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Literature review

# Management of trauma-related nightmares in PTSD: Can doxazosin serve as a pragmatic alternative to prazosin?

## *Traitement des cauchemars traumatiques dans le TSPT : la doxazosine, alternative à la prazosine ?*

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ABSTRACT

*Objectives:* Trauma-related nightmares (TRNs), core features of post-traumatic stress disorder (PTSD), partially or fully replicate the traumatic event and are often associated with nocturnal awakenings and significant emotional distress. In light of the imminent withdrawal of prazosin in France, this review explores the potential of doxazosin as a pharmacological alternative while emphasizing the central role of psychotherapeutic interventions in TRNs management.

*Methods:* Following a brief overview of TRNs and existing therapeutic strategies, both pharmacological and non-pharmacological, this review examines the available evidence on doxazosin, a selective $\alpha_1$-adrenergic receptor antagonist, and proposes a practical initiation protocol for clinicians.

*Results:* Although limited and heterogeneous, the literature suggests that doxazosin may reduce the frequency and intensity of TRNs and improve sleep continuity, particularly in patients with marked adrenergic hyperactivation or those who previously responded to prazosin. Tolerance is generally good and extended-release formulations enable convenient nocturnal dosing. However, randomized controlled trials have produced mixed results due to small sample sizes, population heterogeneity, and comorbidities such as alcohol-related disorders. Across studies, psychotherapeutic interventions remain the most evidence-based and durable treatment for TRNs, and pharmacological options are best considered as adjuncts within an integrated care pathway.

*Conclusions:* Doxazosin may represent a pragmatic pharmacological option for managing TRNs in PTSD, especially in the context of prazosin withdrawal. Its use should complement, rather than replace, first-line psychotherapeutic approaches and be integrated into a comprehensive, coordinated, and individualized treatment plan with careful monitoring of adverse effects. Larger, well-designed randomized controlled trials are needed to determine optimal dosing, treatment duration, and predictors of response.

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RÉSUMÉ

*Objectifs :* Les cauchemars traumatiques, symptômes clés du trouble de stress post-traumatique (TSPT), reproduisent partiellement ou totalement l'événement traumatisant et s'accompagnent de réveils nocturnes et d'une forte détresse émotionnelle. Dans le contexte du retrait prochain de la prazosine en France, cet article explore le potentiel de la doxazosine comme alternative pharmacologique tout en soulignant la place centrale des approches psychothérapeutiques dans la prise en charge des cauchemars traumatiques.
*Méthodes :* Après un rappel clinique sur le cauchemar traumatique et les stratégies thérapeutiques existantes, médicamenteuses et non médicamenteuses, cette revue évalue les données disponibles sur la doxazosine, antagoniste sélectif des récepteurs adrénergiques, et propose un protocole d'initiation pratique pour les cliniciens.
*Résultats :* Bien que limitées et hétérogènes, les données disponibles suggèrent que la doxazosine pourrait réduire la fréquence et l'intensité des cauchemars traumatiques et améliorer la continuité du sommeil, en particulier chez les patients présentant une hyperactivation adrénergique marquée ou ayant répondu préalablement à la prazosine. La tolérance est globalement bonne, et les formes à libération prolongée permettent une prise au coucher adaptée. Toutefois, les essais randomisés contrôlés montrent des résultats contrastés, en raison notamment de petits effectifs, d'une hétérogénéité des populations étudiées et de comorbidités fréquentes telles que les troubles de l'usage de l'alcool. Les interventions psychothérapeutiques demeurent, dans l'ensemble des études, les traitements les plus étayés et les plus durables pour la prise en charge des cauchemars traumatiques. Les options pharmacologiques doivent être envisagées comme des adjuvants dans un parcours de soins structuré.
*Conclusions :* La doxazosine pourrait constituer une alternative pharmacologique pragmatique pour la gestion des cauchemars traumatiques dans le TSPT, en particulier dans le contexte du retrait de la prazosine. Son utilisation doit toutefois venir en complément – et non en substitution – des approches psychothérapeutiques de première intention, au sein d'un plan de traitement individualisé, coordonné et attentif aux effets indésirables. Des essais randomisés contrôlés de plus grande ampleur sont nécessaires pour préciser les posologies optimales, la durée de traitement et les facteurs prédictifs de réponse.

## 1. Trauma-related nightmares: a core symptom of post-traumatic stress disorder

### 1.1. Definition and prevalence

Trauma-related nightmares (TRNs) are defined as vivid, recurring sleep phenomena linked to trauma, either through direct content or through emotionally charged mentation reflecting trauma-associated affect [1,2]. They often recreate traumatic situations in striking detail, provoking intense emotional and sensory distress and may lead to abrupt, highly distressing awakenings with varying levels of recall [3]. More specifically, TRNs span a continuum from replicative (REP) forms that vividly reenact the traumatic event with marked physiological arousal and close association to severe post-traumatic stress disorder (PTSD) [3,4], to partially-replicative (PREP) and non-replicative (NREP) variants that may progressively incorporate symbolic or emotional transformations, reflecting reduced distress and gradual trauma integration [1–3,5].

Clinically, TRNs differ from idiopathic nightmares by their anchoring in autobiographical trauma, their intense sensory realism [1], and the marked physiological arousal upon awakening [3]. They frequently trigger prolonged nocturnal wakefulness, anticipatory anxiety at bedtime, and a progressive avoidance of sleep, leading to significant next-day exhaustion [4,6,7].

TRNs are considered a core symptom of PTSD, especially among military personnel [4,8]. While the lifetime prevalence of nightmares in the general population is estimated at 3–4%, rates increase sharply in trauma-exposed individuals and exceed 80% in military PTSD populations, with some studies reporting up to 97% in combat-related PTSD [7]. Beyond their frequency, TRNs are profoundly disruptive, contributing to sleep fragmentation, hypervigilance, and poor sleep efficiency, as well as maladaptive coping behaviors such as alcohol or sedative use at bedtime [4,8]. Their chronic presence worsens daytime PTSD symptoms, increases the risk of depression and suicidality, and, as shown by longitudinal data, often outlasts improvements in other PTSD clusters – thereby sustaining sleep fragmentation, daytime fatigue, and emotional dysregulation [4,6,9,10]. Moreover, accumulating evidence suggests that TRNs may not merely represent a symptom of PTSD but rather a distinct pathological process that can precede and predict its development, underscoring the need for specific, targeted therapeutic approaches [4,8].

