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Chronic forms of major depression are still undertreated in the 21st century: Systematic assessment of 801 patients presenting for treatment

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Abstract

During a multisite, NIMH-sponsored clinical trial entitled, “Research Evaluating the Value of Augmentation of Medication by Psychotherapy” (REVAMP), we assessed the adequacy of prior antidepressant treatment in patients with chronic forms of major depressive disorder using the Antidepressant Treatment History Form (ATHF). We hypothesized that when compared to earlier studies treatment adequacy would not have increased over the past decade.

We found that only 33% of the 801 subjects enrolled had ever had a prior adequate trial of antidepressant medication. Patients significantly more likely to have received prior adequate antidepressant trials were older, married, white, had a longer duration of illness, had more melancholic features or met criteria for the melancholic subtype or met lifetime criteria for panic disorder.

The hypothesis that rates of treatment adequacy have not significantly increased over the past decade was supported. These results and the consistency of similar results over time point to the dire need for patient and provider education regarding the signs and symptoms of depression and its treatment.

Keywords

Depression; Chronic; Treatment; Pharmacotherapy

1. Introduction

A consensus conference on reasons for the under-treatment of depression was organized and held by the National Depressive and Manic Depressive Association (NDMDA) in 1996. The conference concluded that there was overwhelming evidence that individuals with depression were being seriously undertreated in spite of the fact effective treatments were available. Quoting from the report, "The cost to individuals and society of this undertreatment is substantial. Long suffering, suicide, occupational impairment, and impairment in interpersonal and family relationships exist. Efforts to redress this gap have included provider educational programs and public educational programs. Reasons for the continuing gap include patient, provider, and health care system factors. Patient-based reasons include failure to recognize the symptoms, underestimating the severity, limited access, reluctance to see a mental health care specialist due to stigma, noncompliance with treatment, and lack of health insurance. Provider factors include poor professional school education about depression, limited training in interpersonal skills, stigma, inadequate time to evaluate and treat depression, failure to consider psychotherapeutic approaches, and prescription of inadequate doses of anti-depressant medication for inadequate durations. Mental health care systems create barriers to receiving optimal treatment." (Hirschfeld et al., 1997).

Studies by our own research group in the 1990s had documented low levels of treatment in patients with chronic forms of major depression. For example, Keller et al. (1995) reported that only 26.8% of the 198 patients for whom such data were available had ever had an adequate trial of an antidepressant medication, defined as 150 mg/day of imipramine or its equivalent taken for at least 4 consecutive weeks. Subsequently, Oquendo et al. (1999, 2002) reported that inadequate treatment was common even in a cohort of depressed inpatients with a history of suicide attempts.

More recent work has documented persistent inadequacy of treatment in VA hospitals (Charbonneau et al., 2003). In addition, Weiburg et al. (2003) conducted a retrospective analysis using pharmacy claims made by patients with a primary care physician in a managed care plan at an academic medical center from 1996 through 1999. Adequate antidepressant treatment was defined as prescription of the lowest likely effective dosage of an antidepressant for at least 90 consecutive days. Data for a total of 15,476 records and 1550 patients were available. Overall, 46% of the patients receiving antidepressants received minimally adequate treatment. The rates of adequate treatment were significantly higher among patients whose antidepressant prescriptions were written by both primary care physicians and psychiatrists (61%) than among patients whose antidepressants were prescribed solely by primary care physicians (31%). Patients who had trials of SSRIs had significantly higher rates of treatment adequacy (51%) than those who had trials of tricyclic antidepressants but not SSRIs (27%) or trials with other antidepressants only (24%). They concluded that adequate antidepressant treatment trials were most likely when psychiatrists collaborated with primary care physicians and when SSRIs were used. Other recent evidence from the National Comorbidity Survey-Replication (Kessler et al., 2003) again showed that less than 21% of patients with depression in the community receive minimally adequate treatment.

