

Antidepressant Treatment in the Primary Care Office: Outcomes for Adjustment Disorder Versus Major Depression

USMAN HAMEED, MD, THOMAS L. SCHWARTZ, MD, and KAMNA MALHOTRA, MD

Department of Psychiatry, Upstate Medical University, Syracuse, NY, USA

REBECCA L. WEST, BS, and FRANCESCA BERTONE, BA

Upstate Medical University, Syracuse, NY, USA

Background. Antidepressants are widely used by primary care physicians. Very little comparative data exists regarding the newer antidepressants in regards to efficacy in naturalistic primary care outpatient settings where the treatment of adjustment disorder and major depressive disorder is concerned. Our objective was to determine if there is a difference in antidepressant effectiveness between disorders in the newer antidepressants (SSRIs) in a primary care setting when a formal systematic depression treatment protocol is used.

Method. A retrospective review of 63 major depression patients and 33 adjustment disorder patients in a primary care setting was undertaken. Patients had been prescribed mostly SSRIs. DSM-IV symptoms, PHQ-9 depression rating scale scores, and functional disability reports were systematically used to evaluate partial and full remission from patients' depressive states.

Results. Neither depressed patients, nor adjustment disordered patients demonstrated a difference in clinical response to any particular antidepressant. The main statistical difference was in response rates, where patients diagnosed with adjustment disorder were twice as likely to respond to standard antidepressant treatment as depressed patients. This retrospective database design with moderate sample size limits the statistical power of this study.

Conclusion. Antidepressants are very effective in treating depression in the primary care setting and may even be an effective and efficient treatment for adjustment disorder with depressed mood.

Keywords Major depression, adjustment disorder, antidepressants, primary care, efficacy

INTRODUCTION

Major depressive disorder (MDD) affects 5 to 12% of men and 10 to 25% of women in their lifetime (1, 2). Nearly 75% of patients seeking help for depression go to a primary care physician (PCP) and 5 to 10% of all the patients seen in this setting carry a diagnosis of major depression in addition to other medical conditions (3). Overall, this makes depression one of the most common disorders in primary care (4)(5). There is greater med-

ical morbidity and mortality in depressed patients compared to those who are not depressed (3)(6).

Adjustment disorders fall within the psychiatric taxonomic spectrum between normal mental health and clear psychiatric disorder. Adjustment Disorder with Depressed Mood per the DSM-IV may be considered a "subsyndromal depressive disorder" and reflects the mild end of the depression spectrum. Development of clinically significant emotional or behavioral symptoms, often depressive in nature, occurs after an identifiable stressor (7). The psychological symptoms must occur within 3 months of the occurrence of the stressor and must remit within 6 months following the cessation of the stressor. Although this subsyndromal condition does not meet the full diagnostic criteria for major depressive disorder in

Address correspondence to Thomas L. Schwartz M.D., Assistant Professor, Department of Psychiatry, Upstate Medical University, 750 E Adams Street, Syracuse, NY, 13210. E-mail: schwartzresearch1@yahoo.com

DSM-IV or ICD-10, it is associated with significant costs and disability (8).

This adjustment diagnosis is often used in psychiatry, but is more typically seen in primary care settings (9), and has an estimated incidence of 5–21% in psychiatric consultation services for adults (10). Currently, psychotherapy remains the treatment of choice for adjustment disorders (11), and there are no major pharmacotherapy studies to support antidepressant treatment.

The SSRIs currently approved for use in depression in the U.S. include Paroxetine, Fluoxetine, Sertraline, Citalopram and Escitalopram. These drugs are equally efficacious with a similar side effect profile (12). In 2002, a survey of prescribing practices in depression found that SSRIs were prescribed first to patients in 93% of cases, serotonin-norepinephrine reuptake inhibitors (SNRIs), such as Venlafaxine in 3% cases and Bupropion in 2% of cases (13). However, there have been no naturalistic, comprehensive studies done in the past that compare the efficacy of these frequently used antidepressants in the primary care setting.

The purpose of this study is to compare two primary care cohorts: a group of major depressive disorder patients and a group of adjustment disorder patients with depressed mood from the same primary care centers. The primary comparison evaluated response rates to antidepressants between these two groups.

METHODS

Ninety-six subjects were initially diagnosed with depressive disorder by their primary care physician in one of three group practice settings. Upon initial diagnosis, an antidepressant was started at the clinician's discretion, and then a depression management protocol was started for each patient. The diagnosing physician would assign a case manager to each patient in order to conduct telephone interviews including a brief medical history, DSM-IV depression symptom screening, PHQ-9 depression rating scale (14) and a functional capacity rating scale (an unvalidated local analog scale). One week after medication initiation, a teleconference call to a consulting psychiatrist occurred to confirm diagnosis and treatment regimen. At weeks 4, 8, and 16, follow-up consulting calls are made to the psychiatrist, and a team approach via a case manager occurs with liaison to the primary care physician. Routine assessments are made at these intervals with the scales noted above. This method allows clinical assessments of depressive symptomatology to be compared with systematic patient report outcome measures. Options to begin additional antidepressant medications or to start concurrent psychotherapy occur in this liaison model as well.

