Key Words: antidepressive agents, bipolar disorder, depressive disorder, clinical trial, monoamine oxidase inhibitors, treatment outcome

Revisiting the Effectiveness of Standard Antidepressants in Bipolar Disorder: Are Monoamine Oxidase Inhibitors Superior?

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ABSTRACT ~ **Objective**: *The role of antidepressants in treating bipolar disorder is controversial, and the comparative effectiveness of specific drugs is insufficiently studied. We report here a comparison of monoamine oxidase inhibitors (MAOIs) with the serotonin reuptake inhibitor paroxetine (PAROX).* **Experimental Design:** *We conducted a retrospective analysis of data from a larger study, using the first antidepressant trial administered either after entry (n = 46) or after a recurrent episode during study participation (n = 6). Twenty two patients were treated with PAROX and 30 with an MAOI. Durable recovery was determined from Hamilton depression and Young mania scores, based on published criteria.* **Principal Observations:** *PAROX treatment led to durable recovery in 27% of patients, a result very similar to the 24% recovery rate found in a recent STEP-BD trial. In contrast, patients treated with an MAOI had a 53% durable recovery rate. Survival analysis showed a significantly faster onset of durable recovery with MAOIs ($\chi^2 = 4.77$, $p = 0.029$). Among subjects who were able to complete an adequate treatment trial of at least four weeks duration, durable recovery was attained in a significantly greater proportion of those treated with an MAOI (16 of 23, 70%) as compared to PAROX (6 of 18, 33%)(Fisher's Exact Test, $p = 0.023$).* **Conclusions:** *In these patients with bipolar depression, the antidepressant effectiveness of PAROX was unacceptably low, but rates of recovery with MAOIs were significantly higher.* Psychopharmacology Bulletin. *2009;42(2):64–74.*

INTRODUCTION

The use of standard antidepressants for treating the depressed phase of bipolar disorder is controversial. Historically it has been assumed that all antidepressants have comparable effectiveness in a variety of types of depressive disorders,

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including bipolar depression, despite limited evidence to support this view. However, it is widely believed that antidepressants convey some degree of risk for induction of mania or hypomania. Thus, antidepressant use in bipolar patients is subject to the need for risk/benefit analysis. On the benefit side, Gijsman et al.[1] reviewed the evidence from 12 randomized controlled trials of short-term treatment of bipolar depression involving 1,088 patients and concluded based on data from five trials involving placebo controls that antidepressants were more effective than placebo. The majority of subjects studied (75%) were receiving concurrent mood stabilizer or atypical antipsychotic medication. Since then, findings have been published from a double-blind comparison of adjunctive antidepressant with placebo in the STEP-BD study, showing no benefit from adding paroxetine (PAROX) or bupropion to a mood stabilizer.[2]

There has been surprisingly little research to date on the comparative effectiveness of specific antidepressant agents in bipolar disorder. In the review cited above, Gijsman et al.[1] concluded that the data are inadequate to definitively favor one medicine over another within the several generic categories of the antidepressants. In previous work, our group has reported on the superiority of the monoamine oxidase inhibitor (MAOI) tranlycypromine versus imipramine for treatment of anergic bipolar depression.[3] In the work reported here, we hypothesized that an MAOI would be more effective for treating bipolar depression than PAROX under conditions comparable to the STEP-BD adjunctive antidepressant study cited above. In order to test this hypothesis, we conducted a retrospective analysis of data from an earlier investigation,[4] using the same durable recovery criteria that were employed in the STEP-BD adjunctive antidepressant study.

MATERIALS AND METHODS

Experimental Design

We conducted a retrospective analysis of data from the Maintenance Therapies in Bipolar Disorder (MTBD) study[4] performed at the University of Pittsburgh Medical Center (UPMC). Data were from the first antidepressant trial administered to subjects after study entry (n = 46), or the first antidepressant trial administered for a new episode of depression following a minimum one month symptomatic remission during study participation (n = 6). All subjects gave informed consent for research participation using procedures approved and monitored by the University of Pittsburgh Health Sciences Institutional Review Board.

