ISSN: 2231-3656

International Journal of Pharmacy and Industrial Research (IJPIR)

IJPIR |Vol. 16 | Issue 3 | Jul – Sep 2026

www.ijpir.com

DOI: https://doi.org/10.61096/ijpir.v16.iss3.2026.543-559

Melatonin, *Valeriana Wallichii*, and Vitamin B6 in A Single Nutraceutical Tablet (Melatonin+): A Critical Review of Mechanistic Rationale, Clinical Utility, Formulation Integrity, and Research Priorities

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Published on: 02.08.2026
Published by: Futuristic Publications

Abstract: Chronic insomnia, delayed sleep–wake phase disorder, jet lag, and shift-work-related circadian misalignment rank among the most prevalent and persistent sleep complaints encountered in clinical practice. Although these conditions are clinically distinct entities, they frequently overlap, share underlying physiological mechanisms, and often present as chronic or recurrent forms of sleep–wake dysregulation. First-line management prioritises non-pharmacological behavioural therapies, with pharmacotherapy reserved for cases in which such interventions have proven insufficient; medication is generally limited to short-term use rather than indefinite symptomatic treatment. Pharmaceutical hypnotics and over-the-counter sleep aids nonetheless remain widely used, particularly in older adults, where polypharmacy with sedative-hypnotic agents is regularly documented. Consequently, recent clinical practice guidelines emphasise explicit deprescribing guidance for benzodiazepine-receptor agonists. Multiple network meta-analyses of insomnia therapies have concluded that, for the majority of patients, the absolute benefit of pharmacologic treatment over behavioural intervention is small, supporting time-limited rather than open-ended use of hypnotic medication. Against this backdrop, combination nutraceutical products containing melatonin, valerian root, and B-vitamin cofactors are increasingly marketed as safer, better-tolerated alternatives. This narrative review critically discusses the preclinical and clinical evidence, regulatory positioning, and proposed research priorities for such combination products, using "Melatonin+" — a tablet formulation containing 5 mg melatonin, 25 mg of *Valeriana wallichii* root extract, and 1.4 mg pyridoxine — as a representative worked example.

Keywords: melatonin; *Valeriana wallichii*; valerian; pyridoxine; insomnia; circadian rhythm; nutraceutical; FSSAI; claim substantiation; combination product.

1. Introduction

Insomnia and circadian-rhythm complaints are highly prevalent [1,2]. They are clinically distinct but often overlapping, physiologically related, and may present as chronic or transient/recurrent forms of misalignment [3–5]. First-line management is behavioural and psychological intervention; pharmacotherapy is reserved for cases in which such approaches have proven insufficient [6–8]. Pharmaceutical hypnotics remain widely used, particularly in older adults, prompting explicit deprescribing guidance for benzodiazepine-receptor agonists [9–12]. Comparative network meta-analyses indicate that the absolute

benefit of drug therapy for most patients with insomnia is small, supporting time-limited rather than indefinite symptomatic treatment [6–8]. Pharmacological hypnotics are superior to behavioural interventions for short-term relief, but for chronic insomnia the long-term benefit of hypnotics is no greater than that produced by a single high-dose hypnotic [6,8].

Why this review matters. There is a persistent gap between the consumer-facing marketing of combination sleep nutraceuticals and the published evidence base for individual ingredients and combinations. This review aims to bridge that gap using a single representative product — Melatonin+ — as a worked example.

The commercial category of multi-ingredient sleep nutraceuticals is dominated by melatonin and valerian (alone or, more commonly, in combination with hops, passionflower, lemon balm, magnesium, glycine, L-theanine, and B-vitamins). Within this crowded field, the formulation labelled "Melatonin+" is conceptually minimalist: it combines only three components, each of which addresses a distinct mechanistic node of sleep physiology. The present review is a critical academic synthesis of the evidence supporting the use of Melatonin+, with emphasis on what can be defended scientifically and what must remain speculative.

Glossary of key terms

Term	Definition
MT1 / MT2	High-affinity G-protein-coupled melatonin receptors; MT1 reduces SCN firing, MT2 mediates phase shifts.
DLMO	Dim light melatonin onset — the endogenous circadian phase marker used to time exogenous melatonin.
SCN	Suprachiasmatic nucleus of the hypothalamus — the central circadian pacemaker.
AANAT	Arylalkylamine N-acetyltransferase — rate-limiting enzyme in pineal melatonin synthesis.
AADC	Aromatic L-amino acid decarboxylase — PLP-dependent enzyme converting L-DOPA to dopamine and 5-HTP to serotonin.
PLP	Pyridoxal-5′-phosphate — the biologically active form of vitamin B6.
GABA-A	γ-aminobutyric acid type A receptor — principal inhibitory ligand-gated ion channel in the CNS.
Valerenic acid	Major valerian-specific sesquiterpenoid with partial allosteric GABA-A activity.
DSWPD	Delayed sleep–wake phase disorder — circadian rhythm disorder in which sleep onset is markedly delayed.
ISWRD	Irregular sleep–wake rhythm disorder.
PSQI / ISI	Pittsburgh Sleep Quality Index / Insomnia Severity Index — validated subjective sleep-assessment instruments.
FSSAI	Food Safety and Standards Authority of India — sets the Indian nutraceutical regulatory framework.
VigiBase	WHO global pharmacovigilance database of individual case safety reports.

2. Scope and evidence selection

The scope of this review is the scientific, regulatory, and consumer-communication considerations defining a fixed-dose combination containing melatonin, *Valeriana wallichii* extract, and pyridoxine. Evidence is

drawn from peer-reviewed systematic reviews and meta-analyses, narrative reviews, regulatory documents, and primary reference works on receptor pharmacology [6–9,13–15].