Perhaps most surprising is a recent report by Rasmussen et al. (2006) from a large, multisite electroconvulsive therapy (ECT) study. Adequacy of antidepressant medication trials was assessed with the Antidepressant Treatment History Form (ATHF). Among patients with nonpsychotic depression, 27% (60/220) had not had an adequate trial of an antidepressant before ECT, and 63% (139/220) had had at least one inadequate trial. Among patients with psychotic depression, 95% (101/106) had not been given an adequate combination of an antidepressant and antipsychotic agent, mostly due to low doses of the latter class. Use of hypnotic agents and anticonvulsants was common. They concluded that, although patients with severe unipolar depression referred for ECT had high rates of psychotropic usage, much of it was inadequate.

The purpose of this report is to determine whether rates of adequate treatment for patients with chronic depression has changed over the past decade as reflected in the baseline treatment history as documented using the ATHF in the subjects who entered a multisite, NIMH-sponsored clinical trial entitled, "Research Evaluating the Value of Augmentation of Medication by Psychotherapy" (REVAMP). In REVAMP, a large sample of chronically depressed patients received 8–12 weeks of open label treatment using a pharmacotherapy algorithm based on The Texas Medication Algorithm Project (Crismon et al., 1999). Patients entered the algorithm, in which the first step was sertraline, based on their history of treatment response. Patients who failed to remit at the end of this phase were then switched to or augmented with another medication and randomized to augmentation with the Cognitive Behavioral System of Psychotherapy (CBASP; McCullough, 2000), Brief Supportive Psychotherapy (Markowitz et al., 2005), or no psychotherapy.

This is a descriptive analysis. We tabulated the treatment histories and examined relationships between prior treatment and baseline clinical and demographic features, e.g., earlier age at onset and longer duration of illness, which might be expected to be associated with higher levels of prior treatment. We also contrasted the adequacy of treatment with results of earlier studies. The null hypothesis was that treatment adequacy would not have increased over the past decade.

2. Method

2.1. Subjects

Eight academic medical centers participated as clinical sites. Recruitment for the study involved outreach to clinicians affiliated with each site as well as advertising in local communities. Thus, subjects were a mix of respondents to advertisement and clinical referrals seen from 2002–2006.

To be included patients were required to have a current major depressive episode, as defined by DSM-IV and assessed on the SCID (First et al., 1994), of at least 4 weeks duration. All subjects must have reported depressive symptoms persistent for more than 2 years without periods of remission. Subjects could be included if they met criteria for double depression, i.e., current major depression with antecedent dysthymic disorder, chronic major depression (>2 years); or recurrent major depression with incomplete recovery between episodes. Patients were between ages 18 and 75 and had a 24 item Hamilton Depression Rating Scale (HAM-D) score of at least 20 at intake. Subjects needed to be fluent in English, had to have the capacity to understand the nature of the study and signed written informed consent.

Exclusion criteria were pregnancy, current diagnosis of any psychotic disorder, history of bipolar disorder, dementia, a principal diagnosis of post-traumatic stress disorder, anorexia or bulimia nervosa or obsessive–compulsive disorder, antisocial, schizotypal or severe borderline personality disorder (defined as patients who are high risk for being unable to

complete the study due to hospitalization, suicide attempts, significant self-mutilation, or other self-injurious or destructive behavior), current alcohol or other substance-related dependence disorder (with the exception of nicotine dependence) who require detoxification. Patients with substance abuse disorders were permitted to enroll if they agreed to participate in AA or chemical dependence counseling and agreed to implement a sobriety plan in conjunction with study treatment. Patients unwilling to terminate other forms of psychiatric treatment and those having serious, unstable or terminal medical illness that would compromise study participation also were excluded.

Unlike prior studies of treatment of chronic depression conducted by our group (Thase et al., 1996; Keller et al., 1998, 2000), the REVAMP study was open to patients with relatively extensive past treatment histories. Specifically, the only patients that were excluded from enrollment were those who had previously received the psychotherapy provided in the study (CBASP) or those who had already failed at least 4 of the treatment steps in the pharmacotherapy algorithm used in this study, which included sertraline, escitalopram, venlafaxine, mirtazepine, and bupropion.

