Clinical Pain Research

Maria Torheim Bjelkarøy*, Socheat Cheng, Tahreem Ghazal Siddiqui, Jūratė Šaltytė Benth, Ramune Grambaite, Espen Saxhaug Kristoffersen and Christofer Lundqvist

The association between pain and central nervous system depressing medication among hospitalised Norwegian older adults

https://doi.org/10.1515/sjpain-2021-0120
Received July 7, 2021; accepted November 23, 2021;
published online December 16, 2021

Abstract

Objectives: Central nervous system depressant medications (CNSD) including benzodiazepines, z-hypnotics and opioids are regularly prescribed for the older patient. These medications are linked to dependence and associated with severe side effects in some older patients. Consensus recommendations for this group suggest limiting their use. We have recently described a high proportion of long-term CNSD use and dependence among older in-hospital patients. In this study, we aim to investigate factors associated with pain intensity and presentation of pain among older adults with long-term use of CNSDs compared to non-users.
Methods: Two hundred and forty six elderly hospitalised patients were recruited consecutively in a cross-sectional study. Data was collected from patients and electronic health records (EHR). Independent variables were sex, age, education, emotional symptoms (hospital anxiety and depression scale [HADS]), cognitive function (Mini-mental State Examination test [MMSE]), comorbidity (cumulative illness rating score – geriatrics [CIRS-G]), loneliness (the six-item De Jong Gierveld Loneliness Scale) and prolonged (≥4 weeks) use of any CNSDs or prolonged use of opioids (≥4 weeks). All variables, including pain intensity, were collected at one time point consistent with the cross-sectional study design. Statistical analyses included descriptive statistics and linear regression models using the above mentioned variables and pain intensity (visual analogue scale for pain intensity [VAS] pain 0–100) as outcome. Additional information regarding pain presentation was extracted from the patients' EHR.
Results: Mean pain intensity VAS (SD) was 35.2 (30.4) and 18.1 (24.2) respectively, for patients with vs. without prolonged use of CNSDs. In the multivariable linear regression analysis, prolonged use of CNSDs and opioids were positively associated with pain intensity (VAS) (regression coefficient (95% CI) 20.7 (11.0; 30.3), p<0.001, and 19.8 (5.7; 33.8), p=0.006, respectively), while sex, age, education, MMSE, HADS, CIRS-G and loneliness scores were not. Pain related to back (23.2%) and lower extremities (23.2%) were most common pain sites, and those with one or more pain sites reported overall higher pain intensity compared to those with no reported pain sites (p<0.006).
Conclusions: Prolonged use of CNSD medications as well as prolonged use of opioids are both positively associated with pain intensity. The results may have implications for treatment and long-term pain management for older patients.

Previous presentation of data: Abstract and e-poster presentation: *'Prolonged use of central nervous system depressant medication and cognitive function are associated with pain among older adults'*. 33rd ECNP Congress Virtual 12–15 September 2020. European College of Neuropsychopharmacology (ECNP) url: P.424 Prolonged use of central nervous system depressant medication and cognitive function are associated with experienced pain among older adults – ScienceDirect.

***Corresponding author: Maria Torheim Bjelkarøy**, Health Services Research Unit, Akershus University Hospital, 1478 Lørenskog, Norway; and Institute of Clinical Medicine, Campus Ahus, Faculty of Medicine, University of Oslo, Lorenskog, Norway, E-mail: matobj@ahus.no
Socheat Cheng, Tahreem Ghazal Siddiqui and Jūratė Šaltytė Benth, Health Services Research Unit, Akershus University Hospital, Lorenskog, Norway; and Institute of Clinical Medicine, Campus Ahus, Faculty of Medicine, University of Oslo, Lorenskog, Norway
Ramune Grambaite, Health Services Research Unit, Akershus University Hospital, Lorenskog, Norway; and Department of Psychology, Norwegian University of Science and Technology, Trondheim, Norway
Espen Saxhaug Kristoffersen, Institute of Clinical Medicine, Campus Ahus, Faculty of Medicine, University of Oslo, Lorenskog, Norway; and Department of General Practice, Institute of Health and Society, University of Oslo, Oslo, Norway
Christofer Lundqvist, Health Services Research Unit, Akershus University Hospital, Lorenskog, Norway; Institute of Clinical Medicine, Campus Ahus, Faculty of Medicine, University of Oslo, Lorenskog, Norway; and Department of Neurology, Akershus Univeristy Hospital, Lorenskog, Norway. https://orcid.org/0000-0002-2596-9876

Keywords: benzodiazepines; opioid-induced hyperalgesia; pain in older adults; prescription medication misuse; z-drugs; z-hypnotics.

Introduction

Older adults aged 65 and older are known to be at increased risk of experiencing pain [1]. The explanation of this may be multifaceted and linked to both age-related somatic comorbidity and psychosocial issues [2, 3]. Most common types of chronic pain in older adults are musculoskeletal pain followed by neuropathic pain [4]. Common sites of pain include unspecified joint pain, back pain and neck pain [4, 5]. Multiple pain sites are common amongst older adults and this has been found to be associated with worse function and pain severity [6]. Mild to moderate chronic pain is commonly treated with paracetamol and/or non-steroidal anti-inflammatory drugs (NSAIDs) whereas moderate to severe pain more often is treated with opioid analgesics [7, 8]. Older adults are more likely to receive prescriptions for pain medication [8]. Research has established an association between experiencing loneliness and pain in older adults [9]. A multimodal approach to management of chronic pain in older adults is recommended [10].

Central nervous system depressing medications (CNSDs) including benzodiazepines, z-hypnotics (zolpidem and zopiclone [zaleplon is not registered for use in Norway]) and opioids are used to treat anxiety, sleep disturbance and pain. CNSDs have been found to be associated with severe side effects as wells as tolerance, addiction, comorbidity and increased socio-economic costs [4, 11]. Although known to be effective and frequently used to treat acute to subacute symptoms, the CNSDs are not recommended for long-term use. Regular use of CNSDs among older adults may cause adverse reactions including falls, fractures and cognitive impairment, all of which contribute to considerable costs to the health care system [12–14]. Clinical guidelines such as the BEERS and NORGEP criteria have classified these medications as high-risk drugs that should be avoided for long-term use ≥4 weeks among older adults [15, 16].

