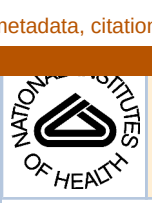

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Accounting for the Sedative and Analgesic Effects of Medication Changes During Patient Participation in Clinical Research Studies: Measurement Development and Application to a Sample of Institutionalized Geriatric Patients

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Abstract

Background: To date, no system has been published that allows investigators to adjust for the overall sedative and/or analgesic effects of medications, or changes in medications, in clinical trial participants for whom medication use cannot be controlled. This is common in clinical trials of behavioral and complementary/alternative therapies, and in research involving elderly or chronically ill patients for whom ongoing medical care continues during the trial. This paper describes the development, and illustrates the use, of a method we developed to address this issue, in which we generate single continuous variables to represent the daily sedative and analgesic loads of multiple medications.

Methods: Medications for 90 study participants in a clinical trial of a nonpharmacological intervention were abstracted from medication administration records across multiple treatment periods. An expert panel of three academic clinical pharmacists and a geriatrician met to develop a system by which each study medication could be assigned a sedative and analgesic effect rating.

Results: The two measures, when applied to data on 90 institutionalized persons with Alzheimer's disease, resulted in variables with moderately skewed distributions that are consistent with the clinical profile of analgesia and sedation use in long-term care populations. The average study participant received 1.89 analgesic medications per day and had a daily analgesic load of 2.96; the corresponding figures for sedation were 2.07 daily medications and an average daily load of 11.41.

Conclusions: A system of classifying the sedative and analgesic effects of non-study medications was created that divides drugs into categories based on the strength of their effects and assigns a

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rating to express overall sedative and analgesic effects. These variables may be useful in comparing patients and populations, and to control for drug effects in future studies.

Keywords

medication; sedative; analgesic; coding; long-term care

Introduction

Early studies of the efficacy and safety of treatments (phase 2 clinical trials) generally control for patient-related factors, such as non-study medications, by holding them constant during the study period. However, the majority of clinical research studies that involve longitudinal data collection -- including many phase 3 clinical trials and virtually all broader effectiveness studies (phase 4 trials; Type 2 translational research) -- are unable to hold all other patient treatments constant during a study period [1]. This problem occurs frequently in studies involving older persons, who often have multiple comorbid conditions, requiring multiple medications, for which treatment changes must occur even while enrolled in a clinical trial. This is also often the case in studies conducted in community settings, where patients may seek alternative medical treatments even while enrolled in a study. It is a particularly challenging issue when the outcome of interest is pain relief, sleep, or alertness, since many medications possess analgesic or sedative properties. Therefore, valid methods need to be available to control for changes in non-study medications that occur during data collection.

Since the 1970s, the World Health Organization (WHO) has developed, maintained, and updated a system that classifies drugs into categories, the anatomical therapeutic chemical (ATC) classification system [2]. Within that system, the relative potency of drugs is classified using the defined daily dose (DDD) however, this system does not classify the side effect potential of drugs, which often does not parallel the DDD. Therefore, an alternative method is needed to classify the sedative and analgesic effects of medications.

A few systems have been published that have attempted to classify sedative and analgesic drug effects. A method of classifying drugs based on their sedative properties was described by Linjakumpu, et al [3], who applied it to a descriptive study of home-dwelling older adults. That system divides all drugs into four categories: primary sedatives and psychotropics (Group 1), drugs with sedation as a prominent side effect or preparations with a sedating component (Group 2), drugs with sedation as a potential adverse effect (Group 3), and drugs with no known sedation (Group 4). The most prominent system for classifying relative analgesic potency is the WHO Analgesic Ladder [4], which is intended more as a broad set of principles than as a rigid framework. The three categories of the WHO Analgesic Ladder are: a non-opioid analgesic, with or without an adjuvant agent (step 1), an opioid for mild to moderate pain, often in combination with one or more step 1 medications (step 2), and an opioid for moderate to severe pain, with or without step 1 medications (step 3). No report has, however addressed how to use such a system in research, and, in particular, how to account for multiple medications in a single patient or medication changes over time.

