Measurement of Compliance With Naltrexone in the Treatment of Alcohol Dependence: Research and Clinical Implications

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Background: Medication compliance is a critical issue in pharmacotherapy. This study evaluated the clinical utility of the Medication Event Monitoring System (MEMS), a newer method for monitoring medication compliance, compared with pill count, a traditional measure, in a sample of patients treated for alcohol dependence with naltrexone.

Method: Ninety-three outpatients meeting DSM-III-R criteria for alcohol dependence participated in a 10-week open-label study of naltrexone. They were provided with naltrexone, 50 mg daily, and concurrent counseling. Measures of medication compliance and drinking during treatment were collected every 2 weeks.

Results: Pill count yielded a significantly ($p < .001$) higher estimate of compliance (87.6% ± 18.1%) than the MEMS (80.4% ± 20.6%). However, the estimate of compliance obtained with the MEMS was more consistently correlated with treatment outcome (percentage of days abstinent, percentage of heavy drinking days, and mean alcohol amount consumed per drinking occasion) than the pill count compliance rate. In addition, classification of the sample into compliant and less compliant groups using the MEMS data yielded groups that differed more clearly on drinking outcomes than did stratification on the basis of pill count.

Conclusion: In pharmacotherapy research, the MEMS may provide more reliable and valid information about subjects' medication compliance than pill count. Clinically, information obtained with the MEMS could be used to provide feedback to patients about their pill-taking behavior to enhance compliance and overall outcome of therapy.

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One of many complex factors faced by clinicians and researchers evaluating the efficacy of a pharmacologic treatment is the issue of medication compliance. Medication compliance "implies a positive behavior in which the patient is sufficiently motivated to adhere to the prescribed medication."[1(p1978)] While a medication might be pharmacologically efficacious, if patients do not comply with treatment, effectiveness is limited. If drug compliance is not taken into account, therapeutic and toxic drug effects can be substantially underestimated, and dosing requirements for optimal efficacy may be overestimated. In clinical practice, medication noncompliance can lead to additional diagnostic and treatment procedures that may be costly and countertherapeutic.[1,2] Medication compliance may also have a major impact on the interpretation of results observed in clinical research. Poor compliance in a trial increases the required sample size needed in order to maintain the same power.[3] Therefore, the measurement of medication compliance plays a crucial role in clinical practice and research.

At this time, there is no true "gold standard" for ascertaining medication compliance, and compliance can be monitored by a variety of indirect methods (e.g., self-report, patient interview, therapeutic outcome, pill count, computerized compliance monitors) or direct methods (e.g., biological marker, tracer compounds, biological assay of body fluid).[1] Computerized compliance monitors using the Medication Event Monitoring System (MEMS; Aprex Corp., Fremont, Calif.) provide an important method of monitoring compliance in clinical practice and research. This system consists of a microprocessor housed in the cap of the medication container. Each time the patient removes the cap, the time and date are recorded in a microprocessor; the accumulated data are retrieved by connecting the microprocessor unit to a computer.[3,4] Besides measuring the number of "presumptive" doses, the MEMS can reveal the pattern of drug intake, such as time of dosing, deviation from prescribed doses, and patient-initiated abstinence from the drug.[4,5]

As reviewed by Bond and Hussar,[1] poorer treatment outcomes have been associated with patient noncompliance in studies of primary hypercholesterolemia, diabe-

tes, epilepsy, infectious disease, hypertension, organ transplants, and other serious chronic diseases. Recently, in clinical trials of antihypertensives, antiepileptics, and ethinyl estradiol, the pattern of medication intake monitored by the MEMS has been related to therapeutic efficacy and adverse events, and, more recently, time of dosing has been associated with the patient's overall rate of compliance.[5–8] Compliance is also an important determinant of outcome in studies of alcohol-dependent patients. For example, medication noncompliance was one of the strongest factors predicting relapse in early studies of disulfiram.[9,10] Following initial studies demonstrating the efficacy of naltrexone in the treatment of alcohol dependence,[11,12] recent reports suggest that medication compliance is also an important determinant of the effectiveness of naltrexone.[13,14]

Given the relationship between compliance and treatment outcome, the goal of this study was to evaluate the utility of the MEMS for monitoring compliance with naltrexone in a sample of alcohol-dependent patients. Previous studies of naltrexone monitored compliance using urine tracer compound (riboflavin) level or pill count,[11–14] but this report is the first to evaluate the utility of the MEMS in a sample of alcohol-dependent patients or with naltrexone pharmacotherapy. We hypothesized that the MEMS estimates of compliance would be lower than estimates obtained by a pill count, the traditional measure of patient compliance, but more valid as measured by their relationship to treatment outcome.

