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Treatment of Benzodiazepine Withdrawal Symptoms with Carbamazepine

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Summary. In 18 patients with a benzodiazepine (BZD) dependency the drug was withdrawn. The dose of BZD was gradually reduced in nine of the patients, while the others were additionally treated with carbamazepine (CBZ) for a further 15 days after BZD discontinuation. Withdrawal symptoms were assessed every third day during the study period. When comparing results in both groups, a clear trend towards less severe withdrawal symptoms could be observed in the group treated with CBZ. Some of the differences were statistically significant on days 9–12 after BZD withdrawal. Fundamental withdrawal symptoms (like hypersensitivity to sensory stimuli, abnormal perception of movement, depersonalisation or derealisation) were also less severe in the group treated with CBZ compared with the group not receiving that treatment. These findings support the results of previous reports indicating a therapeutical effect of CBZ in BZD withdrawal.

Key words: Benzodiazepine withdrawal – Carbamazepine – Anxiolytic effects

Introduction

Until recently benzodiazepines (BZDs) have been regarded as not only safe and effective anti-anxiety drugs but also free of serious side-effects. However, in the past decade there has been a rising concern about the risk of dependency after continuous medication with these drugs. In fact, it has been suggested that one of the reasons for long-term consumption of BZDs is dependency and the subsequent appearance of withdrawal symptoms after discontinuation of BZD [39, 18].

Although most withdrawal symptoms following BZD dependency resemble those associated with anxiety and panic states [33], there are other symptoms that occur very frequently and are regarded as fundamental components of the BZD withdrawal syndrome. These include hypersensitivity to sensory stimuli, depersonalisation and derealisation [34], abnormal perception of movement [16, 18], loss of appetite and weight [18], depressed mood [15] and, less commonly, epileptic seizures [29], psychotic features [24] and other neuropsychiatric symptoms.

Among the factors affecting incidence and severity of withdrawal symptoms are the mode of withdrawal [7], serum half-life of drugs [21, 31] and, probably, duration of intake [25a]. Present evidence does not show any difference in specificity [11, 29, 36], severity and incidence of withdrawal symptoms when comparing high- and low-dose dependency [10], although protracted withdrawal syndromes have mainly been observed in low-dose-dependent patients [26].

Since withdrawal symptoms have been observed even under gradual withdrawal schedules [31] and their appearance has been reported to be one of the main causes for lack of compliance during the withdrawal period [18], the development of alternative strategies for treating withdrawal symptoms appears to be necessary.

The use of a gradual withdrawal schedule or a long-acting BZD that has a built-in tapering action have been shown to be effective strategies for treatment of the BZD withdrawal syndrome [17]. However, there may also be individual differences in responsivity to different BZDs – as there are with different psychotropic drugs of other classes – making withdrawal unresponsive to a switch in BZDs [41]. There have been, however, few controlled studies of non-BZD-pharmacological aids in the treatment of BZD withdrawal. While propanolol, in open trials, has proved to be minimally effective in attenuating some somatic symptoms [2, 8, 25a, 30], clonidine has failed to show significant efficacy under double-blind conditions [9].

During the last few years there have been several reports suggesting that carbamazepine (CBZ) might be effective in attenuating withdrawal symptoms [12, 13, 22, 23, 28]. In the present report, the severity of withdrawal symptoms during gradual tapering is compared between patients treated either with CBZ or without CBZ.

Method

Withdrawal symptoms of 18 inpatients, who were consecutively treated during the last 3 years for BZD withdrawal at the crisis intervention ward of the Max-Planck-Institute of Psychiatry in Munich, were compared. The first 9 patients (Nos. 1–9; group I)

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were gradually tapered, while the other 9 patients (Nos. 10–18; group II) were additionally treated with CBZ, using an identical gradual withdrawal schedule. The two groups were studied one after the other, and all patients received the standard treatment being used at the time of admission. Patients were informed that, although CBZ possibly could be useful for the treatment of BZD withdrawal symptoms, its effectiveness was not well founded in the literature.

Before admission, patients were carefully examined for a history of drug abuse. They were only included in the study if they were solely dependent on BZD medication. A current history of alcohol abuse/dependency or a history of a psychotic disorder were criteria for exclusion. Previous neurological and laboratory tests revealed no evidence for an organic disease. The diagnosis was made according to DSM-III-R criteria [1] by two experienced psychiatrists.

