The role of benzodiazepines in common conditions: a narrative review focusing on lormetazepam

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This review aimed to examine the place of benzodiazepines, specifically lormetazepam, in the treatment of insomnia, including during pregnancy or in patients with psychodermatoses. PubMed was searched for the term "lormetazepam" in association with MeSH terms encompassing anxiety, insomnia/sleep disorders, pregnancy/gestation, and psychodermatoses/skin disorders. English-language articles up to 31 July 2022 were identified. Ad hoc searches for relevant literature were performed at later stages of review development. Multiple randomized, placebo-controlled studies have demonstrated that lormetazepam dose-dependently increases total sleep time, decreases wakefulness over a dosing range of 0.5–2.0 mg, and improves subjective assessments of sleep quality. Lormetazepam is as effective as other benzodiazepines in improving sleep duration and quality, but is better tolerated than the long-acting agents with minimal next-day effects. Benzodiazepines can be used as short-term monotherapy at the lowest effective dose during the second or third trimesters of pregnancy; lormetazepam is also a reasonable choice due to its limited transplacental passage. Insomnia associated with skin disorders or pregnancy can be managed by effective symptom control (especially itching), sleep hygiene, treatment of anxiety/depression, and a short course of hypnotics. *Int Clin Psychopharmacol* 39: 139–147 Copyright © 2024 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Patients often have multiple reasons for consulting a medical practitioner, either because they have more than one condition or because a single condition is impacting their physical and mental well-being in several different ways (Thorsen *et al*., 2001). For example, anxiety and insomnia are both common conditions (Morin *et al*., 2015; Finley *et al*., 2018), which may exist on their own or as part of a complex nexus of symptoms and comorbidities in patients with psychiatric diagnoses and/other underlying conditions, such as chronic illness or disability (Valderas *et al*., 2009).

Insomnia symptoms are highly prevalent in the general population, affecting 30–35% of all people. However, most sleep disturbances last for only a few days or weeks (Morin *et al*., 2015). When sleep disturbances persist and affect daytime functioning, they can be classified as an insomnia disorder (Morin *et al*., 2015). Most patients with insomnia have an underlying condition that affects their ability to sleep; primary insomnia is present in only about 12% of patients presenting to the general practitioner with insomnia (Arroll *et al*., 2012). At least half have neuropsychiatric conditions and approximately 40% have general medical conditions (Arroll *et al*., 2012). While commonalities in the neurobiology and treatment approaches to insomnia and psychiatric conditions have been well described and discussed in the scientific literature, relatively less attention has been paid to the treatment of insomnia in patients with general medical conditions.

Benzodiazepines have been in clinical use since the 1960s and have a valuable place in the treatment of insomnia and anxiety, but can be associated with negative effects, including the potential for dependency (Rosenbaum, 2005; Sim *et al*., 2007). On the other hand, benzodiazepines are highly effective hypnotics and anxiolytics, with similar or greater efficacy in anxiety disorders and insomnia compared with newer drug classes (Rosenbaum, 2005; Dubovsky and Marshall, 2022). Multiple benzodiazepines are available, but they differ in their pharmacology and therefore their onset and duration of effect, dosing and administration, and side effect profiles. Therefore, rational prescribing of benzodiazepines by physicians requires careful and holistic consideration of the patient and their situation, as well as the characteristics of the drug (Sim *et al*., 2007; Dubovsky and Marshall, 2022).

Lormetazepam is a widely used benzodiazepine that has been in clinical use since 1980 and is available as a tablet,

oral solution, and intravenous formulation (Ancolio *et al.*, 2004; Horowski, 2020). Lormetazepam has a receptor-binding profile that distinguishes it pharmacologically from other benzodiazepines (Horowski, 2020).

This narrative review investigates the role of benzodiazepines in patients with insomnia and anxiety associated with common medical conditions, specifically pregnancy and dermatoses, with a particular focus on lormetazepam.

Methods

PubMed was searched using the term "lormetazepam" [Title/Abstract] in association with MeSH terms encompassing anxiety, insomnia/sleep disorders, pregnancy/gestation, psychodermatoses/skin disorders. All English-language articles were identified up to 31 July 2022, with no initial date limit set. Other content for this article was developed based on ad hoc searches for relevant literature.