2.1 Search strategy and evidence-grading rubric

A structured but non-systematic search was conducted in PubMed, Cochrane Library, and Science Direct, last updated in mid-2026. Boolean queries of the form "melatonin AND insomnia", "melatonin AND delayed sleep-wake phase disorder", "valerian AND insomnia", "pyridoxine AND sleep", and "*Valeriana wallichii*" were used to identify primary literature. Reference lists of umbrella reviews and meta-analyses were hand-searched for additional sources. Sources were prioritised in the following hierarchy when assigning qualitative strength of evidence: (i) systematic reviews and meta-analyses [15–18]; (ii) randomised controlled trials [19–24]; (iii) observational and pharmacovigilance data [25,26]; (iv) preclinical and in vitro receptor-pharmacology studies [27–29]; (v) regulatory and consensus statements [6–9,13,14]. Specificity (direct versus indirect evidence on the product itself), consistency across independent sources, and the temporal proximity of the source to current practice were used, alongside the study-design hierarchy, to grade individual claims. No formal risk-of-bias scoring was performed. Searches were restricted to English-language and PubMed-indexed sources.

Limitations of this review

This is a narrative critical review rather than a systematic review. No PRISMA flow diagram, formal risk-of-bias scoring, or quantitative publication-bias assessment was performed; readers should weight claims accordingly. Search was restricted to English-language and PubMed-indexed sources, and the search cut-off preceded manuscript acceptance — newer evidence may have emerged. All claims concerning the finished Melatonin+ product itself represent inferences from indirect evidence on individual ingredients and combinations; no published randomised controlled trial of the specific three-ingredient product exists at the time of writing. Where positive signals exist for adjacent combination products (e.g., the Lemoine 2019 pilot study of melatonin + vitamin B6 + medicinal plants for mild-to-moderate insomnia [22]), these are summarised in §13 as the closest available analogue.

3. Product description and formulation

Melatonin+ is a once-daily oral tablet containing melatonin (5 mg), *Valeriana wallichii* root extract (25 mg, hydro alcoholic extract), and pyridoxine hydrochloride (1.4 mg, providing approximately 1.15 mg pyridoxine). It is positioned as a dietary supplement intended for adults with occasional sleep-onset difficulty, jet lag, or shift-work-related circadian misalignment. The formulation and its positioning are summarised in Table 1, and the product is shown in Figure 1.

Table 1: Product profile and positioning

Property	Value
Product name	Melatonin+
Form	Once-daily oral tablet
Active ingredients	Melatonin 5 mg; *Valeriana wallichii* root extract 25 mg; pyridoxine HCl 1.4 mg
Mechanistic classes	Chronobiotic + GABAergic modulator + neurotransmitter cofactor
Intended population	Non-pregnant, non-lactating adults
Indications	Occasional sleep-onset difficulty; jet lag; shift-work circadian misalignment (adjunctive)
Regulatory route	Health supplement/nutraceutical under FSSAI 2016 schedule [13]
Labelling status	Not a drug; not an Ayurvedic medicine; not a substitute for CBT-I [7,8]

Figure 1. Biotex Life Melatonin+.

The dose selection reflects three convergent rationales:

1. The FSSAI's 2016 schedule sets the permitted melatonin range at 2–10 mg/day and permits *Valeriana wallichii* as a nutraceutical ingredient [13].
2. The European Food Safety Authority's 2011 scientific opinion concluded that intakes of 0.5 mg or more of exogenous melatonin reduce sleep-onset latency (the EFSA "cause-and-effect" relationship was established for the dose and the outcome) [14].
3. A 2024 dose–response meta-analysis identified a near-plateau maximum at approximately 4 mg/day, beyond which additional benefit plateaus while next-day drowsiness risk rises [15].

The pyridoxine dose is a nutritional cofactor level: the EU nutrient reference value for vitamin B6 is 1.4 mg, so the tablet supplies approximately one full daily reference intake rather than a pharmacologically active dose.

The choice to use exactly three ingredients minimises pharmacokinetic complexity and aligns with the principle of combining only those agents whose mechanisms of action are clearly distinct. Mechanistic complementarity in a fixed-dose combination does not, however, translate into pharmacodynamic synergy — synergy requires factorial active-comparator trial evidence, which is the central methodological gap for any multi-ingredient nutraceutical and will be revisited in §9 and §13.

4. Melatonin: biosynthesis, receptor pharmacology, and pharmacokinetics

4.1 Endogenous synthesis and circadian signalling

Melatonin (N-acetyl-5-methoxytryptamine) is synthesised via the tryptophan → 5-hydroxytryptophan → serotonin pathway. Serotonin is N-acetylated by arylalkylamine N-acetyltransferase to N-acetylserotonin and subsequently O-methylated by hydroxyindole-O-methyltransferase to melatonin [31–33]. The pineal gland is the principal source of circulating melatonin. However, melatonin is also synthesised by the retina, gastrointestinal tract, skin, bone marrow, platelets, and lymphocytes, indicating that endogenous systemic melatonin is the integrated output of multiple compartmentally regulated sources rather than exclusively pineal output [32,33]. Circulating melatonin communicates the biological night to tissues expressing its receptors; exogenous melatonin therefore acts on a pre-existing signalling axis rather than introducing a foreign molecular target. The suprachiasmatic nucleus of the hypothalamus receives this nocturnal melatonin signal and transduces it into a stabilised circadian output that coordinates peripheral clocks [4,5].

The two high-affinity G-protein-coupled melatonin receptors, MT1 and MT2, are the principal targets of pharmacological interest [28,31]. MT1 activation reduces SCN neuronal firing rate; MT2 activation

phase-shifts the SCN and advances sleep onset when melatonin is administered in the late subjective day [28]. Melatonin also acts at MT3 (quinone reductase 2), a low-affinity binding site, but this is not the principal target for sleep pharmacology [28]. Figure 2 maps the three ingredients onto their complementary mechanistic nodes.