To be included in the analysis, subjects were required to have a baseline score of 12 or greater on the 25-item Hamilton Rating Scale for Depression (HRSD),[5,6] calculated as the average from two pretreatment ratings. Patients currently in a mixed episode were not included. Clinical outcome was assessed using the criteria for durable recovery employed in the above-cited STEP-BD report (at least eight consecutive weeks of euthymia, with onset by the 16th week of treatment). All subjects categorized as recovered continued to take antidepressant during at least the first five weeks of durable recovery, and 18 (82%) of the 22 recovered patients continued to take antidepressant during the entire eight week durable recovery period. Euthymia was defined as having a score of 12 or less on the 17-item HRSD[7] and 14 or less on the Young Mania Rating Scale (YMRS)[8]. These cutoffs were calculated from published data on the comparability of the above scales with the Clinical Monitoring Form (CMF) used in the STEP-BD study,[9] and were intended to approximate the criterion of no more than two depressive or two manic symptoms that was used in the STEP-BD adjunctive antidepressant study to define durable recovery. Although we consider the 25-item HRSD to provide a more accurate assessment of symptom severity in bipolar depression because it includes reversed vegetative symptoms, the 17-item HRSD was used in the criteria for durable recovery because published data on comparability with the CMF were available only for that version. Mood ratings were routinely performed at all clinic visits by an independent evaluator who was not involved in treating the patients.

The protocol of the MTBD study specified that subjects who presented with an episode of depression were first treated on an open label basis with a mood stabilizer alone (usually lithium unless there was a specific reason to prefer a different medication). Those whose depression failed to remit received open label addition of an antidepressant. Assignment of subjects to specific medication was governed by MTBD study guidelines; earlier in the course of subject acquisition, these guidelines called for use of the MAOI tranylcypromine as first line antidepressant treatment, and later the selective serotonin reuptake inhibitor PAROX was given this role. Treating physicians were occasionally permitted to substitute other drugs as first line treatment if there was a compelling clinical rationale for doing so. Of 175 depressed, manic, and mixed mood patients who participated in the overall MTBD study, we identified 52 who met our inclusion criteria during a first antidepressant trial. Twenty two of these were treated with PAROX and 30 were treated with MAOIs (specifically, 28 received tranylcypromine and two received phenelzine). All patients were treated with ongoing concomitant mood stabilizers. Patients also concurrently received either interpersonal and social rhythm therapy (IPSRT) or intensive clinical management (ICM).[4]

Hypothesis

We hypothesized that MAOI treatment would lead to durable recovery in a greater proportion of cases as compared to PAROX.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 15.0 for Windows, SPSS, Inc., Chicago, IL). Fisher's Exact tests were used to compare groups on categorical measures with two categories, chi-square tests were used for measures with more than two categories, and independent t-tests were used with continuous measures. For continuous measures, Levene's test was used to compare group variances, and Shapiro-Wilk's test was used to test for fit to normality. Except when specified otherwise, significance levels for testing demographic or illness variables and outcome measures were based on $p < 0.05$, two-tailed. In cases where a one-sided test was utilized, the direction of the difference was predicted by our hypothesis, and the comparable results of two-sided tests are also presented. The log rank test was used to compare times to onset of durable recovery for the MAOI and PAROX groups in a Kaplan-Maier survival analysis.

RESULTS

Subject Characteristics

Table 1 summarizes the demographic and clinical characteristics of subjects, categorized by treatment group. Our subjects on average experienced a first depressive episode in their early twenties and first manic episode in their mid twenties. Overall, 38% had a highly recurrent pattern of depressions (10 or more prior episodes), and a somewhat lower proportion (17%) had highly recurrent manias. There were no significant differences between the MAOI and PAROX treatment groups with respect to gender, age at study entry, age at first depression, age at first mania, racial composition, education, marital status, or the proportion of subjects with highly recurrent illness based on having at least 10 prior episodes of mania or depression.

Table 1 also presents the mean (SD) pretreatment 17- and 25-item Hamilton depression scores for subjects grouped by treatment condition. The mean scores reflect depression of moderate severity, and there was no significant difference between the MAOI and PAROX treatment groups in the baseline scores. Symptoms of mania at baseline were minimal, and there was likewise no significant difference between the treatment groups.

Use of mood stabilizers was comparable in the two treatment groups, with the majority of patients being treated with lithium (see Table 1).

