Benzodiazepine Usage During 19.5 Years in Methadone Maintenance Treatment Patients and its Relation to Long-Term Outcome

Einat Peles, PhD,[1,2] Miriam Adelson, MD,[1] and Shaul Schreiber, MD[1,2]

[1] *Dr. Miriam & Sheldon G. Adelson Clinic for Drug Abuse, Treatment & Research, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*
[2] *Department of Psychiatry, Tel Aviv Sourasky Medical Center, affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

ABSTRACT

Background: Benzodiazepines (BDZs) abuse was found to cause diverse harmful effects among MMT patients. The current study evaluates prevalence rates of BDZ usage during 19.5 years in MMT, and its relation to patients' long-term retention in treatment.

Methods: All 787 opiate addicts who were ever admitted to the Adelson MMT clinic in Tel Aviv between 1993 and 2012 were studied. Observed and random urine results for BDZs usage were taken a few times every month. Positive for BDZ was defined in each month if at least one of the urines tested positive. Long-term retention was studied using Kaplan Meier analyses.

Results: BDZ prevalence among the MMT patients (ranged from 26 patients in 1994, and 300 to 350 since 2009) was about 35-40% in the last few years, with a "peak" of 61% followed by low rate of 25.4%. Followed up for up to 19.5 years, those who were negative to BDZ upon admission to MMT stayed longer in treatment (mean 8.5y, 95% Confidence Interval [CI] 7.6-9.4) than those who were positive to BDZ when admitted (mean 6.9y, 95% CI 6.2-7.7) (Kaplan Meier analyses p=0.01).

Conclusion: BDZs abuse is highly prevalent among MMT patients. Abuse of BDZ on entry to treatment predicts worse MMT outcome. High and low rates of BDZ abuse may also be attributed to staff tolerance of this abuse; thus, we strongly recommend a strict attitude by staff in order to reduce patients' harm.

INTRODUCTION

The history of the use of sedative drugs in order to treat anxiety and insomnia has its roots in antiquity, and alcohol is the oldest known sedative, used both medically and non-medically. The development of newer sedative medications throughout the ages has promised safety and efficacy, yet time has taught (too often painfully), the dangers of tolerance, dependency and addiction, and the severe potential complications associated with these drugs (intoxication and even death). The main hallmarks over the last two centuries include valerian, the bromides, the barbiturates and meprobamate (for review see 1).

Introduced in the early 1960s, benzodiazepines (BDZs) (initially chlordiazepoxide) were described as efficacious, safe and lacking risk of addiction, but life (and experience) taught us differently (2). Furthermore, the sociological phenomenon of a "rush for sedation" of wide populations (mostly women) that accompanied the introduction of this class of medications was evident right after their appearance on the market, and described as early as 1965 in a popular song of the epoch that deals with the darker perspective of the use of tranquilizers among housewives (3).

BDZs are positive allosteric modulators of the g-aminobutyric acid type A receptors (GABAARs) (4). GABAARs are ligand-gated chloride-selective ion channels that are physiologically activated by GABA, the major inhibitory neurotransmitter in the brain. GABA also activates GABABRs and GABACRs. GABABRs are metabotropic receptors involved in slow inhibitory neurotransmission (5). GABACRs are ionotropic receptors composed of r (rho) subunits that are both related to and classified by the International Union of Basic and Clinical Pharmacology (IUPHAR) as GABAAR subunits (4).

Address for Correspondence: ✉ Einat Peles, PhD, Adelson Clinic for Drug Abuse, Treatment & Research, Tel Aviv Sourasky Medical Center, 6 Weizman Street, Tel Aviv 64239, Israel einatp@tlvmc.gov.il

BDZs are typically categorized according to their pharmacokinetic properties as short-, intermediate- or long-acting; they possess anxiolytic, hypnotic, sedative and anti-epileptic properties and are prescribed to obtain one of the following major effects: decrease of sleep latency, reduction of anxiety, suppression of epileptic seizures or relaxation of muscle spasms. In general, BDZs are safe and effective for short-term treatment; however, long-term use is controversial due to the development of tolerance and their liability for physical dependence (2).