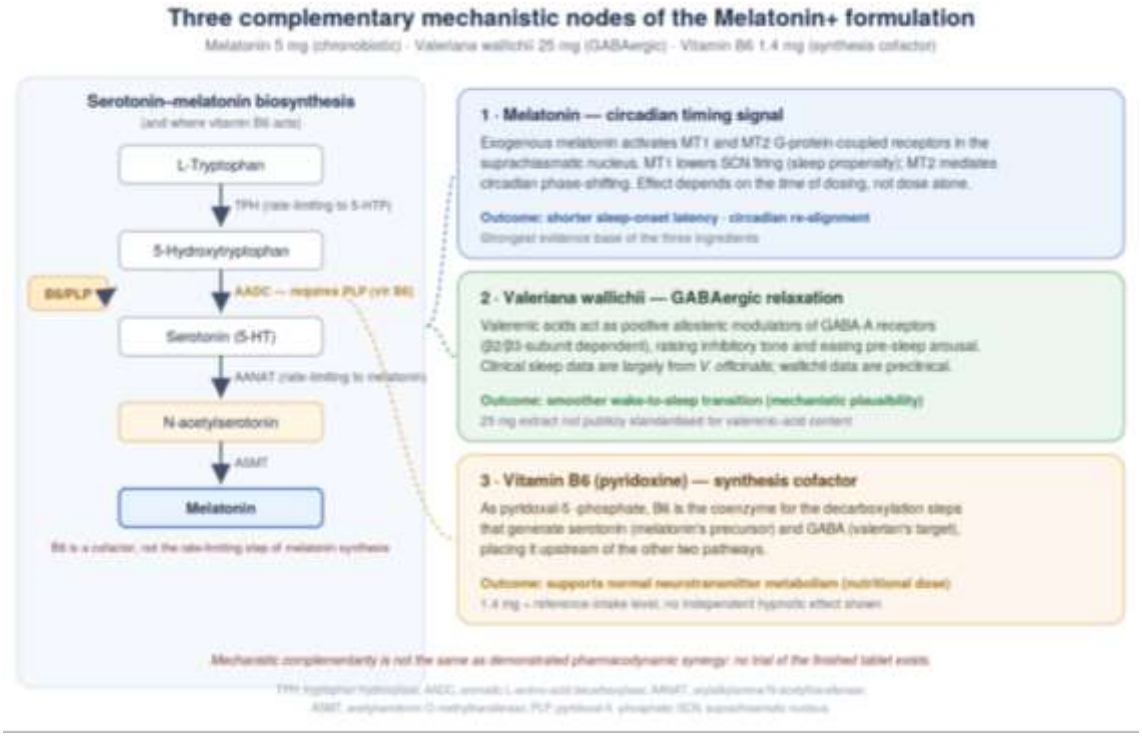

Figure 2. Three complementary mechanistic nodes of the Melatonin+ formulation. Left: the pineal serotonin–melatonin biosynthetic pathway (L-tryptophan → 5-hydroxytryptophan → serotonin → N-acetylserotonin → melatonin), showing the enzymes tryptophan hydroxylase (TPH), aromatic L-amino-acid decarboxylase (AADC), arylalkylamine N-acetyltransferase (AANAT, conventionally rate-limiting), and acetylserotonin O-methyltransferase (ASMT); vitamin B6, as pyridoxal-5′-phosphate (PLP), is highlighted as the AADC cofactor, underscoring that B6 is a cofactor rather than the rate-limiting step. Right: the three actives mapped onto complementary sleep-biology nodes — melatonin as a circadian timing signal at MT1/MT2 receptors, *Valeriana wallichii* valerenic acids as GABA-A positive allosteric modulators, and vitamin B6 as the upstream synthesis cofactor for serotonin and GABA. The figure emphasises that mechanistic complementarity is not the same as demonstrated pharmacodynamic synergy.

4.2 Absorption, metabolism, dose, and timing

Oral melatonin exhibits first-order absorption with peak plasma concentration approximately 40–60 minutes after intake, large inter-individual variability, and a plasma half-life of 30–60 minutes. It is hepatically metabolised primarily by CYP1A2 to 6-hydroxymelatonin, which is sulphated and excreted renally [14,31]. Bioavailability is variable, and food delays Tmax and may alter Cmax. The pharmacokinetic profile favours evening dosing approximately 30–60 minutes before a person's desired sleep-onset time, with magnitude, direction, and sign of any circadian effect depending on administration time relative to the individual's endogenous melatonin onset [3,5,34].

Dose–response is shallow but non-monotonic. EFSA concluded that intakes of 0.5 mg or more reduce sleep-onset latency [14]; Choi 2022 identified a small overall reduction in sleep-onset latency and a modest increase in total sleep time [18]; the Cruz-Sanabria 2024 dose–response meta-analysis suggested a near-plateau above approximately 4 mg/day, with diminishing returns and increasing next-day drowsiness risk above this threshold [15]. For circadian phase disorders, doses in the 0.5–5 mg range administered at biologically appropriate times are efficacious when combined with behavioural scheduling [3,20,34]. Figure 3 shows how the timing of a dose relative to dim-light melatonin onset shapes the response.

Figure 3. Why timing, not milligrams alone, governs the melatonin response. Schematic of the endogenous melatonin rhythm across a 24-hour cycle with the dim-light melatonin onset (DLMO) marked. Dosing in the early evening (before DLMO) advances the circadian clock and is useful for delayed sleep phase; dosing near bedtime produces a predominantly acute sleep-promoting effect; and late or mistimed dosing can cause daytime sleepiness or an unwanted phase shift. Boxed annotations note the dose–response peak near ~4 mg/day and the practical implication that a fixed 5 mg tablet is convenient for occasional sleep onset but often not optimal for circadian indications, which may require earlier and individually timed dosing.

