



# High levels of benzodiazepines after treatment of moderate alcohol withdrawal syndrome: the problem of incomplete detoxification

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## Abstract

**Purpose:** Some alcohol-dependence relapses occur soon after a concluded detoxification treatment. A popular agent used in that treatment is diazepam, which effectively relieves withdrawal symptoms due to its long half-life and affinity to the same receptors. It is hypothesized here that these attributes, after nominally completed detoxification, result in, respectively, persisting benzodiazepine (BZD) influence and a distorted (optimistic) clinical presentation. This could contribute to later reemergence of withdrawal symptoms caused by delayed final elimination of BZDs, as the evidence puts into doubt the concept of a gentle self-taper of a long-acting drug.

**Methods:** Serum-BZD concentration levels were measured with a radioimmunoassay at the end of routine treatment of moderately-intense alcohol withdrawal syndrome. These data were cross-referenced with individual diazepam administration schedules, including the maximal daily dose and the day of its administration, and the day of overall diazepam cessation.

**Results:** Most patients revealed clinically relevant serum-BZD levels. These correlated with the doses but also with the day of maximal-dose administration and the day of diazepam withdrawal.

**Conclusions:** The confrontation with actual abstinence comes after detoxification. Delayed elimination of diazepam may be a contributing factor in the re-emergence of symptoms and early post-detox relapses. The optimization of the procedure has been discussed in terms of concentration evolution and known treatment schedules. Maximal initial dosage compression and further decisive counteracting the tendencies of diazepam towards accumulation increase the patient's chance of going through the low-concentration crisis under medical assistance.

**Key words:** alcohol withdrawal, benzodiazepine concentration, post-detox relapses.

## INTRODUCTION

In the treatment of alcohol withdrawal syndrome (AWS) the benzodiazepines (BZDs) are of primary importance, as they transiently substitute alcohol due to a shared affinity for the GABA-A receptors. Among the several BZDs considered to be the gold standard in AWS treatment (lorazepam, oxazepam, chlordiazepoxide or diazepam [1, 2]), some recommend diazepam as the most adequate drug of choice [2]. With its fast onset and ultra-long half-life ( $T_{1/2}$ ), it provides effective BZD accumulation and resulting satiation. After discontinuation it is eliminated slowly, which is hoped to drive the patient gently into abstinence.

There are different ways to treat AWS [1, 3, 4], beginning with symptom-triggered treatment (only when

moderate symptoms emerge, with the dose repeated hourly as needed [5]), through fixed-dose administration 4 times a day, ending with frontal loading using oral 20-mg doses of diazepam (or their equivalents) repeated every 1-2 hours until the symptoms are controlled [6]. The latter intensive treatment regimen, recommended in severe or complicated cases [4, 7-9], uses the accumulation of consecutive diazepam doses.

Unfortunately, the fact that diazepam can also accumulate in a moderate dose regimen is often ignored. After clinical improvement is achieved, the dose should be reduced to zero in a controlled manner in order to adapt the patient to the state of abstinence. However, it is not clear why the term “abstinence” is taken as the end of the alcohol-substitute (BZD) administration, and not its removal from the body. This notion results in an erroneous belief

that it is reducing the doses, and not a decrease in concentration, that directly adapts the patient to abstinence. As such, tapering is conducted slowly, sometimes ending only on the day of discharge from the detoxification unit (in Poland typically on the 10<sup>th</sup> day after admission). The status of the BZD elimination is completely ignored, which may be due to a conviction that the slow elimination of alleged (but not checked) small diazepam residues will be imperceptible, or even beneficial, to the patient.

However, considering the detoxification of BZD-addicted patients, where their drugs, as with alcohol in AWS treatment, are first replaced by a long(er)-acting BZD (usually diazepam), it has been noted [10] that its initial accumulation, then augmented by a too-slow tapering rate, may falsify the assessment of a patient's adaptation to subsequent dose reductions. Furthermore, it significantly delays the low-concentration phase, indicated as critical for adaptation mechanisms [11, 12], and for the patients themselves as well, by moving it beyond the hospitalization period. That hypothesis has been supported by a study showing the correlation of the decisive withdrawal crisis with the final drug-elimination phase, and at the same time a significant shift of the latter far beyond the time of diazepam withdrawal [13].