### 1.2. Pathophysiology

The sleep fragmentation model offers a robust framework to understand TRNs in PTSD [4]. In healthy sleep, emotional memories thought to be gradually reprocessed and attenuated across Non-Rapid Eye Movement (NREM) – Rapid Eye Movement (REM) cycles through the progressive decoupling of affective charge from mnemonic content [11]. In PTSD, chronic hyperarousal could disrupt this mechanism, maintaining a pathological coupling between emotional and perceptual traces of trauma. Each TRN-related awakening resets this process, fragmenting sleep and preventing the adaptive reintegration of traumatic memories, thereby sustaining emotional dysregulation [1,8].

Ecological physiological data strongly support this model. Although nightmares were traditionally associated with REM sleep, home-based studies have shown that most TRNs (≈ 60–65%) occur during NREM sleep, with distinct temporal distributions across the night – NREM-related forms predominating in the middle of the night and REM-related ones clustering toward the final third [10,12,13]. Ecological analyses further reveal increased micro-fragmentation and autonomic instability in the minutes preceding TRN-related awakenings, particularly during NREM, highlighting stage-specific vulnerabilities and reinforcing the view of TRNs as a disorder of sleep continuity rather than of a single stage [10].

From a psychodynamic and clinical perspective, TRNs may thus reflect a breakdown in the symbolic function of dreaming, where the trauma is re-enacted rather than transformed. Over the course of therapy, a gradual shift can often be observed – from REP vividly replaying the event toward PREP and eventually NREP, integrating symbolic or emotional transformations. This transition from repetition to representation may potentially mark a progressive restoration of the dream's integrative function, signaling a movement toward trauma integration [5,14,15].

### 1.3. Clinical implications and monitoring

Within clinical trajectories, TRNs function less as barometers of PTSD symptom severity than as dynamic indicators of trauma integration.

To monitor these dynamics, both subjective and objective tools have been developed. The Trauma-Related Nightmare Survey (TRNS) and its French adaptation (TRNS-FR) provide standardized assessment of TRNs frequency, replication type (REP, PREP, NREP), emotional intensity, and post-awakening duration [16,17]. Beyond its strong clinical relevance, ecological studies have confirmed that self-reported TRNs frequency closely parallels objective sleep indices, supporting its validity as a reliable marker of nocturnal disturbance [7]. Complementarily, objective multimodal monitoring tools – such as actigraphy, portable Electroencephalography (EEG), and autonomic recordings – can further characterize sleep continuity and physiological instability. Their integration with self-report instruments like the TRNS-FR may enable longitudinal tracking of therapeutic progress and the early detection of relapses.

In the French military health system, such integrated follow-up is increasingly paired with Therapeutic Patient Education (TPE) programs on sleep and trauma [18]. By framing TRNs as modifiable physiological events rather than personal failures, these approaches strengthen patient engagement and foster adaptive coping – facilitating both the reintegration of traumatic memory and the recovery of continuous sleep.

## 2. Non-pharmacological management strategies

### 2.1. Imagery rehearsal therapy

TRNs treatment has traditionally included psychotherapeutic approaches such as Imagery Rehearsal Therapy (IRT). Although its efficacy has been demonstrated, notably among survivors of sexual assault with PTSD [19], the specific therapeutic effect of IRT remains debated, particularly in military populations. IRT involves reworking the narrative of nightmares during the day using mental imagery, with the aim of reducing their intensity and/or frequency at night. Short-term protocols include psychoeducation about nightmares and sleep [20]. This therapy is supported by Grade A recommendations from the American Academy of Sleep Medicine (AASM) for the treatment of TRNs [21,22]. IRT has demonstrated significant efficacy in alleviating dysphoric affect associated with TRNs [23]. A 2019 meta-analysis found no significant difference between prazosin and IRT in terms of TRNs frequency or overall post-traumatic symptomatology [24]. Rather than indicating a strong specific effect of IRT, this equivalence suggests that improvements may stem from non-specific therapeutic factors – such as reduced sleep-related anxiety, improved sleep anticipation, and structured exposure to dream content.

IRT can be combined with therapies targeting insomnia. In a clinical trial, 108 American veterans suffering from TRNs were randomized into two groups: one group received six sessions of Cognitive Behavioral Therapy for Insomnia (CBT-I) combined with IRT, and the other group received CBT-I alone [25]. In both groups, the sleep-focused intervention significantly reduced nightmare frequency (29% reduction) and led to a 23% remission rate. Remission was defined as the absence of nightmares or no more than one TRN every two weeks. This improvement was maintained at the 6-month follow-up. Notably, adding IRT to CBT-I did not provide additional benefit, reinforcing the hypothesis that strengthening sleep continuity may be the primary driver of improvement in many cases. The authors suggest that this absence of added efficacy may be due to the type of traumatic events experienced by military patients, which differ from those encountered in the civilian population [25,26]. Veterans' TRNs are particularly immersive and replicative, often consisting of a reenactment of the traumatic scene, which in most cases involves a confrontation with death [3,26].

Evidence from civilian populations highlights the broader therapeutic potential of IRT in non-military settings. In an open-label trial of 62 crime victims with PTSD, a 10-hour group intervention combining IRT for nightmares with sleep hygiene, stimulus control, and sleep restriction for insomnia led to meaningful improvements across multiple domains. Nightmare frequency, sleep quality, and sleep impairment improved from severe to moderate, while PTSD symptoms decreased from borderline severe to borderline moderate, and anxiety and depression symptoms also showed substantial reductions. Participants who experienced improvements in PTSD symptoms demonstrated significantly greater gains in sleep quality and reductions in nightmare frequency than those whose PTSD symptoms did not improve [27]. IRT has also demonstrated significant benefits in civilian populations without PTSD but with psychiatric comorbidities. In a non-randomized controlled study of 53 adults with major depressive episodes and nightmare disorder, four weekly group-based IRT sessions significantly reduced nightmare severity across multiple dimensions (frequency, emotional, diurnal, and nocturnal impacts) and were associated with reductions in depressive and anxiety symptoms, as well as suicidal ideation [28]. These findings suggest that IRT may be effective in improving sleep and alleviating psychiatric comorbidities and suicide risk, which are clinically relevant considerations for trauma-exposed populations.

