failure and tardive dyskinesia.

Overall, only four studies met the pre-specified low risk of bias criteria for meta-analysis. Figure 7 presents the Forrest plot of serious adverse events, adverse events, and withdrawals due to serious adverse events for studies with low and medium risk of bias over a 3-month period.

Figure 7: Forrest plot of (A) Serious adverse events, (B) Adverse events, (C) Withdrawals due to Serious adverse events, in studies with low and medium risk of bias over 3 months

Populations: Castro, 2011 - Neuroleptic-induced Tardive Dyskinesia, Madsen 2017 - Acute coronary syndrome, Sanchez-Lopez, 2018 - Relapsing-remitting multiple sclerosis treated with Interferon B-1b, Sookprasert, 2014- Non-small-cell lung cancer.

In this small subset of four studies (Figure 7), melatonin was not associated with a detectable increase in serious adverse events (Rate Ratio = 0.88 [0.52, 1.50], p = .64) or withdrawals due to adverse events (0.93 [0.24, 3.56], p = .92). However, melatonin was associated with a significantly increased the risk of adverse events, including drowsiness, headache and dizziness (1.40 [1.15, 1.69], p < .001).

Conclusions: The authors concluded that overall, there has been limited adverse event reporting from high-dose melatonin studies. They added that based on this limited evidence, melatonin appears to have a good safety profile.

Comments:

Based on the study-selection process, it is evident that the risk of bias is difficult to eliminate when comparing high dose melatonin with control.

Although two of the four studies in the forest plot have large sample sizes, pooling them with much smaller studies may add limited value to the overall estimate. Notably, only the Madsen study contributed to Forest plots (A) and (C), thus making the value of these analyses minimal.

Even at a high dose (≥10 mg), melatonin did not appear to markedly increase the frequency of serious adverse events over the short time period of 3 months across a range of clinical conditions in adult populations based on these results. However, the total number of participants of just over 3,000 only allows for detection of events occurring at a frequency of more than 1 in 1000.

3.1.3 Systematic review

3.1.3.1 Long-term effects of melatonin on individuals with depressive, anxiety, or bipolar disorder: a scoping review - Emma, N., et al., 2025 [33]

Purpose: Melatonin has been suggested as a potential therapeutic option for mood and anxiety disorders, highlighting the need to better understand its long-term effects. This review aimed to gather evidence on the long-term (≥ 3 months) efficacy and tolerability of melatonin in children, adults, and elderly people with anxiety, depressive, or bipolar disorders.

Study Type: Systematic review.

Methods: A search was conducted in PubMed, Embase, Web of Science, Scopus, and CENTRAL electronic databases for English and Dutch-language RCTs. Additionally, three clinical trial registries were screened for unpublished studies.

Results: Six RCTs met the inclusion criteria. Of the six RCTs, two studies (Noris et al. and Akhondazadeh et al.) demonstrated a significant positive long-term effect of melatonin on mood or anxiety symptoms, whereas the remaining studies did not.

Table 2: Characteristics and design features of reviewed studies

In the study by Leibenluft et al., two participants experienced partial suppression of endogenous melatonin secretion following discontinuation of melatonin. In the study by Mahableshwarker et al., somnolence and insomnia were reported in 3.4% and 3.0% of participants, respectively, among 434 participants treated with the melatonin receptor agonist ramelteon. Akhondzadeh et al., reported no serious adverse events in the melatonin group; minor adverse events included headache, drowsiness, and nightmares.

Conclusions: The authors concluded that the existing evidence on the long-term efficacy of melatonin and its agonists in patients with mood or anxiety disorders remain limited and inconsistent. They added that the available data are insufficient to enable a comprehensive assessment of its long-term safety profile.

3.1.3.2 Adverse events in long-term studies of exogenous melatonin - Besag, F. M. C. and M. J. Vasey, 2022 [34]

Purpose: There have been concerns about the possible risks of melatonin use in certain populations, including pre-adolescent children and patients with epilepsy or asthma. The aim of this review was to evaluate the evidence on adverse effects associated with both short-term and longer-term melatonin treatment for sleep disorders.

Study Type: Systematic review.

Method: A search of Embase and Medline up to 12 September 2022 was conducted to identify RCTs, open-label studies, and prospective observational studies involving at least six months of treatment in participants of all ages. All indications, including healthy participants, were eligible for inclusion, and studies were required to include systematic, prospective monitoring and reporting of adverse events. The included studies showed considerable variability in methodology and in the specificity of adverse event reporting, which is why the authors did not attempt to aggregate adverse event frequencies.

Results: Only 8 studies, 3 RCTs and 5 open-label studies, were judged to meet the full inclusion criteria.

Long-term RCTs: Wade et al. investigated the safety and efficacy of prolonged release melatonin in 791 adults with primary insomnia, with adverse events categorised by system organ class during the first 3 weeks and again at 26 weeks. Among the serious adverse events reported in the treatment group, one was considered possibly related to prolonged release melatonin. This case involved a 68-year-old woman with a 3-year history of palpitations who experienced palpitations after taking melatonin.

Lubas et al. investigated the effectiveness of time-release melatonin for neurocognitive and/or sleep impairment in 580 adult survivors of childhood cancer, who were randomised to receive 6 months of treatment or placebo. Sleep-related adverse effects (somnolence, fatigue, insomnia) were generally more common among participants with pre-existing sleep impairment, suggesting possible confounding by indication.