The prevalence of BDZs usage in the general population was reported as 5.6% in a large survey from Boston Area Community (6), 3.9% in a regional survey from Thailand (7), 3.3% in a Canadian population sample (8), but mostly characterize psychiatric groups, i.e., 25% among U.S. male veterans with PTSD (9); 62.9% among patients with schizophrenia in Taiwan (10) and particularly, among opiate addicts MMT patients, where it ranged between 40 to above 60% (11-13). There are several possible reasons why drug abusers add benzodiazepines to their "cocktail" of street and prescription drugs (14): 1. BDZs induce euphoria (per se, but moreso when snorted): BDZs like other drugs of abuse increase dopamine release in the nucleus accumbens (4). Specifically, BDZs have a stronger impact on GABA neurons than on dopamine neurons. The GABAAR on the interneuron GABA affected by BDZs and the hyper-polarization cause disinhibition on dopamine cell that project to the NA. The GABAAR on the dopamine neuron is less affected by BDZs and thus does not inhibit the dopamine release. 2. BDZs may attenuate intoxication symptoms of "uppers" (e.g., cocaine), or withdrawal symptoms of "downers" (e.g., opiates) or augment the desirable lightheadness induced by alcohol. 3. BDZs may serve as efficacious self-medication/self-treatment of anxiety, insomnia, other psychiatric illness – or erroneously of depression.

Our aims in the current study were to evaluate: 1. prevalence rate of BDZs among MMT patients during the years 1994 and 2012, and 2. the association between BDZs use upon admission and long term retention in treatment (up to 19.5years), and 3. whether it is possible to discontinue BDZs after one year in treatment.

METHODS

The study was approved by the institutional review board (Helsinki Committee) at TASMC (07-111).

All 787 opiate addicts admitted to the Adelson MMT clinic in Tel Aviv between 1993 and 2012 were studied. All MMT patients routinely provide at least one observed random urine test per month (range through years between 1 to 11) lately two per month. BDZ was analyzed using enzyme immunoassay systems (Diagnostic Reagents Inc [DRI®])(15). Each month since admission, each patient was defined as positive to BDZ if at least one of the urine tests was positive, or negative to BDZ if the entire set of tests over the months was negative. The total number of patients in the clinic increased over the years since it was open until having reached full capacity (i.e., 26 patients were tested in 1994, and 300 to 350 since 2009).

STATISTICAL ANALYSES

All analyses were done using the SPSS-19 package. Prevalence of BDZ was calculated for each month since 1994 and until December 2012. Of all the patients who had urine tests (all current patients), we calculated the proportion of those who had at least one positive urine test for BDZ. Duration in treatment from first admission until the patient left treatment or until the end of follow-up (19.5 years) was used for calculating cumulative retention in treatment using survival analyses (Kaplan Meier) with log rank.

RESULTS

Of all 787 opiate addicts who were ever admitted to the Adelson MMT clinic in Tel Aviv (1993-2012), 58% tested positive to BDZ on entry.

PREVALENCE RATE OF BDZS

Prevalence of patients with positive urines for BDZ range between 1994 and 2012 years with the highest rate of 61% in 2002 and the lowest rate of 25.4% in 2003. The total number of patients in treatment increased from 26 patients in 1994 to 300 and 350 since 2009, when the clinic reached its full capacity. Since 2008 and up to the present, the rate is consistently around 35-40% (Figure 1). In December 2012, 322 patients were tested. Of them, 209 were negative and 113(35.1%) were positive for BDZ.