In contrast to these positive findings in civilian populations, the highly realistic, sensory-driven structure of TRNs in military patients may limit the transformative potential of imagery-based rescripting techniques, contributing to the variable efficacy of IRT. Taken together, current evidence suggests that, while IRT may benefit some patients, its effects appear more consistent in civilian populations and more variable in military populations, likely relying more on general sleep- and anxiety-modulating mechanisms than on specific dream-rescripting processes.

### 2.2. Cognitive-behavioral therapy for insomnia

In contrast to imagery-based approaches, CBT-I directly targets sleep continuity and hyperarousal, which appear to be the central mechanisms driving improvements in TRNs [29]. CBT-I includes psychoeducation on the physiology of sleep, stimulus control, sleep restriction, and cognitive restructuring of sleep-related beliefs. CBT-I has demonstrated its effectiveness in treating insomnia in patients with various comorbidities, such as PTSD and depression [30–32]. Patients with sleep disturbances resistant to conventional PTSD treatments have shown improvements in sleep following insomnia-focused interventions: sleep onset latency and night awakenings decrease, while sleep efficiency increases [33]. Furthermore, a reduction in the frequency of TRNs was observed, likely due to improved sleep quality, particularly deep sleep [25,30]. Improvements in sleep among American veterans following CBT-I sessions were also associated with improvements in overall PTSD symptomatology [25,34].

These findings strongly support the view that the therapeutic benefit in TRNs may arise less from the specific content of psychotherapies than from the restoration of sleep continuity itself. Stabilizing the sleep-wake cycle, reducing hypervigilance in the pre-sleep period, and reinforcing regular sleep routines appear to produce meaningful reductions in nightmare frequency across military and civilian populations [30]. These approaches can be integrated into TPE programs, where the patient is placed at the center of care, with an emphasis on their experiences. In France, a TPE program targeting sleep disturbances associated with PTSD in military and former military has existed since 2022 in two military hospitals [18,35].

### 2.3. Body and movement-oriented interventions

Beyond cognitive and behavioral interventions, body- and movement-oriented approaches contribute to trauma-related nightmare reduction primarily through non-specific mechanisms of autonomic regulation and sleep stabilization. Most therapies targeting veterans' TRNs in the United States include body-based approaches. Relaxation is one of the components of CBT-I interventions that have demonstrated effectiveness in the treatment of TRNs [34]. Body and movement-oriented interventions are characterized by their focus on the use of

bodily activities and physical experiences to help reduce symptoms, enhance mental health, and support psychosocial functioning [36]. A meta-analysis published in 2023 examined the effectiveness of body and movement-oriented interventions (BMOIs) in adults with PTSD [37]. The BMOIs assessed in the meta-analysis included the following approaches: yoga, physical exercise, relaxation techniques, and specific body-based practices. This meta-analysis highlights a significant effect of BMOIs on sleep quality improvement. These interventions may serve as a valuable therapeutic complement for individuals with PTSD experiencing severe sleep disturbances.

Follow-up studies suggest that integrating BMOIs practices into daily routines after the end of treatment is associated with sustained symptom reduction and long-term improvement [38]. Supporting individuals in establishing and maintaining these practices could foster autonomy and promote the long-term maintenance of therapeutic benefits. Professionals trained in psychocorporal and psychomotor approaches can help patients restore bodily regulation, reduce nocturnal hyperarousal, and consolidate more stable sleep architecture – factors that are likely foundational for reducing trauma-related nightmares, regardless of their specific content. Taken together, body-oriented approaches appear to contribute to TRNs improvement by modulating the physiological terrain on which nightmares emerge, rather than by acting on trauma representation itself.

## 3. Pharmacological management strategies

### 3.1. PTSD first-line treatments

Guidelines for the treatment of PTSD and TRNs place pharmacotherapy as a second-line option, to be considered only after non-pharmacological strategies – especially sleep-focused interventions – have been implemented [21,22,39]. Guideline-concordant pharmacotherapy for PTSD prioritizes antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs) and Serotonin-norepinephrine reuptake inhibitors (SNRIs), as first-line agents. Their efficacy spans the core symptom clusters – re-experiencing, avoidance, and hyperarousal – with consistent, although modest, effect sizes across randomized trials [40,41].

In French practice, sertraline, paroxetine, fluoxetine, and venlafaxine are among the most frequently prescribed antidepressants for PTSD. However, only sertraline and paroxetine hold formal marketing authorization (AMM) for PTSD in France, while fluoxetine and venlafaxine are used off-label, following international practices. Mechanistically, SSRIs enhance serotonergic tone within corticolimbic circuits, facilitating affect regulation and fear extinction, whereas venlafaxine's additional noradrenergic engagement may further reduce anxious arousal and somatic tension [42].

Despite these broad effects, sleep disturbances and TRNs often remain the most persistent residual symptoms under SSRI/SNRI monotherapy. In French military cohorts, TRNs remain a major residual burden after several months of antidepressant treatment, marked by frequent nocturnal awakenings and vivid dream re-enactments despite improvement in daytime symptoms [3,7]. These observations align with the sleep fragmentation model described by Saguin et al. [10], where autonomic surges preceding TRN-related awakenings disrupt emotional recalibration during sleep. Within this framework, mirtazapine is frequently prescribed in France as an adjunct or alternative for patients exhibiting marked insomnia, anxiety, or weight loss. Through 5-$HT_2$ and histaminergic antagonism, combined with $\alpha_2$-autoreceptor blockade, mirtazapine enhances sleep continuity and appetite while reducing nocturnal hypervigilance [4].