R-van der Lek et al. investigated the effects of bright light and melatonin on cognitive and non-cognitive function in 189 elderly care-home residents with dementia, with adverse events reported by frequency of occurrence. No severe adverse events were reported; however, the study was limited by the participants' reduced ability to self-report due to dementia.

Open-label studies: Of the five open-label studies, only one included a population other than children. Lemoine et al. investigated the efficacy and safety of prolonged-release melatonin in 244 community-dwelling adults with primary insomnia, with adverse events categorised during the first 6 weeks and again after 6–12 months. The investigator assessed adverse events in 7% of participants as definitely, probably, or possibly related to the study medicine. The most common treatment-related adverse events were dizziness (1.6%) and headache (1.2%).

Fracture: Hypnotic medicines are well known to increase the risk of falls and fracture in older adults. The authors reviewed a retrospective cohort study showing that melatonin was associated with a statistically significant increase in fracture risk compared with controls, based on average exposure duration of 2.6 years. While there is evidence that melatonin may mediate processes involved in bone formation and maintenance of bone health, a study on effects of melatonin on postural balance and muscle function found no long-term hangover effects affecting balance or muscle function.

Laboratory tests: A small open-label study in 14 women reported decreased estradiol and increased somatomedin C and DHEA-S after 6 months of treatment. However, other studies, including an RCT, did not show treatment-related endocrine effects.

Seizure: While a small number of studies have suggested that peak concentrations of endogenous melatonin may be associated with increased susceptibility to seizures in people with epilepsy, short-duration clinical

studies in this population have generally reported neutral or beneficial effects of melatonin on seizure frequency, with only a few reports indicating potential worsening of seizures.

Conclusions: The authors concluded that clinicians continue to reassure their patients about the use of melatonin, as short-term evidence indicates no serious harms and long-term widespread use has not raised major safety concerns. However, as long-term data is sparse, reassurance should be provided with a degree of reservation.

Comments:
Melatonin should be advised not to be taken during the daytime to reduce the risk of falls and subsequent fractures.
Evidence regarding melatonin use in people with epilepsy is inconsistent. The authors highlight a study reporting increased seizure frequency in individuals with no prior history of seizures.

3.1.3.3 A Systematic Review of the Efficacy and Safety of Over-the-Counter Medications Used in Older People for the Treatment of Primary insomnia - Almond, S.-A. M., et al., 2021 [35]

Purpose: The purpose of this systematic review was to evaluate the available evidence for safety and efficacy of over the counter (OTC) sleep aids used for the treatment of insomnia in older people.

Study Type: Systematic review.

Method: A search was conducted up to 8 May 2020, using PubMed, EBSCO, and International Pharmaceutical Abstracts. PubMed, EBSCO, and International Pharmaceutical Abstracts.

Results: Five articles were considered appropriate for inclusion, evaluating diphenhydramine, valerian, and melatonin. Overall, the most evidence was found for melatonin. The authors considered that the data demonstrated a significant positive effect of melatonin on sleep outcomes without notable safety concerns. Across the 3 RCTs, only one participant reported excessive drowsiness while taking both melatonin and placebo at different times, and another participant discontinued therapy due to excessive drowsiness during melatonin use (Table 3).

Table 3: Summary of studies evaluating safety and efficacy results of OTC melatonin

Conclusions: While melatonin and valerian were associated with minimal safety concerns, diphenhydramine resulted in episodes of oversedation and anticholinergic side effects. Valerian did not demonstrate a meaningful improvement in insomnia symptoms.

3.1.3.4 Adverse Events Associated with Melatonin for the Treatment of Primary or Secondary Sleep Disorders: A Systematic Review - Besag, F. M. C., et al., 2019 [36]

Purpose: At the time of publication, melatonin had recently been approved in the United Kingdom for the short-term treatment of jet lag, with limited information available on its potential for adverse effects, particularly with long-term use. At the time, concerns were being raised regarding the use of melatonin in children and in patients with epilepsy or asthma. The purpose of this systematic review was to the evidence for adverse effects associated with short-term and longer-term melatonin treatment for sleep disorders.

Study type: Systematic review.

Method: A literature search of the PubMed, Medline database and Google Scholar was conducted to identify placebo-controlled RCTs of exogenous melatonin administered for primary or secondary sleep disorders. Studies were included if they reported on both the types and frequencies of adverse events. Studies of pre-term infants, studies of < 1 week in duration or involving single doses of melatonin and studies in languages other than English were excluded. Findings from open-label studies that raised concerns relating to adverse event reports in patients were also examined. Studies were assessed for quality of reporting and for risk of bias according to the Consolidated Standards for Reporting Trials (CONSORT) statement guidelines and the Cochrane Collaboration risk-of-bias tool.

Results: Thirty-seven RCTs met the inclusion criteria, comprising a total of 1,625 participants. Daily melatonin doses ranged from 0.15 mg to 12 mg. Study duration ranged from 1 to 29 weeks, with the majority lasting 4 weeks or less. Only three studies extended beyond 12 weeks. Subject ages were between 1 and 93 years. Reported primary or co-morbid medical conditions, aside from primary sleep disorders, included epilepsy (eight studies).

Many studies were published before the introduction of the CONSORT checklist and therefore did not closely adhere to its reporting guidelines. Overall, only one study met the criteria to be judged as 'good'.

