Patterns of Dispensed Disulfiram and Naltrexone for Alcoholism Treatment in a Veteran Patient Population

John A. Hermos, Melissa M. Young, David R. Gagnon, and Louis D. Fiore

Background: Short-term treatment trials indicate that two Food and Drug Administration–approved agents, disulfiram and naltrexone, may each curtail alcohol consumption, but two large 1-year Veterans Administration cooperative studies showed no long-term benefits for these agents over placebo. To assess whether these agents are being prescribed for extended periods, as an indicator of long-term use in nonexperimental settings, we compared dispensing patterns in a veteran patient population.

Methods: The New England Veterans Integrated Service Network outpatient pharmacy files between January 1, 1998, and June 30, 2001, were analyzed; only patients with prescriptions on or after March 1, 1998, were included. Measurements for each patient included data on new and refilled prescriptions of disulfiram, naltrexone, and control medications. Prescription survival curves with right censoring were constructed. Distinct treatment episodes were defined by having six or more months between the end date of a prior prescription and the start date of a new prescription.

Results: From eight New England Veterans Integrated Service Network centers, 754 patients were dispensed disulfiram, and 971 were dispensed naltrexone, encompassing 873 and 1075 treatment episodes, respectively. Treatment episode durations were virtually identical for both drugs: more than 35% of episodes were 1 month or shorter, more than 50% were 2 months or shorter, and 75% were 5 months or shorter. Concurrently prescribed neuroleptic or statin medications predicted longer disulfiram and naltrexone treatment episodes. However, for patients newly prescribed common neuroleptic, antidepressant, or statin agents, the risks for discontinuing disulfiram or naltrexone were 1.4 to 2.3 times greater than for discontinuing these other agents.

Conclusions: In clinical settings, veteran patients were likely to be dispensed either disulfiram or naltrexone for only several months or less. The contexts and reasons for these predominantly short-term treatment episodes or the benefits derived were not known and merit further study.

Key Words: Disulfiram, Naltrexone, Pharmacoepidemiology, Alcoholism Treatment.
Data. Use of the VISN 1 pharmacy database for pharmacoepidemiology kept confidential, no patient-level information has been contained in this sign a confidentiality and usage agreement, which details the responsibilities confined to a limited number of investigators and programmers, who use of this database on the server is doubly password protected. Use of this database magnetic tapes and locked in a secured fireproof safe. Access to the files is checked of days prescriptions of disulfiram and naltrexone outside of study protocols provides a clinically and ecologically relevant indicator of their potential use and, particularly, of their protocols during which the same drug was not prescribed from the VISN 1 pharmacy database for the Veterans Integrated Service Network for the New England region (VISN 1). Our objectives were to determine how long these drugs were dispensed to individual patients, whether these distinctive agents had similar dispensing patterns, and what other factors might influence these patterns. If the results that demonstrated no benefits for disulfiram and naltrexone over placebo from the 1-year Veterans Administration (VA) cooperative studies translated into clinical settings, we expected that the time spans covered by initially dispensed medications and refills for each of these agents would generally be short.

Dispensed prescriptions do not necessarily indicate that patients are taking the medication and are, therefore, not a measure of medication compliance. Discontinued prescriptions, however, whether initiated by the patient or prescribing physician and whether for positive or negative reasons, should be a good indication of nonuse by veteran patients, who typically use the VA as their sole source of prescriptions. Although there are clear limitations to this assumption, we believe that aggregate analysis of dispensed prescriptions of disulfiram and naltrexone outside of study protocols provides a clinically and ecologically relevant indicator of their potential use and, particularly, of their discontinued use.

METHODS

Pharmacy Database

At the time of the analysis, there were eight distinct VA health-care sites in VISN 1, which includes the six New England states Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont. VISN 1 pharmacy files are obtained from Information Resource Management and cleaned via an established, standard process. The data elements of the outpatient pharmacy prescription files include patient identification, date of birth, drug name, dosage, route, quantity, cost, VA drug class, internal drug identification number, date of original prescription, number of days' supply, refill date(s), number of refills remaining, discontinuation date, provider identification, and VA site number. The files are checked quarterly for validity and consistency.

