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Sociodemographic, clinical and pharmacological profiles of medication misuse and dependence in hospitalized older patients: a cross-sectional study

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SOCIODEMOGRAPHIC, CLINICAL AND PHARMACOLOGICAL PROFILES OF MEDICATION MISUSE AND DEPENDENCE IN HOSPITALIZED OLDER PATIENTS: – a cross-sectional study

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ABSTRACT

Objectives

Timely recognition of medication misuse and dependence is crucial to avoid both adverse drug events and increasing health expenditure. Yet, the detection of these disorders in older people remains challenging due to the paucity of evidence on characteristics of patients at risk. This study investigates sociodemographic, pharmacological and clinical characteristics and factors associated with prolonged medication use, misuse and dependence in hospitalized older patients, focusing on three commonly prescribed central nervous system depressants (CNSDs): opioid analgesics, benzodiazepines and z-hypnotics.

Design

A cross-sectional study, complying with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines

Setting

Somatic departments of the Akershus University Hospital, Norway

Participants

246 patients aged 65-90 were included.

Outcome measures

Prolonged use was defined as using CNSDs for ≥4 weeks. Misuse and dependence were assessed with DSM-IV criteria for substance abuse and dependence. Data on sociodemographic and clinical characteristics of patients were collected through self-reported questionnaires. Data analyses were mainly descriptive statistics and regression models.

Results

Forty percent of participants reported using CNSDs for ≥4 weeks. Z-hypnotics were the most-commonly-used drugs. Prolonged users were more frequently female, aged 75-84, living alone, with lower socioeconomic status, polypharmacy, and higher pain intensity and depression scores. Those with and those without misuse or dependence did not differ significantly. The odds for prolonged use were higher among patients aged ≥75 and those with pain and polypharmacy, but lower among those who had completed secondary education. In older patients, concurrent use, rather than the duration of CNSD use increased the likelihood of misuse or dependence.

Conclusion

CNSD overuse is prevalent among hospitalized older patients, raising a concern about an increasing incidence and consequences among elderly. Characteristics of at-risk patients and significant associations identified in this study can be used to inform ways for implementing future research initiatives and interventions.

Key words: characteristics, geriatric patients, risk factors, addiction, prescription drug abuse

Trial registration: ClinicalTrials.gov Identifier: NCT03162081. Registered 3 May 2017

Strengths and limitations of this study

- The first and comprehensive study of characteristics and factors associated with commonly prescribed central nervous system depressants (CNSDs) prolonged use, misuse, and dependence in older hospitalized patients.
- Characteristics of at-risk patients and significant associations revealed in this study can be used to inform ways for implementing future research initiatives and interventions aiming at early detection, prevention and treatment for CNSD overuse among older patients.
- We used validated and generally accepted diagnostic criteria to assess medication misuse and dependence in older patients (DSM-IV criteria for substance abuse and dependence)
- The use of cross-sectional data and a hospital-based sample precludes us from inferring causal relationships and generalizing the study findings to the general population.

INTRODUCTION

Central nervous system depressants (CNSDs) such as opioid analgesics, benzodiazepines and z-hypnotics are commonly prescribed among older patients for the treatment of chronic pain, anxiety and insomnia. While these medications are essential for moderate-severe cases, long-term use is not recommended owing to the risk of adverse events, including hyperalgesia, fractures, falls, cognitive impairment and dependence.[1-3] This underlines the importance of rational use and prescription of CNSDs for older patients. To achieve this, one of the practical steps is for clinicians to be able to timely recognize older patients at risk or suffering from medication misuse and dependence.

According to the Norwegian Prescription Database, the consumption of potentially addictive drugs such as opioid analgesics (i.e. oxycodone and tramadol), benzodiazepines (i.e. diazepam, oxazepam and nitrazepam) and z-hypnotics (i.e. zopiclone and zolpidem) is high among individuals aged 65 and older. These drugs were among the 30 most commonly prescribed drugs to older patients in Norway in 2017.[4]

A Norwegian study showed that the patients' regular general practitioners (GPs) prescribed the largest proportion of addictive drugs to their older patients (77%) compared to other groups of physicians.[5] In line with this, another study, found that CNSDs were frequently prescribed by GPs in large quantities and through indirect contacts without consultation.[6] Both inappropriate prescribing and the high consumption of such addictive medications may put older patients at risk of medication misuse and dependence – a condition characterized by persistent and compulsive use of a medication despite impairment in physical, social and psychological health.[7]

Given the vulnerability to serious adverse effects and interactions as a result of age-related changes in pharmacokinetics and pharmacodynamics, timely recognition and treatment of medication misuse and dependence in older patients are crucial to ensure medication safety and to avoid increasing health expenditure.[8] Yet, the detection of these disorders in older people is challenging. Major hurdles that impede clinicians in arriving at an early identification of at-risk patients may include the paucity of screening tools validated for geriatric patients and the lack of

evidence on disease profiles and factors that add to an older patient's risk for starting and persisting in using a potentially addictive drug.[7 9] Until these knowledge gaps are addressed, early diagnosis and evidence-based interventions for medication misuse and dependence in older patients will remain difficult to attain.

This study investigates sociodemographic, pharmacological and clinical characteristics and factors associated with prolonged medication use, misuse and dependence in hospitalized older patients, focusing on three commonly prescribed central nervous system depressants (CNSDs): opioid analgesics, benzodiazepines and z-hypnotics.

METHODS

Study design

The study was a cross-sectional, in-hospital study and complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Participants and setting

The recruitment process took place between May 2017 and September 2018, at three somatic departments of the Akershus University Hospital: Geriatrics, General Internal Medicine and Neurology. The catchment area of the hospital covers roughly 10% of the total population of Norway. Participants were recruited at the first few days of admission based on predefined inclusion and exclusion criteria (NCT03162081), and not on their vulnerability, reasons for admission, diagnosis or severity of disease. As Norway has an all-covering national health insurance, all patients enter the hospital on the same conditions and with the same in-patient threshold. The study inclusion criteria were hospitalized patients, aged between 65 and 90 years old. The exclusion criteria included Mini-Mental State Examination (MMSE) score ≤ 21 (incapacity to give informed consent); [10 11] pre-existing severe depression, stroke, dementia, psychotic disorders; serious visual or hearing impairment; and insufficient Norwegian language. We precluded

participants who were in a too serious medical condition or palliative treatment, defined by physicians at the study setting.

Data collection

Data collection (by SC, TGS and CL) involved three steps. After consent had been given, all eligible participants were asked to complete a questionnaire on sociodemographic background, pain, anxiety and depression. At this stage, the investigators were blinded to the use of medications as this was registered in the electronic patient record (EPR) which could only be accessed once a written informed consent had been obtained. Having fulfilled this requirement, the EPRs were reviewed to document the use of medications (type, duration, frequency and polypharmacy). Finally, the presence of medication misuse or dependence among participants identified as prolonged users of CNSDs was assessed through a structured interview. Prior to the start of the study, the three data collectors had gone through training sessions in order to optimize congruent use of the interview. More details on definition, data sources, and measurements for variables under investigations are given in the section below.

Sociodemographic and clinical variables

Sociodemographic variables included age (65-74, 75-84, and ≥ 85); sex (Male, Female); education (basic, secondary, and higher education); annual income (<200 000, 200 000 – 349 000, and ≥ 350 000 Norwegian Krone (NOK) per year); and living alone (Yes, No). Clinical variables consisted of pain intensity (continuous, measured using visual analog scale - VAS); Anxiety and depressive symptoms were assessed with the Hospital Anxiety and Depression Scale (HADS). Optimal cut-off values for diagnosing anxiety and depression in older hospitalized patients using HADS remain to be established.[12 13] To avoid underestimation and misclassification bias of anxious and depressed individuals, we used anxiety and depression scores as continuous variables. Higher scores indicate higher levels of anxiety and depressive symptoms.[14] Data for all of these variables were collected through a self-completed questionnaire.

Pharmacological variables

We defined prolonged use of CNSDs as the use of opioid analgesics, benzodiazepines and/or z-hypnotics for four weeks or longer continuously up to the point of recruitment, [15 16] while non-prolonged use was non-use or use of these medications for less than four weeks. Medication misuse and dependence were defined based on DSM-IV criteria for substance abuse and dependence, using the Norwegian version of the Mini-International Neuropsychiatric Interview Guide – MINI.[17] Dependence was defined to be present if patients met three or more of the dependence criteria. Misuse was confirmed if the dependence criteria were not met and the respondents satisfied one or more of the abuse criteria.[18] For the purpose of the present study, and as few patients fulfilled misuse criteria (n=6), misuse and dependence were grouped together as medication misuse or dependence (n=39). Other pharmacological variables entailed types of CNSD medications used (categorized as exclusive or concurrent use), duration of use (continuous, in week); frequency of use (categorized as sporadic use if the medication was taken intermittently < 5 days per week and as daily use if the medication was taken ≥ 5 days per week); Polypharmacy[19] (defined as the use of ≥5 medications daily, coded as Yes or No). Data for theses variables was collected through structured interviews and reviewing EPRs. To ensure the accuracy of data on CNSD use patterns, we checked for evidence of use and consistency across prescriptions and relevant documents reported from both primary care and hospital settings.

Statistical analysis

We compared the characteristics of older patients with and without prolonged use, and that of those with and without misuse or dependence using descriptive statistics and difference inferential statistics. Categorical variables such as sex, age groups, education, annual income, living alone and polypharmacy were analyzed using χ^2 tests. Continuous data on duration of CNSD use, pain intensity, anxiety and depression scores were skewed, and were therefore analyzed with Mann-Whitney test.

We assessed the associations between patient characteristics and the presence of prolonged CNSD use, and misuse or dependence using bivariate and multiple logistic regression analyses. The analyses included adjustment for sociodemographic subgroups, clinical and pharmacological variables as described on page 6 (Methods). Multiple imputation using chained equations (with 20 imputed data sets) were performed to handle missing data. Sensitivity analyses were conducted for the same models using complete case analysis. No multicollinearity was detected. Stata-SE software version 15 was used for all statistical analyses.[20]

Patient and public involvement

A user advisory board established at the Akershus University Hospital (the study setting), which included both representatives of older patients and health service officials, supported this study. The board met on a regular basis throughout the study period. They provided project-specific inputs on ethics, design and methodology as well as highlighted research focus based on patient and public interests. They will also be involved in the dissemination of the findings.

RESULTS

Participants

In total, we consecutively approached 665 adults aged 65-90. Of these, 227 participants declined to participate, while 92 others were precluded due to either being in a too serious medical condition or palliative treatment. Of the remaining patients, 100 were excluded based on predefined exclusion criteria. This resulted in 246 older patients eligible for the study, of which 100 were thereafter identified as prolonged users of CNSDs (≥ four weeks). Figure 1 provides more details on the flow of participants through the study.

There were no missing data in the variables: prolonged use, misuse or dependence, concurrent use, duration of CNSD use, age groups, sex, living alone and polypharmacy. The following variables had missing data: pain intensity 7% (18/246), anxiety scores 7% (17/246), depression scores 7% (17/246), education 6% (14/246), and income 16% (39/246).

Differences in sociodemographic, pharmacological and clinical characteristics of older patients with and without prolonged use, misuse and dependence

Overall, in descriptive analyses, older patients with prolonged use of CNSDs were significantly more often female, aged 75-85, living alone, with lower socioeconomic status (completed ≤ secondary education and earned < 350000 NOK/year), polypharmacy and accompanied by higher pain intensity and depression scores (Table 1). Apart from the variable living alone (69% of those classified as misuse or dependence), we did not find any significant differences between those with and without medication misuse or dependence in terms of their sociodemographic, pharmacological and clinical characteristics. More details are provided in Table 1.

Table1. Sociodemographic, pharmacological and clinical characteristics of older patients with and without prolonged CNSD use, misuse and dependence

Patient characteristics	**Prolonged use of CNSDs** (n = 246)			**CNSD misuse or dependence** (n = 100)		
	No (n=146)	Yes (n=100)	P-value	No (n=61)	Yes (n=39)	P-value
Sex						
Female	71 (49%)	66 (66%)	**0.009**	38 (62%)	28 (72%)	0.39
Male	75 (51%)	34 (34%)		23 (38%)	11 (28%)	
Age groups						
65-74	73 (50%)	28 (28%)		18 (29%)	10 (25%)	
75-84	59 (40%)	51 (51%)	**0.001**	34 (56%)	17 (44%)	0.16
≥ 85	14 (10%)	21 (21%)		9 (15%)	12 (31%)	
Education, years						
Basic education (≤10)	16 (12%)	30 (32%)		17 (29%)	13 (36%)	
Secondary education (11-13)	64 (46%)	31 (33%)	**0.001**	21 (36%)	10 (28%)	0.67
Higher education (≥14)	58 (42%)	33 (35%)		20 (35%)	13 (36%)	
Income (NOK/year)						
< 200 000	8 (7%)	13 (15%)		7 (14%)	6 (18%)	
200 000–349 000	42 (34%)	43 (51%)	**0.001**	24 (46%)	19 (58%)	0.31
≥ 350 0000	72 (59%)	29 (34%)		21 (40%)	8 (24%)	
Living alone						
No	87 (60%)	45 (45%)	**0.03**	33 (54%)	12 (31%)	**0.02**
Yes	59 (40%)	55 (55%)		28 (46%)	27 (69%)	

Polypharmacy (≥ 5 drugs/day)						
No	55 (38%)	8 (8%)	**< 0.001**	6 (10%)	2 (5%)	0.48
Yes	91 (62%)	92 (92%)		55 (90%)	37 (95%)	
Anxiety scores (HADS-A)						
Mean (SD)	4.13 (3.28)	4.97 (3.91)	0.17	4.47 (3.54)	5.68 (4.34)	
Median (Range)	4 (0-14)	4 (0-16)		4 (0-16)	5 (0-15)	0.24
Depression scores (HADS-D)						
Mean (SD)	3.60 (2.98)	5.13 (3.49)		4.89 (3.26)	5.49 (3.81)	
Median (Range)	3 (0-13)	4 (0-15)	**<0.001**	4 (0-12)	5 (0-15)	0.56
Pain intensity (millimeters on VAS scale)						
Mean (SD)	18.07 (24.21)	35.20 (30.35)	**<0.001**	30.56 (28.30)	42.08 (32.34)	
Median (Range)	7 (0-91)	29.50 (0-97)		27 (0-97)	48 (0-93)	0.10
Duration of CNSD use (weeks)						
Mean (SD)	-	71.47 (113.44)	-	72.10 (138.38)	70.48 (57.36)	0.06
Median (Range)		50.50 (4-988)		33 (4-988)	52 (4-232)	
Concurrent use (of >1 CNSDs)						
No (exclusive use)	-	70 (70%)	-	49 (80%)	21 (54%)	**0.007**
Yes	-	30 (30%)		12 (20%)	18 (46%)	

Abbreviations:
CNSD – central nervous system depressant drugs;
HADS–D/A – hospital anxiety and depression scale, depression or anxiety subscore.

Medication use patterns

Forty percent of the older patients enrolled in this study (100 out of 246 participants) were identified as prolonged users (≥4 weeks) of opioid analgesics, benzodiazepines and/or z-hypnotics. Figure 2 illustrates the proportion of prolonged users of the three listed CNSDs and concurrent use of more than one medication group. The dominant group of medications was Z-hypnotics, accounting for 42% (42/100) as exclusive use and 26% (26/100) as concurrent use of Z-hypnotics plus other CNSDs, followed by opioid analgesics, which comprised 21% (21/100) as exclusive use and 23% (23/100) as concurrent use. Benzodiazepines were less commonly used and constituted 7% (7/100) as exclusive use and 13% (13/100) as concurrent use. 30% (30/100) of the prolonged users in our sample concurrently consumed two or more different types of CNSDs. The most prevalent pattern of concurrent use was the combination of z-hypnotics and opioid analgesics, amounting to 57% (17/30) of all forms of current use.

The majority of older patients using CNSDs, did so on long-term and daily basis. The medians for duration of use for opioid analgesics, benzodiazepines and z-hypnotics were 42 (4-988), 51 (4-208)

and 52 (4-232) weeks respectively. More than half of the prolonged users reported using these medications daily (5-7 days per week): opioid analgesics (26/44), benzodiazepines (15/20) and/or z-hypnotics (51/68).

Among all the prolonged users of CNSDs, 39% (39/100) met the DSM-IV criteria for substance abuse or dependence. The non-mutually exclusive proportion of misuse or dependence for opioid analgesics, benzodiazepines and z-hypnotics were 30% (13/44), 40% (8/20) and 41% (28/68) respectively.