Of the 37 studies included, 16 studies (42%) did not report any adverse events. The frequency of adverse events across studies was low, with most events reported as mild in severity and occurring at rates not substantially more than placebo. None of the included studies reported a statistically significant difference in the frequency of adverse events between melatonin and placebo groups; however, most studies did not perform statistical analysis.

Table 4: Number of studies reporting each adverse event with numerical and percentage frequencies for melatonin and placebo groups

The most frequently reported adverse events were daytime sleepiness (1.66%), headache (0.74%), other sleep-related adverse events (0.74%), dizziness (0.74%) and hypothermia (0.62%) (Table 4). Very few adverse events considered to be serious or of clinical significance were reported. These included either an exacerbation of pre-existing condition (e.g., worsening migraine), events related to characteristics of the study population (e.g., agitation and mood swings in patients with ADHD), or more severe episodes of other commonly reported adverse events (e.g., fatigue, nightmares and skin irritation). Few events were assessed as related to melatonin. Most adverse events either resolved spontaneously within a few days with no adjustment in melatonin, or immediately upon withdrawal of treatment.

Seizures: Low endogenous melatonin levels have been reported in some patients with epilepsy, and melatonin demonstrated efficacy in improving sleep in this population. The mechanism may involve modulation of GABA receptor activity. However, no clear evidence of a proconvulsive effect has been identified, and some evidence suggests that melatonin may have neuroprotective effects that may lessen seizure susceptibility. Overall, the available evidence is insufficient to support either a proconvulsive or a neuroprotective effect of melatonin. In this systematic review, no evidence of an increased risk of seizures was identified among participants in the included RCTs. Although eight studies reported epilepsy as either a primary condition or a comorbidity, the authors did not specify how many participants within these studies actually had epilepsy.

Endocrine Effects and Reproductive Dysfunction: It has been proposed that endogenous melatonin mediates a range of neuroendocrine actions; however, the precise nature and extent of these effects are yet to be established, and the available evidence remains inconsistent. The long-term consequences of possible melatonin-induced dysregulation of hormonal balance have not been established.

Diabetes, Glucose Tolerance and Insulin Resistance: The exact relationship between abnormal endogenous melatonin profiles and metabolic disorders in humans remains to be clarified.

Asthma: Lack of evidence does not exclude possible adverse reactions. Asthma is a common and important condition in childhood; additional studies to determine whether there are any positive or adverse effects of melatonin are recommended.

Conclusions: The authors concluded that overall, few adverse effects (generally mild to moderate in severity) were associated with exogenous melatonin. No life-threatening adverse effects or events of major clinical

significance were identified. However, the limited availability of long-term RCTs restricts conclusions regarding the safety of continuous melatonin use over extended periods. There are insufficient robust data to allow a meaningful meaning assessment of concerns that melatonin may be associated with more clinically significant adverse effects in potentially at-risk populations.

Comments:

This systematic review excluded studies of less than one week's duration and studies involving single doses of melatonin. Although melatonin for the treatment of jet lag is intended for short-term use, typically less than one week, such short-term therapy is generally considered to be used without serious adverse consequences. The author noted that the adverse events reported in earlier short-term melatonin studies were similar to those observed in the longer duration RCTs included in this review.

This study further highlighted the lack of high-quality data needed to support a meaningful safety assessment of melatonin use in at-risk populations, such as patients with epilepsy or asthma.

The corrected placebo adverse event frequency of 0.62% reflects that, after adjusting for the expected rate of adverse events in the control group, melatonin therapy shows a 0.62% higher frequency compared with placebo. Of the adverse effects listed in Table 4, hypothermia (0.62%), decreased appetite (0.37%), seizures (0.25%) and enuresis (0.18%) are not listed in the Circadin NZDS.

3.1.3.5 Adverse events associated with oral administration of melatonin: A critical systematic review of clinical evidence - Foley, H. M. and A. E. Steel., 2019 [37]

Purpose: At the time, the authors were unable to identify a comprehensive review addressing the safety of melatonin. Consequently, they conducted a systematic review focused on the adverse effects associated with orally administered melatonin. The aim of the review was to examine the available clinical evidence regarding the safety of oral melatonin supplementation in humans.

Study Type: Systematic review.

Method: A search was conducted 7-9 August 2017, using AMED (EBSCOhost), CINAHL (EBSCOhost) and PubMed (NLM) databases. Four search-strings were combined to identify papers involving melatonin administration, safety assessment, relevant study designs, and human participants.

Results: Of the 50 included articles, 26 reported no statistically significant differences in adverse events between the melatonin and control groups. The remaining 24 studies documented at least one statistically significant adverse event attributed to melatonin.

Fatigue, Sleep and Psychological Effects: Melatonin did not demonstrate an increased risk of fatigue-related or psychological adverse events, as many studies assessing these outcomes found no statistically significant differences compared with placebo.

Physical, Psychomotor and Neurocognitive Performance: In one study involving soccer players, an 8 mg dose of melatonin was associated with statistically significant impairments in physical performance tests for a short time after administration. A similar study using a 5 mg dose also reported adverse effects on physical performance and cognitive reaction time. Another study administering 5 mg of melatonin found that overall performance parameters remained within normal ranges, despite significant reductions in selective attention. Visual tracking and reaction time were likewise adversely affected following a 5 mg daytime dose compared with placebo.

