Summoning the Sandman: Mitigating the rebound effects of hypnotic therapy

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Abstract

Insomnia significantly impairs quality of life, productivity, and mental health. Pharmacotherapy, such as benzodiazepines and Z-drugs, are often used, though notable risks include tolerance, dependence, withdrawal, and rebound insomnia, especially when used beyond short-term recommendations. This review summarises the pharmacological mechanisms and potential adverse effects, and further discusses the deprescribing strategies to reduce the occurrence of rebound and withdrawal effects. These include gradual dose tapering, substitution with longer-acting agents, adjunct use of melatonin, and integration of cognitive behavioural therapy for insomnia to support withdrawal and relapse prevention. Non-pharmacological approaches should be prioritised wherever feasible, and pharmacotherapy should be used judiciously, with patient education and interprofessional support. Ultimately, a balanced, individualised management plan that emphasises resolving the underlying reasons for insomnia, and incorporating judiscious use of non-pharmacological and pharmacotherapeutic options, should be aimed for.

Keywords: benzodiazepines, deprescribing, hypnotics, insomnia, rebound insomnia, withdrawal, Z-drugs

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Introduction

Insomnia is one of the most commonly occurring sleep disorders, characterised by frequent and continuous difficulty in initiating and/or maintaining sleep[1,2] despite appropriate opportunities to do so, with subsequent detriments during the daytime.[1,2] Clinically significant insomnia has a global prevalence of approximately 16.2% in adults ≥ 20 years old, of which half of those affected are considered to live with severe insomnia.[1] South Africa is no different, with various studies highlighting the prevalence of insomnia.[3-5] Prevalence is typically higher in females, the elderly, those of lower socioeconomic status, those living with mental health disorders, or those affected by stressors such as food insecurity.[1,2,3,6] In their systematic review, Campbell et al.[7] highlighted the impact of chronic insomnia in the reduced quality of life of individuals, with an increased potential for the development of psychiatric or behavioural disorders, such as depression and anxiety, worsening of comorbidities, or reduction of cognitive function.[7] Furthermore, insomnia (or the treatment thereof) has been associated with injuries (whether related or unrelated to the workplace), mental health disorders and burnout.[3,5,7,8,9,10] Insomnia further contributes to economic detriments given workplace absenteeism and loss of productivity, however, the workplace itself also contributes to the prevalence of insomnia.[7,11,12] Within the health sector, for example, the impact on the productivity of the health and care workforce invariably affects the quality of service provided to patients, and reciprocally the quality of life of the practitioners. For example, in the health and care workforce, factors such as shift-work, the complex clinical environment and professional inter-working, human-disease interactions (e.g. COVID-19) and working requirements may drive irregularities and difficulties with sleep.[4,9,10,13,14] Various studies have noted insomnia among nurses, physicians, and specialists, which lowers sleep sufficiency, restoration and quality, incurs nap disturbances, and promotes burnout, anxiety, and chronic pain and disease.[4,9,10,12]

This review aims to briefly describe the current pharmacotherapeutic approaches available for insomnia treatment, however, focuses on the potential consequences of such treatments on dependence, withdrawal and rebound insomnia, and strategies to prevent and mitigate their occurrence.

A brief overview of insomnia treatment

Non-pharmacological approaches, such as promoting sleep hygiene and/or cognitive behavioural therapy for insomnia, are recommended, with the latter being considered a first-line approach.[2,15] However, implementing such strategies is difficult, and access to such services is limited.[2,15] Given the chronic nature of many insomnia cases, the focus should be the cure or modification of insomnia, otherwise it precipitates continuous and/or unhealthy practice related to its treatment.[6] However, due to the complexity of such non-pharmacological approaches as lifestyle modifications and the general limited adherence to it, pharmacotherapeutic options are often resorted to (Table I). In-depth South African recommendations for the pharmacotherapeutic management of insomnia are summarised by Lipinska,[16] Marais and Osuch,[17] and Ngomana et al.,[18] however a brief mechanistic summarisation is provided below to facilitate broader discussion of relevant adverse effects of key treatments.[16-18]