Recent developments in pharmacogenetics support a precision approach. Studies conducted by Baldacci et al. [43] and Lorvellec et al. [44] have demonstrated that identifying CYP2D6/CYP2C19 metabolic variants and phenoconversion can optimize antidepressant selection and reduce adverse effects, contributing to the implementation of pharmacogenetics within the French military health system. Such variability may partly explain the persistence of TRNs despite adequate pharmacological exposure.

Overall, ecological recordings and prospective monitoring developed by the French team demonstrate that sleep fragmentation, pre-awakening autonomic surges, and TRNs recurrence are strongly correlated with daytime PTSD severity [7,10]. This supports a dual-track therapeutic model:

- SSRIs/SNRIs to reduce global PTSD burden;
- adrenergic or sleep-focused adjuncts to restore sleep integrity and modulate nocturnal hyperarousal.

### 3.2. Adjunctive or off-label options

When first-line antidepressants provide only partial remission or are poorly tolerated, adjunctive pharmacotherapy becomes necessary. The French approach increasingly favors dimensional augmentation, targeting the dominant residual symptom domain (hyperarousal/irritability, insomnia/TRNs, or intrusive imagery) rather than relying solely on categorical diagnosis. Among atypical antipsychotics, risperidone and olanzapine initially appeared beneficial for re-experiencing and vigilance hyperreactivity, but a large VA multicenter trial demonstrated the absence of superiority of adjunctive risperidone over placebo in antidepressant-resistant PTSD [45]. Moreover, weight gain and metabolic effects limit their long-term applicability.

In contrast, loxapine, a tricyclic antipsychotic with $D_2$, 5-$HT_2$A, and $\alpha_1$ affinities, has regained attention in French settings as a low-dose, off-label option targeting nocturnal hyperarousal and TRNs [46]. In pragmatic military contexts, clinicians report improved sleep continuity, attenuated dream recalls and reduced nocturnal awakenings under loxapine add-on. The drug can be administered in drop formulation, allowing flexible titration between 5 and 40 mg at bedtime, with gradual adjustment often performed by the patient in coordination with the clinician. This flexibility fosters a sense of agency and control over symptoms and sleep. Loxapine thus appears well suited for nighttime use at microdoses, where sedative and adrenergic-blocking properties predominate over antipsychotic action. Moreover, loxapine does not have metabolic side effects typical of second-generation antipsychotics which reduces the risk of exacerbating or precipitating a comorbid sleep apnea. This quality of loxapine is essential as sleep apnea could increase the severity of underlying PTSD through an increase in sleep fragmentation among other things. Nonetheless, controlled trials remain necessary to clarify dose-response relationships and long-term safety.

Other sedative antidepressants, such as trazodone, act through 5-$HT_2$A antagonism and $H_1$ blockade, improving sleep onset and continuity while modestly reducing nightmare intensity [47]. In short-term military contexts – such as post-deployment adaptation – hydroxyzine or cyamemazine may alleviate transient hyperarousal but do not address the adrenergic dysregulation underlying TRNs. Their role remains supportive, particularly during tapering or transitional phases.

Benzodiazepines, though anxiolytic, are avoided in chronic PTSD of deleterious impacts on extinction learning, memory consolidation, respiratory stability, and dependence risks [39,41,46]. Their use should be short-term and closely supervised.

### 3.3. Prazosin and other $\alpha_1$-adrenergic antagonists

Objective and ecological recordings show that pre-awakening autonomic surges – increases in heart rate and electrodermal activity – frequently precede TRN-related awakenings, reflecting persistent sympathetic hyperactivation during sleep [10,12,13]. These findings provide a pathophysiological rationale for the use of adrenergic modulators when TRNs and signs of hyperarousal persist despite optimized PTSD management [48]. When combined with TPE [18], such inter-

ventions may reduce hypnotic misuse and facilitate physiological sleep restoration.

The noradrenergic system is critically involved in PTSD pathophysiology. Sustained locus coeruleus hyperactivity maintains elevated sympathetic tone and impairs emotional memory depotentiation during REM sleep [48,49]. By attenuating postsynaptic $\alpha_1$-adrenergic signaling within central noradrenergic circuits, $\alpha_1$-antagonists such as prazosin may dampen nocturnal sympathetic surges without REM suppression, leading to reduced TRN frequency, fewer abrupt awakenings, and improved sleep continuity [22,50,51]. However, clinical efficacy remains heterogeneous [52], supporting a personalized and adjunctive use alongside non-pharmacological interventions.

Over the past two decades, prazosin has accumulated the strongest body of evidence among adrenergic modulators for reducing TRNs. Early randomized controlled trials demonstrated significant decreases in TRNs frequency and overall PTSD severity [50,53]. Subsequent meta-analyses confirmed these benefits for nightmares, although broader PTSD effects were more modest and heterogeneous [54].

According to the AASM best practice guide [21], prazosin was initially recommended with a "Level A" rating for nightmare disorder associated with PTSD, alongside IRT. However, following the VA Cooperative Study #504 showing no superiority over placebo [52], several guidelines downgraded prazosin's recommendation level. In response, the AASM Position Paper [22] offered a more nuanced view: while acknowledging mixed results, it emphasized that prazosin may remain beneficial for selected patients, particularly when antidepressant co-medications do not interfere with its $\alpha_1$-adrenergic action (interference may occur primarily with SNRIs or other antidepressants that enhance noradrenergic tone, as increased endogenous $\alpha_1$ stimulation can partially blunt prazosin's therapeutic blockade; SSRIs and other serotonergic agents do not pose this issue). IRT thus remained the only treatment formally recommended, but prazosin continued to be considered a reasonable option in individualized care approaches.

In our clinical experience, prazosin does not produce substantial improvement in all patients, and predicting responders remains difficult. Yet in a meaningful subset, the treatment leads to clear benefits: improved sleep continuity, fewer nocturnal awakenings, and a progressive attenuation of TRNs, often acting as a therapeutic catalyst within the broader recovery process. Restoring consolidated sleep frequently serves as a psychological "booster", enhancing engagement in treatment and daily functioning. When titrated gradually (2.5–10 mg at bedtime), prazosin is generally well tolerated; orthostatic hypotension and first-dose syncope remain the primary adverse effects but can be minimized through patient education and slow uptitration.