Reproductive Health: In one study, daily doses of 7.5 to 300 mg of melatonin administered to healthy women resulted in suppression of luteinising hormone and subsequent inhibition of ovulation within a single menstrual cycle. Another study reported disruptions to normal prolactin rhythms following four months of 2 mg melatonin therapy, while a separate investigation found a significant acute increase in prolactin levels in men after a single 2 to 4 mg dose of melatonin. When men received a daily dose of 3 mg of melatonin for 3 months, two of the eight participants experienced reductions in sperm concentration and mobility, along with decreased oestrogen levels. Further research is needed to clarify the role of melatonin in endocrine function,

as some studies have suggested beneficial effects on menstrual regulation and protective effects on sperm in certain populations.

Glucose Metabolism: In one study, a 5 mg dose of melatonin administered before an oral glucose-tolerance test was associated with significantly reduced pancreatic insulin release in the morning and impaired insulin sensitivity in the evening. Another study found that a 5 mg dose of melatonin decreased glucose tolerance, but only in individuals carrying the MTNR1B genetic polymorphism. Similarly, a separate study reported reduced glucose tolerance and impaired insulin sensitivity in postmenopausal women.

Potential Drug Interactions: Seventeen of the reviewed studies administered melatonin to participants who were also taking concomitant medicines including anxiolytics, antipsychotics, antidepressants, mood stabilisers, anticholinergics, surgical anaesthesia, anti-emetics, analgesics, non-steroidal anti-inflammatories, sex hormones (oestradiol) and more, without reporting any apparent drug interactions. Several studies reported potential drug interactions with cardiovascular medicines, but the authors were unable to determine whether the observed effects were attributable to melatonin itself or to its interaction with the medicines. One study demonstrated potentiation of sedative effects when melatonin was taken with zolpidem.

Conclusions: The authors concluded that oral melatonin supplementation in humans appears to be relatively safe, with some notable exceptions in specific populations. Reported adverse events are generally minor, short-lived, manageable, and often avoidable when dosing aligns with the circadian rhythm of endogenous melatonin. However, further research is needed to better understand melatonin's physiological effects and the full spectrum of potential adverse events, particularly as its use continues to expand beyond traditional indications for sleep disorders.

Comments:

Although doses of 5 to 8 mg of melatonin have been shown to affect physical and neurocognitive performance, these effects were observed when the doses were administered during the daytime. This is unlikely to be a concern when melatonin is used appropriately for jet lag or insomnia, where dosing occurs before sleep.

To minimise sedative or hypnotic adverse effects, melatonin should be taken at night before going to bed and it should not be taken immediately before activities requiring a high level of alertness. Also, caution is advised when it is co-administered with other sedative medicines. Given the need for further research on the use of melatonin in patients with hypertension and other conditions, it may be prudent to advise individuals with underlying health conditions to discuss its use with a health professional.

The author was unable to identify any clinical trials evaluating melatonin use in pregnant or lactating women. There were no contraceptives among the studies on potential drug interactions.

The author noted several limitations, including the inability to conduct statistical analyses of adverse events due to methodological heterogeneity across studies. In addition, studies that reported no adverse events were excluded.

3.1.3.6 A systematic review of melatonin for insomnia in older people - Byrne, A., et al., 2016 [38]

Purpose: Some quality trials demonstrated improvements in sleep quality among older people with insomnia treated with melatonin. However, meta-analytic findings were inconsistent, suggesting conflicting results. Therefore, the author aimed to examine quality evidence on the efficacy and safety of melatonin for insomnia in older people.

Study Type: Systematic review.

Method: A search covering 1995 to 2015 was conducted in The Cochrane Library, Medline, Embase, PsycInfo, and NHS Evidence. Eligible studies were double-blinded RCTs comparing melatonin with placebo or hypnotics in individuals aged over 55 years.

Results: Nine RCTs were selected for appraisal; 7 comparing melatonin with placebo and 2 comparing melatonin with zolpidem.

Conclusions: The authors concluded that compared to zolpidem, melatonin demonstrated more favourable side-effect profile, with no significant effects on cognitive or psychomotor performance, postural stability, morning alertness, or driving ability. The authors noted that small sample sizes in some trials were a limitation.

Comments:
Full article was not obtainable.

3.1.4 Prospective study

3.1.4.1 Lasting treatment effects in a postmarketing surveillance study of prolonged-release melatonin - Hajak, G., et al., 2015 [39]

Purpose: To assess discontinuation, withdrawal, and rebound effects of Circadin in a heterogenous population with insomnia treated in outpatient settings in Germany, where physicians prescribed the medicine according to the Summary of Product Characteristics.

Study Type: Prospective cohort study.

Method: Between July 2008 and April 2009, 653 patients were recruited. Eligible participants were adult outpatients with physician-diagnosed insomnia requiring pharmacological treatment. They were instructed to take 2 mg Circadin tablet 2 hours before bedtime for the first 3 weeks, and to return for follow-up approximately 2 weeks after treatment discontinuation as part of routine care. Data were collected at the treatment initiation, within 2 days of discontinuation, and again approximately two weeks after discontinuation.

Baseline data included demographics, insomnia history, other illness/medicines, reasons for starting prolonged release melatonin, and patient-related sleep quality and morning alertness. At follow-up, prolonged release melatonin use, discontinuation details, other sleep medicines, sleep quality, alertness, and adverse events were recorded. Sleep quality and alertness were scored on 1-5 scales, with changes indicating improvement or worsening.