Our research group has been involved in the analysis of data from several therapeutic trials of nonpharmacological agents in persons with Alzheimer's disease, in which the need arose to control for differences and changes in non-study medications that occurred during the study period. We were unable to find a suitable method in the literature, and, therefore, sought to develop and pilot test a classification system that would allow us to represent, as single continuous variables, the estimated total sedative effect and total analgesic load of all medications taken. In developing the system, we sought to: (a) accurately reflect the relative effect of each medication, and (b) allow patients with multiple medications to have the effects

summed. This paper describes the system we developed and illustrates its application, using data from a National Institutes of Health-funded clinical trial of the effect of high intensity light therapy on sleep, depression, and other behavioral symptoms in older persons residing in two geriatric care facilities.

Methods

Medications for all study participants were abstracted from the medication administration records for each data collection period. The following information was recorded on each medication received at least once during the data collection period: name, dosage received at each administration time, frequency of administration, start date, and stop date (if applicable). Both scheduled and "as needed" (i.e., pro re nata [PRN]) medications were recorded. A single pharmacist (JI) reviewed these records to ensure that medication names were spelled correctly and that different brand names corresponding to the same generic drug were recorded as the generic name.

Next, an expert panel of three academic clinical pharmacists (JI, MR, and MR) and a geriatrician (PS) met to develop a system in which each study medication could be assigned a sedative and analgesic effect rating. Each drug received by any participant in either study was reviewed to determine sedative and analgesic effects, to classify it, and to assign a "standard" dose. In categorizing drugs, determining relative effects, and assigning a standard dose to each medication, the expert panel relied on existing literature and their clinical experience.

Sedation ratings were assigned based on a modification of the sedation systematic classification method formulated by Linjakumpu and colleagues [3]. Drugs with sedation as a primary action or side effect were divided into four groups based on a modification of the Anatomical Therapeutic Chemical Classification system (ATC) [5]. Medications that were not specifically included in either of the above classification systems were given a sedation rating based on their pharmacological properties, indication, and therapeutic similarity to other drugs in the respective 4 groups. The groups were then assigned relative potency ratings, based on the team's consensus of the effects of one group vis-à-vis the other, and the cumulative effects of using multiple agents. The four groups are described below:

- Sedation group 1 consists of psychotropic agents whose primary effect is sedation. Medications in Group 1 were given a sedation potency rating of 6.
- Sedation group 2 includes drugs with sedation as a prominent side effect or preparations with a strong sedating component. Medications in Group 2 were assigned a sedation rating of 3.
- Sedation group 3 includes drugs with sedation as a potential adverse effect that can persist beyond initiation of the drug. Medications in group 3 were given a sedation rating of 1.
- Sedation group 4 consists of drugs with no known sedation. Medications in group 4 were given a sedation rating of 0.

Analgesic ratings were assigned using a modification of the WHO Analgesic Ladder [4], and the American Pain Society's principles of analgesia [6]. Based on these and other reference texts [7,4,6,8], all medications within the study were grouped as opioids for the treatment of moderate to severe pain, opioids for the treatment of mild to moderate pain, non-opioid analgesics, adjuvant (co-analgesic) medications, or nonanalgesic agents (drugs without analgesic or adjuvant properties). The groups were then assigned relative potency ratings, based on the team's consensus of the effects of one group vis-à-vis the other, and the cumulative effects of using multiple agents. Each group is described below:

- Opioids for the treatment of moderate to severe pain. Opioids (or medications with similar effectiveness) whose potency was equal to or greater than morphine on a milligram-to-milligram basis are in this category. Drugs in this category were assigned an analgesic potency rating of 9.
- Opioids for the treatment of mild to moderate pain. Opioids (or medications with similar effectiveness) whose common dosage range is less potent than that of morphine are in this category. Drugs in this category were assigned an analgesic potency rating of 6.
- Non-opioid analgesics. These are non-opioid medications that are used primarily for the treatment of pain. Drugs in this category were assigned an analgesic potency rating of 3.
- Adjuvant, or co-analgesic medications. These are drugs with independent analgesic properties in certain situations or the ability to enhance the effects of opioids or non-opioid analgesics. Drugs in this category were assigned an analgesic potency rating of 1.
- Nonanalgesic agents, or drugs without analgesic or adjuvant properties. These were assigned an analgesic potency rating of zero (0).