We have previously in a cross-sectional study among hospitalised older adults, reported that 40% of the participants had prolonged (≥4 weeks) use of CNSDs [17]. Among patients having prolonged use, 39% were found to be dependent on their medication according to DSM-IV criteria for substance abuse. Factors associated with prolonged use included multimorbidity, polypharmacy, increasing age, reduced cognitive function, reduced health-related quality of life and higher levels of pain intensity [18–21]. Increased pain intensity was the sole factor associated with both prolonged use and dependence of CNSDs [18].

Not only is use of CNSDs associated with addiction and side effects. Use of opioids has been found to be associated with opioid-induced hyperalgesia where prolonged use causes neurological sensitisation of pain leading to further use and increasing dosage [22–25]. The relationship between prolonged use of CNSD medication or opioids and experienced pain may be bidirectional. We have previously found that patients with prolonged use of CNSDs had significantly higher pain intensity scores [18], and our aim in this study is to further explore this relationship. We aim to explore this relationship for CNSD use in general and opioid medication specifically. To add to this, we have described the characteristics of pain as it is presented in the electronic health records (EHR) in this hospital sample of older adults with and without prolonged use of CNSD medication.

Methods

Study design and setting

This cross-sectional study among hospitalised older adults was conducted at the Akershus University Hospital (Lørenskog, Norway) from May 2017 to September 2018. Patients were recruited consecutively from three somatic departments including geriatrics, general internal medicine and neurology. The catchment area of the hospital covers about 10% of the total population in Norway. All patients admitted to the hospital are admitted on the basis of the same inpatient threshold and all medical expenses are covered by the Norwegian national public health insurance. The study design has previously been thoroughly described [17–21, 26].

Study participants

Hospital-admitted older adults, 65–90 years of age, were invited to participate in the study on the basis of a set of pre-defined inclusion and exclusion criteria. Exclusion criteria were mini-mental state examination (MMSE) score ≤21 (to avoid inclusion of patients with possible reduced ability to consent), pre-existing diagnosis including moderate to severe depression, stroke, dementia, psychotic disorders, serious visual or hearing impairment and insufficient language skills to complete an interview and questionnaires in Norwegian. Patients receiving palliative treatment or having a serious condition affecting their ability to participate, were precluded from participating in the study.

Data collection

Data was collected by three study investigators (SC, TGS and CL) approaching the patients at study setting (from May 2017 to September

2018) and consisted of a three-step collection including self-conducted patient questionnaires, an investigator-patient interview consisting of special tests and finally data extraction from EHR. A secondary data collection was conducted by a blinded fourth investigator (MTB), between August 10th and September 2nd 2020. This data collection consisted of an additional extraction from the patient EHR from the time of the index hospital stay, and included gathering information regarding presentation of pain, types of non-opioid pain medication and level of activity. Data collection was single time point specific, consistent with the cross-sectional study design and could therefore not be used to ascertain direction of causality.

Measurements

Data collected covered sociodemographic information (sex, age, educational level and smoking) and clinical information (level of anxiety/depression, loneliness and pain as well as CNSD medication use, cumulative illness and assessment of cognitive function). The following instruments were used.

Mini-mental state examination (MMSE): MMSE is an 11-item assessment of cognitive function used to detect cognitive impairment. Test score ranges from 0 to 30, where a score of <25 indicates cognitive impairment [27].

Cumulative illness rating score – geriatrics (CIRS-G): CIRS for geriatric patients is a tool for rating comorbidity. It is a 56 point scale rating severity of chronic disease in major body organ systems. A higher total score reflect higher severity and burden of disease [28].

Hospital anxiety and depression scale (HADS): Hospital anxiety and depression scale (HADS) consists of 14-items each scored 0–3. It may be used as a total score or as two sub-dimensions; anxiety and depression. The score may vary from 0 to 21 where a higher score indicates increased severity of symptoms [29].

The six-item De Jong Gierveld Loneliness Scale: The six-item De Jong Gierveld Loneliness Scale is designed to measure overall emotional and social loneliness. It is scored between 0 and six where zero indicates no loneliness [30].

Visual analogue scale for pain intensity (VAS): VAS is a standardised tool used both in research and clinical practise where patients are asked to mark their level of pain intensity on a 100 mm unmarked line where one end of the line is marked with 'no pain' and the other marked with 'worst possible pain' [31].

Pain sites and type: The following variables on pain sites: head, neck, back, trunk, upper extremity, lower extremity and pain type: neuropathic nociceptive, somatic muscular-skeletal, nociceptive visceral were extracted from the EHR.

Medication use: Prolonged use of CNSD was defined as self-reported use ≥4 weeks. Information regarding CNSD use were collected directly from patient as well as from EHR. Use of other non-opiate pain medication including paracetamol, NSAIDs, cyclooxygenase-2 selective inhibitors (coxibs) and neuropathic pain medication (pregabalin, amitriptyline, gabapentin, duloxetine) were extracted from the EHR.

Level of physical activity: Information regarding level of physical activity was extracted from the EHR. Level of activity was graded as inactive (including unable to move without aid), moderate active (able to move, but preferred not to) and active (regularly active at own initiative).

Statistics

Demographic and clinical patient characteristics are presented as means and standard deviations (SDs) or frequencies and percentages for the whole group, and stratified by groups of users (≥4 weeks) and non-users of CNSD medication. Pearson χ^2-test for categorical variables and independent samples t-test or ANOVA for continuous variables were used to compare the groups. When required, Bonferroni correction was used for multiple comparisons. The associations between reported pain (VAS) and the pre-chosen covariates (sex, age, level of education, CIRS-G, HADS, MMSE, loneliness) were first assessed in a bivariate linear regression analyses. Further, two multivariable regression models were estimated. Model 1, the main model, included being a user/non-user of CNSD medication as main covariate. In model 2, the exploratory model, being a user/non-user of CNSD medication was substituted by being an opioid user alone. In a post hoc analysis, being a CNSD user was replaced by being a user of paracetamol. All regression models were estimated for patients without any missing values of covariates. Results were presented as regression coefficients and 95% confidence intervals (CIs). The assumptions for linear regression models were assessed by applying standard tests. All tests were two-sided and the results with $p<0.05$ were regarded as statistically significant. IBM SPSS Statistics version 26 was used for all statistical analysis.

