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Research report

Correlates of benzodiazepine use in major depressive disorder: The effect of anhedonia

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ABSTRACT

Background: Current treatment guidelines emphasize the limited role of benzodiazepines in Major Depressive Disorder (MDD), mainly due to the absence of long-term data, risk of abuse and potential adverse effects. However, benzodiazepines continue to be prescribed for long-term use in a significant number of patients. This study sought to evaluate benzodiazepine use in a large sample of MDD patients seen at a tertiary care clinic, and determine whether use is related to illness severity or complexity, as well as to identify the clinical predictors of benzodiazepine use.

Methods: This was a naturalistic cross-sectional study conducted in MDD patients seen at the Mood Disorders Psychopharmacology Unit at the University Health Network ($N=326$). Detailed information on current medication regimens was collected. A structured diagnostic interview, in addition to measures of symptom severity, quality of life, and personality were administered. Participants were grouped according to the presence or absence of prescribed benzodiazepines for daily use.

Results: The prevalence of regular benzodiazepine use was 25%. Benzodiazepine users were more likely to be female, unemployed, have a history of child abuse, and have comorbid panic disorder. Depression and anxiety scores were not significantly different between groups, although anhedonia was greater in the benzodiazepine group. A logistic regression revealed anhedonia was the strongest predictor of regular benzodiazepine use.

Conclusion: The groups were similar in clinical profile suggesting benzodiazepine use is not necessarily linked to greater illness complexity or severity. Benzodiazepine use appears to be associated with specific diagnostic and symptom characteristics, possibly providing insight into the potential pharmacodynamic and neurobiological effects of frequent use.

1. Introduction

Benzodiazepines are primarily utilized as sedative hypnotics in patients with Major Depressive Disorder (MDD) to alleviate anxiety (either as a symptom of depression or as a disorder on its own) and insomnia. International guidelines recommend limited use of benzodiazepines in MDD beyond 4 weeks (Davidson, 2010; Higuchi, 2010), due to their addictive potential and negative cognitive effects in the domains of memory, attention, and psychomotor speed (Barker et al., 2004; Lader, 2011). Benzodiazepines are also associated with an increased risk of dementia as well as falls (Lavsa et al., 2010; Billioti de Gage et al., 2012). In addition to lack of efficacy data in prospective trials, there is evidence to suggest that adjunctive benzodiazepine therapy may impede antidepressant response with electroconvulsive therapy (ECT) and transcranial direct current stimulation (Delva et al., 2001; Nordenskjöld et al., 2011; Lader, 2011; Brunoni et al., 2013). Despite these findings and guideline recommendations, prescribing practices have not been significantly affected (Lai et al., 2011; Schneider et al., 2005; Zhang, 2010), and benzodiazepines remain commonly used (Olfson et al., 2015). Current estimates across Canada, the US and Europe indicate upwards of 40% of individuals with MDD are prescribed concomitant benzodiazepine therapy (Sanyal et al., 2011; Demyttenaere et al., 2008; Valenstein et al., 2004). However, chronic benzodiazepine use in depression remains

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sparsely investigated. Therefore, it is unclear whether individuals who receive benzodiazepines represent a more chronically ill and psychiatrically comorbid group or whether long-term use contributes to worse outcomes.

The effect of *acute* benzodiazepine use on depressive symptoms can be understood by its allosteric binding to benzodiazepine receptors on GABA neurons throughout the brain, specifically the GABA-A subtype, resulting in increased GABA release (Luscher et al., 2011). However, reports of decreased GABAergic functioning following *chronic* benzodiazepine administration in preclinical models (Miller et al., 1990; Fahey et al., 2001; Gallager et al., 1984) suggest benzodiazepines could exacerbate depression severity. GABA signaling has been shown to directly modulate processes implicated in the etiopathology of MDD, including HPA axis signaling, neurogenesis, monoamine and glutamate transmission (Luscher et al., 2011; Biswas and Carlsson, 1977). There are also consistent reports of reduced GABA metabolites in plasma and cerebrospinal fluid in MDD compared to healthy controls (Gerner and Hare, 1981; Petty et al., 1992), in addition to neuroimaging evidence of lower concentrations of GABA in depression from adolescence into adulthood (Gabbay et al., 2012; Sanacora et al., 1999; Kugaya et al., 2003; Hasler et al., 2007; Price et al., 2009).