Factors associated with prolonged use of CNSDs

In the multivariate model, factors associated with increasing odds for prolonged use of CNSDs included being aged 75-84 (OR= 2.32, 95%CI: 1.16-4.65) and ≥85 years old (OR= 3.33, 95%CI: 1.25-8.87) compared to age <75; having more intense pain according to the VAS scale (OR=1.02, 95%CI: 1.01-1.04) and polypharmacy (OR=5.16, 95%CI: 2.13-12.55). On the contrary, the odds were lower among patients who had completed at least secondary education (OR= 0.33, 95%CI: 0.13-0.83) compared to only basic education (Table 2). In the sensitivity analysis using complete case analysis, the associations between these factors and the prolonged use of CNSDs remained significant (Appendix 1). Sex, income, anxiety and depression scores were not significantly associated with prolonged use of CNSDs.

Table 2. Logistic regression models for factors associated with prolonged use of CNSDs – estimated using multiple imputations.

Independent variable	Bivariate model		Multivariate model	
	OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Sex				
Male	1		1	
Female	2.05 (1.21-3.47)	**0.007**	1.56 (0.80-3.02)	0.19
Age groups, years				
65-74	1		1	
75-84	2.25 (1.27-4.00)	**0.006**	2.32 (1.16-4.65)	**0.02**
≥ 85	3.91 (1.75-8.74)	**0.001**	3.33 (1.25-8.87)	**0.02**

Education, years				
Basic education (≤ 10)	1		1	
Secondary education (11-13)	0.29 (0.14-0.60)	**0.001**	0.33 (0.13-0.83)	**0.02**
Higher education (≥ 14)	0.34 (0.16-0.71)	**0.004**	0.45 (0.18-1.12)	0.09
Income (NOK/year)				
< 200 000	1		1	
200 000 – 349 000	0.73 (0.27-1.93)	0.52	0.67 (0.20-2.24)	0.52
≥ 350 000	0.33 (0.12-0.88)	**0.03**	0.35 (0.10-1.23)	0.10
Living alone				
No	1		1	
Yes	1.80 (1.08-3.01)	**0.03**	0.94 (0.47-1.88)	0.86
Polypharmacy (≥ 5 drugs/day)				
No	1		1	
Yes	6.95 (3.13-15.41)	**<0.001**	5.16 (2.13-12.55)	**<0.001**
Anxiety scores (HADS-A)	1.06 (0.98-1.14)	0.14	1.01 (0.91-1.13)	0.80
Depression scores (HADS-D)	1.14 (1.05-1.24)	**0.002**	1.08 (0.95-1.22)	0.21
Pain intensity (millimeters on VAS scale)	1.02 (1.01-1.03)	**<0.001**	1.02 (1.01-1.04)	**<0.001**

Abbreviations:
CNSD – central nervous system depressant drugs
HADS–D/A – hospital anxiety and depression scale, depression or anxiety subscore.

Factors associated with CNSD misuse or dependence

Table 3 shows results of bivariate and multiple logistic regression analyses of factors associated with CNSD misuse or dependence, estimated using multiple imputations. We found that concurrent use of CNSDs and pain intensity had a significant association with misuse or dependence. In the multivariate model, we found that compared to exclusive use, concurrent use of two or more CNSDs increased the odds for misuse or dependence by 4 times (OR= 3.99, 95%CI: 1.34-11.88). Moreover, as pain intensity increased by 1 millimeter on 100 mm VAS scale, the odds for misuse or dependence increased by 1.02 units (OR= 1.02, 95%CI: 1.01-1.04). Sensitivity analysis using complete case analysis yield consistent results (Appendix 2).

Table 3. Logistic regression models for factors associated with CNSD misuse or dependence – estimated using multiple imputations.

Independent variables	Bivariate model		Multivariate model	
	OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Sex				
Male	1		1	
Female	1.54 (0.65-3.67)	0.33	1.13 (0.39-3.21)	0.83
Age, years				
65-74	1		1	
75-84	0.90 (0.34-2.37)	0.83	1.37 (0.42-4.50)	0.60
≥ 85	2.40 (0.75-7.65)	0.14	2.30 (0.56-9.45)	0.25
Education, years				
Basic education (≤10)	1		1	
Secondary education (11-13)	0.61 (0.22-1.72)	0.35	0.84 (0.23-3.03)	0.78
Higher education (≥14)	0.86 (0.32-2.34)	0.77	1.09 (0.31-3.81)	0.89
Income (NOK/year)				
< 200 000	1		1	
200 000 – 349 000	0.85 (0.24-2.98)	0.80	1.26 (0.26-6.26)	0.77
≥ 350 000	0.49 (0.13-1.88)	0.30	0.73 (0.11-4.83)	0.75
Living alone				
No	1		1	
Yes	2.65 (1.14-6.18)	**0.02**	2.06 (0.65-6.48)	0.22
Polypharmacy (≥ 5 drugs/d)				
No	1		1	
Yes	2.02 (0.39-10.55)	0.41	1.88 (0.25-14.21)	0.54
Concurrent use (of >1 CNSDs)				
No (exclusive use)	1		1	
Yes	3.5 (1.44-8.54)	**0.006**	3.99 (1.34-11.88)	**0.01**
Duration of CNSD use (weeks)	1.00 (0.99-1.00)	0.94	1.00 (0.99-1.00)	0.33
Anxiety scores (HADS-A)	1.08 (0.97-1.21)	0.14	1.06 (0.88-1.26)	0.55
Depression scores (HADS-D)	1.05 (0.93-1.19)	0.41	0.99 (0.81-1.20)	0.90
Pain intensity (millimeters, VAS scale)	1.01 (0.99-1.03)	0.08	1.02 (1.01-1.04)	**0.04**

Abbreviations: CNSD – central nervous system depressant drugs; HADS–D/A – hospital anxiety and depression scale, depression or anxiety subscore.

DISCUSSION

Our study shows that prolonged, concurrent and daily use of CNSDs is prevalent among hospitalized older patients. Z-hypnotics were the most commonly used drugs, both in exclusive and concurrent use patterns (with other CNSDs). In this particular group of patients, the presence of prolonged CNSD use was more common among patients with the following characteristics: being female, aged 75-84 years old, living alone, with lower socioeconomic status, polypharmacy, higher pain intensity and depression scores. Patients with and without misuse or dependence, according to DSM-IV criteria, did not differ significantly except for the fact that among those living alone there was a high prevalence of these disorders. The odds for prolonged CNSD use were higher among patients aged ≥ 75 years old and those with higher pain intensity and polypharmacy. Having completed secondary education was protective against the prolonged use. In older patients, concurrent use of more than one addictive medication, rather than the duration of use increased the likelihood of CNSD misuse or dependence.

One of the strengths of this study is that it provides evidence on characteristics of older patients with prolonged CNSD use, misuse, and dependence, from many different aspects (sociodemographic, pharmacological and clinical profiles). We adhered strictly to the STROBE reporting guidelines, ethical standards, and outcome measures were predefined (NCT03162081). Moreover, we used validated and generally accepted criteria (DSM-IV criteria) to assess medication misuse and dependence in older patients. Nonetheless, the study has some limitations. We acknowledge that the use of a consecutive hospital-based sample represents a limitation regarding generalizability of the study findings to the general population. However, our study should be reasonably representative for somatic hospital populations of older people. We suggest that hospitals may be good settings for conducting research on medication-related problems as they represent settings where older patients often get their medication regimens changed and also where they may therefore be at risk for adverse drug events and, consequently, where this focus is important. Another issue, which suggests some care in interpretation of our results, is the relatively

high number of patients that declined participation. It may be that those who declined represent either those with the most serious medical conditions or those that were not interested in being queried regarding their medication use, thus suggesting that our sample may be somewhat biased towards milder cases. In addition, the use of cross-sectional data precludes us from inferring causality of the observed associations.

Our study delivers a number of new and important insights pertaining to medication misuse and dependence in older patients. First, our study showed that concurrent use of CNSDs is still common among older patients. This is despite recommendations specified in the national treatment guidelines and evidence on the risk of fatal overdose.[21-25] Second; we comprehensively explored patient characteristics associated with the presence of CNSD prolonged use among hospitalized older patients, which may be useful for raising the awareness of patient groups that may be at increased risk.

Among geriatric patients, age-related pharmacokinetic and pharmacodynamics changes, chronic diseases, polypharmacy, and cognitive impairment can all interact and lead to greater vulnerability to harmful effects of medication overuse. According to both the national (NORGEP) and international (Beers and STOPP) criteria and treatment guidelines, opioid analgesics, benzodiazepines and z-hypnotics are all classified as inappropriate drugs for older patients and should not be used on a long-term basis. Our findings are consistent with three studies previously conducted in Norway and suggest that today's prescribing behavior is suboptimal and that more in-depth research and educational interventions are needed.[6 16 26]

Problematic patterns of CNSD use may derive from different underlying factors. Overprescribing is often unintentional, due to lenient prescribing or unawareness among prescribers about the uncertainty of long-term efficacy of CNSDs.[27 28] Another factor may be the failure to recognize at-risk patients, which may be a consequence of lacking validated instruments. Apart from this, doctor-patient communication may also play a role. Messages on the importance of adherence in order to avoid harmful effects of medication overuse, for instance, may not be

conveyed effectively to older patients. For the older patient counterpart, potential barriers in understanding and adhering to medical advice may include cognitive impairment, low health literacy and lack of family/social support.[29] [30] Furthermore, older patients may hold opposing attitudes regarding the discontinuation of CNSD use, [31] if adverse effects are under-emphasized and hopes of attaining freedom from unnecessary pain, anxiety and sleep disturbances in old age based only on medications are over-stated. Physicians may also experience other challenges in managing CNSD use.[32] Both the magnitude and impacts of such underlying factors on the prolonged use of CNSD in older patients remain poorly understood, and should therefore be elaborated in future research.

Also of note, we found that the concurrent use of CNSDs significantly increased the odds for misuse or dependence in older patients, even adjusted for patients' socio-demographic background and clinically important covariates such as duration of CNSD use and intensity of pain, anxiety and depressive symptoms (Table 3). This finding suggests that co-prescribing of CNSDs for older patients should be done with great care. Moreover, the present study points out significant associations between polypharmacy and CNSD prolonged use, misuse and dependence in older patients. This, to our knowledge, has not been explored by previous research. Such associations can be explained by several factors. Studies suggest that polypharmacy is associated with the co-occurrence of anxiety, sleep difficulties and discomforts,[33-35] and might through unknown side-effects aggravate these conditions, in turn leading to more CNSDs being prescribed for symptom relief.

Pertaining to our finding that living alone in old age is not associated with medication prolonged use and misuse or dependence, previous research yielded inconsistent results. Some reported that older adults who lived alone had significantly poorer sleep quality and tended to use more hypnotic drugs[36] [37] whereas others claimed that living alone is not associated with or even reduced the risk of long-term use of benzodiazepine and z-hypnotics.[38] [39] The issue clearly deserves further focus.

Finally, we found that pain intensity has a highly significant relationship with both prolonged use and misuse or dependence. This may suggest that pain intensity drives problematic use of CNSDs. However, another possibility is that prolonged opioid use does not contribute to improving pain. That opioid-induced hyperalgesia may worsen pain is well-known among younger chronic opioid users.[40 41] However, whether pain may indeed be worsened also by prolonged CNSD use among older patients, remains to be studied. Notably, anxiety and depression, known to be associated with pain intensity, were not, in our study, associated with prolonged CNSD use and misuse or dependence, even though they were reported to be common among chronic z-hypnotics users (the major medication used in our sample).[42 43] The interrelationship between pain, anxiety and depression is complex.[44] Future prospective studies over time are therefore needed to explain the interplay between these entities and their influences on CNSD dependence.

In conclusions, CNSD overuse (prolonged use, misuse and dependence) is still prevalent among hospitalized older patients, despite clear guidelines and recommendations. This raises a concern about an increasing incidence and consequences among elderly. Sociodemographic, clinical and pharmacological profiles of at-risk patients and significant associations identified in this study can be used to inform ways for implementing future research initiatives and interventions aiming at early detection, prevention and treatment for CNSD overuse among older patients.

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Authors' contributions

CL conceptualized, designed and led the study. SC, ESK and CL drafted the study protocol. SC customized the protocol, recruited participants, collected and analyzed data, and drafted this manuscript. TGS was involved in the recruitment and data collection process. MG contributed to the study conception and design. All authors took part in project planning and were involved in the refinement and approval of the final version of this manuscript.

Conflicts of interest

In addition to the funding given above, Dr. Lundqvist reports having received research grants from the South-East Regional Health authority, during the conduct of the study as well as grants and personal fees from Abbvie pharma AS and Roche Norway AS, outside this submitted work. These funders have no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. Other authors declared no conflicts of interest.

Patient consent for publication

Not required.

Ethics

Ethical approval was obtained from the Regional Committee for Medical Research Ethics – South East Norway (Reference number: 2016/2289/REK sør-øst) and the Data Protection Office at Akershus University Hospital (Reference number: 17-054). All participants provided written informed consents. Data handling was done accordingly.

Data sharing statement

The datasets analyzed during this study are not publicly available due to threats to subject privacy but are available from the corresponding author on reasonable request.

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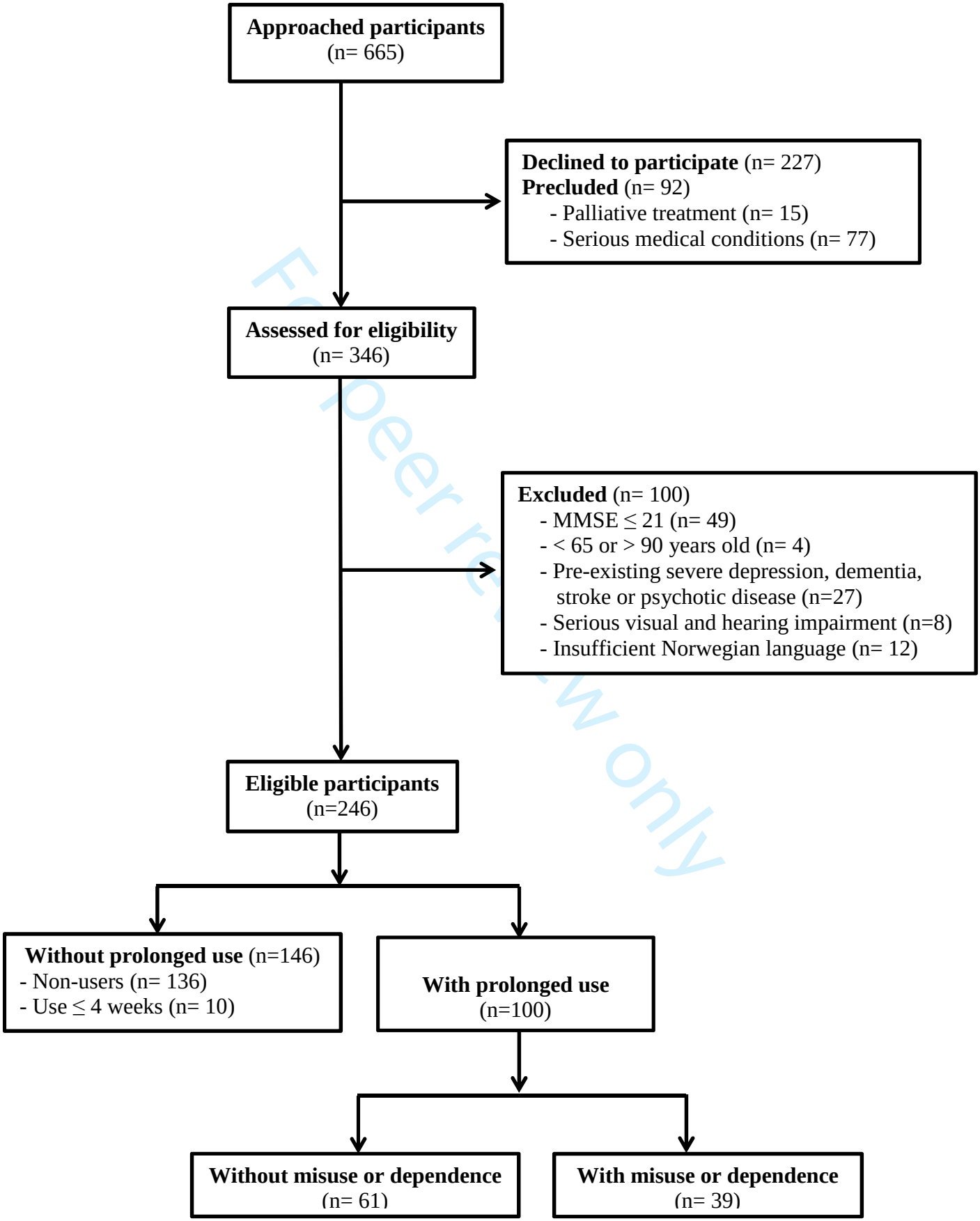
Figure 1. Flow of participants through the study