Subjects were not randomized to any particular medication, combination of medications, or psychotherapy. The depression management team made these choices naturalistically and prospectively. This management protocol was a clinical endeavor and was not a research study. Patients were asked if they would like to be a part of the clinical program by their clinician and

were given verbal informed consent in the course of their usual doctor-patient relationship. This was not a prospective study and written informed consent was not given. There were no placebo controls and blinding was not part of the design of this clinical intervention. This study is a retrospective review of the outcomes of this management program by way of reviewing its database well after treatment had occurred. Appropriate permission was gathered in order to analyze this clinical database without patient identifiers.

This cohort of patients represents a typical population of patients, diagnosed in the primary care setting with varying levels of depressive disorder. Each patient is given the same level of care in regards to number of visits, phone calls, and naturalistic dose titration. This cohort allows for a systematic approach to treating depression and also for evaluating treatment outcomes. As these are unique doctor-patient dyads, variance would occur in regards to medication chosen, dose used, amount of follow-up visits (particularly for co-morbid medical problems), and so on.

Sixty-three patients met full criteria for major depressive disorder according to the DSM-IV and the PHQ-9. Subjects who had four or less depressive disorder symptoms and were lower than the depression score cut-off on the PHQ-9 were deemed to have subsyndromal depression. Most of this group likely had a stressor and adjustment disorder after case review. It is possible that this subsyndromal group would also qualify for minor depressive disorder if their symptoms were to persist long enough to meet DSM-IV provisional criteria. Thirty-three subjects met these subsyndromal depressive criteria and created the second clinical group for comparative analysis.

The authors hypothesized:

1. major depression patients will show lower response rates to antidepressant therapy. The authors evaluated 'response' to treatment versus 'remission' from depression. Response was defined as residual DSM-IV symptoms of 4 or less, a decrease in PHQ-9 score value of 50% from baseline and a decrease in functional impairment by one level (e.g., extreme difficulty at baseline to very difficult at any follow up). Remission was defined as follow up DSM-IV symptoms of 2 or less, a decrease in PHQ-9 score value of 70% or more from baseline and decrease in functional impairment by two or more levels (e.g., very difficult at baseline and none at follow up) and
2. all novel FDA approved antidepressant monotherapies will be equally effective in treating depression and adjustment disorders within each diagnostic cohort.

RESULTS

Table 1 shows patient characteristics for the major depression group and Table 2 the adjustment disorder group. Descriptive statistics were used to quantify group characteristics and Fisher's

Table 1 Predictors of Response and Remission among Depressed Patients

	Symptom				Score				Function			
	Resp.	P-v	Rem.	P-v	Resp.	P-v	Rem.	P-v	Resp.	P-v	Rem.	P-v
Age-split at median												
< 51 (n=29)	14 (48)	0.040	11 (38)	0.155	12 (41)	0.106	8 (28)	0.371	11 (38)	0.098	4 (14)	0.137
>= 51 (n=34)	25 (74)		19 (56)		21 (62)		13 (38)		20 (59)		10 (29)	
Gender												
Male (n=16)	10 (63)	0.955	7 (44)	0.720	9 (56)	0.720	5 (31)	0.838	8 (50)	0.941	3 (19)	1.000
Female (n=47)	29 (62)		23 (49)		24 (51)		16 (34)		23 (49)		11 (23)	
Dysthymia												
Yes (n=41)	24 (59)	0.257	16 (39)	0.034	18 (44)	0.031	11 (27)	0.051	18 (44)	0.165	7 (17)	0.312
No (n=19)	14 (74)		13 (68)		14 (74)		10 (53)		12 (63)		6 (32)	
Q9 (Suicidality)												
Yes (n=9)	7 (78)	0.462	5 (56)	0.725	5 (56)	1.000	4 (44)	0.466	4 (44)	1.000	3 (33)	0.403
No (n=54)	32 (59)		25 (46)		28 (52)		17 (31)		27 (50)		11 (20)	
Medication												
Citalopram (n=17)	13 (76)	0.230	11 (65)	0.174	12 (71)	0.091	8 (47)	0.633	11 (65)	0.065	5 (29)	0.553
Paroxetine (n=14)	6 (43)		4 (29)		5 (36)		3 (21)		8 (57)		3 (21)	
Sertraline (n=11)	5 (45)		4 (36)		4 (36)		3 (27)		3 (27)		1 (9)	
Venlafaxine (n=5)	4 (80)		1 (20)		1 (20)		1 (20)		0 (0)		0 (0)	
Combination (n=10)	7 (70)		6 (60)		7 (70)		3 (30)		5 (50)		3 (30)	
Treatment												
Medication (n=37)	25 (68)	0.270	19 (51)	0.479	22 (59)	0.180	13 (35)	0.717	20 (54)	0.359	10 (27)	0.274
Combination (n=26)	14 (54)		11 (42)		11 (42)		8 (31)		11 (42)		4 (15)	

Definitions of response and remission:

Symptom: A response occurred when any follow-up symptom value was less than or equal to 4 and remission when follow-up value was less than or equal to two.

