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Secular Trends in Central Nervous System-Active Polypharmacy Among Serial Cross-Sections of US Adults, 2009–2020

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Abstract

Background—Data comprehensively examining trends in central nervous system (CNS)-active polypharmacy are limited. The objective of this cross-sectional study was to characterize the composition of and trends in CNS-active medication use in US adults.

Methods—We included all participants ≥ 18 years old in the National Health and Nutrition Examination Study (NHANES), 2009–2020. The primary outcome was the percent of adults with CNS-active polypharmacy. This was defined as ≥ 3 medications among antidepressants [tricyclic, selective and serotonin-norepinephrine reuptake inhibitors (SSRIs and SNRIs), opioids,

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Conflicts of Interest No authors have any relevant competing or conflicts of interest.

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Availability of Data and Material All datasets are freely available for download at https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

Ethics Approval This study was deemed exempt by the University of Michigan Institutional Review Board (HUM00175050), given use of publicly available de-identified datasets.

Consent to Participate Consenting participants for this study was not required, as we used already-existing publicly available de-identified datasets that were deemed exempt as above.

Consent for Publication This article does not contain any identifying media or materials that would require patient consent for publication.

Code Availability Statistical code may be obtained upon request.

antiepileptics, antipsychotics, benzodiazepines, and nonbenzodiazepine receptor agonists ("Z-drugs")]. Secondary outcomes included prevalence of any CNS-active medication and specific medications and classes over time, and their indications. Percentages were weighted according to NHANES's nationally representative sampling frame. log binomial regressions evaluated the relative risk (RR) for each outcome, comparing the last (2017–2020) versus the first (2010–2011) survey cycle.

Results—We included 34,189 adults (18.8% at least 65 years old) from five serial cross-sections (survey cycles). The prevalence of CNS-active polypharmacy was 2.1% in 2009–2010 and 2.6% in 2017–2020 [RR 1.18, 95% confidence interval (CI) 0.94–1.47]. The prevalence of CNS-active polypharmacy did not significantly change within any specific age group (e.g., age at least 65 years: RR 1.29, CI 0.74–2.24). The prevalence of any CNS-active medication was 21.0% in 2009 and 24.6% in 2017–2020 (RR] 1.12, 95% CI 1.02–1.25). A substantial increase occurred for antiepileptics (5.1–8.3%), specifically among participants aged 65 years and older (8.3–13.7%). This was largely driven by increasing gabapentin prevalence (1.4–3.6% overall; 3.3–7.9% age 65 years and older). Anticholinergic, SSRIs/SNRIs, antiepileptics, and benzodiazepines were elevated in most cycles for participants at least 65 years old compared with participants less than 65 years, and opioid use was increased in several cycles for older participants as well. Alprazolam was the most common benzodiazepine and third most common medication for anxiety/depression. Gabapentin was the most common CNS-active medication (3.6% of all participants in 2017–2020), followed by sertraline, citalopram, and acetaminophen-hydrocodone (each ~2%). The most common categories were antidepressants (13.7% in 2017–2020), followed by opioids (5.1% in 2017–2020).

Conclusions—CNS-active medications are increasingly common, particularly gabapentin, and use of any CNS-active medication increased by 12%. Numerous CNS-active classes also increased in older adults throughout the years. Increasing suboptimal medication use highlight the need for further investigation into causes for potentially inappropriate prescribing, particularly for older adults.

1 Introduction

Approximately 60% of US adults take any prescription medication [1], and 20% of prescriptions to older patients may be inappropriate [2, 3]. While medications may be helpful for symptom reduction or prevention, taking at least five medications correlates with adverse drug events [4] and poorer cognitive and physical function [5]. This includes on average a ~10% increase in frailty, disability, mortality, and falls with every additional medication [6]. Approximately 100,000 preventable medication-related hospitalizations occur each year in the USA for adults over 65 years [7]. Central nervous system (CNS)-active medications pose unique risks for side effects such as falls, cognitive impairment, and drug–drug interactions [8-11], particularly when used in combination [12].

Pharmacoepidemiological data monitoring trends in CNS-active polypharmacy prevalence are critical to gain insight into patterns of use and misuse of prescription medications and opportunities for intervention. Prior analyses using the National Ambulatory Medical Care Survey (NAMCS) measured outpatient visits for patients over 65 years old with CNS-active polypharmacy [13]. However, NAMCS captures only visits amongst healthcare seekers and

thus may overestimate national trends, and those data ended in 2013. Also, that study did not consider antiepileptics, which could alternatively markedly underestimate the prevalence of CNS-active polypharmacy and is particularly relevant given the 2019 American Geriatrics Society statement included antiepileptics when considering CNS-active combinations [14]. Other studies of prescription trends among US adults ended over a decade ago and also did not focus on the important category of CNS-active polypharmacy [1], or else focused on only selected populations such as older adults with dementia rather than a broader examination of US adults enabling a comparison between younger versus older patients [15-17].

