

Original and Simple Protocol for Withdrawal of Benzodiazepines to Achieve Sustained Remission

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Abstract

Benzodiazepines are psychotropic medications for effective management of anxiety. However, after over 50 years of unrestrained prescription use, prescribers realize the severity of side effects in select patients. The most challenging of these side effects is the emergence of a physiological dependence that explains virtual impossibility of successful withdrawal that can ensure sustained abstinence. We propose a method for successful withdrawal using substitution and innovative downward tapering of diazepam oral solution for all benzodiazepines to attain sustained remission. Our protocol reported here allowed not only successful withdrawal for all of 20 patients included in this pilot study but also helped in totally weaning them off of benzodiazepines demonstrating absence of relapse even 2 years after the total discontinuance.

Keywords

Benzodiazepine, Withdrawal, Success

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1. Introduction

In the early 1970's, the dangerousness of barbiturates and search for safer drugs resulted in physicians mostly choosing to prescribe benzodiazepines (BZDs) for anxiety. Throughout the last 50 years, BZDs have become the most prescribed drugs in the world as a first line of treatment for anxiety (13). In fact, 12% to 16% of adults in developed countries are taking BZDs consistently. (15). USD \$134 million worth of BZDs were sold in 2010. France had one of the highest rates of hypnotic and anxiolytic drug consumption in Europe (AFSSAPS), (ANSM), [1]-[3].

In addition, the consumption of BZDs tends to soar with age: Lagnaoui *et al.* [4] showed that, regardless of gender, prevalence of BZD use increased from 30% between the ages of 51 and 70 years to over 55% in population over the age of 70 years.

However, the *prima facie* safety of BZDs that is at the root of the BZD popularity in the 70's has turned out to be an illusion. The BZD molecule, whose efficacy is nowadays discussed as beneficial in the treatment of anxiety, as it can be, also is associated with major concerning side effects that have turned this overused drug into a substantial public health risk [5]. Initially intended as temporary or short term prescriptions of BZD tend to last longer than they are intended for, and gradually become more permanent on the patient's medication profile, usually at the subtle or not so subtle urging by the patients themselves. This is coupled with the sincere desire to help seen among the doctors in resolving the problem of anxiety. Such decision for long term use of BZD to relieve anxiety indeed turns out to be a quick and dirty solution for the wide-spread anxiety related syndromes [6]. The continuous consumption of BZD indeed has a strong potential for habituation that results in undesirable unintended physical/psychological dependency in addition to well intended and acceptable therapeutic dependency. It is a common knowledge that nowadays 1/3 of women over 50, 1/5 of men over 50, [6]-[9] and 14% of the non-institutionalized over 60 population uses medically prescribed BZDs on an uninterrupted basis [4] [10]. Yet, more the population grows in age, the more side effects can be observed: falls with or without fractures, memory impairment, confusion, attention deficits that may lead to accidental injuries to patients, etc., [8] [11]. By inducing long term cognitive deficits, BZDs also contribute to precipitating emergence of acquired no-reversible major neurocognitive disorders that mimic Alzheimer's disease [12]-[14] and in emerging cases these disorders are clinically indistinguishable from Dementia of the Alzheimer's type.

All these arguments underline the utmost importance of judicious discontinuance and cessation of BZD use whenever clinically justifiable. However, considerable impediments arise when it comes to withdrawal: the usual impediments are absence or infrequency of demand for such measure initiated by the patients, the frequent, rapid, and even consistently repeated relapses according to some authors even after successful withdrawal, and the regrettably ubiquitous BZD withdrawal syndrome (BZDWS) of varied severity which is most dreaded by the patients. Difficulties faced during withdrawal process mostly depend on the length of treatment, dosages [15] and the withdrawing protocol used as well as the unwillingness of the patients. Numerous strategies have been studied, and their efficiency is limited, especially in the outpatient settings. Indeed, the rapidly graduated decrease of dosage recommended by current protocols is to be used during hospitalization in controlled environments, to minimize the hospital stays and as a rule it is almost impossible to achieve successful implementation of such protocols in outpatient clinics [16]. There is a general consensus that withdrawal discomfort could be eased by the simultaneous use of Selective Serotonin Reuptake Inhibitor [17] [18]. In these cases, even though relapse rate is lowered, the severity of BZDWS remains the same [17] [18]. Some authors also suggest that we combine gradual cessation of BZDs combined with Cognitive Behavior Therapy and/or 12 Step-Program proposed by AA (Alcoholics Anonymous).

