Trazodone in Benzodiazepine Dependence

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Background: The authors set forth to test the usefulness of trazodone as an alternative anxiolytic in benzodiazepine-dependent patients.

Method: Ten benzodiazepine-dependent patients according to DSM-III-R were hospitalized during a 2–4 week period and treated with trazodone (100 mg t.i.d.) while their benzodiazepine intake was progressively tapered; they left the hospital on a regimen of only a 300-mg daily dose of trazodone and were followed as outpatients at monthly intervals. The dose of trazodone was individually adapted according to condition.

Results: Very limited withdrawal phenomena occurred during the benzodiazepine taper period; during the 1-year follow-up, all patients remained off benzodiazepines and showed no evidence of abuse of trazodone. The dose of trazodone was significantly reduced to 185 mg ($p = .003$); the ratings of anxiety and depressive symptoms also significantly improved during follow-up: from 12.3 to 5.4 on the Hamilton Rating Scale for Anxiety ($p = .002$) and from 11.6 to 4.8 on the Hamilton Rating Scale for Depression ($p = .002$).

Conclusion: These findings suggest the usefulness of trazodone as an alternative anxiolytic in patients at risk for benzodiazepine abuse.

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There is growing concern about the potential of benzodiazepines for abuse and dependence and their use over too prolonged periods of time.[1] Therapeutic procedures developed to deal with benzodiazepine-dependent patients, such as gradual taper schedules, taper schedules combined with carbamazepine, psychological interventions, or alternative anxiolytics devoid of abuse potential, have had controversial results.[1,2] The situation is complicated by the fact that a large proportion of anxiety disorder patients exhibit significant chronicity: 50% or more of patients relapse by 1- to 5-year follow-up, even if acute treatment leads to remission.[3] This finding suggests that maintenance drug therapy should be considered a treatment option for some patients.

Trazodone is a second-generation antidepressant[4] that possesses significant anxiolytic and sedative properties.[5] Trazodone has already been demonstrated of interest in the treatment of cocaine and alcohol abuse.[6,7] Interestingly, trazodone seems to be devoid of abuse potential[7] and therefore could represent an interesting alternative in the long-term treatment of anxious patients at risk for benzodiazepine abuse.

In this paper, we report our findings concerning the usefulness of trazodone as an alternative anxiolytic in 10 benzodiazepine-dependent patients followed over a 1-year period.

METHOD

Ten consecutively admitted patients who fulfilled DSM-III-R criteria for anxiolytic (benzodiazepine) dependence (304.10)[8] were included in the trial. None of them was taking other types of psychoactive substances. Their individual characteristics are reported in Table 1. All patients gave their informed consent after the nature of the procedure had been fully explained. Two patients refused participation, both women, aged 39 and 47 years, abusing respectively lorazepam for 14 years at the current daily dose of 15 mg and bromazepam for 12 years at the current daily dose of 48 mg.

All patients were initially admitted for a 2- to 4-week stay in the psychiatric unit of the University of Liège Hospital. After a medical checkup and a careful psychological evaluation, their daily intake of benzodiazepine was cut by half while trazodone was introduced at a daily dose of 300 mg (100 mg t.i.d.). Then the benzodiazepine intake was progressively tapered twice a week over a 2- to 4-week period according to individual schedules presented in Table 2 while the dose of trazodone was maintained stable. The benzodiazepines were always administered in three daily intakes. At each decrease in benzodiazepine dose, all withdrawal symptoms were carefully assessed according to the Ashton scale.[9] The patients left the hospital on a regimen of only a 300-mg daily dose of trazodone and were followed as outpatients at monthly intervals at which time the dose of trazodone was individually adapted according to their

Table 1. Sample of Benzodiazepine Abusers Treated With Trazodone

Patient	Gender	Age (y)	Drug	Abused Benzodiazepine: Mean Daily Dose (mg)	Abused Benzodiazepine: Diazepam Equivalent[a] (mg)	Length (y)	Baseline Rating[b]: Ham-A	Baseline Rating[b]: Ham-D	Trazodone: Initial Dose	Trazodone: 1-Year Dose	1-Year Rating: Ham-A	1-Year Rating: Ham-D
1	F	27	Lorazepam	20	80	3	12	16	300	200	4	3
2	F	46	Lorazepam	15	60	8	15	10	300	150	7	6
3	M	49	Diazepam	60	60	4	19	18	300	250	5	7
4	F	60	Lorazepam	17.5	70	15	13	12	300	200	9	7
5	F	32	Lorazepam	25	100	6	6	8	300	100	7	7
6	F	46	Clorazepate	300	150	4	12	11	300	300	6	4
7	F	29	Bromazepam	72	72	5	17	12	300	200	4	3
8	F	62	Lorazepam	15	60	10	10	10	300	100	3	4
9	M	42	Bromazepam	54	54	3	12	14	300	50	2	1
10	F	30	Clorazepate	250	125	6	7	5	300	300	7	6
Mean ± SD		37.1 ± 11.5			83.1 ± 32.1	6.4 ± 3.7	12.3 ± 4.1	11.6 ± 3.8	300 ± 0	185 ± 85.1	5.4 ± 2.2	4.8 ± 2.1

[a]According to the defined daily doses (DDD) from the World Health Organization.
[b]HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression.