Benzodiazepine pharmacology

Benzodiazepines modulate the activity of gamma-aminobutyric acid (GABA) at $GABA_A$ receptors (Baldwin *et al.*, 2013; Griffin *et al.*, 2013). $GABA_A$ receptors are widely distributed in the human brain, especially the cortex, hippocampus, thalamus, basal ganglia, and cerebellum (Young and Chu, 1990). The $GABA_A$ receptor is comprised of five transmembrane glycoprotein subunits that surround a chloride channel (Baldwin *et al.*, 2013; Griffin *et al.*, 2013). Benzodiazepine agents allosterically increase the receptor's affinity for GABA, thereby increasing the probability of the chloride channel opening and facilitating the subsequent passage of chloride ions through the neuronal membrane (Baldwin *et al.*, 2013; Griffin *et al.*, 2013). The benzodiazepine binding site on $GABA_A$ receptors is distinct from the GABA binding site, and unlike barbiturates, benzodiazepines do not mimic the effects of GABA or directly open chloride channels (Baldwin *et al.*, 2013). Because GABA is an inhibitory neurotransmitter, benzodiazepines reduce neuronal transmission throughout the central nervous system, producing anxiolytic, sedative, and amnesic effects (Griffin *et al.*, 2013).

Table 1 Common benzodiazepines categorized by half-life and duration of action (including metabolites) (Vermeeren, 2004; Griffin *et al.*, 2013; Dubovsky and Marshall, 2022)

Long-acting agents	Intermediate-acting agents	Short-acting agents
Chlordiazepoxide	Clonazepam	Alprazolam
Clobazam	Clorazepate	Bromazepam
Clotiazepam	Loprazolam	Brotizolam
Cloxazolam	Lorazepam	Estazolam
Diazepam	Nitrazepam	Flunitrazepam
Ethyl loflazepate	Oxazepam	Lormetazepam
Flurazepam	Remimazolam	Midazolam
Ketazolam	Temazepam	Triazolam
Nordiazepam	Tetrazepam	
Quazepam		
Prazepam		

The large number of agents in the benzodiazepine drug class may be categorized based on their structure, pharmacokinetic properties, or potency; a common distinction is between long- and short-/intermediate-acting agents (Table 1) (Vermeeren, 2004; Griffin *et al.*, 2013). However, all benzodiazepines have a common mechanism of action and a similar profile of clinical effects (Baldwin *et al.*, 2013).

Common adverse effects of benzodiazepines include cognitive and psychomotor disorders, such as drowsiness, fatigue, mental slowness, and anterograde amnesia. Prolonged use of benzodiazepines is associated with a risk of tolerance and dependence (Baldwin *et al.*, 2013; Griffin *et al.*, 2013; Dubovsky and Marshall, 2022). Therefore, responsible prescribing of a benzodiazepine requires that the physician carefully weighs the risks and benefits of treatment, investigates and trials alternative interventions, and limits the duration of benzodiazepine use to a maximum of 1 month (Baldwin *et al.*, 2013; Dubovsky and Marshall, 2022). Moreover, as recently suggested, it could be helpful to prescribe GABA enhancers intermittently (Davies *et al.*, 2022). In this way, the risk of developing dependence may be reduced with respect to chronic use.

Use of benzodiazepines to treat insomnia

Across the various definitions of clinical insomnia, all include the presence of poor sleep onset, quality, or maintenance that is present on ≥3 days/week for ≥3 months and impairs daytime activities (American Psychiatric Association, 2013; Sateia, 2014; Riemann *et al.*, 2017). Depending on the definition, the reported prevalence of insomnia is between 4% and 22%; this condition can often be very persistent, with a reported median duration of 3 years (Morin *et al.*, 2015).

The prevalence of insomnia is typically higher in women than in men, in older individuals and in people with physical or psychiatric comorbidities (Morin *et al.*, 2015; Riemann *et al.*, 2017; Hollsten *et al.*, 2020). Older patients and those with concomitant comorbidities require particularly careful assessment when determining the optimal treatment as the effects of age and comorbidity on drug pharmacokinetics can impact the risk–benefit profile (Scaglione *et al.*, 2018).

As well as affecting a person's ability to perform their usual daily activities, insomnia increases the risk of cardiovascular disease (e.g. hypertension, myocardial infarction, or chronic heart failure), metabolic disease (e.g. obesity or type 2 diabetes), psychiatric conditions (e.g. depression or suicidal ideation), neurological disorders (e.g. cognitive impairment or cortical atrophy in older people) and work-related or motor vehicle accidents (Riemann *et al.*, 2017).