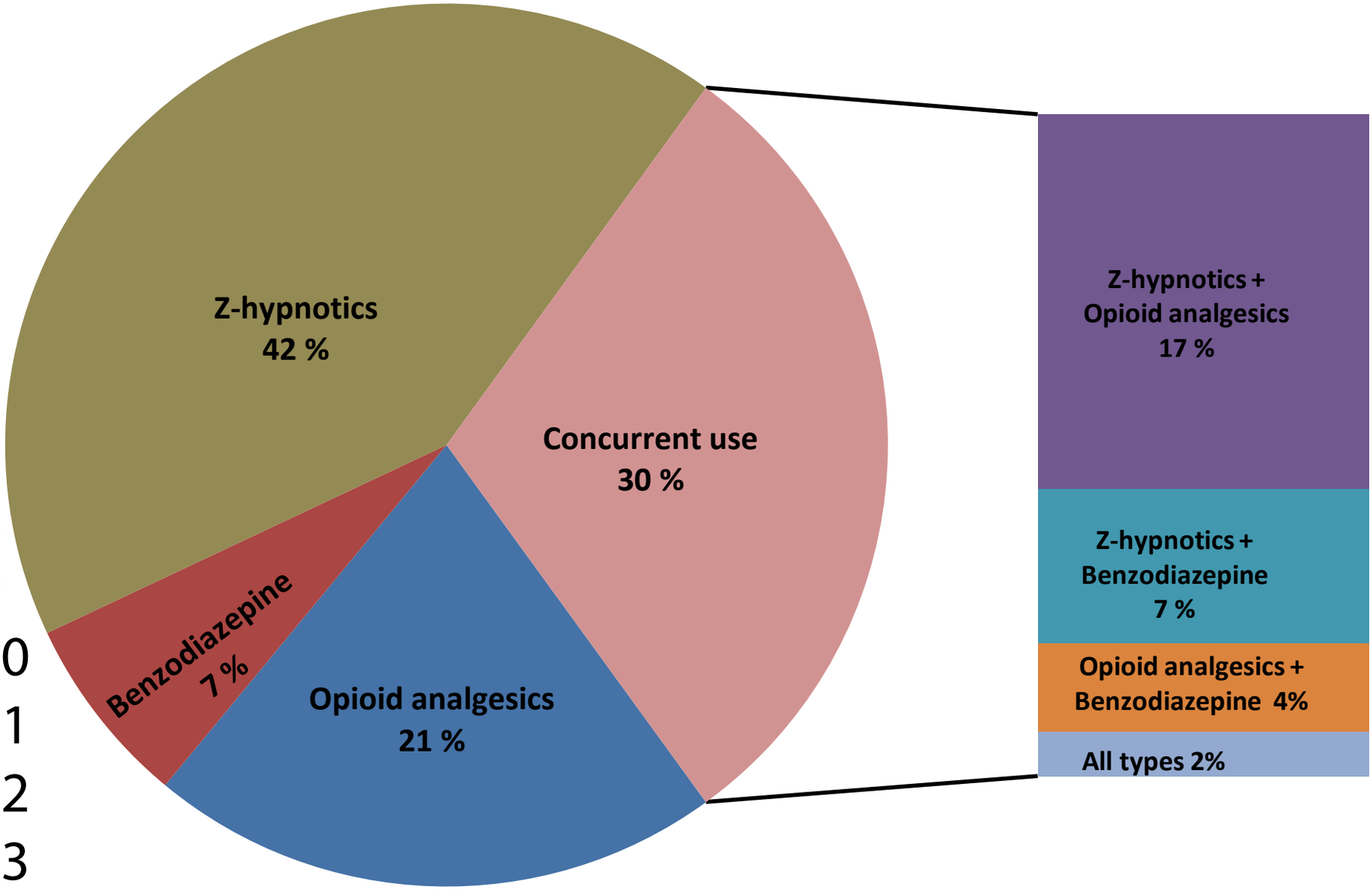


Figure 2. Proportion of prolonged users of CNSDs across medication groups. Of the 100 prolonged users, 70% used opioid analgesics (21%), benzodiazepines (7%) and z-hypnotics (42%) exclusively. The remaining 30% concurrently consumed ≥ 2 different types of CNSDs: z-hypnotics + opioid analgesics (17 %), z-hypnotics + benzodiazepines (7%), opioid analgesics + benzodiazepines (4%), z-hypnotics + benzodiazepines + opioid analgesics (2%).

Appendix 1. Sensitivity analysis for factor associated with prolonged use of CNSDs – Logistic regression models, estimated using complete case analysis

Independent variable	Bivariate		Multivariate	
	OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Sex				
Male	1		1	
Female	2.05 (1.21-3.47)	**0.007**	1.64 (0.77-3.50)	0.20
Age groups, years				
65-74	1		1	
75-84	2.25 (1.27-4.00)	**0.006**	2.31 (1.07-5.01)	**0.03**
≥ 85	3.91 (1.75-8.74)	**0.001**	3.52 (1.11-11.20)	**0.03**
Education, years				
Basic education (≤ 10)	1		1	
Secondary education (11-13)	0.26 (0.12-0.54)	**<0.001**	0.35 (0.13-0.97)	**0.04**
Higher education (≥ 14)	0.30 (0.14-0.64)	**0.002**	0.41 (0.15-1.14)	0.09
Income (NOK/year)				
< 200 000	1		1	
200 000 – 349 000	0.63 (0.24-1.68)	0.36	0.48 (0.14-1.67)	0.25
≥ 350 000	0.25 (0.09-0.66)	**0.005**	0.18 (0.05-0.69)	**0.01**
Living alone				
No	1		1	
Yes	1.80 (1.08-3.01)	**0.03**	0.56 (0.25-1.27)	0.17
Polypharmacy (≥ 5 drugs/day)				
No	1		1	
Yes	6.95 (3.13-15.41)	**<0.001**	4.64 (1.73-12.48)	**0.002**
Anxiety scores (HADS-A)	1.07 (0.99-1.15)	0.08	1.04 (0.92-1.17)	0.54
Depression scores (HADS-D)	1.15 (1.06-1.26)	**0.001**	1.08 (0.95-1.23)	0.23
Pain intensity (millimeters on VAS scale)	1.02 (1.01-1.03)	**<0.001**	1.03 (1.01-1.04)	**<0.001**

Abbreviations:
CNSD – central nervous system depressant drugs
HADS–D/A – hospital anxiety and depression scale, depression or anxiety subscore.

Appendix 2. Sensitivity analysis for factors associated with CNSD misuse or dependence – Logistic regression models, estimated using complete case analysis

Independent variable	Bivariate		Multivariate	
	OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Sex				
Male	1		1	
Female	1.54 (0.65-3.67)	0.33	1.50 (0.43-5.25)	0.52
Age, years				
65-74	1		1	
75-84	0.90 (0.34-2.37)	0.83	1.46 (0.36-5.96)	0.60
≥ 85	2.40 (0.75-7.65)	0.14	3.33 (0.55-20.16)	0.19
Education, years				
Basic education (≤10)	1		1	
Secondary education (11-13)	0.62 (0.22-1.77)	0.37	0.96 (0.20-4.60)	0.96
Higher education (≥14)	0.85 (0.31-2.32)	0.75	0.94 (0.22-3.99)	0.93
Income (NOK/year)				
< 200 000	1		1	
200 000 – 349 000	0.92 (0.27-3.21)	0.90	1.67 (0.28-9.95)	0.57
≥ 350 000	0.44 (0.11-1.73)	0.24	0.83 (0.10-6.94)	0.86
Living alone				
No	1		1	
Yes	2.65 (1.14-6.18)	**0.02**	2.24 (0.53-9.44)	0.27
Polypharmacy (≥ 5 drugs/day)				
No	1		1	
Yes	2.02 (0.39-10.55)	0.41	1.74 (0.14-21.22)	0.66
Concurrent use				
No (exclusive use)	1		1	
Yes	3.5 (1.44-8.54)	**0.006**	8.77 (2.19-35.10)	**0.002**
Duration of CNSD use (weeks)	1.00 (0.99-1.00)	0.94	1.00 (0.99-1.01)	0.11
Anxiety scores (HADS-A)	1.08(0.97-1.21)	0.15	1.01 (0.82-1.25)	0.94
Depression scores (HADS-D)	1.05 (0.93-1.19)	0.42	1.01 (0.81-1.27)	0.92
Pain intensity (millimeters, VAS scale)	1.01 (0.99-1.03)	0.08	1.03 (1.01-1.06)	**0.009**

Abbreviations:
CNSD – central nervous system depressant drugs
HADS–D/A – hospital anxiety and depression scale, depression or anxiety subscore.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6-8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social)	9-10

		and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	9
Outcome data	15*	Report numbers of outcome events or summary measures	8-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	10-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Sociodemographic, clinical and pharmacological profiles of medication misuse and dependence in hospitalized older patients: a prospective cross-sectional study

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Keywords:	Characteristics, geriatric patients, risk factors, addiction, prescription drug abuse

Sociodemographic, clinical and pharmacological profiles of medication misuse and dependence in hospitalized older patients: a prospective cross-sectional study

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ABSTRACT

Objectives

Timely recognition of medication misuse and dependence is crucial to avoid both adverse drug events and increasing health expenditure. Yet, the detection of these disorders in older people remains challenging due to the paucity of evidence on characteristics of patients at risk. This study investigates sociodemographic, pharmacological and clinical characteristics and factors associated with prolonged medication use, misuse and dependence in hospitalized older patients, focusing on three commonly prescribed central nervous system depressants (CNSDs): opioid analgesics, benzodiazepines and z-hypnotics.

Design

A prospective cross-sectional study, complying with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines

Setting

Somatic departments of the Akershus University Hospital, Norway

Participants

246 patients aged 65-90 were included.

Outcome measures

Prolonged use was defined as using CNSDs for ≥4 weeks. Misuse and dependence were assessed with DSM-IV criteria for substance abuse and dependence. We used descriptive statistics to report patients' characteristics and logistic regression to demonstrate factors associated with prolonged use, and misuse or dependence.

Results

Forty percent of participants reported using CNSDs for ≥4 weeks. Z-hypnotics were the most-commonly-used drugs. Prolonged users were more frequently female, aged 75-84, living alone, with lower socioeconomic status, polypharmacy, and higher pain intensity and depression scores. The

odds for prolonged use were higher among patients aged ≥75 and those with pain and polypharmacy, but lower among those who had completed secondary education, compared to the reference categories. In older patients, enhanced pain and concurrent use of ≥2 CNSDs increased the likelihood of misuse or dependence.

Conclusion

CNSD overuse is prevalent among hospitalized older patients, despite clear guidelines and recommendations. Our findings underline a need for stronger focus on responsible prescribing, timely detection and prevention of this issue, with special attention towards older patients, those with enhanced pain, polypharmacy and/or concurrent use of several CNSDs.

Key words: characteristics, geriatric patients, risk factors, addiction, prescription drug abuse

Trial registration: ClinicalTrials.gov Identifier: NCT03162081. Registered 3 May 2017

Strengths and limitations of this study

- The first and comprehensive study of characteristics and factors associated with commonly prescribed central nervous system depressants (CNSDs) prolonged use, misuse, and dependence in older hospitalized patients.
- Characteristics of at-risk patients and significant associations revealed in this study can be used to inform ways for implementing future research initiatives and interventions aiming at early detection, prevention and treatment for CNSD overuse among older patients.
- We used validated and generally accepted diagnostic criteria to assess medication misuse and dependence in older patients (DSM-IV criteria for substance abuse and dependence)
- The use of cross-sectional data and a hospital-based sample precludes us from inferring causal relationships and generalizing the study findings to the general population.

INTRODUCTION

Central nervous system depressants (CNSDs) such as opioid analgesics, benzodiazepines and z-hypnotics are commonly prescribed among older patients for the treatment of chronic pain, anxiety and insomnia. While these medications are essential for moderate-severe cases, long-term use is not recommended owing to the risk of adverse events, including hyperalgesia, fractures, falls, cognitive impairment and dependence.[1-3] This underlines the importance of rational use and prescription of CNSDs for older patients. To achieve this, one of the practical steps is for clinicians to be able to timely recognize older patients at risk or suffering from medication misuse and dependence.

According to the Norwegian Prescription Database, the consumption of potentially addictive drugs such as opioid analgesics (i.e. oxycodone and tramadol), benzodiazepines (i.e. diazepam, oxazepam and nitrazepam) and z-hypnotics (i.e. zopiclone and zolpidem) is high among individuals aged 65 and older. These drugs were among the 30 most commonly prescribed drugs to older patients in Norway in 2017.[4]

A Norwegian study showed that the patients' regular general practitioners (GPs) prescribed the largest proportion of addictive drugs to their older patients (77%) compared to other groups of physicians.[5] In line with this, another study, found that CNSDs were frequently prescribed by GPs in large quantities and through indirect contacts without consultation.[6] Both inappropriate prescribing and the high consumption of such addictive medications may put older patients at risk of medication misuse and dependence – a condition characterized by persistent and compulsive use of a medication despite impairment in physical, social and psychological health.[7]

Given the vulnerability to serious adverse effects and interactions as a result of age-related changes in pharmacokinetics and pharmacodynamics, timely recognition and treatment of medication misuse and dependence in older patients are crucial to ensure medication safety and to avoid increasing health expenditure.[8] Yet, the detection of these disorders in older people is challenging and requires both valid screening tools and evidence-based knowledge on long-term use

of CNSDs, including patients' characteristics related to misuse and dependence.[7 9] Addressing these knowledge gaps forms the basis for developing evidence-based intervention.

This study intends to provide such information by investigating sociodemographic, pharmacological and clinical characteristics and factors associated with prolonged medication use, misuse and dependence in hospitalized older patients, focusing on three commonly prescribed central nervous system depressants (CNSDs): opioid analgesics, benzodiazepines and z-hypnotics.

METHODS

Study design

The study was a prospective cross-sectional, in-hospital study and complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Participants and setting

The recruitment process took place between May 2017 and September 2018, at three somatic departments of the Akershus University Hospital: Geriatrics, General Internal Medicine and Neurology. The catchment area of the hospital covers roughly 10% of the total population of Norway. Participants were recruited at the first few days of admission based on predefined inclusion and exclusion criteria (NCT03162081), and not on their vulnerability, reasons for admission, diagnosis or severity of disease. As Norway has an all-covering national health insurance, all patients enter the hospital on the same conditions and with the same in-patient threshold. The study inclusion criteria were hospitalized patients, aged between 65 and 90 years old. The exclusion criteria included Mini-Mental State Examination (MMSE) score ≤ 21 (incapacity to give informed consent); [10 11] pre-existing diagnosis of severe depression, stroke, dementia, psychotic disorders; serious visual or hearing impairment; and insufficient Norwegian language, all generally assumed to bias participants' responses on self-rated health questions. We precluded participants who were in a too serious medical condition or palliative treatment, defined by physicians at the study setting.

Data collection

Data collection (by SC, TGS and CL) involved three steps. After consent had been given, all eligible participants were asked to complete a questionnaire on sociodemographic background, pain, anxiety and depression. At this stage, the investigators were blinded to the use of medications as this was registered in the electronic patient record (EPR) which could only be accessed once a written informed consent had been obtained. Having fulfilled this requirement, the EPRs were reviewed to document the use of medications (type, duration, frequency and polypharmacy). Finally, the presence of medication misuse or dependence among participants identified as prolonged users of CNSDs was assessed through a structured interview. Prior to the start of the study, the three data collectors had gone through training sessions in order to optimize congruent use of the interview. More details on definition, data sources, and measurements for variables under investigations are given in the section below. The questionnaire and interview guide used to collect data from participants can be found in Additional file 1.