By analogy, it can also be hypothesized that alcohol-addicted patients, leaving the detoxification ward in a good clinical condition, may owe this state not to (as is assumed) their advanced adaptation to sobriety, but to being under the unrecognized influence (as opposed to sobriety) of a significant concentration of the active diazepam derivatives. If this is so, the withdrawal crisis related to the diazepam (the alcohol substitute here) low-concentration phase may surprise the patients after the conclusion of their detox treatment. Without medical assistance and without knowing the causes of the condition, they may resort to alcohol, initiating a relapse into drinking.

The presented study was aimed at checking the plausibility of the above hypothesis. The retrospective analysis involved AWS-treatment records, where each routine and laboratory-blind treatment, when concluded, was followed by a single serum-BZD concentration check (primarily as a reference for further addiction-therapy purposes). In this study, in the case of confirmation of significant serum-BZD concentrations it was intended to determine relationships between the phenomenon and the way the detoxification was carried out, with the attempt of finding clues to solve the problem.

## METHODS

The records came from 120 in-patients, 89% males, at median age 52 (interquartile range 40-59) who were treated, with their informed consent, for moderate, non-complicated AWS. In this retrospective, one-arm, open study the records were taken in the order of admission to the detoxification

ward. Data from patients with severe withdrawal symptoms requiring intensive treatment were excluded from the analysis, and so were data from patients with coexisting addictions (except for cigarettes) and accompanying mental disorders. The enrolled patients had no life-threatening somatic problems at that time and the majority of them showed an average level of nutrition (median BMI 23.2 (20.9-26.1)).

The participants were treated with diazepam according to the daily routine of the detoxification unit, initially with doses of 5-15 mg of diazepam (depending on the severity of their symptoms) administered 3-4 times a day, with the aim of achieving the satiation state. In addition, typical auxiliary treatment (thiamine injections, electrolyte infusions, beta-adrenolytic agents) were applied. For the purposes of this study, records from patients using medications affecting the elimination of diazepam were excluded.

The severity of symptoms was routinely monitored using the Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar) scale [14]. At admission, the median CIWA-Ar score was 16 (15-17). After reaching satiation, as measured by clinical improvement (CIWA-Ar score < 10), diazepam was reduced at a rate adjusted to the patient's condition but with the aim of ending its supply before the patient's discharge. Possible residual withdrawal symptoms were treated with non-benzodiazepine drugs (beta-adrenolytics, tiapride, promethazine).

Patients included in the study stayed on the ward for 10 days. Apart from their condition (CIWA-Ar), data describing the dynamics of diazepam administration were noted, such as daily doses, maximum daily dose and the day of its use, total dose and the day of diazepam withdrawal (the next one after the last dose). On day 10 (the day of discharge), the serum-BZD concentration was measured, as a routine adopted in the ward to provide a baseline for the correct interpretation of the patient's control check when entering subsequent addiction therapy. For the concentration measurements a radioimmunoassay (SBENZ immunoassay/COBAS integra 400 plus analyzer, Roche Diagnostics [15]) was applied.

Data analysis came down to noting the serum-BZD concentration from the 10<sup>th</sup> day of hospitalization and referring it to the data on diazepam administration. Due to possible asymmetries in the distribution of results within the study group, the group averages are described using the median and the span between the first and third quartiles, while correlations between concentration value and detoxification parameters were tested with the non-parametric Spearman's rank correlations test. Statistical analysis was performed using the Statistica 13.3 version [16].

## RESULTS

All patients completed detoxification in good general condition, at their discharge showing no clinically signifi-

cant intensity of withdrawal symptoms (CIWA-Ar scores were below 8).

The data related to the dynamics of diazepam administration are presented in Table 1.

The resulting median serum-BZD level on the day of discharge from the detox unit was at median level 260 (161-495) ng/ml, at the test reference ‘therapeutic’ range 200-300 ng/ml.

The 3 maximal individual serum-BZD levels were: 1252 ng/ml, 1134 ng/ml, 1050 ng/ml, and only in 3 patients was the BZD level below the method’s detection limit (3 ng/ml).