For all medications assigned a non-zero value for sedation and/or analgesia, resident medication records were further abstracted to produce a daily record of the amount received of each drug for each resident. For each resident for each day, the sedative load (SL_{ij}, for resident *i* on day *j*) was then computed according to the following formula:

$$SL_{ij} = \sum_{k=1}^{m} \frac{Dose_{ijk} \times SR_k}{ADMD_k}$$

where

- *m* is the number of sedative medications for resident *i* on day *j*

- $Dose_{ijk}$ is the quantity of medication *k* received by resident *i* on day *j* (in same units as $ADMD_k$)

- SR_k is the sedation rating (1, 3, 6) for sedating medication *k*

- $ADMD_k$ is the average daily maintenance dose for medication *k*

For residents not receiving any sedative medications on a given day, a value of 0 was assigned. The daily analgesic load for each resident (AL_{ij}) was computed in the same way, using the analgesic rating (1, 3, 6, 9) for each analgesic medicine (AR_k). For analyses in which the sedative and analgesic loads were needed at a higher level of summarization than the resident-day (e.g. for the resident-study period), then the daily load scores were averaged over the days in the period. This resulted in a single continuous variable for each study participant and each data collection period. This variable was then used in longitudinal analyses to control for changes in medications at the resident level across the data collection period.

To illustrate how this system was used in analysis of clinical trial data, we present data from our study of a light therapy intervention in two long-term care facilities. That study systematically altered the intensity and timing of lighting in public areas during a series of 3-week study periods, and effects on the sleep and activity pattern of study participants were evaluated. Details of the study design are published elsewhere [9]. Summary statistics for number of daily analgesic medications, daily analgesic load, number of daily sedative medications, and daily sedative load were computed. In order to account for the lack of independence among the multiple daily records for each resident, a two-step procedure was used to compute these summary statistics. First, a resident-level average was generated as the

mean across all observations (days) for a given resident. Second, summary statistics (mean, standard deviation, quantiles) were computed based on these resident-level means.

In order to assess the validity of the analgesic and sedative rating system, we compared the medication scores according to selected participant characteristics for which we might expect variation in use of these medications. These characteristics included site, gender, whether or not the participant had dementia, and if demented, the severity of dementia as rated by the Minimum Data Set Cognition Scale (MDS-COGS), a staff-rated measure of cognitive function [10]. Participants were also categorized with respect to level of agitation and daytime sleepiness during each three-week study period. Agitated behavior was measured using the short form of the Cohen-Mansfield Agitation Inventory [11], which was reported for each resident by caregiving staff on each shift for each study period. Daytime drowsiness was measured using direct observation by research staff, who conducted up to 48 randomly distributed one-minute observations of each participant during the last seven days of each study period, using a modification of the Resident and Staff Observation Instrument [12]; for each participant the proportion of observations for the given study period during which he or she was coded as asleep or drowsy was computed. For purposes of comparison of medication use, agitation scores and daytime drowsiness were dichotomized at the median.

Means of the medication measures were computed across all observations (days) overall, and according to the specified resident characteristics; the standard errors of the means were adjusted for the repeated measures on study participants using Taylor series expansion methods [13]. For the purposes of testing whether the medication measures differed significantly according to the selected participant characteristics, linear mixed models were used for each medication measure and each characteristic, specifying the medication measure as the dependent variable, the given participant characteristic as a single fixed effect and including a random effect for participant [14]. The results are displayed in Table 4.

Results

The study gathered data on 90 participants from two sites – a geropsychiatric hospital and a dementia-specific assisted living facility. The 90 study participants participated in a total of 432 three-week study periods, for a total of 9,072 daily records of sedative and analgesic loads.

A total of 60 different sedative medications and 46 analgesic medications were received by the 90 study participants (Tables 1 and 2). Among the sedative medications, lorazepam was the most commonly prescribed Group 1 drug; olanzapine and risperidone were the most commonly prescribed Group 2 drugs; and donepezil, atenolol, clonidine, levodopa, doxazosin, terazosin, and prazosin were the only prescribed group 3 drugs. Among the analgesic medications in our study data, morphine and methadone were the only prescribed opioids for moderate-to-severe pain, the most common opioid in the mild-to-moderate pain category was hydrocodone; the most common non-opioid analgesics were aspirin, acetaminophen, and ibuprofen; and the most common adjuvant or co-analgesic medications were lorazepam and sertraline.

Descriptive statistics on the analgesia and sedation summary variables are displayed in Table 3. The average study participant received 1.89 analgesic medications per day and had a daily analgesic load of 2.91; the corresponding figures for sedation were 2.07 daily medications and an average daily load of 11.49.

Table 4 displays the mean scores for the analgesic daily load and the sedative daily load, by site, participant gender, dementia status, agitation level, and daytime drowsiness. For comparison purposes, the mean number of analgesic or sedative medications is also displayed. Statistical comparisons indicate, that in these data, differences between all dichotomized

variables were statistically significant at p<.001, with the only exception being gender and sedative load.