Results: Of the 653 enrolled patients, one was excluded for not receiving Circadin. Among the treated patients, 46 (7.1%) reported 79 adverse events, and physicians judged 75 of them as possibly or probably related to melatonin. The most common adverse events were nausea (1.5%), dizziness (<1%), restlessness (<1%), and headache (<1%). No serious adverse events were reported, and no adverse events were reported after treatment was discontinued. Thirteen patients discontinued treatment due to adverse events, including nausea, dizziness, vomiting, insomnia, and headache.

Conclusions: The authors concluded that the data supports the positive benefit-risk profile of short-term use of prolonged release melatonin.

3.1.5 Retrospective study

3.1.5.1 Rethinking Melatonin Dosing: Safety and Efficacy at Higher-than-Usual Levels in Aged Patients with Sleep Disturbances and Comorbidities - Valiensi, S. M., et al., 2025 [40]

Purpose: The study aimed to examine non-communicable diseases before and after high-dose melatonin use and compared patients' lab results with an age- and sex-matched control group.

Study Type: Retrospective uncontrolled cohort analysis and a cross-sectional study.

Method: Patients aged 52 years and older who used immediate release melatonin (40-200mg/day) nightly for sleep disorders in the presence of comorbidities were included in the melatonin group. They were matched with controls by age, sex, CPAP therapy, and having sleep disorders during the same period. Therapeutic response (whether pre-existing conditions improved or worsened) was assessed after 4 months, and blood

tests taken at least 3 months after starting melatonin were compared with those from the melatonin-free control group.

Results: Table 5 shows significant improvements in hypertension, ischaemic heart disease and diabetes mellitus following melatonin treatment, with no changes observed in patients with cancer. "Improvements" were defined as the normalisation of blood pressure in the case of arterial hypertension, clinical assessment of symptom improvement for ischaemic heart disease, and normalisation of blood glucose levels for diabetes mellitus.

Table 5: Chronic diseases before and after receiving high doses of melatonin

For laboratory tests, the control group showed higher mean serum alkaline phosphatase levels than the melatonin ($p = 0.02$). No other significant differences were observed.

Both groups reported occasional symptoms such as headaches or dizziness, but these were not systematically analysed. No clinically significant adverse effects were observed.

Conclusions: The authors concluded that the study demonstrates improvements in arterial hypertension, ischaemic heart disease, and diabetes mellitus, along with favourable modulation of alkaline phosphatase levels, without other laboratory changes.

Comments:

Table 5 reports 54 cases of arterial hypertension before high-dose melatonin and 9 cases after. However, the 'significant improvements' in hypertension, ischaemic heart disease, and diabetes reflect changes in clinical measures rather than resolution of these chronic diseases. Melatonin is not a disease-modifying therapy for ischaemic heart disease, which does not resolve without revascularisation or sustained risk-factor modification. Likewise, hypertension and diabetes are chronic conditions in which improvement typically reflects better control of parameters, not cure. It is also plausible that participants were receiving standard treatments for these conditions concurrently. Interpretation of these findings is limited by the lack of detailed information on comorbidities and concomitant medicines.

3.1.5.2 Investigating the safety profiles of exogenous melatonin and associated adverse events: A pharmacovigilance study using WHO-VigiBase - Ha, M., et al., 2024 [41]

Purpose: This study aimed to characterise patterns of reported adverse events associated with melatonin use and identify any potential safety signals.

Study Type: Retrospective, observational, pharmacovigilance study.

Method: Adverse event data related to melatonin and other sleep medicines used to treat sleep disorders were obtained from the VigiBase database from 1967 to September 2022. The collected data included patient demographics, drug information, and adverse events. The melatonin group was compared with two other comparator settings through disproportionality analysis: all other drugs and other sleep medicines. Adverse

events of special interest were predefined to include those associated with an increased risk of falls and fractures, over-sedation and confusion.