5. *Valeriana wallichii*: botanical rationale and the limits of extrapolation

5.1 Species identity and proposed GABAergic activity

Valeriana wallichii contains valerenic acids, valepotriates (valtrate, isovaltrate), and volatile oils whose pharmacological footprint centres on GABA-A receptor modulation. Valerenic acid and its derivatives are partial allosteric modulators at the GABA-A receptor, with documented subunit specificity for β-containing subtypes [27,29]. Acute anxiolytic-like and sedative effects in rodents have been demonstrated for standardised valerian extracts and isolated valerenic acids [19,35]. The species is referred to in classical Ayurvedic texts (as "Tagar") and is widely used across South Asia for "nervous system" indications, including sleep disturbance [35].

Pharmacognostic caveats. *Valeriana wallichii* (Tagar, Indian/Himalayan valerian) and *Valeriana officinalis* are distinct species; their root chemistries vary by chemotype, geographic origin, harvest timing, drying conditions, and extraction solvent [35]. The bulk of published human sleep evidence is for *V. officinalis* at doses in the grams-of-root range or standardised-extract equivalents, with most systematic reviews and umbrella reviews flagging heterogeneity as the primary limiting factor [16,17]. The 25 mg *V. wallichii* extract dose in Melatonin+ therefore cannot be read across to the substantially higher *V. officinalis* doses or longer treatment durations in the clinical literature without disclosed extract ratio, solvent, marker-compound assay, and chromatographic fingerprint [35]. Combination products containing valerian alongside hops or passionflower have produced stronger subjective-sleep signals than valerian alone, suggesting that any future Melatonin+ iteration might benefit from an additional botanical, though this would also add formulation and claim-substantiation complexity [19,36].

5.2 Sleep evidence

Systematic reviews and meta-analyses consistently report small subjective improvements in sleep latency and quality for valerian, with effect sizes that fail to consistently reach clinical significance under rigorous

meta-analytic scrutiny [16,17,19]. Shinjyo 2020 concluded that valerian may have small subjective benefit on sleep measures, with most studies lacking sufficient methodological rigor to support strong conclusions [16]. The 2024 umbrella review by Valente et al. concluded that while valerian appears safe and is well tolerated, the evidence base is too heterogeneous to support a robust quantitative conclusion of efficacy [17]. A 2023 umbrella review of complementary and alternative therapies [36] similarly concluded that valerian holds promise but lacks definitive trial evidence at clinical-scale doses.

6. Vitamin B6: metabolic role without proven hypnotic activity

Vitamin B6 in its active form, pyridoxal-5′-phosphate, is a cofactor for aromatic L-amino acid decarboxylase, which converts L-DOPA to dopamine and 5-hydroxytryptophan to serotonin. Pyridoxine may therefore, in principle, support neurotransmitter synthesis relevant to mood and sleep regulation [30,37]. B6 is also a cofactor for the enzyme converting tryptophan into niacin and into kynurenine pathway metabolites, some of which are implicated in sleep–wake regulation [37]. Animal models demonstrate that maternal B6 deficiency alters hippocampal expression of GABAergic, serotonergic, and glutamatergic pathway genes in offspring [38].

Despite this mechanistic plausibility, pyridoxine has not been shown in controlled trials to exert an intrinsic hypnotic effect at nutritional doses [23,30]. The Lemoine 2019 prospective pilot study of melatonin + vitamin B6 + medicinal plants for mild-to-moderate insomnia reported a significant improvement in Pittsburgh Sleep Quality Index scores from baseline to week 4 (n = 49) and concluded that the combination was well tolerated — but this is a single-arm, open-label pilot, and the design does not permit causal attribution of the B6 effect [22]. Aspy et al. 2018 reported that pyridoxine (and B-complex) supplementation increased dream vividness and recall but did not alter objective sleep onset, duration, or awakenings [24]. The Melatonin+ tablet contains 1.4 mg pyridoxine, equivalent to approximately 70% of the US RDA — a nutritional cofactor dose, not a pharmacologically active dose. The ingredient's role in the formulation is therefore best characterised as supportive and plausible rather than directly sleep-promoting. Pyridoxine at very high chronic doses (>200 mg/day) can cause peripheral neuropathy, but the 1.4 mg dose in Melatonin+ is many orders of magnitude below this threshold [30,37].

7. Integrated mechanistic rationale

Melatonin+ combines three ingredients acting at three mechanistically distinct nodes:

1. A chronobiotic signal (5 mg melatonin) — addresses circadian alignment and MT1/MT2-mediated sleep-onset facilitation [28,31].
2. A GABAergic relaxation component (25 mg *V. wallichii* extract) — addresses anxiolytic / sedative GABA-A potentiation, useful when sleep-onset difficulty is anxiety-mediated [27,29,35].
3. A neurotransmitter-synthesis cofactor (1.4 mg pyridoxine) — supports serotonin and dopamine synthesis that plausibly supports mood-related aspects of sleep [30,37,38].

Mechanistic complementarity in a fixed-dose combination does not translate into pharmacodynamic synergy, which requires factorial active-comparator trial evidence; this is the central methodological gap for any multi-ingredient nutraceutical.

The empirical case for combination is therefore conditional: the components are individually defensible, but evidence that combining them in a single tablet produces a clinically meaningful advantage over either melatonin alone or over non-pharmacological intervention alone is absent. Only the Lemoine 2019 pilot study [22] provides adjacent combination data — and even that is open-label. This honest gap motivates the research priorities spelt out in §13.

