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How chronic administration of benzodiazepines leads to unexplained chronic illnesses: A hypothesis

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A B S T R A C T

It is thought that an ill defined biochemical cascade may lead to protracted withdrawal symptoms subsequent to discontinuance of routine use of benzodiazepine class drugs and establish chronic illness in some patients. In this review, published findings are presented that support the novel concept that withdrawal from benzodiazepine class drugs can trigger elevated and sustained levels of a potent oxidant called peroxynitrite via potentiation of the L-type voltage-gated calcium channels, and in the later stages of withdrawal, via excessive N-methyl-D-aspartate receptor activity, as well. Potentiation of L-type voltage-gated calcium channels and excessive N-methyl-D-aspartate receptor activity both result in calcium influx into the cell that triggers nitric oxide synthesis. In pathophysiological conditions, such increased nitric oxide synthesis leads to peroxynitrite formation.

The downstream effects of peroxynitrite formation that may occur during withdrawal ultimately lead to further peroxynitrite production in a system of overlapping vicious cycles collectively referred to as the NO/ONOO(−) cycle. Once triggered, the elements of the NO/ONOO(−) cycle perpetuate pathophysiology, perhaps including reduced $GABA_A$ receptor functioning, that may explain protracted withdrawal associated symptoms while the vicious cycle nature of the NO/ONOO(−) cycle may explain how withdrawal becomes a chronic state.

Suboptimal levels of tetrahydrobiopterin may be one risk factor for the development of the protracted withdrawal syndrome as this will lead to partial nitric oxide uncoupling and resultant peroxynitrite formation. Nitric oxide uncoupling results in superoxide production as calcium-dependent nitric oxide synthases attempt to produce nitric oxide in response to L-type voltage-gated calcium channel-mediated calcium influx that is known to occur during withdrawal. The combination of nitric oxide and superoxide produced, as when partial uncoupling occurs, react together in a very rapid, diffusion limited reaction to form peroxynitrite and thereby trigger the NO/ONOO(−) cycle.

The NO/ONOO(−) cycle may explain the nature of the protracted withdrawal syndrome and the related constellation of symptoms that are also common in other illnesses characterized as NO/ONOO(−) disorders such as myalgic encephalomyelitis/chronic fatigue syndrome and fibromyalgia.

Introduction

Benzodiazepines are a class of drugs that are prescribed for treating a wide variety of disorders, including various forms of anxiety disorders, epilepsy, muscle spasms, insomnia, and tinnitus. Benzodiazepines are sometimes characterized as “minor tranquilizers,” due to their potentially sedating effect. Benzodiazepines are thought to exert their anxiolytic effect by enhancing the activity of the inhibitory neurotransmitter, GABA (gamma-aminobutyric acid). Among the most prescribed benzodiazepine drugs are clonazepam, brand name Klonopin, alprazolam, brand name, Xanax, lorazepam, brand name Ativan, and diazepam, brand name, Valium. A major drawback to benzodiazepines, however, is that long term use, including normal therapeutic dosing, can lead to the development of physical dependency and withdrawal symptoms upon discontinuance [1]. For those who use benzodiazepines at therapeutic doses, benzodiazepine dependence is primarily concerned with the negative subjective effects of withdrawal upon discontinuance and not reward-seeking effects of the benzodiazepine use [2].

Observations that benzodiazepine withdrawal associated symptoms can be severe and protracted

According to physician and Emeritus Professor of Clinical Psychopharmacology at Newcastle University, Heather Ashton, it may be appropriate to characterize the constellation of symptoms associated

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with withdrawing from benzodiazepine use as an illness rather than simply "withdrawal" in cases in which symptoms persist for a period of several months to several years after discontinuance.

> "The features of benzodiazepine withdrawal appear to constitute a new syndrome characterised by a particular cluster of symptoms and a protracted clinical course…In addition the course of the benzodiazepine withdrawal syndrome appears to be much longer than that of other drugs of dependence, and in particular longer than that reported for benzodiazepines, which has been stated to last 5–15 days, 2–4 weeks, and 10–54 days" [3].

Malcolm Lader, Emeritus Professor at the Institute of Psychiatry, Psychology, and Neuroscience at King's College in London, echoed Ashton's observations in both his research and public comments. In a radio interview, Lader stated that a subset of patients experience long-term withdrawal lasting two or more years with some reports of patients still experiencing symptoms ten years after discontinuance [4].

