



## Original Article

Symptoms Associated with Long-term Benzodiazepine Use in Elderly Individuals Aged 65 Years and Older: A Longitudinal Descriptive Study<sup>☆</sup>Sari Vaapio<sup>1,2,3\*</sup>, Juha Puustinen<sup>1,2,4</sup>, Marika J. Salminen<sup>1,2,5</sup>, Tero Vahlberg<sup>6</sup>, Maritta Salonoja<sup>7</sup>, Alan Lyles<sup>8,9</sup>, Sirkka-Liisa Kivelä<sup>1,5,8</sup>

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## SUMMARY

**Background:** Recent epidemiologic studies have shown that the use of psychotropics is associated with many symptoms and may result in dependence and tolerance among elderly individuals. The aim of this study was to describe the symptoms related to withdrawal or dose reduction of long-term benzodiazepine (BZD) or BZD-related drugs (RDs) use and to compare them with nonuse of these drugs in community-dwelling individuals aged 65 and older.

**Methods:** The study was a *post hoc* analysis embedded in a 12-month randomized, controlled fall-prevention trial that included withdrawal of BZDs and RDs. The participants ( $n = 248$ ) in the intervention group were divided into the following four groups according to their use of BZDs/RDs at baseline and follow-up: (1) withdrawal (WG), (2) reduction (RG), (3) unchanged (UG), and (4) nonusers (NUG). Differences in symptom changes were compared between and within these four groups.

**Results:** Using BZD/RD was associated with numerous symptoms at baseline and during the intervention. At follow-up, those symptoms reduced significantly among all participants. However, there were no significant differences between the groups in the changes of symptoms during the follow-up. Self-perceived health improved in only NUG ( $p < 0.001$ ), but not in the other groups (WG, RG, and UG).

**Conclusion:** Withdrawal or reduction of BZD/RD produced positive effects on physical, psychological, or cognitive symptoms among all participants, but no differences between the groups were detected. We recommend that clinical goals should be carefully assessed against the risks of long-term BZD/RD use, and that withdrawal interventions should be initiated for community-dwelling users aged 65 and older, especially those long-term users who may already be experiencing adverse drug effects.

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## 1. Introduction

Benzodiazepines and BZD-related drugs (BZDs/RDs) are widely prescribed<sup>1</sup> and long-term BZD/RD use is common. However, psychotropics tend to be overprescribed and overused in patients aged

65 years and older, the age group most vulnerable to their adverse effects. Use of psychotropics is common among patients with memory disturbances or dementia<sup>2</sup>. In Europe, the prevalence of BZD/RD use is about 2–3% in the general population, whereas its prevalence in the aged individuals varies between 10% and 42% worldwide<sup>3</sup>.

Primary insomnia and anxiety are the most common clinical indications for prescribing BZD or RD; however, this is associated with certain risks. Cross-sectional and longitudinal studies show that BZD/RD use among the elderly population is associated with sedation, sleep disorders, depression, psychomotor and cognitive

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impairments, motor vehicle accidents, and increased risk of falls and fall-related injuries<sup>4-6</sup>.

Long-term BZD/RD use may result in dependence and tolerance. These risks are especially high among individuals aged 85 years or over, and among those with cognitive impairment, poor health, mental disorders, previous use of BZDs/RDs, concomitant antidepressant use, multiple drug use, and multiple chronic and psychiatric diseases<sup>6</sup>.

In this study, an intervention implemented by our research team included a one-time individual counseling session followed by a group lecture about the risks of adverse effects from BZD/RD use, and recommendations to reduce or stop long-term BZD/RD use<sup>7</sup>. Using the trial data, we carried out a *post hoc* analysis and assessed whether withdrawal or reduction of BZDs/RDs would be associated with changes in physical, psychological, or cognitive abilities in individuals aged 65 years and older.

## 2. Materials and methods

### 2.1. Participants and study design

Participants ( $n = 591$ ) were 65 years or older in a multifactorial, randomized, controlled fall-prevention trial lasting 12 months (registered in [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00247546), ID = NCT00247546). The trial has been previously described in more detail<sup>8</sup>. The number of regular users of BZDs/RDs decreased significantly by 35% in the intervention group and correspondingly increased by 4% in the controls<sup>7</sup>. Participants ( $n = 248$ ) belonging to the intervention group and participating in follow-up examinations formed the study group for the present study's longitudinal analyses. The use of BZD/RD was not randomized (Fig. 1). Ethics approval was obtained from the Ethics Committee of Satakunta Hospital District and written informed consent from the participants was also obtained.