The European Sleep Research Society (ESRS) guidelines recommend initiating insomnia treatment with

non-pharmacological therapies, principally cognitive behavioral therapy (CBT). Initiation of pharmacological treatment is recommended only once CBT becomes ineffective or is unavailable (Riemann *et al.*, 2017). A short course (≤4 weeks) of benzodiazepines or benzodiazepine receptor agonists is recommended as first-line pharmacotherapy; long-acting benzodiazepines should be avoided to reduce the risk of next-day sedation (Riemann *et al.*, 2017). Meta-analyses have demonstrated that benzodiazepines significantly improve a range of sleep parameters in patients with insomnia, including shortening sleep latency, improving sleep efficiency, increasing total sleep duration, and reducing wake time after sleep onset (Holbrook *et al.*, 2000; Wang *et al.*, 2021).

Older patients may be more vulnerable to the positive and negative effects of benzodiazepines compared with younger patients, because of higher plasma levels (as a result of lower lean body mass, slower metabolism, and reduced clearance) and changes in receptor function/signaling (Dubovsky and Marshall, 2022). To reduce the risk of drug accumulation, elderly patients may benefit from short- or intermediate-acting benzodiazepines and from starting with a lower dose (Dubovsky and Marshall, 2022). Caution is particularly recommended in patients with cognitive impairment, as benzodiazepines can increase the risk of delirium, falls, and accidents in this group (Dyer *et al.*, 2020).

Focus on lormetazepam

Lormetazepam, a benzodiazepine of the 3-droxy-benzo-1,4 diazepine class, has been available in Europe since the 1980s (Horowski, 2020). Lormetazepam is rapidly absorbed (time to maximum concentration is 2 h) (Dorow *et al.*, 1982), with a half-life of 11 h and no active metabolites (Electronic Medicines Compendium, 2021); therefore, this agent is considered to be a short- or intermediate-acting benzodiazepine (Griffin *et al.*, 2013; Horowski, 2020; Dubovsky and Marshall, 2022).

Our literature search identified 88 English-language papers on PubMed focused on lormetazepam, of which 44 were clinical studies. We excluded eight studies, one of which assessed a single intravenous dose of lormetazepam in volunteers and seven that assessed a single oral lormetazepam dose for preoperative anxiety. Of the remaining 36 studies, 14 were in healthy volunteers, 17 were in patients with insomnia, and five were in patients with anxiety, depression, or a mix of conditions.

In randomized, placebo-controlled, crossover studies among healthy volunteers, lormetazepam significantly and dose-dependently increased total sleep time and decreased wakefulness and the duration of drowsy sleep over the 0.5–2.0 mg dose range (Nicholson and Stone, 1982; Cluydts *et al.*, 1995), as well as improving subjective assessments of sleep quality (Subhan and Hindmarch, 1983). Lormetazepam was also shown to induce sleep more quickly than zopiclone (Jobert *et al.*, 1993), but had similar effects on sleep architecture to zopiclone (Jobert *et al.*, 1992) and zolpidem (Cluydts *et al.*, 1995). Compared with another short-acting benzodiazepine flunitrazepam, lormetazepam increased the duration of stage 3 sleep, reduced rapid eye movement (REM) latency and had significantly less marked effects on next-day electroencephalography (Timsit-Berthier *et al.*, 1985). In healthy volunteers, lormetazepam did not have any marked effects on REM patterns, in contrast with triazolam, which suppressed early REM activity resulting in a sub-normal proportion of REM sleep during the night (Kubicki *et al.*, 1987).

In randomized, double-blind, placebo-controlled studies in adults with insomnia, lormetazepam as a tablet or oral solution was associated with significantly improved sleep parameters, measured by subjective and objective parameters (Table 2) (Heidrich *et al.*, 1981; Kales *et al.*, 1982; Meco *et al.*, 1985). In the largest of these studies (n = 62), lormetazepam 2 mg reduced sleep onset latency, improved sleep quality, increased sleep duration, and decreased the number of nighttime awakenings over 14 days of treatment compared with placebo (Heidrich *et al.*, 1981). Two studies assessed how patients felt the next day and reported that patients in the lormetazepam group felt more refreshed during the daytime (Heidrich *et al.*, 1981; Meco *et al.*, 1985). Another study reported that patients were better able to concentrate at work after lormetazepam than after placebo (Heidrich *et al.*, 1981). In the largest placebo-controlled trial, lormetazepam was not associated with any hangover effects the next day or with rebound insomnia after discontinuation (Heidrich *et al.*, 1981). However, in a dose-ranging comparison with placebo, withdrawal of an oral solution of lormetazepam 2 mg was associated with longer sleep latency and wake time after sleep and a shorter percentage of sleep time (Kales *et al.*, 1982). A study comparing the effects of tablets and oral solutions of lormetazepam for 14 days in patients with insomnia found no difference in subjective assessment of sleep parameters (latency, duration, and quality) or vigilance on waking between the formulations (Ancolio *et al.*, 2004). Patients in this study were able to increase or decrease the dose of lormetazepam between days 2 and 14 based on their response; tablets were available in a dose range of 0.5 to 2 mg and the oral solution was available in 0.25 to 2 mg (Ancolio *et al.*, 2004). Mean, maximal, and cumulative doses of lormetazepam were significantly lower with the solution than the tablets (Ancolio *et al.*, 2004).

