

HYPNOTIC DRUGS AND PARASOMNIAS

by Regina Patrick RPSGT



Chlordiazepoxide, which has been marketed since 1960 under the trade name Librium, was the first benzodiazepine used to treat anxiety and insomnia. The development of other benzodiazepines soon followed: diazepam (Valium) in 1963; nitrazepam (Mogadon) in 1965; lorazepam (Ativan) in 1977; triazolam (Halcion) in 1982; and alprazolam (Xanax) in 1981. An infrequent side effect of benzodiazepines is that they can induce sleep walking or other sleep behavior in some people. Interestingly, recently developed classes of hypnotic drugs – the imidazopyridines, pyrazolopyrimidines, and cyclopyrrolones – can similarly cause sleep walking and other sleep behaviors (e.g., sleep-driving, sleep eating) as a side effect. Although the new hypnotics are not in the benzodiazepine class, they interact with the benzodiazepine receptor. It may be this interaction which explains why they can induce sleep walking and other sleep behaviors.

Imidazopyridine substances have been the focus of research since the 1950s. In 1985, zolpidem was the first imidazopyridine investigated for clinical use as a hypnotic. It has been available in Europe since 1988 and in the US since 1993 as a *Ambien*.

Pyrazolopyrimidine substances have been synthesized since the 1970s. In 1993, zaleplon (Sonata) was the first pyrazolopyrimidine investigated for clinical use as a hypnotic. The FDA approved its use in 1999. A second pyrazolopyrimidine, indiplon, has been undergoing clinical investigations since 2002. It currently has no trade name and has not been FDA approved yet.

Cyclopyrrolone substances have been synthesized since the 1980s. Zopiclone (Imovane and Zimovane) was first investigated for clinical use in 1980. It has been available as a prescription drug since 1988 in Europe but has no FDA approval in US. A second cyclopyrrolone, suriclone, was developed in 1983. It currently has no trade name or FDA approval. A third cyclopyrrolone is eszopiclone (Lunesta) has been in use in Europe since 1992; the FDA approved its use as a hypnotic in 2005 in the United States.

The imidazopyridines, cyclopyrrolones, and pyrazolopyrimidines exert their sedative effect by binding to the benzodiazepine portion (the omega receptor) of the gamma-aminobutyric acid/benzodiazepine (GABA-BZD) receptor. The GABA-BZD receptor is a macromolecule that is found on a cell's membrane. One portion of the macromolecule binds with a GABA molecule and a separate portion of the macromolecule binds with a BDZ molecule. When a GABA molecule binds to its site on the macromolecule, negatively charged calcium ions flood into a cell. The increased intracellular negative charge inhibits neuronal firing. When BDZ simultaneously binds to its site on the macromolecule, it enhances the influx of calcium into the cell. Decreased neuronal firing is more pronounced which results in the sedation and hypnotic effects noted with BDZ use.

The omega receptor has three subtypes: omega1, omega2, and omega3. Stimulation of the omega1 and omega3 receptor subtypes results in sedation and reduced anxiety. Unwanted effects from stimulating the omega1 receptor subtype are impaired memory and ataxia (impaired muscle coordination). Stimulation of the omega2 subtype results in muscle relaxation.

Benzodiazepine drugs bind to all three omega receptor subtypes resulting in their sedative, anxiolytic, muscle relaxant effects as well as the unwanted effects of amnesia and ataxia. The new classes of hypnotic drugs bind to the omega1 subtype resulting in their sedative and anxiolytic effects as well as amnesia and ataxia. Unlike benzodiazepines, the new hypnotic drugs do not have a muscle relaxant effect since they do not bind to the omega2 receptor subtype. The omega1 subtype is located on the pars reticulata; the molecular layer of the cerebellar cortex; the Lamina IV fibers in the spinal cord; the ventral thalamic complex; the pons; the inferior colliculi; and the globus pallidus. Some of these brain regions play a role in balance, coordination, body movements, and walking. Stimulation of the areas by hypnotic drugs during sleep may explain the manifestation of sleep-driving, sleep-eating, and sleep walking.

Sleep-driving

A person gets out of bed during sleep to drive. He may drive to a location without incident but have no memory of having driven by the next day, or, he may awaken in a location other than the one he went to sleep with no memory of how he arrived there. If the person has an accident, he will later have no memory of how the accident occurred.

Onlookers may note that the person: is driving erratically or unusually slow; appears drunk or drugged; talks or responds ver-

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bally nonsensically or has slow and slurred speech; appears disoriented; or that the person has slowed reflexes or a lack of balance and coordination.

Sleep-eating

A person gets out of bed to eat, often excessively. The person may eat odd combinations of food (e.g., mayonnaise and sugar sandwich) or inadvertently eat dangerous things (e.g., cleanser).

Later, the person may awaken to food wrappers inexplicably strewn about the house; find evidence that cooking has occurred during the night (e.g., finding a stove burner in the "on" position even though the person had turned it off before going to bed); awaken with traces of food or other substances in their mouth; or have unexplained weight gain. Onlookers may note that a person appears dazed while eating or observe a sleep-eater preparing strange food combinations or eating dangerous substances in a dazed or careless manner.

Sleep walking

A person gets out of bed and walks around aimlessly. He may harm himself by tripping over things or may inadvertently walk into dangerous situations (e.g., leaving the home to walk in traffic). He may awaken to find himself in a location other than where he had gone to sleep with no memory of how he arrived there.

Onlookers may note that the person appears dazed or walks in an haphazard fashion. If an onlooker attempts to question him, the person may answer nonsensically.

Drug-induced sleep walking or other sleep behavior can manifest after improper use of a hypnotic drug. For example, some people use alcohol with a drug thereby intensifying the effects of amnesia, incoordination, etc.; or a person either pur-

posefully or accidentally takes an overdose of a drug; or a person takes a drug at an improper time (such as late afternoon rather than before bedtime) which allows a drug to take effect during driving or other activity rather than at bedtime.

However, not all cases of drug-induced sleep behaviors involve the misuse of a drug. In some cases, sleep behaviors occurred in a person who already had a history of sleep walking. Since the new non-benzodiazepine hypnotics increase slow wave sleep, the likelihood of inducing sleepwalking or other sleep behavior is increased in a person with a history of sleep walking.

Drug-induced sleep walking or other sleep behaviors can occur in people who are using a drug correctly and who do not have a history of sleep walking or other sleep behavior. Researchers Jeffrey Harazin and Timothy R. Berigan report the case of a patient who had zolpidem-induced sleepwalking. The patient had had no history of sleepwalking previous to using the drug which stopped when he stopped taking the drug.

Zolpidem and zaleplon have the most reports of inducing sleep-driving, sleep-eating, and sleep walking. The newer hypnotic drugs do not at this time have this association since they are more recently on the market or are currently in development. However, future research may reveal that all imidazopyridine, pyrazolopyrimidine, and cyclopyrrolone hypnotics can induce these parasomnias. Although sleep-driving, sleep-eating, and sleep walking are rare side effects, they can be dangerous when they occur. Patients – particularly those with a history of sleep walking – who are taking imidazopyridine, pyrazolopyrimidine, or cyclopyrrolone hypnotics may need to be informed about the potentiality of drug-induced sleep behaviors.