Sociodemographic and clinical variables

Sociodemographic variables included age (65-74, 75-84, and ≥ 85); sex (Male, Female); education (basic, secondary, and higher education); annual income (<200 000, 200 000 – 349 000, and ≥ 350 000 Norwegian Krone (NOK) per year); and living alone (Yes, No). Clinical variables consisted of pain intensity (continuous, measured using visual analog scale - VAS); Anxiety and depressive symptoms were assessed with the Hospital Anxiety and Depression Scale (HADS). Optimal cut-off values for diagnosing anxiety and depression in older hospitalized patients using HADS remain to be established.[12 13] To avoid underestimation and misclassification bias of anxious and depressed individuals, we used anxiety and depression scores as continuous variables. Higher scores indicate higher levels of anxiety and depressive symptoms.[14] Data for all of these variables were collected through a self-completed questionnaire.

Pharmacological variables

We defined prolonged use of CNSDs as the use of opioid analgesics, benzodiazepines and/or z-hypnotics for four weeks or longer continuously up to the point of recruitment, [15 16] while non-prolonged use was non-use or use of these medications for less than four weeks. Medication misuse and dependence were defined based on DSM-IV criteria for substance abuse and dependence, through structured interviews, using the Norwegian version of the Mini-International Neuropsychiatric Interview Guide – MINI.[17] Dependence was defined to be present if patients met three or more of the dependence criteria. Misuse was confirmed if the dependence criteria were not met and the respondents satisfied one or more of the abuse criteria.[18] For the purpose of the present study, and as few patients fulfilled misuse criteria (n=6), misuse and dependence were grouped together as medication misuse or dependence (n=39). Other pharmacological variables entailed types of CNSD medications used (categorized as exclusive or concurrent use), duration of use (continuous, in week); frequency of use (categorized as sporadic use if the medication was taken intermittently < 5 days per week and as daily use if the medication was taken ≥ 5 days per week); Polypharmacy[19] (defined as the use of ≥5 medications daily, coded as Yes or No). The main source of pharmacological data was the EPR. We also sought to verify this against information from patients and GP referral documents. To ensure the accuracy of data on CNSD use patterns, we checked for evidence of use and consistency across prescriptions and relevant documents reported from both primary care and hospital settings.

Statistical analysis

We analyzed characteristics of older patients with and without prolonged use, and that of those with and without misuse or dependence using descriptive statistics. We assessed the associations between patient characteristics and the presence of prolonged CNSD use, and misuse or dependence using bivariate and multiple logistic regression analyses. The analyses included adjustment for sociodemographic subgroups (age groups, sex, education, annual income, living alone), clinical

(pain intensity, anxiety and depression scores) and pharmacological variables (polypharmacy, duration and concurrent use of CNSDs). Multiple imputations, under the missing at random assumption, using chained equations (with 20 imputed data sets) were performed to handle missing data. Sensitivity analyses were conducted for the same models using complete case analysis (individuals with missing data are excluded). No multicollinearity was detected. Stata-SE software version 15 was used for all statistical analyses.[20]

Patient and public involvement

A user advisory board established at the Akershus University Hospital (the study setting), which included both representatives of older patients and health service officials, supported this study. The board met on a regular basis throughout the study period. They provided project-specific inputs on ethics, design and methodology as well as highlighted research focus based on patient and public interests. They will also be involved in the dissemination of the findings.

RESULTS

Participants

In total, we consecutively approached 665 adults aged 65-90. Of these, 227 participants declined to participate, while 92 others were precluded due to either being in a too serious medical condition or palliative treatment. Of the remaining patients, 100 were excluded based on predefined exclusion criteria. This resulted in 246 older patients eligible for the study, of which 100 were thereafter identified as prolonged users of CNSDs (≥ four weeks). Figure 1 provides more details on the flow of participants through the study.

There were no missing data in the variables: prolonged use, misuse or dependence, concurrent use, duration of CNSD use, age groups, sex, living alone and polypharmacy. The following variables had missing data: pain intensity 7% (18/246), anxiety scores 7% (17/246), depression scores 7% (17/246), education 6% (14/246), and income 16% (39/246).

Descriptive data

Overall, in descriptive analyses, older patients with prolonged use of CNSDs were more often female, aged 75-85, living alone, with lower socioeconomic status (completed ≤ secondary education and earned < 350000 NOK/year), polypharmacy and accompanied by higher pain intensity and depression scores (Table 1). Patients screening positive on misuse or dependence were mainly those living alone (69%) and those on exclusive use of CNSDs (54%). More details on patient characteristics are provided in Table 1.

Table1. Patient characteristics

Patient characteristics	Prolonged use of CNSDs		CNSD misuse or dependence	
	No (n=146)	Yes (n=100)	No (n=61)	Yes (n=39)
Sex				
Female	71 (49%)	66 (66%)	38 (62%)	28 (72%)
Male	75 (51%)	34 (34%)	23 (38%)	11 (28%)
Age groups				
65-74	73 (50%)	28 (28%)	18 (29%)	10 (25%)
75-84	59 (40%)	51 (51%)	34 (56%)	17 (44%)
≥ 85	14 (10%)	21 (21%)	9 (15%)	12 (31%)
Education, years				
Basic education (≤10)	16 (12%)	30 (32%)	17 (29%)	13 (36%)
Secondary education (11-13)	64 (46%)	31 (33%)	21 (36%)	10 (28%)
Higher education (≥14)	58 (42%)	33 (35%)	20 (35%)	13 (36%)
Income (NOK/year)				
< 200 000	8 (7%)	13 (15%)	7 (14%)	6 (18%)
200 000–349 000	42 (34%)	43 (51%)	24 (46%)	19 (58%)
≥ 350 0000	72 (59%)	29 (34%)	21 (40%)	8 (24%)
Living alone				
No	87 (60%)	45 (45%)	33 (54%)	12 (31%)
Yes	59 (40%)	55 (55%)	28 (46%)	27 (69%)
Polypharmacy (≥ 5 drugs/day)				
No	55 (38%)	8 (8%)	6 (10%)	2 (5%)
Yes	91 (62%)	92 (92%)	55 (90%)	37 (95%)
Anxiety scores (HADS-A)				
Mean (SD)	4.13 (3.28)	4.97 (3.91)	4.47 (3.54)	5.68 (4.34)
Median (Range)	4 (0-14)	4 (0-16)	4 (0-16)	5 (0-15)
Depression scores (HADS-D)				
Mean (SD)	3.60 (2.98)	5.13 (3.49)	4.89 (3.26)	5.49 (3.81)
Median (Range)	3 (0-13)	4 (0-15)	4 (0-12)	5 (0-15)
Pain intensity (millimeters on VAS scale)				
Mean (SD)	18.07 (24.21)	35.20 (30.35)	30.56 (28.30)	42.08 (32.34)
Median (Range)	7 (0-91)	29.50 (0-97)	27 (0-97)	48 (0-93)
Duration of CNSD use (weeks)				
Mean (SD)	-	71.47 (113.44)	72.10 (138.38)	70.48 (57.36)

Median (Range)		50.50 (4-988)	33 (4-988)	52 (4-232)
Concurrent use (of >1 CNSDs)				
No (exclusive use)	-	70 (70%)	49 (80%)	21 (54%)
Yes	-	30 (30%)	12 (20%)	18 (46%)

Abbreviations:
CNSD – central nervous system depressant drugs;
HADS–D/A – hospital anxiety and depression scale, depression or anxiety subscore.

Medication use patterns

Forty percent (100 out of 246 participants) of the older patients enrolled in this study were identified as prolonged users (≥4 weeks) of opioid analgesics, benzodiazepines and/or z-hypnotics. The dominant group of medications was Z-hypnotics, accounting for 42% (42/100) as exclusive use and 26% (26/100) as concurrent use of Z-hypnotics plus other CNSDs, followed by opioid analgesics, which comprised 21% (21/100) as exclusive use and 23% (23/100) as concurrent use. Benzodiazepines were less commonly used and constituted 7% (7/100) as exclusive use and 13% (13/100) as concurrent use. 30% (30/100) of the prolonged users in our sample concurrently consumed two or more different types of CNSDs. The most prevalent pattern of concurrent use was the combination of z-hypnotics and opioid analgesics, amounting to 57% (17/30) of all forms of current use.

The majority of older patients using CNSDs, did so on long-term and daily basis. The medians for duration of use for opioid analgesics, benzodiazepines and z-hypnotics were 42 (4-988), 51 (4-208) and 52 (4-232) weeks respectively. More than half of the prolonged users reported using these medications daily (5-7 days per week): opioid analgesics (26/44), benzodiazepines (15/20) and/or z-hypnotics (51/68).

Among all the prolonged users of CNSDs, 39% (39/100) met the DSM-IV criteria for substance abuse or dependence. The non-mutually exclusive proportion of misuse or dependence for opioid analgesics, benzodiazepines and z-hypnotics were 30% (13/44), 40% (8/20) and 41% (28/68) respectively.

Factors associated with prolonged use of CNSDs

In the multivariate model, factors associated with increasing odds for prolonged use of CNSDs included being aged 75-84 (OR= 2.32, 95%CI: 1.16-4.65) and ≥85 years old (OR= 3.33, 95%CI: 1.25-8.87) compared to age <75; having more intense pain according to the VAS scale (OR=1.02, 95%CI: 1.01-1.04) and polypharmacy (OR=5.16, 95%CI: 2.13-12.55). On the contrary, the odds were lower among patients who had completed at least secondary education (OR= 0.33, 95%CI: 0.13-0.83) compared to only basic education (Table 2). In the sensitivity analysis using complete case analysis, the associations between these factors and the prolonged use of CNSDs remained significant (Additional file 2). Sex, income, anxiety and depression scores were not significantly associated with prolonged use of CNSDs.

Table 2. Logistic regression models for factors associated with prolonged use of CNSDs – estimated using multiple imputations.

Independent variable	Bivariate model		Multivariate model	
	OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Sex				
Male	1		1	
Female	2.05 (1.21-3.47)	**0.007**	1.56 (0.80-3.02)	0.19
Age groups, years				
65-74	1		1	
75-84	2.25 (1.27-4.00)	**0.006**	2.32 (1.16-4.65)	**0.02**
≥ 85	3.91 (1.75-8.74)	**0.001**	3.33 (1.25-8.87)	**0.02**
Education, years				
Basic education (≤ 10)	1		1	
Secondary education (11-13)	0.29 (0.14-0.60)	**0.001**	0.33 (0.13-0.83)	**0.02**
Higher education (≥ 14)	0.34 (0.16-0.71)	**0.004**	0.45 (0.18-1.12)	0.09
Income (NOK/year)				
< 200 000	1		1	
200 000 – 349 000	0.73 (0.27-1.93)	0.52	0.67 (0.20-2.24)	0.52
≥ 350 000	0.33 (0.12-0.88)	**0.03**	0.35 (0.10-1.23)	0.10
Living alone				
No	1		1	
Yes	1.80 (1.08-3.01)	**0.03**	0.94 (0.47-1.88)	0.86

Polypharmacy (≥ 5 drugs/day)				
No	1		1	
Yes	6.95 (3.13-15.41)	**<0.001**	5.16 (2.13-12.55)	**<0.001**
Anxiety scores (HADS-A)	1.06 (0.98-1.14)	0.14	1.01 (0.91-1.13)	0.80
Depression scores (HADS-D)	1.14 (1.05-1.24)	**0.002**	1.08 (0.95-1.22)	0.21
Pain intensity (millimeters on VAS scale)	1.02 (1.01-1.03)	**<0.001**	1.02 (1.01-1.04)	**<0.001**

Abbreviations:
CNSD – central nervous system depressant drugs
HADS–D/A – hospital anxiety and depression scale, depression or anxiety subscore.

Factors associated with CNSD misuse or dependence

Table 3 shows results of bivariate and multiple logistic regression analyses of factors associated with CNSD misuse or dependence, estimated using multiple imputations. We found that concurrent use of CNSDs and pain intensity had a significant association with misuse or dependence. In the multivariate model, we found that compared to exclusive use, concurrent use of two or more CNSDs increased the odds for misuse or dependence by 4 times (OR= 3.99, 95%CI: 1.34-11.88). Moreover, as pain intensity increased by 1 millimeter on 100 mm VAS scale, the odds for misuse or dependence increased by 1.02 units (OR= 1.02, 95%CI: 1.01-1.04). Sensitivity analysis using complete case analysis yield consistent results (Additional file 2).

Table 3. Logistic regression models for factors associated with CNSD misuse or dependence – estimated using multiple imputations.

Independent variables	Bivariate model		Multivariate model	
	OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Sex				
Male	1		1	
Female	1.54 (0.65-3.67)	0.33	1.13 (0.39-3.21)	0.83
Age, years				
65-74	1		1	
75-84	0.90 (0.34-2.37)	0.83	1.37 (0.42-4.50)	0.60
≥ 85	2.40 (0.75-7.65)	0.14	2.30 (0.56-9.45)	0.25
Education, years				
Basic education (≤10)	1		1	
Secondary education (11-13)	0.61 (0.22-1.72)	0.35	0.84 (0.23-3.03)	0.78

Higher education (≥14)	0.86 (0.32-2.34)	0.77	1.09 (0.31-3.81)	0.89
Income (NOK/year)				
< 200 000	1		1	
200 000 – 349 000	0.85 (0.24-2.98)	0.80	1.26 (0.26-6.26)	0.77
≥ 350 000	0.49 (0.13-1.88)	0.30	0.73 (0.11-4.83)	0.75
Living alone				
No	1		1	
Yes	2.65 (1.14-6.18)	**0.02**	2.06 (0.65-6.48)	0.22
Polypharmacy (≥ 5 drugs/day)				
No	1		1	
Yes	2.02 (0.39-10.55)	0.41	1.88 (0.25-14.21)	0.54
Concurrent use (of >1 CNSDs)				
No (exclusive use)	1		1	
Yes	3.5 (1.44-8.54)	**0.006**	3.99 (1.34-11.88)	**0.01**
Duration of CNSD use (weeks)	1.00 (0.99-1.00)	0.94	1.00 (0.99-1.00)	0.33
Anxiety scores (HADS-A)	1.08 (0.97-1.21)	0.14	1.06 (0.88-1.26)	0.55
Depression scores (HADS-D)	1.05 (0.93-1.19)	0.41	0.99 (0.81-1.20)	0.90
Pain intensity (millimeters, VAS scale)	1.01 (0.99-1.03)	0.08	1.02 (1.01-1.04)	**0.04**

Abbreviations: CNSD – central nervous system depressant drugs; HADS–D/A – hospital anxiety and depression scale, depression or anxiety subscore.

DISCUSSION

Our study shows that prolonged, concurrent and daily use of CNSDs is prevalent among hospitalized older patients. Z-hypnotics were the most commonly used drugs, both in exclusive and concurrent use patterns (with other CNSDs). In this particular group of patients, the presence of prolonged CNSD use was more common among patients with the following characteristics: being female, aged 75-84 years old, living alone, with lower socioeconomic status, polypharmacy, higher pain intensity and depression scores. Patients with misuse or dependence, according to DSM-IV criteria, were mainly those living alone and those on exclusive use of CNSDs. The odds for prolonged CNSD use were higher among patients aged ≥ 75 years old and those with higher pain intensity and polypharmacy. Having completed secondary education was protective against the

prolonged use. In older patients, enhanced pain and concurrent use of ≥ 2 different types of CNSDs, rather than the duration of use increased the likelihood of misuse or dependence.

One of the strengths of this study is that it provides evidence on characteristics of older patients with prolonged CNSD use, misuse, and dependence, from many different aspects (sociodemographic, pharmacological and clinical profiles). We adhered strictly to the STROBE reporting guidelines, ethical standards, and outcome measures were predefined (NCT03162081). Moreover, we used validated and generally accepted criteria (DSM-IV criteria) to assess medication misuse and dependence in older patients. Nonetheless, the study has some limitations. We acknowledge that the use of a consecutive hospital-based sample represents a limitation regarding generalizability of the study findings to the general population. However, our study should be reasonably representative for somatic hospital populations of older people. We suggest that hospitals may be good settings for conducting research on medication-related problems as they represent settings where older patients often get their medication regimens changed and also where they may therefore be at risk for adverse drug events and, consequently, where this focus is important. Furthermore, it has recently been pointed out that long-term use of benzodiazepine/z-hypnotics often started in hospitals and the prescription is continued by GPs.[21] Another issue, which suggests some care in interpretation of our results, is the relatively high number of patients that declined participation. It may be that those who declined represent either those with the most serious medical conditions or those that were not interested in being queried regarding their medication use, thus suggesting that our sample may be somewhat biased towards milder cases. In addition, the use of cross-sectional data precludes us from inferring causality of the observed associations.

