Investigating correlates of sedative load among people with chronic non-cancer pain and the association with drowsiness and ambulance use.

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Background

Polypharmacy is extensive in people with chronic non-cancer pain (CNCP) and many of these medications are associated with adverse effects, including sedation.

Unwanted sedation can decrease quality of life and independently, sedative medications and sedation have been associated with hospitalisation [1], particularly in relation to falls [2] and overdose [3].

RCTs on the efficacy on concurrent use of sedative medications report sedation either remains the same or increases in comparison to single medication use [4].

However, these trials do not necessarily reflect the complexity and combinations of medications used by patients within the community.

Sedative load (SL) Index

The cumulative effect of multiple sedative medications has previously been assessed using a number of indices among community samples of the elderly (≥65 years old).

The sedative load (SL) quantifies medications based on their potential to cause sedation, by rating medications according to the level of sedation the medication tends to cause (i.e. whether the action of the medication directly causes sedation or whether sedation is a common or rare adverse effect) [5,6].

Simular sedative indices have reported associations with falls and hospitalisation [7-10].

Aims

1. Measure and describe SL in the sample;
2. Assess whether SL is associated with self-reported drowsiness/fatigue;
3. Assess whether SL is associated with demographic factors, pain, physical health, sleep and anxiety and/or depression.
4. Assess the association of SL and ambulance use.

Methods

Participants were recruited form community pharmacies across Australia.

Eligible participants had current CNCP (pain lasting longer than 3 months) and had been prescribed a schedule 8 opioids for 6 weeks or longer.

This study examines 1166 participants where baseline telephone interview and medication diary data was available (77% of the sample).

Sedative Load Index

Medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification [11]. Using the SL index, medications were classified into 3 groups and had a corresponding sedative rating:

- Group 1- primary sedatives→ sedative rating of 2
- Group 2- medications with a sedating component and medications with sedation as a prominent adverse effect → sedative rating of 1;
- Group 3- medications with sedation as a potential adverse effect and medications with no known sedation → Sedative rating of 0.

The ratings for medications used in the past week were added together to create a total score.

Results

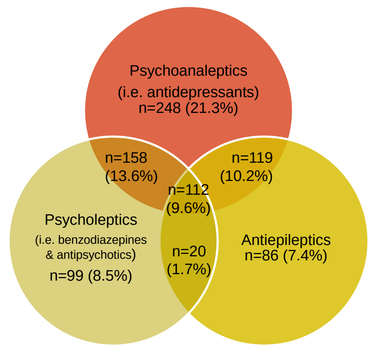
The mean SL for the group was 3.76 (S.D. 2.22) and ranged from 0-13 (Figure 5.0.1) and equates to a mean of 3.2 sedative medications and ranges from 0-10.

Almost half of the sample had taken a primary sedative (group 1; 46%, 95%CI= 42.7-48.4) Most (58%, 95%CI=55.0-60.7) of the sample had also used a non-opioid medication from group 2 (Table 1).

Table 1: Medications used in the last week according to the sedative load index

Sedative load index group	ATC Class	Frequency n (%)
Primary Sedatives- Group 1 (rating of 2)	N01 Anaesthetics	1 (0.1)
	N05 Psycholeptics (e.g. 1st generation antipsychotics, and benzodiazepines.)	354 (30.4)
	N06 Psychoanaleptics (Tricyclic antidepressants)	263 (22.6)
Drugs with sedation as a prominent adverse effect or preparations with a sedating component- Group 2 (rating of 1)	A03 Drugs for functional gastrointestinal disorders	71 (6.1)
	A04 Antiemetics and antinauseants	6 (0.5)
	C02 Antihypertensives	16 (1.4)
	M03 Muscle relaxant	22 (1.9)
	N02 Analgesic	1132 (97.1)
	N03 Antiepileptics	337 (28.9)
	N04 Anti-parkinson	26 (2.2)
	N05 Psycholeptics (e.g. 2nd generation antipsychotics)	74 (6.3)
	N06 Psychoanaleptic (other antidepressants)	432 (37.0)
	N07 Other nervous system drugs	5 (0.4)
	R03 Drugs for obstructive airway diseases	2 (0.2)
	R05 Cough and cold preparations	9 (0.8)

