Sertraline as Monotherapy in the Treatment of Psychotic and Nonpsychotic Depression

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Background: Previous studies suggest that selective serotonin reuptake inhibitors (SSRIs) are effective when used alone in the treatment of unipolar depression with psychotic features. The purpose of the present study was to examine the response to sertraline for patients with and without psychotic features using standard criteria such as recovery and remission.

Method: An 8-week open-label trial of sertraline in depressed inpatients was conducted. Twenty-five subjects had DSM-IV major depressive disorder with psychotic features, and 25 had DSM-IV major depressive disorder without psychotic features. After a 1-week open washout, all subjects were rated using the Hamilton Rating Scale for Depression (HAM-D) and Brief Psychiatric Rating Scale (BPRS) at baseline. The HAM-D was administered weekly, and the BPRS was administered again only at the end of the 8-week trial. Medication dosage was started at 50 mg/day, increased to 100 mg/day after 1 week, and then increased up to 200 mg/day if subjects had not remitted.

Results: Depressed patients without psychosis responded significantly better than did depressed patients with psychosis using the criteria of remission (HAM-D score ≤ 7; p = .001), response (HAM-D score ≤ 50% of baseline score; p = .011), referral for electroconvulsive therapy (HAM-D score ≥ 15; p = .011), or change in HAM-D scores (p = .016). Baseline HAM-D score and psychosis independently predicted response, whereas baseline BPRS scores did not, regardless of whether psychotic status was entered into the analyses.

Conclusion: Psychotic depression responds more poorly than depression without psychosis to sertraline alone. Psychosis was a predictor of response independent of degree of depression and general psychopathology. Limitations due to an open-label design are discussed, as are differences between this study and others using SSRIs for psychotic depression.

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The evaluation of different types of depression is important from both theoretical and treatment perspectives. Some proposed types, such as reactive depression,[1] are now more of historical interest, while other variants, such as atypical depression,[2] have received sufficient support to become codified in DSM-IV.[3] Other proposed subtypes, including mixed anxiety and depression,[4] are in need of more evidence and are presently found in an appendix of DSM-IV.[3]

At present, unipolar depression with psychotic features is not classified as distinct from unipolar depression without psychotic features, although there is mounting evidence that it is distinct.[5,6] However, this evidence presents as group differences with some overlap between the psychotic and nonpsychotic depressive samples. Therefore, these findings could also be interpreted as differences in severity between the groups rather than as evidence of different variants of depression.

One major area that has consistently shown differences between psychotic and nonpsychotic depression is treatment response to tricyclic antidepressants when used as the only medication. Patients with psychotic depression consistently respond more poorly when only a tricyclic antidepressant is used, a result that has been shown with several of the tricyclics.[7–10]

In contrast, 2 groups have published several research projects that consistently show selective serotonin reuptake inhibitors (SSRIs) to be extremely effective in the treatment of psychotic depression, even when used alone.[11–15] Fluvoxamine, paroxetine, and sertraline have all shown this dramatic effect of an approximately 80%

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remission rate in studies that have used neither a placebo control group nor a contrast group with depression without psychotic features. One small study that used desipramine as a contrast group found fluvoxamine alone effective but not desipramine alone.[16] Reasons proposed for the effectiveness of the SSRIs have been speculative, but would argue against viewing psychotic depression as a distinct form of depression.

The effectiveness of the SSRIs for psychotic depression needs replication. The purpose of this study was to examine the efficacy of an SSRI used alone in the treatment of psychotic depression in comparison with its efficacy in nonpsychotic depression.

METHOD

Subjects

Fifty subjects completed this open-label study. In order to have equal representation for the presence or absence of psychotic features, if patients met the other inclusion and exclusion criteria, the first 25 men or women with major depressive disorder without psychotic features and the first 25 men or women with major depressive disorder with psychotic features who presented were included. Patients that did not complete the trial were replaced to enable the analysis of 25 patients in each group.

Eligible subjects had to meet DSM-IV criteria for a major depressive episode with or without psychotic features and be aged 18 to 65 years. Another inclusion criterion was an initial score on the 17-item Hamilton Rating Scale for Depression (HAM-D)[17] of 22 or greater. Further, the score on the HAM-D had to be at that level or higher after a 1-week period of medication washout that was conducted while the subjects were admitted to the inpatient unit where the study was conducted.