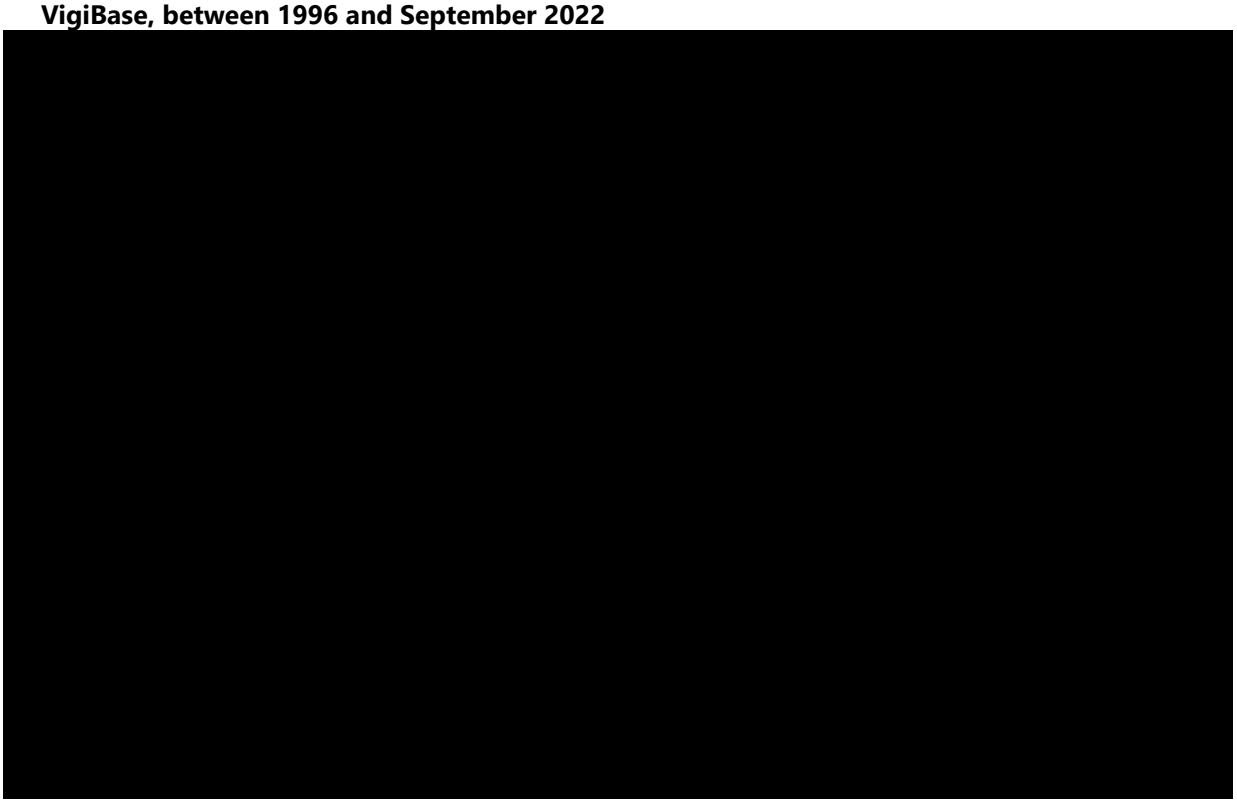
Results: The total number of reported adverse events increased substantially from 1996 to 2021. Because data for 2022 were only collected up to September, the number of adverse event reports for that year is likely underestimated.

The authors identified 21 potential safety signals, including: tics, learning difficulties, social behaviour issues, body temperature fluctuation, and growth delays.

Among the adverse events of special interest, melatonin showed a signal for accidents and injuries, fall, and nightmares. Abnormal dreams were identified as a safety signal for melatonin when compared with all other drugs, but this signal was mitigated when melatonin was compared only with other sleep medicines.

Reports of fatigue, nausea, headache, and insomnia were common, consistent with findings from previous studies.

Figure 8: Temporal trends of individual case safety reports for overall drugs and melatonin reported in VigiBase, between 1996 and September 2022



Conclusions: The authors concluded that the study demonstrated an overall satisfactory safety profile. Although several potential safety signals were identified, the study could not establish a causal relationship between these adverse effects and melatonin use.

3.1.5.3 Differences between paediatric and adult suspected neuropsychiatric adverse drug reactions of Melatonin reported to the European Medicines Agency - Bakalov, D. V., et al., 2021 [42]

This retrospective pharmacovigilance study aimed to identify which neurological and psychiatric adverse drug reactions are reported more frequently for melatonin in children than in adults.

Adverse event reports for melatonin from 2006 to 23 March 2019 were retrieved from the European Medicines Agency's EudraVigilance pharmacovigilance database. The most reported adverse events in adults were dizziness, headache, insomnia, somnolence, agitation, and abnormal dreams.

The authors concluded that neuropsychiatric reactions, such as aggression, abnormal behaviour, and psychomotor hyperactivity were reported more frequently in children than in adults.

3.1.5.4 Association of melatonin use with adverse events in geriatric patients admitted to inpatient medical and surgical care units - Steele, A., et al., 2021

This retrospective electronic chart review examined adverse events associated with melatonin use in elderly patients admitted to inpatient medical and surgical units. Between 2 June 2020 and 31 August 2020, electronic records were reviewed for all inpatients aged 65 years and older who received at least one dose of melatonin at UPMC Mercy Hospital US.

Among the 336 included patients (mean age 77 years), 12 (3.6%) experienced adverse events, including falls, altered mental status, new-onset delirium, and aspiration pneumonia. Patients receiving a median dose of 6 mg had a longer average length of stay compared with those receiving 3 mg. The authors concluded that higher melatonin doses may be associated with increased adverse effects in hospitalised older adults.

Comments:
The publication by Steele was a poster presentation.

3.1.6 Narrative review

3.1.6.1 Melatonin's paradox: From therapeutic benefits to toxicity warnings - Amrollahi-Sharifabadi, M., et al., 2025 [17]

The therapeutic potential of exogenous melatonin across various disorders has attracted increasing attention. However, emerging studies have raised concerns regarding its potential toxicological effects. This paper therefore aimed to summarise current knowledge of melatonin's pharmacological, toxicological, and biochemical properties, with particular emphasis on toxicity mechanisms and safety concerns in susceptible populations.

The authors state that at lower doses (approximately 0.3–5 mg), melatonin is generally well tolerated and associated with minimal adverse effects. However, doses of 10 mg or higher have raised concerns regarding potential long-term endocrine disruption, including suppression of endogenous melatonin secretion. Further, recent studies have highlighted the need for further investigation into the long-term use of melatonin in individuals with hepatic or renal impairment.

The authors highlighted several population-specific risks, particularly in children, elderlies, pregnant, lactating women, and individuals with chronic health conditions.

Paediatric population: The review describes previous research into case studies of melatonin-related paediatric deaths, raising concerns about the need for tighter regulation in children.