Our study delivers a number of new and important insights pertaining to medication misuse and dependence in older patients. First, our study showed that concurrent use of CNSDs is still common among older patients. This is despite recommendations specified in the national treatment guidelines and evidence on the risk of fatal overdose.[22-26] Second; we comprehensively explored

patient characteristics associated with the presence of CNSD prolonged use among hospitalized older patients, which may be useful for raising the awareness of patient groups that may be at increased risk.

Among geriatric patients, age-related pharmacokinetic and pharmacodynamics changes, chronic diseases, polypharmacy, and cognitive impairment can all interact and lead to greater vulnerability to harmful effects of medication overuse. According to both the national (NORGEP) and international (Beers and STOPP) criteria[27-29] and treatment guidelines,[22 23] opioid analgesics, benzodiazepines and z-hypnotics are all classified as inappropriate drugs for older patients and should not be used on a long-term basis. Our findings are consistent with three studies previously conducted in Norway[6 16 30] and suggest that today's prescribing behavior is suboptimal and that more in-depth research and educational interventions are needed.[31 32]

Problematic patterns of CNSD use may derive from different underlying factors. Overprescribing is often unintentional, due to lenient prescribing or unawareness among prescribers about the uncertainty of long-term efficacy of CNSDs.[33 34] Another factor may be the failure to recognize at-risk patients, which may be a consequence of lacking validated instruments. Apart from this, doctor-patient communication may also play a role. Messages on the importance of adherence in order to avoid harmful effects of medication overuse, for instance, may not be conveyed effectively to older patients. For the older patient counterpart, potential barriers in understanding and adhering to medical advice may include cognitive impairment, low health literacy and lack of family/social support.[35 36] Furthermore, older patients may hold opposing attitudes regarding the discontinuation of CNSD use,[21] if adverse effects are under-emphasized and hopes of attaining freedom from unnecessary pain, anxiety and sleep disturbances in old age based only on medications are over-stated. Physicians may also experience other challenges in managing CNSD use.[37] Both the magnitude and impacts of such underlying factors on the prolonged use of CNSDs in older patients remain poorly understood, and should therefore be elaborated in future research.

Also of note, we found that the concurrent use of CNSDs significantly increased the odds for misuse or dependence in older patients, even adjusted for patients' socio-demographic background and clinically important covariates such as duration of CNSD use and intensity of pain, anxiety and depressive symptoms (Table 3). This finding suggests that co-prescribing of CNSDs for older patients should be done with great care. Moreover, the present study points out a significant association between polypharmacy and CNSD prolonged use in older patients. This, to our knowledge, has not been explored by previous research. Such associations can be explained by several factors. Studies suggest that polypharmacy is associated with the co-occurrence of anxiety, sleep difficulties and discomforts,[38-40] and might through unknown side-effects aggravate these conditions, in turn leading to more CNSDs being prescribed for symptom relief.[41]

Pertaining to our finding that living alone in old age is not associated with medication prolonged use and misuse or dependence, previous research yielded inconsistent results. Some reported that older adults who lived alone had significantly poorer sleep quality and tended to use more hypnotic drugs[42 43] whereas others claimed that living alone is not associated with or even reduced the risk of long-term use of benzodiazepine and z-hypnotics.[44-46] The issue clearly deserves further focus.

Finally, we found that pain intensity has a highly significant relationship with both prolonged use and misuse or dependence. This may suggest that pain intensity drives problematic use of CNSDs. However, another possibility is that prolonged opioid use does not contribute to improving pain. That opioid-induced hyperalgesia may worsen pain is well-known among younger chronic opioid users.[47-48] However, whether pain may indeed be worsened also by prolonged CNSD use among older patients, remains to be studied. Notably, anxiety and depression, known to be associated with pain intensity, were not, in our study, associated with prolonged CNSD use and misuse or dependence, even though they were reported to be common among chronic z-hypnotics users (the major medication used in our sample).[49 50] The interrelationship between pain, anxiety and

depression is complex.[51 52] Future prospective studies over time are therefore needed to explain the interplay between these entities and their influences on CNSD dependence.

In conclusions, CNSD overuse (prolonged use, misuse and dependence) is still prevalent among hospitalized older patients, despite clear guidelines and recommendations. Our findings underline a need for stronger focus on responsible prescribing, timely detection and prevention of medication misuse and dependence, with special attention towards older patients, those with enhanced pain, polypharmacy and/or concurrent use of several CNSDs.

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Authors' contributions

CL conceptualized, designed and led the study. SC, ESK and CL drafted the study protocol. SC customized the protocol, recruited participants, collected and analyzed data, and drafted this manuscript. TGS was involved in the recruitment and data collection process. MG contributed to the study conception and design. All authors took part in project planning and were involved in the refinement and approval of the final version of this manuscript.

Competing interests

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Patient consent for publication

Not required.

Ethics

Ethical approval was obtained from the Regional Committee for Medical Research Ethics – South East Norway (Reference number: 2016/2289/REK sør-øst) and the Data Protection Office at Akershus University Hospital (Reference number: 17-054). All participants provided written informed consents. Data handling was done accordingly.

Data sharing statement

The datasets analyzed during this study are not publicly available due to threats to subject privacy but are available from the corresponding author on reasonable request.

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Figure legends

Figure 1. Flow of participants through the study

Table 1. Patient characteristics

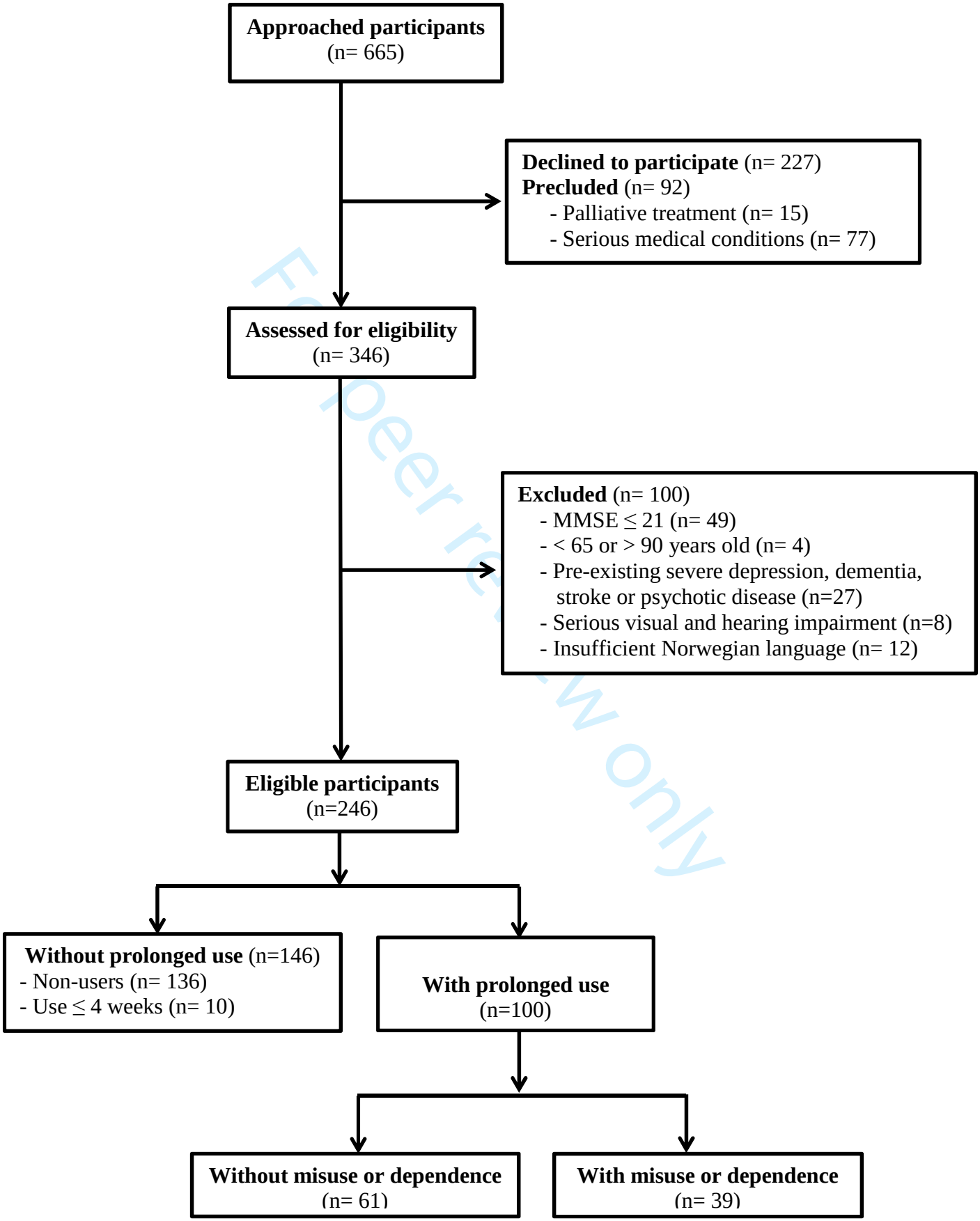
Table 2. Logistic regression models for factors associated with prolonged use of CNSDs – estimated using multiple imputations

Table 3. Logistic regression models for factors associated with CNSD misuse or dependence – estimated using multiple imputations

Additional file 1. Questionnaire and interview guide

Additional file 2. Sensitivity analyses

Figure 1. Flow of participants through the study



SOCIODEMOGRAPHIC BACKGROUND

1. **Sex**

☐ Male

☐ Female

2. **The year you were born:** …….

3. **Your highest education level:**

☐ Basic education

☐ Secondary education

☐ College or university (number of years:……..)

4. **Your annual income (NOK per year)**

☐ < 200 000

☐ 200 000–349 000

☐ ≥ 350 0000

5. **Do you live alone?**

☐ No

☐ Yes

THE HOSPITAL ANXIETY AND DEPRESSION SCALE

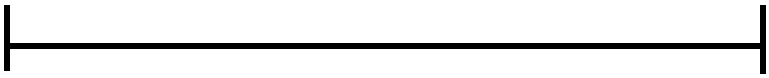
1. I feel tense or 'wound up':	**2. I still enjoy the things I used to enjoy**
3 ☐ Most of the time	**0** ☐ Definitely as much
2 ☐ A lot of the time	**1** ☐ Not quite so much
1 ☐ From time to time, occasionally	**2** ☐ Only a little
0 ☐ Not at all	**3** ☐ Hardly at all
3. I get a sort of frightened feeling as if something awful is about to happen:	**4. I can laugh and see the funny side of things:**
3 ☐ Very definitely and quite badly	**0** ☐ As much as I always could
2 ☐ Yes , but not too badly	**1** ☐ Not quite so much now
1 ☐ A little, but it doesn't worry me	**2** ☐ Definitely not so much no
0 ☐ Not at all	**3** ☐ Not at all
5. Worrying thoughts go through my mind:	**6. I feel cheerful:**
3 ☐ A great deal of the time	**3** ☐ Not at all
2 ☐ A lot of the time	**2** ☐ Not often
1 ☐ From time to time but not too often	**1** ☐ Sometimes
0 ☐ Only occasionally	**0** ☐ Most of the time
7. I can sit at ease and feel relaxed:	**8. I feel as if I have slowed down:**
0 ☐ Definitely	**3** ☐ Nearly all the time
1 ☐ Usually	**2** ☐ Very often
2 ☐ Not often	**1** ☐ Sometimes
3 ☐ Not at all	**0** ☐ Not at all
9. I get a sort of frightened feeling like 'butterflies' in the stomach:	**10. I have lost interest in my appearance:**
0 ☐ Not at all	**3** ☐ Definitely
1 ☐ Occasionally	**2** ☐ I don't take so much care as I should
2 ☐ Quite often	**1** ☐ I may not take quite as much care
3 ☐ Very often	**0** ☐ I take just as much care as ever
11. I feel restless as if I have to be on the move:	**12. I look forward with enjoyment to things:**
3 ☐ Very much indeed	**0** ☐ As much as ever I did
2 ☐ Quite a lot	**1** ☐ Rather less than I used to
1 ☐ Not very much	**2** ☐ Definitely less than I used to
0 ☐ Not a t all	**3** ☐ Hardly at all
13. I get sudden feelings of panic:	**14. I can enjoy a good book or radio or TV programme:**
3 ☐ Very often indeed	**0** ☐Often
2 ☐ Quite often	**1** ☐ Sometimes
1 ☐ Not very often	**2** ☐ Not often
0 ☐ Not at all	**3** ☐ Very seldom

Total anxiety score:

Total depression score:

PAIN INTENSITY
(Visual analogue scale)

Please mark on the line to describe how much pain you are currently feeling:



No pain **Worst pain**

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

DSM-IV criteria, Version 6.0.0

PSYCHOACTIVE SUBSTANCE USE DISORDERS (NON-ALCOHOL)

➡ **MEANS: GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)**

Now I am going to show you/read to you a list of street drugs or medicines.

		➡	
J1	**Have you in the past 12 months ever taken** any of these drugs more than once to get high, to feel better, or to change your mood?	NO	YES

CIRCLE EACH DRUG TAKEN:

Stimulants: amphetamines, "speed", methamphetamine (crystal meth), “crank”, “rush”, Dexedrine, Ritalin, diet pills.

Cocaine: cocaine, snorting, IV, freebase, crack, "speedball".

Opiates: heroin, morphine, opium, methadone, codeine, OxyContin.

Hallucinogens: LSD ("acid"), mescaline, peyote, psilocybin, STP, "mushrooms", “ecstasy”, MDA, MDMA.

Phencyclidin: PCP ("Angel Dust", "PeaCe Pill", “Tranq”) or ketamin (”special K”).

Inhalants: glue, ethyl chloride, "rush", dinitrogen monoxide ("laughing gas"), amyl or butyl nitrate ("poppers").

Cannabis: marijuana, hashish ("hash"), THC, "reefer", "grass".

Anxiolytics: Valium, Vival, Stesolid, Xanor (alprazolam), Seconal, Librium, Ativan, Halcion, barbiturates, GHB, Rohypnol (“Roofies”).

Miscellaneous: steroids, nonprescription sleep or diet pills, cough syrup. Any others?

SPECIFY MOST USED DRUG(S): _____

WHICH SUBSTANCE(S)/MEDICATION(S) CAUSE THE MAJOR PROBLEMS? _____

J2 Considering your use of (name the drug / drug class selected), in the past 12 months:

a.	Have you found that you needed to use more (name of drug / drug class selected) to get the same effect that you did when you first started taking it?	NO	YES
b.	When you reduced or stopped using (name of drug / drug class selected), did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable, or depressed)? Did you use any drug(s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better?	NO	YES
	IF **YES** TO EITHER QUESTION, CODE **YES**.		
c.	Have you often found that when you used (name of drug / drug class selected),	NO	YES

you ended up taking more than you thought you would?

d. Have you tried to reduce or stop taking (name of drug / drug class selected), but failed? NO YES

e. On the days that you used (name of drug / drug class selected), did you spend substantial time (> 2 hours) in obtaining, using or in recovering from drug(s), or thinking about drug(s)? NO YES

f. Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use? NO YES

g. Have you continued to use (name of drug / drug class selected) even though it caused you health or mental problems? NO YES

ARE **3** OR MORE **J2** ANSWERS CODED **YES**?

SPECIFY DRUG(S): _____

NO	**YES**
SUBSTANCE DEPENDENCE	

J3 Considering your use of (name the drug / drug class selected), in the past 12 months:

a. Have you been intoxicated, high, or hungover from (name of drug / drug class selected) more than once, when you had other responsibilities at school, at work, or at home? Did this cause any problems? (CODE **YES** ONLY IF THIS CAUSED PROBLEMS.) NO YES

b. Have you been high or intoxicated from (name of drug / drug class selected) more than once, in any situation where you were physically at risk, (for example, driving a car, riding a motorbike, using machinery, boating, etc.)? NO YES

c. Did you have legal problems more than once, because of your drug use, for example, an arrest or disorderly conduct? NO YES

d. Did you continue to use (name of drug / drug class selected) even though it caused problems with your family or other people? NO YES

ARE **1** OR MORE **J3** ANSWERS CODED YES?

SPECIFY DRUG(S): _____

NO	**YES**
SUBSTANCE ABUSE	
CURRENT	

ADDITIONAL QUESTIONS TO CONFIRM MEDICATION USE PATTERNS

1. How long have you been using this medication?

2. How many days per week do you need to take the medication (on average)?

3. Do you need to take it every day?

   If yes, ask: for how long the patient has used the medication every day?

