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Adverse performance effects of acute lorazepam administration in elderly long-term users: Pharmacokinetic and clinical predictors

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ABSTRACT

Background: The benzodiazepine lorazepam is widely utilized in the treatment of elderly individuals with anxiety disorders and related conditions. Negative effects of acute lorazepam administration on cognitive performance, especially memory, have been reported in both previously untreated elderly and in individuals who have received short term (up to three weeks) treatment with therapeutic doses. However, it remains unclear if these adverse cognitive effects also persist after long-term use, which is frequently found in clinical practice.
Methods: Cognitively intact elderly individuals ($n = 37$) on long-term (at least three months) daily treatment with lorazepam were studied using a double-blind placebo-controlled cross-over study design. Subjects were administered their highest daily unit dose of lorazepam (0.25–3.00 mg) or placebo on different days, approximately 1 week apart in a random order, and were assessed on memory, psychomotor speed, and subjective mood states.
Results: Subjects had significantly poorer recall and slowed psychomotor performance following acute lorazepam administration. There were no significant effects on self-ratings of mood, sedation, or anxiety in the whole group, but secondary analyses suggested a differential response in subjects with Generalized Anxiety Disorder.
Conclusions: The reduced recall and psychomotor slowing that we observed, along with an absence of significant therapeutic benefits, following acute lorazepam administration in elderly long-term users reinforces the importance of cognitive toxicity as a clinical factor in benzodiazepine use, especially in this population.

1. Introduction

Benzodiazepines (BZPs) are among the most widely prescribed drugs in the rapidly increasing elderly population. A number of surveys indicate that 13%–25% of community-dwelling individuals (aged 65 or over) report current or recent BZP use (Jackson et al., 2014; Lister and File, 1984; Tamblyn et al., 2005; Woods et al., 1992). However, it is a concern that impairments in multiple cognitive domains (e.g., memory, psychomotor performance) have been demonstrated consistently following acute doses of BZPs, in both healthy and anxious participants (Curran, 1986; Mintzer and Griffiths, 2007; Satzger et al., 1990; Woods et al., 1992). These impairments have been observed with lorazepam, the BZP frequently recommended for the elderly, due in part to a lack of active metabolites, a relatively shorter elimination half-life, and a presumed better safety profile compared to other BZPs (Tamblyn et al., 2005).

In the elderly, administration of even a single dose of a BZP impairs performance (Bertz et al., 1997; Nikaido et al., 1990; Pomara et al., 1988, 1998, 2005; Satzger et al., 1990), and elderly individuals may show greater sensitivity than younger subjects to the adverse effects of BZPs on psychomotor performance (Bertz et al., 1997; Nikaido et al., 1990; Satzger et al., 1990) and memory (Pomara et al., 1989). Following chronic treatment with BZPs for 1–3 weeks, significant adverse effects can be observed following an acute dose — although partial tolerance may develop (Curran, 1986; Ghoneim et al., 1981; Pomara et al., 1989, 1998). However, clinical treatment often extends beyond 3 weeks (e.g., years), increasing the associated morbidity and mortality (Hampton et al., 2014; Pariente et al., 2008; Tamblyn et al., 2005). Conversely, discontinuation of BZPs in long-term users is generally associated with an improvement in cognitive function, with no significant adverse effects (Kitajima et al., 2012; Rickels et al., 1999).

In spite of the prevalence of long-term administration of BZPs, few studies have examined the impact of acute doses of BZPs on cognitive

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performance in populations of elderly long-term users, and none have included a placebo condition (Curran, 1992; Gorenstein et al., 1994; Lucki et al., 1986; van Steveninck et al., 1997). Their findings suggest that acute administration of the patient's *usual* daily unit dose may still result in significant impairment, even after several years of continuous BZP treatment. One study only examined saccadic eye movements and body sway (van Steveninck et al., 1997) and another did not report psychiatric diagnoses (Curran, 1992). Older participants were either not included (Gorenstein et al., 1994) or were underrepresented (Curran, 1992; Lucki et al., 1986; van Steveninck et al., 1997), questioning the relevance of these results in the elderly population.

In the present study, we examined the effects of a single acute dose of lorazepam in elderly long-term users treated with this drug for anxiety and related conditions. Memory and psychomotor performance was assessed and self-report measures of mood states and anxiety levels were obtained. We also determined the degree to which various factors (e.g., strength of daily unit dose, total daily dose, dosing frequency, and duration of treatment) contributed to the acute adverse effects. Because prolonged use of benzodiazepines is reported to be more prevalent in older individuals, especially women (Kruse, 1990), we also examined if age and gender influenced the effects of an acute lorazepam challenge.