The patients were withdrawn using the same BZD (diazepam). Therefore, the total daily dosage of BZDs during the week before admission was calculated, and the patients were switched to a (clinically defined) equivalent dose of diazepam at the beginning of the study (day 0) [6]. Every 3 days, starting at the fourth day of treatment, diazepam was reduced by 5 mg/day. Patients belonging to group II were treated from day 0 (day on which they were switched to an equivalent dose of diazepam) with CBZ. The CBZ treatment was discontinued 2 weeks after ceasing the administration of diazepam (day X). Carbamazepine was given as a syrup in varied dosages (300–600 mg), according to clinical requirements (defined as a deterioration of the clinical state due to withdrawal symptoms). Dosages of CBZ started at 200–300 mg the first day, 300–400 mg the second day and 400–600 mg after the third day. During the entire withdrawal period up to 150 mg/day of promethazine were available in both groups for sleep promotion. Heart rate and blood pressure were measured every day.

Psychopathometric instruments were applied at the beginning of the study (day 0), at discontinuation of diazepam (day X), and every third day during the following 2 weeks. The patients were asked to answer three self-rating questionnaires every third day: BWSQ-2 (Benzodiazepine Withdrawal Symptoms Questionnaire [34]); SAS (Self-rating Anxiety Scale [43]); and SDS (Self-rating Depression Scale [42]). Several items of the BWSQ-2 known to be related to the most fundamental BZD-withdrawal symptoms, were added up to form a subscore. Those items were [34]: item 1: "feeling unreal"; item 2: "feeling very sensitive to noise"; item 3: "feeling very sensitive to light"; item 4: "feeling very sensitive to smell"; item 5: "feeling very sensitive to touch"; item 6: "feeling a peculiar taste in mouth"; item 14: "feeling depressed"; item 16: "feelings of things moving when they are still"; item 17: "seeing or hearing

Table 1. Description of sample

Group I Pat. No.	Gender	Age (years)	Benzodiazepine daily dose	Diazepam equivalent dose (mg)	Duration of dependency (years)	Promethazine (mg/day)	Additional DSM-III-R diagnosis
1	female	46	diazepam 20 mg	20.0	7.0	10.4	300.02
2	female	49	diazepam 10 mg	10.0	12.0	29.0	300.40
3	female	42	diazepam 40 mg	40.0	17.0	29.4	300.40
4	female	61	flunitrazepam 3 mg	15.0	2.0	25.0	
5	female	24	diazepam 15 mg	15.0	3.0	0	300.30
							300.01
6	male	42	lorazepam 25 mg	167.00	5.0	41.0	303.90
7	female	28	bromazepam 7 mg	15.0	5.0	24.0	300.30
							300.40
8	female	45	lorazepam 7.5 mg	50.0	20.0	0	300.50
9	female	41	diazepam 10 mg	10.0	11.0	0	300.01
							296.31
Mean		42		38.0	9.1	17.6	
± S.E.M.		3.6		16.7	2.1	5.1	

Group II Pat. No.	Gender	Age (years)	Benzodiazepine daily dose	Diazepam equivalent dose (mg)	Duration of dependency (years)	Prome-thazine (mg/day)	Mean Dose of CBZ	Additional DSM-III-R diagnosis
10	male	30	lorazepam 7.5	50.0	5.0	0	426.0	300.02
11	female	41	diazepam 10 mg	10.0	16.0	0	420.0	300.02
12	female	35	diazepam 95 mg	95.0	20.0	0	620.0	
13	female	49	bromazepam 6 mg	13.5	3.0	0	342.0	296.31
14	female	33	bromazepam 6 mg	13.5	7.0	0	404.0	300.40
15	male	39	diazepam 30 mg	30.0	3.0	0	274.0	300.01
								303.50
16	female	27	chlordiazepoxide 60 mg	20.0	4.0	0	444.0	
17	female	59	diazepam 30 mg	30.0	20.0	0	344.0	296.21
18	female	32	clonazepam 2 mg	10.0	5.0	0	420.0	300.40
Mean		38.3		30.2	9.2	0	410.4	
± S.E.M.		3.4		9.2	2.4	0	31.9	