Of those that suffer from a protracted withdrawal, most recover from associated anxiety and depression long before resolution of physical symptoms such as muscle spasm [5]. Ashton listed several common "somatic" withdrawal symptoms which she distinguished from the common psychiatric symptoms associated with withdrawal, such as anxiety [3]. Among the somatic symptoms, Ashton noted paresthesia, pain and stiffness in various parts of the body, tremors in hand and jaw, muscle fasciculation, myoclonic jerk, ataxia, visual disturbances, photophobia along with increased sensitivities to noise, taste and smell, gastrointestinal disturbances, "influenza-like" symptoms including weakness, postural dizziness, aches and pains, but not accompanied by fever [3]. Among common withdrawal symptoms, Brett and Murnion noted tinnitus along with many other symptoms, including several that are identical to the ones reported by Ashton [6]. While many of the withdrawal symptoms experienced by patients may be similar in nature to their symptoms for which the drug was originally prescribed [6], old symptoms often return with pronounced severity, and indeed, new symptoms commonly emerge in withdrawal never before experienced by the patient [5]. Additionally, Pittman et al. conducted a survey of 493 self-selected participants from the benzodiazepine withdrawal support website, Benzobuddies.org, indicating the cluster of symptoms experienced by withdrawal sufferers was consistent notwithstanding the symptoms the participant experienced prior to benzodiazepine use [7]. Most interestingly, when comparing participants with no prior psychiatric history to those with a history of psychiatric disorder, Pittman et al. found no significant differences in reporting of psychiatric symptoms (with the exception of suicidal and panic symptoms) experienced during withdrawal [7]. Of the 493 surveyed, 156 participants reported that they had discontinued benzodiazepine use and that their withdrawal symptoms had subsided [7]. The average length of time that withdrawal symptoms persisted *after withdrawal from the drug was complete* for these 156 participants was 14 months [7].

Benzodiazepine Information Coalition (BIC), a patient-driven non-profit organization that raises awareness of the risks associated with benzodiazepine administration, reports a wide range of common symptoms associated with withdrawal, including those observed by Ashton, Lader and Pittman, as well as the potential for withdrawal symptoms to persist for a period of several months or even several years [8,9]. While the epidemiology of protracted withdrawal syndrome (PWS) has not been rigorously studied, based on informal patient surveys and reporting, Ashton and BIC agree the number who are severely affected in the long term to comprise a significant minority, perhaps representing somewhere between 10% and 15% of all chronic benzodiazepine users [5,8]. Given the astounding number of prescriptions for benzodiazepines, this significant minority might represent upward of over one million individuals in the United States alone. Emergence of PWS from chronic use of benzodiazepines appears to be independent of dosing [2,5,8]. To date, there has been no detailed proposal for how PWS is initiated and perpetuated and what factors predispose one to PWS upon discontinuance from routine use of benzodiazepines.

Background: prior research concerning pathophysiological effects of benzodiazepine sensitization & withdrawal

Research has demonstrated why benzodiazepines tend to lose their effectiveness with chronic use over time and lead to physical dependency. Essentially, GABAergic function is diminished after chronic benzodiazepine treatment [10], and up-regulation of glutamatergic neurotransmission occurs, although resultant glutamatergic over-activity may not be observed until subsequent to withdrawal [11]. After withdrawal occurs, glutamatergic over-activity is no longer masked by the benzodiazepine's heightened inhibitory effect on the GABAergic system [11].

Previously studied effects of benzodiazepine withdrawal on L-type voltage gated calcium channels

Benzodiazepines' action on voltage activated calcium channels appear to play an important role in benzodiazepine dependency and withdrawal [12]. Benzodiazepine administration can regulate L-type voltage-gated calcium channel (L-type VGCC) expression [12]. Benzodiazepines can directly inhibit L-type VGCC-mediated calcium influx and high voltage-activated (HVA) currents [13–15]. Benzodiazepines' inhibition of L-type VGCC's may partially explain the therapeutic effect of clonazepam, a benzodiazepine class drug, in the treatment of ME/CFS, in lowering over-activity of the brain [16].

Benzodiazepines, however, can have a paradoxical effect on L-type VGCC expression, especially during withdrawal [12]. Xiang et al. cited the finding that [^{3}H]diltiazem (a calcium channel blocking drug) binding sites were up-regulated in mouse cortical cultures with concomitant increase in L-type VGCC subunit expression after 3-day exposure of mouse cortical cultures to 1,4- or 1,5-benzodiazepines and in diazepam-treated mice exhibiting withdrawal signs [17] as part of the foundation for their experiment that revealed "a doubling of HVA calcium current density was detectable [in rat hippocampal CA1 pyramidal neuron cell cultures] immediately after ending 1-week flurazepam (a benzodiazepine) administration and was sustained for at least 2 days after ending treatment before tapering off 3 days after treatment" [12].

Summarizing the role of L-type VGCCs in withdrawal, Xiang et al. states:

> "The accumulated evidence supports the possibility that L-type VGCCs may be a source for diverse intracellular messengers or transcription factors to increase glutamatergic strength during benzodiazepine withdrawal and contribute to benzodiazepine physical dependence" [12].

Role of AMPA receptors in benzodiazepine withdrawal

α-amino-3-hydroxy-5-methylisoxasole-4-propionic acid (AMPA) receptors appear to play a significant role in the initial stages of benzodiazepine withdrawal pathophysiology [11]. AMPA receptor mediated mEPSC amplitude increased an additional 30 to 50% in 2-day flurazepam-withdrawn rats; however, pretreatment with the L-VGCC antagonist, nimodipine, abolished the transient increase in AMPAR-current potentiation, demonstrating L-VGCC's role in benzodiazepine dependence and withdrawal [12]. Such AMPAR current enhancement is linked to severity of withdrawal anxiety [18], at least during the early stages of withdrawal.

Role of NMDA receptors in benzodiazepine sensitization and withdrawal

While N-methyl-D-aspartate (NMDA) receptor EPSC amplitude has been found to be significantly decreased in hippocampal slices