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Title: Opioids and other CNS-active polypharmacy among older adults in the United States

Running Title: CNS-active polypharmacy among older adults

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ABSTRACT

Background/Objectives: Central Nervous System (CNS)-active medication polypharmacy, defined by the Beers Criteria as ≥3 CNS-active medications, poses significant risks for older adults. Among adults ages ≥65 seen in U.S. outpatient medical practice, we determined patterns and trends in contributions to CNS polypharmacy of each medication class.

Design: The National Ambulatory Medical Care Survey (2004-2013).

Setting: U.S. outpatient medical care.

Participants: Visits by older adults to outpatient physicians (n=97,910).

Exposure: Patient visits including ≥3 CNS medications including antipsychotics, benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonist hypnotics (NBRAs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and opioids.

Measurements: We determined the proportion of CNS polypharmacy contributed by each medication class during 2011-2013 and then used logistic regression to determine trends from 2004 to 2013 in the contribution of individual medication classes to such polypharmacy.

Results: Among recent CNS polypharmacy visits, 76.2% included opioids and 61.8% included benzodiazepines. Approximately two-thirds (66.0%) of the polypharmacy visits with benzodiazepines included opioids and

approximately half (53.3%) of the polypharmacy visits with opioids included benzodiazepines. Between 2011 and 2013, opioid and benzodiazepine co-prescribing occurred at approximately 1.50 million visits (CI 1.23-1.78 million) annually. From 2004 (reference) to 2013, the proportion of polypharmacy visits with opioids rose from 69.6% to 76.2% (AOR 2.15 [CI 1.19-3.91], p=0.01), while the corresponding proportion that included benzodiazepines fell. Among the polypharmacy visits, the odds of SSRI, NBRA, and antipsychotic use were unchanged, while TCAs decreased.

Conclusions: Among older adults, the recent national increase in CNS polypharmacy appears to be largely driven by opioid use. Although concomitant use of opioids and benzodiazepines is associated with increased mortality, they are the most common contributors to CNS polypharmacy in older adults.

Key Words: polypharmacy, opioids, benzodiazepines

INTRODUCTION

When the Beers Criteria for potentially inappropriate medication use in the elderly were first introduced twenty years ago, a select number of psychotropic medications were included, primarily due to their sedating effects: long-acting benzodiazepines, short-acting benzodiazepines above a low dosage, amitriptyline, and doxepin [1]. With each subsequent revision of the criteria, the list of psychotropic medications has grown along with the evidence of associated risks [2-5]; the 2015 version now includes virtually every class of psychotropic medication [6]. The potential harms for older adults are particularly concerning given growing evidence that a significant proportion of psychotropic prescribing in older adults occurs in the absence of significant psychiatric symptoms [7] or a clearly-defined mental health disorder [8, 9].

As the number of psychotropic medications in the Beers Criteria increased, opioids were not previously featured prominently. However, their use is now included as potentially inappropriate in a measure of central nervous system (CNS) polypharmacy, defined as ≥3 prescriptions from the following classes: antipsychotics; benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonist hypnotics (NBRAs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and opioids [6]. This revision follows evidence that CNS polypharmacy (opioids included) is associated with increased risk of falls [5] and cognitive decline [10]. In light of the opioid epidemic, there is now even greater attention on combined use of CNS medications. Co-prescribing of opioids and benzodiazepines is a particular cause for concern given their common role together in pharmaceutical overdose deaths. The risk of mortality increases with the dose of benzodiazepine prescribed [11]. The U.S. Food and Drug Administration recently issued a black-box warning advising of slowed breathing and death caused by co-prescribing opioids with CNS-depressants including

benzodiazepines, NBRAs, and antipsychotics [12], all of which are included within the Beers polypharmacy measure.