METHOD

Subjects

Subjects were recruited through advertisements in New Haven, Connecticut, area newspapers and from patients seeking treatment at the outpatient Alcohol Treatment Unit of the Connecticut Mental Health Center. Prospective patients were screened briefly by telephone and invited to participate in an intake interview. Individuals 18 to 65 years old were eligible to participate if they (1) met DSM-III-R criteria for alcohol dependence,[15] (2) had achieved between 5 and 30 days of abstinence, (3) were able to read and write English, and (4) had a stable residence and phone. Criteria for exclusion included (1) current abuse of or dependence on a substance other than nicotine; (2) acute major psychiatric illness or psychotic illness; (3) liver cirrhosis, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels more than 3 times normal, or any elevation in bilirubin; (4) unstable medical condition; (5) more than 5 previous treatments for alcohol dependence; (6) current use of disulfiram; and (7) among women, pregnancy, nursing, or refusal to use a reliable form of birth control. The protocol was approved by the Human Investigation Committee at Yale University, and informed consent was obtained from all subjects.

Of 100 eligible subjects, 93 (93.0%) were included in the analyses comparing pill count and MEMS. The 7 subjects (7.0%) who discontinued treatment prior to attending the assessment interview at the end of week 2 (at which time compliance was assessed) were excluded. These subjects included 1 who suffered an adverse reaction to naltrexone, 1 who was referred to other more intensive treatment owing to clinical deterioration, and 5 who dropped out of treatment.

The sample was primarily male (N = 62, 66.7%), white (N = 87, 93.5%), Catholic (58/93, 62.4%), married (40/93, 43.0%), well educated (beyond high school graduate, 57/93, 61.3%), and employed full-time (61/93, 65.6%). The mean ± SD age was 45.4 ± 8.8 years. The mean ± SD number of prior episodes of treatment for alcohol dependence was 1.1 ± 2.2. The mean ± SD baseline score of the Alcohol Dependence Scale (ADS) was 15.4 ± 7.4, which is in the "moderate" dependence range.[16] On average, they drank on 60.2% ± 24.0% of the days during the 90-day pretreatment baseline period, and consumed a mean of 9.3 ± 6.2 standard drinks per drinking occasion.

Procedures

In the initial intake sessions prior to beginning treatment, informed consent was obtained, eligibility criteria were assessed, and baseline assessments, including a physical examination, laboratory testing, and psychiatric assessment, were completed. Drinking behavior for 90 days prior to entering the study was assessed using the time-line follow-back assessment method.[17] Diagnoses of substance use disorders and other psychiatric disorders were obtained using the Structured Clinical Interview, patient version, for DSM-III-R.[18]

Following at least 5 days of abstinence, patients received naltrexone, 25 mg, for 1 day followed by 50 mg daily for a total period of 10 weeks. Naltrexone tablets were dispensed in pill bottles with caps containing the MEMS microelectronic chip that recorded the date and time of day the bottle was opened. The subject also received either a primary-care–based model of counseling[19] or coping skills therapy.[20] Pills were dispensed every 2 weeks, and concurrent psychosocial therapy was provided at least weekly for the first 4 weeks and at least every 2 weeks thereafter. For each subject, pill count data were obtained and recorded on a computerized pill count flow sheet, and MEMS data were retrieved using MEMS data retrieval software. Information on quantity and frequency of drinking during the treatment period was elicited using the time-line follow-back technique.[17] Follow-up assessments, including compliance monitoring, were completed weekly for the first 4 weeks and then every 2 weeks at each follow-up clinical visit. Patients were informed that the MEMS and pill counts were being used to monitor their medication compliance and were given gen-

Table 1. Correlation Between Medication Compliance and Treatment Outcome (N = 93)[a]

Outcome Measure	MEMS Compliance Rate	Pill Count Compliance Rate
% Days abstinent	.2327[b]	.2173[b]
% Days of heavy drinking	–.2548[b]	–.1232
Mean number of drinks per drinking occasion	–.2512[b]	–.1336

[a]Abbreviation: MEMS = Medication Event Monitoring System.
[b]$p < .05$ with Spearman rank order correlation.

eral feedback and encouragement based on reports generated from MEMS software at each assessment session.