We used nationally representative data to provide updated trends in the prevalence of CNS-active polypharmacy, evaluate what specific medication classes are most contributing to CNS-active polypharmacy, and assess indications for various CNS-active medications that are often not available in other claims datasets. Our aim was to characterize the composition of and trends in CNS-active medication prescribing in US adults.

2 Methods

2.1 Study design and dataset

We used five serial cross-sections from the National Health and Nutrition Examination Survey (NHANES) from January 2009 to February 2020. Data after 2020 were not yet publicly available. We included adults at least 18 years old with no upper age restriction, to compare older versus younger adults. Because NHANES considers old age to be a potential identifier in this publicly available dataset, NHANES lists age 80 years for all participants at least 80 years old.

NHANES is a long-standing semi-annual cross-sectional study run by the Centers for Disease Control and Prevention. Its goal is to understand broad trends in health and nutrition in the USA. NHANES samples a new population of approximately 5000–10,000 noninstitutionalized US civilians from 15 counties across the USA each year, and oversamples certain individuals (over 60 years old, African Americans, Hispanics) selected from the US Census to ensure it is nationally representative. Because it samples only noninstitutionalized individuals, it does not include those living in long-term care facilities or nursing homes. It uses complex, stratified, multistage probability cluster sampling and collects data including respondents' prescribed medications and health conditions. Health interviews are conducted in a participant's home, and in-person physical examination by a physician is conducted in a traveling mobile center. The design and operation of NHANES are available online (https://wwwn.cdc.gov/nchs/nhanes/default.aspx).

2.2 Variables

Baseline factors describing the population included age, sex, race, family income to poverty ratio, insurance status, self-rated health status, and numerous self-reported health conditions available from NHANES questionnaire data. We calculated the number of chronic conditions from available data elements considering the following self-reported conditions ("has a doctor or other health professional ever told you that you have…"):

arthritis, asthma, cancer, coronary heart disease, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, liver disease, stroke, and thyroid disease.

Participants were asked to show the examiner their containers of all prescription medications taken in the last 30 days, regardless of whether daily versus only as needed, excluding those available only over the counter. The interviewer verified all medications to ensure a match from known drugs in Lexicon Plus®. Lexicon Plus®, a proprietary database of Cerner Multum, Inc., is a comprehensive database of all prescription drug products available on the US drug market [18, 19].

Our primary outcome was CNS-active polypharmacy. This was defined according to the 2019 American Geriatrics Society Beers Criteria [13, 14] as three or more medications among antiepileptics, antipsychotics, benzodiazepines, nonbenzodiazepine receptor agonists (NBRAs, i.e., “Z-drugs”), opioids, selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs).

We captured numerous secondary outcomes. We evaluated the prevalence of any prescription medication or at least five prescription medications (i.e., polypharmacy) [20, 21]. We defined CNS-active medications using Lexicon Plus® Level 1 categories of “central nervous system” or “psychotherapeutic” agents, excluding non-steroidal anti-inflammatory drugs and salicylates, which Lexicon Plus® includes as CNS medications but are not specific to the nervous system. To further broadly characterize CNS-active medication use, we described the most common Level 2 (e.g., antipsychotics, analgesics, etc.) and Level 3 (e.g., atypical antipsychotics, opioids, etc.) classifications and the most common medications within each class, several important drug–drug combinations with warnings for increased mortality (i.e., opioid–benzodiazepine [22], opioid–gabapentinoid [23]), and strongly anticholinergic medications according to the Beers statement [14].

Finally, we reported the most common indications for various medications and classes and the most common medications for various indications. Starting in 2013, participants were asked for the main indications for using each prescription medication. The interviewer chose up to the three closest indications matching International Classification of Diseases (ICD)-10 codes [24].

2.3 Statistical analysis

All analyses were survey weighted to account for NHANES’s sampling frame, unless stated otherwise. For this reason, raw percentages (the number of participants in our sample taking each medication class divided by the number of participants in our sample) may not exactly correspond to displayed survey-weighted percentages (which estimate the number of US adults taking each medication class in those years divided by the number of US adults in those years). Note that in Sect. 3.3 we also reported prevalence rates averaging all cycles together (i.e., the number of US adults taking each medication class across all years divided by the number of US adults across all years). Note that the 2019–2020 cycle was stopped prematurely in February 2020 due to onset of the COVID-19 pandemic. To accommodate this protocol deviation, participants from 2019 to February 2020 were incorporated into the

2017–2018 cycle, which was reweighted to still provide a single nationally representative cross-section [25].