Predictors of *long-term* benzodiazepine use include older age, female gender, presence of MDD or Anxiety Disorder, antidepressant initiation and pain (Hawkins et al., 2012; Manthey et al., 2011; Liu et al., 2010; Patten et al., 2010; Préville et al., 2011; Valenstein et al., 2004). However, in addition to demographic predictors, it is important to identify clinical symptoms that may predict benzodiazepine use in order to address the questions of whether exposure exacerbates illness or is a confound by association (i.e., patients with greater illness complexity are more likely to receive benzodiazepines). Therefore, the objective of this study is to evaluate benzodiazepine use in a large sample of MDD patients seen at a tertiary care clinic, and determine whether use is related to illness severity or complexity, as well as to identify the clinical predictors of benzodiazepine use.

2. Methods

2.1. Design

Data for this study were extracted from the Mood Disorder Psychopharmacology Unit (MDPU) database at the Department of Psychiatry, University Health Network, Toronto. The methodology has been previously published (McIntyre et al., 2010). Briefly, patients referred for consultation to the MDPU were enrolled into a naturalistic cross-sectional study following written informed consent. Participants underwent a battery of clinician administered and self-report questionnaires during a single visit. The clinical characteristics of a subset of subjects diagnosed with MDD were assessed in relation to benzodiazepine use.

2.2. Subjects

Subject selection criteria for data inclusion were: male and female patients who were between the ages of 18–60, outpatient status, met DSM-IV criteria for MDD in a current major depressive episode, confirmed through the Mini-International Neuropsychiatric Interview-Plus (MINI-Plus) (Sheehan et al., 1998). Psychiatric and medical comorbidities were allowed, as effects of comorbidity were directly related to the study aims. Only those with confirmed daily benzodiazepine use or no use were included in the analysis.

2.3. Procedure

Eligible subjects provided informed consent before undergoing a battery of clinician administered and self-report questionnaires during a single visit. Assessment data used in the current study included demographic and medication information, the MINI-Plus (Sheehan et al., 1998), the HRSD-17 (Hamilton, 1960), Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979), the Trimodal Anxiety Questionnaire (TAQ) (Lehrer and Woolfolk, 1982), the Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ) (Endicott et al., 1993), the Sheehan Disability Scale (SDS) (Sheehan et al., 1996), the Endicott Work Productivity Scale (EWPS) (Endicott and Nee, 1997), the NEO-Five Factor Inventory (NEO-FFI) (Costa and McCrae, 1992) and the Klein Trauma and Abuse-Neglect scale (Lizardi et al., 1995).

2.4. Statistical analysis

Exploration of between group differences, using Student *t*-tests and Mann Whitney *U* tests corrected for multiple comparisons, were conducted. In order to determine group differences based on depression and anxiety scores with a power of 0.80 and an alpha of 0.05, a minimum of 60 participants per group was needed. A logistic regression was performed to determine the model that best predicted benzodiazepine use. Specifically, data were entered into a stepwise logistic regression with benzodiazepine use as the dependent variable. Differences identified in the between group analysis were included in the model as covariates.

3. Results

3.1. Subjects

Of the 1861 subjects in the MDPU database, 851 subjects had a diagnosis of MDD. After excluding inpatients ($n=502$) and "unconfirmed" benzodiazepine users ($n=23$), a final sample size of 326 was achieved. Participant characteristics are presented in Table 1. Benzodiazepine users were more likely to be slightly older, female, unemployed, have a history of hospitalization or child abuse and reported lower scores on the dimension of "Openness" as measured by the NEO. The overall prevalence of benzodiazepine use was 25%. Clonazepam and lorazepam were the most frequently utilized (50.6% and 45.6% of benzodiazepine users, respectively), although use with alprazolam, diazepam, temazepam,

Table 1
Participant characteristics.

	Non-BZD user ($n=247$)	Daily BZD user ($n=79$)	*P*-value
Age	**39.8 (12.6)**	**44.1 (11.3)**	**0.006**
Gender (% female)	**59.5%**	**72.2%**	**0.043**
Education achieved	**College/ University**	**College/ University**	**0.394**
Employment status			
% Full-time	**76.4%**	**56.3%**	**0.019**
% unemployed	**23.6%**	**43.8%**	
History of MDD hospitalization	**16.2%**	**31.7%**	**0.006**
Age of MDD onset	**22.5 (12.2)**	**20.8 (11.5)**	**0.305**
# Lifetime MDEs	**11.1 (23.2)**	**11.0 (17.2)**	**0.619**
Family history of mental illness	**70.2%**	**83.7%**	**0.054**
History of child abuse (Physical/sexual)	**26.8%**	**40.0%**	**0.031**

BZD: Benzodiazepine; MDD: Major Depressive Disorder; MDE: Major Depressive Episode.