In France, prazosin (ALPRESS L.P.®) has long been a cornerstone for TRN management in both military and civilian psychiatry. Its withdrawal as of September 1st, 2025 – a commercial decision unrelated to safety – creates a significant therapeutic gap [55]. Structured transition protocols are necessary to avoid rebound adrenergic symptoms (irritability, nocturnal awakenings, intensified dream recall) during tapering or switching. With prazosin no longer available, clinicians must identify alternative strategies to maintain adrenergic regulation. Doxazosin currently appears the most plausible substitute, sharing $\alpha_1$-antagonist properties and offering a longer half-life that may provide steadier nocturnal coverage. The next section examines the available evidence supporting its use in TRNs.

## 4. Clinical use of doxazosin in trauma-related nightmares

### 4.1. Review of clinical evidence

Doxazosin, a selective $\alpha_1$-adrenergic antagonist, was first approved in France in 1999 for essential hypertension and benign prostatic hyperplasia (BPH). Initially available in immediate-release formulations (1, 2, 4, and 8 mg), only prolonged-release (PR) tablets remain marketed since 2006, and reimbursement for BPH treatment has been maintained [56]. Although its psychiatric use was not anticipated at the time of approval, doxazosin has recently gained clinical interest as a potential therapeutic option for TRNs in PTSD. Like prazosin, it reduces central noradrenergic hyperactivation through $\alpha_1$-receptor blockade, but its longer half-life allows more stable nocturnal adrenergic coverage. In the French context, this pharmacological continuity has become particularly relevant following the discontinuation of prazosin, creating a need for effective and well-tolerated substitutes.

Preliminary evidence comes from case reports and small case series describing significant reductions in TRNs frequency, intensity, or associated distress following doxazosin treatment. Calegaro et al. reported three cases of PTSD patients experiencing full or partial remission of TRNs, although outcomes were based solely on patient self-reports [57]. Pallesen et al. described a patient who maintained a nightmare diary and achieved complete symptom relief with 8 mg/day of doxazosin, whereas lower doses were ineffective [58]. In another report, Sethi and Vasudeva observed improvement in both PTSD Checklist scores and sleep parameters in a military patient after gradual titration from 1 to 4 mg/day [59]. More recently, Hessel et al. [60] and Khan et al. [61] presented four cases in which switching to doxazosin after symptom relapse following prazosin discontinuation led to renewed improvement, suggesting therapeutic continuity between both $\alpha_1$-antagonists. While anecdotal, these reports consistently highlight reductions in TRNs frequency, improved sleep continuity, and good tolerability across diverse clinical contexts.

Two early exploratory studies provided initial controlled evidence. In an open-label pilot trial of 12 civilians and veterans, De Jong et al. observed significant reductions in Clinician-Administered PTSD Scale (CAPS) scores [62]. Similarly, Rodgman et al. conducted a within-subject, double-blind, placebo-controlled study ($n = 8$) and reported lower PTSD Checklist-Military (PCL-M) scores after four days of 16 mg/day doxazosin, with parallel – but nonsignificant – improvements on the CAPS hyperarousal subscale [63]. A larger retrospective chart review of 51 patients found a significant reduction in TRNs frequency over 12 weeks, with one quarter achieving full remission and early sleep recovery within the first month [64]. These findings support a favorable therapeutic signal, though replication in larger samples is warranted.

Conversely, a randomized controlled trial in veterans with comorbid PTSD and alcohol use disorder did not show significant differences between doxazosin and placebo groups, despite significant global symptom reduction across both groups [65]. The authors suggested that the co-occurring substance use disorder may have masked doxazosin's potential benefit on PTSD symptoms. Most recently, a randomized, double-blind, placebo-controlled trial by Richards et al. ($n = 65$, including 60 veterans and 21 women) assessed doxazosin for TRNs [66]. Although CAPS-IV and PSQI scores did not differ significantly from placebo, the doxazosin group showed statistically significant improvements in sleep maintenance and TRNs severity on prespecified sleep diary measures. The authors noted that a strong placebo effect may have limited between-group differentiation.

Taken together, available evidence – though limited in scale and methodological rigor – suggests that doxazosin may alleviate TRNs and improve sleep quality in PTSD. Benefits appear most pronounced in patients with marked adrenergic hyperarousal or those previously responsive to prazosin. Tolerability is generally good, and PR formulations may offer practical advantages for once-daily dosing and sustained overnight action. The mixed outcomes observed in randomized controlled trials likely reflect methodological factors including small sample sizes, heterogeneous populations (e.g., civilians vs. veterans, comorbidities such as alcohol use disorder), variable outcome measures (CAPS, PSQI, sleep diaries), and short trial durations, as well as potential placebo responses. Further large-scale studies are required to establish optimal dosing, treatment duration, and predictors of response. In light of prazosin's market withdrawal and the need to maintain adrenergic modulation in PTSD, doxazosin currently represents a pragmatic alter-

