RESEARCH

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Validation of the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (ATRQ)

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The low rate of response to antidepressants in treatment resistant depression (TRD) justifies studies of next-step therapies following a treatment failure. In TRD clinical trials, it is important to verify the accurate diagnosis of treatment resistance for all enrolled subjects using a reliable and valid instrument. Self-rated scales can reduce the impact of investigator bias and reduce the time burden for clinical researchers. The Massachusetts General Hospital (MGH) Antidepressant Treatment Response Questionnaire (ATRQ) is a self-rated scale used to determine treatment resistance in major depressive disorder (MDD). The ADAPT-A study is a multi-center double-blind, placebo-controlled study of low-dose aripiprazole adjunctive to ADT among outpatients with TRD. At the screening assessment, potential subjects completed the MGH ATRQ. The ADAPT-A medical monitors subsequently performed remote patient interviews and obtained detailed medication histories. The data obtained from the MGH ATRQ and by the medical monitors were compared for congruency. Of the 186 patients enrolled by the local sites, no subjects deemed treatment resistant by the MGH ATRQ were found to be nonresistant by the medical monitors. In 76.3% (n = 142) of the subjects, the number of failed adequate antidepressant trials reported by the MGH ATRQ was concordant with the data collected by medical monitors. In 16.1% (n = 30) of all cases, the medical monitors found a greater number of failed trials; in 7.5% (n = 14) of cases, the medical monitors found fewer failed medication trials. The discrepancy was by more than one medication trial in only 4.0% (n = 7) of cases. We found the MGH ATRQ to be relatively concordant in its assessment of treatment resistance in depression compared with independent clinical researchers. Although the MGH ATRQ tended to underreport the number of unsuccessful treatment trials relative to the clinical interviews, its accuracy in cases it detected was confirmed by raters.

Introduction

Treatment resistant depression (TRD) refers to an insufficient response to at least one trial of an antidepressant medication which has demonstrated efficacy in clinical trials [1]. There is a modest rate of response to commercially available first-line antidepressants in major depressive disorder (MDD) and an even more modest response in TRD [2]. Consequently, it is imperative to prospectively study next-step antidepressant therapies and to develop treatment algorithms that can guide clinicians' treatment decisions following a treatment failure. In order to provide meaningful data for TRD clinical trials, it is important to ensure that patients enrolled in such trials are actually treatment resistant. This requirement necessitates both making the proper diagnosis of MDD and determining that past antidepressant trials yielded nonresponse and were of an adequate dose and duration [3].

It is important to employ a reliable and valid instrument to provide consistency between clinicians and clinical researchers in this assessment.

A standardized scale for the assessment of TRD can help ensure that patients entering TRD trials are truly treatment resistant. As with other psychiatric instruments, there is the option of using self-rated scales or clinician-rated scales. Self-rated scales can help reduce the impact of clinical researchers' biases to promote enrollment in their studies, as well as reduce the time burden for clinical researchers [4]. The clinician-rated scales, such as the Antidepressant Treatment History Form (ATHF) [5], and the Harvard Antidepressant Treatment History (HATH) [6], offer the advantage of incorporating clinical judgment in the assessment of treatment resistance, but they are quite burdensome on the clinical researchers and do not address the risk of clinicians' bias.

The Massachusetts General Hospital (MGH) Antidepressant Treatment Response Questionnaire (ATRQ) is a self-rated scale used to determine treatment resistance in MDD. The MGH ATRQ defines 6 weeks on an adequate dose of antidepressant medication as an adequate duration of treatment. It also provides specific operational criteria for adequate dosage for each of the most commonly used antidepressants.

The MGH ATRQ has been used in several multi-center studies in TRD, including those involving the study of duloxetine [7,8], mirtazapine [9], and aripiprazole [10,11] in TRD. It is currently being used in the ADAPT-A study, a double-blind, placebo-controlled study of low-dose aripiprazole adjunctive to antidepressant therapy (ADT) study among outpatients with MDD who have responded inadequately to prior ADT. However, despite its broad use in clinical trials, the MGH ATRQ has never been formerly validated. In the current report, we have used data collected in the ADAPT-A study to compare the information acquired with the ATRQ with that obtained by independent clinicians remotely assessing the nature of treatment resistance, including the number of medication trials of adequate dose and duration reported by the patients. In addition, we compared the specific medications listed on the MGH ATRQ by the patients with the information obtained by the remote assessors' findings. We believe that comparisons of both the number of trials and specific nature of the medications are critical for the validation of the MGH ATRQ.

Methods

The ADAPT-A study is a multi-center, double-blind, placebo-controlled study of low-dose aripiprazole adjunctive to ADT among outpatients with MDD who have responded inadequately to antidepressant treatment in the current major depressive episode. Patients who failed to respond to at least one and no more than three medication trials of adequate dose and duration were eligible for this study [12]. At the screening assessment, potential subjects were asked to complete the MGH ATRQ. Assuming that the subject met the remainder of the screening inclusion criteria, this information was entered into the study's electronic database. Within 2 weeks of the screening visit, the ADAPT-A medical monitors, who functioned as independent assessors and are all MGH psychiatrists, performed a remote patient interview by telephone. As part of their independent assessment of patient eligibility, the medical monitors obtained a detailed medication history and assessed treatment resistance. Although medical monitors had access to the MGH ATRQ entered by the study sites, they were instructed to perform their evaluation of treatment resistance prior to viewing previously entered information, including the ATRQ. The medical monitors were then asked to input their findings into the electronic database.

Statistical Methods

The data obtained from the MGH ATRQ and by the medical monitors were extracted from the electronic data records. This medication information was compared and checked for congruency. The number of medication trials recorded by the patients on the ATRQ and by the medical monitors in the separate remote interview was compared. Additionally, the congruency of the actual types of medications recorded for all trials was assessed.