For our primary analysis regarding how CNS-active polypharmacy changed over time, we conducted an unadjusted log binomial regression to obtain a relative risk (RR) over the study period with a 95% confidence interval (CI) similar to previous work [13]. We chose log binomial rather than logistic regressions because the former computes relative risks, whereas the latter computes odds ratios. RR is a more intuitive measure of association than odds ratios, and odds ratios exaggerate apparent associations compared with relative risks particularly when outcomes are common, as was the case for several of our outcomes [26, 27]. The main predictor was ([survey year—2009] / 8). In other words, the 2009–2010 cycle was "0," the 2011–2012 cycle was "0.25," all the way to final cycle 2017—February 2020, which was "1" in the model, such that a one-unit step represented the full study timespan. We then produced RRs for CNS-active polypharmacy stratified over baseline factors and then also obtained overall RRs for trends in our secondary outcomes. We particularly stratified the prevalence of each medication class by age less than versus at least 65 years old, given age's critical importance in medication appropriateness and adverse effects (Fig. 1).

We performed an additional analysis to evaluate for change in the composition of CNS-active polypharmacy over time by age (Fig. 2). For each cycle, we added up the number of prescriptions in each medication class contributing to the definition of CNS-active polypharmacy (e.g., the number of antipsychotics, etc.) divided by the total number of prescriptions in any class contributing to the definition of CNS-active polypharmacy (e.g., the number of antipsychotics, NBRAs, benzodiazepines, opioids, antidepressants, or antiepileptics). This produced 100% stacked bar graphs displaying relative shifts in the percent of CNS-active medication belonging to each class over time, which we also stratified by age < 65 versus ≥ 65 years old. We performed a Chi-squared for each age group, which was unweighted given the denominator was participant–medications rather than participants. Because some overlap exists between classes (e.g., benzodiazepines can be used as antiepileptics or antidepressants/anxiolytics), we considered benzodiazepines to be its own separate class to keep categories mutually exclusive.

Data were analyzed using SAS 9.4 (Cary, NC) and Stata 17.0 (College Station, TX).

3 Results

3.1 Population description

NHANES contained 55,999 participants between 2009 and February 2020. This included 34,189 (76.1%) participants at least 18 years old, which represented 238 million US adults averaging all cohorts together. Among adults, there were 7868 (18.8%) participants at least 65 years, 51.8% female, and 64.6% non-Hispanic White. Table 1 provides further characteristics.

3.2 Trends in medication use across 2009–2020

An estimated 7 million US adults reported CNS-active polypharmacy (the cross-sectional prevalence), per the 2017–2020 (last) cycle. In the last cycle, 82.2% of participants used no CNS-active Beers medications, 11.5% used one, 4.3% used two, and 2.6% used at least three (CNS-active polypharmacy). The prevalence of CNS-active polypharmacy did not change significantly between the first (2.1%) and last (2.6%) cycles (RR 1.18, 95% CI 0.94–1.47; $p = 0.15$; Table 1). Prevalence did not change in most strata except, for example, participants with fair or poor health status (RR 2.20, 95% CI 1.45–3.33).

An estimated 61 million US adults used any CNS-active medication, per last cycle. The prevalence of any CNS-active medication use increased between the first (21.0%) and last (24.6%) cycle [relative risk (RR) 1.12, 95% confidence interval (CI) 1.02–1.25; $p = 0.03$). Use of antidepressants, antipsychotics, and antiepileptics increased, while NBRAs decreased (Table 1).

The largest and most consistent increase of any class occurred in antiepileptics, from 5.1% in 2009 to 8.3% in 2017–2020 (RR 1.64, 95% CI 1.39–2.00). The increase was particularly notable in participants at least 65 years old (from 8.3 to 13.7%; RR 1.69, 95% CI 1.28–2.25; Fig. 1). The increase was particularly driven by gabapentin, which increased from 1.4 to 3.6% overall (RR 2.62, 95% CI 1.86–2.67) and from 3.3 to 7.9% in participants at least 65 years old (RR 2.61, 95% CI 1.75–3.87). Across time, Fig. 1 also demonstrates that anticholinergic, SSRIs/SNRIs, antiepileptics, and benzodiazepines were also mostly elevated for participants at least 65 years old compared with participants less than 65 years, and opioid use was increased in several cycles for older patients as well. As a specific important example due to its teratogenicity, valproate use in females 18–45 years was 27 (0.3%) in 2009–2010, 22 (< 0.1%) in 2011–2012, 34 (0.4%) in 2013–2014, 34 (0.7%) in 2015–2016, and 48 (0.2%) in 2017–2020 ($p = 0.59$ for trend).