The use of individual psychotropic medication classes and prescription opioids has increased among older adults in the U.S. [13, 14], with CNS polypharmacy visits for older adults more than doubling between 2004-2006 and 2011-2013 [15]. While polypharmacy has risen overall, it is unclear which specific medication classes account for this growth. In order to address CNS polypharmacy, it is important to understand which medications and medication combinations are most common. In the present study we use data from the National Ambulatory Medical Care Survey (NAMCS), a nationally representative survey of visits to office-based physicians in the U.S., to better characterize the relative contribution of specific medication classes to CNS-polypharmacy and how this has changed over time.

METHODS

Sample

The analysis uses data from NAMCS, years 2004 through 2013, the most recent year available. NAMCS is a national probability sample survey of office-based and community health center-based physicians conducted annually and designed to "provide objective, reliable information about the provision and use of ambulatory medical care services in the United States" [16]. Non-federally employed physicians engaged in office-based practice are sampled from the American Medical Association and American Osteopathic Association master files; physicians in anesthesiology, pathology, and radiology are excluded.

Throughout the year, each participating physician is assigned a one-week reporting period, with data collected from a random sample of visits during that week. For very small practices, every visit may be included; for large practices, 10% of visits may be included [17]. Encounters such as house calls or those to institutional settings (e.g., nursing homes) are not included. For survey years prior to 2012, data for selected visits were recorded on a standardized form by the physician, their office staff, or field representatives of the U.S. Census Bureau. Beginning in 2012, NAMCS implemented computer-assisted data collection, which was performed primarily by Census staff. The 2013 NAMCS public use data file does not currently include visits to community health centers; therefore, such visits from other years were excluded from analysis, as recommended by NAMCS. Additional technical information concerning the survey sampling design and non-response adjustment is provided elsewhere [17]. The current analysis was drawn from visits by patients ≥65 years to all outpatient providers (n=97,910).

Medications and Other Visit Characteristics

Survey data included up to 8 medications prescribed, ordered, supplied, administered, or continued during each visit. While the 2012 and 2013 surveys include up to 10 medications, this analysis used only the first 8 listed medications to be consistent across all years. The 2015 AGS Beers Criteria includes use of ≥3 CNS medication classes as potentially inappropriate: antipsychotics, benzodiazepines, NBRAs, TCAs, SSRIs, and opioids. Medications in NAMCS are assigned to therapeutic classes according to Lexicon Plus®, a proprietary database of Cerner Multum, Inc [17]. A patient visit was classified as meeting the Beers CNS polypharmacy criteria if it included ≥3 medications from any of these classes.

For this analysis, we also include basic demographic data collected such as patient age, sex, and race/ethnicity. NAMCS classifies physicians into fifteen specialty groups; this analysis includes visits to all physicians, categorized as family medicine, internal medicine, psychiatry, or other medical specialties.

Statistical Methods

We grouped survey years (2004-2006, 2007-2010, and 2011-2013) as recommended by NAMCS to produce more reliable annual visit rate estimates [18]. All analyses were completed using survey design elements for visit weight, clustering within physician practice, and stratification to allow national inferences [17]. First, we compared all older adult visits across the study period on basic demographic and visit characteristics using difference in proportion tests. Next, for the most recent time period (2011-2013), we determined the relative contribution of each medication class to CNS polypharmacy overall. Finally, we determined the contribution of these medication classes to CNS polypharmacy during each time period and used logistic regression to determine how odds of use for each class changed over time. For example, an odds ratio of 2.0 means that, relative to a visit in 2004, a visit in 2013 had twice the odds of that medication class contributing to CNS polypharmacy visits. Regression models were adjusted for age, gender, and race/ethnicity. Because the Beers polypharmacy measure does not include diagnosis-based exclusions, the analyses were not adjusted for clinical diagnosis. Analyses were conducted in Stata 13.1 (College Station, TX) using two-sided tests with $\alpha = .05$.