4. Have there been periods that you have not used the medication at all?

Sensitivity analysis for factor associated with prolonged use of CNSDs – Logistic regression models, estimated using complete case analysis

Independent variable	Bivariate		Multivariate	
	OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Sex				
Male	1		1	
Female	2.05 (1.21-3.47)	**0.007**	1.64 (0.77-3.50)	0.20
Age groups, years				
65-74	1		1	
75-84	2.25 (1.27-4.00)	**0.006**	2.31 (1.07-5.01)	**0.03**
≥ 85	3.91 (1.75-8.74)	**0.001**	3.52 (1.11-11.20)	**0.03**
Education, years				
Basic education (≤ 10)	1		1	
Secondary education (11-13)	0.26 (0.12-0.54)	**<0.001**	0.35 (0.13-0.97)	**0.04**
Higher education (≥ 14)	0.30 (0.14-0.64)	**0.002**	0.41 (0.15-1.14)	0.09
Income (NOK/year)				
< 200 000	1		1	
200 000 – 349 000	0.63 (0.24-1.68)	0.36	0.48 (0.14-1.67)	0.25
≥ 350 000	0.25 (0.09-0.66)	**0.005**	0.18 (0.05-0.69)	**0.01**
Living alone				
No	1		1	
Yes	1.80 (1.08-3.01)	**0.03**	0.56 (0.25-1.27)	0.17
Polypharmacy (≥ 5 drugs/day)				
No	1		1	
Yes	6.95 (3.13-15.41)	**<0.001**	4.64 (1.73-12.48)	**0.002**
Anxiety scores (HADS-A)	1.07 (0.99-1.15)	0.08	1.04 (0.92-1.17)	0.54
Depression scores (HADS-D)	1.15 (1.06-1.26)	**0.001**	1.08 (0.95-1.23)	0.23
Pain intensity (millimeters on VAS scale)	1.02 (1.01-1.03)	**<0.001**	1.03 (1.01-1.04)	**<0.001**

Abbreviations:
CNSD – central nervous system depressant drugs
HADS–D/A – hospital anxiety and depression scale, depression or anxiety subscore.

Sensitivity analysis for factors associated with CNSD misuse or dependence – Logistic regression models, estimated using complete case analysis

Independent variable	Bivariate		Multivariate	
	OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Sex				
Male	1		1	
Female	1.54 (0.65-3.67)	0.33	1.50 (0.43-5.25)	0.52
Age, years				
65-74	1		1	
75-84	0.90 (0.34-2.37)	0.83	1.46 (0.36-5.96)	0.60
≥ 85	2.40 (0.75-7.65)	0.14	3.33 (0.55-20.16)	0.19
Education, years				
Basic education (≤10)	1		1	
Secondary education (11-13)	0.62 (0.22-1.77)	0.37	0.96 (0.20-4.60)	0.96
Higher education (≥14)	0.85 (0.31-2.32)	0.75	0.94 (0.22-3.99)	0.93
Income (NOK/year)				
< 200 000	1		1	
200 000 – 349 000	0.92 (0.27-3.21)	0.90	1.67 (0.28-9.95)	0.57
≥ 350 000	0.44 (0.11-1.73)	0.24	0.83 (0.10-6.94)	0.86
Living alone				
No	1		1	
Yes	2.65 (1.14-6.18)	**0.02**	2.24 (0.53-9.44)	0.27
Polypharmacy (≥ 5 drugs/day)				
No	1		1	
Yes	2.02 (0.39-10.55)	0.41	1.74 (0.14-21.22)	0.66
Concurrent use				
No (exclusive use)	1		1	
Yes	3.5 (1.44-8.54)	**0.006**	8.77 (2.19-35.10)	**0.002**
Duration of CNSD use (weeks)	1.00 (0.99-1.00)	0.94	1.00 (0.99-1.01)	0.11
Anxiety scores (HADS-A)	1.08(0.97-1.21)	0.15	1.01 (0.82-1.25)	0.94
Depression scores (HADS-D)	1.05 (0.93-1.19)	0.42	1.01 (0.81-1.27)	0.92
Pain intensity (millimeters, VAS scale)	1.01 (0.99-1.03)	0.08	1.03 (1.01-1.06)	**0.009**

Abbreviations:
CNSD – central nervous system depressant drugs
HADS–D/A – hospital anxiety and depression scale, depression or anxiety subscore.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	5-8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social)	9-10

		and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	8
Outcome data	15*	Report numbers of outcome events or summary measures	8-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Sociodemographic, clinical and pharmacological profiles of medication misuse and dependence in hospitalized older patients in Norway: a prospective cross-sectional study

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Secondary Subject Heading:	Addiction, Mental health, Patient-centred medicine, Pharmacology and therapeutics
Keywords:	Characteristics, geriatric patients, risk factors, addiction, prescription drug abuse

Sociodemographic, clinical and pharmacological profiles of medication misuse and dependence in hospitalized older patients in Norway: a prospective cross-sectional study

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ABSTRACT

Objectives

Timely recognition of medication misuse and dependence is crucial to avoid both adverse drug events and increasing health expenditure. Yet, the detection of these disorders in older people remains challenging due to the paucity of evidence on characteristics of patients at risk. This study investigates sociodemographic, pharmacological and clinical characteristics and factors associated with prolonged medication use, misuse and dependence in hospitalized older patients, focusing on three commonly prescribed central nervous system depressants (CNSDs): opioid analgesics, benzodiazepines and z-hypnotics.

Design

A prospective cross-sectional study, complying with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines

Setting

Somatic departments of the Akershus University Hospital, Norway

Participants

246 patients aged 65-90 were included.

Outcome measures

Prolonged use was defined as using CNSDs for ≥4 weeks. Misuse and dependence were assessed with DSM-IV criteria for substance abuse and dependence. We used descriptive statistics to report patients' characteristics and logistic regression to demonstrate factors associated with prolonged use, and misuse or dependence.

Results

Forty percent of participants reported using CNSDs for ≥4 weeks. The odds of prolonged use were higher for patients aged 75-84 (OR=2.32, 95%CI: 1.16-4.65) and ≥85 (OR=3.33, 95%CI: 1.25-8.87) versus <75 years, for pain intensity (OR=1.02, 95%CI: 1.01-1.04) and polypharmacy versus

no polypharmacy (OR=5.16, 95%CI: 2.13-12.55). The odds were lower for patients who completed secondary education (OR= 0.33, 95%CI: 0.13-0.83) compared to those with only basic education. Factors associated with misuse or dependence were pain intensity (OR=1.02, 95%CI: 1.01-1.04) and concurrent use of ≥2 CNSDs (OR=3.99, 95%CI: 1.34-11.88).

Conclusion

CNSD overuse is prevalent among hospitalized older patients, despite clear guidelines and recommendations. Our findings underline a need for stronger focus on responsible prescribing, timely detection and prevention of this issue, with special attention towards older patients, those with enhanced pain, polypharmacy and/or concurrent use of several CNSDs.

Key words: characteristics, geriatric patients, risk factors, addiction, prescription drug abuse

Trial registration: ClinicalTrials.gov Identifier: NCT03162081. Registered 3 May 2017

Strengths and limitations of this study

- The first and comprehensive study of characteristics and factors associated with commonly prescribed central nervous system depressants (CNSDs) prolonged use, misuse, and dependence in older hospitalized patients.
- Characteristics of at-risk patients and significant associations revealed in this study can be used to inform ways for implementing future research initiatives and interventions aiming at early detection, prevention and treatment for CNSD overuse among older patients.
- We used validated and generally accepted diagnostic criteria to assess medication misuse and dependence in older patients (DSM-IV criteria for substance abuse and dependence)
- The use of cross-sectional data and a hospital-based sample precludes us from inferring causal relationships and generalizing the study findings to the general population.

INTRODUCTION

Central nervous system depressants (CNSDs) such as opioid analgesics, benzodiazepines and z-hypnotics are commonly prescribed among older patients for the treatment of chronic pain, anxiety and insomnia. While these medications are essential for moderate-severe cases, long-term use is not recommended owing to the risk of adverse events, including hyperalgesia, fractures, falls, cognitive impairment and dependence.[1-3] This underlines the importance of rational use and prescription of CNSDs for older patients. To achieve this, one of the practical steps is for clinicians to be able to timely recognize older patients at risk or suffering from medication misuse and dependence.

According to the Norwegian Prescription Database, the consumption of potentially addictive drugs such as opioid analgesics (i.e. oxycodone and tramadol), benzodiazepines (i.e. diazepam, oxazepam and nitrazepam) and z-hypnotics (i.e. zopiclone and zolpidem) is high among individuals aged 65 and older. These drugs were among the 30 most commonly prescribed drugs to older patients in Norway in 2017.[4]

A Norwegian study showed that the patients' regular general practitioners (GPs) prescribed the largest proportion of addictive drugs to their older patients (77%) compared to other groups of physicians.[5] In line with this, another study, found that CNSDs were frequently prescribed by GPs in large quantities and through indirect contacts without consultation.[6] Both inappropriate prescribing and the high consumption of such addictive medications may put older patients at risk of medication misuse and dependence – a condition characterized by persistent and compulsive use of a medication despite impairment in physical, social and psychological health.[7]

Given the vulnerability to serious adverse effects and interactions as a result of age-related changes in pharmacokinetics and pharmacodynamics, timely recognition and treatment of medication misuse and dependence in older patients are crucial to ensure medication safety and to avoid increasing health expenditure.[8] Yet, the detection of these disorders in older people is challenging and requires both valid screening tools and evidence-based knowledge on long-term use

of CNSDs, including patients' characteristics related to misuse and dependence.[7 9] Addressing these knowledge gaps forms the basis for developing evidence-based intervention.

This study intends to provide such information by investigating sociodemographic, pharmacological and clinical characteristics and factors associated with prolonged medication use, misuse and dependence in hospitalized older patients, focusing on three commonly prescribed central nervous system depressants (CNSDs): opioid analgesics, benzodiazepines and z-hypnotics.

METHODS

Study design

The study was a prospective cross-sectional, in-hospital study and complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Participants and setting

The recruitment process took place between May 2017 and September 2018, at three somatic departments of the Akershus University Hospital: Geriatrics, General Internal Medicine and Neurology. The catchment area of the hospital covers roughly 10% of the total population of Norway. Participants were recruited at the first few days of admission based on predefined inclusion and exclusion criteria (NCT03162081), and not on their vulnerability, reasons for admission, diagnosis or severity of disease. As Norway has an all-covering national health insurance, all patients enter the hospital on the same conditions and with the same in-patient threshold. The study inclusion criteria were hospitalized patients, aged between 65 and 90 years old. The exclusion criteria included Mini-Mental State Examination (MMSE) score ≤ 21 (incapacity to give informed consent); [10 11] pre-existing diagnosis of severe depression, stroke, dementia, psychotic disorders; serious visual or hearing impairment; and insufficient Norwegian language, all generally assumed to bias participants' responses on self-rated health questions. We precluded participants who were in a too serious medical condition or palliative treatment, defined by physicians at the study setting.

Data collection

Data collection (by SC, TGS and CL) involved three steps. After consent had been given, all eligible participants were asked to complete a questionnaire on sociodemographic background, pain, anxiety and depression. At this stage, the investigators were blinded to the use of medications as this was registered in the electronic patient record (EPR) which could only be accessed once a written informed consent had been obtained. Having fulfilled this requirement, the EPRs were reviewed to document the use of medications (type, duration, frequency and polypharmacy). Finally, the presence of medication misuse or dependence among participants identified as prolonged users of CNSDs was assessed through a structured interview. Prior to the start of the study, the three data collectors had gone through training sessions in order to optimize congruent use of the interview. More details on definition, data sources, and measurements for variables under investigations are given in the section below. The questionnaire and interview guide used to collect data from participants can be found in Additional file 1.

Sociodemographic and clinical variables

Sociodemographic variables included age (65-74, 75-84, and ≥ 85); sex (Male, Female); education (basic, secondary, and higher education); annual income (<200 000, 200 000 – 349 000, and ≥ 350 000 Norwegian Krone (NOK) per year); and living alone (Yes, No). Clinical variables consisted of pain intensity (continuous, measured using visual analog scale - VAS); Anxiety and depressive symptoms were assessed with the Hospital Anxiety and Depression Scale (HADS). Cronbach alpha coefficient for the HADS-anxiety and depression subscale, reported by Helvik et al. (2011), was 0.78 and 0.71 respectively.[12] Optimal cut-off values for diagnosing anxiety and depression in older hospitalized patients using HADS remain to be established.[12 13] To avoid underestimation and misclassification bias of anxious and depressed individuals, we used anxiety and depression scores as continuous variables. Higher scores indicate higher levels of anxiety and depressive symptoms.[14] Data for all of these variables were collected through a self-completed questionnaire.

Pharmacological variables

We defined prolonged use of CNSDs as the use of opioid analgesics, benzodiazepines and/or z-hypnotics for four weeks or longer continuously up to the point of recruitment, [15 16] while non-prolonged use was non-use or use of these medications for less than four weeks. Medication misuse and dependence were defined based on DSM-IV criteria for substance abuse and dependence, through structured interviews, using the Norwegian version of the Mini-International Neuropsychiatric Interview Guide – MINI.[17] Dependence was defined to be present if patients met three or more of the dependence criteria. Misuse was confirmed if the dependence criteria were not met and the respondents satisfied one or more of the abuse criteria.[18] For the purpose of the present study, and as few patients fulfilled misuse criteria (n=6), misuse and dependence were grouped together as medication misuse or dependence (n=39). Other pharmacological variables entailed types of CNSD medications used (categorized as exclusive or concurrent use), duration of use (continuous, in week); frequency of use (categorized as sporadic use if the medication was taken intermittently < 5 days per week and as daily use if the medication was taken ≥ 5 days per week); Polypharmacy[19] (defined as the use of ≥5 medications daily, coded as Yes or No). The main source of pharmacological data was the EPR. We also sought to verify this against information from patients and GP referral documents. To ensure the accuracy of data on CNSD use patterns, we checked for evidence of use and consistency across prescriptions and relevant documents reported from both primary care and hospital settings.

Statistical analysis

We analyzed characteristics of older patients with and without prolonged use, and that of those with and without misuse or dependence using descriptive statistics. We assessed the associations between patient characteristics and the presence of prolonged CNSD use, and misuse or dependence using bivariate and multiple logistic regression analyses. The analyses included adjustment for sociodemographic subgroups (age groups, sex, education, annual income, living alone), clinical (pain intensity, anxiety and depression scores) and pharmacological variables (polypharmacy,

duration and concurrent use of CNSDs). Multiple imputations, under the missing at random assumption, using chained equations (with 20 imputed data sets) were performed to handle missing data. Sensitivity analyses were conducted for the same models using complete case analysis (individuals with missing data are excluded). No multicollinearity was detected. Stata-SE software version 15 was used for all statistical analyses.[20]

Patient and public involvement

A user advisory board established at the Akershus University Hospital (the study setting), which included both representatives of older patients and health service officials, supported this study. The board met on a regular basis throughout the study period. They provided project-specific inputs on ethics, design and methodology as well as highlighted research focus based on patient and public interests. They will also be involved in the dissemination of the findings.

RESULTS

Participants

In total, we consecutively approached 665 adults aged 65-90. Of these, 227 participants declined to participate, while 92 others were precluded due to either being in a too serious medical condition or palliative treatment. Of the remaining patients, 100 were excluded based on predefined exclusion criteria. This resulted in 246 older patients eligible for the study, of which 100 were thereafter identified as prolonged users of CNSDs (≥ four weeks). Figure 1 provides more details on the flow of participants through the study.

There were no missing data in the variables: prolonged use, misuse or dependence, concurrent use, duration of CNSD use, age groups, sex, living alone and polypharmacy. The following variables had missing data: pain intensity 7% (18/246), anxiety scores 7% (17/246), depression scores 7% (17/246), education 6% (14/246), and income 16% (39/246).

Descriptive data

Overall, in descriptive analyses, older patients with prolonged use of CNSDs were more often female, aged 75-85, living alone, with lower socioeconomic status (completed ≤ secondary education and earned < 350000 NOK/year), polypharmacy and accompanied by higher pain intensity and depression scores (Table 1). Patients screening positive on misuse or dependence were mainly those living alone (69%) and those on exclusive use of CNSDs (54%). More details on patient characteristics are provided in Table 1.