- Barbiturates function as central nervous system depressants by positively modulating the binding of γ-aminobutyric acid

(GABA) to the $GABA_A$ receptor and extending chloride channel opening duration.[19,20] Given the prolonged chloride ion influx into neurons, widespread neuronal inhibition occurs due to hyperpolarisation and sedation is promoted.[19,20] Barbiturates positively modulate GABA binding at a site separate from the benzodiazepine-binding site.[19,20]

- Benzodiazepines depress central nervous system function due to high affinity binding to the benzodiazepine-binding site on the $GABA_A$ receptor, which promotes chloride channel opening and chloride ion influx in a similar way to barbiturates.[18] Sedative effects are associated with the α_1 subunit, while anxiolytic effects are mediated by α_2, α_3, and α_5 subunits.[20,21]
- The non-benzodiazepine $GABA_A$ receptor agonists, also known as Z-drugs, selectively bind to the α_1 subunit of the $GABA_A$ receptor to enhance inhibitory neurotransmission and promote sedation with little anxiolytic or muscle-relaxant activity.[20,21]
- Melatonin receptor (MT) agonists, including melatonin and ramelteon, selectively stimulate MT_1 and MT_2 receptors in the suprachiasmatic nucleus, subsequently aligning circadian rhythms and facilitating physiological sleep onset without direct GABAergic inhibition.[19,20]
- Antihistamines induce sleep by antagonising central histamine receptor-1, inhibiting histaminergic neurotransmission from the tuberomammillary nucleus which is involved with wakefulness.[20]
- Although not primarily designated as hypnotics, selective serotonin reuptake inhibitors (SSRIs) may promote circadian stabilisation due to increased serotonergic activity (although initial worsening of sleep-onset latency or induction of vivid dreams may occur).[17] The long-term effects on sleeping patterns are typically neutral or slightly restorative when mood symptoms are managed, possibly due to emotional regulation of underlying contributing factors.[22]

Despite their global recognition as significant advances in insomnia treatment, dual orexin receptor antagonists and melatonergic drugs (such as ramelteon), are currently unavailable in South Africa likely due to broader economic and regulatory constraints and market authorisation.[17,18] This regulatory gap underscores a disparity between global therapeutic innovation and local treatment accessibility, especially regarding the shift towards non-GABAergic hypnotic alternatives.[2] Consequently, conventional medicines (Table I) with proven efficacy but well-documented safety issues remain the predominant form of pharmaceutical treatment for insomnia in South Africa.

Current guidelines advise against the use of barbiturates due to their non-selective cortical suppression, which raises considerable cognitive and safety issues in comparison to safer alternatives, such as benzodiazepines, Z-drugs, and non-GABAergic options.[17] Insomnia treatment, particularly with benzodiazepines and Z-drugs, are currently recommended to not exceed a maximum of two to four weeks, and requires gradual tapering off with parallel reevaluation of the clinical profile.[6,17,22,23] Similarly, antihistamines are discouraged for routine or prolonged use, and are advised for short-term or situational insomnia when non-pharmacological approaches fail.[18] Should symptomatic treatment be the only option, long-term pharmacotherapeutic approaches should be carefully investigated.[6] Recommendations have been made that use of hypnotic medication requires personalised consideration of each individual's unique circumstances and their benefit-risk ratio.[24] However, as summarised by Mcgee et al.,[8] prescription of such hypnotics have increased over time, presenting a concerning view of the potential inappropriate use as opposed to non-pharmacological strategies, or an increased long-term use.[8]