Results

Participants

A total of 665 patients were approached for participation. Two-hundred and twenty-seven declined participation and 92 were precluded due to serious disease leaving a number of 346 patients that were assessed for eligibility. Of these, 246 patients met the inclusion criteria and were included in the study. The study population flow chart is presented in Figure 1. The mean age (SD) of the included patients was 77 (6.6) years and 137 (55.7%) of them were women. The basic characteristics of the population have previously been reported [18, 21] and are summarised in Table 1. Of the 246 included patients, 100 (40.7%) were found to have a prolonged use (≥4 weeks) of CNSD. Twenty-one (21%) of these were exclusively using opioids, 42 (42%) were exclusively using z-hypnotics and 7 (7%) patients were exclusively using benzodiazepines on a regular basis. Thirty percent of the CNSD users used two or more CNSDs concurrently. The most common opioid medication was per oral (PO) administered codeine with nine patients using this, followed by five patients using oxycodone hydrochloride (PO), four using

tramadol (PO) and three patients using buprenorphine (transdermal skin patch).

The patients who had a prolonged use of CNSD medication were more often female (p=0.007), older (p<0.001), had lower education (p=0.002), were more lonely (<0.001), had higher HADS score (p=0.003), lower cognitive function (p=0.015), higher comorbidity (p<0.001) and higher levels of pain (VAS) (p<0.001) than those patients that did not have prolonged use of CNSD medication (Table 1). This has been previously reported [18, 21].

Covariates associated with pain (VAS)

Among the variables included in the regression analysis, education was missing for 10 (4.1%), loneliness scale for 12 (4.9%), HADS for 17 (6.9%), MMSE for 31 (12.6%) and pain VAS for 18 (7.3%) patients. Excluding cases with missing variables, data on 192 patients were included in the regression analysis. Results from the bivariate linear regression as well as the two multivariable models are presented in Table 2.

In the bivariate models, higher score of HADS and increased comorbidity were found to be positively associated with pain (p=0.042 and p=0.023, respectively). Also, having prolonged use of CNSD medication and opioid medication alone was positively associated with pain (p<0.001 and p=0.004, respectively).

In the main multivariable linear regression model (model 1) prolonged use of CNSD medication was the only covariate positively associated with pain (p<0.001). In model 2 where prolonged opioid use was included as covariate instead of overall CNSD use, we found that prolonged opioid use (p=0.006) was the only covariate positively associated with pain.

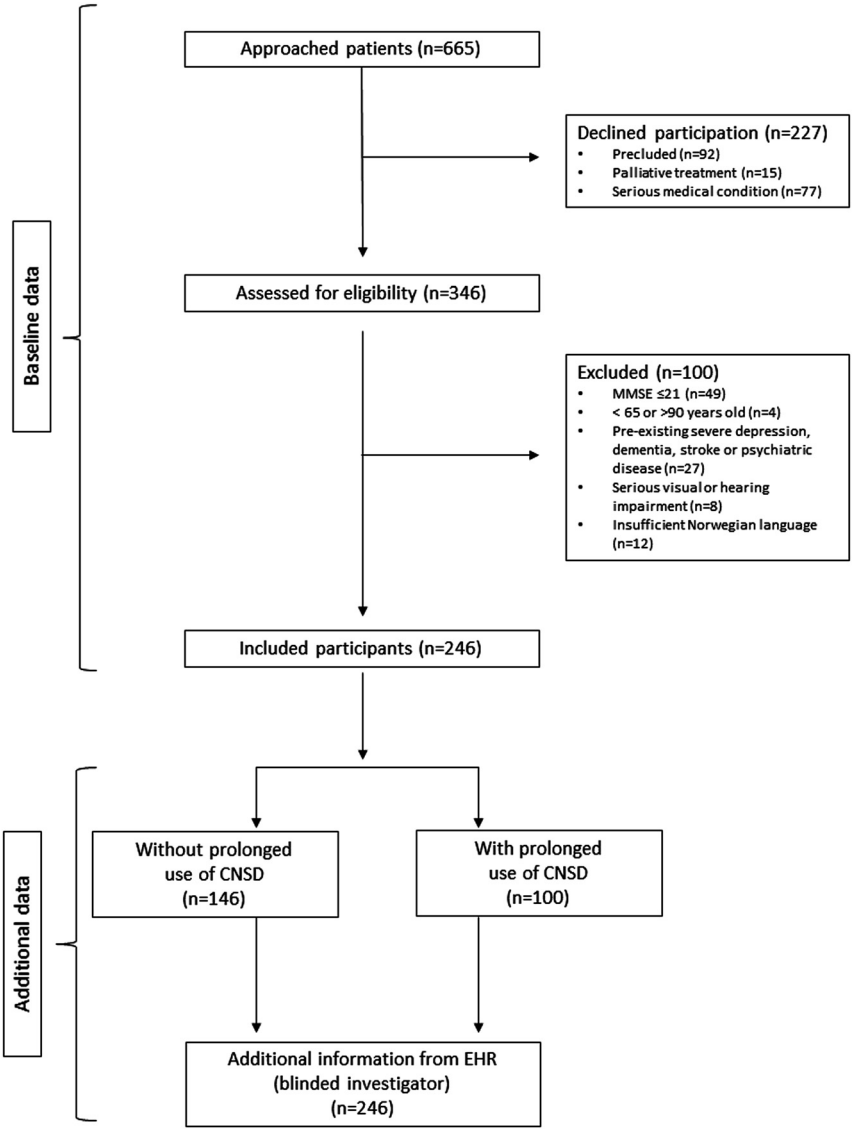

Figure 1: Study population flow chart
EHR, electronic health records.

Table 1: Demographic data for the study population and stratified groups for user and non-user of CSND medication (also previously reported [18, 21]).