There were shifts in the contributing classes over time for both age groups (Fig. 2; $p < 0.001$). Antiepileptics grew from 13.5 to 28.4% of participant–medications, while opioids decreased from 27.6 to 17.7% of participant–medications.

Online resources 1-5 describe the most common medications within each class across study years.

3.3 Medication use pooling all study years

Antidepressants were the most common Level 2 class (12.9%), and SSRIs were the most common Level 3 class (8.0%) (Online Resource 6). Gabapentin was the most common CNS-active medication (2.5%), followed by sertraline, citalopram, and acetaminophen-hydrocodone (all ~2%) (Online Resource 7). There were 1.2% of participants who reported both an opioid and benzodiazepine, and 1.0% who reported an opioid plus gabapentinoid (either gabapentin or pregabalin) (Online Resource 8).

There were 12.7% of participants who reported at least one medication for anxiety/depression, 6.9% for pain, and 5.0% for sleep (Online Resource 9). Online resources 10 and 11 describe the most common indications for each class or specific medication,

respectively. Online Resource 12 describes the most common medications used for selected indications. The most common medications used for sleep disturbances were trazodone and zolpidem, the most common medication for pain was gabapentin, and there was a wide range of medications used for anxiety/depression (most common: sertraline, citalopram, and alprazolam).

4 Discussion

We described national trends in CNS-active medication use from 2009 to 2020 in US adults. While no single CNS-active medication was overly common, by the end of the study period one-fourth of adults used any CNS medication (cross-sectional prevalence: 61 million US adults), 2.6% of adults fulfilled criteria for CNS polypharmacy (7 million), and ~1–2% of adults used opioid combinations with black box warnings (e.g., benzodiazepines or gabapentinoids, both 2–3 million). While CNS-active polypharmacy did not significantly increase, use of any CNS-active medication increased by 12%. Analgesics, antidepressants, and antiepileptics comprised the largest categories contributing to CNS polypharmacy, with antiepileptics representing an increasingly larger share over time, and 13% of participants reported at least one prescription medication for anxiety/depression and 7% for pain.

Whereas a previous study using NAMCS estimated that visits in older adults with CNS-active polypharmacy increased from 1.5 to 3.7 million per year between 2004 and 2013 [13], our study found a prevalence of about 7 million US adults fulfilling criteria for CNS-active polypharmacy. Our number was likely higher because we included all adults and included antiepileptics in the definition of CNS-active polypharmacy. Another previous study also using NHANES found that prevalence of certain CNS-active medications increased then plateaued 1999–2012 (e.g., SSRIs/SNRIs, opioids, benzodiazepines, muscle relaxants) [1]. The authors theorized this trend could have been due to market saturation, direct to consumer advertising, or increasing awareness regarding the potential for medication abuse, though such theories are untestable from NHANES data other than indirectly by considering secular US trends. Our findings update such results by about 8 years to show that CNS-active medication use has continued to increase.

One of the largest increases over time among all medications was for gabapentin, with a nearly three-fold increase over this decade of observation. Gabapentin was consistently the most common CNS-active medication and was more than twice as common as any other prescription medication for pain. Gabapentin is approved in the USA only for postherpetic neuralgia and focal seizures. Yet our data found 16 different self-reported indications and only 3% of indications were on-label. Off-label use appears widespread ranging from diabetic neuropathy to restless legs to mood disorders to insomnia to migraines, despite, at best, mixed evidence, for example, in painful diabetic neuropathy, evidence against efficacy in low back pain or radiculopathy, and a statistically significant but fairly small effect size in fibromyalgia [28]. While gabapentinoids may be increasing as a low-cost alternative to opioids, they still have known possible adverse effects such as fall risk, somnolence, dizziness, and possibly suicidal ideation as a controlled substance in many states [29]. However, our data did not support a significant decline in opioids corresponding with rising

gabapentin use. Note that other data have found declining opioid use concomitant with rising gabapentin use, such as in older Veterans [17].

Aging presents unique clinical considerations related to CNS-active prescribing given the higher potential for drug–drug interactions, altered drug metabolism, and side effects that can impair cognition and functional status. Numerous CNS-active medications classes are identified in the Beers criteria as potentially dangerous medications in older adults, such as anticholinergics, antipsychotics, barbiturates, benzodiazepines, muscle relaxants, and opioids, particularly when used in conjunction with gabapentinoids or benzodiazepines [14]. However, despite CNS-active polypharmacy prevalence appearing comparable or slightly less in older versus younger adults (Table 1), nearly all individual medication classes in Fig. 1 demonstrated increased use among older adults across study years. In particular, benzodiazepine use increased among older adults (increasing from 4 to 7% of participants between 2009 and 2020), which is a concerning trend given the high risk of adverse drug effects in older adults, including falls and cognitive impairment [30, 31]. Similarly, antiepileptic use increased, consistent with recent studies demonstrating growth in use, particularly among older adults [32]. In contrast, our data showed that antipsychotic use doubled in younger participants but remained stable among older adults. Antipsychotic use among adults is often off-label prescribing (e.g., behavioral and psychological symptoms in dementia or depression), and at least the lack of increase among older adults may be encouraging as there is growing recognition of medication-related harms including sedation, extrapyramidal side effects, and in the case of treatment of dementia-related behaviors, mortality [33, 34].