8. Clinical evidence and potential applications

8.1 Sleep-onset difficulty and chronic insomnia

For sleep-onset insomnia in adults, meta-analytic evidence supports a small but statistically significant effect of melatonin on reducing sleep-onset latency (typically 7–12 minutes) and modestly increasing total

sleep time [15,18]. Choi 2022 reported that melatonin's effect on subjective sleep quality is small, while objective polysomnographic effects are inconsistent [18]. Systematic reviews of herbal medicines for insomnia report small subjective benefits for valerian preparations but considerable heterogeneity [16,17,36]. These findings indicate that no published evidence supports a clinically meaningful advantage of a melatonin + *V. wallichii* + pyridoxine combination over melatonin alone for chronic insomnia. The 2023 AASM behavioural and psychological treatments guideline reiterates CBT-I as first-line, with no nutraceutical combination recommended as monotherapy for chronic insomnia [7]. Table 2 summarises the strength of evidence by ingredient and indication.

Table 2: Strength of evidence by ingredient and indication

Indication	Ingredient	Evidence type	Strength	Key citations
Sleep-onset latency reduction	Melatonin	Multiple meta-analyses + EFSA opinion	Moderate-strong	[14,15,18]
Sleep-onset latency reduction	*V. wallichii*	Heterogeneous meta-analyses	Weak	[16,17,19,36]
Total sleep time increase	Melatonin	Meta-analyses	Weak-moderate	[15,18]
Circadian phase advance	Melatonin	RCT + CPG	Strong	[3,20,34]
Circadian phase advance	*V. wallichii* / pyridoxine	No RCT data	Absent	—
Jet-lag symptom reduction	Melatonin	Cochrane review	Moderate	[34,40]
Subjective sleep quality	Combination (Lemoine 2019 pilot)	Open-label single-arm	Weak (suggestive only)	[22]
Cognitive enhancement	Melatonin	Mechanistic plausibility, no RCT signal	Not substantiable	[31,44]
Anxiolysis	Valerenic acids	In vitro GABA-A + animal	Weak (extrapolated)	[27,29,35]

8.2 Delayed sleep–wake phase disorder

DSWPD is the condition for which melatonin has the strongest mechanistic and clinical support. Sletten et al. 2018 demonstrated in a double-blind randomised trial that evening melatonin (0.5 mg) combined with scheduled morning bright-light avoidance advances circadian phase and shortens sleep-onset latency in adolescents and young adults with DSWPD [20]. Standard practice and consensus guidance recommend low-dose evening melatonin (0.5–1 mg) administered approximately 4–5 hours before endogenous DLMO, with parallel morning bright-light exposure to consolidate the phase advance [3,5,34]. Mantle 2020 reviewed the use of supplemental melatonin in children with DSWPD and concluded that low-dose melatonin is well tolerated and pharmacologically appropriate in this population [39]. The Melatonin+ 5 mg dose is within the higher end of tested doses; for DSWPD specifically, a 0.5–1 mg dose administered earlier in the evening may be pharmacologically more rational than the 5 mg dose used in a general-purpose formulation.

8.3 Jet lag and shift work

For jet lag following eastward travel across five or more time zones, evening melatonin (0.5–5 mg) taken at destination bedtime reduces subjective jet-lag symptoms and accelerates realignment [34,40]. The Herxheimer & Petrie 2002 Cochrane review remains the canonical synthesis [40]. No major update has superseded the 2002 Cochrane synthesis, although the underlying primary RCT evidence base has expanded modestly. This is a relevant application for Melatonin+, where the traveller's combination of sleep-onset difficulty, circadian misalignment, and travel-related anxiety matches the formulation's mechanistic footprint.

For permanent night-shift workers, the evidence for melatonin as a chronobiotic is more equivocal: while melatonin is modestly useful in accelerating circadian adaptation when scheduling is fixed night after night, complete adaptation rarely occurs, and chronic melatonin use does not neutralise the cardiometabolic risks of shift work [34,41]. Melatonin+ is therefore a poor long-term solution for night-shift-related sleep complaints; scheduled sleep hygiene, light-exposure management, and short-term hypnotics (when indicated) are the evidence-supported interventions.

8.4 Cognition, memory, hormones, and wellbeing

Claims that melatonin improves cognitive performance, memory consolidation, mood, antioxidant defence, and immune function in healthy adults are mechanistically plausible but only weakly supported by controlled-trial evidence [31,42]. Aromatase inhibition by high-dose melatonin and its effect on reproductive hormones are documented in animal models but have not been demonstrated to produce clinically significant effects in adults at standard sleep doses [31]. "Melatonin as the next vitamin D" is an aspirational framing rather than an established equivalence, and broad antioxidant and longevity claims are not supported by the regulatory standard of substantiation for sleep-indication claims and should not be used as primary product communication [14,43,44]. Figure 4 provides a clinical decision flowchart for candidate selection.