Covariate (missing)	Total (n=246)	Non-user (n=146)	User (n=100)	p-Value
Sex, n (%)				
Female	137 (55.7)	71 (48.6)	66 (66.0)	0.007[a]
Age mean, SD	76.6 (6.6)	75.3 (6.4)	78.5 (6.5)	<0.001[b]
Education, years (10) (%)				
Basic ≤10	47 (19.9)	17 (12.2)	30 (30.9)	0.002[a]
Secondary 11–13	99 (41.9)	65 (46.8)	34 (35.1)	
Higher ≥14	90 (38.1)	57 (41.0)	33 (34.0)	
Smoking, (34) (%)				
Yes	31 (14.6)	16 (12.6)	15 (17.6)	0.308[a]
Loneliness mean, SD (12)	1.5 (1.6)	1.2 (1.5)	2.0 (1.8)	<0.001[b]
HADS total, SD (17)	8.7 (6.0)	7.7 (5.3)	10.1 (6.7)	0.003[b]
Anxiety score	4.5 (3.6)	4.1 (3.3)	5.0 (3.9)	0.082[b]
Depression score	4.2 (3.3)	3.6 (3.0)	5.1 (3.5)	<0.001[b]
MMSE mean, SD (31)	25.4 (2.7)	25.7 (2.7)	24.8 (2.6)	0.015[b]
CIRS-G mean, SD	5.9 (2.8)	4.7 (2.1)	7.7 (2.7)	<0.001[b]
Opioid user, n (%)	21 (8.5)	0	21 (21.0)	<0.001[a]
Outcome				
Pain VAS mean, SD (18)	25.0 (28.1)	18.1 (24.2)	35.2 (30.4)	<0.001[b]
Pain VAS median, min; max	10.5 (0.0; 97.0)	7.0 (0.0; 91.0)	29.5 (0.0; 97.0)	

[a]χ^2-test. [b]Independent samples t-test. CIRS-G, cumulative illness rating score – geriatrics; HADS, hospital anxiety depression scale; MMSE, mini-mental state examination; Pain VAS, visual analogue scale for pain intensity.

In a post hoc multivariable regression model, we found that paracetamol use was the sole covariate significantly positively associated with pain VAS (regression coefficient (95% CI) 17.1 (8.3; 25.9), p<0.001).

Secondary descriptive data

Pain patterns

Additional data regarding pain extracted from the EHR of the 246 patients showed that the most common sites of pain was back pain, lower extremity pain and headache. Fifty-seven (23.2%) patients suffered from back pain, 57 (23.2%) had pain in the lower extremities (hip, knee, legs) and 41 (16.6%) patients suffered from headache. Comparing experienced pain between single pain sites, there was overall no significant difference between the pain sites (Figure 2).

The dominating types of pain documented in the EHR were pain associated with musculoskeletal issues such as arthrosis and myalgia in 54 (21.8%) patients and neuropathic pain in 16 (6.5%). Paracetamol was the most commonly used non-opioid pain medication with 70 (28.2%) users followed by 21 (8.2%) patients using neuropathic pain medication and 12 (4.9%) patients using NSAIDs. Among patients using pain medication, three patients using opioids (14.3%) and 22 (31.4%) patients using paracetamol did not have any recordings regarding experiencing pain in their EHR.

Table 2: Results of bivariate and multivariate linear regression (n=196).

Covariate	Bivariate Reg. coef. (95% CI)	(p-Value)	Model 1 Multivariable Reg. coef. (95% CI)	(p-Value)	Model 2 Multivariable Reg. coef. (95% CI)	(p-Value)
Sex						
Women	5.3 (−2.9; 13.5)	(0.203)	4.4 (−3.6; 12.4)	(0.279)	5.9 (−2.2; 14.1)	(0.154)
Age	−0.003 (−0.6; 0.6)	(0.992)	−0.2 (−0.9; 0.4)	(0.476)	−0.09 (−0.7; 0.6)	(0.789)
Education						
Cat1 primary	−4.0 (−15.7; 7.7)	(0.501)	−8.4 (−19.8; 3.0)	(0.147)	−5.4 (−17.0; 6.2)	(0.361)
Cat2 secondary(ref)						
Cat3 higher	−3.5 (−12.5; 5.5)	(0.443)	−5.2 (−14.0; 3.4)	(0.233)	−5.0 (−13.9; 3.9)	(0.266)
CIRS-G	1.7 (0.2; 3.2)	**(0.023)**	−0.04 (−1.7; 1.7)	(0.964)	1.3 (−0.3; 2.8)	(0.114)
HADS	0.7 (0.02; 1.3)	**(0.042)**	0.3 (−0.4; 1.0)	(0.397)	0.6 (−0.1; 1.3)	(0.114)
MMSE	0.7 (−0.8; 2.3)	(0.351)	1.0 (−0.6; 2.6)	(0.215)	0.9 (−0.7; 2.5)	(0.265)
Loneliness	2.1 (−0.4; 4.6)	(0.094)	0.2 (−2.4; 2.9)	(0.874)	1.04 (−1.7; 3.8)	(0.446)
CNSD use	20.1 (12.3; 28.0)	**(<0.001)**	20.7 (11.0;30.3)	**(<0.001)**		
Opioid use	20.1 (6.4; 33.8)	**(0.004)**			19.8 (5.7; 33.8)	**(0.006)**

CIRS-G, cumulative illness rating score – geriatrics; HADS, hospital anxiety depression scale; MMSE, mini-mental state examination. Bold values shows p-values that are statistically significant.

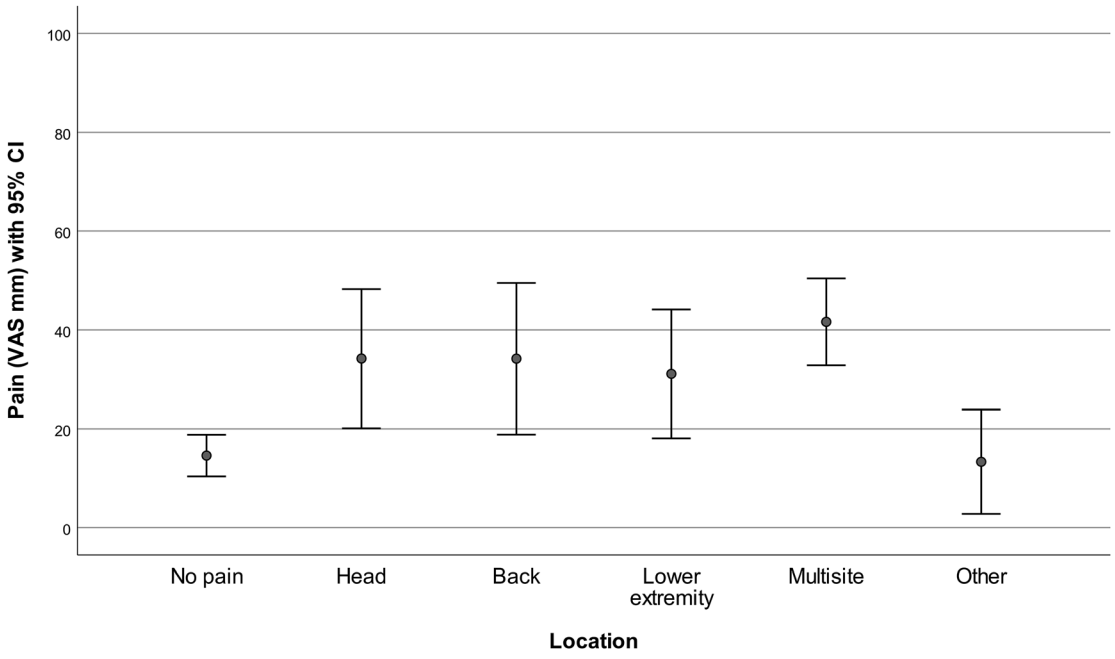

Figure 2: Mean pain VAS between unique pain sites.