Table 2. Time series of the groups' mean score (S.E.M.) for the BWSQ-2, SAS, SDS, and BAS

		Day 0	X	X+3	X+6	X+9	X+12	X+15	X+20	Slope (0–X+15)	*P* (slope gr I vs II)
BWSQ-2	Group I	13.4 (2.1)	11.6 (2.5)	11.8 (2.7)	14.0 (3.2)	16.0 (3.4)	15.0 (3.6)	14.2 (3.4)	13.6 (2.8)	0.46 (0.5)	[b]
	Group II	14.4 (1.8)	12.5 (2.6)	11.2 (1.9)	11.4 (2.6)	10.1 (3.1)	8.6 (2.3)	8.1 (2.4)	7.6 (2.4)	−0.99 (0.5)	
	P					[a](1)	[b](1)				
SAS	Group I	27.0 (2.9)	22.5 (2.5)	23.2 (2.3)	26.0 (2.7)	25.8 (3.5)	24.8 (3.4)	23.4 (3.2)	–	−1.15 (0.4)	
	Group II	28.3 (2.4)	24.8 (3.7)	23.5 (3.1)	23.3 (4.3)	23.3 (3.4)	21.3 (3.5)	19.0 (3.1)	–	−1.25 (0.6)	
SDS	Group I	31.7 (3.5)	27.2 (2.7)	27.2 (1.9)	30.1 (2.8)	31.4 (2.1)	29.6 (3.0)	28.2 (2.3)	–	−0.05 (0.5)	[a]
	Group II	34.8 (1.8)	29.2 (3.0)	28.0 (3.1)	27.4 (3.9)	26.2 (4.0)	26.0 (3.9)	23.4 (3.9)	–	−1.51 (0.64)	
BAS	Group I	16.5 (2.8)	17.1 (2.9)	16.4 (2.8)	21.4 (3.0)	22.0 (4.0)	20.6 (2.88)	16.7 (2.0)	–	0.47 (0.5)	[a]
	Group II	18.5 (2.7)	17.1 (2.7)	17.0 (3.0)	15.8 (3.7)	15.0 (3.6)	12.7 (3.7)	12.0 (3.7)	–	−1.08 (0.6)	
	P						[a](1)				

[a], [b] Significance at the 0.05 and 0.01 (respectively) levels comparing the original scores (Mann-Whitney U-test)

(1) *P* is obtained comparing both groups "transformed scores", previously dividing each score by its initial (day 0) score (Mann-Whitney U-test)

things that are not really there (hallucinations)"; item 18: "feeling unable to control one's movements"; item 20: "feeling loss of appetite".

A brief anxiety rating scale (BAS) [32] of the Comprehensive Psychopathological Rating Scale [4] was applied in the form of a semistandardized interview by the psychiatrist responsible for treatment on the same days as the other scales were used.

Statistical Procedure

Apart from an exploratory search (look for outliers, range, minima, maxima, trends, etc.), a confirmatory statistical analysis (test of hypotheses) was carried out with the scores of the various scales. Since the scores at the beginning of the study (day 0) for group II were somewhat higher than the corresponding ones of group I, in order to obtain comparable score values of subsequent days, only the transformed scores (each score divided by its initial score) have been used in the confirmatory statistical analysis. For these scores, a statistical comparison between the two groups at the various time points and within the various scales was carried out by means of the nonparametrical Mann-Whitney U-test. The level of significance 0.05 was properly adjusted to the number of the tests.

Results

a) Description of Sample

A description of the main characteristics of the patient sample can be seen in Table 1. The gender distribution, mean age, dose of BZD, proportion of low-dose dependencies (five in group I vs four in group II) and duration of dependency were comparable in both groups.

b) Drop-outs

All 18 patients completed the period of study. Severe withdrawal reactions, such as psychotic symptoms or epileptic seizures, were not observed. Group II did not report any typical side effects of CBZ, such as dizziness, ataxia or seeing double.