Figure 1. *Benzodiazepine rate (%) by month and years.*

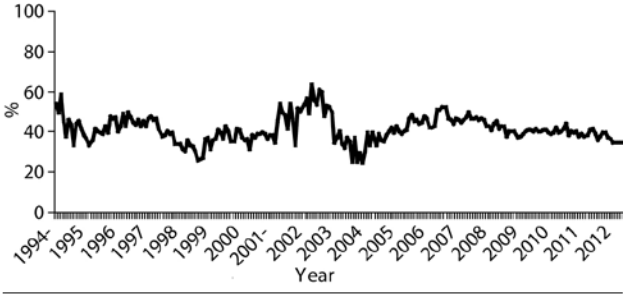
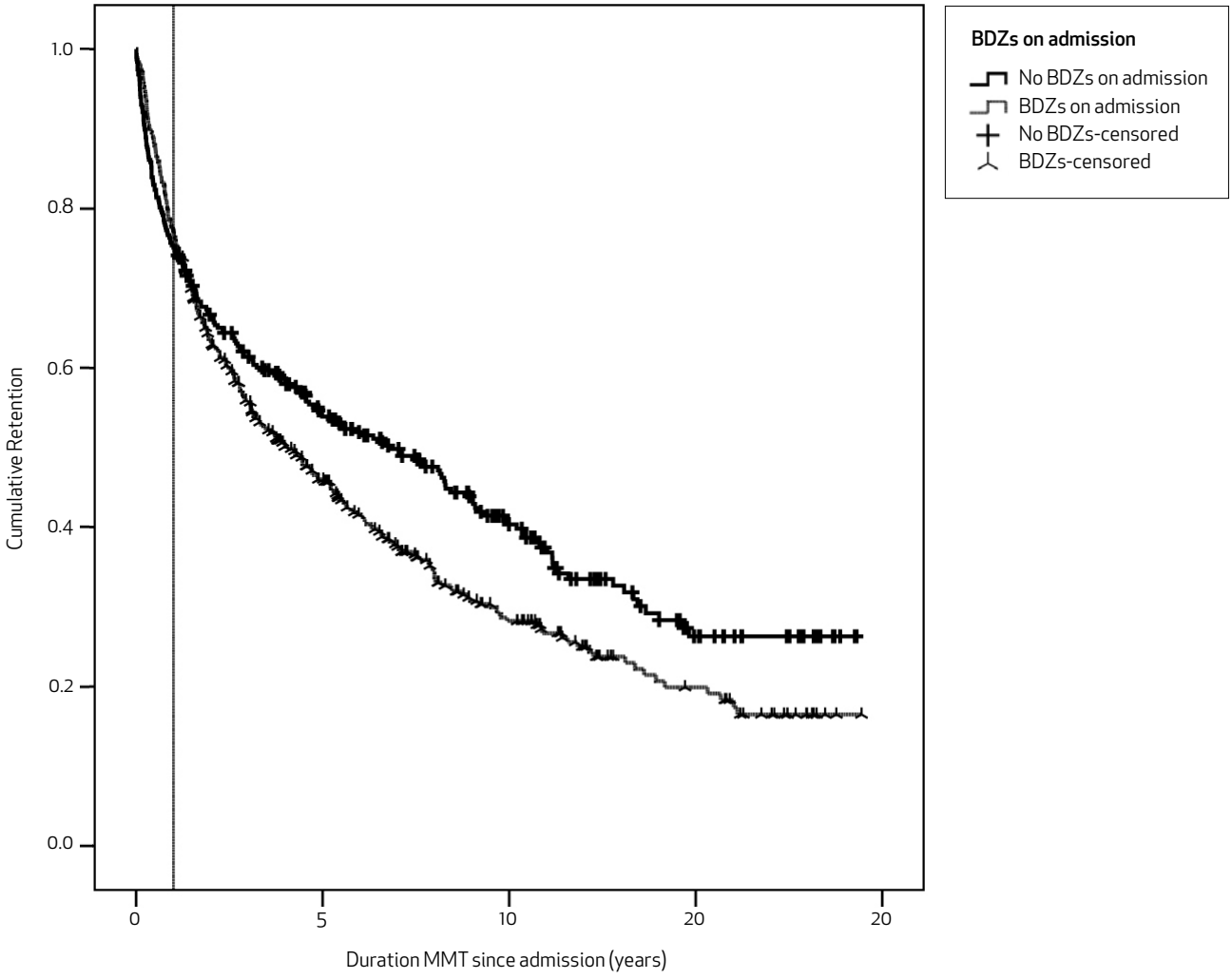


Figure 2. *Long term retention in treatment (up to 19.5years) by being positive to BDZ (dashed line, with 141 censored cases) or negative to BDZ (continuous line, with 126 censored cases) on admission to treatment (Kaplan Meier survival analyses, Chi Square 5.7, p 0.01).*



LONG-TERM RETENTION IN TREATMENT AND USE OF BDZS AT ADMISSION

Cumulative retention (up to 19.5 years) of the 761 patients who were admitted until December 2011 was 6.9y (95% CI 6.2-7.7) for those who tested positive to BDZs on admission, as compared to 8.5y (95% CI 7.6-9.4) for those who tested negative to BDZ (Figure 2).

DISCONTINUE BDZS AFTER ONE YEAR IN TREATMENT

Of the 761 who were admitted until December 2011, 76.1% (n=579) remained in treatment at least one year. Of them, 340 (58.7%) were positive and 239 were negative to BDZs on admission. Of the 340 who were positive to BDZ on admission, 36.5% stopped BDZ abuse after one year, but 25.1% of the 239 who were negative on admission started BDZ abuse during treatment, producing a net reduction of 11.4% in BDZ usage after one year (36.5% minus 25.1%).