Clinical studies using objective (sleep clinic) and subjective (questionnaire) parameters indicate that lormetazepam is effective and safe in older patients (≥55 years) with insomnia, even at doses as low as 0.5 mg (Jovanović *et al.*, 1980; Vogel, 1984; Overstall and Oldman, 1987; Richards and Vallé-Jones, 1988; Jobert *et al.*, 1995; De Vanna *et al.*, 2007). Where reported, lormetazepam was

well tolerated in these studies with a low incidence of adverse events at doses of 0.5 or 1 mg (Jovanović *et al.*, 1980; Richards and Vallé-Jones, 1988; De Vanna *et al.*, 2007). One double-blind, comparative study in frail elderly inpatients with insomnia ($n = 62$) reported similar effects on sleep and comparable tolerability with lormetazepam 1 mg and chlormethiazole (Overstall and Oldman, 1987). Lormetazepam does not undergo oxidative metabolism in the liver, and therefore, may be safer in older patients than other benzodiazepines that require oxidation (e.g. triazolam, alprazolam, or estazolam) (Vermeeren, 2004). Based on dose-ranging studies, the optimal starting dose of lormetazepam in elderly patients is 0.5 mg with the option of increasing to a higher dose if needed (Jovanović *et al.*, 1980; Richards and Vallé-Jones, 1988).

Lormetazepam has been directly compared with other hypnotics including benzodiazepines and a barbiturate (Sastre y Hernández *et al.*, 1981; Ansseau and Diricq, 1983; Pöldinger *et al.*, 1983; Melo de Paula, 1984). In an early randomized, double-blind comparison, lormetazepam had effects on sleep that were comparable with those of a barbiturate (amobarbital sodium) in psychiatric outpatients with insomnia ($n = 50$), but was better tolerated (Ansseau and Diricq, 1983). The comparative studies with benzodiazepines have had more varied results (Table 3) (Sastre y Hernández *et al.*, 1981; Pöldinger *et al.*, 1983; Melo de Paula, 1984). Two studies compared lormetazepam with long-acting benzodiazepines (diazepam or flurazepam) (Sastre y Hernández *et al.*, 1981; Melo de Paula, 1984) and one with the short-acting agent triazolam (Pöldinger *et al.*, 1983). Lormetazepam 1 mg was significantly more effective at improving subjective sleep parameters, and was better tolerated, than diazepam 5 mg in 50 patients with insomnia and concomitant medical conditions ($P < 0.05$) (Sastre y Hernández *et al.*, 1981). In a separate study, both lormetazepam (1 or 2 mg) and flurazepam (30 mg) were effective in improving sleep parameters, but for some subjective sleep parameters, only lormetazepam 2 mg was significantly better than placebo (Melo de Paula, 1984). A comparative study in general practice suggested that triazolam was more effective than lormetazepam but less tolerated; however, it should be noted that this study did not use equieffective doses of the two benzodiazepines, with the lowest dose of lormetazepam (0.5 mg) being compared with a moderate dose of triazolam (0.5 mg) (Pöldinger *et al.*, 1983).

A large, general practice, single-arm study similarly reported that lorazepam improved sleep parameters and daytime functioning compared with baseline in patients with insomnia ($n = 665$) (Hill and Harry, 1983). In this

Table 2 Placebo-controlled trials with lormetazepam in patients with insomnia

Reference	Design	N	Treatments	Active treatment duration, days	Effects of lormetazepam vs. placebo
Heidrich *et al.* 1981 (Heidrich *et al.*, 1981)	R, DB, PC, parallel	62	Lormetazepam 2 mg or placebo	14	Statistically significant improvement in subjective sleep parameters[a] and daytime functioning[b] vs. placebo
Kales *et al.* 1982 (Kales *et al.*, 1982)	R, DB, PC, crossover	24	Lormetazepam 0.5, 1, 1.5 or 2 mg or placebo	6	Statistically significant improvements in wake time after sleep onset (0.5 mg), total wake time (0.5, 1.5 or 2.0 mg), and percent sleep time (0.5, 1.5 or 2.0 mg) vs. placebo
Meco *et al.* 1985 (Meco *et al.*, 1985)	R, DB, PC, crossover	20	Lormetazepam 1 mg (as oral solution) or placebo	2	Statistically significant improvement in subjective assessment of sleep parameters[a] and sense of being "rested" the next day vs. placebo

DB, double-blind; PC, placebo-controlled; R, randomized.
[a]Sleep quality, sleep duration, sleep latency, number of awakenings.
[b]Morning freshness, evening freshness, concentration at work.