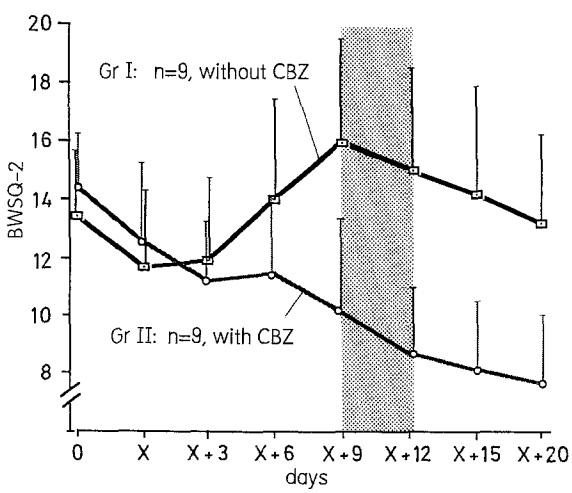

Fig. 1. Time course (SEM) of the BWSQ-2 mean scores X: Time point when BZDs were completely withdrawn. The *shaded area* describes the time parameter for which significant differences between the transformed scores is given. Mann-Whitney U-test ($P < 0.05$)

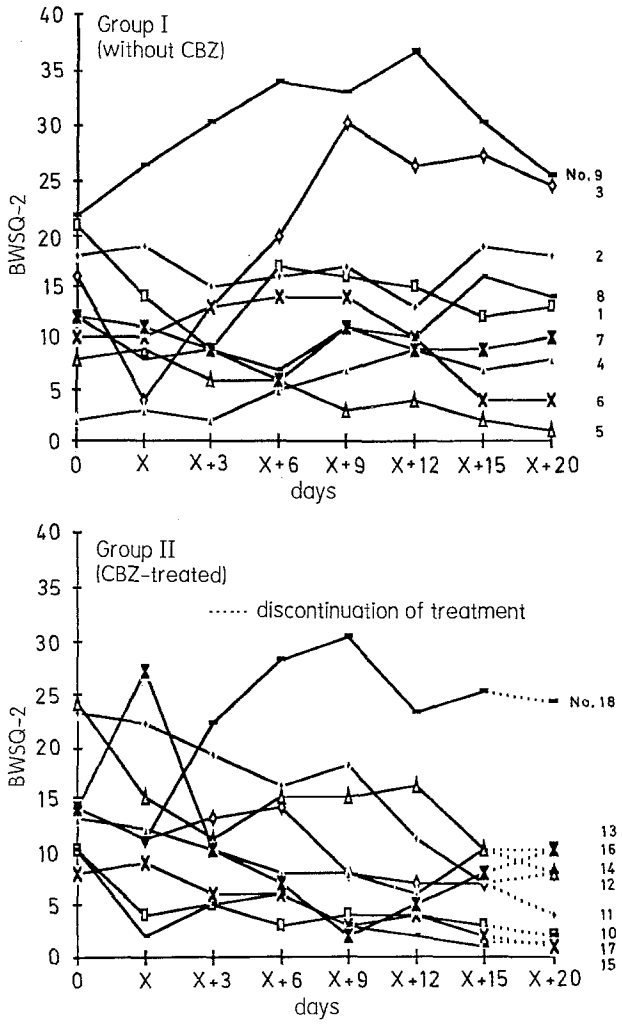

Fig. 2. Time course of individual BWSQ-2 scores

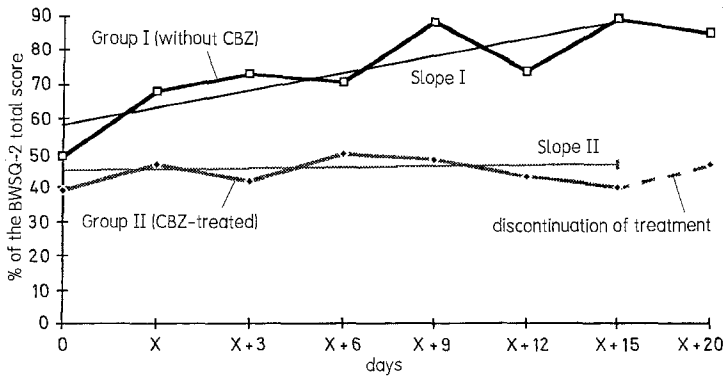

Fig. 3. Percentage of the BWSQ-2 total score comprised by the subscore of the fundamental withdrawal symptoms