That final BZD level correlated with the diazepam administration data (c.f. Table 2). Additionally, it correlated also with patients’ age ( $\rho = +0.025$ ,  $p = 0.009$ ) and BMI ( $\rho = +0.16$ ,  $p = 0.049$ ).

## DISCUSSION

At the conclusion of the rather standard detoxification procedure, the serum-BZD at discharge in the majority of patients fitted within or exceeded the nominal ‘therapeutic range’. Regardless of tolerance issues, these clinically significant levels following treatment with diazepam (the ethanol substitute here) might have contributed to a low expression of withdrawal symptoms, encouraging patient’s discharge from the detoxification ward. This result raises a point of concern about the patients’ actual and unassisted confrontation with their real abstinence from GABA-A agonists, unintentionally shifted beyond the hospitalization period.

That concern is justified despite the opinions that diazepam, after its discontinuation, gently tapers itself due to its slow elimination rate. Following that point of view, some researchers even recommend cessation of additional diazepam doses once satiation has been achieved [17]. However, such opinions would be correct only if elimination and adaptation processes were mutually synchronized. The expectations of a concordance between the PK- and PD-phenomena, however, are unjustified and success, even though possible, may only be fortuitous. Analogous treatment using a long-acting barbiturate ended with the need for additional doses [18]. In the large-sample study on BZD-dependent patients converted to diazepam prior to detoxification, at the final low-concentration detox stage a re-emergence of withdrawal crises occurred regularly, with varying but significant delay (2-95 days) after diazepam cessation [13].

Thus, in terms of AWS treatment it is plausible that the delayed arrival at actual abstinence, meant as a ceased impact of a GABA-A receptor agonist, may trigger the late re-emergence of withdrawal symptoms. Moving this critical stage into a not-medically-assisted setting may contribute to early post-detox relapses.

**Table 1.** Data related to the dynamics of diazepam administration across the detoxification procedure

Diazepam administration data	Median (1-3 interquartile)
Maximal daily dose (mg)	30 (24-40)
Application of the maximal daily dose (day of the procedure)	1 (1-2)
Total dose (mg)	83 (50-115)
Discontinuation (day of the procedure)	6 (5-8)

**Table 2.** Correlations between final serum-benzodiazepine (BZD) level and the dynamics of diazepam administration

Diazepam administration data	Correlation with final serum-BZD level Spearman’s rho; significance $p$
Maximal daily dose (mg)	+0.41; 0.000003
Application of the maximal daily dose (day of the procedure)	+0.23; 0.011
Total dose (mg)	+0.56; < 0.0000005
Discontinuation (day of the procedure)	+0.49; < 0.0000005

The question is whether a physician can prevent this scenario, which arose as a consequence of actually unfinished detoxification from GABA-A agonists.

Routine prolongation of hospitalization beyond the set limit, and despite a currently good clinical condition, regardless of patients’ protests, has no rationale for economic reasons. What a physician can do is optimize the way detox is carried out.

The relationships between the dynamics of diazepam administration and the concentration of BZD residual in the patient’s body (Table 2) seem obvious: the earlier elimination starts, and the lower the level at the beginning of this process, the more advanced the elimination will be at discharge. Certainly, the amount of diazepam needed to control withdrawal symptoms is absolutely determined by the individual patient’s needs. However, it is the doctor who has a say in how the administration of that amount is spread over time: at the same loading (satiating) amounts of BZD, earlier both satiation and discontinuation would help, according to the proposal below.

### Fast loading

The sooner the patient becomes satiated, the faster the next stages of detoxification can follow. Although the loading dose depends on the body’s needs, it is up to the doctor to determine when the satiating concentration level is reached. Both frontal loading and symptom-triggered techniques (dedicated for in-patient settings) aim for rapid control over the symptoms. Certainly, the popular, somewhat eclectic “3-4 times a day” regimens in

moderate syndromes will also eventually result in satiation. However, the necessary accumulation, slowed down by longer inter-dose intervals, will be reached by many patients only in the later days of their stay. Restrained dosing, in the face of a determined level of the body's needs, not only prolongs the phase of symptoms but, paradoxically, results in a higher total cumulative dose, due to the partial elimination of the drug between consecutive doses. Satiation by titration, similar to the classical loading regimen [6] but with smaller doses allowed, promises to achieve the required concentration already on the first day.

