Veteran adherence to oral versus injectable AUD medication treatment

Hayden Stewart, PharmD[1]; Brian G. Mitchell, PharmD, BCPS, BCPP[2]; Daniel Ayanga, MD, MPH[3]; Annette Walder, MS[4]

Abstract

Introduction: AUD medication treatment has been shown to improve outcomes compared with placebo when confined to per-protocol analysis. The same outcomes, however, have not always been maintained in intent-to-treat analysis, thus suggesting adherence may have a significant impact on efficacy outcomes. There is conflicting evidence present in the literature comparing adherence to oral versus injectable AUD pharmacotherapy and a paucity of information in the veteran population on risk factors for low adherence.

Methods: The primary end point of this retrospective chart review was to determine whether adherence rates differ between oral and injectable AUD treatments in veterans during the first year of treatment (at 3, 6, 9, and 12 months) using the portion of days covered model. Secondary end points were to determine differing characteristics between patients with high versus low adherence and compare alcohol-related readmission rates and discontinuation rates between groups.

Results: Adherence to injectable extended-release (XR) naltrexone was significantly higher than oral naltrexone at all time points and was significantly higher than disulfiram at 3, 6, and 9 months, but it was not significantly different from acamprosate at any time point. At months 9 and 12, acamprosate had significantly higher adherence compared with oral naltrexone. Patients with higher adherence were seen more frequently in the mental health clinic and had previously tried more AUD medications. The discontinuation rates and alcohol-related admission rates were not significantly different between groups at 1 year.

Discussion: XR naltrexone may improve adherence rates compared with oral naltrexone or disulfiram, but not acamprosate based on these outcomes. Patients may have increased adherence if they are seen more often in clinic and have trialed more AUD medications.

Keywords: alcohol use disorder, AUD, adherence, naltrexone, acamprosate, disulfiram

[1] (Corresponding author) PGY-2 Psychiatric Pharmacy Resident, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas, hay.m.higg@gmail.com, ORCID: https://orcid.org/0000-0003-2018-5391; [2] Clinical Pharmacy Specialist, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; Assistant Professor, Department of Psychiatry & Behavioral Sciences, Baylor College of Medicine, Houston, Texas, ORCID: https://orcid.org/0000-0003-1735-5601; [3] Addiction Psychiatrist, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; Assistant Professor, Department of Psychiatry & Behavioral Sciences, Baylor College of Medicine, Houston, Texas, ORCID: https://orcid.org/0000-0002-2116-5467; [4] Statistician, IQuESt, Houston, Texas, ORCID: https://orcid.org/0000-0003-4799-6039

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Introduction

Alcohol is the most widely used substance in the United States, with nearly 140 million people reporting use within the past month.[1] Of those, nearly half (67.1 million) admit to binge drinking (more than 5 drinks per occasion for men or 4 drinks per occasion for women), and 11.8% of alcohol users (16.6 million) admit to heavy alcohol use, defined as binge drinking on 5 or more days in the past month.[1] Misuse of alcohol is common both among civilians and military veterans. For veterans establishing

care with the Department of Veterans Affairs (VA) for the first time, 10.5% of men and 4.8% of women will meet criteria for AUD, defined in the *DSM-5* as a pattern of use that results in marked distress and/or impairment, with 2 or more associated symptoms occurring in the past year.[2]

There are currently 4 FDA-approved agents for the treatment of AUD, including 3 oral options—naltrexone, acamprosate, and disulfiram—and the extended-release (XR) naltrexone injection that is administered intramuscularly once a month. Previous studies[3-6] have shown that pharmacologic treatment for AUD significantly reduces alcohol cravings, number of drinking days, heavy drinking, and relapses compared with placebo. However, a systematic review[7] found that few efficacy studies of naltrexone for AUD have incorporated high-assurance assessments of adherence into their methods. In some of these studies, when patients who were less adherent or nonadherent were included in intent-to-treat analysis, pharmacologic treatment either did not significantly affect drinking outcomes relative to placebo or did so to a lesser extent compared with patients with higher adherence in per-protocol analysis.[7] Because adherence is a defining difference between intent-to-treat and per-protocol analysis, adherence level appears to be a factor impacting the efficacy of pharmacologic treatment for AUD, which makes identifying contributors to nonadherence of the utmost importance in order to improve outcomes in this patient population.