Even considering the heterogeneity of recommend protocols, presenting difficulties in implementing them in outpatient clinics, [3] [19] [20], the obvious benefits of these protocols outweigh the risks and inconvenience of withdrawal. Among such benefits the most desirable is the significant decline in psychiatric morbidity 6 months [21] after successful discontinuance. We have been thinking of a protocol that could be used in our daily practice that could offer not only this benefit but also a total remission from BZD dependence. In this paper we would like to share a clinical experience of BZD withdrawal undertaken by following a simple empirical protocol that can have tremendous public health impact.

2. Material & Methods

2.1. Sample

This study took place in a health service nursing home "Maison d'Accueil Spécialisée" in Denain in North re-

gion of France. The experience begins in April 2013 and ends in September 2013.

All participants were under guardianship. We explained to guardians the benefits and purpose of BZD withdrawal: better alertness, fewer side effects, etc. They all accepted the value of such effort and consented to withdrawal and discontinuance of BZDs. Out of a total of 42 only 20 patients treated with BZD were selected. The inclusion criteria were informed consent by guardians and willingness of the healthy participants. Patients suffering from chronic pain and other serious chronic ailments were excluded from the study.

We also communicated with the nurses who prepare and administer medications, the details and the usefulness of this approach. In addition we organized many meetings in order to inform nurse's aids (Mental Health Technicians—MHTs) and paramedics. They all understood the ins and outs of this study, the utmost importance of their role and the fact that, in the long haul, fewer users of BZDs would mean lower amount of work for care-givers.

We put together a sample of 20 patients (10 men, 10 women, mean age: 48.4 ± 11.3) with known severe predominantly genetically transmitted psychiatric disorders namely subjects with significant intellectual disability, psychotic disorders, and pervasive developmental disorder, as defined by DSM-IV. It is acknowledged here that the diagnosis of pervasive developmental disorder is officially deleted from DSM V but was commonly used during the time this clinical trial was conducted.

The severity of the psychopathologies had led to long term care ($13 \text{ years} \pm 7 \text{ years}$) in an institution that would be described as long term residential care facility (Nursing Home).

Patients were well known to the attending physicians and caregivers. There was no turn-over and it was a steady long term population. Medication administration and the actual consumption of medications were systematically checked by nurses and were tallied as well as cross-checked.

Characteristics of patients are summarized in **Table 1**. Patients were taking BZDs for $27 \text{ years} \pm 5 - 6 \text{ years}$. Over time, behavioral symptoms, self-mutilation, increased aggression and combativeness towards others, agitation, sleep disorders, etc. were all used as legitimized indications for BZD prescriptions and the fear of resurgence of these symptoms seemed to be the reason for sustained long term use of BZD prescriptions. Thus, in order to maintain the initial effect, it progressively became necessary to increase dosage, because of the phenomenon of tolerance. Many previous withdrawal attempts failed due to high dependency on BZDs, patients becoming decompensated and the resultant institutional imbalance or sometimes stormy disruption of milieu as an immediate consequence of BZD discontinuance.

2.2. Protocol

This proposed protocol was inspired by the work of Professor Heather Ashton (<http://www.benzo.org.uk/freman/bzcha01.htm>). We used the same protocol as reported by Zitman & Couvec [18] based on the correspondence or equivalence between targeted BZD and 10 mg diazepam tablets (<http://www.benzo.org.uk/freman/bzcha01.htm>). The originality of our idea is that we transformed the diazepam tablets in drops of diazepam oral solution. We converted the tablet form dosage of every BZD of every patient into solution form, following the equivalence: 10 mg of diazepam tablet = 30 drops of oral solution of diazepam for oral administration. However, some BZDs were already prescribed in solution or liquid form at the beginning of our study. We calculated the equivalence to a hydrate form of other specific BZDs, and then used the same previous rule or methodology of gradual reduction of dosage utilizing diazepam oral solution. We substituted diazepam oral solution for the original BZD in every patient.

For example, 0.5 milligrams (mg) of alprazolam (Xanax) is approximately equivalent to 10mg of diazepam (Valium) (<http://www.benzo.org.uk/manual/bzcha01.htm>). And 1 ml contains 30 drops, corresponding to 10 mg of diazepam (<http://www.onmeda.fr/medicament/valium-roche-93111303.html>). <https://dailymed.nlm.nih.gov/dailymed/index.cfm>.

Daily scheduled administration of dosage of the diazepam oral solution was identical to that of the a hydrate BZD.