**Table 1**
Contraindications and safety considerations.

| |
|---|
| Contraindications |
| – Hypersensitivity to the active substance, doxazosin, to other quinazolines, or to any of the excipients |
| – History of symptomatic orthostatic hypotension |
| – Benign prostatic hyperplasia associated with upper urinary tract congestion, chronic urinary tract infections, or bladder stones |
| – History of esophageal or gastrointestinal obstruction, or any degree of narrowing of the gastrointestinal lumen[a] |
| – Patients with clinically significant hypotension[b] |
| – Bladder overflow (urinary retention), anuria, or progressive renal insufficiency |
| Acute cardiac conditions |
| As with all antihypertensive agents that have vasodilatory effects, doxazosin should be administered with caution in patients suffering from any of the following acute cardiac conditions: |
| – Pulmonary edema secondary to aortic or mitral stenosis |
| – High-output heart failure |
| – Right-sided heart failure due to pulmonary embolism or pericardial effusion |
| – Left ventricular failure with low filling pressure |
| In hypertensive patients with one or more cardiovascular risk factors, doxazosin should not be used due to a possible increased risk of developing heart failure |
| Hepatic impairment |
| – Being extensively metabolized by the liver, doxazosin should be administered with caution in patients with established hepatic impairment |
| – Due to the lack of clinical data, doxazosin use is not recommended in patients with severe hepatic impairment |
| – Caution is advised when doxazosin is administered concomitantly with medicinal products that may affect hepatic metabolism |
| Renal impairment |
| The pharmacokinetics of doxazosin are not significantly altered in patients with renal impairment; therefore, no dose adjustment is recommended |
| Fertility, pregnancy and lactation |
| Excretion of doxazosin into human breast milk was found to be very low (with a relative dose to the infant of less than 1%). However, as clinical data are lacking, the benefit–risk balance should be carefully assessed in consultation with the prescribing physician |
| Elderly patients |
| Pharmacokinetic studies of doxazosin in elderly patients have shown no significant alterations compared to younger subjects |
| Use with PDE-5 inhibitors: |
| – The concomitant administration of doxazosin with a phosphodiesterase type 5 (PDE-5) inhibitor may cause symptomatic hypotension in some patients. To reduce the risk of orthostatic hypotension, initiation of PDE-5 inhibitors is recommended only in hemodynamically stable patients already receiving alpha-blocker therapy |
| – PDE-5 inhibitor treatment should be started at the lowest possible dose, and a minimum interval of at least 6 hours should be respected between the intake of doxazosin and the PDE-5 inhibitor. No studies have been conducted with prolonged-release formulations of doxazosin |
| Use in patients undergoing cataract surgery: |
| – Intraoperative Floppy Iris Syndrome (IFIS), a variant of the small pupil syndrome, has been observed during cataract surgery in some patients treated or previously treated with tamsulosin |
| – Isolated cases have also been reported with other alpha-1 blockers, and a class effect cannot be excluded |
| – Since IFIS may cause additional technical difficulties during cataract surgery, any current or prior use of alpha-1 blockers should be reported to the ophthalmic surgeon before the procedure |

National Agency for the Safety of Medicines and Health Products (ANSM). Summary of product characteristics – doxazosin. Updated June 10th, 2024. Accessed October 12th, 2025. Available at: https://base-donnees-publique.medicaments.gouv.fr/medicament/67970560/extrait#tab-rcp.

[a] Applicable only to patients treated with the prolonged-release tablets.

[b] Applicable only to the indication of benign prostatic hyperplasia.

native. The following section presents a clinical framework for its safe initiation, monitoring, and integration into multimodal care strategies for TRNs.

### 4.2. Doxazosin clinical toolbox and initiation protocol

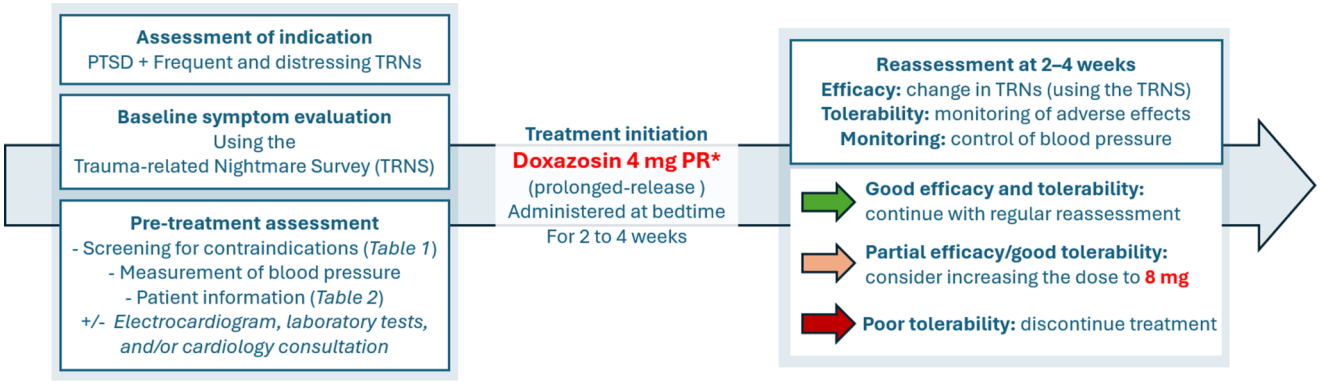
In France, doxazosin is available in two non-divisible PR formulations: 4 mg PR tablets and 8 mg PR tablets. For its two approved indications – essential hypertension and lower urinary tract symptoms associated with benign prostatic hyperplasia – treatment is initiated at 4 mg PR once daily, which may be increased to 8 mg PR per day depending on efficacy and tolerability. In studies evaluating its effects on TRNs, doxazosin was generally initiated at a 1 mg bedtime dose (using non-PR formulations when available), then gradually increased to a maximum of 10 mg at night, according to clinical response and tolerance [66,67]. In the French context, initiation below 4 mg is not feasible with PR tablets; however, starting at 4 mg PR is commonly used safely for other indications, and adherence to standard precautions and monitoring is expected to allow safe titration in TRNs.

Before initiating doxazosin, contraindications must be ruled out, and specific precautions should be observed (Table 1). The baseline assessment should include an evaluation for hypotension or orthostatic hypotension, which may be exacerbated by doxazosin. Blood pressure monitoring is recommended at treatment initiation and after any subsequent dose increase. Depending on the clinical context, a standard laboratory work-up (including hepatic function tests), an electrocardiogram, and a cardiology consultation may be warranted. Patients should be provided with detailed information regarding the benefit-risk balance, correct use of the medication, and management of potential adverse effects (Table 2).

The TRNS can thus be used to perform an initial assessment of TRNs [3], particularly regarding their frequency and associated distress. It also serves as a standardized monitoring tool, enabling clinicians to track symptom evolution and to inform the clinical discussion surrounding sleep disturbances in patients with PTSD.

Fig. 1 presents a proposed algorithm for doxazosin initiation and titration using the 4 and 8 mg prolonged-release formulations.