Table1. Patient characteristics

Patient characteristics	Prolonged use of CNSDs		CNSD misuse or dependence	
	No (n=146)	Yes (n=100)	No (n=61)	Yes (n=39)
Sex				
Female	71 (49%)	66 (66%)	38 (62%)	28 (72%)
Male	75 (51%)	34 (34%)	23 (38%)	11 (28%)
Age groups				
65-74	73 (50%)	28 (28%)	18 (29%)	10 (25%)
75-84	59 (40%)	51 (51%)	34 (56%)	17 (44%)
≥ 85	14 (10%)	21 (21%)	9 (15%)	12 (31%)
Education, years				
Basic education (≤10)	16 (12%)	30 (32%)	17 (29%)	13 (36%)
Secondary education (11-13)	64 (46%)	31 (33%)	21 (36%)	10 (28%)
Higher education (≥14)	58 (42%)	33 (35%)	20 (35%)	13 (36%)
Income (NOK/year)				
< 200 000	8 (7%)	13 (15%)	7 (14%)	6 (18%)
200 000–349 000	42 (34%)	43 (51%)	24 (46%)	19 (58%)
≥ 350 0000	72 (59%)	29 (34%)	21 (40%)	8 (24%)
Living alone				
No	87 (60%)	45 (45%)	33 (54%)	12 (31%)
Yes	59 (40%)	55 (55%)	28 (46%)	27 (69%)
Polypharmacy (≥ 5 drugs/day)				
No	55 (38%)	8 (8%)	6 (10%)	2 (5%)
Yes	91 (62%)	92 (92%)	55 (90%)	37 (95%)
Anxiety scores (HADS-A)				
Mean (SD)	4.13 (3.28)	4.97 (3.91)	4.47 (3.54)	5.68 (4.34)
Median (Range)	4 (0-14)	4 (0-16)	4 (0-16)	5 (0-15)
Depression scores (HADS-D)				
Mean (SD)	3.60 (2.98)	5.13 (3.49)	4.89 (3.26)	5.49 (3.81)
Median (Range)	3 (0-13)	4 (0-15)	4 (0-12)	5 (0-15)
Pain intensity (millimeters on VAS scale)				
Mean (SD)	18.07 (24.21)	35.20 (30.35)	30.56 (28.30)	42.08 (32.34)
Median (Range)	7 (0-91)	29.50 (0-97)	27 (0-97)	48 (0-93)
Duration of CNSD use (weeks)				
Mean (SD)	-	71.47 (113.44)	72.10 (138.38)	70.48 (57.36)

Median (Range)		50.50 (4-988)	33 (4-988)	52 (4-232)
Concurrent use (of >1 CNSDs)				
No (exclusive use)	-	70 (70%)	49 (80%)	21 (54%)
Yes	-	30 (30%)	12 (20%)	18 (46%)

Abbreviations:
CNSD – central nervous system depressant drugs;
HADS–D/A – hospital anxiety and depression scale, depression or anxiety subscore.

Medication use patterns

Forty percent (100 out of 246 participants) of the older patients enrolled in this study were identified as prolonged users (≥4 weeks) of opioid analgesics, benzodiazepines and/or z-hypnotics. The dominant group of medications was Z-hypnotics, accounting for 42% (42/100) as exclusive use and 26% (26/100) as concurrent use of Z-hypnotics plus other CNSDs, followed by opioid analgesics, which comprised 21% (21/100) as exclusive use and 23% (23/100) as concurrent use. Benzodiazepines were less commonly used and constituted 7% (7/100) as exclusive use and 13% (13/100) as concurrent use. 30% (30/100) of the prolonged users in our sample concurrently consumed two or more different types of CNSDs. The most prevalent pattern of concurrent use was the combination of z-hypnotics and opioid analgesics, amounting to 57% (17/30) of all forms of current use.

The majority of older patients using CNSDs, did so on long-term and daily basis. The medians for duration of use for opioid analgesics, benzodiazepines and z-hypnotics were 42 (4-988), 51 (4-208) and 52 (4-232) weeks respectively. More than half of the prolonged users reported using these medications daily (5-7 days per week): opioid analgesics (26/44), benzodiazepines (15/20) and/or z-hypnotics (51/68).

Among all the prolonged users of CNSDs, 39% (39/100) met the DSM-IV criteria for substance abuse or dependence. The non-mutually exclusive proportion of misuse or dependence for opioid analgesics, benzodiazepines and z-hypnotics were 30% (13/44), 40% (8/20) and 41% (28/68) respectively.

Factors associated with prolonged use of CNSDs

In the multivariate model, factors associated with increasing odds for prolonged use of CNSDs included being aged 75-84 (OR= 2.32, 95%CI: 1.16-4.65) and ≥85 years old (OR= 3.33, 95%CI: 1.25-8.87) compared to age <75; having more intense pain according to the VAS scale (OR=1.02, 95%CI: 1.01-1.04) and polypharmacy (OR=5.16, 95%CI: 2.13-12.55). On the contrary, the odds were lower among patients who had completed at least secondary education (OR= 0.33, 95%CI: 0.13-0.83) compared to only basic education (Table 2). In the sensitivity analysis using complete case analysis, the associations between these factors and the prolonged use of CNSDs remained significant (Additional file 2). Sex, income, anxiety and depression scores were not significantly associated with prolonged use of CNSDs.

Table 2. Logistic regression models for factors associated with prolonged use of CNSDs – estimated using multiple imputations.

Independent variable	Bivariate model		Multivariate model	
	OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Sex				
Male	1		1	
Female	2.05 (1.21-3.47)	**0.007**	1.56 (0.80-3.02)	0.19
Age groups, years				
65-74	1		1	
75-84	2.25 (1.27-4.00)	**0.006**	2.32 (1.16-4.65)	**0.02**
≥ 85	3.91 (1.75-8.74)	**0.001**	3.33 (1.25-8.87)	**0.02**
Education, years				
Basic education (≤ 10)	1		1	
Secondary education (11-13)	0.29 (0.14-0.60)	**0.001**	0.33 (0.13-0.83)	**0.02**
Higher education (≥ 14)	0.34 (0.16-0.71)	**0.004**	0.45 (0.18-1.12)	0.09
Income (NOK/year)				
< 200 000	1		1	
200 000 – 349 000	0.73 (0.27-1.93)	0.52	0.67 (0.20-2.24)	0.52
≥ 350 000	0.33 (0.12-0.88)	**0.03**	0.35 (0.10-1.23)	0.10
Living alone				
No	1		1	
Yes	1.80 (1.08-3.01)	**0.03**	0.94 (0.47-1.88)	0.86

Polypharmacy (≥ 5 drugs/day)				
No	1		1	
Yes	6.95 (3.13-15.41)	**<0.001**	5.16 (2.13-12.55)	**<0.001**
Anxiety scores (HADS-A)	1.06 (0.98-1.14)	0.14	1.01 (0.91-1.13)	0.80
Depression scores (HADS-D)	1.14 (1.05-1.24)	**0.002**	1.08 (0.95-1.22)	0.21
Pain intensity (millimeters on VAS scale)	1.02 (1.01-1.03)	**<0.001**	1.02 (1.01-1.04)	**<0.001**

Abbreviations:
CNSD – central nervous system depressant drugs
HADS–D/A – hospital anxiety and depression scale, depression or anxiety subscore.

Factors associated with CNSD misuse or dependence

Table 3 shows results of bivariate and multiple logistic regression analyses of factors associated with CNSD misuse or dependence, estimated using multiple imputations. We found that concurrent use of CNSDs and pain intensity had a significant association with misuse or dependence. In the multivariate model, we found that compared to exclusive use, concurrent use of two or more CNSDs increased the odds for misuse or dependence by 4 times (OR= 3.99, 95%CI: 1.34-11.88). Moreover, as pain intensity increased by 1 millimeter on 100 mm VAS scale, the odds for misuse or dependence increased by 1.02 units (OR= 1.02, 95%CI: 1.01-1.04). Sensitivity analysis using complete case analysis yield consistent results (Additional file 2).

Table 3. Logistic regression models for factors associated with CNSD misuse or dependence – estimated using multiple imputations.

Independent variables	Bivariate model		Multivariate model	
	OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Sex				
Male	1		1	
Female	1.54 (0.65-3.67)	0.33	1.13 (0.39-3.21)	0.83
Age, years				
65-74	1		1	
75-84	0.90 (0.34-2.37)	0.83	1.37 (0.42-4.50)	0.60
≥ 85	2.40 (0.75-7.65)	0.14	2.30 (0.56-9.45)	0.25
Education, years				
Basic education (≤10)	1		1	
Secondary education (11-13)	0.61 (0.22-1.72)	0.35	0.84 (0.23-3.03)	0.78

Higher education (≥14)	0.86 (0.32-2.34)	0.77	1.09 (0.31-3.81)	0.89
Income (NOK/year)				
< 200 000	1		1	
200 000 – 349 000	0.85 (0.24-2.98)	0.80	1.26 (0.26-6.26)	0.77
≥ 350 000	0.49 (0.13-1.88)	0.30	0.73 (0.11-4.83)	0.75
Living alone				
No	1		1	
Yes	2.65 (1.14-6.18)	**0.02**	2.06 (0.65-6.48)	0.22
Polypharmacy (≥ 5 drugs/day)				
No	1		1	
Yes	2.02 (0.39-10.55)	0.41	1.88 (0.25-14.21)	0.54
Concurrent use (of >1 CNSDs)				
No (exclusive use)	1		1	
Yes	3.5 (1.44-8.54)	**0.006**	3.99 (1.34-11.88)	**0.01**
Duration of CNSD use (weeks)	1.00 (0.99-1.00)	0.94	1.00 (0.99-1.00)	0.33
Anxiety scores (HADS-A)	1.08 (0.97-1.21)	0.14	1.06 (0.88-1.26)	0.55
Depression scores (HADS-D)	1.05 (0.93-1.19)	0.41	0.99 (0.81-1.20)	0.90
Pain intensity (millimeters, VAS scale)	1.01 (0.99-1.03)	0.08	1.02 (1.01-1.04)	**0.04**

Abbreviations: CNSD – central nervous system depressant drugs; HADS–D/A – hospital anxiety and depression scale, depression or anxiety subscore.

DISCUSSION

Our study shows that prolonged, concurrent and daily use of CNSDs is prevalent among hospitalized older patients. Z-hypnotics were the most commonly used drugs, both in exclusive and concurrent use patterns (with other CNSDs). In this particular group of patients, the presence of prolonged CNSD use was more common among patients with the following characteristics: being female, aged 75-84 years old, living alone, with lower socioeconomic status, polypharmacy, higher pain intensity and depression scores. Patients with misuse or dependence, according to DSM-IV criteria, were mainly those living alone and those on exclusive use of CNSDs. The odds for prolonged CNSD use were higher among patients aged ≥ 75 years old and those with higher pain intensity and polypharmacy. Having completed secondary education was protective against the

prolonged use. In older patients, enhanced pain and concurrent use of ≥ 2 different types of CNSDs, rather than the duration of use increased the likelihood of misuse or dependence.

One of the strengths of this study is that it provides evidence on characteristics of older patients with prolonged CNSD use, misuse, and dependence, from many different aspects (sociodemographic, pharmacological and clinical profiles). We adhered strictly to the STROBE reporting guidelines, ethical standards, and outcome measures were predefined (NCT03162081). Moreover, we used validated and generally accepted criteria (DSM-IV criteria) to assess medication misuse and dependence in older patients. Nonetheless, the study has some limitations. We acknowledge that the use of a consecutive hospital-based sample represents a limitation regarding generalizability of the study findings to the general population. However, our study should be reasonably representative for somatic hospital populations of older people. We suggest that hospitals may be good settings for conducting research on medication-related problems as they represent settings where older patients often get their medication regimens changed and also where they may therefore be at risk for adverse drug events and, consequently, where this focus is important. Furthermore, it has recently been pointed out that long-term use of benzodiazepine/z-hypnotics often started in hospitals and the prescription is continued by GPs.[21] Another issue, which suggests some care in interpretation of our results, is the relatively high number of patients that declined participation. It may be that those who declined represent either those with the most serious medical conditions or those that were not interested in being queried regarding their medication use, thus suggesting that our sample may be somewhat biased towards milder cases. In addition, the use of cross-sectional data precludes us from inferring causality of the observed associations.

Our study delivers a number of new and important insights pertaining to medication misuse and dependence in older patients. First, our study showed that concurrent use of CNSDs is still common among older patients. This is despite recommendations specified in the national treatment guidelines and evidence on the risk of fatal overdose.[22-26] Second; we comprehensively explored

patient characteristics associated with the presence of CNSD prolonged use among hospitalized older patients, which may be useful for raising the awareness of patient groups that may be at increased risk.

Among geriatric patients, age-related pharmacokinetic and pharmacodynamics changes, chronic diseases, polypharmacy, and cognitive impairment can all interact and lead to greater vulnerability to harmful effects of medication overuse. According to both the national (NORGEP) and international (Beers and STOPP) criteria[27-29] and treatment guidelines,[22 23] opioid analgesics, benzodiazepines and z-hypnotics are all classified as inappropriate drugs for older patients and should not be used on a long-term basis. Our findings are consistent with three studies previously conducted in Norway[6 16 30] and suggest that today's prescribing behavior is suboptimal and that more in-depth research and educational interventions are needed.[31 32]

Problematic patterns of CNSD use may derive from different underlying factors. Overprescribing is often unintentional, due to lenient prescribing or unawareness among prescribers about the uncertainty of long-term efficacy of CNSDs.[33 34] Another factor may be the failure to recognize at-risk patients, which may be a consequence of lacking validated instruments. Apart from this, doctor-patient communication may also play a role. Messages on the importance of adherence in order to avoid harmful effects of medication overuse, for instance, may not be conveyed effectively to older patients. For the older patient counterpart, potential barriers in understanding and adhering to medical advice may include cognitive impairment, low health literacy and lack of family/social support.[35 36] Furthermore, older patients may hold opposing attitudes regarding the discontinuation of CNSD use,[21] if adverse effects are under-emphasized and hopes of attaining freedom from unnecessary pain, anxiety and sleep disturbances in old age based only on medications are over-stated. Physicians may also experience other challenges in managing CNSD use.[37] Both the magnitude and impacts of such underlying factors on the prolonged use of CNSDs in older patients remain poorly understood, and should therefore be elaborated in future research.

Also of note, we found that the concurrent use of CNSDs significantly increased the odds for misuse or dependence in older patients, even adjusted for patients' socio-demographic background and clinically important covariates such as duration of CNSD use and intensity of pain, anxiety and depressive symptoms (Table 3). This finding suggests that co-prescribing of CNSDs for older patients should be done with great care. Moreover, the present study points out a significant association between polypharmacy and CNSD prolonged use in older patients. This, to our knowledge, has not been explored by previous research. Such associations can be explained by several factors. Studies suggest that polypharmacy is associated with the co-occurrence of anxiety, sleep difficulties and discomforts,[38-40] and might through unknown side-effects aggravate these conditions, in turn leading to more CNSDs being prescribed for symptom relief.[41]

Pertaining to our finding that living alone in old age is not associated with medication prolonged use and misuse or dependence, previous research yielded inconsistent results. Some reported that older adults who lived alone had significantly poorer sleep quality and tended to use more hypnotic drugs[42 43] whereas others claimed that living alone is not associated with or even reduced the risk of long-term use of benzodiazepine and z-hypnotics.[44-46] The issue clearly deserves further focus.

Finally, we found that pain intensity has a highly significant relationship with both prolonged use and misuse or dependence. This may suggest that pain intensity drives problematic use of CNSDs. However, another possibility is that prolonged opioid use does not contribute to improving pain. That opioid-induced hyperalgesia may worsen pain is well-known among younger chronic opioid users.[47-48] However, whether pain may indeed be worsened also by prolonged CNSD use among older patients, remains to be studied. Notably, anxiety and depression, known to be associated with pain intensity, were not, in our study, associated with prolonged CNSD use and misuse or dependence, even though they were reported to be common among chronic z-hypnotics users (the major medication used in our sample).[49 50] The interrelationship between pain, anxiety and

depression is complex.[51 52] Future prospective studies over time are therefore needed to explain the interplay between these entities and their influences on CNSD dependence.

In conclusions, CNSD overuse (prolonged use, misuse and dependence) is still prevalent among hospitalized older patients, despite clear guidelines and recommendations. Our findings underline a need for stronger focus on responsible prescribing, timely detection and prevention of medication misuse and dependence, with special attention towards older patients, those with enhanced pain, polypharmacy and/or concurrent use of several CNSDs.

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Authors' contributions

CL conceptualized, designed and led the study. SC, ESK and CL drafted the study protocol. SC customized the protocol, recruited participants, collected and analyzed data, and drafted this manuscript. TGS was involved in the recruitment and data collection process. MG contributed to the study conception and design. All authors took part in project planning and were involved in the refinement and approval of the final version of this manuscript.