Each week, we reduced only 2 drops at each scheduled dose of the day (**Figure 1**). Volumes of oral diazepam solution for weekly use were stored in small plastic containers closed with a waterproof lid. A picture of the patient was stuck on the external side of the container including his/her identification by name and date of birth to be verified at administration of each dose.

The preparation of 20 containers required specific attention by the pharmacists and the nurses. Weekly changes in the 20 dosage schedules were a major and difficult challenge of this approach. Each patient had an

Table 1. Characteristics of patients who benefited from the withdrawal.

		M = male F = femelle	Diagnosis: Severe Intellectual disability	Treatment	Age	former treatment	dosages	DIAZEP AM equivalent	Withdrawal Duration in weeks	Cost per year
1	BB	M	idiopathic	AD + TR + BZD	50	Alprazolam 0.25 mg	1-1-1	15-15-15	8	65
2	BL	F	idiopathic	TR + AE + ED + AP + BZD	40	Diazepam 10 mg	0-0-1	0-0-30	15	25
3	DE	M	idiopathic	AD + AP + BZD	25	Prazepam 10 mg	1-0-1	20-0-30	15	30
4	DP	F	idiopathic	AD + AE + AP + BZD	53	Oxazepam 10 mg	1-0-1	15-15-15	8	25
5	DR	M	Tuberous sclerosis	AD + TR + AE + AP + BZD	23	Clorazepat 10 mg Clorazepat 20 mg	0-1-0 1-0-1	40-20-40	20	48 152
6	NJC	F	malformation syndrome	AE + AP	55	Prazepam 10 mg	0-0-1	0-0-30	15	47
7	PM	F	idiopathic	AD + AP	61	Alprazolam 0.25 mg	0-0-1	0-0-15	8	18
8	RD	M	idiopathic	AD + BZD	41	Alprazolam 0.25 mg	1-1-1	15-15-15	8	65
9	WD	M	Autism	AE + AP + BZD	42	Prazepam 10 mg	0-0-1	0-0-30	15	42
10	BM	F	Trisomy 21	BZD	60	Clobazepam 5mg	0-0-1	0-0-8	4	22
11	BR	F	very serious psychosis	AD + AP + BZD	49	Oxazepam 10 mg	1-0-1	15-0--15	8	38
12	DJP	F	Autism	AD + AP + BZD	61	Oxazepam 10 mg	2-0-2	30-0-30	15	141
13	EMN	M	Synd. Polymalforma- -tions	AE + BZD	37	Oxazepam 10 mg	2-0-2	30-0-30-	15	125
14	GA	M	idiopathic	AD + AP + BZD	61	Zolpidem 10 mg	0-0-1	0-0-15	8	66
15	VS	F	Autism	AE + BZD	53	Zolpidem 10 mg	0-0-1	0-0-15	8	31
16	BC	F	idiopathic	AD + BZD	45	Zolpidem 10 mg	0-0-1	0-0-15	8	66
17	CN	M	idiopathic	AE + AD + BZD	48	Oxazepam 10 mg	1-1-1	15-15-15	8	140
18	LN	M	Kernicterus	AD + AP + TR + BZD	47	Alprazolam 0.25 mg	2-2-2	30-30-30	15	120
19	VM	F	Irradiation in utero	AD + BZD	57	Alprazolam 0.25 mg	0-0-1/2	0-0-8	4	17
20	VJR	M	idiopathic	AD + AP + BZD	60	Oxazepam 10 mg	1-1-1	15-15-15	8	140

AD: antidepressants, AE: antiepileptic, PA: antipsychotics, BZD: Benzodiazepines, TR: thymus-regulators.

individualized calendar for his medication administration record for every week and the withdrawal protocol was running for months.

3. Results

This protocol goes on for several months as against the rapid withdrawal schedules used in acute care settings.

