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Persistence with Oral Naltrexone for Alcohol Treatment: Implications for Healthcare Utilization

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Abstract

Aims—Concerns have been raised about patients' failure to persist in alcohol treatment. We examined prescriptions for oral naltrexone in a large, nationally distributed treatment population to identify characteristics and healthcare utilization patterns associated with persistence.

Design—Data from the 2000-2004 MarketScan[®] Commercial Claims and Encounters Database were used to identify patients with alcohol-related claims who were prescribed naltrexone.

Measurements—Analysis identified patient characteristics that predicted persistence with naltrexone (defined as having filled prescriptions for $\geq 80\%$ of the 6-month treatment period) and its association to healthcare utilization.

Findings—Of 1,138 patients, 162 (14.2%) were persistent in obtaining naltrexone. Non-persistent patients were significantly younger, more likely to be hourly employees and to live in an area with a lower median income, and less likely to be newly diagnosed with an alcohol-related disorder. Non-persistence in obtaining naltrexone was associated with significantly more intensive treatments, including inpatient detoxification, emergency room visits, and hospitalizations.

Conclusions—Over a 6-month period, more than 85% of patients who filled an initial prescription for naltrexone did not persist in obtaining the medication. Non-persistence was associated with significantly greater use of costly healthcare services. Because the study was correlational, it is not possible to conclude that persistence reduced healthcare costs, since better prognosis patients may have been more persistent. Research is needed to determine whether interventions that enhance persistence with naltrexone therapy improve treatment outcomes and reduce healthcare costs.

Keywords

Naltrexone; Persistence; Healthcare Utilization; Alcohol Treatment

Introduction

Alcohol use disorders (AUDs, including alcohol abuse and dependence) occur commonly in the general population, with recent estimates of their current (i.e., past-year) prevalence of

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8.46% (1). In addition to their high prevalence, AUDs are associated with a variety of adverse medical, psychiatric, family, legal, and work-related problems (2), with an estimated annual cost in the United States of nearly \$185 billion (3). Not uncommonly, individuals with an alcohol use disorder are identified as needing treatment by virtue of having co-occurring medical or psychiatric problems.

Despite the adverse effects of AUDs, most individuals with such a diagnosis never receive treatment (4-8). In an effort to improve both the efficacy and the acceptability of alcohol treatment to both patients and the treatment community, there has been considerable research on interventions for these disorders. One particular focus of research has been the identification and evaluation of medications to treat alcohol dependence, which since 1994 has resulted in the approval by the U.S. Food and Drug Administration of three medications to treat the disorder: oral naltrexone, acamprosate, and extended-release naltrexone. These represent the first three medications approved since disulfiram became available for clinical use in 1949.

The use of available medications is substantially limited by poor adherence to prescribed regimens. Medication adherence is a problem in many therapeutic areas and it is of particular concern among individuals who drink alcohol, particularly those who drink heavily (9-13). Poor medication adherence has been identified as the basis for the failure of some medication trials to show a drug-placebo difference despite other evidence of the efficacy of the medications (14,15). Although efforts have been made to quantify adherence to oral medication in clinical trials (16-18), data are not available to indicate the extent to which patients in real-world clinical practice adhere to oral medications.

Although daily medication adherence can be difficult to measure, it is feasible retrospectively to analyze patient refills of oral naltrexone prescriptions through point-of-sale pharmacy data. Since this approach does not directly measure pill-taking compliance, it is not herein referred to as adherence, but rather as prescription persistence. The present study was conducted to determine the extent and predictors of persistence with oral naltrexone prescriptions in clinical practice. A second objective of the study was to ascertain the patterns of healthcare utilization associated with poor persistence. Such factors might be expected to help identify alcoholic patients who could benefit most from an intervention aimed at improving persistence with naltrexone treatment.