The database is housed on a secure server in the Massachusetts Veterans Epidemiology and Research Information Center at the VA Boston Healthcare System. Periodic backups of this database are housed on magnetic tapes and locked in a secured fireproof safe. Access to the database on the server is doubly password protected. Use of this database is confined to a limited number of investigators and programmers, who sign a confidentiality and usage agreement, which details the responsibilities for safety and security of the files. All patient information has been kept confidential, no patient-level information has been contained in this report, and all information for this publication is presented as aggregate data. Use of the VISN 1 pharmacy database for pharmacoepidemiology research and for this study was approved by the Institutional Review Board of the VA Boston Healthcare System.

Prescription and Patient Variables

Pharmacy data were analyzed for the 42-month period from January 1, 1998, through June 30, 2001. All naltrexone prescriptions were for 50-mg tablets; 6937 (99.91%) disulfiram prescriptions were for the 250-mg tablets, and only 6 (0.09%) were for 500-mg tablets. For disulfiram, 93.6% of prescriptions dispensed medication supplies for 30 days or fewer, and 5.4% dispensed 90-day supplies; for naltrexone, 96.6% were supplies for 30 days or less, and only 2.2% were for 90 days. The relatively few 90-day prescriptions for each agent were calculated as prescriptions dispensed for three continuous months, that is, similar to three consecutive 30-day prescriptions. It is not the policy of the VA to have 30- or 90-day prescription refills mailed to patients without the request of the patient either directly to the pharmacy or through the prescribing physician; thus, these data should not include automatically dispensed and mailed prescriptions from the VISN 1 pharmacies without a request from patients or physicians.

To provide uniformity to our database, we excluded patients who received these prescriptions during the first 2 months (January and February 1998) of our observation window; this was done to exclude patients who were possibly receiving these medications on a continual basis before December 31, 1997. This process excluded 228 patients who had received disulfiram prescriptions and 116 patients who had received naltrexone prescriptions during January and February 1998. The remaining patients—those whose first prescription in the window of observation occurred on or after March 1, 1998—included 754 patients who received disulfiram prescriptions and 971 patients who received naltrexone prescriptions; these subjects provided the data for analysis. Distinct treatment episodes for each patient were determined by imposing a limit of 6 months between the end date of the previously dispensed prescription and the dispense date of the following prescription. Thus, an individual patient could have two or more treatment episodes if there were 6-month intervals during which the same drug was not prescribed from the VISN 1 pharmacies.

Two of these medical centers participated in VACSP 425, “Naltrexone in the Treatment of Alcoholism,” conducted between 1997 and 2000 (Krystal et al., 2001). The active medication or placebo in these studies was dispensed as study medication to the study coordinators, was not distributed to the patients at these two participating sites, and was not recorded as prescribed naltrexone in the VISN 1 pharmacy database. During this study, naltrexone was also prescribed clinically to patients not enrolled in VACSP 425. Disulfiram was not being used in any large-scale protocols during the time period of our analysis. None of the eight VISN 1 sites had formal programs in which naltrexone was prescribed as primary treatment for opioid dependence. Personal communications with key physicians at major sites indicated that prescribing naltrexone for opioid dependence was, at most, done very infrequently.