TABLE 1

DEMOGRAPHICS, SEVERITY OF ILLNESS, AND TREATMENT VARIABLES

	MAOI *N = 30*	PAROXETINE *N = 22*	
	n (%)	*n (%)*	*p (2-tailed)*
Education			0.88
• Some or Completed High School	9 (30)	8 (37)	
• Some After High School	11 (37)	7 (32)	
• Associate, Technical, or College Degree	10 (33)	7 (32)	
Marital status			0.18
• Married	13 (43)	5 (23)	
• Divorced, Widowed, or Separated	6 (20)	9 (41)	
• Never Married	11 (37)	8 (36)	
Previous Episodes			
• Depression (≥10)	9 (30)	11 (50)	0.16
• Mania (≥10)	4 (13)	5 (23)	0.47
Race (Caucasian)	28 (93)	22 (100)	0.50
Sex (Male)	10 (33)	11 (50)	0.26
Psychosocial Treatment (IPSRT)	17 (57)	9 (41)	0.40
Completed 4 Weeks Treatment	23 (77)	18 (82)	0.74
Mood Stabilizer Treatment			
• Lithium (Li)	25 (83)	16 (73)	
• Valproate (VPA)	4 (13)	2 (9)	
• Carbamazepine (CBZ)	0 (0)	1 (5)	
• Combination	0 (0)	3 (14)	
• Li, VPA	0 (0)	2 (9)	
• Li, VPA, CBZ	0 (0)	1 (5)	
• None	1 (3)	0 (0)	
	Mean (SD)	*Mean (SD)*	*p (2-tailed)*
Age			
• First Depression	21.9 (7.3)	22.3 (8.1)	0.61
• First Mania	26.1 (9.0)	27.1 (10.2)	0.55
• Study Entry	33.4 (8.8)	39.0 (11.8)	0.13
Mood (Baseline)			
• HDRS (17 Item)	16.4 (5.1)	15.7 (4.5)	0.60
• HDRS (25 Item)	21.4 (5.3)	21.0 (5.1)	0.79
• YMRS	1.9 (1.8)	1.9 (1.8)	0.93

The percentage of subjects treated with lithium as the only mood stabilizer was 83% in the MAOI-treated group and 73% in the PAROX-treated group. Mood stabilizer combinations utilized also included lithium. In the single case where no traditional mood stabilizer was used, the subject was treated with the atypical antipsychotic risperidone.

Because only a subgroup of patients received IPSRT and this psychotherapy could potentially affect treatment outcome, we examined group differences in this variable. As is shown in Table 1, IPSRT was administered to comparable proportions of MAOI-treated and PAROX-treated patients (57% vs 41%, respectively, $p = 0.40$). Overall, attainment of durable recovery was comparable in the groups treated with IPSRT (10 of 26 subjects, 38%) and ICM (12 of 26 subjects, 46%), and this small difference was not significant (Fisher's Exact Test, $p = 0.38$).

Treatment Outcome

Durable recovery was attained in 6 of 22 patients (27%) treated with PAROX. In contrast, for patients treated with MAOIs, durable recovery was attained in 16 of 30 (53%), a near-twofold difference in response rate. Treatment response over time is shown in Figure 1. Survival analysis showed significantly faster onset of durable recovery with MAOI treatment ($\chi^2 = 4.77$, $p = 0.029$).

Among 41 of the original 52 subjects who were able to complete an adequate treatment trial of at least four weeks duration, the rate of

FIGURE 1

PROPORTION OF SUBJECTS ATTAINING THE ONSET OF DURABLE RECOVERY OVER TIME WITH MONOAMINE OXIDASE INHIBITOR (MAOI, SOLID LINE) OR PAROXETINE (DASHED LINE). CENSORED OBSERVATIONS ARE REPRESENTED BY +