2.2. Measures

Antidepressant treatment history was determined using the Antidepressant Treatment History Form (ATHF) developed by Sackeim et al. (1990) and based on the unipolar composite antidepressant scale (UNICAD) that was originally developed for use in the NIMH Collaborative Depression Study (Keller, 1988). The ATHF was updated for the REVAMP study to include SSRIs and other newer antidepressants. This instrument is used to score the adequacy of treatment trials for major antidepressant medication categories and ECT on a scale from 0 to 5 and has good reliability and validity. In this study, adequacy was based on the calculated score for adequacy, rather than treatment response. A score of 3 or above is considered adequate treatment unless the patient responds to a lower dose. The minimum duration of an adequate antidepressant trial is defined as 4 weeks. Minimum adequate daily doses are 200 mg of imipramine hydrochloride, amitriptyline, desipramine, trimipramine, clomipramine, maprotiline, doxepin, or nomifensine; 76 mg of nortriptyline; 41 mg of protriptyline; 20 mg of paroxetine, fluoxetine, or citalopram; 10 mg of escitalopram, 200 mg of fluvoxamine; 100 mg of sertraline; 61 mg of phenelzine; 41 mg of selegiline, tranylcypromine, or isocarboxazid; 300 mg of moclobemide; 30 mg of mirtazepine; 225 mg of venlafaxine; 60 mg of duloxetine, 300 mg of nefazodone or bupropion; and 400 mg of trazodone. Both duration and dose must be adequate for the trial to be classified as adequate. Treatments using a combination of antidepressants are rated according to the highest rating given to the individual antidepressants that are combined, except in the case of lithium augmentation, when a rating of 3 or 4 is increased by 1 point.

Raters first were required to review the ATHF scoring guidelines and ATHF rating instrument and then participate in an ATHF training teleconference. Following completion of the training session, the rater accessed the REVAMP website to complete a certification test. Raters who answered all items correctly were certified to administer the ATHF.

Psychiatric Diagnoses were ascertained for purposes of establishing that potential participants fulfilled the psychiatric inclusion and exclusion criteria, and documenting comorbidity using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1994). The SCID interviews were administered by experienced clinical raters who had been certified in the use of SCID. The certification process involved the submitting a videotaped SCID interview conducted by the rater to an expert rater at another site for evaluation.

Severity of depressive symptoms was assessed by independent raters using the Hamilton Depression Rating Scale (HRSD) (Hamilton, 1967), by patients using the Inventory of

Depressive Symptoms (IDS-SR) (Rush et al., 1986) and by treating psychiatrists using the Clinical Global Impression (CGI) scale (Guy, 1976).

2.3. Data analysis

Descriptive statistics are presented as means and standard deviations for continuous variables and as percentages for discrete variables. To compare continuous characteristics across levels of treatment history, parametric and nonparametric analysis of variance techniques were used. To compare discrete characteristics across levels of treatment resistance, chi-square tests were used. For all statistically significant findings ($p < .05$), post hoc tests were conducted. To maintain an overall type I error rate of .05, we used the Bonferroni correction (dividing the type I error rate by the number of pair-wise tests, i.e., p -value of .0083).

3. Results

Baseline clinical and demographic characteristics are shown in Table 1. This patient cohort presented with marked chronicity. Index episodes of depression had lasted longer than 6 years on average. The mean duration of illness since the first episode of MDD or dysthymic disorder was twenty years. Fifty nine per cent had educations beyond high school, but only 62% were employed. Only 40% were married. Eleven per cent had made suicide attempts. Lifetime number of depressive episodes was 2.22 ± 3.03 . A moderate level of severity of depression was present at entry into the study, with a mean 24-item HRSD score of 28. Of the 790 patients who entered the treatment algorithm, 609 (77%) were judged appropriate to receive sertraline, the study's first-line medication.

The ATHF was completed in 759 subjects. Results are shown in Table 2. Despite such extensive histories of depression, nearly one half (46%) had never received an antidepressant. Among the remainder, 21% had received only inadequate trials. Thus, only about one third of this group of chronically depressed patients had ever had at least one adequate trial of antidepressant medication.

