Drugs Used in Parasomnia

Paola Proserpio, MD[a], Michele Terzaghi, MD[b], Raffaele Manni, MD[b], Lino Nobili, MD, PhD[a,c,*]

KEYWORDS

• Disorders of arousal • REM behavior disorder • Sleep-related eating disorder • Sleep enuresis • Benzodiazepines • Clonazepam • Melatonin • Antidepressant drugs

KEY POINTS

- Nonrapid eye movement (NREM) parasomnias, especially during childhood, are often benign conditions, and pharmacologic therapy is usually unnecessary.
- There are no properly powered randomized controlled studies evaluating the efficacy of pharmacologic therapy for NREM parasomnias.
- The most commonly used drugs for NREM parasomnias are intermediate- and long-acting benzodiazepines and antidepressants. Anecdotal cases reported the efficacy of melatonergic agents and hydroxytryptophan.
- The pharmacologic treatment of rapid eye movement sleep behavior disorder is symptomatic, and the most commonly used drugs are clonazepam and melatonin.

INTRODUCTION

Parasomnias are defined as "undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousal from sleep."[1] Depending on the sleep stage of occurrence, they are classified as nonrapid eye movement (NREM)-related parasomnias (confusional arousals, sleepwalking, sleep terrors, and sleep-related eating disorder), rapid eye movement (REM)-related parasomnias (REM sleep behavior disorder [RBD], recurrent isolated sleep paralysis, and nightmare disorder), and other parasomnias (exploding head syndrome [EHS], sleep-related hallucinations, and sleep enuresis [SE]).[1]

Parasomnias are not generally associated with a primary complaint of insomnia or excessive sleepiness, although this last one may be present in some of them. On the other hand, parasomnias can be associated with possible resulting injuries, adverse health, and negative psychosocial effects. Moreover, the clinical consequences of parasomnias can affect the patient, parents, or both.

Parasomnias, especially disorders of arousal (DOA) during childhood, are often relatively benign and transitory and do not usually require a pharmacologic therapy. A relevant aspect in both NREM and REM parasomnia treatment is to prevent sleep-related injuries by maintaining a safe environment. Physicians should always evaluate the possible presence of favoring and precipitating factors (sleep disorders and drugs). A pharmacologic treatment may be indicated in case of frequent, troublesome, or particularly dangerous events. The aim of this article is to review current available evidence on pharmacologic treatment of different forms of parasomnia.

NON RAPID EYE MOVEMENT PARASOMNIAS

Disorder of Arousal from Non Rapid Eye Movement Sleep

DOA are the subgroup of parasomnias arising from NREM sleep, encompassing confusional arousals, sleep terrors, and sleep walking.[1] They are most prevalent during childhood and normally cease

[a] Department of Neuroscience, Centre of Sleep Medicine, Centre for Epilepsy Surgery, Niguarda Hospital, Piazza Ospedale Maggiore, Milan 3-20162, Italy; [b] Sleep Medicine and Epilepsy, IRCCS Mondino Foundation, Via Mondino, Pavia 2-27100, Italy; [c] Department of Neuroscience (DINOGMI), University of Genoa, Child neuropsychiatry, Gaslini Institute, Via Gerolamo Gaslini, Genoa 5-16147, Italy
* Corresponding author. Department of Neuroscience, Centre of Sleep Medicine, Niguarda Hospital, Piazza Ospedale Maggiore, Milan 3-20162, Italy
E-mail address: lino.nobili@ospedaleniguarda.it

Sleep Med Clin ■ (2018) ■–■
https://doi.org/10.1016/j.jsmc.2018.02.003

by adolescence, but onset or persistence during adulthood is well recognized.[2] More than one type may coexist within the same patient.[3] Many clinical features are common to these manifestations.[4,5] First, they generally occur during deep NREM sleep (N3) and, thus, most often take place in the first third of the night. During the episode, patients are usually unresponsive to the environment and completely or partially amnestic after the event. A positive family history is frequently found in DOA. Finally, any factor that deepens (sleep deprivation, stress, febrile illness, medications, alcohol) or fragments sleep (external or internal stimuli, sleep disorders, mental activity) may increase the occurrence of DOA.