Medication-specific factors impacting adherence commonly include either administration or adverse effects. For example, acamprosate is a generally well-tolerated medication, but it requires administration three times per day, which may prove challenging for some patients.[6] Disulfiram, on the other hand, is only taken once daily but may require some lifestyle changes to avoid alcohol-containing products. Alternatively, XR naltrexone is administered only once per month but requires a clinic visit and may result in injection site reactions.[8]

As with other long-acting injectables, XR naltrexone is commonly preferred for patients who have poor adherence to oral medications. In fact, XR naltrexone has previously been shown to have a lower discontinuation rate compared with oral alternatives for AUD, including naltrexone, disulfiram, and acamprosate.[3] However, in a more recent study[6] no significant difference was found in adherence rates between oral and XR naltrexone, which is converse to what is widely accepted in clinical practice. This study also found that oral naltrexone significantly reduced the number of alcohol-related admissions (ARAs) at 30 days, whereas XR naltrexone did not. Bear in mind that this was a retrospective study[6] with a small sample size. At present, there is conflicting evidence on this topic and a paucity of information specifically in the veteran population regarding adherence to oral versus injectable AUD pharmacotherapy and patient-specific risk factors for low adherence.

Methods

The primary objective of this study was to determine whether adherence rates differ between oral naltrexone, disulfiram, or acamprosate and injectable XR naltrexone in veterans during the first year of treatment using the portion of days covered (PDC) model. The PDC model computes an adherence percentage based on the number of days during a time period that a patient has an adequate medication supply based upon refill data.[9] For XR naltrexone, *refills* were determined for the PDC by documentation of injections by clinic nurses (because this is a clinic-administered medication). The PDC is an indirect measure of adherence and does not assess for actual medication administration for oral drugs. Secondary objectives were to determine differing characteristics between patients with high ($\geq$80%) versus low ($\leq$60%) adherence at 3 months and to compare medication discontinuation and ARA rates between medication groups at 12 months.[9,10]

A retrospective chart review was conducted to include mental health patients identified from the VA Informatics and Computing Infrastructure database who were initially prescribed the AUD medication between June 30, 2015 and June 30, 2018. Included patients were adults newly started on the AUD medication who had an AUD diagnosis on the index date and were treated outpatient for the first year of treatment (except for ARAs). Patients were excluded if prescribed the AUD medication on an as-needed basis, if they had cognitive impairment (neurocognitive disorder, dementia, history of cerebrovascular accident), and if they were diagnosed with bipolar disorder, schizophrenia, or a personality disorder.

Data collected for the primary outcome included the AUD medication prescribed, route of administration, and the PDC calculated every 3 months through the first year of treatment following AUD medication initiation. For the secondary objectives, information collected included demographic information, psychiatric diagnoses, psychotropic medications, involvement in psychotherapy, number of mental health visits with a prescriber during the first year, any previous AUD medication trials since 1995 as documented in the electronic medical record, number of standard drinks per day per patient report on the index date, ARA rate, and discontinuation rate (number of patients discontinuing treatment out of the total for each medication group). Patient data were collected through the computerized patient record system by manual chart

TABLE 1: Baseline characteristics of the study

	XR-NTX n = 39	NT n = 37	DIS n = 37	ACA n = 37	P Value[a]
Age, y, mean	46.9	48.4	45.9	43.6	.531
Male, %	97.4	91.9	94.6	91.9	.628
Ethnicity, n (%)					
White	26 (67)	23 (62.2)	15 (40.5)	16 (43.3)	**.025**
African American/Black	13 (33)	11 (29.7)	15 (40.5)	8 (21.6)	.362
Hispanic	0	1 (2.7)	4 (10.8)	8 (21.6)	**.013**
Other	0	2 (5.4)	3 (8.2)	5 (13.5)	.306
Stable housing, %	87.2	91.2	94.6	100	.131
Psychiatric diagnoses, mean	1.79	1.92	1.6	1.81	.496
Psychiatric diagnoses, %					
Depression	53.8	67.6	51.4	70.3	. . .
PTSD/trauma-related disorder	51.3	56.8	51.4	51.4	. . .
SUD	25.6	16.2	27	16.2	. . .
Psychiatric medications, mean	2.32	1.35	1.7	2.03	**.004**
Psychiatric medications, %					
Antidepressant	36	30	27	31	. . .
Antipsychotic	5	4	4	5	. . .
Sleep aid	25	12	17	21	. . .
Previous AUD medications, mean	1.23	0.05	0.51	0.41	**.00001**
Drinks per day, mean	6.46	6.67	9.1	7.57	.511
Average AUD medication dose, mg	380/mo	50/d	318/d	1593/d	. . .

ACA = acamprosate; DIS = disulfiram; NTX = naltrexone; TID = 3 times daily; XR = extended release.
[a]Boldface values indicate statistical significance ($P < .05$).

reviews. For the statistical analysis, baseline characteristics were analyzed using analysis of variance and χ^2 analysis. The primary outcome was determined using Mann-Whitney U test. Tests used for secondary outcomes depended upon the type of data and sample size and included Student t test, Fisher exact test, and χ^2 test.