Measurement of Compliance and Statistical Analysis

Two measures of compliance were computed using data obtained by either pill count or the MEMS, as described below:

1. Pill count compliance rate = [(Number of pills dispensed – Number of pills returned) / Number of pills prescribed] × 100. This reflects the percentage of doses presumably taken.
2. MEMS compliance rate = (Number of days on which the MEMS cap was opened at least once / Number of days of monitoring by MEMS) × 100. This reflects the percentage of days on which at least 1 naltrexone dose was presumed taken. If a subject did not open the pill bottle on a particular day, that day was coded as a noncompliant day.

In addition to the MEMS compliance rate, several other compliance indices can be computed using MEMS data, such as the percentage of doses presumably taken over the monitoring period or the percentage of days naltrexone was taken as prescribed, that is, once a day (in this case, taking 2 pills on the same day would be coded as noncompliant). However, we chose to focus on the number of days on which a dose of naltrexone was taken (MEMS compliance rate) as the most clinically meaningful measure, since taking 1 or more doses of naltrexone on a given day should provide opioid blockade over the course of at least 24 hours.[21]

In order to evaluate the relationship between compliance estimates and treatment outcome, subjects were classified into 2 groups by means of a median split: compliant and less compliant. This classification was done separately using the median of the MEMS data and the median of the pill count data. *Relapse* or *heavy drinking* was defined as drinking 5 or more standard drinks on an occasion for men and as drinking 4 or more standard drinks on an occasion for women.[11,22] Given that compliance did not differ as a function of the type of counseling patients received (i.e., primary care or coping skills therapy), the data were collapsed across these 2 conditions in the analyses.

The comparison of pill count and MEMS compliance rates was conducted using the Wilcoxon matched-pair signed rank test and the McNemar test. The Spearman rank order correlation and chi-square test were used to examine the relationship between the compliance measures and measures of treatment outcome (i.e., percentage of days abstinent, percentage of heavy drinking days, and mean number of drinks consumed on a drinking occasion), due to the skewed distributions of the measures.

All statistical analyses were performed using the Statistical Package for Social Science (SPSS) for Windows, Version 7.0.

RESULTS

Comparison of Compliance Indices Measured by MEMS and Pill Count

Subjects were retained in treatment for a mean ± SD of 8.9 ± 2.4 weeks, and 79.6% (74/93) of the subjects completed the 10 weeks of therapy. As expected, pill counts obtained during treatment yielded a higher estimate of compliance than did the MEMS compliance data ($z = 5.78$, $p < .001$ using the Wilcoxon signed rank test). The pill count compliance rate was 87.6% ± 18.1%, and the MEMS compliance rate was 80.4% ± 20.6%. In addition to reporting mean compliance, many studies use a cutoff, most often 90% or 80% compliance, to classify study participants into highly and less compliant groups.[2,13,23–25] Using these cutoffs, the percentage of participants who were presumed to have taken ≥ 90% of their prescribed doses by pill count was 69.9%, which was substantially higher than the percentage of patients (39.8%) who took at least 1 dose on more than 90% of study days by the MEMS ($\chi^2 = 22.78$, $p < .001$ using the McNemar test). Similarly, the percentage of the subjects with 80% or higher pill count compliance rate was significantly higher than the percentage of those with 80% or higher MEMS compliance rate (83.9% vs. 66.7%, $p < .001$).

Relationship Between Compliance Indices and Treatment Outcome

The MEMS compliance rate was significantly correlated with treatment outcome as measured by percentage of days abstinent, percentage of heavy drinking days, and the mean number of drinks consumed per drinking occasion (Table 1). In contrast, pill counts were significantly correlated only with percentage of days abstinent.

To further examine the relationship of treatment outcome and compliance measured by the 2 monitoring methods, rates of continuous abstinence and not relapsing to heavy drinking during the treatment period were compared for the compliant and less compliant groups as derived using median splits on the pill count and MEMS compliance measures (median = 94.3% and 87.2%, respectively). When compliance was determined using the MEMS data

Table 2. Comparison of Treatment Outcome Between Medication Compliant and Less Compliant Subjects Determined by Median Split Using the MEMS Versus Pill Count (N = 93)

	MEMS					Pill Count				
	Less Compliant (N = 50)		Compliant (N = 43)			Less Compliant (N = 46)		Compliant (N = 47)		
Outcome Measure	N	%	N	%	p Value[a]	N	%	N	%	p Value[a]
Abstinent during treatment period	17	34.0	26	60.5	.010	16	34.8	27	57.4	.028
Never relapsed during treatment period	27	54.0	34	79.1	.011	27	58.7	34	72.3	.166

[a]p = Significance in χ^2 test.