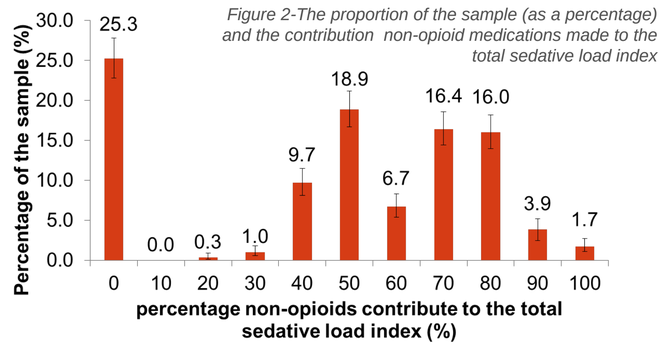
Figure 1- Non-opioid nervous system medication use combinations.



There were many combinations of medication use in the sample (Figure 1) with 10% of the sample taking at least 1 psychoanaleptic, psycholeptic and antiepileptic.

Non-opioid medications contributed on average 45% (S.D. 29.9%) of the SL scores. However, this vary considerably (Figure 2).

Figure 2-The proportion of the sample (as a percentage) and the contribution non-opioid medications made to the total sedative load index



SL was significantly associated with drowsiness and/or fatigue from current pain relievers even when controlling for sex, age and total oral morphine equivalence. However, only explained 3% of the variance in drowsiness and/or fatigue.

Table 2: Logistic regression analysis of the association between sedative load and level of drowsiness and fatigue.

	None to mild drowsiness or fatigue (n=792)	Moderate to severe drowsiness or fatigue (n=373)	Unadjusted OR (95%CI), p	Adjusted OR (95%CI), p
Age: mean (S.D.)	59.2 (13.7)	57.1 (13.0)	0.98 (0.98-1.00), p=0.011*	0.99 (0.99-1.00), p=0.235
Female: n (%)	457 (57.7)	210 (56.3)	1.06 (0.83-1.36), p=0.652	1.07 (0.83-1.39), p=0.582
Sedative load: mean (S.D.)	3.5 (2.1)	4.2 (2.3)	1.13 (1.07-1.20), p<0.001*	1.12 (1.05-1.18), p<0.001*
Total oral morphine equivalence (mg/day): median (I.Q.R.)	61.4 (101.9)	76.2 (122.5)	1.00 (1.00-1.00), p=0.010*	1.00 (1.00-1.00), p=0.203

* p<0.05

Notes: OR=Odds ratio, 95% CI= 95% confidence intervals. The multivariate model was statistically significant (χ^2=24.8, df=4, p<0.001) and explained 3.0% (Nagelkerke R^2) of the variance in drowsiness and fatigue. Linearity assumptions were met for all continuous variables.

The Difference is Research

Being female, younger, unemployed, having more severe pain, having anxiety and/or depression and a higher total oral morphine equivalent dose were associated with a higher SL (Table 3).

Table 3: Bivariate multiple regression analysis of demographic, physical, mental health, substance use and treatment-related behaviour characteristics associated with sedative load severity.

	Sedative load n=1166	
	Total	Unadjusted (B (SE), β, p)
Age: mean (S.D.)	58.5 (13.5)	-0.04 (0.01), -0.25, p<0.001*
Female: n (%)	668 (57.3)	-0.33 (0.13), -0.07, p<0.001*
Unemployed: n (%)	543 (46.6)	1.01 (0.13), 0.23, p=0.011*
BPI pain severity: mean (S.D.)	5.0 (1.8)	0.31 (0.04), 0.25, p<0.001*
Anxiety or depression (mod-severe): n (%)	541 (46.5)	1.06 (0.13), 0.23, p=0.001*
Total oral morphine equivalence (mg/day): median mg/day (I.Q.R.) ^	67.9 (112.3)	1.00 (0.00), 0.24, p<0.001*^

p<0.05, ^ regression used increments of 100mg/day.
Notes: B= unstandardized coefficient, β= standardised coefficient, SE= standard error.