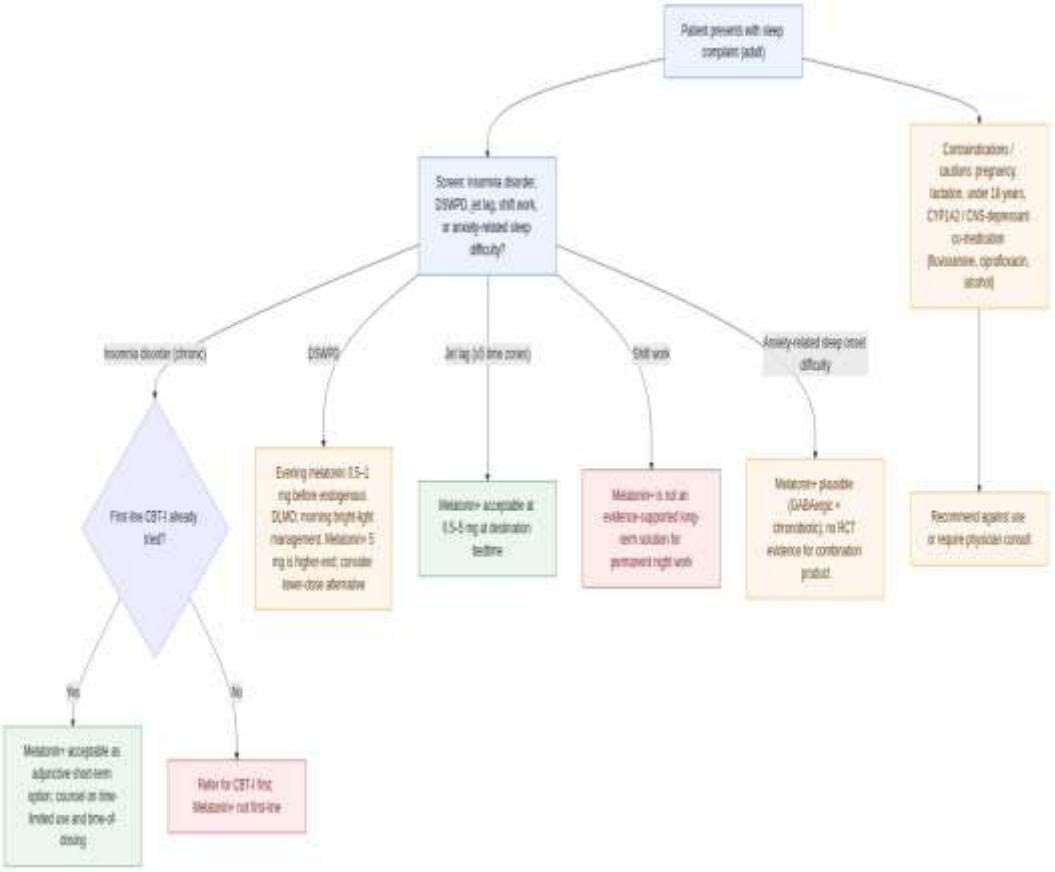

Figure 4. Clinical decision flowchart for candidate selection for Melatonin+. Based on evidence summarised in §§4–12 and the European Insomnia Guideline [8], the AASM chronic insomnia clinical practice guideline [7,9], the AASM intrinsic circadian rhythm sleep-wake disorders CPG [3], and the Sletten 2018 DSWPD-specific RCT [20].

9. Synergy: plausible network or demonstrated advantage?

The case for "synergy" between melatonin, valerian, and pyridoxine is mechanistically plausible but not empirically demonstrated. No factorial active-comparator trial has randomised Melatonin+ against melatonin alone, against valerian alone, and against placebo. The combination is not, however, equivalent

to demonstrated efficacy — this distinction must be transparently conveyed to consumers and reflected in any marketing communication [13,14,26,42,45]. Absence of synergy evidence does not mean the combination is ineffective; it means the available evidence base for the specific combination is too thin to support superlative product claims that suggest superiority. The closest analogue, Lemoine 2019 [22], reported positive results but was open-label, single-arm, and combined a different set of plant ingredients, so its evidentiary weight for Melatonin+ specifically is suggestive but not confirmatory. Table 3 compares Melatonin+ against guideline first-line therapies.

Table 3: Comparative profile against guideline first-line therapy

Attribute	Melatonin+	CBT-I	Benzodiazepine / Z-drug
Guideline-recommended first-line status	No (adjunct only)	Yes [7–9]	Limited, short-term only [6,8]
Strength of evidence	Indirect; no combination RCT	Strong	Moderate
Dependence liability	None at standard doses [42,45]	None	Significant; deprescribing guidance [10,11]
Next-day sedation risk	Small, predictable [21,42]	None	Significant [11,12]
Onset of benefit	Days to weeks	Weeks	Days
Long-term safety data	Limited	Strong	Limited; signal of harm in elderly [11,12]

10. Formulation integrity, regulation, and quality requirements

In India, the regulatory classification of Melatonin+ depends on the formulation's marketed positioning. Under the Food Safety and Standards Regulations, 2016, the FSSAI includes "melatonin 2–10 mg/day" and "*Valeriana wallichii*/Tagar" within permitted nutraceutical ingredient schedules [13]. FSSAI also caps permitted health-supplement and nutraceutical claims to a closed list of function claims (e.g., "supports sleep", "helps reduce sleep onset latency") rather than disease-treatment claims. The general regulatory framework for Indian nutraceuticals is reviewed by Bhupathiraju et al. [43]. Under Indian law, ASU formulations containing *Valeriana wallichii* may also sit under the AYUSH Ministry's pharmacopoeial framework (the *Ayurvedic Pharmacopoeia of India*), giving dual regulatory pathways depending on the marketed positioning [13,43]. Melatonin+ is positioned under the FSSAI schedule, not as an Ayurvedic medicine; as such, it cannot make classical Ayurvedic claims and must substantiate function claims by reference to the evidence set out in this review.

Beyond regulatory positioning, formulation-level quality requirements include:

1. Marker-compound assay of melatonin by HPLC-UV or HPLC-MS against USP / Ph. Eur. reference standards.
2. Marker-compound assay of total valerenic acids, valepotriates, and a chromatographic fingerprint for *Valeriana wallichii* extract [35].
3. Pyridoxine assay by HPLC.
4. Content-uniformity testing per pharmacopoeial methods.
5. Dissolution testing to demonstrate release of actives.
6. Microbial and heavy-metals testing per FSSAI Schedule V.
7. Absence-of-adulterant testing for serotonin or other monoamines that have been reported as contaminants of low-grade commercial melatonin products [46].