RESULTS

Background characteristics of NAMCS visits by adults ≥65 years are presented in **Table 1**. During the study period there were a total of 97,910 office visits; 1,062 of which met criteria for CNS polypharmacy. As reported previously, between 2011 and 2013 polypharmacy occurred at 1.3% of all outpatient encounters by older adults [15]. Opioids were the most commonly prescribed medication group among CNS polypharmacy encounters (76.2%), followed by benzodiazepines (61.8%) and SSRIs (51.5%) (**Table 2**). While opioids and

benzodiazepines were the most common medications in polypharmacy visits, they were also most commonly used with each other. Among patients with CNS polypharmacy that included an opioid, 53.3% were co-prescribed a benzodiazepine; among patients with CNS polypharmacy that included a benzodiazepine, 66.0% were co-prescribed an opioid. Between 2011 and 2013 this opioid and benzodiazepine co-prescribing occurred at approximately 1.50 million visits (95% confidence interval [CI] 1.23-1.78 million) annually. Opioid co-prescribing was the least common among CNS polypharmacy that included an antipsychotic, just 35.9% of whom were also prescribed an opioid. Overall, TCAs were the least common class, prescribed at just 10.8% of CNS polypharmacy encounters overall and the least commonly prescribed with each other medication class.

Among CNS polypharmacy encounters, opioids were both the most common medication class and the only class where the odds increased from 2004 to 2013 (adjusted odds ratio [AOR] 2.15 [CI 1.19-3.91], p=0.01) (**Table 3**). While the odds of benzodiazepines as a polypharmacy component decreased during the study period, they were still the second most commonly prescribed medication group. The odds of SSRIs, NBRAs, or antipsychotics as a polypharmacy component were unchanged during the study period. TCA use decreased significantly, falling from 23.9% to 10.8% (AOR 0.31 [CI 0.15-0.66], p=0.002).

DISCUSSION

Opioids are the most common component of CNS polypharmacy among older adults in the U.S. and, against the background of overall increase in CNS polypharmacy, account for the greatest share of this growth. Although the odds of benzodiazepine use decreased slightly during the study interval, benzodiazepines remained the second-most common polypharmacy component. While the Beers CNS polypharmacy measure cites the risk of falls as its primary rationale, the recent FDA black box warning primarily concerns increased risk of respiratory suppression and death due to concomitant use of opioids and other CNS-depressants, most notably benzodiazepines. Over 30% of overdose deaths among US Veterans related to opioids also include benzodiazepines [19]. Therefore, it is particularly concerning that opioids and benzodiazepines are the two medication groups that most contribute to CNS polypharmacy in older adults.

From 2004 to 2013, while polypharmacy grew overall, the odds of SSRIs, NBRAs, or antipsychotics as a polypharmacy component were unchanged. This is consistent with previous analyses suggesting growth of these individual medication classes [15, 20-22]. While the opioid-specific growth may be attributed to the emphasis on treatment of pain, growth of other medications classes may reflect polypharmacy used to target other specific indication (e.g., depression) or more widespread use of medications for multiple off-label indications. For

example, increased use of the quetiapine may reflect indication expansion from its FDA approval in 2009 as an augmentation strategy to antidepressants for depression as well as growth in off-label use for insomnia, anxiety, or both. Over the study period, use of TCAs declined significantly. This decline may be due to greater recognition by providers of adverse effects associated with medications with high anticholinergic burden in older adults [23], with many alternative medications with more favorable side effects available for depression, anxiety, and neuropathy.

Our work has several limitations. NAMCS does not account for whether a prescribed medication is taken regularly versus as needed, so it is possible that the extent of regular use is overestimated. As the data are multiple cross-sectional samples, we cannot report on outcomes associated with medication use. Because NAMCS is a survey of office-based medical practice, it does not include physicians practicing in other settings or non-physician providers. In addition, as a survey of U.S. physicians, our results only examine trends in the U.S. health care system and do not generalize internationally. Physician non-response might introduce bias into the results, but the survey weights designed by NAMCS account for this to produce unbiased national estimates [16]. Finally, in 2012 NAMCS began using Census Field Representatives rather than physician office staff to conduct data collection. NAMCS reports that these changes did not affect diagnosis results, while the number of medications reported did decrease, for which NCHS staff "have researched . . . [all] possible contributing factors" without clear explanation [16]. This suggests that our results may potentially underestimate the actual increase in CNS polypharmacy visits.