For the longitudinal analyses, participants were divided into four groups according to their usage of BZDs/RDs at the baseline and after the 12-month intervention: (1) those participants who totally stopped BZD/RD use formed the withdrawal group (WG); (2) those who reduced BZD/RD use formed the reduction group (RG); (3) those who did not change their BZD/RD use formed the unchanged group (UG); and (4) those not using BZD/RD at baseline and after 12 months formed the nonuser group (NUG). Interventions (geriatric assessment, guidance, lectures, and psychosocial support) performed in all groups were identical.

At the baseline and after the 12-month intervention, a senior clinical geriatrician (M.S.) collected drug-utilization data (1) by interviewing the participants, and (2) from the medical records. All participants were asked to take their prescriptions and pillboxes of regularly or irregularly used drugs to the interviews. For those who had higher Geriatric Depression Scale (GDS) scores, the geriatrician prescribed antidepressant treatment with caution. Antidepressant treatment was started only if the participant was diagnosed to suffer from major depression. Drugs were coded using a Finnish translation of the Anatomical Therapeutic Chemical (ATC) Classification System<sup>9</sup>. BZDs and RDs consisted of medications included in the following ATC codes: N05BA, N05CD, N05CF, A03CA, N03AE01, R06AE53, and N06CA01. Participants received individually designed withdrawal program by the geriatrician. The program has been previously described in more detail<sup>7</sup>.

The participants' physical symptoms were measured at baseline and during the follow-up examination. These used structured questions about palpitation, hand tremor, incontinence, dizziness while walking and dizziness while arising, tendency to fall, and heavy perspiration without physical exercise. For every symptom, participants were asked: "Have you had the following symptoms during the most recent 14 days, and if so, how frequently?" The

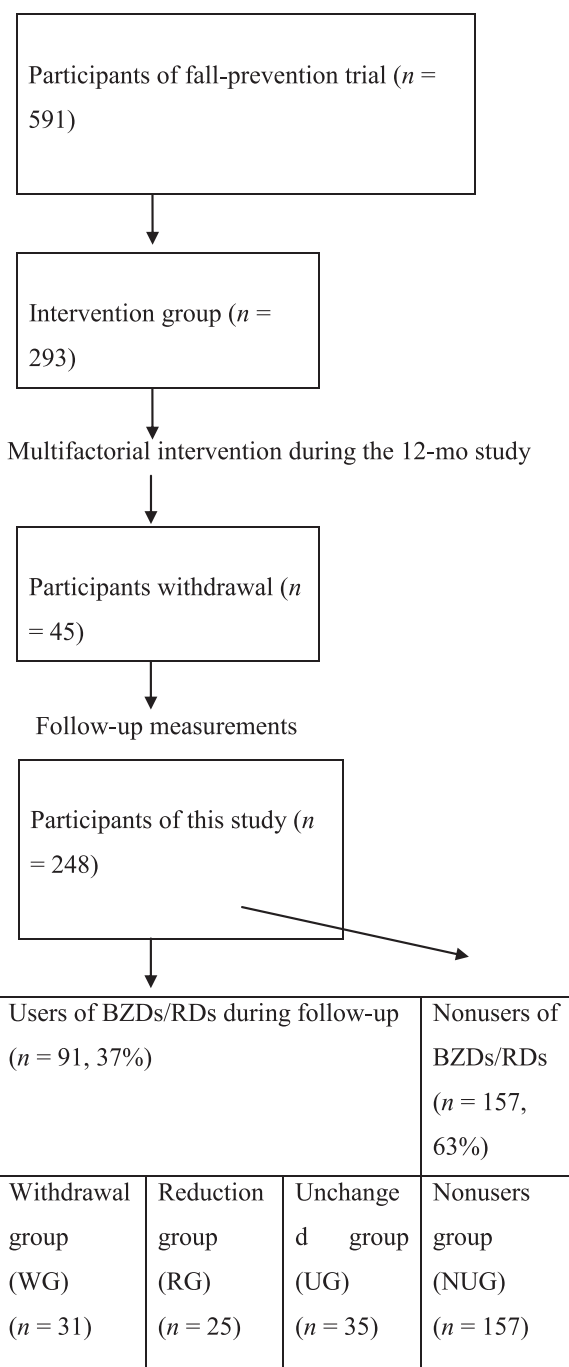


Fig. 1. Flowchart for the identification of participants from the longitudinal fall-prevention trial. BZDs = benzodiazepine; RDs = BZD-related drugs.

occurrence and frequency of these symptoms were rated on scales covering the following four frequencies: 1 = not at all; 2 = every now and then; 3 = almost daily; and 4 = daily. Psychological and cognitive symptoms were ascertained from questions about insomnia, lack of confidence while walking, unwillingness and powerlessness, tiredness and weakness, anxiety, memory loss, and global cognitive abilities. For every symptom, participants were asked: "Have you had the following symptoms during the most recent 14 days, and if so, how frequently?" For statistical analyses, answers in symptom items were combined into two categories (yes/no), because of the small numbers of observations in some of the categories.

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