The double-edged sword to pharmacothepareutic approaches to insomnia

As with all pharmacotherapy, adverse effects are important to consider when using medication for a disease, but also to inform associated considerations (such as the length of treatment and benefit-to-risk ratio). Pharmacotherapy for insomnia, as drugs affecting the central nervous system, have common and unique side-effects of concern (Table 1), though for relevance of the discussion, focus will be on tolerance, dependence and rebound insomnia of certain drug classes. Tolerance, dependence with associated withdrawal symptoms, and rebound insomnia have been linked to barbiturates, benzodiazepines and Z-drugs.[7] Individuals may relapse into use of hypnotics for various reasons, such as living with chronic insomnia, having associated poor health outcomes, and present with high levels of dependency.[2,19,20] The latter is likely given iatrogenic drug dependence, a physiological reliance on medication after use.[2]

As mentioned previously, barbiturates are generally not preferred given risks involved, including a narrow therapeutic index and a high potential for fatal overdose caused by severe respiratory depression,[18,22] which often positions benzodiazepines and Z-drugs as more appropriate alternatives.[21] Campbell et al.[7] and Del Rio Verduzco et al.[20] highlight several central nervous system adverse effects, while Mcgee et al.[8] further describes their increased potential to promote falls and fractures, and associations with dementia and mortality.[8] According to Baldwin et al., long-term benzodiazepine and Z-drug exposure causes tolerance and withdrawal symptoms, even at recommended therapeutic doses.[21] Tolerance to benzodiazepines is thought to occur due to reduced ability of benzodiazepines to bind to the benzodiazepine-binding site on the $GABA_A$-receptor, modifications to the $GABA_A$-receptor expression, and physiological compensation from glutaminergic, monoaminergic and neurosteroidal factors.[21] Dependence and habit formation is subject to mechanisms not fully understood, but may include increased dopaminergic neuron conduction in the ventral tegmental area downstream to the $GABA_A$-receptor's α1-subunit, with subsequent drug reinforcement.[21] Mechanisms underlying withdrawal symptoms, are similarly not fully determined, but are likely due to benzodiazepine binding site downregulation, increased calcium flux, and serotonergic activity.[21] Withdrawal symptoms from benzodiazepines, for example, can be quite varied and difficult to separate from the underlying conditions' clinical profiles, however, may present as psychological (e.g. anxiety; nervousness; restlessness),

physical (e.g. sweating; cardiovascular activation), and health complications (e.g. sensitivity to stimuli; altered cognitive state).[21] Withdrawal symptoms may persist for 5 to 28 days, however, some occurrences beyond that may occur.[8]

Although there is a concern regarding long-term safety of hypnotic use, it is more associated with benzodiazepines than Z-drugs, with the latter being considered a safer option for such approaches.[6,7,24] However, similar levels of dependence have been

Table I: Pharmacotherapeutic approaches in South Africa for insomnia treatment[36]