Comparing information on pain (VAS) collected at baseline, 111 (45.1%) did not have any information in the EHR regarding pain and among these (excluding 11 missing) the reported mean pain VAS (SD) was 14.5 (21.5). Eighty-two (33.3%) patients had one pain location with mean pain VAS 27.7 (28.3) (five missing), 37 (15.0%) patients had two pain locations with mean pain 42.8 (31.0) (one missing) and 16 (6.5%) patients had three or more pain locations with mean pain VAS 38.5 (28.0) (two missing) (Figure 3). There was an overall significant difference in mean VAS score when stratified by number of reported pain sites ($p<0.001$). Post hoc tests identified significantly higher pain VAS in patients with 1–3 sites of pain compared to those where no pain site was reported ($p=0.006$, $p<0.001$ and $p=0.006$, respectively).

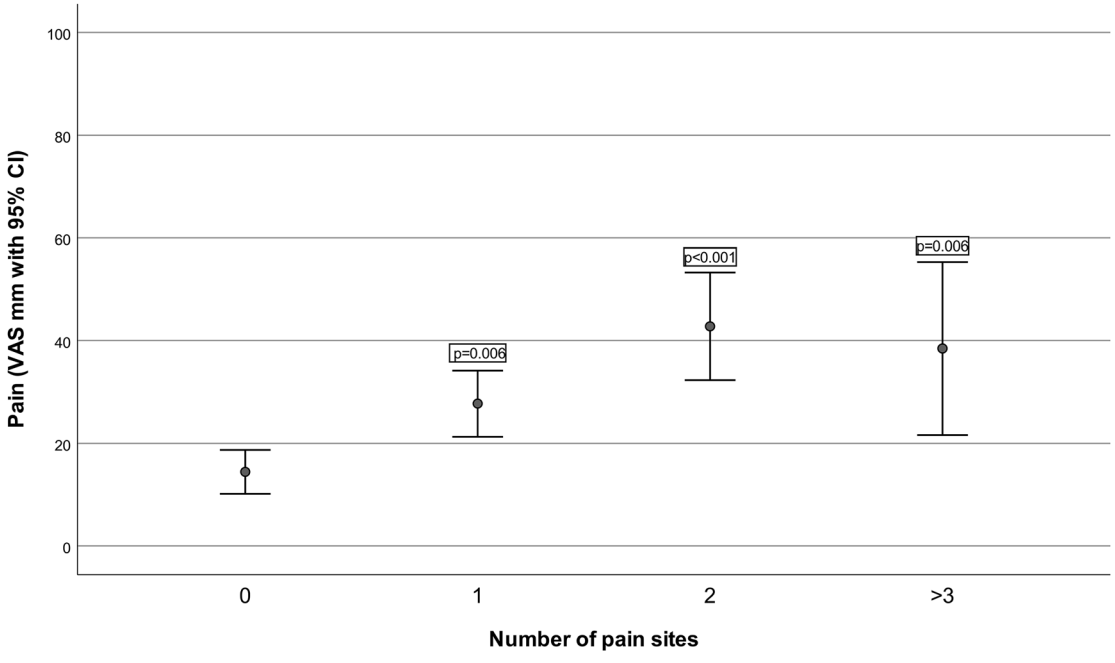

Figure 3: Mean pain VAS vs. number of pain sites.
p-value: ANOVA between-groups difference.

Pain in CNSD users vs. CNSD non-users

Comparing with the non-users (Table 3) the CNSD users used significantly more paracetamol and neurogenic medication (p=0.001 and p=0.038, respectively). Patients that were using paracetamol and were CNSD users had a significantly higher pain VAS (p=0.026) than those that were not CNSD users.

The proportion of patients having musculoskeletal pain was significantly higher in the CNSD user group (p=0.012) and these patients had significantly higher levels of pain (p=0.013). The proportion of patients with an active lifestyle was significantly higher among the non CNSD users compared to the CNSD user group (p<0.001). The distribution of pain sites stratified by CNSD users and non-users is described in Table 3.

Discussion

In this study among hospitalised older adults, we found that having prolonged (≥4 weeks) CNSD use or opioid pain medication use were the sole variables positively associated with experiencing pain. Further, we found that musculoskeletal pain related to back, hip, knees and legs were the most common pain presentation and that those that had multiple pain sites reported overall more pain intensity. The most common non-opioid pain medication was paracetamol and the most common opioid pain medication was codeine-based per oral medication.

Interpretation; association between pain experience and CNSD use

Epidemiological studies of pain presentation in older adults have found that being female and older, having a lower educational level, being lonely, having anxiety and depression, having reduced cognitive function and higher levels of comorbidity are all known factors associated with experiencing increased levels of pain [2, 3, 32–35]. In our cohort of hospitalised older adults these factors were also significantly associated with prolonged use of CNSDs. Regardless of this, the multivariable analysis found that the only variable positively associated with pain intensity was prolonged use of CNSD medication and opioid medication specifically.

CNSD medications are known to have addictive properties causing withdrawal symptoms and tolerance [36]. Prolonged use may lead to an increase in symptoms

Table 3: Patterns of pain, activity level and non-opioid pain medication in CNSD users and non-users.