Methods

A retrospective database analysis was conducted: 1) to determine rates of persistence with naltrexone prescriptions, 2) to identify pretreatment patient characteristics associated with non-persistence, and 3) to determine healthcare utilization patterns associated with persistence with oral naltrexone prescriptions among patients with alcohol-related diagnosis. To be included, patients had to have at least one medication claim for oral naltrexone and no medication claims for disulfiram or acamprosate in the 3 months before the earliest naltrexone claim. They also had to have at least one claim for an alcohol-related diagnosis code using the criteria of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) in the six months before or six months after the earliest naltrexone claim. To be as inclusive as possible, we used a list of diagnoses from Harwood et al. (3). The following alcohol-related conditions were represented: Alcohol psychoses; alcohol dependence syndrome; nondependent abuse of alcohol; alcoholic polyneuropathy; alcoholic cardiomyopathy; alcoholic gastritis; alcoholic fatty liver; acute alcoholic hepatitis; alcoholic cirrhosis of the liver; alcoholic liver damage, unspecified; fetal alcohol syndrome; excessive blood level of alcohol; toxic effects of ethyl alcohol; and accidental poisoning by alcohol. The data were obtained prior to the availability of extended-release naltrexone for

clinical use, so there were no claims for that medication. Patients also had to have ≥ 6 months of continuous enrollment both prior to and following the earliest oral naltrexone claim.

Data were obtained from the MarketScan[®] Commercial Claims and Encounters Database from Thomson Healthcare (Ann Arbor, MI) for healthcare services incurred during the period January 1, 2000 through December 31, 2004. This database contains inpatient, emergency department, outpatient, and outpatient pharmacy claims for more than 5 million employees and their dependents annually from approximately 50 large U.S. employers. Health plan offerings of these employers include point-of-service, HMO, and traditional indemnity plans. Because some plans do not cover or carve out substance abuse treatment, the study sample was limited to patients with substance abuse coverage through their health plans.

Statistical Analysis

Persistence was derived using outpatient pharmacy claims and was defined as the number of days that oral naltrexone was supplied from all claims for the medication during the 6-month period after the first prescription was filled, divided by 180 (total) days. Oral naltrexone users were divided into a non-persistent group [i.e., those filling prescriptions for oral naltrexone for $< 80\%$ of the 6-month period (i.e., less than approximately 5 months)] and a persistent group (i.e., those filling prescriptions for oral naltrexone for $\geq 80\%$ of the 6-month period). Clinically, this is an optimistic threshold, since even with prescriptions filled for $\geq 80\%$ of the 6-month period it is possible that a patient could have taken medication for considerably fewer than 80% of the days of that period. Nevertheless, this categorization is similar to that used in studies measuring adherence to other treatments (19-21). Descriptive analyses were used to compare the persistence groups on demographic and clinical characteristics during the 6 months prior to the first oral naltrexone prescription (pretreatment period) and the healthcare utilization rates in both the pretreatment and 6-month treatment period. We used a standard approach to determine disease-specific utilization in claims analyses. Specifically, we divided utilization into alcohol- or non-alcohol-related based on the primary diagnosis on each claim, using the same alcohol-related diagnosis codes as those used to identify the sample. Medical comorbidities present in the pretreatment period were assessed using two measures (higher scores on either of which indicate a greater burden of comorbidity): the Charlson Comorbidity Index (CCI; based on ICD-9-CM diagnosis codes) and the Chronic Disease Score (CDS; based on drug claims). Patients with claims for an alcohol- or drug-related diagnosis in the pretreatment period were flagged. The former was used as a proxy for being in treatment for an alcohol-related disorder prior to the start of oral naltrexone therapy, while the latter was indicative of having comorbid drug abuse or dependence.

The number of oral naltrexone prescriptions filled over the 6-month treatment period was defined as the number of unique dates of service for oral naltrexone from the treatment start date to the treatment start date plus 180 days. The treatment start date was the date of the earliest naltrexone claim and represented the initiation of naltrexone therapy, following at least 3 months without evidence of such therapy. The percentage of patients having a filled oral naltrexone prescription for at least 1 day during a given month was based on oral naltrexone prescription fill dates and the number of days for which the supply was dispensed each time.

Univariate (chi-square analysis and t-tests) and multivariate (logistic regression) analyses were used to determine the demographic and clinical characteristics that were associated with persistence status. Chi-square tests were used to compare the persistent and non-

persistent groups on categorical measures of treatment utilization (i.e., yes/no service-use variables).