### Stopping the accumulation

Once satiation is reached (symptom control, CIWA-A score < 10), dose reduction should be immediate. If it is delayed or slow, it causes the further accumulation of diazepam.

The real process of reducing the impact of diazepam does not start with dose reduction but with the descent to the dose that stops further (unnecessary) accumulation. Given  $T_{1/2}$  36-200 hours [19], reducing the dose by 50% on the next day may be not enough to stop it even in the faster metabolizers. In the others, maintenance doses will be much lower, especially in elderly and obese patients. Due to the large span of diazepam  $T_{1/2}$  values in the general population, the maintenance dose is difficult to estimate in advance. Therefore, if available, concentration checks are advised.

### Efficient reduction of the impact of diazepam

Only a dose lower than the maintenance dose initiates the effective elimination of BZDs. That dose, although unknown in advance (laboratory feedback is recommended), once reached places the patient already in the advanced stage of diazepam tapering. Therefore, the discussion at this point should refer to residual doses, and only these really serve to smoothen the adaptation course during decreasing BZD concentration (slowing this decrease). At this stage, diazepam should be administered in the lowest doses that meet this goal. Their action can be supplemented or replaced by administering auxiliary non-benzodiazepine drugs (tiaprid, promethazine, trazodone, beta adrenergic antagonists). It is worth noting that in the present study, diazepam was withdrawn on average 4 days before the concentration check (Table 1). If a slow tapering of diazepam doses is mistakenly assumed to gently adjust the patient to abstinence (while serum-BZD is often increasing) and intentionally prolonged until the last day of their stay, the inflation of BZD concentration at discharge is expected to be even greater. Obviously, it would be at its lowest when diazepam administration is stopped immediately after reaching satiation. However, as discussed above this may fail if the adaptation processes do not keep up with elimination. In any case, this approach is worth considering in older or obese patients, if medically assisted.

The above model, apart from the new concentration issues, resembles the symptom-triggered approach [5]. The latter, introduced a few years later than the loading treatment [4], actually constitutes its variant but with the doses individually adjusted. Although resulting in lower total diazepam use as compared with the fixed-dose regimen [4] and recommended for hospital conditions [3, 20], it is often abandoned due to the associated requirement of the careful monitoring of the patient's state, in favor of a "3-4 times a day" schedule. The discussion above shows the consequences of such choices for the BZD post-detox concentration.

One may ask, why the spontaneous elimination of diazepam at home is supposed to be tolerated worse than the (seemingly) accelerated elimination in the detox ward. It should be stressed here that the aim of the above proposal is not to accelerate elimination (which would be challenging for adaptation mechanisms), but to hasten its commencement. Restrictive dosing of diazepam after reaching satiation also allows for the lowering of the level of the start, by avoiding further BZD accumulation that is too high and too long with respect to the body's needs. This, assuming a similar rate of BZD elimination, increases the patient's chance of going through the low-concentration crisis in the ward. Quantifying the impact of the proposed modifications on the discussed post-detox issues is the expected next in further investigation.

However, even though the model proposed above aims to minimize the post-detox serum-BZD concentration, it does not assure the possibility of reducing it to zero in every case. Therefore, the second postulate, apart from the process optimization, is to educate the patient and provide him with post-discharge outpatient consultation. Knowing about the possibility of transient symptoms re-emerging at home, and about the available medical intervention, will reduce the patient's anxiety and improve prognosis.

## CONCLUSIONS

1. In the majority of alcohol-dependent patients leaving the detox unit after nominally completed AWS treatment using diazepam, clinically significant serum-BZD level persists. This state shifts the patient's confrontation with sobriety into the post-discharge period. A possible re-emergence of withdrawal symptoms may contribute to early post-detox relapses into drinking.
2. Post-detox residual serum-BZD concentration can be minimized by using the same (or lower) satiating amounts of diazepam, but concentrating them in the initial detox phase. The proposed modification offers a chance to reduce errors without increasing the patient's stress.
3. Providing the patient necessary information and scheduling an outpatient post-detox visit further reduces the risk of relapse in the case of a delayed crisis.

### Conflict of interest

Absent.

### Financial support

Absent.

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