Early Morning Insomnia, Daytime Anxiety, and Organic Mental Disorder Associated with Triazolam

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A psychiatric syndrome characterized by agitation, paranoid ideation, depersonalization, and depression, as well as paresthesias and hyperacusis, has been attributed to administration of triazolam (Halcion).[1] The occurrence of these reactions led to the removal of the drug from the market in the Netherlands. Isolated behavioral side effects that include amnesia[2-4] and hallucinations[5] have also been reported with administration of triazolam.

Rebound insomnia[6] and early morning insomnia,[7] both associated with increases in daytime anxiety,[7,8] are withdrawal syndromes known to occur with rapidly eliminated benzodiazepine hypnotics such as triazolam. Rebound insomnia consists of a marked increase in wakefulness above baseline levels following drug withdrawal. With early morning insomnia, an increase in wakefulness above baseline values occurs during the last two or three hours of the sleep period on nights of actual drug administration.

This communication describes the occurrence of early morning insomnia, daytime anxiety, and organic mental disorder associated with triazolam use and dependence. The rapid disappearance of these symptoms following withdrawal of the drug is also documented.

Case Report

A 36-year-old single man with a complaint of severe insomnia of approximately 18 months' duration was referred by his family physician to the Sleep Disorders Clinic. He began taking triazolam at bedtime in a 0.5-mg dose eight months before his referral. Although the drug was effective initially, tolerance developed, causing the patient to gradually increase the dosage until eventually he was taking a total of 1.5 mg nightly.

The physical examination revealed no contributory conditions. However, assessment of the patient's mental status revealed that he was extremely guarded and suspicious and preoccupied with his sleeplessness to the degree that this hypochondriacal concern had a delusional quality. He also described two episodes indicating memory impairment; both incidents occurred in the late afternoon and involved preparing to eat certain foods, which he had no recollection of having already consumed the previous night. He also related an episode suggesting paranoid ideation in that he described returning to his apartment one evening to find the door unlocked and immediately wondered whether someone was trying to "play tricks" with his mind. Based on the complete assessment, a tentative DSM-III (American Psychiatric Association Diagnostic and Statistical Manual) diagnosis of organic mental disorder secondary to hypnotic drug dependence was made, and the patient was hospitalized for withdrawal of triazolam and treatment of his emotional condition.

On each of the first seven nights following the patient's hospitalization, his sleep was monitored in the sleep laboratory for an eight-hour period. The patient received three identical capsules on each of these nights. During this week baseline measurements were obtained, triazolam was withdrawn, and flurazepam was substituted (Table 1). On the first two nights he was given 0.5 mg of triazolam in each capsule; on nights 3 through 7 he was withdrawn from triazolam while the drugs and placebo were administered in the following fashion: night 3, 0.5 mg triazolam, 15 mg flurazepam,

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Table 1. Assessment of Sleep and Psychiatric Status During Triazolam Withdrawal

Night	Triazolam (mg)	Flurazepam (mg)	Sleep Latency (min)	WTASO (min)	TWT (min)	BPRS	HAM-A	POMS
1 and 2	1.5	0.0	53.4	187.7	241.1	52	24	100
3	0.5	15	28.3	54.1	82.4	52	20	108
4	0.0	30	67.6	22.1	89.7	51	20	50
5	0.0	30	16.5	53.6	70.1	36	16	91
6	0.0	30	21.3	91.7	113.0	21	13	53
7	0.0	30	22.7	44.4	67.1	21	13	42

WTASO = Wake time after sleep onset
TWT = Total wake time
BPRS = Brief Psychiatric Rating Scale
HAM-A = Hamilton Anxiety Scale
POMS = Profile of Mood States

and a placebo capsule; and nights 4 through 7, 15 mg flurazepam in each of two capsules and a placebo capsule. The patient, sleep laboratory and ward personnel, as well as the patient's attending physician, were blind to the withdrawal schedule.