In the bivariate analysis, SL was significantly associated with past month ambulance use (Table 4).

However, after controlling for demographics, physical and mental health comorbidities, SL was not associated with past month ambulance use.

Table 4: Sedative load, demographic, physical, mental health, substance use and medication characteristics associated with ambulance use.

	Ambulance use in the past month (n=1166)			
	No (n=1087)	Yes (n=77)	Unadjusted OR (95% CI), p	Adjusted OR (95% CI), p
Sedative load: mean (S.D.)	3.7 (2.2)	4.0 (2.8)	1.14 (1.03-1.25), p=0.008*	1.11 (1.00-1.23), p=0.054
Age: mean (S.D.)	58.5 (13.4)	59.0 (14.5)	1.00 (0.99-1.02), p=0.741	1.01 (1.00-1.03), p=0.355
Female: n (%)	624 (57.4)	43 (55.8)	1.07 (0.67-1.70), p=0.789	1.09 (0.67-1.76), p=0.740
Unemployed: n (%)	496 (45.6)	45 (58.4)	1.68 (1.05-2.68), p=0.031*	1.88 (1.08-3.27), p=0.026*
BPI pain severity: mean (S.D.)	5.00 (1.8)	5.26 (2.02)	1.09 (0.95-1.24), p=0.223	
No of physical health problems: median (I.Q.R.)	0.0 (1.0)	1.0 (3.0)	1.74 (1.45-2.08), p<0.001*	1.72 (1.43-2.08), p<0.001*
Anxiety or depression (mod-severe): n (%)	496 (45.6)	44 (57.1)	1.59 (0.99-2.53), p=0.053	
5+ drinks ≥monthly in last 12m: n (%)	121 (11.1)	6 (7.8)	0.67 (0.29-1.58), p=0.365	
Overdose last 12 m: n (%)	24 (2.2)	4 (5.2)	2.43(0.82-7.18), p=0.109	
Oral morphine equivalence (mg/day): median (I.Q.R.)	67.5 (110.0)	80.0 (138.8)	1.00 (1.00-1.00), p=0.096	

*** p<0.05**
Notes: OR=Odds ratio, 95% CI= 95% confidence intervals. The multivariate model was statistically significant (χ^2=43.3, df=5, p<0.001) and explained 9.5% (Nagelkerke R^2) of the variance in past month ambulance use. The model correctly classified 1.3% of ambulance use cases. Linearity assumptions were met for all continuous variables.

Conclusions

Non-opioids contributed to half of the SL index and many combinations of non-opioid nervous system sedative medications were used.

SL was higher than most previous studies in the elderly [5,6].

Sedative load associated increasingly complex health and demographic profiles.

SL was not associated with ambulance use when controlling for other factors including other physical health problems and this is not surprising considering the comorbidity in the sample and CNCP more widely.

The SL is just one approach to assessing outcomes related to polypharmacy in CNCP. Further research is needed to assess whether SL is associated with other medication related outcomes.

References

1. Nielsen S, *et al.* Pain Med. 2015.16(2):356-66.
2. Woolcott JC *et al.* Arch Intern Med, 2009. 69(21):1952-60.
3. Roxburgh A, *et al.* Med J Aust. 2011.195(5):280-4.
4. Chaparro LE, *et al.* Cochrane Database Syst Rev, 2012. 7(7).
5. Linjakumpu TA, *et al.* Int J Geriatr Psychiatry, 2003. 18(6):542-4.
6. Linjakumpu TA, *et al.* Ann Pharmacother, 2004. 38(12):2017-22.
7. Gnjidic, D, *et al.* PLoS One, 2014. 9(1):e8322
8. Nishtala, PS, *et al.* Pharmacoepidemiol Drug Saf, 2014.
9. Wilson, NM *et al.* J Am Geriatr Soc, 2011. 59(5):875-80.
10. Hanlon, *et al.* J Gerontol A Biol Sci Med Sci, 2009. 64(4):492-8.
11. Anatomical Therapeutic Chemical Classification and Defined daily dose Assignment 2013. http://www.whocc.no/atc_ddd_index/.

POINT
PAIN AND OPIOIDS IN TREATMENT