

U.S. Prescribing of On-and-Off-Label Medications for Alcohol Use Disorder in Outpatient Visits: NAMCS 2014 to 2016



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INTRODUCTION

In the United States (U.S.), it is estimated that only 4% of people with alcohol use disorder (AUD) receive a Food and Drug Administration (FDA)–approved medication for treatment, such as disulfiram, naltrexone, or acamprosate.¹ There are six additional medications available in the U.S., not FDA-approved for the treatment of AUD, for which there is clinical trial evidence suggestive of safety and efficacy when used for AUD treatment: baclofen, gabapentin, ondansetron, topiramate, varenicline, and zonisamide.² Physicians can legally prescribe these medications for AUD or another clinical indication, based on their individual judgment of patients' likelihood of benefit and risk, even without formal FDA approval, a practice known as off-label prescribing. However, little is known about the extent to which both on-and-off-label medications for AUD are used in outpatient care. Using nationally representative prescribing data from ambulatory visits in the U.S., we estimated the prevalence of and factors associated with on-and-off-label medication prescription for AUD.

METHODS

We used data from the 2014–2016 National Ambulatory Medical Care Survey (NAMCS), an annual nationally representative survey of office-based physician visits administered by the Centers for Disease Control and Prevention.³ We identified all visits made by patients with AUD, based on whether patients had an AUD-related diagnostic code and/or were categorized as having “alcohol misuse, abuse, or dependence.” Next, we determined whether these visits by patients with AUD were associated with an active prescription for oral naltrexone, acamprosate, and/or disulfiram, which were categorized as on-label treatment, or associated with baclofen, gabapentin, ondansetron, topiramate, varenicline, and/or zonisamide, which were categorized as off-label treatment.

We did not consider nalmefene because the oral formulation, which is used for AUD in Europe, is not available in the U.S.

We used a multivariable-adjusted logistic regression analysis to examine associations between any AUD medication use with age, sex, race/ethnicity, and patient/prescriber characteristics (with $p < 0.05$ from bivariate analyses). Analyses were conducted in Stata (v.15.1, StataCorp.) and accounted for the complex survey sampling design in NAMCS using *svy* commands. This study was deemed exempt from review by Yale School of Medicine's Institutional Review Board because we used de-identified, publicly available data.

RESULTS

In 2014–2016, there were 687 outpatient visits, among adults aged ≥ 18 with a known diagnosis of AUD, nationally representative of 7,197,178 visits (Table 1). Of these, 15.4% (95% CI, 11.6–20.2%) were associated with an active prescription for any AUD medication, including 3.6% (1.8–7.2%) who received on-label treatment and 11.8% (8.7–15.9%) who received only off-label treatment.

Several factors were independently associated with greater likelihood of receiving any AUD medication, including current tobacco use (adjusted odds ratio = 2.32; 95% CI, 1.09–4.93), receiving ≥ 6 concomitant medications (2.99; 1.05–8.42), being prescribed antidepressants (2.92; 1.19–7.15), and being prescribed opioids (2.48; 1.70–8.54) (Table 2).

DISCUSSION

From 2014 to 2016, fewer than one in seven outpatient visits to physicians in the U.S. made by patients with AUD were associated with an active prescription for AUD treatments with clinical trial evidence suggestive of safety and efficacy, three-quarters of which were for off-label treatments that had not been formally approved by the FDA as safe and effective for use for AUD. While this evaluation indicates low rates of on-label treatment for AUD, similar to what has been observed among commercially insured and Veterans Health Administration patients,^{4, 5} it also suggests that most AUD treatment is off-label. It is possible that off-label medications are being prescribed to treat multiple indications and reduce unnecessary polypharmacy (e.g., gabapentin for AUD and anxiety). However, our findings raise concerns

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Table 1 Characteristics of Adults (Weighted %) According to AUD Medications Received in Office-Based Outpatient Visits: 2014–2016 National Ambulatory Medical Care Survey