DOA are generally considered benign phenomena. However, especially in adults, they can be characterized by complex behavior with potentially violent or injurious features[6] or be associated with significant functional impairment, such as daytime sleepiness, fatigue, and distress.[7] Therefore, evaluation and treatment are recommended in these cases, especially when violent manifestations are frequent or very disturbing for the patient or other family members.

The management of DOA is not well codified. No drug has yet been approved, and there are no properly powered randomized controlled studies evaluating the efficacy of behavioral or pharmacologic interventions for DOA.[8] Current treatment recommendations are based on scarce evidence derived from expert opinions, case reports, and only few case series. To date, the largest retrospective case series, analyzing treatment options and efficacy in DOA, refers to a population of 103 adults.[9]

Only recently, a self-administered scale has been developed with the aim of providing a valid and reliable tool able to assess the diagnosis and severity of NREM parasomnia as well as to monitor the efficacy of treatment.[10] Considering that evidence is lacking for off-label use of pharmacologic agents, clinicians may wish to ensure that patients are fully informed about all therapeutic options.[8]

Nonpharmacologic treatment

As previously discussed, if the episodes are rare, or not associated with harm potential, treatment is often unnecessary. Management includes reassuring patients about the usual benign nature of the episodes. Parents or bed partners should be instructed to keep calm and not to insist in trying to awaken the patient because this may aggravate or lengthen the episodes.[11] Precautions should be taken to ensure a safe sleep environment. Simple safety measures can include the removal of obstructions in the bedroom, securing windows, sleeping on the ground floor, and installing locks or alarms on windows, doors, and stairways.[4,11]

Every priming or triggering factor should be investigated and avoided. For instance, every effort should be made to ensure regular and adequate sleep routines, to prevent sleep loss or disruption of the sleep-wake cycle. Sleep disorders (sleep apnea or periodic leg movements) must be recognized and treated.[12] Moreover, patients should avoid the intake of drugs or substances that could favor the occurrence of episodes (alcohol, hypnotics, antipsychotics, antidepressants, antihistamines).

Some investigators proposed “scheduled awakenings” in the case of DOA occurring nightly and consistently at or around the same time each night.[13] In adults, a psychological approach may be considered (hypnosis, relaxation therapy, or cognitive behavioral therapy), although studies evaluating its efficacy have provided contrasting results.[14,15]

Pharmacologic treatment

The main indications for a pharmacologic treatment in patients with DOA encompass the following: (1) persistence of frequent episodes despite resolution and removal of all potential predisposing and precipitating factors; (2) high risk of injury for the patient or the family; (3) significant functional impairment (such as insomnia, daytime sleepiness, weight gain from nocturnal eating); (4) potential legal consequences related to sexual or violent behavior.

As illustrated above, if drug therapy is planned, patients or their parents should be advised that drugs for DOA are considered “off label” and, if the decision is to prescribe, a patient’s written consent is recommended.

Benzodiazepines Intermediate and long-acting agents in the benzodiazepine class of sedative hypnotics (BZD) are the most frequently used treatment of DOA,[4,11,16] although they have never been approved for this indication. They act by increasing the chloride conductance through GABA A receptors,[17] thus inducing a hypnotic-sedative effect. It is worth reminding that BDZ may have muscle-relaxing properties and should be used with caution if comorbid sleep-disordered breathing is suspected. The use of BZD in the treatment of DOA is apparently paradoxic, considering that other sedative-hypnotics such as non-BZD receptor agonists can induce amnestic nocturnal behavior.[18] The exact mechanism by which BZD suppress DOA is unknown. Probably, their effectiveness may be related to