Score: A 50% or more decrease in the score value from baseline to follow-up was defined as a response, whereas a 70% decrease was interpreted as remission.

Function: A response was defined as a decrease of one or more (e.g., extreme difficulty at baseline to very difficult at any follow-up time), whereas a decrease of two or more (e.g., very difficult at baseline and none at any follow-up time) suggested the patient was in remission.

Exact tests were used to compare the proportion of patients who experienced treatment response between subgroups.

Major Depression Cohort

Overall response to treatment in the depression group was 43–80% ($x/\bar{x} = 46.6$) and remission was achieved for 20–65% ($x/\bar{x} = 29.0\%$) of patients depending upon medication(s) used (see Table 1). No single antidepressant was found to be more effective than another agent in treating depression to a response ($p = 0.091$) or remission ($p = 0.633$). Combining antidepressants did not improve depression symptom relief over monotherapy at four months in regards to response or remission rates ($p = 0.091$ and 0.633). The addition of psychotherapy did not improve response ($p = 0.180$) or remission ($p = 0.717$) rates. Patients who acknowledged “dysthymia” or symptom duration exceeding 2 years demonstrated equal response to treatment statistically ($p = 0.31$), but were less likely to remit completely ($p = 0.051$). Neither age ($p = 0.106$ and 0.371) nor gender ($p = 0.720$ and 0.838) played a role in treatment outcome.

Adjustment Disorder Cohort

Overall response to treatment in this group was 33–100% ($x/\bar{x} = 74.4$) and sustained response over 4 months was achieved

for 33–100% ($x/\bar{x} = 70\%$) of patients (see Table 2). No single antidepressant was found to be more effective than another agent in treating adjustment disorder symptoms ($p = 0.399$). Combining antidepressants did not improve symptom relief over monotherapy at 4 months in regards to response or sustained response rates ($p = 0.652$ and 1.000). Patients who acknowledged “dysthymia” or symptom duration exceeding 2 years demonstrated equal response to treatment statistically ($p = 0.169$), but were also equally likely to maintain a sustained response ($p = 0.060$). However a clinical trend towards being less responsive to treatment was noted. Neither age ($p = 0.106$ and 0.371) nor gender ($p = 0.720$ and 0.838) played a role in treatment outcome.

DISCUSSION

The purpose of this research was to determine the effectiveness of newer antidepressants in the treatment of major depressive disorder and adjustment disorders in the primary care setting. The sustained response rates of adjustment disorders were compared to those seen in the treatment of major depressive disorder. Response and remission rates of subjects with major depressive disorder were compared to those seen when additional antidepressants or psychotherapy were added to monotherapy as a separate analysis. The major strength of this database review is that each patient was treated with an

Table 2 Predictors of Response in Adjustment Disorder Patients

	Symptom Quantity				PHQ9 Score			
	AR	Pv	SR	Pv	AR	Pv	SR	Pv
Age-split at median								
< 51 (n=17)	13 (76)	1.000	11 (65)	1.000	10 (59)	1.000	8 (47)	0.732
>= 51 (n=16)	13 (81)		11 (69)		9 (56)		9 (56)	
Gender								
Male (n=7)	6 (86)	1.000	6 (86)	0.378	4 (57)	1.000	4 (57)	1.000
Female (n=26)	20 (77)		16 (62)		15 (57)		13 (50)	
Dysthymia *4 missing								
Yes (n=14)	10 (71)	0.169	10 (71)	1.000	6 (43)	0.060	6 (43)	0.272
No (n=15)	14 (93)		11 (73)		12 (80)		10 (67)	
Q9 (Suicidality)								
Yes (n=1)	N too small							
No (n=32)								
Medication *2 missing								
Celexa (n=5)	4 (80)	0.399	3 (60)	0.425	3 (60)	0.418	3 (60)	0.193
Paxil (n=4)	4 (100)		4 (100)		4 (100)		4 (100)	
Zoloft (n=14)	11 (79)		8 (57)		8 (57)		7 (50)	
Effexor (n=3)	1 (33)		1 (33)		1 (33)		1 (33)	
Combination (n=5)	4 (80)		4 (100)		2 (40)		1 (20)	
Celexa/Paxil/Zoloft (n=27)	22 (81)	0.212	18 (67)	0.601	16 (59)	1.000	15 (56)	0.333
Other (n=4)	2 (50)		2 (50)		2 (50)		1 (25)	
Treatment								
Medication (n=25)	19 (76)	0.652	17 (68)	1.000	15 (60)	0.695	14 (56)	0.438
Combination (n=8)	7 (88)		5 (63)		4 (50)		3 (38)	
6 (40)								

AR=any response, SR=sustained response.