Pregnant and lactating women: The authors considered the safety of melatonin use in pregnant and lactating women to be under-researched.

Ovulation: The authors stated that parenteral or oral administration of melatonin may inhibit ovulation and is therefore not considered suitable for women attempting to conceive. In terms of drug-drug interactions, the author highlighted the involvement of CYP1A2 enzyme inhibitors and inducers.

Elderly and individuals with chronic conditions: The authors noted that, in elderly individuals, melatonin's effects on thermoregulation have been associated with an increased risk of hypothermia and hypotension. They also noted that in patients with autoimmune disorders, melatonin's immunomodulatory activity may worsen underlying symptoms. the authors emphasised the need for a clearer understanding of melatonin's role in immune regulation to better mitigate risks in these groups.

Conclusions: The authors concluded that several preclinical and clinical studies indicate that melatonin is generally safe, with predominantly mild adverse effects. However, this review identified recent reports raising concerns about the use of exogenous melatonin in special populations, including older adults, paediatric patients, pregnant women, and individuals with comorbidities and chronic conditions.

Comments:

Narrative reviews have been added to the literature list to provide a brief overview of the current state of knowledge.

The review included brief statements, such as "parenteral or oral melatonin might also inhibit ovulation and therefore, it is not suitable for women who are trying to get pregnant," which was referenced from a comment on a single website. There is some evidence that melatonin may influence sexual maturation and reproductive cycles in mammals; however, its effect on human reproductive function remains incompletely understood [43]. In contrast, a recent systematic review and meta-analyses of RCTs have reported improved reproductive outcomes when melatonin is used as an adjunct in assisted reproductive technologies [44].

Hypertension is listed as an ADR in the NZDS for Circadin and ApoHealth Melatonin, but hypotension is not.

While melatonin is suspected to have immunomodulatory and thermoregulatory effects, current evidence is insufficient to clearly characterise them. As a result, the clinical risk associated with melatonin use in elderly individuals and those with autoimmune disorders remains uncertain. As mentioned earlier, section 4.4 of the Circadin NZDS contains information regarding use in individuals with autoimmune disorders.

3.1.6.2 What do we really know about the safety and efficacy of melatonin for sleep disorders - Kennaway, D. J., 2022 [4]

Melatonin is widely marketed as a supplement despite being a pineal hormone. This review summarises what has been learned in the 60 years since its discovery. Although the exact risks during pregnancy remain uncertain, the author emphasises the need for caution when using melatonin for any therapeutic purpose in this population.

Regarding diabetes, the review discusses several studies examining the effects of melatonin administration on glucose control in health subjects. The author advises caution when prescribing melatonin to individuals with poor glycaemic control or established diabetes. This recommendation stems from emerging evidence that that MTNr1B melatonin receptor gene represents a novel risk factor for type 2 diabetes. Carriers of the risk genotype exhibit increased receptor activity, which appears to exacerbate melatonin's adverse effects on glucose tolerance.

Notably, this narrative review was the only article to address the interaction between melatonin and oral contraceptives. The cited pharmacokinetic study (Hilli et al.) found that oral contraceptives use significantly inhibited CYP1A2-mediated melatonin metabolism. Among 29 healthy subjects, oral contraceptive users showed substantially higher melatonin exposure (AUC and Cmax) and reduced clearance after a single 6 mg melatonin dose, indicating a significant inhibitory effect [45].

The review concludes that, because melatonin is sold as a dietary supplement to millions of people with diverse comorbidities, appropriate monitoring is difficult to achieve. While short-term use appears to carry low risk and may help support healthy sleep routines, long-term therapy without adequate clinical assessment may not be justified.

Comments:

The author notes, oestrogens have been shown to increase melatonin levels by inhibiting its metabolism via CYP1A1 and CYP1A2, as noted in the NZDS for Circadin.

3.1.6.3 The Safety of Melatonin in Humans - Andersen, L. P. H., et al., 2016 [46]

This review aims to evaluate the literature on the potential adverse effects and overall safety of exogenous melatonin use in humans. Across both animal and human studies, short-term melatonin use was associated only with mild adverse effects, such as dizziness, headache, nausea, and sleepiness, and no serious adverse effects were identified. In RCTs evaluating longer-term use, the reported adverse effects remained mild and were comparable to those observed with placebo. The authors concluded that the evidence regarding the long-term safety of melatonin in children and adolescents is limited, and there is insufficient safety data to support its use during pregnancy or breastfeeding.

3.2 Regulatory review

3.2.1 Australia (Therapeutic Goods Administration)

In September 2025, the TGA highlighted an increase in Australians purchasing melatonin products online, particularly for use in children [47]. This was followed by a safety alert in January 2026 regarding concerns about imported counterfeit melatonin products [48], and a further blog post in February 2026 outlining the risks of buying melatonin online [49].

3.2.2 The United Kingdom (Medicines and Healthcare products regulatory Agency)

In August 2025, the MHRA published a press release regarding concerns about use of specific brand of kids' magnesium gummies due to the presence of undeclared melatonin, a prescription-only medicine [50].

