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# Quality of life in a cohort of high-dose benzodiazepine dependent patients

Fabio Lugoboni[a], Antonio Mirijello[b], Marco Faccini[a], Rebecca Casari[a], Anthony Cossari[c], Gessica Musi[a], Giorgia Bissoli[a], Gianluca Quaglio[a], Giovanni Addolorato[b,*]

[a] Addiction Unit, Department of Medicine, Verona University Hospital, Verona, Italy
[b] Alcohol Addiction Unit, Department of Internal Medicine, Catholic University of Rome, Rome, Italy
[c] Department of Economics, Statistics and Finance, University of Calabria, Rende, Italy

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ABSTRACT

*Background:* Benzodiazepines (BZD) are among the most widely prescribed drugs in developed countries. Since BZD can produce tolerance and dependence even in a short time, their use is recommended for a very limited time. However, these recommendations have been largely disregarded. The chronic use of BZD causes a number of serious side effects, i.e., cognitive impairment, falls, traffic accidents, dependence and tolerance. The aim of the present study was to evaluate quality of life (QoL) in a cohort of 62 consecutive high-dose BZD-dependent patients seeking a BZD detoxification.
*Methods:* Patients seeking BZD detoxification were evaluated using the General Health Questionnaire (GHQ-12) and the short form-36 questionnaire (SF-36).
*Results:* Patients showed a significant reduction of QoL as measured by either SF-36 or GHQ-12. In particular, the greater impairment was observed in the items exploring physical and emotional status. Physical functioning was the item more influenced by the length of BZD abuse. Female patients showed a greater reduction of QoL compared to male, at least in some of the explored items. Social functioning scores were greatly reduced.
*Conclusions:* The present study shows for the first time that high-doses BZD dependent patients have a reduced QoL and a reduced social functioning, along with high levels of psychological distress.


## 1. Introduction

Benzodiazepines (BZD) represent a wide group of molecules with GABA-ergic activity. After the approval in 1960 for its use in the treatment of insomnia, a rapid spread of the use of these drugs occurred and in the 1970s diazepam became the best-selling drug in UK and USA (Lader, 2011).

BZD can rapidly produce tolerance and dependence, thus their use is recommended for a very limited time (Lader, 2011). BZD tolerance was first reported by Hollister et al. (1961), but this phenomenon was often obscured during the 1960s and 1970s by the enthusiastic use of these drugs, which were able to replace barbiturates. Although BZD have been ranked at high risk of dependence among licit and illicit drugs (Nutt et al., 2010), at present, BZD dependence remains still substantially unweighted (Lader, 2011).

The long-term use of BZD, which represent the main risk factor for tolerance and dependence, is a phenomenon affecting almost 2% to 7.5% of the population in developed countries (Fang et al., 2009). Few epidemiological studies are available on BZD abuse and dependence. In a population based cross-sectional study with 520,000 patents, Petitjean et al. (2007) estimated that 1.6% used BZD in high doses, exceeding more than twice the maximal recommended daily dose. Surveys carried out in the 1990s in France, Germany, Italy, and the United Kingdom showed that 3.9% of hypnotic users and 3.2% of anxiolytic users had been taking a dose exceeding the recommended one (Lader, 2011; Ohayon and Lader, 2002). Thus, high-dose BZD abuse/dependence involves almost 3–4% of patients taking anxiolytic drugs (Lader, 2011; Petitjean et al., 2007; Ohayon and Lader, 2002).

The low toxicity of BZD coupled with a high potential of tolerance can raise doses to an extremely high level of abuse (Lader, 2011; Quaglio et al., 2005, 2012a; Faccini et al., 2012). In the past, high dose BZD users (HDUs) were categorised as patients with major psychiatric disorders or drug addiction (O'Brien, 2005;

* Corresponding author. Tel.: +39 06 30154334; fax: +39 06 35502775.
*E-mail address:* g.addolorato@rm.unicatt.it (G. Addolorato).

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Lequeille et al., 2009; Marini et al., 2013). At present, a significant proportion of these patients seems not to have major psychiatric disorders (Faccini et al., 2012), but are part of the general population.

Drug abuse and/or dependence can reduce quality of life (QoL; Ventegodt and Merrick, 2003; De Maeyer et al., 2010; Domingo-Salvany et al., 2010). The evaluation of the effects of BZD abuse/dependence on QoL has been conducted in the setting of alcohol and/or poly-drug abuse (Beccaria et al., 2012; Chen et al., 2011; Brands et al., 2008; Vorma et al., 2004), psychiatric facilities (Brunette et al., 2003; Colpaert et al., 2012), or in elderly populations (González-Salvador et al., 2000; Gelatti et al., 2006). In particular, studies conducted on a population of heroin addicts in methadone maintenance showed that the co-occurrence of BZD abuse worsened the QoL of these patients (Chen et al., 2011; Brands et al., 2008; Vorma et al., 2004; Brunette et al., 2003; Colpaert et al., 2012). However, in these settings BZD are usually prescribed for the management of withdrawal symptoms, of major psychiatric disorders or represent a co-dependence. Although BZD are widely prescribed, potential misuse/abuse of these drugs have been almost neglected by medical community and by regulatory authorities until recent years.