Classification	Active ingredient	Examples	Formulation	Dose	Administration	Drug class adverse effects
Antihistamines	Diphenhydramine	Betasleep; Sleepeze-PM	Tablets; Capsules	25 mg, 50 mg	1 to 2 doses at bedtime	Antimuscarinic side-effects (dry mouth, confusion, constipation, and residual daytime sedation),[17,20] paradoxical excitement[20]
	Doxylamine	Nomowake; Somnil	Tablets	25 mg	1 to 2 doses at bedtime	
Barbiturates	Phenobarbitone	Adco Phenobarbitone; Sedabarb	Elixir; Tablets	Elixer (phenobarbitone [16 mg], vitamin B1 [3 mg] and B2 [1 mg], B6 [0.25 mg], and nicotine [10 mg/5mL] Tablet (30 mg)	Elixer: two to three times daily between 2.5 to 5 mL, 5 to 10 mL and 10 mL for infants, children and adults, respectively Tablets: 1 dose 1 hour before bedtime	Tolerance, dependence, withdrawal, hepatic enzyme induction[16]
Benzodiazepines	Loprazolam	Dormonoct	Tablets	2 mg	Lowest recommended dose immediately before bedtime	Dizziness, daytime sedation, reduced motor activity, falls, headaches,[20] rebound insomnia,[7,20] psychological dependence, anxiety[7]
	Midazolam	Dormicum	Tablets	7.5 mg, 15 mg	Lowest recommended dose immediately before bedtime	
	Temazepam	Normison	Capsules	10 mg, 20 mg	Dose before bed	
	Triazolam	Halcion	Tablets	0.125 mg, 0.25 mg	Lowest recommended dose immediately before bedtime	
Melatonin receptor agonists	Melatonin	Cadiatev; Melnoc XR 2 MG	Tablets	2 mg	Once daily 1 to 2 hour before bedtime after food	Nausea, headaches and dizziness[20]
Non-benzodiazepine hypnotics (Z-drugs)	Zolpidem	Adco -Zolpidem Hemitartrate; Ivedal; Medploz; Nyx; Silnox; Zizz 10; Zolnorem; Zolnoxs; Zolpihexal	Tablets	5 mg, 10 mg, 12.5 mg	Dose immediately before bed; half of dose for elderly or those with renal/hepatic concerns	Headaches, dizziness, confusion, falls, unpleasant taste,[20] memory and balance impairment, night-time behavioural shifts (e.g. sleep-eating), suicide attempts, dependence[7]
	Zopiclone	Adco-Zopimed; Alchera; Austell-Zopiclone; Bio Zopiclone; Sandoz Zopiclone; Zopiclone Unicorn; Zopisleep; Zopivane	Tablets	7.5 mg	Dose shortly before bed; half of dose for elderly or those with renal/hepatic concerns	
Selective serotonin reuptake inhibitors	Citalopram	Austell-Citalopram; Bio Citalopram; Citalopram 20 Oethmaan	Tablets	10 mg, 20 mg, 40 mg	Low dose administration[17]	Vivid dreams, headaches, dizziness, somnolence,[20] day-time fatigue, restlessness, anxiety[17,18]
	Escitalopram	Accord Escitalopram; Escitalopram Unicorn; Escitalopram-Winthrop	Tablets	5 mg, 10 mg, 20 mg		
	Fluoxetine	Fluoxetine Biotech 20; Fluoxetine Oethman; Zydus Fluoxetine	Capsules	20 mg		
	Paroxetine	Adco-Paroxetine; Paroxetine Unicorn	Tablets	20 mg		
	Sertraline	Austell-Sertraline; Dyna Sertraline	Tablets	50 mg, 100 mg		

reported between benzodiazepines and Z-drugs.[19] Curado et al.[19] reported that 77% and 69% of benzodiazepine and Z-drug users exceeded the ICD-10 criteria for depedence, however, Roehrs et al.[25] noted that discontinuing Z-drugs in participants with objective hyperarousal and impaired sleep efficiency was more difficult in comparison to benzodiazepines.[25] As such, receptor-specific variations in withdrawal potential exist.[25]

Prevention and management of rebound insomnia

Recommendations to support the clinical prevention and management of hypnotic dependence and withdrawal include non-pharmacotherapeutic and pharmacotherapeutic factors.[21] Patient education is important to ensure that any strategy followed is understood, adhered to, and supported by evidence-based practice, which draws from interprofessional modalities and involvement of the patient in the discussion thereof.[23,26,27,28] As good practice, cognitive behavioural therapy for insomnia should be considered for all strategies.[21] Underlying triggers of the original insomnia should be addressed through psychological and/or pharmacotherapeutic interventions, with additional support to prevent potential relapse, for example, when linked to anxiety or depression.[21] For rationale prescribing, judicious use of medication is needed; for example, benzodiazepines should be avoided in lieu of alternative therapies or short-term therapy, including appropriate patient consultation, preparation and support for withdrawal strategies upon cessation.[21] Abrupt cessation of treatment with benzodiazepines or Z-drugs is likely to incur rebound insomnia and withdrawal symptoms.[15] As such, gradual tapering is recommended to reduce the occurrence of such withdrawal effect, often with cognitive behavioural therapy for insomnia or drug substitution.[15] For deprescribing, polypharmacy should be consolidated to monotherapy, with sensible and appropriate gradual reduction of the doses considered alongside the potential need for inpatient admission where necessary.[21] Aoki et al.[29] demonstrated that cognitive behavioural therapy for insomnia improved the effectiveness of benzodiazepine tapering, which shortens sleep-onset latency, reduces nocturnal awakenings and improves sleep efficiency.[29] Similarly, systematic review and meta-analysis and guidelines support such combined efforts to reduce rebound and withdrawal effects.[30,31]