2. Methods

2.1. Subjects

Thirty-seven psychiatric outpatients on long-term (between 3 and 252 months of treatment; median = 60 months) treatment with lorazepam for anxiety and related conditions were recruited for participation from outpatient psychiatric clinics, newspaper advertisements, and outreach efforts to senior citizen groups in the New York City area and Rockland County, NY. The study was conducted at the NYU-Bellevue General Clinical Research Center in New York City and the Nathan S. Kline Institute in Orangeburg, NY. Subjects ranged in age from 60 to 91 years (mean = 70.7, standard deviation (SD) 8.1). Absence of current DSM-IV psychotic illness, dementia, and current alcohol or substance abuse/dependence was also included in the criteria. DSM-IV diagnoses were determined by clinical psychiatric interview and the Structured Clinical Interview (First et al., 2002). Subjects with severe neurological or medical illnesses, as determined by medical history, physical evaluation and routine laboratory tests, were excluded. All subjects were free of cognitive impairment, as determined by a score of ≥28 on the Mini Mental State Examination (Folstein et al., 1975), an age-corrected score of at least 7 in the vocabulary subtest of the Wechsler Adult Intelligence Scale — Revised (Wechsler, 1981), and a score of ≥85 on the General Memory Index of the Wechsler Memory Scale — Revised (Wechsler, 1987). Other demographic characteristics and screening measures are presented in Table 1. Each participant was paid $200 for their participation.

2.2. Procedure

All participants provided written informed consent prior to participation. A double-blind, placebo-controlled, crossover study design on two different days was used. Following diagnostic and screening evaluation, individuals participated in two five-hour experimental sessions on separate days, one-week apart. Lorazepam and placebo doses were prepared by the institutional pharmacy and dispensed at the experimental sessions by research staff. Subjects were randomly assigned to receive the sequence "lorazepam–placebo", or "placebo–lorazepam". Following a morning baseline assessment, each subject was either administered his/her highest daily unit dose of lorazepam as the challenge dose, or placebo. The highest daily unit doses ranged from 0.5 mg to 3.0 mg lorazepam. Experimental sessions began at approximately 9:00 a.m. under non-fasting conditions. The Buschke Selective Reminding Test (BSRT; Buschke, 1973, 1974) and the Purdue Pegboard Test (PPT; Lezak, 1995; Tiffin, 1968) tests, and both the Mood Rating Scale (MRS; Bond and Lader, 1974) and the State-Trait Anxiety Inventory scale (STAI-S; Spielberger et al., 1983) were administered at baseline, and again at 1, 2.5 and 5 h following oral administration of the drug or placebo. Vital signs and blood samples were also obtained at each assessment point.

2.3. Plasma lorazepam determination

Blood samples for determination of plasma lorazepam levels were collected at baseline, and at 1, 2.5 and 5 h post-drug administration. Quantitation of plasma drug levels was determined by electron-capture gas chromatography, as previously described (Greenblatt et al., 1978).

2.4. Neuropsychological measures

The BSRT consists of a list of 16 nouns presented verbally to the subject at a rate of one word every 2 s. The subject is asked to recall as many words as possible and to indicate when no more can be recalled. After the initial presentation, the subject is presented only with those words that were not recalled on the immediately preceding trial, although they are asked to recall the entire list on each trial. Seven presentation and recall trials of the same list are given in immediate succession. Total recall is defined as the total number of words correctly recalled across the seven learning trials.

The PPT requires participants to place as many pegs as possible into a row of holes in a 30 s period. Participants complete three pegboard

Table 1
Demographics of the study population. The values represent group means with standard deviations in parentheses (WAIS-R = Wechsler Adult Intelligence Scale — Revised; WMS-R = Wechsler Memory Scale — Revised; BSRT = Buschke Selective Reminding Test).

Characteristics	Total sample ($N = 37$)	Completer group ($n = 31$)	Non-completer group ($n = 6$)
Age, yrs	70.7 (8.1)	70.0 (7.8)	73.8 (9.4)
Weight, lbs	169.3 (53.3)	174.1 (54.2)	145.7 (45.8)
Education	15.3 (2.6)	15.2 (2.1)	15.7 (4.8)
Sex, no. M/F	18/19	16/15	2/4
Highest prescribed unit dose of lorazepam, mg	1.0 (0.6)	0.9 (0.6)	1.3 (0.5)
Duration of lorazepam use, months	82.1 (67.6)	79 (70.9)	98 (48.8)
Total daily dose lorazepam, mg	1.4 (1.3)	1.2 (1.1)	2.5 (1.9)
Hamilton Rating Scale for Anxiety (HAM-A)	9.8 (5.6)	9.3 (5.6)	12.5 (5.5)
Hamilton Rating Scale for Depression (HAM-D)	9.5 (8.4)	9.0 (8.7)	11.7 (6.9)
Mini-Mental Status Examination score	29.2 (0.8)	29.4 (0.8)	28.3 (0.5)
WAIS-R Total Vocabulary score	13.1 (2.3)	13.2 (2.0)	12.5 (3.6)
WMS-R Total Verbal score	99.3 (15.4)	99.5 (16.0)	98.2 (12.7)
WMS-R Total Visual score	105.4 (20.1)	104.1 (20.4)	111.8 (18.5)
WMS-R General Memory Index score	102.7 (14.0)	102.4 (13.7)	104.3 (16.9)
BSRT Screening Total Recall	62.2 (13.8)	62.7 (13.6)	59.6 (16.0)