Patients who did not have any symptom or score value at baseline and at least one follow-up time were deleted from the analysis. The Fisher's Exact test was used to compare the proportion of patients who experienced a response between subgroups.

Definitions of response

Symptom: A response occurred when any follow-up symptom value was equal to 0. Patients who continued to have 0 symptoms throughout the follow-up period were defined as a sustained response.

Score: Responders were defined as having a PHQ9 score less than or equal to 2 during follow-up. Sustained response occurred when values less than or equal to 2 persisted through follow-up.

Table 3 Major Depressive Disorder Versus Adjustment Disorder Response to Treatment

	Symptom Quantity				PHQ9 Score			
	AR	Pv	SR	Pv	AR	Pv	SR	Pv
Depression								
Minor (n=33)	26 (79)	0.001	22 (67)	0.012	18 (55)	0.004	17 (52)	0.008
Major (n=47)	20 (43)		17 (36)		10 (21)		10 (21)	

AR=any response, SR=sustained response.

antidepressant medication, and received a controlled and uniform level of follow-up care within a nurse case management system where routine interviews, rating scales and psychiatric consultation were used as treatment tools.

This study found that all antidepressants worked equally well, combining antidepressants did not improve response or remission rates over monotherapy, and the addition of psychotherapy to pharmacotherapy did not improve response or remission rates over pharmacotherapy alone during a 4-month period in either group. The study also found that patients with

adjustment disorder experienced sustained response rates approximately 70% of the time, which is double the rate of response compared to the major depression group. Absence of dysthymia was the best predictor of patient remission rates in the full major depression group, as dysthymic patients were less likely to achieve full remission of symptoms compared to other members of the cohort.

The strength of this research lies in that every patient received approximately the same level of care allowing for variance based on specific doctor-patient dyads. These systematic

efforts to improve depression treatment also ensure that adequate trials of medication and psychotherapy are carried out for the patients. This protocol allowed for real time, prospective systematic use of outcome measures, which lends to the reliability of our data. For patients diagnosed with adjustment disorders, a 70% sustained response rate was quite remarkable and suggests that short term antidepressant use in this population may be clinically useful and cost effective.

Limitations to this study are apparent in that it is a retrospective analysis of a database. The authors were not treating clinicians, but were liaison psychiatrists and database reviewers. Patients were not seen weekly to collect rating scales as in prospective studies. There were no clinician-administered scales. Some confounding may occur as many family physicians were in charge of treating many patients, which allows for heterogeneity not seen in single site prospective studies. Again, this allows for more naturalistic, real-world data which often is missed in prospective studies with non-co-morbid subjects. Our data may also be confounded by usual predictors of poor outcome in depression; severity and duration of current depressive episode and that adjustment-based illness may remit without any intervention. Additional studies are needed to compare individual outcomes at specific time intervals, and it is difficult to compare our findings with those of other investigators as this was a database review. Despite these drawbacks, we feel our findings remain valuable and clinically relevant given the relative lack of comparative data in this area of study.

Many patients in the primary care setting suffer from mild to moderate depressive episodes, and still others suffer from adjustment disorders. Though they tend to respond well to antidepressant treatment, optimizing treatment as much as possible for these patients is crucial. Although some patients would prefer counseling to antidepressant therapy if given the choice, our study has demonstrated that antidepressants work very well in the treatment of depression, and that combining antidepressants or adding psychotherapy to pharmacotherapy did not improve response or remission rates over pharmacotherapy alone. Our data also yielded results that demonstrated that patients with adjustment disorder tend to respond very well to antidepressant treatment, and may respond twice as well as patients with major depressive disorder. Importantly, early recognition and treatment of adjustment disorders may reduce the duration of episodes and prevent further progression to a more serious depressive disorder. As long as a disparity continues to exist between health insurance coverage for mental health and general medical treatment, a careful balance must be achieved in order to offer high quality mental health services while making sensible use of our health care resources in primary care.

We hope to continue this study by improving our database and increasing our sample size in order to address some of these limitations and reconfirm our findings. We hope that future investigations will replicate these findings in a matched prospective study in a large group of patients with major depressive disorder and adjustment disorder.

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