Our data suggest several opportunities to improve prescribing practices.

Numerous medications of concern were likely more common than ideal. Alprazolam is approved for acute treatment of generalized anxiety disorder and panic disorder. That said, there are known potentially serious risks of taking benzodiazepines in terms of overdose, falls, sedation, and cognitive dysfunction, all of which may be particularly magnified with alprazolam due to its rapid onset/offset and addictive potential [35]. Alprazolam was the most common benzodiazepine and was reported by 1–2% of adults (about 4 million adults at any given time) throughout the study period. Despite the availability of more effective, less addictive/dangerous alternatives, alprazolam was the third most common medication for anxiety/depression.

Our data suggest that other medications may also be over-used. For example, approximately 30–50% of adults have short-term and 5–10% have chronic insomnia [36]. In our sample, 5% of participants used at least one prescription medication for sleep, chiefly trazodone and zolpidem, in addition to a wide variety of benzodiazepines, antipsychotics, tricyclics, gabapentinoids, and muscle relaxants. Evidence is generally weak in favor of hypnotics for chronic insomnia, and the American Society of Sleep Medicine recommends against trazodone for sleep onset or sleep maintenance insomnia [36], in favor of optimizing sleep hygiene and utilizing nonmedication strategies, which have shown effectiveness and greater long-term safety.

As another example, phenytoin was the second most common antiepileptic used for epilepsy treatment. This is despite first-generation enzyme-inducing antiepileptics exerting greater drug–drug interactions and adverse effects such as cognitive dysfunction compared with newer-generation antiepileptics [37]. Older-generation medications may be used despite, or even because of, their sedating properties (similarly, quetiapine was nearly twice as common as aripiprazole). Our work reinforces previous findings that lamotrigine may be an underutilized, effective medication, with a more favorable side effect profile than others [38]. Previous epilepsy guidelines recommended several options such as gabapentin, lamotrigine, topiramate, and oxcarbazepine for monotherapy in newly diagnosed epilepsy [39], though those guidelines were updated in 2018 [40] (toward the end of our observation period) favoring lamotrigine and levetiracetam amongst first-line medications. Thus, future monitoring will be needed to understand how recent guideline updates affect prescribing patterns. Fortunately, we found other certain high-risk medications were relatively rare, such as valproate in women of childbearing potential. This is favorable news in the USA, mirroring generally declining valproate use in European women of childbearing potential, [41] given valproate is a particularly noteworthy teratogen.

Our data highlight other psychiatric examples. For instance, citalopram outpaced escitalopram throughout the observation period despite only citalopram containing a warning (issued in 2011) regarding QTc prolongation at higher doses [42, 43]. Other interesting findings exist, such as quetiapine being used slightly more commonly for anxiety/depression than aripiprazole, despite only aripiprazole having evidence favoring its use in unipolar depression aug-mentation therapy, and 17% of valproate indications being for major depression. despite not typically being endorsed for this purpose. Additionally, for example, only 0.3% of participants reported pharmacotherapy for posttraumatic stress disorder (PTSD), despite the prevalence of PTSD being 10–20 times higher than that in adults [44-46], likely reinforcing persistent undertreatment despite increasing recognition and public health importance.

Our study had several limitations. These data did not contain over the counter medications or dietary supplements (e.g., melatonin for sleep, magnesium for migraines, B12 for cognition, etc.). Also, participants reported only medications taken within the last 30 days, and numerous elements were not captured (e.g., daily versus as-needed, doses, mode of administration, level of adherence). Medication lists also do not directly inform appropriateness without full clinical details. For example, our data do not provide a precise denominator regarding who should be treatment candidates for each medication, by which to judge possible underuse—the existing START criteria suggest certain neurological indications to start treatment such as levodopa in Parkinson’s disease, antidepressants in moderate–severe depression or persistent anxiety, or cholinesterase inhibitors for mild–moderate dementia. [47] Thus, future work may seek to evaluate both neurological overtreatment but also potential undertreatment. NHANES also lacks ICD codes for more granular stratification according to specific physician-confirmed diagnoses to look for trends [48], and patients could misreport indications particularly given older adults may not understand the indication for each medication [49]. Moreover, for example lamotrigine and valproate are both categorized by Lexicon Plus® as antiepileptics, whereas they can both be used for many other reasons such as mood stabilization. This is why we analyzed