In light of the serious health consequences for older adults associated with CNS polypharmacy, potentially including falls and death, it is concerning that such prescribing continues to rise [15]. While this combination of medications may be appropriate in select populations, use should only be considered after careful assessment of the risks, benefits, and alternatives. Public attitudes have grown more favorable towards psychotropic medications [24] and older adults have become more open to mental health treatment. While this may lead to improved treatment for some older adults, it may also lead to inappropriate overtreatment for others. In light of the recent FDA warning, co-prescribing of opioids and benzodiazepines is particularly concerning. It is critical to reduce this common and potentially lethal prescribing. There have been promising studies implementing structured algorithms to reduce polypharmacy, including psychotropic medications, demonstrating success in discontinuing medication without adverse effect, and often with significant improvement in health outcomes [25]. Direct patient education about the harms of potentially associated with medications that contribute to CNS polypharmacy may also lead some patients to initiate a discussion about appropriate prescribing, as demonstrated with chronic benzodiazepine use [26]. Lastly, improving access to evidence-based non-

pharmacologic treatments for insomnia, anxiety, or pain might also limit polypharmacy. In treatment of older adults the adage “less is more” holds true and further work is needed to place greater emphasis on deprescribing during the care of older adults.

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Elements of Financial/Personal Conflicts	*Author 1 LBG		Author 2 MO		Author 3 HCK		Author 4 DTM	
	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		x		x		x		x
Grants/Funds		x	x			x		x
Honoraria		x		x		x		x
Speaker Forum		x		x		x		x
Consultant		x		x		x		x

Stocks		x		x		x		x
Royalties		x		x		x		x
Expert Testimony		x		x		x		x
Board Member		x		x		x		x
Patents		x		x		x		x
Personal Relationship		x		x		x		x

***Authors can be listed by abbreviations of their names.**

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Table 1. Characteristics of Visits by Older Adults to Office-Based Physicians in the US, 2004-2013

	2004-2006 (n=21,029)	2007-2010 (n=31,516)	2011-2013 (n=45,365)		
	%[a]	%[a]	%[a]	Chi Square	p
Demographics					
Age					
65-74 years	47.8	49.7	51.2	15.88	<0.001
75-84 years	40.1	37.1	34.7		
85+ years	12.1	13.2	13.5		
Sex					
Male	41.5	42.9	43.2	4.06	0.02
Female	58.6	57.1	56.8		
Ethnicity					
Non-Hispanic white[b]	85.6	84.2	84.9	0.91	0.45
Non-Hispanic black	7.2	7.9	7.2		
Hispanic	7.2	7.9	7.9		
Clinical Characteristics					
Diagnoses[c]					
Depression	1.7	1.8	2.1	2.45	0.09
Anxiety	0.9	1.0	1.5	7.58	<0.001
Insomnia	0.4	0.6	0.7	4.97	0.007
Dementia	0.7	0.5	1.1	11.39	<0.001
Pain	15.6	15.8	17.0	1.93	0.15
Substance use disorder	0.3	0.3	0.3	0.73	0.48
No mental health or pain diagnosis	80.3	80.0	78.1	3.93	0.02
Provider Type					

Family practice	19.6	18.1	20.9	1.70	0.14
Internal medicine	21.5	22.1	19.8		
Psychiatry	1.1	1.0	1.6		
Other medical specialty	57.8	59.0	57.8		

[a] Represents the weighted percentage of visits by older adults within the time interval.