Patients with bipolar disorder were excluded, as were patients who had been treated previously with any of the SSRIs. Patients with unstable medical illnesses were excluded, as were patients with substance dependence and those judged unable to give informed consent. The study was approved by the local Institutional Review Board, and all subjects gave written informed consent.

Design

The trial was an open-label 8-week trial of sertraline, during which all subjects were inpatients. The study was conducted at the University of Alexandria Hospital in Alexandria, Egypt. The HAM-D was administered to all subjects at screening, at baseline, and weekly for the next 8 weeks. The Brief Psychiatric Rating Scale (BPRS)[18] was administered at baseline and at the end of the 8-week trial. All ratings were performed by the same psychiatrist (A.R.), who also was in charge of treatment for the subjects and who is familiar with the rating scales used.

After a 7-day washout during which subjects were given no psychotropic medications except lorazepam for sleep as needed, subjects were rated on the HAM-D for a baseline score and begun on sertraline, 50 mg in the morning. After 1 week, all subjects had their sertraline dose raised to 100 mg, again administered in the morning. At the end of 3 weeks, subjects who had not responded had their morning dose of sertraline raised to 150 mg. Response was defined as a decrease in HAM-D score of 50% or greater. At the end of the fifth week, based on the same criteria, patients who had not remitted began to receive sertraline, 200 mg in the morning. At the conclusion of the 8-week trial, subjects with a HAM-D score of 15 or greater were evaluated for electroconvulsive therapy (ECT). Subjects were permitted lorazepam for insomnia, but no other psychotropic medication during the trial.

Statistical Analysis

All subjects entered into this trial completed the trial, and there were no missing data. The primary analysis was the number of subjects in each group who met the criterion for remission (HAM-D score ≤ 7) at the end of the 8-week trial. A secondary analysis included the numbers of subjects who met the criterion for response (HAM-D score ≤ 50% of baseline score) at the end of the trial. These results were analyzed using the chi-square test.

Other analyses included repeated-measures analyses of variance of the HAM-D scores at baseline and over the 8-week trial and total BPRS score at baseline and at the end of the trial to examine differences in rate of response, with sex and presence or absence of delusions as grouping variables. All analyses were performed using SYSTAT 8.0.[19] Alpha was set at .05.

RESULTS

Fifty subjects with DSM-IV unipolar major depressive disorder completed this study, with 25 meeting criteria for unipolar major depressive disorder with psychotic features and 25 meeting criteria for unipolar major depressive disorder without psychotic features. Of these, 12 in the psychotic group and 15 in the nonpsychotic group had single-episode illnesses. No subject's depression converted to mania during the course of this trial. Although subjects were not selected to equalize sex distribution, 13 of each of these groups were male and 12 were female. No subject's HAM-D or BPRS score increased over the trial.

Three additional subjects entered this trial but did not complete the entire 8 weeks. One subject who dropped out was experiencing her first episode of nonpsychotic depression. This 38-year-old woman had a baseline BPRS score of 38 and a baseline HAM-D score of 33. She dropped out at the end of week 4 with a HAM-D score of 14 and a daily sertraline dose of 100 mg, stating she was satisfied with treatment. Two subjects with psychotic de-

Table 1. Remission in Sertraline-Treated Men and Women With Psychotic and Nonpsychotic Depression[a]

Subject Group	Week 1	Week 3	Week 5	Week 8
Psychotic depression, N				
Total	0	0	1	4
Men	0	0	1	1
Women	0	0	0	3
Nonpsychotic depression, N				
Total	0	0	10	16
Men	0	0	9	10
Women	0	0	1	6

[a]Remission = Hamilton Rating Scale for Depression score of 7 or less. Men: N = 13 and women: N = 12 for each group.

pression failed to complete the trial. One, a 36-year-old man with 1 previous episode of psychotic depression, had a baseline BPRS score of 53 and a baseline HAM-D score of 32. At the end of week 5 and on a sertraline dose of 150 mg/day, he dropped out with a HAM-D score of 22, because his entire family was moving away. The second was a 44-year-old man with 1 previous episode of psychotic depression. He entered the trial with a baseline BPRS score of 44 and a baseline HAM-D score of 31. After 3 weeks, he dropped out with a HAM-D score of 32 while on 100 mg/day of sertraline, stating that he wished to continue treatment at another hospital. Inclusion of these 3 subjects and use of an intent-to-treat analysis did not change the direction or significance of any result. Therefore, these 3 subjects are excluded from the reported results.