In the absence of formal recommendations regarding prazosin tapering or discontinuation, and in patients without hypertension, a gradual dose reduction of 2.5 mg per week until cessation may be considered prior to initiating doxazosin.




*PR Prolonged-Released; PTSD Post-Traumatic Stress Disorder; TRNs Trauma-related Nightmares; TRNS Trauma-related Nightmare Survey.*
**See Tables 1 and 2 for safety.*

**Fig. 1.** Doxazosin initiation and follow-up protocol (prolonged-release formulations).

**Table 2**
Information to be provided to the patient.

| |
|---|
| – Due to the prolonged-release formulation, the tablets must be swallowed whole and must not be chewed, divided, or crushed |
| – Patients may experience postural dizziness or orthostatic hypotension, characterized by dizziness and weakness or, rarely, syncope, particularly at the beginning of treatment. They should be advised to avoid situations in which these symptoms could lead to injury at the start of doxazosin therapy. In case of severe or disabling adverse effects, the patient should discontinue the medication and consult the prescribing physician immediately |
| – In the event of sexual dysfunction, the patient should consult their physician to discuss the potential initiation of treatment with a PDE-5 inhibitor; self-medication is contraindicated |
| – In the event of priapism, medical advice should be sought immediately |

National Agency for the Safety of Medicines and Health Products (ANSM). Summary of Product Characteristics–Doxazosin. Updated June 10th, 2024. Accessed October 12th, 2025. Available at: https://base-donnees-publique.medicaments.gouv.fr/medicament/67970560/extrait#tab-rcp.

### 4.3. *Doxazosin integration into the care pathway*

Doxazosin should not be viewed as a stand-alone or curative treatment, but rather as one component within a multimodal therapeutic strategy for PTSD. Its use should emerge from a global clinical reflection integrating the patient's trauma history, comorbidities, and previous therapeutic responses, in accordance with the pharmacological and non-pharmacological approaches detailed in Sections 2 and 3. The rationale for prescribing doxazosin lies in its potential to reduce TRNs and improve sleep continuity, thereby facilitating engagement in trauma-focused psychotherapies and overall functional recovery. However, its introduction should always be embedded within a comprehensive, individualized care plan, coordinated across psychiatry, primary care, and psychotherapy. Fig. 2 illustrates the integrated PTSD care framework, highlighting the position of doxazosin among complementary therapeutic domains and intervention targets.

## 5. Discussion

This review addresses the major clinical challenge posed by trauma-related nightmares (TRNs), a core feature of PTSD known to severely disrupt sleep continuity, emotional processing, and engagement in trauma-focused treatments. TRNs often perpetuate hyperarousal, avoidance, and maladaptive sleep habits, contributing to a self-reinforcing cycle of sleep fragmentation and symptom worsening [25,30]. In this context, the recent withdrawal of prazosin in France has created a critical therapeutic gap. The present work proposes a timely synthesis of emerging evidence supporting doxazosin as an alternative $\alpha_1$-adrenergic antagonist, while situating its use within a multimodal and clinically coherent approach.

### 5.1. *Doxazosin: limitations, clinical positioning, and future directions*

Doxazosin, like prazosin, is prescribed off-label for PTSD in France. This requires explicit informed consent, careful documentation, and clear clinical justification. The place of $\alpha_1$-adrenergic antagonists within PTSD treatment remains debated. Earlier randomized trials supported prazosin's efficacy [50,53], leading to a Level A recommendation by the American Academy of Sleep Medicine [21]. However, subsequent mixed findings, including the VA Cooperative Study #504 [52], led to a reassessment: the 2018 AASM Position Paper maintained imagery rehearsal therapy (IRT) as the only strongly recommended intervention for nightmares, while prazosin was reclassified among treatments that may be used depending on individual clinical profiles [22].

In this landscape, doxazosin emerges as a potential alternative rather than a replacement. Evidence supporting its use remains limited to small sample sizes, controlled studies and case reports, but consistently suggests improvement in TRN frequency, distress, and sleep continuity [57,58,64]. Yet randomized trials yield mixed results, with some benefits observed only on sleep diary parameters [66]. These inconsistencies highlight the need for large, methodologically robust trials assessing optimal dosing, predictors of response, and long-term outcomes.

Doxazosin's potential therapeutic role may extend to specific PTSD phenotypes characterized by marked adrenergic hyperarousal, heightened autonomic reactivity, or long-standing TRNs unresponsive to first-line psychotherapies. This aligns with dimensional approaches to PTSD treatment and future directions in precision psychiatry.

### 5.2. *TRNs within a broader sleep pathology framework*

Although TRNs represent a central symptom, they rarely occur in isolation. Sleep disorders are ubiquitous in PTSD, including insomnia, sleep fragmentation, circadian disruption, and obstructive sleep apnea (OSA). Insomnia is one of the most disabling features and a major treatment target. Cognitive Behavioral Therapy for Insomnia (CBT-I) has shown robust efficacy across comorbid populations, reducing sleep onset latency, nighttime awakenings, and improving sleep efficiency [30–32]. Importantly, CBT-I alone can reduce TRN frequency – sometimes as effectively as IRT – and facilitate improvement in overall PTSD severity [25,34].

Body- and movement-oriented interventions (e.g., relaxation, yoga, structured physical activity) also demonstrate beneficial effects on sleep