At present, few data on quality of life (QoL) in long-term BZD users are available and data on BZD HDUs are lacking. The present study aims to evaluate the QoL in a cohort of BZD highly dependent patients without alcohol or illicit drugs co-dependence.

## 2. Methods

Between January, 2010, and December, 2012, all BZD dependent patients consecutively referred to the Addiction Unit, Verona University Hospital, Verona, Italy seeking BZD detoxification were evaluated for this prospective study. The proposed detoxification program consisted of a continuous (7–9 days) flumazenil infusion in an inpatient setting (Faccini et al., 2012; Quaglio et al., 2012b; Hood et al., 1997; Lugoboni and Quaglio, 2014), followed by a BZD relapse prevention program consisting of counseling or cognitive-behavioral psychotherapy in addition to pharmacological therapy (Quaglio et al., 2012b).

Inclusion criteria were: age older than 18 years; diagnosis of BZD dependence according to DSM-IV criteria (American Psychiatric Association (APA), 2000) with BZD abuse lasting more than 6 months; high dose BZD abuse.

The lack of a consensus among researchers regarding clinical criteria for high-dose have led us to define a high use of BZD, such as to indicate an inpatient treatment, as intake exceeding at least 5 times the maximum daily recommended dose (Liebrenz et al., 2010; Egan et al., 2001). In Italy, the maximum approved dose of diazepam for extra-hospital use is 10 mg/day. Consequently, a dose exceeding 50 mg of diazepam equivalents have been considered as "high-dose". Exclusion criteria were: major psychiatric disorders; addiction to alcohol and/or drugs other than nicotine, even if in remission.

All BZD utilized were standardized as diazepam dose equivalents. The imidazopyridine hypnotic zolpidem, chemically distinct from BZDs, has been included among BZDs in the present study since its binding to the alpha-1 subtype of BZD receptor and since its behavioral effects, generally similar to those of BZDs (Quaglio et al., 2005; Hajak et al., 2003).

A total of 62 BZD HDUs dependent patients who meet the eligibility criteria were enrolled in the study. The study protocol fully adhered to guidelines of the ethics committee of the Verona University Hospital, Verona, Italy, where the study was done. Eligible patients provided written informed consent to take part in the study.

**Table 1**
Socio-demographic characteristics of the 62 patients evaluated.

| | |
|---|---|
| Sex | |
| Female | 39 (62.9%) |
| Male | 23 (37.1%) |
| Mean age (SD) | 45.4 (10.2) |
| Education level | |
| Grade school | 14 (22.6%) |
| High school | 34 (54.8%) |
| University | 14 (22.6%) |
| Employment status | |
| Full time | 29 (46.8%) |
| Part time | 20 (32.3%) |
| Not employed | 13 (20.9%) |
| Marital status | |
| Married | 27 (43.6%) |
| Divorced | 10 (16.1%) |
| Never married | 25 (40.3%) |
| Children | |
| Yes | 34 (54.8%) |
| No | 28 (45.2%) |

### 2.1. Psychometric evaluation

At the preliminary clinical evaluation, before hospitalization, a questionnaire exacting information on level of education, work status, socio-economic and marital status (Table 1) and psychometric evaluation was given to all the 62 enrolled patients. The psychometric evaluation was performed using the General Health Questionnaire (GHQ-12; Goldberg and Hillier, 1979) and the short form-36 questionnaire (SF-36; Brazier et al., 1992).

The General Health Questionnaire (GHQ) is one of the most widely used screening instruments to detect psychological health among individuals (Goldberg and Hillier, 1979). The 12-items questionnaire (GHQ-12) is a validated instrument to detect psychiatric morbidity with high sensitivity (96.7%) and specificity (90%; Montazeri et al., 2003; Jacob et al., 1997), extensively used in many countries, including Italy (Piccinelli et al., 1993).

The GHQ-12 includes 12 statements, describing mood states over the previous two weeks: lost sleep, feelings of being under strain, could not concentrate, felt unable to play a useful role, could not face problems, could not make decisions, could not overcome difficulties, felt unhappy, did not enjoy day-to-day activities, felt depressed, lost confidence, and felt worthless. Answers are scored on a two-point scale (coded 0-0-1-1; Goldberg and Hillier, 1979). Total score range was 0–12, with higher values indicating more severe distress. A cut-off value of $\geq$4 was used; in particular patient scoring $\geq$4 were considered having high levels of distress and a high probability to develop psychiatric disorders (non-psychotic), such as anxiety and depression (Montazeri et al., 2003; Jacob et al., 1997).

The SF-36 consists of 36 multiple choice questions. These questions are ordered in eight dimensions, from mainly physical to mainly psychological: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE) and mental health (MH). The sum of the SF-36 item scores within each dimension is transformed into a scale ranging from 0 (poor health) to 100 (good health; Brazier et al., 1992; Felce and Perry, 1995; Apolone and Mosconi, 1998).

### 2.2. Statistical analysis

A number of statistical procedures were used to analyze the data. Each variable studied, both numerical and categorical, was first summarized, mainly through usual measures of data location (mean and quantiles) and dispersion (standard deviation). Standard two-sample *t*-tests were then run in order to compare mean values of the various numerical variables, primarily the SF-36 item scores, for binary variables such as gender. In the case of