Discussion

Classifying sedative and analgesic medications in a manner that allows investigators to compare individuals across time periods and across studies is a challenging issue in the design and analysis of clinical trials. This paper describes a method whereby, based on the existing literature on the comparative effects of medications and a consensus-development process involving three clinical pharmacists and a geriatrician, drugs were categorized in a manner that enabled a clinical trial to represent sedation and analgesia as single continuous variables. The two measures, when applied to data from a study of 90 institutionalized persons with Alzheimer's disease, resulted in variables with moderately skewed distributions (Table 3) that are consistent with the clinical profile of analgesia and sedation use in a long-term care population, and that yielded statistically significant associations in bivariate analyses using selected participant characteristics for which variation in medication use could be expected (Table 4).

Such a method will, if validated by further use, have several advantages. It will facilitate the comparison across studies of the amount of analgesia and sedation received by specific populations and samples. More importantly, it will for the first time allow investigators to incorporate the relative potencies of medications into a single continuous variable. Because its method is based on general principles, it can be used by other investigators with different patient populations and can accommodate changing trends in medication use.

There are, of course, limitations to this method. Assignment of drugs to categories, of relative potencies to each category, and the resultant summation formula are derived based on the literature and expert consensus, rather than on physiological studies. However, given the vast array of drugs currently marketed and the absence of head-to-head comparisons, this method was the only one available to the study team. Such a system does, of course result in some decisions that could be debated. In spite of these limitations, we believe that this method constitutes a considerable improvement over previous strategies used to accommodate for medication effects.

Further validation will be critical to determining the usefulness of this methodology and, if necessary, in making modifications. Among the validation approaches that could be considered in future studies include: confirmation of face validity through a more formal consensus process with a multidisciplinary panel; criterion validation of the absolute values assigned to categories or category combinations through comparison with, for example, self-ratings of pain or drowsiness by volunteers to whom various sample medications and medication combinations are administered; concurrent validation through comparison with caregiver self-report of sedation or analgesia; and convergent validation through use of the instrument in multiple studies.

In conclusion, we have developed, and successfully used in the analyses of clinical trial data, a method of classifying the sedative and analgesic effects of non-study medications. Our method divides all drugs into categories based on the relative strength of their effects and generates a continuous variable expressing sedation load and another expressing analgesic load. These variables can then be applied to describe and compare participants and populations, to compute change over time in longitudinal studies, and to control for drug effects in studies where drug effects could confound the primary relationship being studied.

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Table 1

Listing of all Sedative Medications Received by Study Participants, by Sedation Rating Category (N=90 participants; 9,072 participant-days)

Sedation Group	Sedation Rating	Medication Name	# of Study Participants Receiving at Least Once	Total # of Participant-Days for this Medication
3	1	DONEPEZIL	25	1,739
3	1	ATENOLOL	6	729
3	1	CLONIDINE	5	791
3	1	LEVODOPA	3	151
3	1	DOXAZOSIN	2	378
3	1	TERAZOSIN	2	291
3	1	PRAZOSIN	2	280
2	3	OLANZAPINE	25	1,962
2	3	RISPERIDONE	23	1,514
2	3	SERTRALINE	21	1,144
2	3	QUETIAPINE	16	1,232
2	3	TRAZODONE	15	996
2	3	HALOPERIDOL	13	548
2	3	VALPROIC ACID	11	866
2	3	MIRTAZAPINE	9	593
2	3	ESCITALOPRAM	6	895
2	3	CITALOPRAM	6	548
2	3	VENLAFAXINE	5	391
2	3	PHENYTOIN	4	659
2	3	PAROXETINE	5	344
2	3	BUPROPION	5	158
2	3	BENZTROPINE	4	517
2	3	HYDROCODONE	4	128
2	3	GABAPENTIN	3	389
2	3	OXCARBAZEPINE	3	300
2	3	TOPIRAMATE	3	179
2	3	PROPOXYPHENE	3	168
2	3	METOCLOPRAMIDE	2	82
2	3	DIVALPROATE	2	26
2	3	INDOMETHACIN	2	19
2	3	ARIPIPRAZOLE	2	17
2	3	MORPHINE	2	14
2	3	PROMETHAZINE	2	2
2	3	CARBAMAZEPINE	1	168
2	3	TRAMADOL	1	168
2	3	VALPROATE	1	168
2	3	METHADONE	1	104
2	3	DEXTROMETHORPHAN	1	15
2	3	FLUOXETINE	1	15
2	3	CHLORPROMAZINE	1	6
2	3	PERGOLIDE	1	4
2	3	DOXEPIN	1	3
2	3	HYDROXYZINE	1	2
2	3	ATROPINE	1	1
2	3	DIPHENOXYLATE	1	1
2	3	FOSPHENYTOIN	1	1
1	6	LORAZEPAM	43	1,337
1	6	CLONAZEPAM	6	340
1	6	CHLORAL HYDRATE	5	92
1	6	DIPHENHYDRAMINE	2	209
1	6	CHLORDIAZEPOXIDE	2	189
1	6	ZOLPIDEM	2	53
1	6	DIAZEPAM	2	42
1	6	ZALEPLON	1	168
1	6	CLORAZEPATE	1	105
1	6	TEMAZEPAM	1	55
1	6	ALPRAZOLAM	1	41
1	6	PHENELZINE	1	12
1	6	MOLINDONE	1	9