Belanger et al.[32] proposed a gradual weekly or biweekly reduction of 25% of the initial dose, with the introduction of drug-free nights at the minimum dose.[32] These nights can be selected to coincide with days that are less likely to require support from medication, such as less stressful times, or on pre-selected nights so that the behavioural link to medication use is broken.[32] Similarly, a step-wise benzodiazepine deprescription of 10% to 25% every one to two weeks can be done to prevent rebound insomnia, occasionally substituting short-acting agents (e.g. triazolam) with long-acting agents (e.g. diazepam) to facilitate smoother withdrawal trajectories.[8,21] Similar adjunct treatment with melatonin has yielded mixed results in supporting tapering strategies and reducing rebound and withdrawal effects. A systematic review by Wright et al.[33] highlighted differential results in melatonin's ability to support benzodiazepine tapering, with no significant improvement was seen overall.[33] However, more recent systematic reviews by Morera-Fumero et al.[34] and Das et al.[35] presented more supportive data, suggesting melatonin's ability to reduce benzodiazepine, Z-drug and other hypnotics' tapering and associated withdrawal effects. Sustained release formulations of melatonin appear to offer a greater benefit in this strategy.[15]

Alternative therapies have been discussed to support movement away from more traditional hypnotics, however, data concerning their efficacy and safety are insufficient. Valerian, chamomile, and L-tryptophan have been investigated for insomnia regulation, which allows for mild GABAergic or serotonergic regulation.[20] These supplements are widely used, however, evidence shows little or no improvement in sleep quality.[2,18] Despite mild side-effects (headache, dizziness, and gastrointestinal pain), the medication is well tolerated.[22] Complementary sleep aids may thus be used as adjuncts in a multimodal approach, but ultimately insufficient data debilitates recommendations for their use as primary insomnia therapies.

Conclusion

Although pharmacotherapeutic approaches to insomnia management are commonplace, it does come paired with several complications, such as dependence and rebound insomnia. Given the prevalence of insomnia, as well as the increased frequency of pharmacotherapy prescriptions, pharmacotherapy should be considered holistically between health practitioners and patients. Underlying reasons for the occurrence of insomnia need to be investigated, which include a variety of factors, such as personal (e.g. mental health and stress) and work-related (e.g. environment and shifts), with sufficient support to mitigate their precipitation of insomnia, effect on sleep quality, and downstream implications. Non-pharmacological approaches, such as cognitive behavioural therapy for insomnia, should be referred to for treatment where possible, and where not feasible, care should be taken to mitigate potential adverse effects and development of dependence. Short-term pharmacotherapy should be aimed for, which generally involves use of benzodiazepines and Z-drugs, though abrupt cessation should be avoided, given risks of withdrawal and rebound insomnia effects. Supportive deprescribing and psychotherapeutic management strategies should be used to reduce the potential for rebound and withdrawal effects, which include gradual tapering, supportive cognitive behavioural therapy for insomnia, and drug substitution or adjunct use. However, given the propensity for poor adherence to and uptake of lifestyle changes, such strategies should actively involve the patient to ensure thorough education and consultation, thereby supporting a healthier sleep cycle.

Conflict of interest

The authors have no conflict of interest to disclose.

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