Medication	CNSD user (n=100) n, %	CNSD non-user (n=146) n, %	p-Value[a]	Mean VAS (SD) within group[d]	CNSD user pain VAS, SD	CNSD non-user pain VAS, SD	p-Value[b]
Paracetamol	40 (40)	30 (20.5)	**0.001**	39.0 (30.8)	46.3 (29.6)	29.4 (30.1)	**0.026**
NSAIDs	4 (4)	8 (5.5)	n.s.	47.2 (36.0)	65.6 (29.2)	37.9 (37.0)	n.s.
Neurogenic medication[e]	13 (13)	8 (5.5)	**0.038**	42.8 (32.2)	40.2 (34.7)	47.7 28.9)	n.s.
Pain site[c]							
Head	15 (15)	19 (13)	n.s.	34.3 (30.4)	38.9 (29.1)	30.8 (31.7)	n.s.
Migraine	4 (4)	3 (2.1)	n.s.	27.3 (35.0)	47.7 (41.2)	7.0 (11.3)	n.s.
Neck	6 (6)	9 (6.2)	n.s.	36.5 (33.8)	47.6 (33.0)	28.5 (34.5)	n.s.
Back	28 (28)	29 (19.9)	n.s.	42.6 (30.6)	47.3 (32.1)	37.7 (28.7)	n.s.
Trunk	6 (6)	15 (10.3)	n.s.	19.7 (23.7)	38.7 (27.6)	11.5 (17.0)	n.s.
Over extremity	7 (7)	10 (6.8)	n.s.	32.8 (25.2)	33.4 (21.6)	32.3 (29.0)	n.s.
Under extremity	28 (28)	29 (19.9)	n.s.	40.4 (30.2)	45.8 (30.0)	35.3 (30.4)	n.s.
Pain type							
Musculoskeletal	30 (30)	24 (16.4)	**0.012**	34.8 (30.5)	43.8 (30.5)	23.0 (26.7)	**0.013**
Neurogenic	7 (7)	9 (6.2)	n.s.	58.6 (23.4)	57.0 (30.0)	59.8 (18.5)	n.s.
Activity level							
Active	6 (6)	44 (30.1)	**<0.001**	21.6 (20.8)	65.8 (7.8)	16.5 (24.8)	n.s.
Moderate	32 (32)	41 (28.1)	n.s.	25.2 (26.6)	35.7 (28.5)	16.0 (21.2)	n.s.
Inactive	50 (50)	34 (23.3)	n.s.	26.9 (29.5)	32.5 (31.0)	18.8 (25.6)	n.s.
No info	12 (12)	27 (18.5)	n.s.	25.2 (28.6)	30.0 (34.5)	23.1 (26.3)	n.s.

[a]χ^2-tests. [b]Independent samples t-test. [c]Pain sites are non-exclusive and may overlap (patients having more than one site). [d]When variable is present. [e]Neurogenic medication included when used in pain management: amitriptyline, pregabalin, gabapentin, duloxetine. n.s., means not significant, significant p-values are shown.

associated with experiencing pain such as symptoms of anxiety and depression including pain itself through modulation of the nervous system. Severe pain may drive analgesic use. However, prolonged use of opioid medication particularly has also been suggested to cause opioid-induced hyperalgesia leading to an experience of increased, widespread pain [37–39]. It is therefore important to consider whether experiencing increased levels of pain, in some cases, may be a consequence of prolonged CNSD use and that the use itself perpetuate the patients' pain issues instead of managing them. A large Norwegian study investigating analgesic use and pain sensitivity, has in fact found that use of pain medication in general was associated with increased pain sensitivity [40]. There is little research on the presence of opioid-induced hyperalgesia in older adults using opioids and this association needs to be further investigated. Nonetheless, in our cross-sectional design we have not investigated causality and it is reasonable to suggest that the result of our analysis may simply reflect that patients with pain use pain medication. This may resonate with the post hoc analysis showing that being a paracetamol user was also positively associated with experiencing pain. Considering clinical guidelines recommending older adults to avoid use of CNSDs over a prolonged period of time [15, 16], further research is needed with regards to use of CNSDs and opioids especially for long-term management of pain in older adults.

On a general note on the observed non-opioid medication and CNSD use in this study, we noted that overall 4.9% patients in the cohort were using NSAIDs. And in the CNSD-user group, 2.8% were exclusively using benzodiazepines on a regular basis. This might reflect the focus that has been set upon these two medication groups in recent decade. With NSAIDs being linked to severe vascular and gastrointestinal events in older adults [41] and benzodiazepines linked to increased mortality [42], the relatively low proportion of users may suggest that the medical care for this cohort is more in line with updated clinical guidelines for these two medication groups. Regardless of this, further focus on caution is needed for these medication groups when prescribed to the older adult. This is particularly so for use of NSAIDs which also have over-the-counter availability. NSAIDs should only be used for the shortest duration possible and with careful surveillance with particular focus on polypharmacy and drug interaction [43, 44].

Information regarding pain and pain medication use in the EHR

In this study we used a combination of information collected directly from the participants and information collected from the EHR pertaining the index stay. We were interested in learning more about the presentation of pain in this population based also on how this was reported in the EHR. Approximately one third of patients using paracetamol (22 of 70) and three out of 21 patients using opioids on a regular basis did not have recordings regarding the pain they were medicated for in the EHR. This is a notable observation considering an episode of hospitalisation as a good opportunity to review prescriptions according to STOPP/START criteria in older adults [45].

We found that the most common type of pain in the study population was pain associated with musculoskeletal problems and specifically pain sites including back, hip, knee and legs. Musculoskeletal low back pain issues are known to be the most common pain issue in the general population across all ages [46]. Adding hip and knee pain issues which is found to commonly occur in the older adult, our sample of hospitalised older adults appeared to reflect the general population when it comes to presentation of pain [4, 5].

Multisite pain and pain per site between CNSD users and non-users

Multiple pain sites have been suggested to be associated with worse function and pain severity in older adults [6]. As expected, there was a significantly higher pain intensity (VAS) in patients that had one or more pain sites compared to those that had none. Further, in patients with more than one pain site we observed an increase in mean VAS. We could not find any difference in reported pain according to pain sites between the CNSD user and non-user group, however. Due to low numbers it is difficult to draw any conclusions from this.

Level of physical activity

There were significantly more people described as active among those that did not use any CNSDs. Further, there were significantly more patients suffering from musculoskeletal pain issues among the CNSD users, and pain intensity (VAS) was significantly higher among the patients that were CNSD users and had musculoskeletal pain. From this one may query whether the patients in the CNSD user group had more pain issues than those in the non-user group and therefore were less active. This may also suggest that the patients in the non-user group were generally more active as a lifestyle habit. Research has found that activity may reduce the experience of pain [47, 48]. Here again it is difficult to discern whether pain has led to inactivity among

these older adults or being inactive has led to an increased experience of pain. Nevertheless, a multimodal approach to pain management needs to be considered for patients of all physical abilities as activity level and psychosocial factors is suggested as beneficial in pain management [47, 49, 50].