Results

A total of 16 079 patients during the specified study time period met criteria based only on alcohol-related ICD codes. Of those, 1523 patients were newly started on an AUD medication and had been seen at least once within the year following initiation. Following application of exclusion criteria, 1158 patients remained (n = 131 acamprosate, n = 65 disulfiram, n = 884 naltrexone, and n = 78 XR naltrexone). Of those, a total of 150 patients were selected for review using a random number generator (n = 37 in each of the oral medication groups, n = 39 in the XR naltrexone group).

Of those included, 21% (n = 32) had high adherence (PDC ≥80%) and 37% (n = 56) had low adherence (PDC ≤60%). The average age of patients included was mid-40s and most of those included were male (Table 1). There was a significant difference between the groups at baseline for ethnicity, specifically for the proportion of white and Hispanic patients. There was also a significant difference in the number of current psychiatric medications, which was highest in the XR naltrexone and acamprosate groups, and the number of previous AUD medication trials, which was more than twice as high in the XR naltrexone group.

For the primary outcome (Table 2), XR naltrexone had significantly higher adherence compared with oral naltrexone at 3, 6, 9, and 12 months. XR naltrexone also had significantly higher adherence compared with disulfiram at 3, 6, and 9 months and trended toward significance at 12 months. Adherence to XR naltrexone was not significantly different from acamprosate at any time point. There were no significant differences between oral treatment options at either 3 or 6 months, but at 9 and 12 months adherence to acamprosate was significantly better than it was to oral naltrexone.

For the secondary end points (Tables 3 and 4), 2 characteristics that were significantly different between those with high versus low adherence were the number of

TABLE 2: Oral versus injectable AUD medication adherence rates

	PDC, %	P Value[a]
3-mo Average PDC comparison		
XR-NTX	68.37	
NTX	48.64	**.006**
DIS	49.96	**.011**
ACA	59	.171
NTX	48.64	
DIS	49.96	.850
ACA	59	.139
DIS	49.96	
ACA	59	.201
6-mo Average PDC comparison		
XR-NTX	57.47	
NTX	33.88	**.003**
DIS	36.78	**.018**
ACA	44.62	.186
NTX	33.88	
DIS	36.78	.569
ACA	44.62	.059
DIS	36.78	
ACA	44.62	.153
9-mo Average PDC comparison		
XR-NTX	49.75	
NTX	22.69	**.003**
DIS	29.9	**.034**
ACA	38.65	.289
NTX	22.69	
DIS	29.9	.177
ACA	38.65	**.013**
DIS	29.9	
ACA	38.65	.174
12-mo Average PDC comparison		
XR-NTX	45.07	
NTX	19.43	**.023**
DIS	23.87	.066
ACA	34.93	.603
NTX	19.43	
DIS	23.87	.238
ACA	34.93	**.029**
DIS	23.87	
ACA	34.93	.174

ACA = acamprosate; DIS = disulfiram; NTX = naltrexone; PDC = portion of days covered; XR = extended release.

[a]Boldface values indicate statistical significance ($P < .05$).

mental health visits during the first 3 months of treatment and the number of previous AUD medications, which were both more than twice as high in the highly adherent group. After 1 year of treatment, there were no significant differences between groups in terms of either the ARA rate or rate of medication discontinuation.

Discussion

To date, there is limited evidence when comparing adherence between oral and injectable AUD medications. The findings of this study are more consistent with those by Bryson et al,[3] which found a superior adherence rate with XR naltrexone. This trend of higher adherence with long-acting injectables has also been seen in other psychiatric illnesses, such as schizophrenia and opioid use disorder.[11,12] However, in this study this trend only held true in comparison with oral naltrexone and disulfiram. It is important to note that ~40% of the acamprosate group was prescribed the renally adjusted dose of 333 mg 3 times daily. Of those prescribed acamprosate at the renally adjusted dose (n = 15), only 2 patients actually met criteria for the reduced dose based on their creatinine clearance. It is possible that this could have resulted in fewer adverse effects and improved tolerability in these patients, thus helping to explain the adherence outcomes.

It is interesting to note that despite the suboptimal dosing, which could reasonably reduce efficacy, ARA for the acamprosate group was the lowest (0 ARA), although not significantly different from other groups. Furthermore, acamprosate has been demonstrated to be most effective for sustaining rather than inducing remission, but in this study most patients were not in remission when initiated on acamprosate, as demonstrated by a lack of difference in the baseline alcohol consumption.[5] Another potential explanation for the lack of difference in adherence between XR naltrexone and acamprosate could be that the XR naltrexone patients had a seemingly higher severity of AUD, as indicated by an increased number of previously trialed AUD medications as well as a nonsignificantly higher baseline number of psychiatric comorbidities. A study with more well-matched patient populations could elucidate this further.

