Perils in Benzodiazepine Withdrawal: Case Report

V. F. H Macfarlane, L. J. Moore

***Abstract* — The discovery that clonazepam prescribed for the treatment of migraines caused obstructive sleep apnea led to a rapid taper of clonazepam and substitution of lorazepam. Lack of accurate knowledge about the different pharmacokinetics and actions of different benzodiazepines at GABA-A receptors and the risks associated with rapid benzodiazepine withdrawal resulted in the development of the benzodiazepine protracted withdrawal syndrome. Moderately severe disability continued after 2 years. Insufficient knowledge about benzodiazepines and their withdrawal is a serious problem as doctors across the world are under extreme pressure to stop prescribing them but do not have an understanding of the potential perils involved. The pathophysiology of protracted withdrawal syndrome remains poorly understood and there is no recognised treatment. Information about appropriate management of withdrawal and the protracted withdrawal syndrome are available on Professor Ashton's website at www.benzo.org.uk.**

***Index Terms* — Benzodiazepine Withdrawal, Protracted Benzodiazepine Withdrawal Syndrome, Benzodiazepine Pharmacology, CNF Effects.**

I. Case Report

A 59-year-old female married with two children was seen by her neurologist for the treatment of migraines and referred for a sleep study. The migraines began in 2009 after exercise as well as airline flights. Magnetic resonance imaging of the brain was normal. After a trial of clonidine for menopausal symptoms precipitated a severe headache in the middle of the night, magnetic resonance imaging with contrast showed an almost completely obstructed left carotid artery. Endarterectomy was undertaken without complications but the migraines did not resolve. Multiple trials or medication were recommended by the neurologist without success. An increased dose of progesterone was effective and this began trials of GABAergic medications including gabitril, gabapentin, valproate, and eventually clonazepam which was effective along with propranolol 20mg and ranitidine 150 mg both taken twice daily.

Repeated attempts were made to stop clonazepam including three trials of gabapentin, two serotonin reuptake inhibitors, a tricyclic antidepressant, mirtazapine, buspirone, oxcarbazepine, topiramate and lamotrigine. The neurologist suspected that clonazepam was causing obstructive sleep apnea and that this was either exacerbating or causing the migraines. The patient was referred to a pain specialist who used acupuncture to treat the migraines and converted the clonazepam to lorazepam over a period of 17 days. The obstructive sleep apnea resolved on repeat testing after conversion to lorazepam. Lorazepam was substituted because it is short acting with no active metabolites and is considered favorable for use in the elderly. A very rapid conversion and an inadequate substitution were made and the patient developed multiple physical symptoms. It took more than four months before an addiction specialist instituted appropriate treatment with a low dose of diazepam and recognised the symptoms were due to the benzodiazepine protracted withdrawal syndrome. None of the patient's previous doctors had any understanding of benzodiazepine withdrawal or recognised the challenges associated with conversion of one benzodiazepine for another. A very slow titration of 0.5 to 1 mg diazepam every 2-3 months was recommended by the addiction specialist; however, a new treating doctor reduced the dose of diazepam by half from 5 mg twice daily to 2.5 mg twice daily. The patient developed xerostomia that did not respond to intensive hydration, persistent gastrointestinal symptoms, cardiovascular symptoms and general malaise. Pepto-Bismol for gastrointestinal distress was helpful but unfortunately led to tinnitus and impaired hearing. Pepto-Bismol was stopped and hearing was restored over a period of 1.5 months. Hypotensive episodes became more frequent and were associated with palpitations when the patient was supine. With an increase in diazepam to 2.5 mg mane and 5 mg nocte, palpitations reduced but xerostomia, severe orthostasis and tachycardia persisted. When these symptoms did not resolve over several months it was felt the patient had developed sensitivity to diazepam. The treating physician stopped diazepam and began clonazepam 0.5mg four times a day.

The gastrointestinal distress continued and treatment included ranitidine 150mg twice daily until new evidence suggested it was carcinogenic. Famotidine 20 mg four times a day was substituted, sucralfate 1 gm twice daily was trialed and finally after almost 2 years, omeprazole was commenced, tolerated well and increased to 20 mg twice daily. Lack of appetite, difficulty with digestion, abdominal pain, palpitations and orthostasis persisted.

II. Differential Diagnosis

Ovarian Cancer with neuroendocrine activity. Subsequent laparoscopic surgery showed no pathology.

III. Coexisting Conditions and Drug Sensitivities

Ophthalmic Migraine with Aura treated with clonazepam that with aging caused Obstructive Sleep Apnea.

Osteopenia with History of Osteoporosis and Compression Fracture of 11th Thoracic Vertebra requiring HRT after 3 years without hormones and multiple HRT

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trials that appeared to precipitate migraines.