Covariables assessed included patient age as of March 1, 1998, in 10-year intervals; the VISN 1 VA health-care site where the prescription was issued; and other prescriptions, determined from the VA Classification System based on the National Drug File, that these patients were receiving. We chose to use as covariables neuroleptics, antidepressants, the 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors (statins), and the diuretic hydrochlorothiazide as markers for patients receiving commonly prescribed medications as part of ongoing medical or psychiatric care. Specifically, neuroleptics and, to a far lesser extent, antidepressants were used to identify patients with major comorbid psychiatric disorders who would be treated in psychiatric clinics. Similarly, patients prescribed statins or hydrochlorothiazide would most likely receive these from primary care or internal medicine clinics. These covariables, however, do not directly determine from where patients were receiving naltrexone or disulfiram but indicate participation in some type of chronic care in addition to treatment for an alcohol use disorder.
To control for individual variations in the use of common prescription drugs during the window of observation, we compared the durations of treatment episodes for the most commonly dispensed representative drugs newly prescribed to subsamples of these same patients. These drugs were the neuroleptic agents risperidone and olanzapine; the antidepressant agents fluoxetine, sertraline, and paroxetine; and the statins simvastatin and lovastatin. Treatment episodes with these drugs were defined similarly to those for disulfiram and naltrexone.

### RESULTS

The 754 patients who received disulfiram as a new prescription between March 1, 1998, and June 30, 2001, had 873 distinct treatment episodes with this agent; similarly, 971 patients who first received naltrexone in that time span had 1075 treatment episodes. In total, close to 90% of patients had only one treatment episode within the 40-month window of observation, accounting for approximately 79% of the treatment episodes (Table 1). Within these 2 groups of disulfiram and naltrexone users, 178 patients received both of these agents at some time during the 40-month period and accounted for 81.6% of the treatment episodes with disulfiram and for 86.5% of those with naltrexone.

The survival curves in total months' supply for dispensed naltrexone and disulfiram for the study population are shown in Fig. 1. The survival curves for these treatment episodes are identical (log-rank, 0.3245; \( p = 0.569 \)). The median duration of prescriptions per treatment episode for disulfiram and naltrexone was 2.0 months (means were 4.6 and 4.2 months, respectively). The 25, 50, and 75% quartiles for the duration of treatment episodes for each drug, including episodes that were completed and censored, were 1.0, 2.0, and 5.0 months, respectively. For disulfiram, 339 (38.8%) of the 873 treatment episodes were only for 1 month or less, and for the naltrexone users, 392 (36.5%) of the 1075 treatment episodes were only for 1 month or less.

For disulfiram users, 22.7% of treatment episodes were for 6 months or more and 10.9% for 1 year or more; for naltrexone users, these proportions were 21.8% and 8.6%, respectively.

To determine some of the factors that may influence the duration of dispensed prescriptions, proportional hazard analyses were performed for each agent for the 873 treatment episodes for disulfiram and 1075 treatment episodes for naltrexone (Table 2). In addition to age (in 10-year cohorts), and controlling for the VA site from which the

### Table 1. Frequency of Treatment Episodes for Disulfiram and Naltrexone by Patient

<table>
<thead>
<tr>
<th>No. treatment episodes</th>
<th>Disulfiram</th>
<th>Naltrexone</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>% of 873 Episodes</td>
<td>No. patients</td>
</tr>
<tr>
<td>1</td>
<td>651</td>
<td>74.6</td>
</tr>
<tr>
<td>2</td>
<td>88</td>
<td>20.2</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>4.8</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Total</td>
<td>754</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 2. Cox Proportional Hazards Models for Months per Treatment Episode for Disulfiram and Naltrexone