During the two-night period when administration of 1.5 mg of triazolam was continued, the patient was awake each night an average of more than four hours. Specifically, it took him about one hour to fall asleep, and he did not sleep at all during the last one third of each of these eight-hour recording periods. As soon as the withdrawal of triazolam was initiated, accompanied by the substitution with flurazepam, the patient's sleeplessness decreased markedly (about 65 percent) on both the first withdrawal night and on the next four withdrawal nights combined. Equally important, the patient was finally able to sleep fairly well throughout the night. In fact, during the last one third of the night on the five nights of withdrawal, he averaged 14.9 percent of the time awake compared with 100 percent during the triazolam baseline period.

During the mornings and days following the two nights of administration of 1.5 mg of triazolam, the patient's assessment of mood based on the Profile of Mood States (POMS), and the physician's ratings on the Hamilton Anxiety Scale (HAM-A) and Brief Psychiatric Rating Scale (BPRS) revealed him to be extremely tense, anxious, suspicious, and confused. On the first day following the initiation of withdrawal of triazolam, the patient rated himself as being somewhat less anxious and tense, while on the days following the second through fifth nights of withdrawal, his level of tenseness and anxiety was further markedly decreased.

By the fourth day of withdrawal, the patient was not only less anxious, agitated, confused, and suspicious, but became at the same time more communicative and related much greater detail than he had previously regarding his behavior before admission. He indicated his major concern was a markedly impaired memory for recent events. For example, often he would arrive at work and "have no recollection of having driven there." Also, when at home in the late afternoon or evening, he frequently could not recall having been at work that same day. He also related evidence of paranoid-like thinking in that he wondered whether something had been put into his drink at a local tavern—"How else could I explain why I wasn't sleeping when I was taking three sleeping pills at night?" He also recalled an episode of uncontrollable laughter with no apparent stimulus while waiting in his family physician's office.

Most disturbing to him during this eight-month period was the extreme agitation he felt at around 2 or 3 AM when he would experience his inevitable final awakening. On several occasions he was so agitated that he went outdoors and ran seven to ten miles in an attempt to calm himself. He also indicated that he was unable to nap during the day, no matter how little he had slept the night before,

although previous to this illness he had been able to nap when he wished. Further, careful questioning of the patient did not reveal any evidence of psychotic or organic symptomatology prior to triazolam use.

During his hospital stay, after one week of receiving flurazepam, 30 mg nightly, the patient's dosage was decreased to 15 mg. In addition to triazolam withdrawal and flurazepam substitution, the patient received individual supportive psychotherapy, group therapy, and behavior therapy including progressive relaxation training to be employed at bedtime. One week later the flurazepam order was changed to an as-needed basis, and the patient was instructed to take the drug only if he felt so tense that relaxation exercises were not sufficient to calm him.

Comment

The history of this patient's illness and its clinical course indicate that when he developed tolerance to triazolam, he experienced manifestations of central nervous system hyperexcitability such as early morning insomnia and daytime anxiety. Further, prolonged use of the relatively high dose of this drug was associated with characteristics of an organic mental disorder, including severe memory impairment. His paranoid tendencies were most likely related to this organic condition because he did not have a history of any psychotic symptomatology before triazolam use or following its withdrawal. All of the patient's behavioral side effects rapidly improved during triazolam withdrawal and flurazepam substitution.

It is noteworthy that during flurazepam administration not only were rebound phenomena absent because of this drug's long elimination half-life,[6,9] but the symptoms of organic mental disorder abated. A number of studies have demonstrated early morning insomnia[7] and daytime anxiety[7,8] during triazolam use and rebound insomnia[2,10-14] following its withdrawal. Other rapidly eliminated benzodiazepines, although found to produce rebound phenomena[15-20] and memory impairment,[15,21] have not been reported to be associated with confusion, agitation, or other manifestations of organic mental disorder. Thus, the side effects of early morning insomnia and daytime anxiety that may occur during triazolam administration are probably due to its rapid rate of elimination.[9] However, the occurrence of various manifestations of organic mental disorder are most likely associated with this drug's high potency or other pharmacologic properties related to its chemical structure.

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