Results

Of 1,138 oral naltrexone patients identified, 162 (14.2%) were categorized as persistent, while the vast majority of patients (85.8%) failed to fill prescriptions for $\geq 80\%$ of the 6-month treatment period. The majority (51.8%) of oral naltrexone users filled only a single prescription for the medication [mean=2.24 (SD=1.7); median=1; range=1–8]. For the non-persistent group, the mean number of oral naltrexone prescriptions filled in the 6-month study period was 1.74 (SD=1.12), with a median of 1. For the persistent group, the mean was 5.28 (SD=1.38), with a median of 6. A comparison of non-persistent and persistent patients on insurance plan types revealed no significant differences.

As shown in Figure 1, the percentage of patients that filled an oral naltrexone prescription for at least 1 day during a given month decreased by 55.9% from month 1 to month 2; it then decreased steadily such that there was a 78.2% reduction by the end of the 6-month treatment period.

Demographics and Clinical Characteristics Differentiating the Groups

Univariate analysis showed that the persistent patient group was significantly older, less likely to be from the South, more likely to have been a salaried employee and less likely to be an hourly employee, less likely to be actively employed and more likely to be a retiree, and likely to live in an area with a higher median income and a higher percentage of college-educated individuals than the non-persistent group (Table 1). During the pretreatment period, measures of comorbidity did not differ by persistence group (Table 2). However, non-persistent patients were more likely to have alcohol-related claims prior to the initiation of naltrexone therapy, indicating that persistent patients were more likely than non-persistent patients to be newly diagnosed with an alcohol-related disorder during the treatment period.

Table 3 shows the significant predictors in the logistic regression analysis. As can be seen there: 1) for each year of additional age the predicted probability of persistence with oral naltrexone increased by nearly 3%, 2) being a salaried employee increased the likelihood of persistence by 54%, 3) each \$1,000 increase in median income increased the likelihood of persistence by 1%, and 4) a pre-treatment claim with an alcohol-related diagnosis decreased the likelihood of persistence by nearly 38%.

Healthcare Utilization

During the pretreatment period, the healthcare utilization rates did not vary significantly by persistence group. Pretreatment inpatient detoxification claims were present for 10.5% of patients who persisted with oral naltrexone therapy, compared to 12.8% of non-persistent patients ($P=0.4$). Only about 1% of either group had outpatient detoxification claims during the same period ($P=0.7$). The proportion of patients who used alcohol-related psychotherapy in the pretreatment period was also similar between the persistent and non-persistent groups (16.3% vs. 18.5%, $P=0.5$), as were the mean number of alcohol-related psychotherapy visits among patients who utilized such services (5 vs. 7, among patients with any utilization, $P=0.2$).

During the treatment period, however, the percentage of non-persistent patients requiring alcohol-related inpatient detoxification was more than twice that of persistent patients (Figure 2A). The proportion of patients with any claims for psychotherapy for an alcohol diagnosis during the treatment period did not differ between the non-persistent and persistent groups (23% vs. 28%, $P=0.17$), but non-persistent patients had significantly fewer

such psychotherapy visits, on average, than persistent patients (1.4 vs. 2.8, $P < 0.03$) [which was partially attributable to the fact that the maximum number of psychotherapy visits was 37 ($n=1$) for the non-persistent group and 73 ($n=1$) for the persistent group].

Also, during treatment, significant differences were seen between non-persistent and persistent patients in the use of non-alcohol-related healthcare services (Figure 2B). Specifically, non-persistent patients had significantly more non-alcohol-related (e.g., general medical and surgical) inpatient admissions and emergency department visits than persistent patients. In contrast, persistent patients had significantly more non-alcohol-related outpatient physician visits and prescription drug claims than did patients who were non-persistent with oral naltrexone.

Discussion

Concern about poor adherence with oral pharmacotherapy by patients with substance use disorders has often been raised in the literature. Nevertheless, there has been a limited effort to measure the problem, despite the recognition that it adversely affects treatment outcomes (13,22). The results of the present analysis underscore the magnitude of this problem: less than 15% of patients treated with oral naltrexone for AUDs over a 6-month period were able to persist with refills for at least 80% of the time, while more than 85% were identified as non-persistent. This finding contrasts with the situation that exists in clinical trials, where a concerted effort is generally made to enhance adherence with the medication (15,22). In this database, more than half of patients filled only 1 prescription for naltrexone during the assessment period. Because the database did not permit us to determine the number of patients who were prescribed naltrexone but did not fill the first prescription, the low rate of persistence is likely an underestimate of the poor adherence to naltrexone oral therapy.