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% Hazard ratio confidence limits</th>
<th>Hazard ratio</th>
<th>95% Hazard ratio confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.899</td>
<td>0.820–0.967</td>
<td>0.941</td>
<td>0.888–1.020</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>0.772</td>
<td>0.660–0.903</td>
<td>0.768</td>
<td>0.667–0.884</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>0.768</td>
<td>0.640–0.922</td>
<td>0.876</td>
<td>0.729–1.052</td>
</tr>
<tr>
<td>Lovastatin/simvastatin</td>
<td>0.645</td>
<td>0.501–0.829</td>
<td>0.804</td>
<td>0.660–0.979</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>0.949</td>
<td>0.708–1.273</td>
<td>0.935</td>
<td>0.720–1.215</td>
</tr>
</tbody>
</table>
prescriptions were dispensed, commonly prescribed classes of psychiatric and medical drugs were used as control variables. One of eight VA sites, a large urban tertiary care facility, had shorter durations for naltrexone prescriptions ($p = 0.049$), and one site, primarily for psychiatric care, had longer durations for disulfiram prescriptions ($p = 0.011$). For disulfiram users, a longer duration of dispensed prescriptions was associated with older age ($p < 0.01$) and the use of neuroleptics, antidepressants, and statins; for naltrexone users, a longer duration of dispensed prescriptions was associated with dispensed neuroleptics and statins (95% hazard ratio confidence limits are reported in Table 2).

To determine whether the survival curves for disulfiram and naltrexone for these patients were unique for these drugs, survival curves were compared with those for other medications that these same patients were commonly prescribed during the window of observation. We analyzed new treatment episodes (from March 1, 1998, on) for the most commonly prescribed neuroleptic, antidepressant, and statin medications in VISN 1 within subsamples of patients who had received these medications, comparing the curves by Cox proportional hazard regression model with gamma frailties (Clayton and Cuzick, 1985). The hazard ratio presented is the likelihood that the survival of the disulfiram or naltrexone treatment episode would be shorter than that of the control medications tested. For patients who received either of the antidipsogenic agents and either one or two commonly prescribed neuroleptic medications, olanzapine or risperidone, the prescription survival curves for the neuroleptics were significantly longer than for disulfiram (log rank $p = 0.0046$; hazard ratio, 1.8) and for naltrexone ($p < 0.0001$; hazard ratio, 1.9; for naltrexone versus neuroleptics, see Fig. 3A). For patients taking one or more of three commonly prescribed antidepressant medications—paroxetine, sertraline, or fluoxetine—the survival curves for the antidepressants were significantly longer than for disulfiram ($log-rank p < 0.0001$; hazard ratio, 2.0) and for naltrexone ($p < 0.0001$; hazard ratio, 2.3; for naltrexone versus antidepressants, see Fig. 3A).
Fig. 3B). For patients taking one of two commonly prescribed statins, simvastatin and lovastatin, the survival curves for the statins were significantly longer for patients taking naltrexone (log-rank p < 0.0001; hazard ratio, 2.3), but not for those taking disulfiram (log-rank p = 0.1657; hazard ratio, 1.4).

**DISCUSSION**

Using archival data from eight VA medical centers and their affiliated clinics in the VISN 1 pharmacy database, we have determined the patterns by which two FDA-approved drugs for treating alcohol dependence—disulfiram and naltrexone—were dispensed to veteran patients. This pharmacoepidemiology analysis is a study neither of medication compliance nor of drinking outcomes. For the patients whose pharmacy data we analyzed, we were not privy to the contexts in which they were prescribed these agents, their actual medication-taking behaviors, drinking behaviors, health status, or psychosocial functioning or whether they were also engaged in alcohol counseling or self-help groups. However, we believe that these data provide a unique descriptive analysis of how these agents are dispensed in nonexperimental settings and that the findings are independent of medication compliance data typically obtained in clinical studies. We are quite confident that in analyzing aggregate data from patients who typically use the VA as their sole source for medications, discontinuation of VA prescriptions, either by the patient or provider and regardless of the reasons, is a good indicator that the medication is being used either not at all or not on a regular basis.

Although disulfiram would be prescribed only for treating alcohol-use disorders, naltrexone is approved for use in treating opioid dependence. The VISN 1 sites had no formal programs for providing naltrexone for opioid dependence during this period, and addiction specialist physicians at the major sites reported to us that prescribing naltrexone to outpatients for this purpose at their VA medical centers would have occurred rarely. There seem to be no conclusive data indicating long-term efficacy for naltrexone maintenance in opioid dependence (Kirmayer et al., 2002), and this practice has not been generally incorporated into opioid treatment programs at VA VISN 1 sites. Thus, we are confident that close to all naltrexone prescriptions within our sample were for treatment of alcohol-use disorders.