Table 3 Studies comparing lormetazepam with other benzodiazepines in patients with insomnia

Reference	Design	N	Treatments	Active treatment duration, days	Results
Sastre y Hernández *et al.* 1981 (Sastre y Hernández *et al.*, 1981)	R, DB, parallel	100	Lormetazepam 1 mg, diazepam 5 mg	7	Lormetazepam is significantly more effective than diazepam for improving subjective sleep parameters[a] (all $P < 0.05$). No AEs in lormetazepam group vs. AEs in 7.5% of diazepam group
Pöldinger *et al.* 1983 (Pöldinger *et al.*, 1983)	R, DB, parallel	94	Lormetazepam 0.5 mg, triazolam 0.5 mg	7	Triazolam 0.5 mg more effective than lormetazepam 0.5 mg for improving subjective sleep parameters[a], but lower incidence of AEs (16% vs. 38%) and discontinuation due to AEs (4.4% vs. 12.8%) with lormetazepam vs. triazolam (both $P < 0.05$)
Melo de Paula, 1984 (Melo de Paula, 1984)	R, DB, PC, parallel	60	Placebo, flurazepam 30 mg, lormetazepam 1 mg, lormetazepam 2 mg	14	All active treatments relieved insomnia vs. placebo; for some subjective parameters only lormetazepam 2 mg showed significant difference vs. placebo

AE, adverse events; DB, double-blind; PC, placebo-controlled; R, randomized.
[a]Sleep quality, sleep duration, sleep latency, number of awakenings.

study, patients who had previously received benzodiazepine therapy preferred lormetazepam to nitrazepam or temazepam (Hill and Harry, 1983). Patients who are chronically using a longer-acting benzodiazepine (such as nitrazepam) can be switched to lormetazepam. A lormetazepam dose of 2 mg is recommended (or 1 mg in elderly patients), for at least the first 5 days to limit rebound effects from nitrazepam withdrawal (Chima and Beaumont, 1986). Thereafter lower doses of lormetazepam can be trialed until the best dose for that patient is determined.

For the treatment of anxiety, lormetazepam is as effective as diazepam and significantly better than placebo according to a double-blind comparative study (de Leo and Ceccarelli, 1986). Lormetazepam is also effective in improving sleep parameters in patients with depression and insomnia (Nolen *et al.*, 1993; Benedetti *et al.*, 2004). One of these studies suggested that the timing of lormetazepam administration affected efficacy, with better results seen when lormetazepam was taken at 10 pm (compared with 8 pm or midnight) (Benedetti *et al.*, 2004). In a placebo-controlled comparison with flunitrazepam (another short-acting benzodiazepine) in depressed patients receiving tricyclic antidepressants (TCAs) ($n = 53$), lormetazepam 2 mg was significantly more effective than placebo at reducing depression symptom severity using the Hamilton Depression Rating Scale and Hamilton Depression Subscale, whereas flunitrazepam was comparable with placebo (Nolen *et al.*, 1993). Sleep studies conducted in the absence of TCAs showed a significant reduction in awake time, total sleep time, and sleep latency, as well as an increase in REM latency and the duration of REM sleep, slow-wave sleep, and stage 2–4 sleep with both benzodiazepines compared with placebo. Lormetazepam also significantly increased the duration of slow-wave sleep, stage 4 sleep, and REM sleep compared with flunitrazepam (Nolen *et al.*, 1993). Further research directly comparing individual benzodiazepines will assist physicians in therapeutic decision-making.

The most common adverse events during lormetazepam treatment are dizziness, tiredness, muscle weakness, and ataxia (Electronic Medicines Compendium, 2021). Like all benzodiazepines, lormetazepam may affect psychomotor performance (Vermeeren, 2004). However, a study in healthy volunteers showed placebo-equivalent effects on psychomotor and cognitive performance with lormetazepam 1 mg in the first 6 h after administration (Fabbrini *et al.*, 2005). A placebo-controlled study in elderly volunteers demonstrated no effect of lormetazepam in 10 out of 12 neurobehavioral tests, but a small and statistically significant impairment in the remaining two tests (Deijen *et al.*, 1991). One of these tests (associate recognition) suggests an amnesic effect consistent with the expected effects of benzodiazepines, and the other test (pattern comparison) indicated a slight slowing of visual organization (Deijen *et al.*, 1991). Another study in healthy elderly volunteers showed significantly worse psychomotor proficiency in two tests after repeated doses of nitrazepam compared with both placebo and lormetazepam ($P < 0.05$), but no significant difference between lormetazepam and placebo (Morgan, 1985).