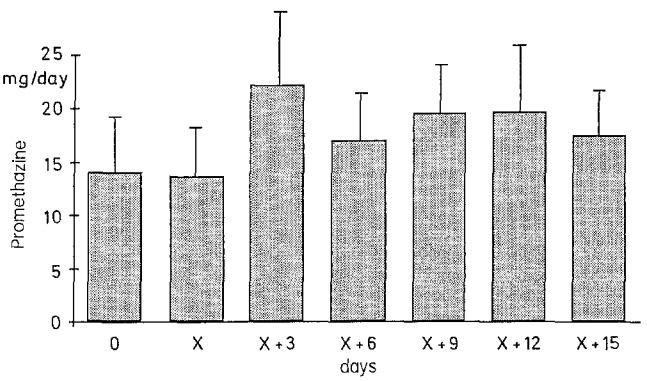

Fig. 4. Mean requirements of promethazine (± SEM) during the study (group I, without CBZ)

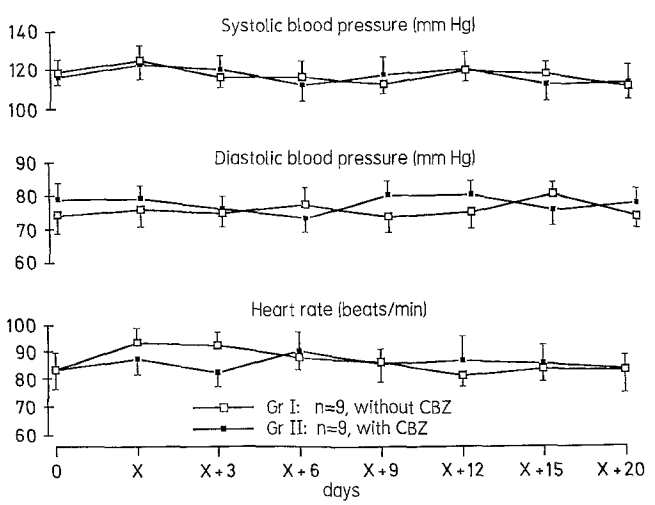

Fig. 5. Mean values of blood pressure and heart rate (± SEM) during the study

c) *Psychopathometry*

As can be seen in Table 2, the severity of withdrawal symptoms, anxiety and depressive symptoms were comparable in both groups at the beginning of the study. During the withdrawal period, group II reported fewer symptoms in all self-rating questionnaires than the other group. Statistically significant differences could be observed in the BWSQ-2 transformed scores on day X + 9 and X + 12 (see Fig. 1) and in BAS transformed scores on day X + 12 (see Table 2). Comparing the mean slope for each patient group drawn from the individual BWSQ-2 graphics (Fig. 2), group II showed a mean slope of −0.99, while group I had a slope of +0.46 ($P < 0.01$).

The individual scores on BWSQ-2 during the whole withdrawal period can be seen in Fig. 2. Withdrawal symptoms did not increase after discontinuation of treatment with CBZ (day X + 20).

As can be seen in Fig. 3, the importance of the BWSQ-2 subscore, containing fundamental withdrawal symptoms described in the previous section in the BWSQ-2 total score (measured as a percentage of the total mean group score at any given time) increased during the withdrawal period in group I, while the same value remained constant in group II.

d) *Additional Medication*

Six patients belonging to group I needed additional sedative medication, as can be seen in Table I. In comparison, no patients in group II required such medication. The requirements of promethazine during the entire study are shown in Fig. 4. As can be seen, there was no coincidence between the requirements of co-medication and the maximum of withdrawal effects.

e) Parameters of Autonomic Function

Data obtained from monitoring withdrawal parameters of autonomic function, such as blood pressure and heart rate, are shown in Fig. 5. As can be seen, neither heart rate nor systolic nor diastolic pressure showed any statistically significant differences between the two groups during the withdrawal period.

Discussion

Statistically significant differences were found when comparing the severity of withdrawal symptoms in both groups using the BWSQ-2 and the BAS scales, while in the other scales a clear trend towards fewer symptoms during the treatment period could be observed in group II. Since the tests used for comparison between the group means were nonparametric and the size of the samples was small, the statistical significance found on days X + 9 and X + 12 points to greater values for most patients of one group compared to the other. For this reason, the statistically significant differences found between both groups cannot be attributed solely to patients No. 3 and 9, as Fig. 2 might suggest.