Results

One hundred and eighty six patients were screened by local sites and submitted for assessment by the MGH ADAPT-A medical monitors. The demographic information for these patients is presented in Table 1. As per the protocol, all of these patients were deemed to be treatment resistant in their current episode by the information collected on the MGH ATRQ.

Of the patients assessed, 62.9% (n = 117) were female and 74.7% (n = 139) were Caucasian. The majority were employed (59.1%, n = 110) and all but six patients (4.3%) had at least a high school education.

None of the subjects deemed treatment resistant by the MGH ATRQ (i.e., on an antidepressant for at least 6 weeks at an adequate dose as defined by the MGH ATRQ, e.g., 20 mg/d fluoxetine or its equivalent) were found to be nonresistant by the remote interview of the MGH ADAPT-A medical monitor. However, four patients (2%) who reported one to three antidepressant

Table 1 Demographics

	Percentage (n = 186)
GENDER	
Female	62.9% (117)
Male	37.1% (69)
ETHNICITY	
White	74.7% (139)
African American	15.5% (27)
Hispanic	7.5% (14)
Other	3.2% (6)
EDUCATION	
Graduate Degree	11.8% (22)
College	30.6% (57)
Some College	16.7% (31)
Technical or associates degree	12.4% (23)
High school or GED	24.3% (45)
Other	4.3% (8)
EMPLOYMENT STATUS	
Employed	59.1% (110)
Unemployed	28.0% (52)
Disability recipient	4.8% (9)
Student	3.2% (6)
Other	3.2% (6)

trials during the current episode on the MGH ATRQ were found to have had four or more such trials by the MGH ADAPT-A medical monitor and thus were ruled ineligible by protocol for the study.

There was absolute concordance between the number of failed adequate past antidepressant trials reported by the MGH ATRQ and the MGH ADAPT-A medical monitors in 76.3% (n = 142) of the potential study subjects. In 16.1% (n = 30) of all cases, the medical monitors found a greater number of failed trials; in 7.5% (n = 14) of cases, the medical monitors found fewer failed medication trials during the episode. The discrepancy was by more than one medication trial in only 4.0% (n = 7) of cases. Among the 32 cases where the patient self-report underreported the number of medication trials, medical monitors found an average of 0.5 extra medication trials (patients self-reported 48.7% of the actual number of trials as judged by the medical monitors). In the 14 cases where the patients overreported the number of medication trials, medical monitors found an average of 1.2 fewer medication trials per patient (patients reported 194.4% of the actual number of trials as judged by the medical monitors).

Discussion

In this study to evaluate whether patient self-reporting of their medication history using the MGH ATRQ could provide accurate information that would be comparable to that gathered by expert clinicians, the rate of absolute concordance between the number of trials reported by the self-rated MGH ATRQ and the independent assessment of the MGH ADAPT-A medical monitors was over 75%. In the majority of the discrepant cases, patients tended to underreport the number of trials compared to the history obtained by the MGH ADAPT-A medical monitors. It is possible that discussion and probing by the MGH ADAPT-A medical monitors stimulated patients' recollection of prior treatments. Given this finding, it is possible that the MGH ATRQ may slightly underestimate the degree of treatment resistance when used to evaluate that issue. However, as none of the subjects deemed treatment resistant by the MGH ATRQ were found to be nonresistant by a clinical interview, the instrument appears to have excellent specificity in defining caseness.

As demonstrated by the STAR-D trials [13], multiple interventions are often required before achieving a treatment response; this may include combination therapy or augmentation with another psychotropic medication. Therefore, there is a clear need to study prospectively in randomized clinical trials the efficacy and effectiveness of next-step treatments in TRD. In these trials, clinical researchers need to verify that a patient is truly treatment resistant and a correct classification is therefore methodologically critical. Patients often report numerous unsuccessful medication trials, but upon probing it may be determined that these treatments were given at subtherapeutic doses or discontinued early due to undesirable side effects. Methods to ensure an accurate determination of the treatment resistance of depressed patients are therefore critical to clinical studies as well as to clinical practice. For example, when patients have not previously undergone an adequate antidepressant trial, monotherapy with a SSRI or SNRI is a reasonable treatment strategy prior to initiating more complex treatment regimens [14].

Limitations of this study include the lack of access to actual source documents that would provide objective documentation of patients' histories. As mentioned, the MGH ATRQ was provided to the patients for independent completion and subsequent input by local clinical sites. However, when patients answered unclearly, clarification was obtained by representatives of the local clinical sites. There may have been patients who completed the MGH ATRQ as if they were treatment resistant, but eliminated from consideration by the clinician researcher at the site.

The MGH ATRQ does not ask the patient to rate their medication adherence, which would provide additional information about treatment intensity. In addition, by collecting the information retrospectively from the patient, the data are subject to recall bias. Patients often have difficulty in accurately remembering the details of

their treatment. They may also lack the ability or education to distinguish discrete major depressive episodes from ongoing depression, either because they cannot recall periods of wellness or because their concept of an episode is different (usually shorter) than what is defined in the DSM. Prospective assessment of treatment resistance is preferable, but due to time and cost, it may be impractical in the context of clinical trials.

In summary, the MGH ATRQ was found to be relatively concordant in its assessment of treatment resistance in depression with independent clinical researchers established during a remote clinical interview. Although the MGH ATRQ tended to underreport the number of unsuccessful treatment trials relative to the clinical interviews, its accuracy in cases it detected was confirmed by raters.

Conflict of Interest

The authors declare no conflict of interest.

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