Characteristics	Patients with AUD*	At least one on-label medication, row % (95% CI)*	At least one off-label medication, row % (95% CI)†
Unweighted sample, no.	687	28	88
Weighted sample [§]	7,197,178	3.6 (1.8–7.2)	11.8 (8.7–15.9)
Type of clinician seen			
General/family/internal medicine	2,874,617	4.4 (1.3–14.1)	14.8 (9.3–22.8)
Psychiatry	2,086,884	5.4 (2.4–11.6)	12.7 (7.7–20.2)
Other	2,235,677	0.9 (0.1–6.1)	7.2 (3.9–12.7)
Geographic region			
Northeast	1,777,200	7.3 (2.1–22.1)	6.8 (3.1–14.4)
South	1,958,494	3.4 (1.1–9.9)	8.7 (4.3–16.8)
Midwest	1,699,400	2.2 (0.6–8.3)	18.3 (11.1–28.5)
West	1,762,084	1.5 (0.5–4.4)	14.1 (8.1–23.3)
Age			
Young (18–45)	2,105,583	7.6 (3.6–15.2)	8.9 (5.0–15.3)
Middle-aged (45–65)	3,699,758	2.5 (1.1–5.8)	15.2 (10.2–22.2)
Older (65+)	1,391,837	0.5 (0.1–3.6)	7.2 (3.5–14.0)
Sex			
Female	2,517,543	1.8 (0.7–4.5)	14.5 (9.0–22.4)
Male	4,679,635	4.5 (2.2–9.2)	10.4 (7.0–15.1)
Race/ethnicity			
Non-Hispanic white	6,133,375	3.6 (1.6–7.9)	11.5 (8.2–15.9)
Other	1,063,803	3.4 (1.0–11.5)	13.6 (7.2–24.3)
Insurance type			
Private	3,297,184	5.7 (2.6–12.2)	5.6 (3.1–10.0)
Medicare	1,607,705	1.8 (0.6–5.5)	17.2 (10.5–27.1)
Medicaid/chip	769,414	0.0	23.2 (12.4–39.0)
Other	1,159,164	1.9 (0.6–6.0)	10.4 (4.2–23.2)
Current tobacco use			
No	3,369,567	1.9 (0.8–4.6)	6.3 (3.2–12.1)
Yes	2,594,151	5.0 (1.7–13.5)	14.6 (9.2–22.4)
No. of visits within the past 12 months			
0	1,324,528	1.6 (0.3–7.1)	7.4 (3.2–16.3)
1+	5,872,650	4.1 (2.01–7.8)	12.8 (9.3–17.3)
No. of chronic conditions			
<2	1,026,812	0.0	6.2 (1.5–22.1)
2+	6,170,366	4.2 (2.1–8.4)	12.7 (9.3–17.2)
No. of concomitant medications			
<6	5,244,730	4.1 (1.8–9.0)	5.7 (3.4–9.6)
6+	1,952,449	2.2 (0.9–5.4)	28.2 (19.7–38.5)
Substance use disorder [#]			
No	4,588,602	2.3 (0.8–6.1)	9.5 (5.9–14.8)
Yes	2,608,576	5.9 (3.0–11.4)	15.9 (10.8–22.9)
Depression			
No	4,301,770	1.3 (0.5–3.4)	10.3 (6.8–15.3)
Yes	2,895,408	7.0 (3.0–15.5)	14.1 (8.9–21.5)
Schizophrenia			
No	7,072,840	3.6 (1.7–7.3)	11.7 (8.5–15.9)
Yes	124,338	3.4 (0.5–20.4)	17.5 (5.1–45.7)
Bipolar disorder			
No	6,305,074	2.8 (1.1–7.0)	11.8 (8.4–16.2)
Yes	892,104	9.1 (2.7–20.9)	12.0 (6.3–21.4)
Anxiety disorder			
No	6,136,412	2.2 (1.0–4.4)	11.9 (8.5–16.3)
Yes	1,060,766	11.7 (4.3–28.5)	11.5 (6.3–19.8)
Liver disease			
No	6,719,553	3.9 (1.9–7.7)	11.5 (8.4–15.7)
Yes	477,625	0.0	15.9 (6.3–34.8)
Antidepressants prescribed			
No	4,587,430	2.1 (1.0–4.8)	6.2 (3.9–9.7)
Yes	2,609,748	6.2 (2.9–12.7)	21.7 (15.0–30.2)
Opioids prescribed			
No	6,198,511	4.0 (1.9–8.1)	8.3 (5.7–11.9)
Yes	998,667	1.2 (0.3–5.4)	33.6 (19.9–50.7)
Opioid agonists prescribed (buprenorphine and methadone)			
No	6,856,225	3.8 (1.8–7.6)	11.8 (8.6–16.0)