Competing interests

In addition to the funding given above, Dr. Lundqvist reports having received research grants from the South-East Regional Health authority, during the conduct of the study as well as grants and personal fees from Abbvie pharma AS and Roche Norway AS, outside this submitted work. These funders have no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. Other authors declared no conflicts of interest.

Patient consent for publication

Not required.

Ethics

Ethical approval was obtained from the Regional Committee for Medical Research Ethics – South East Norway (Reference number: 2016/2289/REK sør-øst) and the Data Protection Office at Akershus University Hospital (Reference number: 17-054). All participants provided written informed consents. Data handling was done accordingly.

Data sharing statement

The datasets analyzed during this study are not publicly available due to threats to subject privacy but are available from the corresponding author on reasonable request.

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Figure legends

Figure 1. Flow of participants through the study

Table 1. Patient characteristics

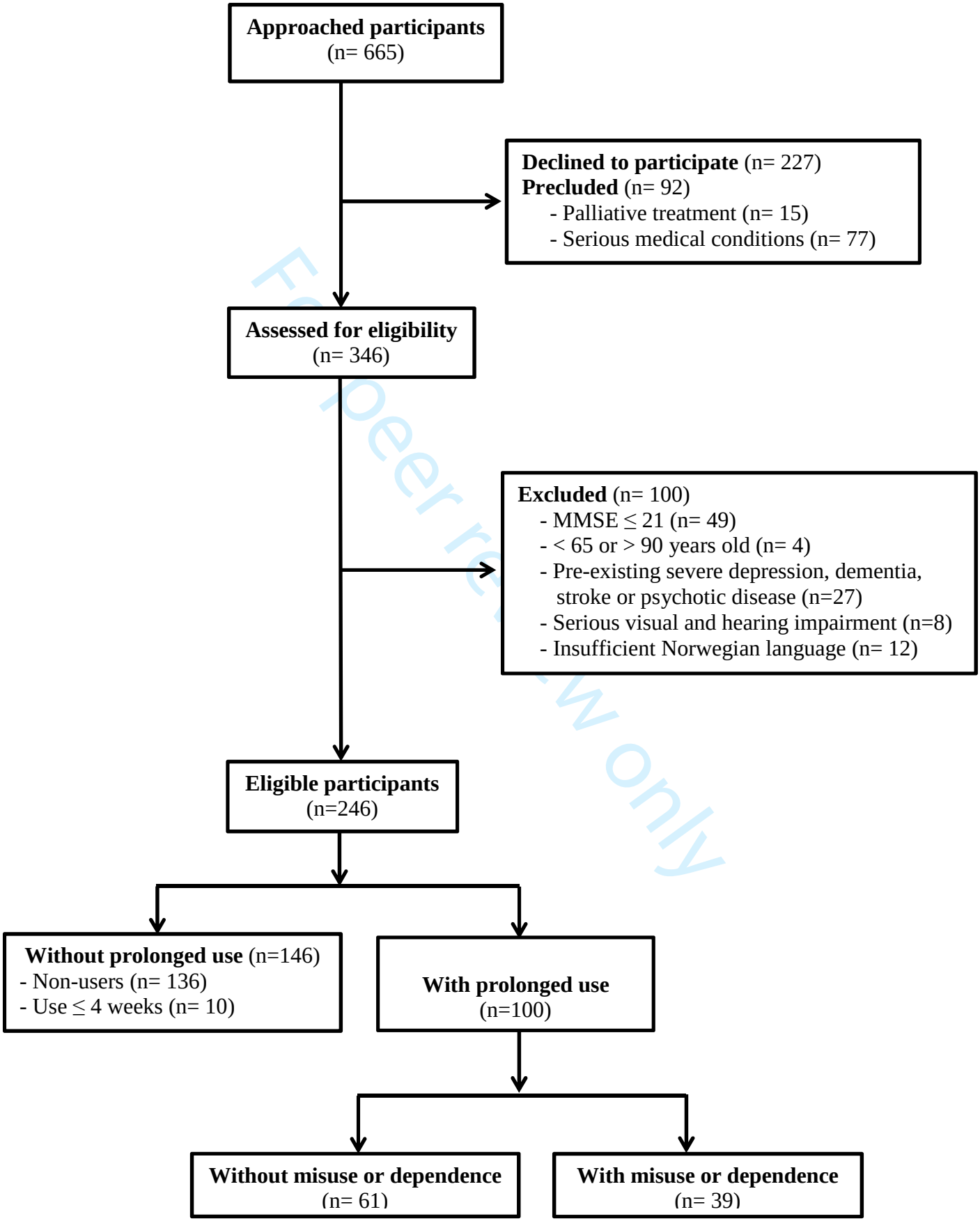
Table 2. Logistic regression models for factors associated with prolonged use of CNSDs – estimated using multiple imputations

Table 3. Logistic regression models for factors associated with CNSD misuse or dependence – estimated using multiple imputations

Additional file 1. Questionnaire and interview guide

Additional file 2. Sensitivity analyses

Figure 1. Flow of participants through the study



SOCIODEMOGRAPHIC BACKGROUND

1. **Sex**

☐ Male

☐ Female

2. **The year you were born:** …….

3. **Your highest education level:**

☐ Basic education

☐ Secondary education

☐ College or university (number of years:……..)

4. **Your annual income (NOK per year)**

☐ < 200 000

☐ 200 000–349 000

☐ ≥ 350 0000

5. **Do you live alone?**

☐ No

☐ Yes

THE HOSPITAL ANXIETY AND DEPRESSION SCALE

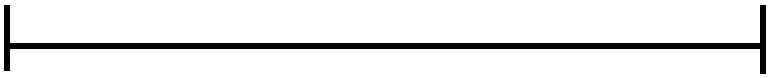
1. I feel tense or 'wound up':	**2. I still enjoy the things I used to enjoy**
3 ☐ Most of the time	**0** ☐ Definitely as much
2 ☐ A lot of the time	**1** ☐ Not quite so much
1 ☐ From time to time, occasionally	**2** ☐ Only a little
0 ☐ Not at all	**3** ☐ Hardly at all
3. I get a sort of frightened feeling as if something awful is about to happen:	**4. I can laugh and see the funny side of things:**
3 ☐ Very definitely and quite badly	**0** ☐ As much as I always could
2 ☐ Yes , but not too badly	**1** ☐ Not quite so much now
1 ☐ A little, but it doesn't worry me	**2** ☐ Definitely not so much no
0 ☐ Not at all	**3** ☐ Not at all
5. Worrying thoughts go through my mind:	**6. I feel cheerful:**
3 ☐ A great deal of the time	**3** ☐ Not at all
2 ☐ A lot of the time	**2** ☐ Not often
1 ☐ From time to time but not too often	**1** ☐ Sometimes
0 ☐ Only occasionally	**0** ☐ Most of the time
7. I can sit at ease and feel relaxed:	**8. I feel as if I have slowed down:**
0 ☐ Definitely	**3** ☐ Nearly all the time
1 ☐ Usually	**2** ☐ Very often
2 ☐ Not often	**1** ☐ Sometimes
3 ☐ Not at all	**0** ☐ Not at all
9. I get a sort of frightened feeling like 'butterflies' in the stomach:	**10. I have lost interest in my appearance:**
0 ☐ Not at all	**3** ☐ Definitely
1 ☐ Occasionally	**2** ☐ I don't take so much care as I should
2 ☐ Quite often	**1** ☐ I may not take quite as much care
3 ☐ Very often	**0** ☐ I take just as much care as ever
11. I feel restless as if I have to be on the move:	**12. I look forward with enjoyment to things:**
3 ☐ Very much indeed	**0** ☐ As much as ever I did
2 ☐ Quite a lot	**1** ☐ Rather less than I used to
1 ☐ Not very much	**2** ☐ Definitely less than I used to
0 ☐ Not a t all	**3** ☐ Hardly at all
13. I get sudden feelings of panic:	**14. I can enjoy a good book or radio or TV programme:**
3 ☐ Very often indeed	**0** ☐Often
2 ☐ Quite often	**1** ☐ Sometimes
1 ☐ Not very often	**2** ☐ Not often
0 ☐ Not at all	**3** ☐ Very seldom

Total anxiety score:

Total depression score:

PAIN INTENSITY
(Visual analogue scale)

Please mark on the line to describe how much pain you are currently feeling:



No pain **Worst pain**

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

DSM-IV criteria, Version 6.0.0

PSYCHOACTIVE SUBSTANCE USE DISORDERS (NON-ALCOHOL)

➡ **MEANS: GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)**

Now I am going to show you/read to you a list of street drugs or medicines.

		➡	
J1	**Have you in the past 12 months ever taken** any of these drugs more than once to get high, to feel better, or to change your mood?	NO	YES

CIRCLE EACH DRUG TAKEN:

Stimulants: amphetamines, "speed", methamphetamine (crystal meth), “crank”, “rush”, Dexedrine, Ritalin, diet pills.

Cocaine: cocaine, snorting, IV, freebase, crack, "speedball".

Opiates: heroin, morphine, opium, methadone, codeine, OxyContin.

Hallucinogens: LSD ("acid"), mescaline, peyote, psilocybin, STP, "mushrooms", “ecstasy”, MDA, MDMA.

Phencyclidin: PCP ("Angel Dust", "PeaCe Pill", “Tranq”) or ketamin (”special K”).

Inhalants: glue, ethyl chloride, "rush", dinitrogen monoxide ("laughing gas"), amyl or butyl nitrate ("poppers").

Cannabis: marijuana, hashish ("hash"), THC, "reefer", "grass".

Anxiolytics: Valium, Vival, Stesolid, Xanor (alprazolam), Seconal, Librium, Ativan, Halcion, barbiturates, GHB, Rohypnol (“Roofies”).

Miscellaneous: steroids, nonprescription sleep or diet pills, cough syrup. Any others?

SPECIFY MOST USED DRUG(S): _____

WHICH SUBSTANCE(S)/MEDICATION(S) CAUSE THE MAJOR PROBLEMS? _____

J2 Considering your use of (name the drug / drug class selected), in the past 12 months:

a.	Have you found that you needed to use more (name of drug / drug class selected) to get the same effect that you did when you first started taking it?	NO	YES
b.	When you reduced or stopped using (name of drug / drug class selected), did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable, or depressed)? Did you use any drug(s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better?	NO	YES
	IF **YES** TO EITHER QUESTION, CODE **YES**.		
c.	Have you often found that when you used (name of drug / drug class selected),	NO	YES

you ended up taking more than you thought you would?

d. Have you tried to reduce or stop taking (name of drug / drug class selected), but failed? NO YES

e. On the days that you used (name of drug / drug class selected), did you spend substantial time (> 2 hours) in obtaining, using or in recovering from drug(s), or thinking about drug(s)? NO YES

f. Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use? NO YES

g. Have you continued to use (name of drug / drug class selected) even though it caused you health or mental problems? NO YES

ARE **3** OR MORE **J2** ANSWERS CODED **YES**?

SPECIFY DRUG(S): _____

NO	**YES**
SUBSTANCE DEPENDENCE	

J3 Considering your use of (name the drug / drug class selected), in the past 12 months:

a. Have you been intoxicated, high, or hungover from (name of drug / drug class selected) more than once, when you had other responsibilities at school, at work, or at home? Did this cause any problems? (CODE **YES** ONLY IF THIS CAUSED PROBLEMS.) NO YES

b. Have you been high or intoxicated from (name of drug / drug class selected) more than once, in any situation where you were physically at risk, (for example, driving a car, riding a motorbike, using machinery, boating, etc.)? NO YES

c. Did you have legal problems more than once, because of your drug use, for example, an arrest or disorderly conduct? NO YES

d. Did you continue to use (name of drug / drug class selected) even though it caused problems with your family or other people? NO YES

ARE **1** OR MORE **J3** ANSWERS CODED YES?

SPECIFY DRUG(S): _____

NO	**YES**
SUBSTANCE ABUSE	
CURRENT	

ADDITIONAL QUESTIONS TO CONFIRM MEDICATION USE PATTERNS

1. How long have you been using this medication?

2. How many days per week do you need to take the medication (on average)?

3. Do you need to take it every day?

   If yes, ask: for how long the patient has used the medication every day?

4. Have there been periods that you have not used the medication at all?

Sensitivity analysis for factor associated with prolonged use of CNSDs – Logistic regression models, estimated using complete case analysis

Independent variable	Bivariate		Multivariate	
	OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Sex				
Male	1		1	
Female	2.05 (1.21-3.47)	**0.007**	1.64 (0.77-3.50)	0.20
Age groups, years				
65-74	1		1	
75-84	2.25 (1.27-4.00)	**0.006**	2.31 (1.07-5.01)	**0.03**
≥ 85	3.91 (1.75-8.74)	**0.001**	3.52 (1.11-11.20)	**0.03**
Education, years				
Basic education (≤ 10)	1		1	
Secondary education (11-13)	0.26 (0.12-0.54)	**<0.001**	0.35 (0.13-0.97)	**0.04**
Higher education (≥ 14)	0.30 (0.14-0.64)	**0.002**	0.41 (0.15-1.14)	0.09
Income (NOK/year)				
< 200 000	1		1	
200 000 – 349 000	0.63 (0.24-1.68)	0.36	0.48 (0.14-1.67)	0.25
≥ 350 000	0.25 (0.09-0.66)	**0.005**	0.18 (0.05-0.69)	**0.01**
Living alone				
No	1		1	
Yes	1.80 (1.08-3.01)	**0.03**	0.56 (0.25-1.27)	0.17
Polypharmacy (≥ 5 drugs/day)				
No	1		1	
Yes	6.95 (3.13-15.41)	**<0.001**	4.64 (1.73-12.48)	**0.002**
Anxiety scores (HADS-A)	1.07 (0.99-1.15)	0.08	1.04 (0.92-1.17)	0.54
Depression scores (HADS-D)	1.15 (1.06-1.26)	**0.001**	1.08 (0.95-1.23)	0.23
Pain intensity (millimeters on VAS scale)	1.02 (1.01-1.03)	**<0.001**	1.03 (1.01-1.04)	**<0.001**

Abbreviations:
CNSD – central nervous system depressant drugs
HADS–D/A – hospital anxiety and depression scale, depression or anxiety subscore.

Sensitivity analysis for factors associated with CNSD misuse or dependence – Logistic regression models, estimated using complete case analysis

Independent variable	Bivariate		Multivariate	
	OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Sex				
Male	1		1	
Female	1.54 (0.65-3.67)	0.33	1.50 (0.43-5.25)	0.52
Age, years				
65-74	1		1	
75-84	0.90 (0.34-2.37)	0.83	1.46 (0.36-5.96)	0.60
≥ 85	2.40 (0.75-7.65)	0.14	3.33 (0.55-20.16)	0.19
Education, years				
Basic education (≤10)	1		1	
Secondary education (11-13)	0.62 (0.22-1.77)	0.37	0.96 (0.20-4.60)	0.96
Higher education (≥14)	0.85 (0.31-2.32)	0.75	0.94 (0.22-3.99)	0.93
Income (NOK/year)				
< 200 000	1		1	
200 000 – 349 000	0.92 (0.27-3.21)	0.90	1.67 (0.28-9.95)	0.57
≥ 350 000	0.44 (0.11-1.73)	0.24	0.83 (0.10-6.94)	0.86
Living alone				
No	1		1	
Yes	2.65 (1.14-6.18)	**0.02**	2.24 (0.53-9.44)	0.27
Polypharmacy (≥ 5 drugs/day)				
No	1		1	
Yes	2.02 (0.39-10.55)	0.41	1.74 (0.14-21.22)	0.66
Concurrent use				
No (exclusive use)	1		1	
Yes	3.5 (1.44-8.54)	**0.006**	8.77 (2.19-35.10)	**0.002**
Duration of CNSD use (weeks)	1.00 (0.99-1.00)	0.94	1.00 (0.99-1.01)	0.11
Anxiety scores (HADS-A)	1.08(0.97-1.21)	0.15	1.01 (0.82-1.25)	0.94
Depression scores (HADS-D)	1.05 (0.93-1.19)	0.42	1.01 (0.81-1.27)	0.92
Pain intensity (millimeters, VAS scale)	1.01 (0.99-1.03)	0.08	1.03 (1.01-1.06)	**0.009**

Abbreviations:
CNSD – central nervous system depressant drugs
HADS–D/A – hospital anxiety and depression scale, depression or anxiety subscore.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	5-8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social)	9-10

		and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	8
Outcome data	15*	Report numbers of outcome events or summary measures	8-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.