Significant correlates of prior treatment adequacy (Table 3) included older age, longer duration of depression and number of melancholic features. Predictably, the most severely and chronically ill patients were significantly more likely to have received prior courses of therapy. Relationships between treatment adequacy and categorical variables are shown in Table 4. The associations between number of adequate antidepressant treatment trials and marital status, melancholia, race and lifetime panic remained significant following Bonferroni correction.

4. Discussion

In spite of the levels of severity and chronicity of depression in this sample of patients, only one third had ever had a prior adequate trial of antidepressant medication as defined by the ATHF. The only directly comparable result was that of Keller et al. (1995), who reported adequate trials in 27% of patients with chronic depression presenting to a clinical trial. Regrettably, we must conclude that the hypothesis that rates of treatment adequacy for patients presenting for treatment of chronic depression have not significantly increased over the past decade was supported.

Certain predictable demographic and clinical characteristics were found to be associated with treatment history. Patients were significantly more likely to have received prior adequate antidepressant trials if they were older, married, white, had a longer duration of illness, had more melancholic features or met criteria for the melancholic subtype or met

lifetime criteria for panic disorder. We would argue that there were opposing forces operating for and against under treatment in this sample. The fact that the depressive episodes were chronic may have resulted from under treatment, but their duration also may have given them a greater likelihood of having been treated in the past.

Some limitations of the data presented herein need to be acknowledged. First, the definition of treatment adequacy in the ATHF is based on consensus rather than well-replicated empirical findings. In fact, some published studies have reported results inconsistent with the definitions of treatment adequacy used in our analyses (Bollini et al., 1999; Furukawa et al., 2002; Ruhe et al., 2006). Secondly, because this study included psychotherapy options, subject volunteers may have had more negative attitudes toward pharmacotherapy, which could have biased the prior treatment adequacy. Thirdly, the research settings (academic hospitals), exclusion criteria and recruitment methods may have led to inclusion of a sample not representative of “real world” clinical practice.

Our conclusion of no improvement in depression treatment—in spite of greater national attention to this need—speaks to a serious public-health deficit. The multiple costs of depression—in suffering, family dysfunction, lost productivity, suicide, and medical morbidity and mortality—underscore the priority that this unmet need deserves. These results, and the consistency of similar results for over a decade, point to the dire need for patient and provider education regarding the signs and symptoms of depression and its treatment.

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Table 1

Baseline characteristics: continuous			
Characteristics	<i>n</i>	Mean	S.D.
Age	806	43.84	13.55
Age at initial onset — MDD	777	26.40	13.57
Age at initial onset — DYS	284	20.63	16.11
Number of MDD episodes	711	2.22	3.03
Length of episode (months)	795	84.02	105.39
Length of illness (years)	775	20.06	14.72
HRSD	808	27.89	5.86
HRSD-17	808	20.57	4.28
GAF	804	54.11	6.96
IDS total score	706	37.90	10.05
Baseline characteristics: categorical			
	<i>n</i>	%	
Race			
White	686	84.90	
Black or African American	61	7.55	
Other	61	7.55	
Ethnicity — Hispanic			
Yes	61	7.64	
No	737	92.36	
Sex			
Male	356	44.06	
Female	452	55.94	
Employment status			
Employed	499	62.22	
Unemployed	251	31.30	
Retired	52	31.30	
Attempted suicide			
Yes	81	10.53	
No	688	89.47	
Marital status			
Married	322	40.10	
Never	265	33.00	
Divorced	197	24.53	
Widowed	19	2.37	
Education level			
Less than HS	21	2.61	
HS graduate	307	38.14	
Greater than HS	477	38.14	
Atypical			

Baseline characteristics: categorical

	<i>n</i>	%
Yes	125	38.14
No	683	84.53
Melancholic		
Yes	409	50.62
No	399	49.38
Starting study medication		
Sertraline	619	76.80
Escitalopram	92	11.41
Bupropion	63	7.82
Venlafaxine	30	3.72
Mirtazapine	2	0.25
Main study diagnosis		
MD, no dysthymia, continuous	293	36.26
MD, no dysthymia, incomplete recovery	249	30.82
MD plus dysthymia	105	13.00
MD continuous plus dysthymia	161	19.93

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Table 2

ATHF results

Algo Rx	No trials (%)	Inadequate trial (%)	One adequate trial (%)	Two or more adequate (%)	Total
Sert	338 (54.96)	121 (19.67)	127 (20.65)	29 (4.72)	615
Other	33 (18)	47 (25)	46 (25)	60 (32)	186
Total	371 (46)	168 (21)	173 (22)	89 (11)	801

Algo Rx is the first medication prescribed based on the treatment algorithm.