Left Carotid Endarterectomy 2009.

Unexpected Sensitivities and Complications During Protracted Withdrawal:

1. Prolonged recovery from colonoscopy: 3 months.
2. Prolonged recovery from laparoscopy: 3 months.
3. Intolerance to medications including propranolol, lamotrigine, diazepam, omeprazole, NSAID gel-induced renal impairment that resolved upon cessation after 20 years of use.
4. Pepto-Bismol-induced tinnitus and hearing impairment that resolved upon cessation, vitamin D toxicity on the same dose used for 10 years.

IV. Discussion

Contrary to the belief of most doctors and psychiatrists, all benzodiazepines are not equivalent. They have distinctive pharmacokinetics and act at different GABA-A receptors that are distributed in particular areas of the brain. Lorazepam is a highly potent and short acting benzodiazepine and is one of the most difficult to withdraw [1]. More than one trial of lorazepam had been given over the years and they were all associated with a significantly low mood and the development of multiple health problems. The recent failed trial was almost certainly due to the unanticipated protracted withdrawal syndrome that developed due to rapid conversion from clonazepam. The subsequent large reduction of diazepam in contradiction to the addiction specialist's advice exacerbated the protracted withdrawal symptoms and ultimately resulted in the restarting of clonazepam.

Contemporary guidelines for benzodiazepine withdrawal usually recommend conversion of all benzodiazepines to diazepam followed by withdrawal over four to six weeks and do not go into any detail about the process of conversion, dose equivalents, the risks of prescribing diazepam to the elderly or the need to individualise withdrawal to avoid the development of the protracted withdrawal syndromes [2], [3].

Dr. Malcom Lader has written extensively on benzodiazepine withdrawal and is clear that withdrawal must be differentiated from rebound, the increase in anxiety and restlessness after cessation of medication. Withdrawal is a more serious phenomenon that is comprised of a characteristic grouping of signs and symptoms that ensues on changing to a different benzodiazepine or reducing the dose of benzodiazepine and in some cases can be protracted [1], [4]. A detailed discussion of benzodiazepine withdrawal and recommendations for treatment are provided by Professor Heather Ashton [5] at her website www.benzo.org.uk. Most doctors are not aware of her recommendations that include a caution that rapid withdrawal of benzodiazepines that have been taken for a long period of time can precipitate a protracted withdrawal syndrome that may last up to one to ten years.

An understanding of the structure of GABA-A receptors including subtypes, distribution and function is important when managing both conversion from one benzodiazepine to another as well as during withdrawal. The GABA-A receptor is comprised of 5 subunits that are assembled in a ring-like complex with a central chloride channel [1]. The subunits vary but the major sub-unit complex consists of $\alpha 1$, $\beta 2$ and $\gamma 2$. Different isoforms of the GABA-A receptor are distributed in different parts of the brain and other parts of the body and have different actions and different affinities for agonists including benzodiazepines [1]. A thorough discussion of these issues is beyond the scope of this paper [4]-[8]. These complicated neuro-receptor characteristics together with different pharmacokinetics of the benzodiazepines result in a syndrome of withdrawal that has fluctuating, varied and unpredictable responses involving multiple organ systems that also varies widely amongst individual patients.

It is not surprising given the current guidelines for benzodiazepine withdrawal that clinicians are unaware of what to do. Some guidelines suggest there is no concern about seizures [3], for example, and others emphasise this risk [4].

The fragmentation of medicine by specialisation has contributed to the lack of understanding of managing benzodiazepine withdrawal. Alcohol and drug services that currently specialise in the management of benzodiazepine withdrawal are separate from psychiatric services, general medical practitioners and other specialists. Benzodiazepines are prescribed by a wide range of doctors but withdrawal knowledge is restricted to alcohol and drug services. Despite the commonly held notion that benzodiazepines must be withdrawn in all patients there are clinical situations in which long-term benzodiazepine use may be considered defensible. The first is in psychiatric illness for the treatment of severe and persistent severe anxiety or insomnia, panic disorder, generalized anxiety disorder, social phobia, dysphoric disorder and anxiety due to medical illness [9]. The second is in benzodiazepine users where all attempts at withdrawal have failed and the patient has persistent, debilitating and intolerable withdrawal symptoms that fail to resolve. It is recommended that if benzodiazepines are going to be prescribed long term that the following criteria must be met:

1) treatment must be for a recognised illness for which all alternative agents have been unsuccessful;

2) the benefits of continuing treatment outweigh the risks of withdrawal;

3) a collaborative decision is made with the patient who accepts the increased risks including memory problems, emotional suppression and dependency;

4) treatment is strictly individualised and reviewed periodically;

5) the prescribing clinician must be able to justify the clinical decision and document an appropriate discussion with details noted in the clinical record [9], [10].