The effects of lormetazepam on memory are interesting. A double-blind, placebo-controlled study in healthy volunteers indicated that benzodiazepines (lormetazepam or flunitrazepam) actually enhanced memorization of material learned before drug ingestion compared with placebo (i.e. had a negative effect on retrograde amnesia with enhanced memory) (Ott *et al.*, 1988). On the other hand, flunitrazepam 2 mg had a more marked anterograde amnesic effect compared with lormetazepam 2 mg or 1 mg. The effect of lormetazepam 1 mg on anterograde amnesia was similar to that of placebo (Ott *et al.*, 1988). This is consistent with other data in healthy volunteers showing a less marked amnesic effect with lormetazepam compared with longer-acting benzodiazepines, specifically temazepam and flurazepam (Roehrs *et al.*, 1984).

At recommended doses (0.5–1.5 mg), lormetazepam has minor or no residual effects on psychomotor performance, visual reaction times, and driving ability after ≥8 h (Vermeeren, 2004), with effects similar to those of placebo (Iudice *et al.*, 2002), as would be expected based on its half-life and lack of active metabolites (Horowski, 2020). The lack of residual next-day effects has been noted with repeated doses of lormetazepam in several studies in volunteers (Subhan and Hindmarch, 1983; Iudice *et al.*, 2002), consistent with the low incidence of hangover effects reported in clinical studies (Heidrich *et al.*, 1981).

While all benzodiazepines are associated with a risk of tolerance and dependence, data from animal studies suggest that the potential for dependence is lower with lormetazepam than with nitrazepam or lorazepam (Horowski, 2020). The oral solution of lormetazepam has been associated with a high incidence of abuse in studies from Italy (Faccini *et al.*, 2012; Cosci *et al.*, 2016; Faccini *et al.*, 2019). However, the same studies reported a low incidence of abuse with lormetazepam tablets; for example, in the largest cohort, only 13 of the 1112 patients with benzodiazepine dependence (1.2%) were using lormetazepam tablets (Faccini *et al.*, 2019). Various authors have speculated on the reasons for the high rate of abuse with lormetazepam oral solution, suggesting that this is related to the drip rate, excipients, α_1-receptor selectivity or a combination of these factors, but the exact reason is not clear (Faccini *et al.*, 2019; Horowski, 2020; Costa *et al.*, 2021). Until there is more clarity about the exact cause of any relationship between lormetazepam oral solution and the risk of abuse, and the extent to which any relationship may be

related to the formulation or patient characteristics, clinicians would be advised to preferentially prescribe the tablet formulation. The oral solution still has a valuable role in the therapeutic armamentarium for anxiety and/or insomnia but may be best reserved for an inpatient or similar setting where patients can be closely monitored for signs of dependence.

As with other benzodiazepines, gradual dose tapering is advised during lormetazepam withdrawal (Electronic Medicines Compendium, 2021), but flumazenil can be used to ameliorate withdrawal symptoms in patients with prolonged exposure (Gerra *et al.*, 1996).

Table 4 Potential risks associated with insomnia in pregnant women (Okun, 2015; Reichner, 2015; Chaudhry and Susser, 2018; Querejeta Roca *et al.*, 2020; Sweet *et al.*, 2020; Deforges *et al.*, 2021)

Maternal health	Delivery	Fetal/neonatal health
Depression during pregnancy	Cesarean delivery	Preterm birth
Gestational hypertension	Increased length of labor	Stillbirth
Pre-eclampsia	Elevated perception of pain during labor	Low birth weight
Gestational diabetes		
Childbirth-related PTSD		
Postpartum depression		

PTSD, post-traumatic stress disorder.

Use of benzodiazepines during pregnancy

Many women experience some level of sleep disturbance during pregnancy, particularly during the third trimester (Sedov *et al.*, 2021), with more nocturnal awakenings, decreased total sleep time, increased time spent awake, a reduction in REM sleep latency, less slow-wave sleep and an increase in REM sleep (Okun, 2015; Sweet *et al.*, 2020). Stress can contribute to poor sleep quality during pregnancy, and the physiological impact of stress (e.g. inflammation and neuroendocrine activation) may contribute to sleep disturbances, anxiety, and reduced concentration (Gupta and Rawat, 2020).