(Table 2), the compliant and less compliant groups were significantly different on these 2 dependent variables. Of the compliant group, 60.5% (26/43) remained abstinent compared with 34.0% (17/50) of the less compliant group ($\chi^2 = 6.51$, $p < .05$), and 79.1% (34/43) avoided relapse to heavy drinking compared with 54.0% (27/50) of the less compliant group ($\chi^2 = 6.43$, $p < .05$). In contrast, the difference between compliant and less compliant subjects determined on the basis of pill count data was nonsignificant for the rate of not relapsing to heavy drinking (72.3% [34/47] vs. 58.7% [27/46]; $\chi^2 = 1.92$, $p > .05$), although it was significant for the rate of continuous abstinence (57.4% [27/47] vs. 34.8% [16/46]; $\chi^2 = 4.80$, $p < .05$).

DISCUSSION

Studies of medication compliance indicate that partial compliance is an important problem across a variety of diseases and populations and that patients take on average only about three fourths of the doses as prescribed.[7,26,27] Although compliance may not always be easily defined or accurately measured, the crucial role of compliance in the design, analysis, and interpretation of clinical trials is of importance to clinicians, researchers, and consumers of the medical literature.[3] This study is the first in which the medication compliance of patients with alcohol dependence has been monitored by the MEMS. Previous studies of medication compliance in patients with alcoholism have typically relied on either pill count, riboflavin markers,[11–14] or, in the case of disulfiram, breath tests for carbon disulfide or urine tests for disulfiram metabolites.[9,10,28]

Comparisons of MEMS data with pill count data yielded several important distinctions. As expected, the mean compliance rate obtained by pill count was significantly higher than the rate ascertained with the MEMS. In addition, significantly more subjects were classified as compliant by pill count than MEMS, using standard cutoffs of 80% and 90%. The MEMS compliance rate was consistently related, albeit moderately, to treatment outcome, whereas the pill count compliance rate was not. This later finding suggests that the MEMS provides a more valid assessment of patient compliance.

Many researchers have already indicated the drawbacks of pill counts.[23] For many years, the pill count has been the standard objective method of measuring medication compliance.[3] However, pill counts tend to overestimate compliance[7,24,25] in patients who attempt to discard medication in an effort to appear compliant and gain approval from the treatment provider, and in patients who lose or deliberately do not return the bottle.[1,5,29] In addition, an erroneous picture of compliance can result when patients who have missed pills on some days take extra pills on other days.[7,29] In contrast with pill counts, the MEMS provides an alternative method for therapeutic drug monitoring that contributes to understanding how patients actually take their medication each day.[5] Reports generated from the MEMS data can also be used to provide feedback to patients about their dosing patterns and lapses to help them develop more effective pill-taking routines.[8] Although patients were seen frequently for assessments in this study, the MEMS may be particularly well suited for studies in which subjects are seen less frequently (e.g., monthly). In this regard, the MEMS should provide a better indication of when doses were missed than pill count. Finally, the potential for missing data is reduced because the information stored in the MEMS cap can be retrieved at any time, even if the subject discontinues treatment and is later persuaded to return the cap at a follow-up appointment.

Of course, the MEMS also has a number of limitations. First, it must be assumed that a bottle opening means the drug was ingested and that the absence of a bottle opening means the dose was not taken.[7,29] However, it is unlikely that a patient would open the lid at regular intervals without intending to take the drug,[30] and this limitation of presumed dosing is also inherent in pill counts. The major disadvantages of the MEMS are its expense (approximately $70 per unit plus the cost of the software and communicator), and the fact that it is somewhat more bulky than a typical pill bottle.[2,3,30]

The results of this study cannot be generalized to all samples of alcohol-dependent patients since the subjects were relatively older, better educated, more socially stable, and were only moderately dependent on average. Therefore, caution may be needed in generalizing these results to other alcohol-dependent populations and other psychiatric disorders.

In conclusion, the finding that the MEMS, compared with pill counts, provided lower but more valid estimates of compliance with naltrexone by alcohol-dependent patients is consistent with the results of studies of compliance with other pharmacotherapies in other disorders.[2,23–25,30] Thus, these results suggest that the

MEMS provides a sensitive method for clarifying the relationship between medication compliance and therapeutic response. In pharmacotherapy research, the MEMS can be used to provide valid data about medication compliance that can aid in the interpretation of the study's results. Clinically, monitoring the patient's dosing pattern and using this knowledge to provide feedback to patients has the potential to increase patients' compliance with naltrexone and, ultimately, the outcome of treatment for alcohol dependence.

Drug names: disulfiram (Antabuse), naltrexone (ReVia).

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