Table 2

Listing of all Analgesic Medications Received by Study Participants, by Analgesic Potency Rating Category (N=90 participants; 9,072 participant-days)

Analgesic Group *	Analgesic Rating	Medication Name	# of Study Participants Receiving at Least Once	Total # of Participant-Days for this Medication
Adjuvant	**1**	LORAZEPAM	43	1,337
Adjuvant	**1**	SERTRALINE	21	1,144
Adjuvant	**1**	TRAZODONE	15	996
Adjuvant	**1**	VALPROIC ACID	11	866
Adjuvant	**1**	MIRTAZAPINE	9	593
Adjuvant	**1**	ESCITALOPRAM	6	895
Adjuvant	**1**	CITALOPRAM	6	548
Adjuvant	**1**	CLONAZEPAM	6	340
Adjuvant	**1**	CLONIDINE	5	791
Adjuvant	**1**	DILTIAZEM	5	648
Adjuvant	**1**	VENLAFAXINE	5	391
Adjuvant	**1**	PAROXETINE	5	344
Adjuvant	**1**	CHLORAL HYDRATE	5	92
Adjuvant	**1**	OXCARBAZEPINE	3	300
Adjuvant	**1**	CHLORDIAZEPOXIDE	2	189
Adjuvant	**1**	PREDNISONE	2	69
Adjuvant	**1**	PHENAZOPYRIDINE	2	45
Adjuvant	**1**	DIVALPROATE	2	26
Adjuvant	**1**	PROMETHAZINE	2	2
Adjuvant	**1**	CARBAMAZEPINE	1	168
Adjuvant	**1**	VALPROATE	1	168
Adjuvant	**1**	ZALEPLON	1	168
Adjuvant	**1**	CLORAZEPATE	1	105
Adjuvant	**1**	TEMAZEPAM	1	55
Adjuvant	**1**	ALPRAZOLAM	1	41
Adjuvant	**1**	FLUOXETINE	1	15
Adjuvant	**1**	CHLORPROMAZINE	1	6
Adjuvant	**1**	DOXEPIN	1	3
Adjuvant	**1**	HYDROXYZINE	1	2
Adjuvant	**1**	DIPHENOXYLATE	1	1
Non-opioid	**3**	ASPIRIN	55	4,418
Non-opioid	**3**	ACETAMINOPHEN	44	2,076
Non-opioid	**3**	IBUPROFEN	21	1,225
Non-opioid	**3**	ROFECOXIB	4	64
Non-opioid	**3**	GABAPENTIN	3	389
Non-opioid	**3**	PROPOXYPHENE	3	168
Non-opioid	**3**	SALSALATE	2	105
Non-opioid	**3**	INDOMETHACIN	2	19
Non-opioid	**3**	VALDECOXIB	1	123
Non-opioid	**3**	NABUMETONE	1	18
Non-opioid	**3**	CELECOXIB	1	4
Opioid, mild/mod	**6**	HYDROCODONE	4	128
Opioid, mild/mod	**6**	TRAMADOL	1	168
Opioid, modsevere	**9**	MORPHINE	2	14
Opioid, mod/severe	**9**	METHADONE	1	104

Table 3

Summary Statistics on the Analgesic Load and Sedative Load Variables for the 90 Study Participants[a]