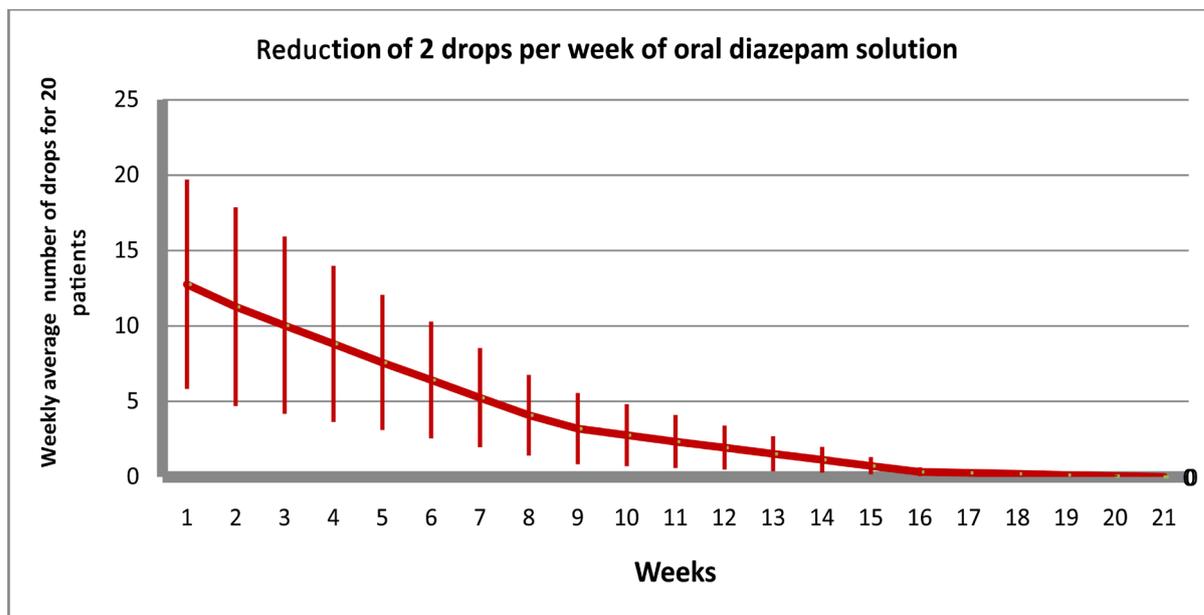


Figure 1. Decrease of 2 drops per week of oral DIAZEPAM solution; profile for 20 residents.

Withdrawal schedules were individualized. What is of note is that there was no emergence of symptoms that constituted the usual BZDWS such as: withdrawal discomfort or uneasiness, tremor, nausea, constipation, difficulties in urination, headaches, musculo-skeletal aches and pains, muscle weakness, massive rebound anxiety, agitation, irritability, nightmares, anorexia, diarrhea, diaphoresis, sweating, mood changes, depression, depersonalization, disorientation, hallucinations, paranoid psychosis, hypersensitivity to noise lights and odors, numbness, tingling, dysgeusia, hyperthermia and rhabdomyolysis, [22] nor any life-threatening condition, such as severe confusion or delirium [22] non-epileptic withdrawal seizures, or aggravation of pre-existing seizure disorder and this, despite the small prevalence of co-morbid epilepsy in this population.

Moreover, after 2 years, no relapses have been detected. Increase in cognitive competencies couldn't be measured nor evaluated due to the original severity of intellectual disability. Nonetheless, patients showed no worsening of their behavioral disorder [10] after the total and complete discontinuance.

Caregivers also reported a lower incidence of daytime drowsiness in patients. They could all participate more easily in daily activities, had higher muscle tone, and could walk more steadily.

Patients were also able to ambulate more independently, according to caregivers. Unfortunately, no standard neurological examination to assess motor strength was serially performed to objectively evaluate the improvement in muscle strength, gait or steadiness.

4. Discussion

Our protocol was effective. We were pleasantly surprised to notice that even though some BZDs had very short half-life, no BZDWS was observed in the case of short half-life BZDs. Indeed, it is widely known that more shorter are half-life, more severe are the BZDWS [22]. This makes us confident that our protocol is highly efficient in controlling the emergence of BZDWS.

However, a few limitations of this study have to be emphasized. First, the small size of the sample makes generalization of these results impossible. Moreover, the experimental group in this study comprised of institutionalized long term patients, and consequently necessarily compliant in controlled environment, whereas, outpatients, who would be our wider public health-wise target population, would have been harder to convince to follow a prescription where come down regimen of the dosage varies weekly. Thus, a study based on only highly motivated outpatients would be beneficial or worth undertaking to verify if the results of this study can be replicated in outpatient population. Another point is that our study was not randomized double blind study. We did not use control subjects in this pilot study. Considering the lack of consensus, our goal was limited to empirically come up with a protocol that could be handily used in daily practice in helping highly motivated patients; and

we were hoping that this clinical experience in real life verified anecdotally by many practitioners may lead the path to further experimental clinical research trials to prove the efficacy of this protocol.