At the end of the 8-week trial, the mean dose of sertraline was 188 mg/day (SD = 26) for the subjects with psychotic depression and 148 mg/day (SD = 44) for those with nonpsychotic depression. This difference in ending dosage of sertraline between the 2 groups was highly significant ($t = 3.879$, $df = 48$, $p < .001$).

Age did not differ for the psychotic versus the nonpsychotic groups (mean ± SD = 35.4 ± 6.65 and 35.96 ± 5.59 years, respectively) ($F = 0.085$, $df = 1,46$; $p = .77$) or for men versus women (34.69 ± 6.43 and 36.75 ± 5.64 years, respectively) ($F = 1.399$, $df = 1,46$; $p = .24$). The interaction between sex and psychotic status also was not significant ($F = 0.593$, $df = 1,46$; $p = .445$). Further, although all parametric analyses were run using age as a covariate, in no case did age reach significance or alter the results. Therefore, analyses will be presented without age as a covariate.

At baseline, men with psychotic depression had a mean ± SD HAM-D score of 30.769 ± 2.743, women with psychotic depression had a mean HAM-D score of 30.667 ± 1.670, men with nonpsychotic depression had a mean HAM-D score of 29.154 ± 2.882, and women with nonpsychotic depression had a mean HAM-D score of 32.917 ± 3.753. Analysis showed no significant difference between subjects with psychotic versus nonpsychotic depression ($F = 0.154$, $df = 1,46$; $p = .697$), but women overall had higher HAM-D scores than men ($F = 5.120$, $df = 1,46$; $p = .028$). Although the nonpsychotic women had a nonsignificantly higher HAM-D score than psychotic men or women and nonpsychotic men, nonpsychotic men showed a nonsignificantly lower HAM-D score than the other groups. Together, these led to a significant interaction of sex by psychotic status ($F = 5.709$, $df = 1,46$; $p = .021$).

Baseline BPRS scores also showed differences between groups. The mean ± SD score for men with psychotic depression was 45.615 ± 9.036; for women with psychotic depression, it was 40.833 ± 8.569; for men with nonpsychotic depression, it was 34.538 ± 2.817; and for women with nonpsychotic depression, it was 38.417 ± 3.753. Analysis showed that those with psychotic depression had significantly higher BPRS scores than those without psychosis ($F = 12.643$, $df = 1,46$; $p = .001$) and that, overall, men and women did not significantly differ on their BPRS scores ($F = 0.057$, $df = 1,46$; $p = .813$). A significant interaction between sex and psychotic status ($F = 5.208$, $df = 1,46$; $p = .027$) appeared due to nonpsychotic men having significantly lower BPRS scores than nonpsychotic women ($t = 2.938$, $df = 23$, $p = .007$), while psychotic men had nonsignificantly higher BPRS scores than psychotic women ($t = 1.344$, $df = 23$, $p = .191$).

Table 1 presents the number of psychotic and nonpsychotic men and women who had remitted (HAM-D score ≤ 7) at the end of week 1 when sertraline was increased to 100 mg/day, at the end of week 3 when sertraline was increased to 150 mg/day if their depression had not responded (HAM-D score ≤ 50% of baseline), at the end of week 5 when sertraline was raised to 200 mg/day if patients had not remitted, and at the end of week 8. By week 5, significantly more of the nonpsychotic group had remitted than the psychotic group ($\chi^2 = 9.441$, $df = 1$, $p = .002$). The significant difference between the nonpsychotic and psychotic groups persisted through the end of week 8 ($\chi^2 = 12.000$, $df = 1$, $p = .001$). The number of nonpsychotic men who remitted at the end of 8 weeks did not significantly differ from the number of nonpsychotic women ($\chi^2 = 1.963$, $df = 1$, $p = .161$), and the number of psychotic men who remitted did not significantly differ from the number of psychotic women ($\chi^2 = 1.391$, $df = 1$, $p = .238$).