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Table 1. (continued)

Characteristics	Patients with AUD*	At least one on-label medication, row % (95% CI)*	At least one off-label medication, row % (95% CI)†
Yes	340,953	0.0	11.6 (4.0–29.0)
Alcohol use disorder counseling [#]			
No	5,947,058	3.5 (1.5–7.9)	11.5 (8.2–15.9)
Yes	1,250,120	3.9 (1.3–12.3)	13.5 (6.6–25.7)
Substance use disorder counseling [#]			
No	6,667,959	3.5 (1.7–7.4)	11.6 (8.3–15.9)
Yes	529,219	4.3 (1.6–11.2)	14.8 (5.8–32.6)

AUD, alcohol use disorder; No., number

*U.S. Food and Drug Administration–approved medications for AUD treatment: acamprosate, naltrexone, or disulfiram (with or without off-label medications)

†Off-label medications for AUD treatment: baclofen, gabapentin, ondansetron, topiramate, varenicline, and zonisamide

‡Patients were categorized as having AUD if they: (1) had at least one AUD-related diagnostic code (International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification) among the five diagnoses provided for each patient visit and/or (2) were categorized as having AUD based on a survey section asking “Regardless of the diagnosis previously entered, does the patient now have:”, which included the response category “alcohol misuse, abuse, or dependence”

§Unweighted counts; weighted counts: patients with AUD (n=687; 89,243) receiving acamprosate (n=6; 60,904), disulfiram (n=6; 45,454), naltrexone (n=19; 182,888), gabapentin (n=66; 714,289), topiramate (n=13; 72,273), varenicline (n=5; 48,992), zonisamide (n=4; 3405), baclofen (n=9; 89,243), and ondansetron (n=6; 35,656)

||The “Other” category includes non-Hispanic Blacks, Hispanics, and non-Hispanic Others

¶Of 14 chronic conditions for which the National Ambulatory Medical Care Survey collected information (e.g., arthritis, congestive heart failure, diabetes)

#In the Survey, these are referred to as “abuse” or “abuse and dependence”

Table 2 Prevalence of AUD Medication Prescriptions (Weighted %) in Office-Based Outpatient Visits According to Subgroups of U.S. Adults: 2014–2016 National Ambulatory Medical Care Survey