When comparing the mean BWSQ-2 score's slopes in both groups, statistically significant differences were also found (Table 2). In addition, fundamental BZD withdrawal symptoms, such as hypersensitivity to sensory stimuli, abnormal perception of movement, feelings of depersonalisation and derealisation, scored lower in group II (measured as a percentage of the total BWSQ-2 score) during the whole withdrawal period, which suggests a specific effect of CBZ on typical withdrawal symptoms. The lack of statistical significance at other points and in other scales can be partly explained by the small size of the samples as well as by the use of nonparametric tests, which are somewhat less efficient than the parametric ones.

Only group I required sedative medication. This finding appears to be of importance, since it demonstrates that the beneficial effects of CBZ cannot be attributed to a solely sedative type of action. In addition, CBZ given in a rather low dose, if compared with dosages generally accepted for the treatment of epileptic seizures, did not show any side-effects.

We used a rather fast tapering scheme, especially for low-dose-dependent patients; however, since the proportion of low-dose dependents was quite similar in both groups, it seems unlikely that this factor influenced the results.

The question arises whether CBZ might have been exerting its therapeutic effects on recurrent anxiety symptoms. If this had been the case, an increase of those symptoms would be expected after the discontinuation of CBZ. However, after discontinuation of treatment, no increase in psychopathology scores occurred. This suggests a bell-shaped pattern of symptoms over time, as is the case in a withdrawal syndrome. Furthermore, our BWSQ-2 data from the postwithdrawal period provide a conservative estimate of baseline psychopathology. Since the postwithdrawal anxiety level was low, it is unlikely that a reemergence of anxiety associated with the primary disease occurred. These findings suggests that CBZ exerted its therapeutic effect on BZD withdrawal symptoms.

Our results support those of previous reports indicating a therapeutic effect of CBZ in BZD withdrawal symptoms. CBZ seemed to be an effective treatment, both concomitant to gradual BZD tapering and after discontinuation of BZDs. So far, the results are in agreement with previous well-documented studies showing therapeutic properties of CBZ in alcohol withdrawal [5]. Furthermore, recent findings indicate that other anticonvulsants, such as valproic acid, may be effective in the treatment of withdrawal symptoms in BZD dependency [3].

Despite the fact that our study included a control group, it was not carried out under double-blind conditions. Another bias may arise from patient assignment to treatment groups because of the non-parallel group design. Patients of the non-CBZ group were allowed promethazine upon request, and to that extent were not free of supportive medication. However, since placebo-like effects cannot be completely ruled out, further evaluations of CBZ's efficacy in this regard should be performed using placebo-controlled, double-blind designs.

A great variety of neuropharmacological effects have been described regarding the mode of action of CBZ: it does not have any effects on the central BZD receptors, but its action on the peripheral BZD receptor, increasing its numbers [38], might account for its anxiolytic effects, which are of special importance in BZD withdrawal. On the other hand, CBZ has been reported to decrease central norepinephrine activity [19]. Similar to buspirone (and in contrast to most anxiolytic drugs, like BZDs), it increases locus ceruleus firing [20], and it appears to be of interest that both drugs seem to be effective in treating generalised anxiety, but not in panic states [27, 35]. Thus, the neurochemical findings described above do not explain the positive CBZ-induced effects in BZD withdrawal, especially the finding that the GABAergic effects of CBZ are only very weak (for review see [40]). However, amygdaloid kindling might be regarded as an especially suitable animal model for evaluating proconvulsive and anxiogenic CNS processes, like BZD withdrawal, and it has been shown by Post's group [20] that preferentially CBZ and valproate are anticonvulsants which are effective in this paradigm. An alternative explanation of its mechanism of action could be obtained by its effects on the adrenocorticotrophic hormone response to corticotrophin-releasing hormone (CRH) [25b, 37], which imply increased sensitivity to CRH at pituitary CRH receptors, which might be due to an attenuation of CRH release. The vasopressin agonist effects of CBZ might be responsible for this, because vasopressin itself stimulates the hypothalamic-pituitary-adrenocortical axis, and vasopressin agonist-like effects of CBZ could substitute for CRH [25b]. This explanation appears to be plausible, since BZD withdrawal induces a rebound-hypercortisolemia [14], which could be due to hypersecretion of hypothalamic CRH.

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