medication indications, to supplement Lexicon Plus's fixed ingredient-based categorization. Still, NHANES is superior to insurance claims dataset for nationally representative data, and the availability of directly reported indications is a major strength. Also, medication lists for each patient were likely highly accurate because interviewers came to the participant's home, visualized all pill bottles of all medications taken in the last 30 days, and recorded drug names directly from pill bottles [24]. NHANES does not include institutionalized or nursing home patients or contain reliable data on dementia for whom psychiatric conditions would be increased. Though, NHANES did allow us to examine the US population more broadly rather than focusing on any single specific subpopulation. Lastly, these data do not inform trends since the onset of the COVID-19 pandemic, which would be important to investigate in future work. The newest 2023 Beers statement released after completion of our study further includes muscle relaxants in the definition of CNS-active polypharmacy [50], thus future work could examine the degree to which guideline updates affect practice.

5 Conclusions

Our study provided a comprehensive evaluation of CNS-active prescribing trends and composition among US adults. Nearly one-fourth of adults (61 million) take at least one CNS-active medication, and 3% (7 million) take at least three. Use of any CNS-active medication increased by 13% between 2009 and 2020. We found numerous concerning findings. For example, benzodiazepines increased over time particularly in older adults, and opioid use was increased in older adults. Acetaminophen–hydrocodone was amongst the most common CNS-active medications, alprazolam was the third most common medication for anxiety/depression and the most common benzodiazepine, and 3 million US adults report both a benzodiazepine plus an opioid. Implications of our work include that future efforts are needed to evaluate reasons for and address underuse of pharmacotherapy for certain indications (e.g., PTSD treatments, escitalopram, lamotrigine) and overuse of other potentially inappropriate medications (e.g., valproate for depression). Gabapentin was the most common CNS medication, its use has increased nearly three-fold over this decade-long observation period, particularly for older adults who may be most susceptible to adverse effects, and it is being widely used for off-label conditions despite oftentimes weak evidence. Evaluating postpandemic trends and the impact of updating Beers criteria remain unmet research needs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

In this multicycle cross-sectional study, nearly one-fourth of adults used any central nervous system (CNS)-active prescription. Three percent used at least three concurrent CNS-active medications.

Gabapentin prevalence more than doubled and antiepileptic and benzodiazepines increased particularly among older participants.

Acetaminophen–hydrocodone was amongst the most common CNS-active medication, and alprazolam was the third most common medication for anxiety.

CNS-active medication use is common. Efforts are warranted to ensure balancing medication benefits versus harms.

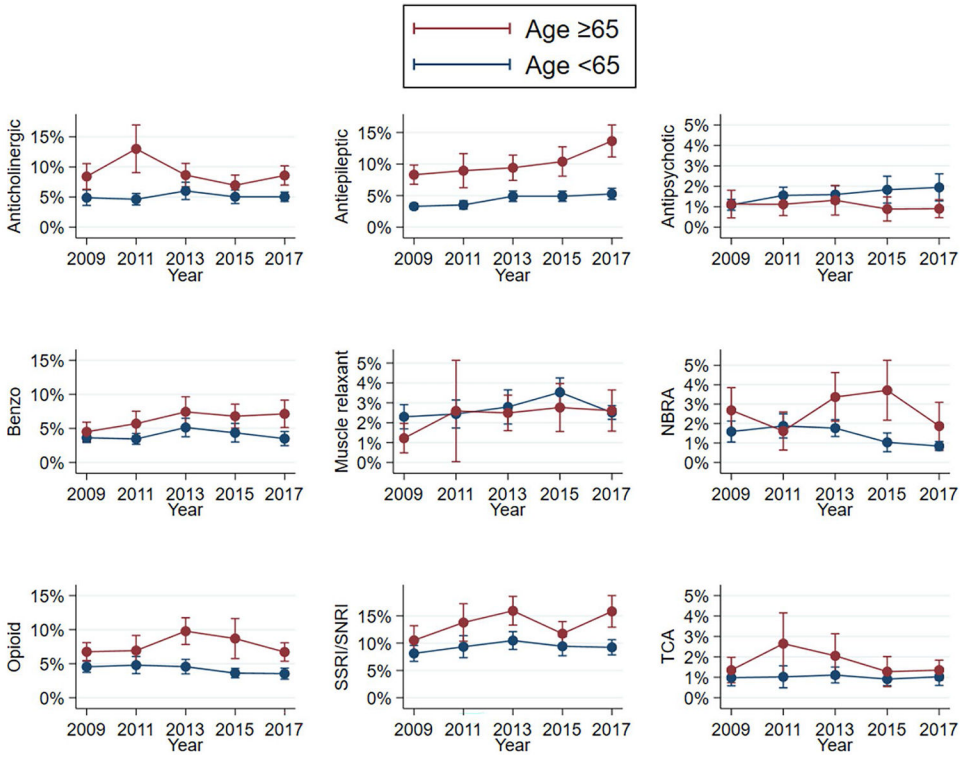

Fig. 1.