	N	Mean	(SD)	Min	25th %-ile	Median	75th %-ile	Max
# Daily analgesic meds received	90	1.89	(1.07)	0.0	1.1	1.84	2.6	4.9
Daily Analgesic Load	90	2.91	(3.52)	0.0	0.6	1.55	3.1	16.4
# Daily Sedative meds received	90	2.07	(1.17)	0.1	1.1	2.00	3.0	5.5
Daily Sedative Load	90	11.49	(13.98)	0.1	3.0	6.45	14.0	61.2

[a]Each measure is computed for each resident for each day of all study periods in which that resident participated, based on the dosage and sedation or analgesic ratings of each drug the resident received. A resident-level mean is then computed by averaging across all days for each resident. These resident-level means are then averaged to estimate the summary statistics shown.

Table 4

Means and Associated Standard Errors for Sedative and Analgesic Medications, by Selected Resident Characteristics

	# of residents	# of days	Analgesic medications				Sedative medications			
			Number of medications		Daily load		Number of medications		Daily load	
			Mean (SE)[a]	p-value[b]	Mean (SE)[a]	p-value[b]	Mean (SE)[a]	p-value[b]	Mean (SE)[a]	p-value[b]
Resident-level										
Overall	90	9072	2.14 (0.18)	--	3.77 (0.64)	--	2.35 (0.18)	--	13.17 (2.48)	--
Site										
Geropsychiatric hospital	70	5985	2.18 (0.26)	<0.001	4.47 (0.84)	<0.001	2.55 (0.24)	<0.001	17.62 (3.40)	<0.001
Dementia-specific AL	20	3087	2.06 (0.20)		2.39 (0.81)		1.98 (0.21)		4.55 (0.83)	<0.001
Gender										
Men	49	4662	2.04 (0.27)	<0.001	4.40 (0.99)	0.360	2.44 (0.27)	<0.001	15.57 (3.80)	<0.001
Women	41	4410	2.24 (0.24)		3.09 (0.78)		2.26 (0.24)		10.64 (3.03)	
Dementia Status										
Dementia	66	7098	1.97 (0.19)	<0.001	3.21 (0.69)	<0.001	2.20 (0.20)	0.001	9.83 (2.13)	<0.001
No dementia	24	1974	2.74 (0.41)		5.75 (0.41)		2.90 (0.40)		25.18 (7.11)	
Dementia Severity[c]										
Mild/moderate	21	2667	1.85 (0.37)	<0.001	3.67 (1.28)	<0.001	2.56 (0.39)	<0.001	13.44 (5.10)	<0.001
Severe/ very severe	45	4431	2.04 (0.21)		2.94 (0.79)		1.99 (0.19)		7.66 (1.16)	
Resident-period-level	**# of resident-periods**	**# of days**								
Agitation – 1st shift[d]										
Low	240	5040	1.81 (0.19)	<0.001	3.16 (0.71)	<0.001	1.98 (0.15)	<0.001	9.81 (2.47)	<0.001
High	192	4032	2.54 (0.25)		4.52 (0.83)		2.82 (0.28)		17.38 (3.78)	
Agitation – 2nd shift[d]										
Low	259	5439	1.86 (0.18)	<0.001	3.08 (0.64)	<0.001	2.02 (0.14)	<0.001	9.67 (2.14)	<0.001
High	173	3633	2.55 (0.26)		4.79 (0.91)		2.86 (0.28)		18.42 (4.10)	
Daytime drowsiness[e]										
Low	207	4347	1.89 (0.27)	<0.001	3.03 (0.80)	<0.001	2.30 (0.25)	<0.001	12.73 (2.96)	<0.001
High	225	4725	2.36 (0.18)		4.44 (0.84)		2.40 (0.17)		13.58 (2.77)	

[a] Means are computed across all days of study participation, categorized according to the specified characteristic; the standard errors are adjusted for repeated measures on residents using Taylor series expansion methods.

[b] P-values are based on a linear mixed model for the given medication measure, specifying the resident characteristic as a single fixed effect and including a random effect for resident to account for repeated measures on residents.

[c] Includes only those with dementia.

[d] Based on the CMAI reported by staff on each shift (possible range 14-70), with the cutpoint set at the overall median (20); low indicates a score of 14-20 and high indicates a score 21 or greater

[e] Based on the proportion of daytime observations that a resident was asleep or drowsy in up to 48 one-minute observations of residents during the third week of each study period, with the cutpoint set at the overall median (14% of observations)