Approximately 15–20% of pregnant women develop clinical insomnia; factors significantly associated with insomnia during pregnancy include anxiety and depression (Wołyńczyk-Gmaj *et al.*, 2017; Sedov and Tomfohr-Madsen, 2021). Insomnia during pregnancy can have detrimental effects on both the mother and fetus (Table 4), increasing the risk of poor pregnancy outcomes, a more complicated delivery, and postnatal mood disorders (Reichner, 2015; Querejeta Roca *et al.*, 2020; Sweet *et al.*, 2020; Deforges *et al.*, 2021). A 2018 meta-analysis indicated that, like insomnia, anxiety during pregnancy was associated with an increased risk of low birth weight and preterm birth (Grigoriadis *et al.*, 2018), consistent with an etiological relationship between anxiety and insomnia mediated by inflammatory and endocrine influences (Gupta and Rawat, 2020). There is also evidence from animal research that insomnia during pregnancy affects fetal brain development, with reduced hippocampal neurogenesis, impacting cognitive and emotional function (Peng *et al.*, 2016).

Although there are limited data on the effects of insomnia treatment during pregnancy, there is evidence that treatment during the third trimester can reduce the risk of postnatal depression (Khazaie *et al.*, 2013). The primary treatment for insomnia during pregnancy should be non-pharmacological interventions (e.g. stimulus control techniques and improved sleep hygiene practices) (Chaudhry and Susser, 2018), particularly during the first trimester when active organogenesis is taking place (Iqbal *et al.*, 2002). Later in the pregnancy, pharmacological therapy may be appropriate in women who are experiencing significant effects from insomnia. Benzodiazepines and benzodiazepine receptor agonists are recommended in the ESRS guidelines for pregnant women with insomnia who do not respond to non-pharmacological therapy (Riemann *et al.*, 2017). All benzodiazepines cross the placenta to varying degrees (Chaudhry and Susser, 2018), but lormetazepam has shown low transplacental passage in animal studies, with maternal concentrations being consistently higher than fetal or placental levels after oral administration (Girkin *et al.*, 1980). In addition, there is no evidence of mutagenic, teratogenic, or embryotoxic effects with lormetazepam in preclinical toxicity analyses (Horowski, 2020).

A small percentage of women (<1%) take benzodiazepines during pregnancy (Sheehy *et al.*, 2019; Bais *et al.*, 2020). Data suggest that benzodiazepine use during early pregnancy may be associated with an increased risk of spontaneous abortion (Sheehy *et al.*, 2019), supporting recommendations to avoid their use during the first trimester. However, in women who have taken benzodiazepines during pregnancy and carried to term, there does not appear to be a significant increase in the risk of congenital or neonatal cardiac malformations, including those exposed to benzodiazepines during the first trimester (Enato *et al.*, 2011; Bellantuono *et al.*, 2013; Grigoriadis *et al.*, 2019). There is, however, a small and statistically significant increase in the risk of malformations with the use of combined benzodiazepines and antidepressants (Grigoriadis *et al.*, 2019).

Taken together, these data suggest that benzodiazepines can be used in pregnant women who are experiencing significant insomnia during the second or third trimester, and after non-pharmacological options have been tried (Iqbal *et al.*, 2002). If prescribed, benzodiazepines should be used as monotherapy at the lowest effective dose and for a short period during pregnancy (Iqbal *et al.*, 2002). While all benzodiazepines cross the placenta to some extent, transplacental passage of lormetazepam is limited (Girkin *et al.*, 1980), so this agent may be a reasonable option during pregnancy (Chaudhry and Susser, 2018).

Use of benzodiazepines to manage psychodermatoses

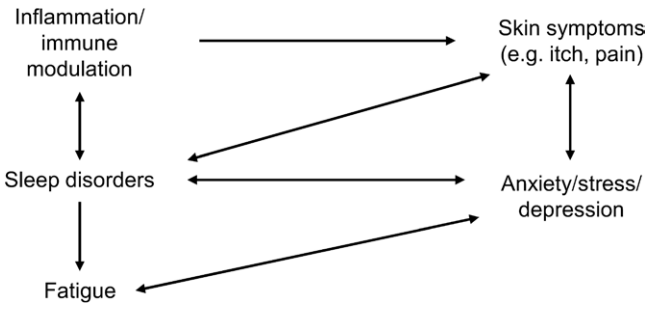
The term psychodermatoses is used to describe a range of dermatological conditions that are caused or affected by psychophysiological processes or treatments (Table 5) (Weber *et al.*, 2020). Many psychodermatoses are associated with sleep disturbances and anxiety/depression (Thorburn and Riha, 2010; Kaaz *et al.*, 2019; Guo *et al.*, 2020), with clinical insomnia present in 20–50% of patients with psychodermatoses (Tamschick *et al.*, 2021). Both skin symptoms (particularly pruritus) and anxiety are common causes of sleep disorders in patients with skin conditions (Tamschick *et al.*, 2021).