For the treatment episodes of patients whose first prescription in our database was recorded on or after March 1, 1998, the striking findings were the similar patterns by which prescriptions for these two agents were discontinued and the typically short durations of dispensed prescriptions. Specifically, more than 35% of the patients received only a 1-month prescription, and more than half of the patients had prescriptions filled and dispensed for 2 months or less; conversely, approximately 20% of patients received prescriptions for six or more months and 10% for 1 year or more for each of the drugs. Taken at face value, these data indicate that most patients starting on these drugs have quite quickly had these medications discontinued either on their own initiative or on their providers’ initiatives. A substantially smaller proportion were being dispensed these drugs for extended periods. We did not determine whether or to what extent either short-term or long-term alcoholism treatment goals may have been met for these patients by using disulfiram or naltrexone. Thus, it is quite possible that within the group of patients receiving these agents for short periods, treatment goals had been met and, conversely, that longer periods of prescribing did not necessarily indicate long-term sobriety.

Within our cohorts, we were able to identify correlates of longer treatment episodes. Older age and treatment with prescribed neuroleptic drugs, antidepressants, or cholesterol-lowering agents (statins) were each associated with longer durations for prescribed disulfiram and were, except for antidepressants, also associated with longer treatment episodes with naltrexone. These findings may be due to a number of factors not necessarily related to direct beneficial effects of the agents; such patients likely represent a stable, health-conscious, medically compliant patient population who are regularly attending psychiatric or medical clinics and are regularly prescribed a variety of medications.

Using the same methods for analyzing the duration of prescriptions, we have shown that for subsamples within this cohort, patients were significantly more likely to discontinue disulfiram or naltrexone than to discontinue new prescriptions for commonly prescribed neuroleptic, antidepressant, or statin medications. These differences were not great (hazard ratios ranging from 1.4 to 2.3) but provide some evidence that the typically short durations for disulfiram and naltrexone use were not solely due to these patients simply discontinuing all medications or dropping out of psychiatric or medical care.

We do not know to what extent these shorter or longer courses of medication may have been associated with beneficial outcomes. The natural course of drinking behaviors is highly variable, and measuring long-term treatment effects within diverse heavy-drinking populations has proven to be extremely challenging (Babor et al., 1987; Institute of Medicine, 1989). Prospective studies indicate that for alcoholism treatment populations, periods of sobriety for approximately two or more years may be necessary to stabilize long-term favorable outcomes (Finney and Moos, 1992; Polich et al., 1981). To the extent that long-term administration of disulfiram or naltrexone may be critical in curtailing alcohol use, the immediate prognoses for most of the veteran patients in our database were probably not favorable. Conversely, because close to 20% of patients in each group had these medications dispensed for six or more months, these data might be interpreted as not very different from the approximate rates of retention for patients entering alco-
holism treatment programs (Polich et al., 1981) or self-help groups (Schulz and Chappel, 1998).

We did not determine to what extent these patients were receiving concomitant cognitive/behavioral therapies or whether they attended self-help groups. Considering the availability of cognitive/behavioral therapies within the VISN 1 sites and the ready access to Alcoholics Anonymous in the community, it is likely that many of this cohort had at least some exposure to these treatment approaches. Most of the short-term and long-term studies cited previously (see the introduction) have included one form or another of cognitive/behavioral therapies. In the VACSP study of naltrexone (Krystal et al., 2001), compliance with medication, 12-step facilitation counseling, and attendance at Alcoholics Anonymous meetings were each associated with longer periods to relapse, but these associations were independent of whether subjects were receiving naltrexone or placebo. Hence, although it is likely that some patients who achieve sobriety by using combined therapies may choose to stop taking antidipsogenic agents, it is also likely that continuing to take these agents may be tied to overall motivation to remain compliant with a successful multimodality treatment plan.