Strengths and limitations

The main strength of this study is that it addresses use of CNSD and opioid medication and pain experience among older adults. The study has however, some limitations. The main limitation is the cross-sectional design of the study with no follow-up making it difficult to discern a direction of causality. Further, the hospital-based sample may not correctly reflect the general population. Recruitment was however, done by consecutively approaching patients as they were admitted to the hospital and without relations to health issues or medication use. The second data collection where data was obtained from the patient EHR (from August to September 2020) is informative regarding information that is registered in the patients EHR, but it would have been an advantage to also obtain the same information directly from the patients. Finally, when investigating the patterns of pain and comparing pain intensity in CNSD users and non-users, low numbers may have affected the power.

Conclusions

Prolonged use of CNSD medications and opioids is positively associated with experiencing pain. The dominating sites of pain among older patients were back pain, lower extremity pain and headache. The question of whether pain issues may cause prolonged use of CNSD medications or prolonged use of CNSD medications may cause higher levels of pain requires further investigation. Thorough recordings of pain experience in the EHR should be emphasised in patients using CNSD medications. In view of current clinical guidelines and risks involved with long-term use of CNSDs among older adults, further research on long-term pain management in the older adults is needed.

Acknowledgements: We are grateful for the support during data collection from department secretaries, occupational therapists, physiotherapists, care assistants, nurses and doctors in Geriatric, General Neurology, Internal Medicine and Stroke departments at Akershus University Hospital. We also recognise the extraordinary commitment of patients that participated in this study.

Research funding: This work was funded by the Norwegian Research Council (256431) and the Health Services Research Unit of the Akershus University Hospital. CL also received funding from the South Eastern Norway Regional health authority. MTB received funding from ELIB (Stiftelsen Et Liv i Bevegelse, Norway). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Author contribution: All authors have agreed to the entire content of this manuscript and approved its submission.

Competing interests: CL has participated on an advisory board and received payment for lectures arranged by Abbvie Pharma AS, Novartis AS, Lundbeck AS and Roche AS, Norway. He has also received research sponsorship from Abbvie Pharma. The other authors state no conflict of interest.

Informed consent: A written informed consent has been obtained from all individuals included in the study.

Ethical approval: The data collection and storage were approved by the Akershus University Hospital data protection officer and the Regional Committees for Medical and Health Research Ethics (2016/2289).

Trial registration: NCT03162081, 22 May 2017.

References

1. Akugizibwe R, Calderon-Larranaga A, Roso-Llorach A, Onder G, Marengoni A, Zucchelli A, et al. Multimorbidity patterns and unplanned hospitalisation in a cohort of older adults. J Clin Med 2020;9:4001.
2. Zimmer Z, Zajacova A, Grol-Prokopczyk H. Trends in pain prevalence among adults aged 50 and older across Europe, 2004 to 2015. J Aging Health 2020;32:1419–32.
3. Gibson SJ, Lussier D. Prevalence and relevance of pain in older persons. Pain Med 2012;13(2 Suppl):S23–6.
4. Domenichiello AF, Ramsden CE. The silent epidemic of chronic pain in older adults. Prog Neuro-Psychopharmacol Biol Psychiatry 2019;93:284–90.
5. Hartvigsen J, Christensen K. Pain in the back and neck are with us until the end: a nationwide interview-based survey of Danish 100-year-olds. Spine 2008;33:909–13.
6. Rundell SD, Patel KV, Krook MA, Heagerty PJ, Suri P, Friedly JL, et al. Multi-site pain is associated with long-term patient-reported outcomes in older adults with persistent back pain. Pain Med 2019;20:1898–906.
7. Enthoven WT, Scheele J, Bierma-Zeinstra SM, Bueving HJ, Bohnen AM, Peul WC, et al. Analgesic use in older adults with back pain: the BACE study. Pain Med 2014;15:1704–14.
8. Macfarlane GJ, Beasley M, Jones EA, Prescott GJ, Docking R, Keeley P, et al. The prevalence and management of low back pain across adulthood: results from a population-based cross-sectional study (the MUSICIAN study). Pain 2012;153:27–32.
9. Loeffler A, Steptoe A. Bidirectional longitudinal associations between loneliness and pain, and the role of inflammation. Pain 2021;162:930–7.