Several factors were associated with persistence with oral naltrexone prescriptions, including having been a salaried rather than hourly employee at the time of treatment or being retired, living in an area with a higher median household income, and not having both alcohol- and drug-related claims prior to treatment. Further, differences in healthcare utilization were associated with persistence during the treatment period. Specifically, persistent patients were more likely to utilize counseling and outpatient general medical care, while non-persistent patients were more likely to undergo inpatient detoxification, emergency room visits, and inpatient admissions. The greater use of outpatient services in the group that was persistent with naltrexone prescriptions may reflect a greater motivation on their part to change drinking behavior, though it could also reflect a beneficial effect on adherence of more frequent contact with a healthcare professional. The correlational nature of the findings makes it impossible to ascertain the causal direction of this association. Greater medication compliance has been associated with better drinking outcomes irrespective of treatment group in a large, placebo-controlled trial of naltrexone for alcohol dependence (25). The adverse effects of naltrexone could also have reduced the rate of persistence.

There are considerable public health and economic implications of non-persistence with oral naltrexone therapy. In clinical practice, however, given the preponderance of non-persistence, efforts to increase persistence will be needed for the vast majority of patients. Such efforts can include a variety of behavioral interventions that have been shown to enhance adherence with alcohol pharmacotherapy (22-25) and the use of extended-release naltrexone (26).

These findings must be interpreted in light of some relevant study limitations. The retrospective and naturalistic design of the study limits the degree to which bias can be

controlled for in the two patient groups. This is balanced to a degree by the fact that the assessment process is transparent to patients and seemingly has little chance of influencing patient behavior. Some factors that may have an impact on medication persistence (e.g., out-of-pocket expenses by patients) were not measured. Another issue is the persistence measure itself. There is no universally accepted method to measure adherence in either research or clinical practice (13). The measurement of persistence in medication usage by quantifying prescription refills means is only a proxy for day-to-day pill taking adherence. In reality, persistence is probably an overly optimistic measure, i.e., although approximately 14% of patients were in possession of naltrexone for 80% of the intended time, the proportion that actually took the medicine during this period was probably lower. Also, the approach we used to differentiate healthcare costs into alcohol-related and non-alcohol-related is limited by the fact that a patient may receive alcohol-related services during a visit with a different primary diagnosis, thereby understating the alcohol-related utilization rates. Finally, the healthcare utilization data were analyzed for only a six-month period. This is a relatively short duration for comparative analysis of healthcare utilization patterns following an alcohol treatment intervention; many studies use a 2-year trial design. The relatively short interval over which utilization was monitored may make the finding of a consistent pattern of over utilization of more intensive medical services by the non-persistent patients more compelling.

These findings can be compared to two prior analyses of oral pharmacotherapy adherence rates in patients with alcohol use disorders (27,28). In a retrospective analysis of data on naltrexone prescriptions in a large mid-Atlantic health plan, approximately 50% of patients received only 30 days or less of medication, a rate that did not improve over a three-year period (27). In an analysis of utilization of medications for alcoholism treatment in a Veterans Administration population, Hermos and colleagues found that only 21.8% of 921 patients filled oral naltrexone prescriptions and only 22.7% of 754 patients filled oral disulfiram prescriptions for 6 months (28). The duration of treatment episodes was similar for both drugs, with more than 35% of episodes being 1 month or shorter, more than 50% being 2 months or shorter, and 75% being 5 months or shorter. Although the study by Hermos et al. (28) and the present study involve different populations, medications, and treatment systems, the similarity of findings between the studies (which together examined the behavior of approximately two thousand patients) demonstrates the limitations of oral pharmacotherapy for the rehabilitation treatment of alcoholism: less than 25% of patients are able to complete a course of therapy lasting only 6 months.

There are serious implications of the very high rates of non-persistence to oral naltrexone and the pattern of significantly greater utilization of intensive medical services among non-persistent patients that were seen in this study. In view of the low rates at which medications are prescribed for the treatment of alcoholism (27,29), the fact that only a small percentage of patients who are prescribed oral naltrexone persist in using the medication is of particular concern. These findings underscore the need to educate physicians in the use of medications with demonstrated efficacy for the treatment of alcohol dependence and in methods to enhance patients' adherence with the treatments.