Prevalence of specific central nervous system-active medication classes over time by age. The *Y* axis for each panel represents each medication class's prevalence in each cycle with 95% confidence interval error bars. Red: age ≥ 65 years; blue: age < 65 years. Note these graphs have some overlap (e.g., antiepileptics and benzodiazepines). Additionally, numerous tricyclic antidepressants (TCAs; e.g., amitriptyline, nortriptyline, etc.) and selective serotonin reuptake inhibitors (SSRIs; e.g., paroxetine) per Table 7 of the Beers statement[14] were considered anticholinergics. NBRA: nonbenzodiazepine receptor agonist (i.e., "Z-drugs"); SNRI: serotonin–norepinephrine reuptake inhibitor.

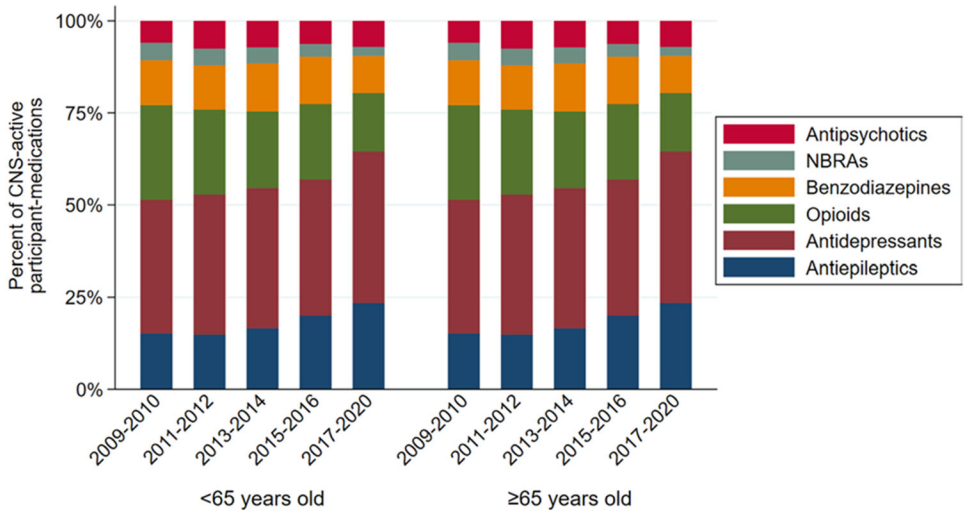

Fig. 2.

Change in composition of central nervous system (CNS)-active polypharmacy over time, stratified by age. This figure presents data like Table 1's "% of CNS participant–meds" but additionally stacks each medication class to add up to 100% of all relevant medications within each cycle and stratifies estimates by age. The distributions changed for both age groups across cycles (Chi-squared for both age groups: $p < 0.001$). Antiepileptics and antidepressants both exclude benzodiazepines. Antidepressants refer to selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and tricyclic antidepressants.

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Table 1

Trends in medication use

Characteristic	% of pooled population	% by cycle					RR (95% CI)[a]
		2009–2010	2011–2012	2013–2014	2015–2016	2017-2020	
N		6527	5864	6113	5992	9693	
Medications, overall							
Any medication	56.8	55.8	56.9	57.1	56.2	57.5	1.02 (0.96–1.09)
Polypharmacy (≥ 5 medications)	15.0	12.6	13.8	15.6	15.7	16.4	**1.28 (1.13–1.44)***
Any CNS-active medication	23.6	21.0	23.2	25.0	23.3	24.6	**1.12 (1.02–1.25)***
CNS-active polypharmacy	2.7	2.1	2.7	3.2	3.1	2.6	1.18 (0.94–1.46)
Antidepressants							
% of participants	12.9	10.5	12.6	14.6	12.5	13.7	**1.20 (1.03–1.41)***
% of CNS participant–meds	38.4	36.2	37.9	38	36.9	41.0	
Antiepileptics[b]							
% of participants	5.0	3.5	3.5	4.8	5.5	6.4	**1.65 (1.39–1.96)***
% of CNS participant–meds	18.7	15.2	14.9	16.6	20.0	23.5	
Antipsychotics							
% of participants	1.5	1.1	1.5	1.6	1.7	1.7	**1.44 (1.01–2.07)***
% of CNS participant–meds	6.8	5.9	7.5	7.2	6.2	7.1	
Benzodiazepines							
% of participants	4.4	3.7	3.8	5.6	4.8	4.2	1.14 (0.89–1.46)
% of CNS participant–meds	11.8	12.2	12.0	13.1	12.9	10.1	
NBRAs							
% of participants	1.6	1.8	1.8	2.1	1.6	1.1	**0.61 (0.45–0.83)***
% of CNS participant–meds	3.7	4.8	4.6	4.4	3.5	2.4	
Opioids							
% of participants	6.0	6.3	6.6	6.8	5.7	5.1	0.79 (0.63–1.00)
% of CNS participant–meds	20.5	25.8	23.2	20.8	20.6	15.9	
CNS-active polypharmacy, within strata							
Age (years)							
18–49	55.7	1.5	2.5	1.9	2.0	1.6	0.91 (0.58–1.42)

