Anxiolytic and sedative polypharmacy among US opioid users: a cross-sectional study

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INTRODUCTION

The adverse risks of concurrent use of opioids and benzodiazepines[1–4] may be elevated even further in patients who are also prescribed non-benzodiazepine sedatives, such as trazodone, commonly used to treat sleep disorders. Therefore, we sought to identify the prevalence of dual anxiolytic/sedative therapy among US adult opioid users.

METHODS

We conducted a cross-sectional study using nationally representative data from the Medical Expenditure Panel Survey (MEPS). Administered by the Agency for Healthcare Research and Quality, the MEPS includes US data on healthcare expenditures, health status, and health services for non-institutionalized Americans.[5] A unique feature of the MEPS is that detailed surveys of participants are conducted in 6-month intervals that are followed with extensive data collection from administrative records (to supplement subjective data on specific health service use).

The MEPS uses a strategic sampling strategy designed to generate estimates for the US population known as complex survey design. Complex survey design methods include both strategic and random elements. Geographic areas are selected based on known population socioeconomic factors to improve the likelihood of selecting under-represented groups. Then, within selected areas, random households and individuals (within households) are selected with an annual sample size of approximately 30 000. Weights are applied to extrapolate up to the entire population (and account for clustering within units). Uncertainty regarding national estimates is reflected in the SE (and CI).

After aggregating the 4 most recent years of MEPS data (2016–2019), we identified a sample of 10 700 adult (18+ years) prescription opioid users. Prescription opioids, benzodiazepines, and miscellaneous non-benzodiazepine sedative medications were identified using a list of established National Drug Codes in the respective calendar year. The miscellaneous sedative list was generated based on a classification system from the American Hospital Formulary Service[6] and supplemented by identifying clinically relevant and commonly used sedating medications (online supplemental appendix 1). Medical conditions were established

Population Characteristic	Among Opioid Users, Percent on Dual Therapy (95% CI)	Estimated No. of Dual Therapy Users in U.S., millions
Overall	9.1 (9.0, 9.2)	2.60
Sociodemographic Characteristics		
Age category, years		
18 to 44	6.6 (5.4, 8.1)	0.57
45 to 64	11.3 (9.9, 12.8)	1.24
65 and older	9.1 (7.8, 10.5)	0.79
Sex		
Male	6.1 (5.2, 7.2)	0.70
Female	11.2 (10.1, 12.4)	1.90
Race/Ethnicity		
Non-Hispanic White	10.4 (9.4, 11.5)	2.15
Non-Hispanic Black	5.4 (4.3, 6.8)	0.18
Hispanic	6.8 (5.4, 8.7)	0.19
Other or multiple races	5.1 (3.5, 7.4)	0.86
Marital status		
Married	8.0 (6.9, 9.2)	1.18
Divorced, separated or widowed	13.1 (11.6, 14.8)	1.11
Never married	6.1 (4.9, 7.5)	0.31
Education		
Highschool or less	9.0 (7.9, 10.1)	1.16
Some college or Bachelor's degree	9.2 (8.0, 10.5)	1.15
Advanced degree	0.3 (0.2, 3.8)	0.29
Health insurance status		
Private	7.3 (6.4, 8.3)	1.29
Public	13.1 (11.7, 14.6)	1.27
Uninsured	4.5 (0.0, 7.6)	0.04
Health Status		
Anxiety	32.9 (30.4, 35.6)	1.84
Depression	23.6 (21.4, 26.5)	1.28
Stress-related disorder	25.9 (20.9, 31.7)	0.34
"Fair" or "Poor" overall health	16.8 (15.1, 18.7)	1.39
Sleep disorder	26.5 (22.2, 31.2)	0.51
Self-reported pain level		
None or little	4.6 (3.8, 5.5)	0.63
Moderate	10.1 (8.3, 12.3)	0.43
Severe	16.9 (15.0, 18.9)	1.29
Surgical Procedure in Past Year		
Inpatient surgery	10.3 (8.6, 12.5)	0.53
Outpatient surgery	7.9 (6.7, 9.4)	0.43