Regarding patient-specific risk factors for low adherence, patients seen less frequently in the mental health clinic and those who had previously been exposed to fewer AUD medications were less likely to be adherent. It is hypothesized that adherence was higher for those seen more frequently in clinic because of provider-driven refills placed during the mental health visits. Also, patients who attend more of their scheduled appointments may be inherently more likely to be adherent to their medications, although in this study we did not assess the appointment no-show rate of included patients.

TABLE 3: Secondary outcomes of the study: 3-month outcomes

	High Adherence (PDC $\geq$ 80)	Low Adherence (PDC $\leq$ 60)	P Value[a]
Age, y, mean	48.06	44.27	.238
Male, %	100	91.1	.154
Ethnicity, %			
White	61.29	52.83	.501
African American/Black	29.03	32.08	.81
Hispanic	9.68	9.43	.293
Asian	0	5.66	1
Stable housing, %	90.63	91.84	1
Psychiatric diagnoses, mean	1.81	1.76	.824
Psychiatric medications, mean	1.88	1.71	.56
Psychotherapy, % yes	43.75	26.79	.157
Mental health visits, mean	1.53	0.71	**.0001**
Previous AUD medication trials, mean	0.72	0.32	**.005**
Drinks per day, mean	6.06	8.03	.28

ACA = acamprosate; ARA = alcohol-related admission; DIS = disulfiram; NTX = naltrexone; PDC = portion of days covered.
[a]Boldface values indicate statistical significance ($P < .05$).

Regarding previous AUD medication trials, it is possible that failure of initial AUD medications may be more characteristic of the disease state itself rather than the specific medication chosen. Up to 90% of patients with a diagnosis of AUD experience at least 1 relapse prior to achieving sobriety.[13] Therefore, the duration of AUD could be a potential confounder for adherence outcomes because regardless of the initial agent chosen, patients are at high risk for treatment failure due to the relapsing and remitting nature of AUD. More study in this area is needed.

An interesting trend noticed was that patients prescribed oral naltrexone had the fewest previous AUD medication trials. This is in accordance with the most recently published guidelines,[8] which recommend either naltrexone or acamprosate first-line for AUD. Given the once-daily dosing for naltrexone, this option is typically favored as the initial agent of choice. It should also be noted that XR naltrexone had the highest number of previous AUD medication trials, likely because it entered the market most recently and many providers may choose to establish tolerance to naltrexone with the oral formulation prior to administering the injectable, although this is not required.

Lastly, as previously stated in Methods, specific psychiatric disease states were excluded in this study. This was done to account for an increased risk of medication nonadherence for the aforementioned disease states. Patients with PTSD, however, were not excluded and in this study more than 60% of patients had a diagnosis of PTSD. Therefore, it is worth noting that PTSD has also been shown to be an independent risk factor for medication nonadherence in multiple settings, including HIV, hypertension, and other medical comorbidities, and might have confounded adherence to AUD medications in this study.[14-16]

Limitations of this study include: (1) a retrospective study design that introduced inherent bias; (2) the relatively small sample size and absence of power calculation; (3) the

TABLE 4: Secondary outcomes of the study: 12-month outcomes

Group (No.)	ARA, No.	ARA, %	Discontinuation, No.	Discontinuation, %
XR-NTX (39)	4	10.3	14	35.9
NTX (37)	2	5.4	18	48.7
DIS (37)	4	10.8	14	29.7
ACA (37)	0	0	11	37.8
P value	.472	. . .	.403	. . .

ACA = acamprosate; ARA = alcohol-related admission; DIS = disulfiram; NTX = naltrexone; PDC = portion of days covered; XR = extended release.

lack of access to non-VA data specifically for ARA and previous medication trials, which increases the possibly of collecting inaccurate data; (4) patients identified by AUD medication use rather than via a standard *DSM* AUD diagnosis; and (5) the lack of excluding patient prescribed gabapentin and topiramate, which are both prescribed off-label for AUD. Although there were relatively few patients prescribed topiramate, approximately 1 in 5 patients was taking gabapentin, which could have confounded outcomes for those patients, especially for the acamprosate (37.8%) and XR naltrexone (38.5%) groups, which had the highest number of patients taking gabapentin.

In conclusion, the results of this study suggest that use of XR naltrexone may improve adherence rates in patients with AUD compared with oral naltrexone or disulfiram, but not in comparison with acamprosate. Patients may have increased adherence if they are seen more often in clinic and have trialed more AUD medications.

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