10. Reid MC, Eccleston C, Pillemer K. Management of chronic pain in older adults. BMJ 2015;350:h532.
11. Sakshaug S, Handal M, Hjellvik V, Berg C, Ripel A, Gustavsen I, et al. Long-term use of Z-hypnotics and Co-medication with benzodiazepines and opioids. Basic Clin Pharmacol Toxicol 2017; 120:292–8.
12. Parekh N, Ali K, Stevenson JM, Davies JG, Schiff R, Van der Cammen T, et al. Incidence and cost of medication harm in older adults following hospital discharge: a multicentre prospective study in the UK. Br J Clin Pharmacol 2018;84:1789–97.
13. Bakken MS, Engeland A, Engesaeter LB, Ranhoff AH, Hunskaar S, Ruths S. Risk of hip fracture among older people using anxiolytic and hypnotic drugs: a nationwide prospective cohort study. Eur J Clin Pharmacol 2014;70:873–80.
14. Glass J, Lanctot KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ 2005;331:1169.
15. Rognstad S, Brekke M, Fetveit A, Spigset O, Wyller TB, Straand J. The Norwegian General Practice (NORGEP) criteria for assessing potentially inappropriate prescriptions to elderly patients. A modified Delphi study. Scand J Prim Health Care 2009;27:153–9.
16. Berryman SN, Jennings J, Ragsdale S, Lofton T, Huff DC, Rooker JS. Beers criteria for potentially inappropriate medication use in older adults. Medsurg Nurs 2012;21:129–32.
17. Cheng S, Siddiqui TG, Gossop M, Kristoffersen ES, Lundqvist C. The Severity of Dependence Scale detects medication misuse and dependence among hospitalized older patients. BMC Geriatr 2019;19:174.
18. Cheng S, Siddiqui TG, Gossop M, Kristoffersen ES, Lundqvist C. Sociodemographic, clinical and pharmacological profiles of medication misuse and dependence in hospitalised older patients in Norway: a prospective cross-sectional study. BMJ Open 2019;9:e031483.
19. Cheng S, Siddiqui TG, Gossop M, Stavem K, Kristoffersen ES, Lundqvist C. Health-related quality of life in hospitalized older patients with versus without prolonged use of opioid analgesics, benzodiazepines, and z-hypnotics: a cross-sectional study. BMC Geriatr 2020;20:425.
20. Cheng S, Siddiqui TG, Gossop M, Wyller TB, Kristoffersen ES, Lundqvist C. The patterns and burden of multimorbidity in geriatric patients with prolonged use of addictive medications. Aging Clin Exp Res 2021;33:2857–64.
21. Siddiqui TG, Cheng S, Gossop M, Kristoffersen ES, Grambaite R, Lundqvist C. Association between prescribed central nervous system depressant drugs, comorbidity and cognition among hospitalised older patients: a cross-sectional study. BMJ Open 2020;10:e038432.
22. Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. Clin J Pain 2008;24:479–96.
23. Chu LF, Clark DJ, Angst MS. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: a preliminary prospective study. J Pain: Off J Am Pain Soc 2006;7: 43–8.
24. Chen L, Sein M, Vo T, Amhmed S, Zhang Y, Hilaire KS, et al. Clinical interpretation of opioid tolerance versus opioid-induced hyperalgesia. J Opioid Manag 2014;10:383–93.
25. Lavand'homme P, Steyaert A. Opioid-free anesthesia opioid side effects: tolerance and hyperalgesia. Best Pract Res Clin Anaesthesiol 2017;31:487–98.
26. Siddiqui TG, Cheng S, Mellingsaeter M, Grambaite R, Gulbrandsen P, Lundqvist C, et al. "What should I do when I get home?" treatment plan discussion at discharge between specialist physicians and older in-patients: mixed method study. BMC Health Serv Res 2020;20:1002.
27. Creavin ST, Wisniewski S, Noel-Storr AH, Trevelyan CM, Hampton T, Rayment D, et al. Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. Cochrane Database Syst Rev 2016;13:CD011145. PMID: 26760674.
28. Salvi F, Miller MD, Grilli A, Giorgi R, Towers AL, Morichi V, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926–31.
29. Helvik AS, Engedal K, Skancke RH, Selbaek G. A psychometric evaluation of the Hospital Anxiety and Depression Scale for the medically hospitalized elderly. Nord J Psychiatr 2011;65:338–44.
30. De Jong Gierveld J, Van Tilburg T. The De Jong Gierveld short scales for emotional and social loneliness: tested on data from 7 countries in the UN generations and gender surveys. Eur J Ageing 2010;7:121–30.
31. Herr KA, Spratt K, Mobily PR, Richardson G. Pain intensity assessment in older adults: use of experimental pain to compare psychometric properties and usability of selected pain scales with younger adults. Clin J Pain 2004;20:207–19.
32. Donovan NJ, Wu Q, Rentz DM, Sperling RA, Marshall GA, Glymour MM. Loneliness, depression and cognitive function in older U.S. adults. Int J Geriatr Psychiatr 2017;32:564–73.
33. Nicolson PJA, Williamson E, Morris A, Sanchez-Santos MT, Bruce J, Silman A, et al. Musculoskeletal pain and loneliness, social support and social engagement among older adults: analysis of the Oxford Pain, Activity and Lifestyle cohort. Muscoskel Care 2021;19:269–77.
34. IsHak WW, Wen RY, Naghdechi L, Vanle B, Dang J, Knosp M, et al. Pain and depression: a systematic review. Harv Rev Psychiatr 2018;26:352–63.
35. Whitlock EL, Diaz-Ramirez LG, Glymour MM, Boscardin WJ, Covinsky KE, Smith AK. Association between persistent pain and memory decline and dementia in a longitudinal cohort of elders. JAMA Intern Med 2017;177:1146–53.
36. Maree RD, Marcum ZA, Saghafi E, Weiner DK, Karp JF. A systematic review of opioid and benzodiazepine misuse in older adults. Am J Geriatr Psychiatr 2016;24:949–63.
37. Hay JL, White JM, Bochner F, Somogyi AA, Semple TJ, Rounsefell B. Hyperalgesia in opioid-managed chronic pain and opioid-dependent patients. J Pain: Off J Am Pain Soc 2009;10:316–22.
38. Roeckel LA, Le Coz GM, Gaveriaux-Ruff C, Simonin F. Opioid-induced hyperalgesia: cellular and molecular mechanisms. Neuroscience 2016;338:160–82.
39. Shurman J, Koob GF, Gutstein HB. Opioids, pain, the brain, and hyperkatifeia: a framework for the rational use of opioids for pain. Pain Med 2010;11:1092–8.
40. Samuelsen PJ, Nielsen CS, Wilsgaard T, Stubhaug A, Svendsen K, Eggen AE. Pain sensitivity and analgesic use among 10,486 adults: the Tromso study. BMC Pharmacol Toxicol 2017;18:45.
41. Coxib, traditional NTC, Bhala N, Emberson J, Merhi A, Abramson S, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013;382: 769–79.

42. Charlson F, Degenhardt L, McLaren J, Hall W, Lynskey M. A systematic review of research examining benzodiazepine-related mortality. Pharmacoepidemiol Drug Saf 2009;18: 93–103.
43. Wongrakpanich S, Wongrakpanich A, Melhado K, Rangaswami J. A comprehensive review of non-steroidal anti-inflammatory drug use in the elderly. Aging Dis 2018;9:143–50.
44. Loboz KK, Shenfield GM. Drug combinations and impaired renal function – the 'triple whammy. Br J Clin Pharmacol 2005;59: 239–43.
45. O'Mahony D. STOPP/START criteria for potentially inappropriate medications/potential prescribing omissions in older people: origin and progress. Expet Rev Clin Pharmacol 2020;13:15–22.
46. Hartvigsen J, Hancock MJ, Kongsted A, Louw Q, Ferreira ML, Genevay S, et al. What low back pain is and why we need to pay attention. Lancet 2018;391:2356–67.
47. Schwan J, Sclafani J, Tawfik VL. Chronic pain management in the elderly. Anesthesiol Clin 2019;37:547–60.
48. Naugle KM, Ohlman T, Naugle KE, Riley ZA, Keith NR. Physical activity behavior predicts endogenous pain modulation in older adults. Pain 2017;158:383–90.
49. Bicket MC, Mao J. Chronic pain in older adults. Anesthesiol Clin 2015;33:577–90.
50. Dentino A, Medina R, Steinberg E. Pain in the elderly: identification, evaluation, and management of older adults with pain complaints and pain-related symptoms. Prim Care 2017;44:519–28.