DISCUSSION

We found that abusing BDZs on entry to methadone maintenance treatment predicts shorter retention in treatment. Our previous findings with respect to treatment outcome, retention, survival, hepatitis C sero-conversion and polydrug abuse, support the current finding: positive urine test for BDZs on entry to MMT (urine tested positive during the first month in MMT) is an independent predictor for a shorter retention in treatment, as was already found in a long-term follow-up of up to 10 years (16) and now expanded our follow-up and sample to up to 19 years. Furthermore, in a

study of long-term retention in MMT and survival since admission to MMT (using the Israeli Ministry of Health's Registry for vital status), we found that BDZs abuse is not just a predictor for lower retention in treatment; it predicted also a shorter survival (17). As most of those who died were not in treatment, and deaths cause were not definitely established (with post-mortem autopsy) in some of the cases, we could not report whether they were abusing BDZs when found dead. However, since they did not stop BDZ use prior to dropping out of treatment, it would be highly unlikely that they managed to stop once they "returned to the street," the assumption that BDZs were part of the abused drugs at the time of death is plausible. The combination of opiates and BDZs abuse and increased death risk is well established (for review, see 18). BDZ poisoning (based on underlying cause of death) was found to be present among 17% of the opiate deaths in U.S. (19).

In 2007, we screened in a random way a sample of our patients for the presence of tricyclic antidepressants (TCAs) (12) and found 15.8% of the patients to abuse amitriptyline. Not surprisingly, logistic regression found that testing positive for amitriptyline was higher in BDZs abusers (Odds Ratio=11.6, 95% CI 4.4-30.7). Such a combination constitutes a potential cardiac hazard (with the prolongation of the QTc interval on ECG, a risk factor for torsades de pointes and sudden death, as one of the cardinal dangers). Due to this hazard, and together with the finding that 12 (7.5%) of the "privileged" group of patients (stabilized patients who, based on their long-standing cessation of any type of street drug abuse and prolonged normative behavior in treatment are granted "take home" methadone doses) were also found to be amitriptyline abusers, we have since then added the TCAs to the routine monitoring in our clinic, a fact that lead to reduction of abuse (about 5% in 2012).

About one half of the MMT patients in our clinic are hepatitis C sera positive on admission to treatment. Although they do not differ from others in their overall outcome success, more of them were found to be BDZs abusers after one year in MMT (20). Moreover, among those who are negative for hepatitis C, being positive for BDZ, is associated with increased risk to become hepatitis C sera-positive (of the BDZ abusers as compared to the non-abusers 3.6 patients as compared to 1 patient per 100 person years of follow-up respectively developed hepatitis C $p = 0.005$) (21).

Although there is a high rate of BDZ abuse among MMT patients, BDZ abuse rate tends to decrease after one year in treatment, as is the case with other substances abused on admission (opiates, cocaine, cannabis, amphetamines), although to a lesser extent than the other drugs mentioned. The net reduction (proportion of those who tested positive on admission and stopped it [tested negative] after one year, minus the proportion of those who tested negative on admission but started later on [tested positive] after one year) is small as compared to other substances, mainly because a high proportion of patients tend to start BDZs abuse during treatment – perhaps in an effort to get a "high" sensation that the methadone does not induce.

Reviewing the prevalence changes over the years, the high prevalence of BDZs abuse during the years 2001-2002 period was parallel to the time when some of the clinic policies were less enforced, a fact that probably had a significant influence on patients' misbehavior. Towards the end of 2002, a strict and clear behavioral program was started (immediate loss of take-home dose privileges for those with positive urines tested to BDZ) and, indeed, in 2003, the rate of BDZs abuse dropped to only 25.4%. This suggests that BDZ abuse may be influenced, in part, by staff attitudes (tolerance or intolerance) towards the phenomenon, and that adhering to the contingency management principles (where "take-home" privileges are the positive incentive) and to the guidelines with no exception may prove beneficial for all.

As data from many MMT clinics world-wide indicate that prolonged or total abstinence from BDZs is actually unreachable for many patients (22), the feasibility of an "agonist substitution / maintenance treatment" for BDZs abuse that will follow the principles of the MMT for opioids abuse should be evaluated. However, investigators should avoid the failed trials in the 1990s (when clonazepam was thought to serve as the substitute, and proved to be more problematic in several aspects than the other BDZs abused) (23, 24).

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