[b] Includes other race/ethnicity

[c] Diagnosis groups are not mutually exclusive (e.g., a visit of a patient with depression and pain would be represented in both diagnosis row

Table 2. Patterns of CNS Polypharmacy at Visits by Older Adults Seen in Office-Based Medical Care in the US, 2011-2013

Medication[a]	**Opioid n=465**	**Benzodiazepine n=393**	**SSRI n=300**	**NBRA n=150**	**Antipsychotic n=117**	**TCA n=87**
Overall[b], % (CI[c]) n=618	76.2 (70.8-80.9)	61.8 (56.5-66.9)	51.5 (45.7-57.2)	25.6 (20.9-31.0)	18.1 (13.7-23.7)	10.8 (8.2-14.0)
Opioid	x	66.0 (58.4-72.8)	62.8 (54.5-70.5)	64.8 (52.8-75.1)	35.9 (24.0-49.8)	61.1 (46.8-73.7)
Benzodiazepine	53.3 (47.3-59.6)	x	66.5 (59.1-73.2)	45.3 (34.7-56.5)	67.5 (53.8-78.7)	54.9 (40.8-68.3)
SSRI	42.4 (36.0-49.2)	55.3 (48.0-62.5)	x	47.7 (36.2-59.5)	54.3 (40.2-67.8)	47.4 (34.1-61.0)
NBRA	21.8	18.8	23.8	x	26.3	18.7

	(16.8-27.7)	(13.8-25.1)	(17.6-31.3)		(15.4-41.2)	(10.7-30.5)
Antipsychotic	8.5 (5.5-13.1)	19.8 (14.0-27.2)	19.1 (13.0-27.3)	18.6 (10.5-30.9)	x	13.9 (7.0-25.7)
TCA	8.6 (6.0-12.2)	9.5 (6.5-13.9)	9.9 (6.5-14.8)	7.8 (4.5-13.4)	8.2 (4.4-14.9)	x

[a] SSRI: selective serotonin reuptake inhibitors; NBRA: nonbenzodiazepine benzodiazepine receptor agonist hypnotics; TCA: tricyclic antidepressants

[b] The "overall" row reflects the % of CNS polypharmacy overall that includes a given medication class from 2011-2013. Within the column for each class, the rows reflect the proportion of polypharmacy within that specific class that includes the other medication groups. For example, 76.2% of CNS polypharmacy encounters overall from 2011-2013 included an opioid; among those on an opioid, 8.5% were also prescribed an antipsychotic. In contrast, 18.1% of CNS polypharmacy encounters overall from 2011-2013 included an antipsychotic; among those on an antipsychotic, 35.9% were also prescribed an opioid.

[c] CI: confidence interval

Table 3. Trends in CNS Polypharmacy Constituent Medication Classes at Visits by Older Adults to Office-Based Physicians in the U.S., 2004-2013

	% of CNS polypharmacy visits (N=1,062)					
Medication group[a]	**2004-2006**	**2007-2010**	**2011-2013**	**OR[b]**	**(95% CI[c])**	**p**
Opioid	69.6	67.5	76.2	2.15	(1.19-3.91)	0.01
Benzodiazepine	68.9	78.7	61.8	0.36	(0.17-0.74)	0.006
SSRI	52.5	58.5	51.5	0.63	(0.35-1.15)	0.13
NBRA	22.3	26.4	25.6	1.23	(0.67-2.27)	0.51
Antipsychotic	18.6	22.5	18.1	0.88	(0.48-1.62)	0.68
TCA	23.9	12.0	10.8	0.31	(0.15-0.66)	0.002

[a] SSRI: selective serotonin reuptake inhibitors; NBRA: nonbenzodiazepine benzodiazepine receptor agonist hypnotics; TCA: tricyclic antidepressants.

[b] The odds ratio (OR) is associated with a transformed survey year variable ([survey year – 2004] / 9) and therefore estimates the change in odds of a visit with the particular medication class among all CNS polypharmacy visits over the entire 2004-2013 study period. For example, in 2013, the odds of a TCA contributing to CNS polypharmacy were 0.31 relative to 2004. Logistic regression models were adjusted for age, gender, and race/ethnicity.

[c] CI: confidence interval