Table 2. Individual Schedules of Benzodiazepine Taper Under the Protection of Trazodone 100 mg t.i.d. and Withdrawal Symptoms

Patient	Benzodiazepine	Daily Dose (mg): Day 1	Day 4	Day 8	Day 11	Day 15	Day 18	Day 22	Day 25	Day 29	Withdrawal Symptoms (1 = Mild, 2 = Moderate, 3 = Severe)
1	Lorazepam	10	7.5	5	3	2	1	0	0	0	Insomnia (2)
2	Lorazepam	7.5	5	3	2	1	0	0	0	0	0
3	Diazepam	30	25	20	15	10	5	0	0	0	Headache (1)
4	Lorazepam	9	7.5	5	3	2	1	0	0	0	Thirst (1), sweating (1)
5	Lorazepam	12.5	10	7.5	5	3	2	1	0	0	Insomnia (2), tremor (1)
6	Clorazepate	150	125	100	75	50	30	20	10	0	Insomnia (1), irritability (1), sweating (1)
7	Bromazepam	36	30	24	18	12	6	3	0	0	Headache (1), palpitations (1)
8	Lorazepam	7.5	5	3	2	1	0	0	0	0	0
9	Bromazepam	27	21	15	12	6	3	0	0	0	Nightmares (1), dry mouth (1), irritability (1)
10	Clorazepate	125	100	75	50	30	20	10	0	0	0

conditions. Ratings performed at admission and at each visit included the Hamilton Rating Scale for Anxiety (HAM-A) and Hamilton Rating Scale for Depression (HAM-D).[10,11] Comparisons of trazodone doses and clinical ratings used paired t tests (two-tailed).

RESULTS

Individual results are reported in Tables 1 and 2. For each subject, all withdrawal symptoms determined by the Ashton scale that appeared during benzodiazepine tapering under the protection of trazodone and their level of severity are described in Table 2. All symptoms remained mild and transitory, except two cases of moderate but transitory insomnia, and did not necessitate any intervention or a slowing in the planned benzodiazepine taper schedules.

All patients remained in the treatment program after 1 year. The mean dose of trazodone used after 1 year of therapy was significantly decreased ($t = 4.27$, $df = 8$, $p = .003$). Interestingly, no patient resumed his/her benzodiazepine intake during this period. Mean ratings of anxiety and depression also showed significant improvement during this 1-year period: respectively, $t = 4.42$, $df = 8$, $p = .002$ and $t = 4.50$, $df = 8$, $p = .002$. Besides slight sedative effect experienced by 4 patients at the initiation of trazodone therapy, the treatment was perfectly tolerated. In particular, no priapism, hypotension, or serotonin syndrome was noted.

DISCUSSION

The results of the present trial suggest the usefulness of trazodone as an alternative anxiolytic in benzodiazepine abusers. Despite the use of fairly high dosages of benzodiazepines in these 10 patients, the taper schedules were conducted under the protection of trazodone 300 mg/day without the occurrence of severe withdrawal phenomena. Indeed, withdrawal symptoms always remained mild and transitory, except two cases of moderate insomnia. It should be noted, however, that benzodiazepine tapering was always performed very progressively, a strategy that represents a major factor in the prevention of withdrawal phenomena.[1,2] Therefore, our study is unable to assess the potential for trazodone to prevent side effects of abrupt benzodiazepine withdrawal. Interestingly, no patient in the trazodone study used benzodiazepines during the 1-year evaluation

period. It should be acknowledged that the abstinence from benzodiazepines was determined by history as well as by contacting the general practitioner in charge of each patient but that drug screens were not performed. Such assessment cannot totally exclude that some patients were using benzodiazepines without the investigators' knowledge. In this sample of patients particularly at risk, there was no evidence of abuse, dependence, or escalation of dosage for trazodone. These results confirm a previous report of the beneficial activity of trazodone in substance-abusing outpatients, mainly alcoholics.[7] Several reports already suggested the potential of trazodone to treat opiate dependence.[6,12] Silvestrini et al.[13] have hypothesized that the α-blocking properties of trazodone are suitable for treating some forms of drug abuse and providing relief of symptoms of both withdrawal and depression eventually associated with this condition.

The antidepressant properties of trazodone may play an important role in its beneficial activity in our sample of benzodiazepine abusers. Indeed, several patients exhibited a significant level of depressive symptoms, as assessed by the HAM-D, at inclusion. This confirms that a significant proportion of chronic benzodiazepine users actually represent depressed patients who could benefit from antidepressant therapy.[3] In this context, the particular profile of trazodone which combines antidepressant,[4] anxiolytic,[5] hypnotic,[14] and withdrawal blockade[6,12,13] makes it an alternative of choice for benzodiazepine abusers, a claim that is supported by the present pilot report.

Drug names: bromazepam (Lectopam), carbamazepine (Tegretol and others), clorazepate (Tranxene), diazepam (Valium and others), lorazepam (Ativan and others), trazodone (Desyrel and others).

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