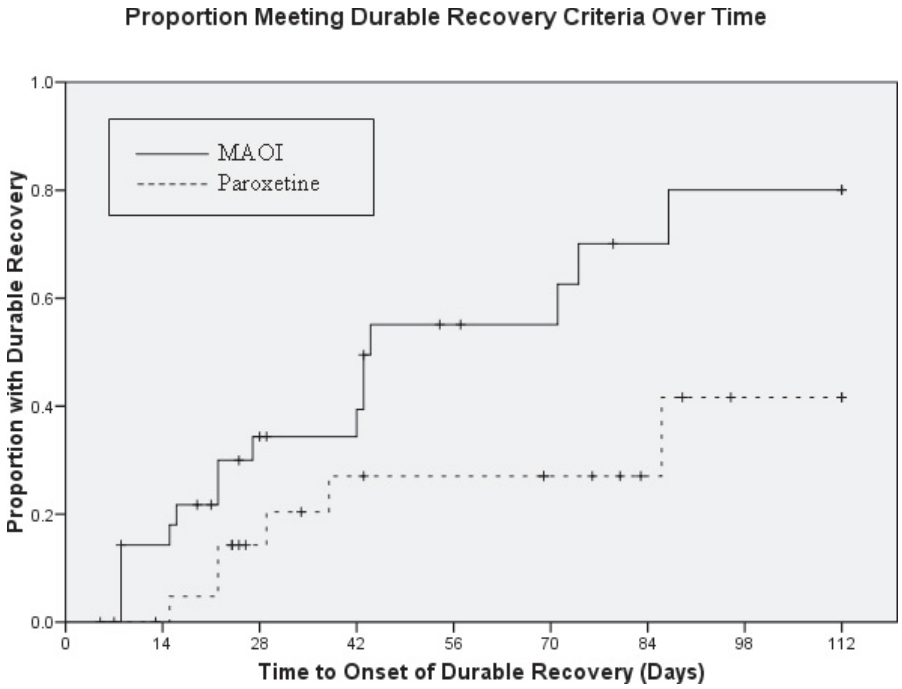

TABLE 2

MINIMUM FOUR WEEKS DURATION ADEQUATE TREATMENT TRIAL

	RESPONSE TO TREATMENT	
TREATMENT GROUP	*DURABLE RECOVERY*	*NOT RECOVERED*
MAOI	16	7
Paroxetine	6	12

Fisher's Exact Test, p (1-tailed) = 0.023
Fisher's Exact Test, p (2-tailed) = 0.030

durable recovery was significantly greater for MAOI-treated patients (70%) as compared to PAROX-treated patients (33%) (Fisher's Exact Test, p = 0.023, one tailed). These data are shown in Table 2. Overall, 82% of PAROX patients and 77% of MAOI patients were able to complete at least four weeks of treatment, and the small difference between groups was not statistically significant (Fisher's Exact Test, p = 0.74).

Comparisons with STEP-BD Treatment Conditions

Treatment parameters for PAROX in this investigation were similar to those reported by the STEP-BD investigators.[2] Table 3 shows a comparison of the present study with published data from the STEP-BD adjunctive antidepressant study. The doses of PAROX utilized (both the maximum and at the time of study exit) were similar in both settings, although no statistical comparison was possible due to the nature of the summary data reported from STEP-BD. Likewise, both studies treated patients for a similar length of time (89.0 ± 58.8 days of PAROX treatment in our study versus 88.0 ± 63.65 days of antidepressant treatment in the STEP-BD adjunctive antidepressant study; t = 0.07, p = 0.94, data presented as means ± SDs), with most subjects in both studies participating over a more extended period in a larger investigation that included both acute and maintenance treatment components.

All of the patients in our study received concomitant adequate treatment with a mood stabilizer (as defined in the published STEP-BD report cited above) both at the time PAROX was started and during ongoing PAROX treatment. In the STEP-BD adjunctive antidepressant study, a significantly lower proportion of patients (76%) were receiving adequate mood stabilizer at antidepressant initiation (Fisher's Exact Test, p = 0.005, see Table 3), although the proportion receiving adequate mood stabilizer increased subsequent to antidepressant initiation (87%) and was only marginally lower than in

TABLE 3

PAROXETINE TREATMENT GROUP COMPARISON TO RESULTS OF STEP-BD

	PAROXETINE *N = 22*	STEP-BD *N = 177*	
	n (%)	*n (%)*	*p (2-tailed)*
Adequate mood stabilizer when antidepressant is started	22 (100)	135 (76)	0.005
Adequate mood stabilizer after antidepressant is started	22 (100)	154 (87)	0.08
	Median (IQR)	*Median (IQR)*	
Maximum dose (mg)	20 (10−60)	30 (20−40)	
Dose at exit (mg)	20 (5−40)	30 (20−40)	
	Mean (SD)	*Mean (SD)*	*p (2-tailed)*
Days receiving treatment	89.0 (58.8)	88.0 (63.65)	0.94
Drug			
• Lithium (n = 19)			
• Dose (mg)	1231.5 (413.3)		
• Level (mmol/L)	0.83 (0.15)		
• Valproate (n = 5)			
• Dose (mg)	1500.0 (176.7)		
• Level (mcg/mL)	69.1 (4.7)		
• Carbamazepine (n = 2)			
• Dose (mg)	600.0 (0.0)		
• Level (mcg/mL)	5.98 (0.40)		

our study (p = 0.08). Table 3 also summarizes mean mood stabilizer levels and doses for subjects in our study, although comparable data were not available for the STEP-BD subjects.