Characteristic	% of pooled population	% by cycle					RR (95% CI)[a]
		2009–2010	2011–2012	2013–2014	2015–2016	2017-2020	
50–64	25.6	3.1	3.1	5.7	5.4	4.1	1.36 (0.91–2.04)
≥ 65	18.8	2.4	3.1	3.8	3.0	3.5	1.29 (0.74–2.24)
Sex							
Male	48.2	1.6	2.0	2.4	2.1	2.0	1.11 (0.76–1.63)
Female	51.8	2.4	3.4	4.0	3.9	3.3	1.21 (0.94–1.56)
Race/ethnicity							
NHW	64.6	2.6	3.5	3.9	3.9	3.1	1.12 (0.87–1.46)
NHB	11.5	1.2	1.9	1.9	1.7	1.4	0.98 (0.63–1.52)
MA	8.7	0.6	0.7	1.9	1.4	1.3	1.82 (0.73–4.53)
Other/multiracial	15.2	0.8	1.1	2.2	1.8	2.4	**2.38 (1.07–5.27)***
Family income-to-poverty ratio							
< 1	17.0	2.7	3.3	5.7	5.0	2.9	1.13 (0.82–1.58)
≥ 1	83.0	2.0	2.8	3.0	2.8	2.7	1.19 (0.91–1.55)
Insurance							
None	16.7	0.9	0.6	1.8	2.6	0.2	0.98 (0.52–1.83)
Any private	60.7	2.6	2.2	2.3	2.0	2.0	1.11 (0.75–1.64)
Government only	22.6	5.3	6.6	7.4	6.1	5.2	0.87 (0.59–1.20)
Self-rated health status							
At least good	82.3	1.4	1.6	1.7	2.0	n/a[c]	1.57 (0.84–2.95)
Fair or poor	17.7	4.8	7.6	9.8	9.3	n/a[c]	**2.20 (1.45–3.33)***
Number chronic conditions[d]							
0	37.3	0.5	0.8	0.7	0.9	0.8	1.56 (0.69–3.53)
1–2	43.9	2.0	3.0	3.1	2.8	1.7	0.78 (0.55–1.11)
≥ 3	18.8	6.8	7.1	8.8	7.6	7.7	1.09 (0.82–1.46)

CI confidence interval, *CNS* central nervous system, *MA* Mexican American, *NBRA* nonbenzodiazepine receptor agonist (i.e., "Z-drugs"), *NHB* non-Hispanic Black, *NHW* non-Hispanic White, *RR* relative risk.

N = 34,189 pooling all five cycles. "Pooled %" refers to combining all cycles together (the first column)—all subsequent columns list each cycle separately. "% of CNS participant–meds" represents the total number of CNS medications reported in each class, divided by the total number of reported CNS medications; these percentages were not survey weighted, given they represent the proportion of medications rather than participants. The bottom half of the table describes demographics of the pooled sample (first column) and then the percent of each demographic strata reporting CNS-active polypharmacy in each cycle (subsequent columns). Relative risk (RR) evaluates how the % of participants taking a given medication class changed across the study period—results were bolded if

confidence intervals excluded 1. Age and number of non-CNS medications had no missingness, race had < 1% missingness, and number of non-CNS medications had 6% missingness, justifying listwise deletion without imputation methods.

[a] To compute relative risks, we transformed each survey year's variable to ([cycle's first year – 2009] / 8), such that a one-unit step in time represented the entire study period. Relative risks were estimated by a log-binomial model for each row, either overall (top half of table) or within strata (bottom half of table).

[b] Excluding benzodiazepines.

[c] Item not assessed in 2017–2020.

[d] Chronic conditions were based on self-report ("has a doctor or other health professional ever told you that you have…") of the following: arthritis, asthma, cancer, coronary heart disease, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, liver disease, stroke, and thyroid disease.