The strength of our work lies in the initial stability of patient population, the absolute certainty of therapeutic compliance, and the involvement and motivation of caregivers. Thus, this protocol cannot be used alone, it has to be complemented with psycho-educational meetings with caregivers and patients to explain the predicted outcomes, by winning the total trust of the motivated patients, and a concerted effort by all the parties involved including the patients' guardians. People in the nursing homes have a similar profile as our population as regards the compliance plan and benefits to stop their BZD medications. Therefore, this study could further guide clinical research trials in gero-psychiatric residential care settings (nursing homes) provided the patients and guardians willingly participate without undue anxiety. Human subject protection considerations should be in favor of such studies if IRBs (Institutional Review Boards) were to note that the benefits far outweigh the risks afforded to experimental subject populations. Simply keeping statistical track of falls, injuries from falls, other accidents, pre and post cognitive assessments, accidental overdose episodes, etc, before starting such studies with similar quantification six months, one year, two year after this study will provide useful data to help popularize this protocol. "Granato-Vinekarprotocol". Naming this protocol will help uniformity of communication in future clinical trials. The originality and possibility of extrapolation or generalization in withdrawing other addictive medications is likely to encourage future research to replicate our findings.

The economic benefit of such protocol has a potential of staggering proportion. This successful withdrawal enabled a saving of minimum USD \$1500 yearly, that is to say a mean cost saving of USD \$ 75 per patient per year even considering use of cheaper generic formulations.

From this pilot study, we understand that the widespread use of this approach could be profitable for a country, not only from the economic point of view, but also from the global public health point of view, since it enhances patient's quality of life, and reduces in the long run the amount of work for caregivers. This cost saving does not include the indirect savings, especially for senior health care costs entailed in diagnoses and treatment of fractures caused by falls, cases of delirium, and preventable hospitalizations for medical and psychiatric complications related to widespread BZD use, etc.

5. Conclusions

Indiscriminate BZD prescribing habits of physicians can be compared to antibiotics prescriptions. In both instances, we have to wait many decades to notice harmful consequences of large and unrestrained use of prescriptions. We now have to cope up with the consequences. Habituation and addiction potential of BZDs being the main issue, our daily challenge as physicians is to help our patients manage to kick the habit of taking BZDs. The model proposed in this paper for a "*come down schedule*" or "*downward titration*" can be implemented in our highly motivated out-patients who are currently under treatment. This is where our withdrawal method can make a difference. Its success is based not only on the use of liquid form instead of an a hydrate tablet forms, but also on the diligence and involvement of nurses and support staff. To go further, equivalences between any of the BZDs and oral solution of diazepam, and individualization of prescriptions can be facilitated by the creation of a software program, accessible on-line only for doctors and pharmacists' use in the institutions. This program will dictate "*prescription calendar for every patient*" and help reduce medication dosage errors and save time needed for monitoring prescriptions. A smartphone application will carefully follow the weekly variations of dosage prescribed by the doctor. We propose the following website

www.benzodiazepine-withdrawal.com.

A complementary way to handle the BZD overuse issue is for us prescribing physician to be extremely cautious when prescribing these drugs: to base our thoughts on their action on precise target symptoms, to pre-determine with each patient the length of treatment, to always use the minimal dosage, and to avoid mechanically written prescriptions (in auto-pilot rapid speed mode of practice). The high risk of dependency linked to BZD legitimizes strict supervision, and is actually everyone's business/concern. This is the rationale behind the mandated prescription monitoring programs (PMP) adopted by many states in the United States.

Our paper demonstrates that the subjects can be totally and permanently withdrawn from BZDs with no craving for BZDs or necessity for other substitute central nervous system depressants (hypnotic-sedatives) in long term care facilities. The remission from BZD dependence is total remission and can last for good. This finding must be emphasized in addition to the side benefits of reducing energy and effort expended by the care-givers,

lowering the risk of potentially dangerous side effects of BZDs, and of course, finally the cost to the society in paying for expensive BZDs year after year for the BZD dependent individuals.

This pioneering work is empirical, but we observed no relapse in 2 years after successful discontinuance, granting no one had access to BZDs in controlled environment. The methodology is simple but significant in overcoming cravings for BZDs. However, more scientific studies are needed to confirm or refute the findings of this clinical trial. BZD dependence is a public health problem as much as the abuse of numerous other natural or synthetic drugs of abuse. The weaning is extremely difficult in the treatment of chemical dependency. Also, confirmation of the success of this method starting with BZDs can be extended to all of these drugs of abuse as well as extrapolated to tapering down of corticosteroids and other therapeutic agents presenting the problem of difficult weaning.

Last but not the least, this protocol can also be used for all other addictive medication molecules presenting challenge to successful withdrawal and discontinuation to attain sustained total remission.

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