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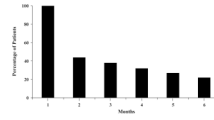


Figure 1.
The Percentage of All Patients with an Oral Naltrexone Prescription in Any Given Month (i.e., Non-cumulative)

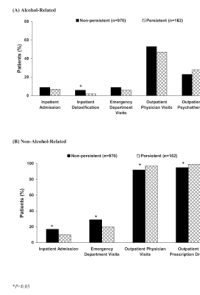


Figure 2. Differences in the Percentage of Persistent and Non-Persistent Oral Naltrexone Users Utilizing (A) Alcohol-Related Healthcare Services and (B) Non-Alcohol-Related Healthcare Services. * $P < 0.05$ Non-Persistent vs. Persistent

Table 1

Demographics of Oral Naltrexone Users in Relation to Persistence Status

| | Patients | | P value |
|---------------------------------|---------------------------|-----------------------|---------------|
| | Non-persistent (n=976) | Persistent (n=162) | |
| Gender | 367 (38%) | 70 (43%) | 0.2 |
| Female, n | | | |
| Age, years | 44.4 (10.7) | 47.6 (9.5) | 0.0003 |
| Mean (SD) | | | |
| Geographic Region, n | | | 0.011 |
| Northeast | 227 (23%) | 49 (30%) | 0.06 |
| North Central | 360 (37%) | 54 (33%) | 0.4 |
| South | 264 (27%) | 29 (18%) | 0.007 |
| West | 125 (13%) | 30 (19%) | 0.08 |
| Employee Type, n | | | 0.007 |
| Salaried | 253 (26%) | 55 (34%) | 0.03 |
| Hourly | 336 (34%) | 34 (21%) | 0.0002 |
| Other | 48 (5%) | 8 (5%) | 1.0 |
| Unknown | 339 (35%) | 65 (40%) | 0.2 |
| Employment Status, n | | | 0.028 |
| Active | 757 (78%) | 110 (68%) | 0.01 |
| Retiree | 194 (20%) | 46 (28%) | 0.03 |
| Other/Unknown | 25 (3%) | 6 (4%) | 0.5 |
| Median Household Income* | | | |
| Mean (SD) | \$48,379 (\$20,204) | \$54,138 (\$22,683) | 0.003 |
| % College Education* | | | |
| Mean (SD) | 27 (17) | 30 (18) | 0.01 |

* By ZIP code.

Table 2
Pretreatment Clinical Characteristics of Oral Naltrexone Users in Relation to Persistence Status

| | Patients | | <i>P</i> -value |
|----------------------------------|---------------------------|-----------------------|-----------------|
| | Non-persistent (n=976) | Persistent (n=162) | |
| CCI, Mean (SD)* | 0.53 (1.01) | 0.59 (1.00) | 0.5 |
| CDS, Mean (SD)* | 1.43 (1.88) | 1.56 (1.99) | 0.4 |
| Substance abuse-related claims** | | | |
| Alcohol-related claims | 806 (83%) | 122 (75%) | 0.03 |
| Drug-related claims | 258 (26%) | 32 (20%) | 0.07 |

* For the Charlson Comorbidity Index (CCI) and the Chronic Disease Score (CDS), higher scores indicate a greater burden of comorbidity.

** For the 6 months prior to the start of treatment; groups not mutually exclusive, so that patients could have had both alcohol- and drug-related claims

Table 3
Demographic and Clinical Characteristics Uniquely Related to Persistence with Oral Naltrexone

| Variable | Parameter Estimate* | Standard Error | Odds Ratio | 95% Confidence Interval | P-Value |
|-------------------------|---------------------|----------------|------------|-------------------------|---------|
| Age | 0.029 | 0.010 | 1.029 | 1.010-1.049 | 0.003 |
| Salaried Employee | 0.433 | 0.195 | 1.542 | 1.053-2.258 | 0.026 |
| Median Income* | 0.010 | 0.004 | 1.010 | 1.002-1.019 | 0.015 |
| Alcohol-Related Claim** | -0.471 | 0.210 | 0.624 | 0.414-0.941 | 0.025 |

* Likelihood of persistence as a function of each increase of \$1000 in median income in the area of residence

** During the six-month pretreatment period