Characteristics (reference group)	Patients with AUD No. (column %) [95% CI]*	Any AUD medication No. (column %) [95% CI]†	Any AUD medication vs. no medication adjusted odds ratios [95% CI] ‡
Total, weighted visits	7,197,178	1,108,211	
Type of clinician seen (General/family/internal medicine)			
Psychiatry	29.0 (22.4–36.6)	378,218 (34.1) [22.1–48.7]	0.63 [0.13–3.11]
Other	31.1 (23.6–39.7)	179,690 (16.2) [9.4–26.6]	0.51 [0.19–1.38]
Geographic region			
Northeast	24.7 (18.9–31.6)	249,764 (22.5) [11.5–39.5]	–
South	27.2 (19.8–36.2)	236,653 (21.3) [12.5–34.1]	–
Midwest	23.6 (18.10–30.18)	348,190 (31.4) [19.6–46.2]	–
West	24.5 (18.6–31.6)	273,603 (24.7) [14.6–38.6]	–
Age (young (18–44 years))			
Middle-aged (45–64 years)	51.4 (45.0–57.7)	655,050 (59.1) [47.1–70.1]	1.68 [0.71–4.02]
Older (65+ years)	19.3 (15.4–24.0)	106,884 (9.6) [4.9–18.1]	0.40 [0.10–1.67]
Sex (female)			
Male	65.0 (58.1–71.3)	697,691 (63.0) [50.3–74.1]	1.32 [0.54–3.24]
Race/ethnicity (non-Hispanic white)			
Other [§]	14.8 (11.4–19.0)	181,093 (16.3) [9.3–27.1]	1.23 [0.30–4.96]
Insurance type			
Private	48.3 (41.3–55.2)	374,950 (37.5) [24.9–52.0]	–
Medicare	23.5 (18.7–29.1)	305,101 (30.5) [19.4–44.5]	–
Medicaid/chip	11.3 (7.9–15.8)	178,130 (17.8) [9.6–30.6]	–
Other	17.0 (11.8–23.8)	141,537 (14.2) [6.3–28.9]	–
Current tobacco use (No)			
Yes	43.5 (37.5–49.8)	507,474 (64.7) [48.5–78.0]	2.32 [1.09–4.93]
No. of visits within the past 12 months (0)			
1+	81.6 (75.8–86.3)	988,802 (89.2) [80.2–94.4]	–
No. of chronic conditions (<2)			
2+	85.7 (79.9–90.1)	1,044,181 (94.2) [79.7–98.5]	–
No. of concomitant medications (<6)			
6+	27.1 (21.7–33.3)	591,899 (53.4) [38.5–67.8]	2.99 [1.05–8.42]
Substance use disorder [¶] (No)			
Yes	36.2 (30.2–42.7)	570,359 (51.5) [38.4–64.4]	1.92 [0.82–4.47]
Depression (No)			
Yes	40.2 (34.6–46.1)	610,200 (55.1) [40.8–68.6]	1.78 [0.62–5.10]
Schizophrenia (No)			
Yes	1.7 (0.8–3.8)	25,982 (2.3) [0.8–6.6]	–
Bipolar disorder (No)			
Yes	12.4 (8.9–17.0)	188,509 (17.0) [9.8–27.8]	–
Anxiety disorder (No)			
Yes	14.7 (11.1–19.4)	246,224 (22.2) [13.1–35.2]	–
Liver disease (No)			
Yes	6.6 (3.9–11.1)	75,734 (6.8) [2.9–15.1]	–
Antidepressants prescribed (No)			
Yes	36.3 (30.2–42.8)	725,821 (65.5) [55.9–74.7]	2.92 [1.19–7.15]
Opioids prescribed (No)			
Yes	13.9 (10.1–18.8)	347,458 (31.4) [19.3–46.5]	2.48 [1.70–8.54]
Opioid agonists prescribed (buprenorphine and methadone) (No)			
Yes	4.7 (2.4–9.0)	39,393 (3.6) [1.3–9.1]	–
Alcohol use disorder counseling ^{¶¶} (No)			
Yes	17.4 (13.1–22.6)	19.7 (10.7–33.3)	–
Substance use disorder counseling ^{¶¶} (No)			
Yes	7.4 (4.8–11.1)	9.1 (4.2–18.7)	–

AUD, alcohol use disorder; CI, confidence interval; No., number

*Patients were categorized as having AUD if they (1) had at least one AUD-related diagnostic code (International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification) among the five diagnoses provided for each patient visit and/or (2) were categorized as having AUD based on a survey section asking “Regardless of the diagnosis previously entered, does the patient now have:”, which included the response category “alcohol misuse, abuse, or dependence”

†Off-label medications for AUD treatment: baclofen, gabapentin, ondansetron, topiramate, varenicline, and zonisamide

‡The multivariate model includes variables that were statistically significant based on bivariate analyses with Bonferroni adjusted $P < 0.05$. “–” denotes variables that were not included in the multivariable-adjusted analyses

§“Other” category: non-Hispanic Blacks, Hispanics, and non-Hispanic Other

||Of 14 chronic conditions for which the National Ambulatory Medical Care Survey collected information (e.g., arthritis, congestive heart failure, diabetes)

¶In the Survey, these questions use the language “abuse” or “abuse and dependence”

about the underutilization of FDA-approved medications in outpatient clinical practice.

Limitations include small number of eligible records; limited generalizability outside of outpatient physician visits; lack of information on medication dosing (e.g., strengths, duration,

and route of administration); inability to determine whether on-and-off-label medications may have been prescribed for reasons other than AUD; and non-accounting for other prescribed medications that may have been used for off-label AUD treatment. While efforts to increase AUD treatment in ambulatory care settings might be improved by targeting

certain patients and physicians,⁶ further research is necessary to confirm the effectiveness and safety of off-label treatments. In addition, more work should be done to determine reasons for low AUD medication prescribing, including the impact of treatment goals, uncertainties about whether and for whom different medications may work, and patient preferences.¹

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Author Contribution Dr. Wallach had had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved with the concept and design of the study. Drs. Wallach and Rhee conducted the statistical analyses. Dr. Wallach drafted the manuscript. All authors contributed to the critical revisions of the manuscript for important intellectual content.

Data Availability The datasets analyzed during the current study are available at https://www.cdc.gov/nchs/ahcd/ahcd_questionnaires.htm.

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Declarations:

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