DISCUSSION

The findings from this investigation must be considered preliminary in view of the retrospective analysis, open label treatment, and limited number of subjects. They thus require replication by prospective study of a larger number of subjects. Nevertheless, this report complements our previously reported finding (from a double-blind, prospective study) on the superiority of the MAOI tranylcypromine versus the reuptake-blocking antidepressant imipramine in the treatment of anergic bipolar depression[3]. In that previous investigation, the response rate for subjects who were able to complete at least four weeks of treatment was 81%, which is comparable to the 70% rate of durable recovery found in the present study (in the previous investigation, patients were not considered nonresponders and were excluded from the analysis unless they completed at least four weeks of

treatment). Thus, despite the differences in criteria for defining outcome that were utilized in our current and previous investigations, MAOIs emerged in a consistent way as being substantially more effective than conventional reuptake-blocking antidepressants in bipolar depression (notwithstanding that in the current investigation, comparable proportions of MAOI and PAROX subjects were able to complete at least four weeks of antidepressant treatment).

The findings presented here are consistent with a recent report by Nolen and associates.[10] Although their findings were based on a small group of subjects and were not statistically significant, they observed during a first trial that 63% of treatment refractory bipolar depressed patients responded to tranylcypromine (n = 8), whereas only 36% responded to lamotrigine (n = 11). Nevertheless, some authors believe that older MAOIs such as tranylcypromine should not be recommended for first line use because of the dietary limitations required and the frequency of adverse events.[11]

The irreversible and nonselective MAOIs utilized in the present investigation (primarily tranylcypromine, see Methods) may have a therapeutic advantage over newer reversible and selective agents. Silverstone and colleagues[12] compared a reversible inhibitor of MAO-A (moclobemide) with imipramine in a randomized, double-blind, parallel group, multicenter study of 156 patients with bipolar depression. Although they did not use a measure of durable recovery, acute response to treatment was similar with moclobemide (46%) or imipramine (53%). Mean score on the 17-item Hamilton Depression Scale after eight weeks of treatment was 13.1 with moclobemide and 9.5 with imipramine, indicating no therapeutic advantage for moclobemide. Lotufo-Neto and associates[13] performed a meta-analysis of moclobemide effectiveness, and found that both intention-to-treat and adequate treatment trial data tended to favor nonselective MAOIs. However, only four studies were available, and for the one trial in which moclobemide was superior to tranylcypromine, the dosage of this latter drug was clearly subtherapeutic (10–30 mg/day).

Selegiline is an irreversible inhibitor of MAO that at low doses is selective for MAO-B.[14] This agent has recently been introduced in a transdermal formulation that conveys some safety advantages, and comparative studies in bipolar depression would be of interest.

An important difference from our previously reported study on tranylcypromine in bipolar depression is that, unlike the previous work, patients in the present investigation received concomitant mood stabilizer treatment. This more closely reflects the standard of care in clinical practice, although it also raises issues related to the possible confounding influence of the mood stabilizer on antidepressant response. In our

current investigation, all subjects were treated with adequate mood stabilizer for at least one month before starting antidepressant, although this was not the case in the STEP-BD adjunctive antidepressant study.

Administration of IPSRT was a possibly confounding factor in this work. However, IPSRT assignment did not differ significantly between the medication groups, and in fact IPSRT and ICM were associated with comparable rates of durable recovery. In the STEP-BD adjunctive antidepressant study, 36% of subjects received intensive psychotherapy and 29% received brief psychoeducation in a concurrent investigation of psychosocial treatments; in that study, augmentation of drug therapy with intensive psychotherapy or brief psychoeducation carried no significant benefit.

As noted previously, the observed rate of durable recovery with PAROX treatment in the present study was 27%. This finding is very similar to the 24% antidepressant recovery rate noted in the STEP-BD adjunctive antidepressant study. In contrast, MAOIs produced significantly higher rates of durable recovery as compared to PAROX, both in an intention-to-treat analysis, and among patients who could complete an adequate treatment trial of at least four weeks duration. MAOIs may offer unique advantages over reuptake-blocking antidepressants for treatment of bipolar depression.✤

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