The etiology of the relationship between dermatological conditions, sleep disturbance, and anxiety is likely to be multifactorial (Fig. 1), with sleep deprivation contributing to immune modulation, which in turn affects skin symptoms. This is supported by data showing that sleep disorders are worse in patients with inflammatory than non-inflammatory skin disorders (Mostaghimi and Hetzel, 2019). Moreover, etiological factors and consequences, such as symptom severity, fatigue, and anxiety, exacerbate one another to promote a vicious cycle of impaired sleep, dermatological worsening, and psychiatric comorbidities (Thorburn and Riha, 2010; Walia and Mehra, 2016; Kaaz *et al.*, 2019; Li *et al.*, 2019; Misery *et al.*, 2020; Myers *et al.*, 2021).

Table 5 **Different types of psychodermatoses (Weber *et al.*, 2020)**

Classification	Definition	Examples
Psychophysiological disorders	Primary dermatological conditions that are exacerbated by emotional factors and stress	Psoriasis, atopic dermatitis
Primary psychiatric disorders	Self-inflicted skin manifestations as secondary to a primary psychiatric disease	Trichotillomania, parasitic delirium, dermatitis artefacta, neurotic excoriations
Secondary psychiatric disorders	Psychiatric conditions that arise because of the psychosocial effects of an existing dermatological disease	Social phobia or depression secondary to psoriasis, alopecia areata
Sensitive skin disease	Psychogenic dermatological symptoms (e.g. burning, pain, itch) in the absence of a skin disease or other medical condition	Vulvodynia, glossodynia
Drug reaction	Dermatological conditions caused by psychoactive medications	Pruritus, rash, Stevens-Johnson syndrome
Multifactorial disease	Conditions in which psychoneuroimmunology factors trigger or aggravate skin conditions	Atopic dermatitis, psoriasis, alopecia areata, chronic pruritus

Fig. 1



The multidirectional relationship of skin disorders, sleep disturbances, and anxiety/stress.

Data from an observational study indicated that European dermatologists are likely to underestimate the prevalence and severity of anxiety among patients with skin disorders, particularly those with long-standing or chronic conditions, eczema, and leg ulcers (Dalgard *et al.*, 2018).

Despite the prevalence and consequences of sleep disorders and anxiety/depression in patients with skin disorders, there has been relatively little research on the optimal approach to treatment, with a suggestion that dermatologists may over-rely on the sedating effects of antihistamines to manage sleep disorders (Thorburn and Riha, 2010).

As with most sleep disorders, non-pharmacological measures should be tried first, including improved sleep hygiene, control of nocturnal stimuli, relaxation techniques, and CBT (Thorburn and Riha, 2010; Walia and Mehra, 2016; Kuhn *et al.*, 2017). Psychiatric comorbidities, such as anxiety and depression, should be treated appropriately; patients who are experiencing sleep disorders may benefit from a short course of hypnotics, such as benzodiazepines (Kuhn *et al.*, 2017). As these agents also have anxiolytic effects, they may benefit patients with skin conditions for whom anxiety contributes to sleep disturbances (Kuhn *et al.*, 2017). However, given the limited evidence base, more research is needed into the impact of different treatments on skin symptoms, anxiety/depression severity, and sleep disturbances in patients with psychodermatoses.

Conclusion

Benzodiazepines have an important role in the short-term treatment of anxiety and insomnia and may be useful in the management of patients with psychodermatoses or during pregnancy. However, the use of these agents requires careful consideration of the patient's complete clinical picture and treatment characteristics. Among the benzodiazepines, lormetazepam has been shown to be effective in the management of insomnia, with minimal hangover effects, and is likely a safe choice for insomnia during the second and third trimesters of pregnancy.

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S. Pallanti conceptualized the article, analyzed the search results for intellectual content, reviewed and critically revised all drafts of the manuscript, read and approved the final version for publication, and therefore meets the criteria for authorship as established by the International Committee of Medical Journal Editors. S. Pallanti confirms that this manuscript represents honest work and that he is able to verify the validity of the results reported.

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Conflicts of interest

S. Pallanti has served as a consultant for Neopharmed gentili in 2022.

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