V. Conclusion Bullet Points

• Doctors are being pressured to stop prescribing benzodiazepines and often do not give patients correct advice about withdrawal.

• This, coupled with lack of knowledge about the complexity of the benzodiazepine family of medications and their diverse neuroreceptor functions, can lead doctors to incorrectly convert one benzodiazepine to another and rapidly withdraw medications patients have been using for

extended periods.

• Both of these potential hazards may precipitate the protracted withdrawal syndrome that may be debilitating and persist for 1 year to 10 years.

• Professor Aston has clear guidelines on her website www.benzo.org.uk [5] for safe withdrawal. She cautions against pushing forward with rapid withdrawal even though the patient may request this. Complete withdrawal may not always be possible. [9,10].

• Inadequate understanding of the neurobiology of benzodiazepines in withdrawal may contribute to doctors blaming patients for their reliance on medications when, in fact, the doctors do not understand the potential perils involved in the appropriate management of benzodiazepine withdrawal.

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Dr. Vicki Macfarlane was born in Auckland, New Zealand, graduated from the University of Auckland in 1989, and completed a Fellowship in General Practice to become a Fellow of the Royal New Zealand College of General practitioners in 2004. She spent 19 years working as a General Practitioner in Auckland and Wellington, New Zealand. In 2011 she commenced work with the Community Alcohol and Drug Services (CADS) in Auckland and trained in Addiction Medicine with the Royal Australasian College of Physicians. She became a Fellow of the Chapter of Addiction Medicine in 2015. Dr Macfarlane has been the New Zealand Branch Chair on the Chapter of Addiction Medicine Committee since 2015.

Since 2011 she has been the Lead Clinician of the Medical Detoxification Services providing clinical leadership for both a community detoxification service and an 11 bed inpatient unit. The multidisciplinary service provides detoxification services for all substances to the population of Auckland, approximately 1.8 million people. Since 2015 the Community Detoxification Service has been the sole service supporting patients in Auckland that require oversight of benzodiazepine withdrawal and she has treated over 300 clients with benzodiazepine dependence.

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Dr. Laurie Jo Moore was born in Seattle, Washington, USA, graduated from the University of California at Berkeley cum laude in 1969, completed Medical School in Oregon and spent seven years working as a General Practitioner in Portland, Oregon. Psychiatry residency, Chief Residency and Fellowship in Public Psychiatry with the American Psychiatric Association (1982-1987) were completed at Oregon Health Sciences University (OHSU) followed by ten years as an Assistant Professor at OHSU. Lifetime Board Certification was gained with the American Board of Psychiatry and Neurology in 1990, a ten-year Addictions Subspecialty Board Certification in 1993 and a ten-year Geriatric Board Certification in 1996. A year sabbatical was spent in Wellington, New Zealand in 1994-1995, then a year on an inpatient ward with the Veteran's Administration at OHSU followed by two locums in Northern Michigan and Charlotte, North Carolina before returning to New Zealand where she became a lifetime Fellow with the Royal Australian and New Zealand College of Psychiatrists in 2001 and worked at each of the three major District Health Boards in Auckland including 8 years in leadership positions. Academic work included appointment as a Clinical Instructor for the University of Auckland Faculty of Medicine and Health Sciences University. This was followed by five years in integrated inpatient/outpatient work in rural remote Cairns, Queensland, Australia, then outpatient work at the Veteran's Administration at Loma Linda University as an Associate Professor 2015-2018 and a two years of locum work in New Zealand including Geriatrics, Intensive Case Management and Maori Services.

She worked with Multnomah County as a general physician in the county jails, detox center, urban crisis clinics and established a cooperative treatment program for alcoholic patients with the community services in the 1970's. Work with both Vietnam Veterans at OHSU and the Indochinese Refugees who came to America in the 1980's following the fall of Saigon led to publishing her first book The Secret Fire: When the Land of a Million Elephants Turned Red, 2000, Sid Harta Press, about how twelve Lao men survived an average of ten years in the Pathet Lao Death Camps. As Assistant Professor at OHSU she provided inpatient, outpatient adult and geriatric work, psychotherapy, consultation-liaison, provision of care and supervision of a psychiatric unit in the men's, women's and children's jails and Clinical Direction for the Alcohol and Drug Treatment and Training Center (AT&TC) associated with OHSU (the oldest alcohol treatment program in the USA). For five years she was the psychiatrist for Odyssey House, a therapeutic community, in New Zealand. She has published in the areas of bipolar disorder, depression, PTSD, addictions, personality disorders, existentialism, cultural and social psychiatry. Her recent book is called What's Behind Social Hatred, 2019, IngramSparks, USA.

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