SLEEP MEDICINE PHARMACEUTICALS: THE TREATMENT OF PARSOMNIAS

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This month's column will focus on Parasomnias, which are undesirable motor, sensory, or behavioral phenomena that occur primarily during sleep. These phenomena range from normal to abnormal, from benign to potentially lethal, and can be associated with normal developmental processes or neurodegeneration. The International Classification of Sleep Disorders, revised in 2000, lists 24 Parasomnias encompassing non-REM, or arousal disorders, REM-related disorders, sleep-wake transition disorders, and "other parasomnias." We will focus on common non-REM and REM parasomnias in this article.

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Non-REM parasomnias, also termed "arousal disorders", such as Confusional Arousals, Sleep Terrors, or Sleep Walking can be considered "primary sleep disorders" or "secondary" when associated with an identifiable cause such as a seizure disorder, obstructive sleep apnea, nocturnal cardiac ischemia, or nocturnal paroxysmal dystonia, for example.

The pathophysiological mechanisms underlying arousal disorders are still unclear, but current hypotheses suggest that they may result from the brain being in a state of partial wakefulness and non-REM sleep, *simultaneously*. This leads to an ability to perform complex motor and/or verbal actions without conscious awareness, and thus responsibility, for these actions.

Primary arousal disorders share several common factors including familial clustering which suggests a genetic predisposition, a childhood predominance, and that they typically occur during non-REM sleep.

Confusional Arousals are characterized by episodes of marked mental confusion during or after an arousal from sleep. They typically occur during the first third of the night, last from 30 seconds up to five minutes, and may be accompanied by mumbling and/or automatic behaviors. During the event, the person does not leave their bed and there are no signs of fear or terror. Following a Confusional Arousal, the person usually falls back to sleep with no recollection of the event (retrograde amnesia) upon awakening the next morning.

Triggers for Confusional Arousals include anything that either fragments sleep or else enhances slow wave sleep. Examples include environmental factors (noise, temperature, etc), stress, fever, pain, pregnancy, recovery from sleep deprivation, or medications acting upon the central nervous system. As mentioned earlier, youth, family history, as well as a history of being a "deep" sleeper are also associated with confusional arousals.

Sleep Terrors, much like Confusional Arousals, occur during the first third of the night. They also emerge from slow wave sleep and can last from 30 seconds up to five minutes. The triggers for Sleep Terrors are also similar to those for Confusional Arousals. The primary difference being, unlike Confusional Arousals, Sleep Terrors are accompanied by an abrupt awakening, an intense scream, and inconsolable fear or terror.

Sleep Terrors most frequently occur in children aged 5-7 years, and appear with equal prevalence between boys and girls. Most children with Sleep Terrors "outgrow" these events by the age of 8 years. Up to 36% may continue to experience them into adolescence while only 1% experience Sleep Terrors as adults.

Another non-REM parasomnia, Somnambulism (sleep walking), also emerges from slow wave sleep, but is also characterized by the presence of automatic behaviors of varying complexity, including walking, eating, mumbling, and rarely, violence. The duration of these events can be from 15 minutes to hours. The event is usually self-limited, and terminates with a return to sleep. Clinical evidence demonstrates that attempts to intervene may be met with resistance and outbursts.

As with other non-REM parasomnias, the familial clustering of Somnambulism suggests a genetic predisposition. Triggers for Somnabulism, such as sleep fragmentation and increased depth and/or duration of slow wave sleep, are also similar as that of other arousal disorders. The initial age of onset for Somnabulism is 5 years while the highest prevalence occurs in 12 year olds. Up to 15-30% of children and early adolescents experience Somnambulism, with boys and girls equally affected. Most children who are sleep walkers will typically "outgrow" it by age 15. Up to 1% continues with episodes into adulthood.

Another clinically identifiable category of parasomnias occur during Rapid Eye Movement (REM) sleep, and for this reason typically occur in the second half of the night. These include REM Sleep Behavior Disorder (RBD), Nightmare Disorder and Isolated Sleep Paralysis. Unlike non-REM

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parasomnias, or arousal disorders, REM parasomnias usually affect adults more often than children and do not follow a similar genetic pattern of inheritance. RBD, in particular, is associated with neurodegenerative disorders such as Parkinson's disease and Multiple Systems Atrophy and usually occurs in older men. The symptoms include violent dream-enactment behavior due to a loss of atonia during REM sleep. If left untreated, RBD can cause serious injury to sufferers as well as bed partners.

Treatment for non-REM and REM parasomnias frequently include avoidance of potential triggers, and in the case of Somnabulism and RBD, also necessitate a safe well-monitored sleeping environment. The most common pharmaceutical intervention for REM and non-REM parasomnias is longer-acting benzodiazepines. Through pharmacological reduction of slow wave sleep, as well as potential reduction in the number of transitions between sleep-states, benzodiazepine's reduce the "triggers" that may potentiate the onset of an arousal disorder or RBD episode.

Benzodiazepine's were initially developed in the early part of the 1950's by Dr. Leo Sternbach an Austrian scientist at Hoffman-LaRoche. The first benzodiazepine, to be synthesized was chlordiazepoxide, which later became known as Librium. The tranquilizing effects of Librium soon led to its use in the treatment of anxiety. This, coupled with the lack of adverse effects that were frequently observed in patients taking barbituates, soon led to clinical utility and acceptance.

The success of Librium led to further research and development of the Benzodiazepines. Among the more notable drugs in this class are diazepam (Vaium), nitrazepam (Mogadon), temazepam (Restoril), and flurazepam (Dalmane), all of which were introduced between 1963 and 1973. Currently, over 20 benzodiazepines are known. Some of these, such as midazolam (Versed) are employed frequently as acute hypnotics, while others, such as clonazepam (Klonopin) are popular parasomnia treatments and even anti-epileptics.

Considerations for employing benzodiazepines include their half-life, the amount of time required for one-half of the active drug to be metabolized or eliminated from the body. Short-acting benzodiazepines have half-lives of 12 hours or less while long-acting benzodiazepines have half-lives which often exceed 24 hours. A gradual increase in the blood levels of a longer-acting drug has the potential to cause residual effects. For example, a benzodiazepine taken in the evening to reduce the likelihood of experiencing an arousal event may induce residual sleepiness that intrudes into the next day's normal waking period.

With regards to pharmaceutical intervention for arousal disorders, the role of benzodiazepines is to suppress the overall amount of time spent in slow wave non-REM sleep. In terms of the mechanism of action that benzodiazepines exert in treating REM parasomnias such as RBD, there are no clear conclusions. Although little is known regarding the precise pharmacologic action of benzodiazepines on neural systems underlying parasomnias, it is clear that many parasomnias are effectively treated with longer-acting benzodiazepines such as clonazepam. Of course judicious selection of the appropriate benzodiazepine for a particular patient is essential in order to reduce the likelihood of residual daytime sleepiness. This is especially important to consider when treating parasomnias as many of the patients who experience them are children or older adults.

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