Because of the substantial proportion of patients in our cohorts who were also receiving neuroleptic medications (these patients accounted for 20% of treatment episodes), it is likely that many of the patients were followed up frequently in psychiatric clinics and were regularly prescribed disulfiram or naltrexone as part of long-term, closely monitored treatment for dual diagnoses. For the patients treated for psychoses, this finding is consistent with the conclusions of Larson et al. (1992): that close supervision of disulfiram therapy was superior to nonsupervised use in improving treatment outcomes and that, at a dose of 250 mg, there were no adverse psychiatric complications or untoward drug interactions. It is noteworthy that in the two long-term VACSP studies, patients with major psychiatric disorders or those taking major psychotropic drugs were excluded from participation (Fuller et al., 1986; Krystal et al., 2001). Whether the inclusion of patients with overt psychiatric disorders would have altered either overall adherence rates or outcomes in these two studies, however, is speculative.

Both naltrexone and disulfiram are prescribed to relatively few patients with alcohol-use disorders in the VA health-care system (Petrakis et al., 2003). By analyzing VA administrative databases for a 6-month period (October 2000 to March 2001), these investigators found that only 1.9% of 194,001 patients with outpatient visits generating International Classification of Diseases, 9th edition, diagnoses of alcohol abuse or dependence were prescribed naltrexone. Patients more likely to be prescribed naltrexone were younger, had a number of associated drug abuse or psychiatric diagnoses, and were more likely to use inpatient mental health services. In concert with those findings, our data indicate that those who were prescribed neuroleptic drugs (that is, those typically cared for in psychiatric clinics) would be more likely to remain on these drugs for longer periods than would other patients.

Among United States addiction specialists, disulfiram and naltrexone are prescribed relatively infrequently to patients with alcohol use disorders. Mark et al. (2003) found in a mailed survey of addiction specialists that only approximately 13% of patients with alcohol use disorders were prescribed naltrexone and 9% were prescribed disulfiram. The key reason cited was only modest confidence in the effectiveness of these agents. Thomas et al. (2003), also from a mailed survey, found that only 15% of addiction specialists prescribed naltrexone either “often” or “to almost all (alcoholic) patients.” Reasons cited in this survey for the generally infrequent use included inadequate knowledge about naltrexone, only modest confidence in its effectiveness, and issues of cost. Physician factors associated with the adoption of naltrexone were time spent in research, affiliation with organizations or programs that actively recommend its use, and having a higher proportion of “alcoholic only” patients. In this study, we did not determine to what extent attitudes regarding the effectiveness of disulfiram or naltrexone influenced disulfiram and naltrexone prescribing practices, but within the VA system, it is likely that many prescribers are involved in research, are connected with an alcoholism treatment program, and do not have the cost concerns of those in private medical settings.

Disulfiram and naltrexone, approved for use for alcoholism treatment almost 50 years apart, have markedly different mechanisms of action and offer distinct expectations to drinkers as to how they may be beneficial. The striking similarities in the patterns in which dispensed prescriptions were discontinued in our large patient cohort suggest that their use is not determined by their distinct pharmacological actions, but rather by many other factors that may influence whether providers or patients choose to discontinue treatment with these drugs. Coupled with the negative results from the two long-term randomized controlled studies conducted by the VACSP (Fuller et al., 1986; Krystal et al., 2001), we conclude that physicians might typically not expect substantial long-term use of these two FDA-approved medications. Whether there will be similar patterns for dispensing acamprosate, the next promising agent likely to be FDA-approved in the United States for alcoholism treatment (Berglund et al., 2003), remains to be determined. Our data do lend support, however, to further studying the potential benefits of these and newer antidipsogenic agents within specifically targeted short- and long-term treatment plans for patients with chronic psychiatric or medical conditions and for those engaged in other forms of alcoholism treatment.
REFERENCES