3.2.3 Canada (Health Canada)

On 9 September 2025, Health Canada added "melatonin or its salts" to the Prescription Drug List (PDL) when sold for the treatment of insomnia in children and adolescents aged 2–17 years with ASD and/or Smith-Magenis Syndrome (SMS). This amendment followed the authorisation of Slenyto, an extended-release melatonin product, as a prescription medicine for this population. [51]

Health Canada subsequently launched a public consultation from 16 September 2025 to 30 December 2025 to consider expanding this prescription requirement to include all sleep-related uses of melatonin in children and adolescents under 18 years of age. The outcome of the consultation has not yet been published. [52]

3.3 Adverse drug reaction reports

3.3.1 New Zealand

As of 12 February 2026, the New Zealand Pharmacovigilance Database contains 32 reports in which melatonin was identified as the suspect medicine. None of these reports included concomitant use of hormonal contraceptives. The most commonly reported System Organ Classes for age group 18-55 years and over 55 years are presented in Figure 9 and 10 respectively.

[redacted]

Comments:

Due to the low number of reports, further data analysis was not meaningful.

3.3.2 International

VigiLyze is a signal detection tool that uses data from VigiBase, the World Health Organisation (WHO) global database of ADR reports for medicines.

Source: VigiLyze dataset date 15 February 2026. URL: vigilyze.who-umc.org/ (accessed 18 February 2026)

Source: VigiLyze dataset date 15 February 2026. URL: vigilyze.who-umc.org/ (accessed 18 February 2026)

Source: VigiLyze dataset date 15 February 2026. URL: vigilyze.who-umc.org/ (accessed 18 February 2026)

Note: $N_{observed}$= A total number of case reports for the active ingredient(s) and reaction in question, $N_{expected}$= The expected number of case reports, based on the number of case reports for the active ingredient(s) and reaction in question, IC025= The lower endpoint of a 95% credibility interval for the Information Component

Source: VigiLyze dataset date 15 February 2026. URL: vigilyze.who-umc.org/ (accessed 18 February 2026)

Source: VigiLyze dataset date 24 February 2026. URL: vigilyze.who-umc.org/ (accessed 26 February 2026)

Source: VigiLyze dataset date 24 February 2026. URL: vigilyze.who-umc.org/ (accessed 26 February 2026)

Source: VigiLyze dataset date 15 February 2026. URL: vigilyze.who-umc.org/ (accessed 18 February 2026)

4 DISCUSSION AND CONCLUSIONS

Melatonin is a hormone made primarily by the pineal gland in response to darkness. Its main function is to regulate the sleep-wake cycle by acting on brain centres controlling circadian rhythms. Melatonin affects multiple body systems through MT1 and MT2 receptors located in the brain, retina, cardiovascular system, digestive system, immune system, and peripheral tissues. It is also thought to act as an antioxidant and to contribute to immune and metabolic regulation.

The purpose of this review was to investigate the safety profile of melatonin and consider if it is adequately described in data sheets and package labelling. Currently, there is no mandatory warning label statement required for melatonin products in New Zealand.

The literature review indicated that there is a paucity of good information. The data identified indicated that, when used as intended in adults, melatonin had generally mild and transient adverse effects, supporting an overall satisfactory safety profile. Alteration in physical and neurocognitive performance were mainly observed when melatonin was administered during the daytime.

There was insufficient evidence available to support any reduction in contraceptive effectiveness associated with melatonin use. Although melatonin has demonstrated CYP enzyme induction *in vitro*, there is currently no evidence that this translates into clinically meaningful effects *in vivo*.

The following potential side effects have been noted but are not listed in the current NZDS:

- Suicide attempt/ideation
- Coma

- Serotonin syndrome
- Seizures
- Cardiac arrest
- Tachycardia
- Hypotension

The mechanism of action of melatonin in patients with autoimmune disorders, hepatic or renal impairment, pregnancy, breastfeeding, cardiovascular disease, or diabetes remains complex and not fully understood. Even though no clear causal risk has been identified, the absence of a risk cannot be assumed. These populations have been highlighted as requiring clinical input in the non-prescription products and in the data sheets. However, the Committee may consider that there is enough evidence to warrant mandating some of these statements in the LSD.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Is the known safety profile adequately reflected in the current data sheet and package labelling?
    - If the answer is no, what further actions do the Committee recommend?

6 ANNEXES

Annex 1 - Long-term effects of melatonin on individuals with depressive, anxiety, or bipolar disorder: a scoping review. Emma, N., et al., 2025

Annex 2 - Adverse events in long-term studies of exogenous melatonin. Besag, F. M. C. and M. J. Vasey, 2022

Annex 3 - A Systematic Review of the Efficacy and Safety of Over-the-Counter Medications Used in Older People for the Treatment of Primary insomnia. Almond, S.-A. M., et al., 2021

Annex 4 - Adverse Events Associated with Melatonin for the Treatment of Primary or Secondary Sleep Disorders: A Systematic Review. Besag, F. M. C., et al., 2019

Annex 5 - Adverse events associated with oral administration of melatonin: A critical systematic review of clinical evidence. Foley, H. M. and A. E. Steel., 2019

Annex 6 - A systematic review of melatonin for insomnia in older people. Byrne, A., et al., 2016

Annex 7 - Association of melatonin use with adverse events in geriatric patients admitted to inpatient medical and surgical care units. Steele, A., et al., 2021

Annex 8 - Melatonin's paradox: From therapeutic benefits to toxicity warnings. Amrollahi-Sharifabadi, M., et al., 2025

Annex 9 - What do we really know about the safety and efficacy of melatonin for sleep disorders. Kennaway, D. J., 2022

Annex 10 - The Safety of Melatonin in Humans. Andersen, L. P. H., et al., 2016

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