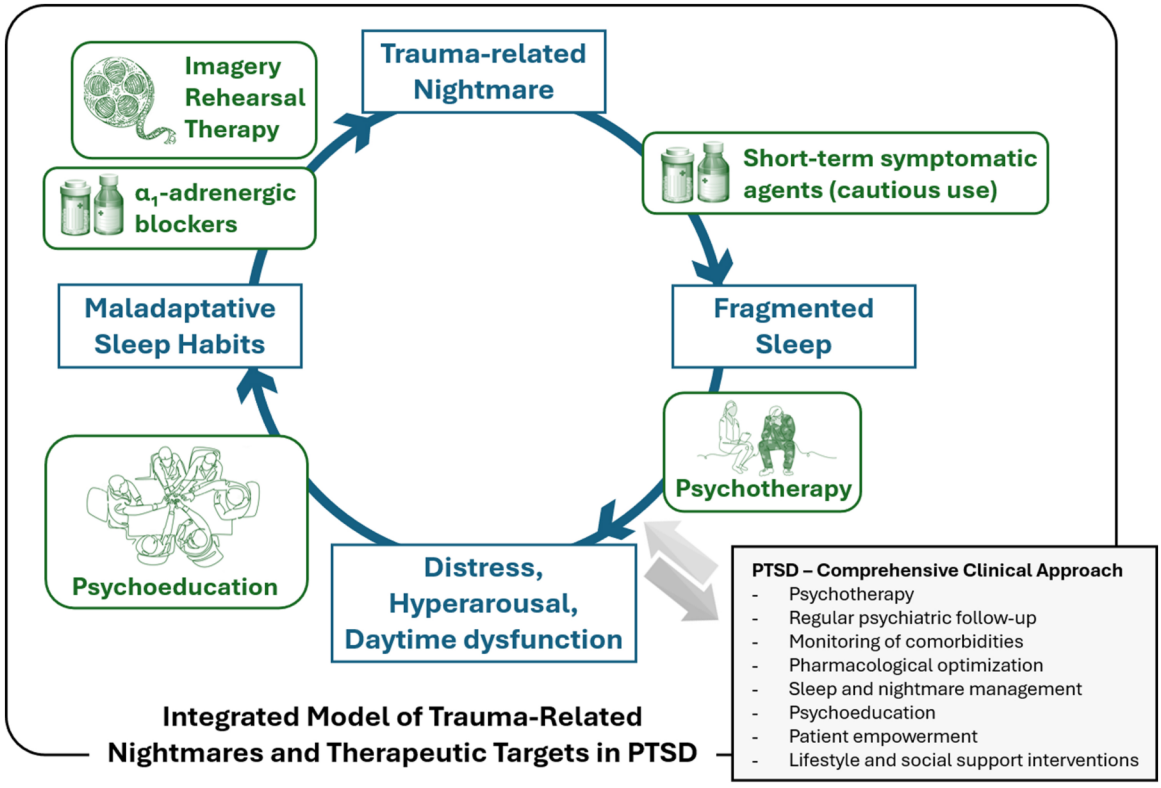



**Fig. 2.** PTSD Management Model with Nightmare-Focused Interventions.

quality and emotional regulation [37,38], and are increasingly integrated into multimodal PTSD programs.

OSA remains underdiagnosed in PTSD, despite its high prevalence and clinical relevance. Shared symptoms – including nocturnal awakenings, fatigue, cognitive attenuation, and irritability – can obscure diagnosis. Untreated OSA has been associated with poorer outcomes in trauma-focused therapy and heightened daytime hyperarousal. Systematic screening and access to sleep studies are therefore essential components of comprehensive PTSD care [68–71].

These findings highlight the need to conceptualize TRNs not as an isolated symptom but as part of a broader sleep disturbance ecosystem requiring comprehensive evaluation and multimodal intervention.

### *5.3. Integrating doxazosin into personalized and coordinated PTSD care*

PTSD treatment relies on coordinated, staged, and individualized care pathways. IRT remains the cornerstone psychotherapeutic approach for TRNs, supported by high-quality evidence and international recommendations [20,23]. However, IRT may be less effective in military populations whose nightmares are immersive and replicative, often reenacting the traumatic scene and confronting death [26]. In such cases, reducing adrenergic reactivity and improving sleep maintenance via pharmacological modulation may facilitate engagement in psychotherapies.

Doxazosin should therefore be conceptualized not as a curative treatment but as a facilitator – an agent that restores sleep continuity, reduces nighttime adrenergic spikes, and creates the conditions for psychological work. Its integration must be embedded within a comprehensive plan including psychotherapy, psychoeducation, sleep hygiene, treatment of comorbidities, and structured follow-up.

Therapeutic education programs, already implemented in French military hospitals, strengthen patient empowerment and integrate behavioral, pharmacological, and psychoeducational strategies to target sleep disturbances [18,35]. This model aligns perfectly with the positioning of doxazosin as an adjunctive, not primary, intervention.

Most evidence on doxazosin for TRNs comes from military PTSD populations. In contrast, studies in civilian populations suggest that psychotherapeutic interventions such as IRT can reduce nightmare frequency, improve sleep quality, and alleviate associated psychiatric symptoms, not only in trauma-exposed individuals but also in patients with depression, anxiety, or suicidal ideation [19,27,28]. These findings highlight potential differences in clinical profiles and treatment responsiveness between military and civilian populations. While doxazosin may hold promise for civilian patients experiencing adrenergic hyperarousal, its safety and efficacy outside military PTSD remain largely untested. Dedicated trials in civilian cohorts are therefore needed to clarify its role and to guide individualized, multimodal care strategies that combine pharmacological and psychotherapeutic approaches.

## 6. Conclusion

Trauma-related nightmares are a disabling manifestation of PTSD and contribute to a self-reinforcing cycle of sleep disruption and daytime symptom exacerbation. With prazosin's market withdrawal in France, doxazosin offers a pharmacologically coherent and potentially useful alternative, especially for patients exhibiting pronounced adrenergic hyperarousal or persistent TRNs despite psychotherapy. However, current evidence remains limited and heterogeneous, underscoring the need for large, randomized trials.

Effective PTSD management extends far beyond pharmacology. Doxazosin should be used as part of a coordinated, staged, and individualized treatment pathway, supporting sleep restoration, psychological stabilization, and long-term functional recovery.

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## Authors' contributions

G.S. and E.S. jointly designed the structure and objectives of the manuscript, coordinated the overall writing process, and supervised the integration of clinical and pharmacological perspectives. All authors contributed to drafting specific sections according to their expertise: J.-B.R., D.F., S.H.-P., C.L., M.R., D.D., F.G.-F., and S.A. participated in the literature review, manuscript writing, and critical revision for important intellectual content. G.S. finalized the manuscript for submission. All authors approved the final version and agreed to be accountable for all aspects of the work.

## Disclosure of interest

The authors declare that they have no competing interest.

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