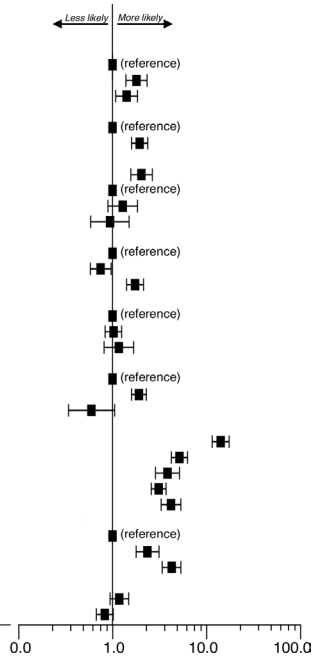

Figure 1 Dual therapy use among opioid users in the USA according to population characteristics. All estimates weighted to represent the US adult population. Dual therapy defined as receiving a prescription for a benzodiazepine and miscellaneous sedative in the same calendar year.

Table 1 Dual therapy use among opioid users in the USA according to level of the amount of opioid use

Opioid use	Per cent on dual therapy* (95% CI)	Estimated number of dual therapy users in the USA, millions
Any opioid prescription	9.2 (8.4 to 10.0)	2.6
By level of opioid use		
Single use (1 prescription)	3.9 (3.3 to 9.7)	0.54
Regular (2–4 prescriptions)	9.4 (7.9 to 11.2)	0.65
Heavy use (≥5 prescriptions)	18.4 (15.5 to 20.5)	1.41

All estimates are weighted to represent the US non-institutionalized population.
*Dual therapy defined as receiving a prescription for a benzodiazepine and miscellaneous sedative in the same calendar year.

using truncated International Classification of Diseases, Tenth Revision, Clinical Modification Codes (online supplemental appendix 2). Complex survey design methods were used to make national estimates by weighting the sample population. ORs were used to estimate the associations between independent variables and dual anxiolytic/sedative use (ie, benzodiazepine and non- benzodiazepine sedative) among opioid users.

RESULTS

Annually, we estimate 2.60 million adult Americans (1.0% of the US adult population) received prescriptions for an opioid, benzodiazepine, *and* non-benzodiazepine sedative. Among the 28.4 million prescription opioid users, we identified 9.2% (95% CI 8.4 to 10.0) who were also prescribed dual anxiolytic/sedative therapy. Within this group, the annual average number (SD) of prescriptions filled for opioids, benzodiazepines, and non-benzodiazepine sedatives was 24.7 (95% CI 23.3 to 26.2) per person. Figure 1 reveals dual anxiolytic/sedative therapy patient characteristics. Among opioid users, dual sedative/anxiolytic therapy use was most common among middle-aged adults, women, and non-Hispanic white individuals. The highest rates of dual therapy were observed among opioid users with severe pain, anxiety, depression, stress-related disorders, and sleep disorders. When stratified by opioid prescription number, high-volume prescribing (five or more per year) had a dual prescription rate of 18.4% (table 1).

DISCUSSION

To our knowledge this is the first study to document that several million American adults (9.1% of all opioid users and 18.4% of high prescription opioid users) receive the combination of an opioid, benzodiazepine, and non-benzodiazepine sedative medication. Patients with severe pain, sleep disorders (eg, obstructive sleep apnea), and mental illness had the highest likelihood of receiving dual therapy. No current guidelines exist regarding the safety of this prescribing practice, especially in subpopulations that may be particularly susceptible to sedation.

Our data are limited as the MEPS does not allow for identification of the sequencing of the medications over the calendar year. Second, our list of non-benzodiazepine sedatives may have been incomplete and underestimated the national totals, in effect biasing our findings toward lower rates. Hence, the prescribing practice may be even more common than in our results.

There are complex interactions among mental illness, pain, and sleep disorders.[7] We find that a surprisingly high number of Americans prescribed opioids are also undergoing treatment that includes a dual combination of anxiolytic and sedative medications. Given the potential dangers of this polypharmacy approach, future studies are warranted to determine the level of safety, especially among vulnerable populations.

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