Independent analytical surveys of over-the-counter melatonin products in North America have documented variability of melatonin content ranging from less than 80% to more than 400% of label claim, and the presence of serotonin as a contaminant in a non-trivial fraction of products [46]. This is the single most

actionable quality-control failure mode for a combination product such as Melatonin+ and warrants explicit manufacturer commitment to batch-level HPLC-MS verification.

11. Safety, tolerability, and interactions

Across adult doses in the 0.5–10 mg range, short-term oral melatonin is generally well tolerated. Besag 2019 reported that the most common complaints across more than 60 trials were headache, dizziness, nausea, and drowsiness — but found no consistent evidence of serious adverse drug reactions [42]. Menczel Schrire 2021 reported that melatonin at doses up to 8 mg/day did not significantly increase adverse events relative to placebo [45]. The pharmacovigilance analysis of WHO-VigiBase by Ha et al. [26] reported common adverse event reports of **headache, sedation, dizziness, and nausea**, with disproportionate reporting concentrated in paediatric and overdose subsets; this is consistent with the controlled-trial adverse-event pattern. Tuft 2023 reviewed the specific risks of melatonin in older adults and concluded that long-term data remain limited and that risks of next-day sedation and falls warrant conservative dosing and counselling [25].

Drowsiness is foreseeable and is the principal adverse effect relevant to driving safety; users should be counselled not to drive or operate heavy machinery within 6–8 hours of melatonin intake [21,42,45].

For valerian, short-term use is well tolerated in younger adults, with the primary reported complaints being mild gastrointestinal upset and morning grogginess [16,17,42]; in older adults, however, valerian may compound next-day sedation when combined with other CNS-depressants and warrants caution [11,12]. For pyridoxine, dose-dependent peripheral neuropathy is reported only at chronic high doses (>200 mg/day) and is not a concern at the 1.4 mg dose in Melatonin+ [30,37].

Drug interactions are generally modest. Melatonin is metabolised by CYP1A2; concurrent strong CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin) may increase exposure and accentuate next-day drowsiness [14,31]. Valerian may potentiate CNS depression when combined with alcohol, benzodiazepines, or sedative antihistamines [11,21,42]. Pyridoxine may reduce the efficacy of levodopa when given without a peripheral decarboxylase inhibitor — an irrelevant consideration for Melatonin+ users but a counselling point in Parkinson's disease [37].

Pregnancy, lactation, and paediatric populations. Melatonin is not recommended as a sleep aid in pregnancy or in children under 18 years unless specifically indicated by a physician [13,14,42]; valerian is not recommended in pregnancy or lactation. The Melatonin+ label should therefore restrict use to non-pregnant, non-lactating adults and recommend physician consultation in paediatric use. Where paediatric DSWPD is the indication, specialist-led low-dose melatonin (0.5 mg) is more appropriate than Melatonin+ [39]. Table 4 summarises the safety and interaction profile.

Table 4: Safety and interaction profile

Risk	Ingredient(s)	Mitigation
Next-day sedation, driving impairment	Melatonin >3 mg, valerian	Counsel no driving within 6–8 h; do not combine with alcohol or BzRAs [21,42]
CYP1A2 interaction (fluvoxamine, ciprofloxacin)	Melatonin	Avoid or monitor
Cumulative CNS depression	Valerian	Avoid concurrent BzRAs, opioids, sedative antihistamines [11]
Falls in older adults	Melatonin + sedatives	Review indication; lowest effective dose; avoid in frail elderly [12,25]
Pregnancy/lactation	All three	Not recommended [39,42]
Paediatric use	All three	Specialist-led only; Melatonin+ not indicated [39]

12. Claim-substantiation matrix

The claim-substantiation matrix below maps each likely marketing claim category for Melatonin+ to (a) the ingredient it principally relies on, (b) the regulatory status of the claim type (FSSAI function claim;

EFSA-recognised claim; not-substantiable), and (c) the defensible wording pattern. Where existing reviews support a function, claims may be made; where evidence is absent or misleading, claims should be softened or removed.

Table 5: Quantitative synthesis of numeric claims used in this review

Claim	Quantitative figure	Source cited
Melatonin reduces sleep-onset latency (cause-and-effect) at this dose	≥ 0.5 mg	EFSA 2011 [14]
Dose–response plateau above this threshold	near 4 mg/day	Cruz-Sanabria 2024 [15]
Sleep-onset latency reduction (chronic insomnia, melatonin)	7–12 minutes	Choi 2022 [18]
DSWPD advance dose range tested in RCT	0.5 mg, 1 h before habitual bedtime, fixed advance of ~2 h	Sletten 2018 [20]
Jet-lag efficacy dose range	0.5–5 mg at destination bedtime	Herxheimer 2002 [40]
FSSAI permitted daily melatonin range	2–10 mg/day	FSSAI 2016 [13]
Valerian typical doses in published trials (extract, root equivalence)	300–900 mg root extract; 1–3 valerian combinations	Valente 2024 [17]; Shinjyo 2020 [16]
Pyridoxine peripheral neuropathy threshold (>chronic)	> 200 mg/day	Kennedy 2016 [30]; Calderón-Ospina 2020 [37]
Pyridoxine dose in Melatonin+	1.4 mg	Product specification
Pilot combination (melatonin + B6 + plants) PSQI improvement	Baseline 13.99 ± 3.71 → week 4: marked improvement	Lemoine 2019 [22]
Consumer melatonin content variability	−83% to +478% of label	Erland 2017 [46]