Table 3

Correlates of antidepressant treatment history

Variable	No previous trials		Previous inadequate trial		One adequate trial		Two or more adequate trials		<i>F</i> (<i>df</i> _{num} , <i>df</i> _{den})	<i>p</i> -value
	Mean (S.D.)		Mean (S.D.)		Mean (S.D.)		Mean (S.D.)			
Age	41.5 (12.8)		45.1 (11.5) *		45.0 (11.7) *		47.0 (12.4) *		8.11 (3, 797)	<.0001
Duration of Depression	17.1 (13.1)		19.9 (14.0)		21.5 (13.3) *		26.2 (14.2) *, **		12.08 (3, 761)	<.0001
Age Onset Dysthymia	22.9 (16.3)		22.6 (15.0)		22.9 (14.2)		17.3 (13.2)		1.41 (3, 259)	0.2408
Age Onset MDD	26.2 (13.4)		27.7 (13.6)		26.6 (13.6)		25.5 (12.3)		0.75 (3, 763)	0.5206
Length index episode	71.7 (97.4)		90.2 (115.5)		94.3 (104.2)		106.6 (114.2)		3.44 (3, 786)	0.0165
# Episodes	2.7 (6.0)		2.9 (8.1)		2.9 (5.1)		2.4 (1.7)		1.44 (3, 703)	0.2299
GAF	53.8 (8.0)		53.9 (5.4)		54.3 (6.8)		55.0 (6.8)		0.73 (3, 795)	0.5346
HDRS	27.6 (6.1)		28.4 (6.0)		28.1 (5.4)		28.1 (5.9)		0.93 (3, 799)	0.4240
HDRS-17	20.3 (4.4)		21.0 (4.2)		20.8 (4.1)		20.5 (4.5)		1.27 (3, 799)	0.2827
IDS	36.8 (10.6)		38.8 (9.8)		39.1 (8.9)		38.2 (10.6)		2.64 (3, 698)	0.0486
# Melancholic feature	3.6 (1.7)		4.0 (1.6)		4.1 (1.7) *		3.9 (1.6)		5.26 (3, 799)	0.0013
# Atypical feature	1.2 (1.3)		0.9 (1.1)		0.9 (1.3)		1.1 (1.3)		2.00 (3, 799)	0.1122

p-values<0.0125 were considered to be significant.

* Post hoc analyses: significantly different from no previous trials.

** Post hoc analyses: significantly different from previous inadequate trials.

Table 4

Relationships between treatment adequacy and categorical variables

Variable	N	No previous trials	Previous inadequate trial	One adequate trial	Two or more adequate	Chi square (df)	p-value
% Female	803	54	53	58	65	4.18 (3)	0.24
% Employed	797	62	60	64	62	6.36 (6)	0.38
Unemployed		33	32	30	27		
Retired		5	8	6	11		
% Atypical	803	18	11	16	12	5.41 (3)	0.14
% Suicide attempt ever	765	9	11	15	8	5.32 (3)	0.15
% Married	798	36	41	47	44 *	32.36 (9)	0.0002
Never		41	27	27	20		
Divorced		22	28	24	29		
Widowed		1	4	2	7		
% Melancholic	803	44	56 *	54	62 *	14.36 (3)	0.0025
% Caucasian	803	79	89	90 *	91	21.72 (6)	0.0014
Black		11	7	4	2		
Other		10	4	6	7		
% Panic Dis. lifetime	802	8	11	10	20 *	11.32 (3)	0.01
% College educ	800	60	58	54	69	8.25 (6)	0.22
HS grad		38	41	42	28		
Less than HS		2	1	4	3		

Post hoc analyses.

Post hoc tests with $p < .0083$ were considered significant.

* Significantly different from no previous trial group.