Table 6: Valerian-specific claim rows

Likely marketing claim	Substantiation status	Defensible wording
"Reduces anxiety-induced sleeplessness"	Small subjective benefit for sleep measures; anxiety measure not consistently demonstrated [16,17,19,36]	"May help reduce occasional sleep difficulty associated with daily stress."
"Promotes deep/restorative sleep"	Not directly substantiated; slow-wave sleep not differentially reported [16,18]	"Supports a normal sleep architecture" — preferable wording, or avoid.
"Improves sleep quality"	Subjective improvement supported for melatonin; not for the combination product [17,18,22]	"Helps support restful sleep".
"Improves next-day energy/mood"	Not substantiated for any ingredient alone or in combination [31,42]	Avoid.
"Non-addictive and non-habit-forming"	Reasonable broad claim; no published signal of dependence [17,42,45]	"Not associated with dependence at standard doses" — preferable wording.

13. Research priorities for Melatonin+

The following research priorities are derived directly from the evidence gaps identified in §§4–12.

1. **Product-specific RCT versus melatonin monotherapy and placebo.** A randomised, double-blind, three-arm trial of Melatonin+ against melatonin-only and placebo, in adults with DSM-5 insomnia disorder, with both subjective (sleep diary, ISI, PSQI) and objective (actigraphy, polysomnography) outcomes, is the single highest-priority study. The Lemoine 2019 pilot study [22] is the closest analogue and provides a feasible design template.

2. **Factorial trial to assess synergy rigorously.** A 2 × 2 factorial trial crossing melatonin (±) and *V. wallichii* (±) at the Melatonin+ doses, with a fixed pyridoxine content, would establish whether the combination produces an additive or interactive advantage.
3. **Product-to-product variability monitoring.** Periodic independent assay of marketed lots (e.g., quarterly HPLC-MS against reference standards for melatonin, valerenic acids, and pyridoxine) is a precondition for generalising any clinical conclusion to the retail product and for detecting drift introduced by raw-material substitution or process change [46].
4. **Standardisation of the *V. wallichii* extract.** Disclosure of extract ratio, extraction solvent, marker-compound assay (valerenic acids), and a chromatographic fingerprint is needed before any read-across from published *V. officinalis* evidence can be defensible [35,36].
5. **DSWPD-specific dose-response of a 5 mg melatonin dose.** Most DSWPD evidence is for lower doses (0.5–1 mg) administered earlier in the evening [3,20,34,39]; whether the 5 mg dose in Melatonin+ is optimal at this circadian-stage indication deserves direct testing.
6. **Long-term safety registry.** A pharmacovigilance-style registry of chronic Melatonin+ users, ideally combined with data linkage to spontaneous-report databases such as WHO-VigiBase [26], would substantially strengthen the long-term safety statement for chronic insomnia and post-marketing surveillance.

14. Conclusion

Melatonin+ is mechanistically coherent: it combines a chronobiotic dose of melatonin (within the FSSAI-permitted range and above the EFSA-recognised efficacy threshold), a GABAergic *Valeriana wallichii* extract whose direct clinical evidence in standardised comparative trials is modest but whose preclinical pharmacology is plausible, and a nutritional dose of pyridoxine whose presence is supportive but not directly sleep-promoting. The formulation has regulatory clarity, a defensible and restrained safety profile, and a substantial body of indirect evidence on its individual components. The principal deficiency of Melatonin+ as currently formulated is the absence of any combination-specific randomised trial evidence — a gap which no narrative review or rationale-based defence can fully bridge. Conservative, function-only claim language, periodic independent assay verification, and the research priorities outlined in §13 are the most defensible paths forward.

15. Strengths and limitations of Melatonin+ as positioned

Strengths

- Mechanistically coherent: each ingredient maps onto a distinct, complementary node of sleep physiology — a chronobiotic signal, a GABAergic relaxation component, and a neurotransmitter-synthesis cofactor.
- Regulatory dose alignment: the melatonin content (5 mg) lies within the FSSAI-permitted 2–10 mg range and exceeds the EFSA-recognised sleep-onset efficacy threshold of 0.5 mg [13,14].
- Convenient single-tablet presentation combining three ingredients.
- Low dependence liability relative to benzodiazepine-receptor agonists; the melatonin component is well tolerated in adults at standard doses over short-term use [42,45].
- Adjacent positive pilot evidence supports plausibility of melatonin + B6 + plant combinations [22].

Limitations

- No published randomised controlled trial of the finished three-ingredient product.
- The *V. wallichii* dose (25 mg root extract) is not standardised against the *V. officinalis* doses used in published sleep trials [16,17,35].
- The pyridoxine content (1.4 mg) is a nutritional cofactor dose, not a demonstrated sleep-promoter dose [24,30,37].

- The evidence base for chronic insomnia, shift work, and cognitive enhancement is at most modest for melatonin in isolation and cannot be claimed for the combination [15,18,44].
- Long-term, high-dose, paediatric, and pregnancy safety data remain incomplete [25,39,42].

16. Declarations

Funding and commissioning

This manuscript was prepared for and commissioned by Biotex Life Solutions. The funder had no role in the design, conduct, analysis, interpretation, or conclusions of the review.

Conflicts of interest

The authors declare no financial conflicts of interest beyond the commissioning relationship disclosed above.

Author contributions

All authors (L.R., S.C., S.P.) contributed to the conception and design of the review, the appraisal and interpretation of the literature, and the drafting and critical revision of the manuscript; all authors read and approved the final version for submission.

Data availability

All data referenced in this review are drawn from published sources cited in the manuscript. Product-level information was obtained from publicly available summary documents provided by the commissioning party.

Acknowledgements

The authors thank the Biotex Life Solutions product information team for providing the product specification sheet used in §3.

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