Table 2 presents the number of psychotic and nonpsychotic men and women whose depression had responded (HAM-D score ≤ 50% of baseline) at the end of weeks 1, 3, 5, and 8 of treatment. By week 3, significantly more of the nonpsychotic group had responded than the psychotic group ($\chi^2 = 8.42$, $df = 1$, $p = .004$). The significant difference between the nonpsychotic and psychotic groups persisted through the end of weeks 5 ($\chi^2 = 9.742$, $df = 1$, $p = .002$) and 8 ($\chi^2 = 6.48$, $df = 1$, $p = .011$). The number of nonpsychotic men who responded at the end of 8 weeks

Table 2. Response in Sertraline-Treated Men and Women With Psychotic and Nonpsychotic Depression[a]

Subject Group	Week 1	Week 3	Week 5	Week 8
Psychotic depression, N				
Total	0	2	6	8
Men	0	2	2	2
Women	0	0	4	6
Nonpsychotic depression, N				
Total	0	11	17	17
Men	0	9	10	10
Women	0	2	7	7

[a]Response = Hamilton Rating Scale for Depression score ≤ 50% of baseline score. Men: N = 13 and women: N = 12 for each group.

Table 3. Men and Women With Psychotic and Nonpsychotic Depression Referred for Electroconvulsive Therapy[a]

Subject Group	N
Psychotic depression	
Total	17
Men	11
Women	6
Nonpsychotic depression	
Total	8
Men	3
Women	5

[a]Referral based on endpoint Hamilton Rating Scale for Depression score of 15 or greater. Men: N = 13 and women: N = 12 for each group.

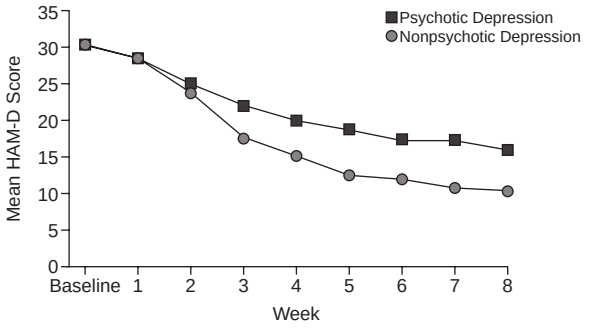
did not significantly differ from the number of nonpsychotic women ($\chi^2 = 0.991$, df = 1, p = .319), and the number of psychotic men who responded did not significantly differ from the number of psychotic women ($\chi^2 = 3.436$, df = 1, p = .064).

Table 3 presents the number of psychotic and nonpsychotic men and women who finished the 8-week trial with a HAM-D score of 15 or greater who were referred for ECT. Overall, significantly more subjects with psychotic depression were referred for ECT than subjects with nonpsychotic depression ($\chi^2 = 6.480$, df = 1, p = .011), which was also true for male subjects ($\chi^2 = 9.905$, df = 1, p = .002). Female subjects with and without psychosis did not show significantly different rates of referral for ECT ($\chi^2 = 0.168$, df = 1, p = .682).

Examining the HAM-D total scores for baseline and the 8-week trial showed much the same results. All groups showed some improvement on the HAM-D. For those without psychosis, the mean endpoint HAM-D score was 32.6% of their baseline score (men, 28.6%; women, 36.9%), while for those with psychotic depression, the mean endpoint HAM-D score was 52.1% of their baseline (men, 60%; women, 43.5%). Over all the weeks of the trial, HAM-D scores decreased significantly (F = 358.127, df = 8,368; p < .001), and the presence or absence of psychosis led to significant differences in HAM-D total scores (F = 6.263, df = 1,46; p = .016), although sex of the subjects did not (F = 1.319, df = 1,46; p = .257). The difference between psychotic and nonpsychotic depression appeared to be due to different rates of response, with those with psychotic depression responding more slowly (F = 14.461, df = 8,368; p < .001; Figure 1A). The between-subjects interaction of sex and presence or absence of psychosis was significant (F = 5.795, df = 1,46; p = .020), although the change in HAM-D scores over weeks by sex (F = 3.070, df = 8,368; p = .052) and the change in HAM-D scores over weeks in interaction with sex and presence or absence of psychosis (F = 2.448, df = 8,368; p = .093) were only borderline significant. These findings appear to be due to men with psychosis responding slightly more slowly than women with psychosis, while men without psychosis responded slightly more quickly than women without psychosis (Figure 1B).

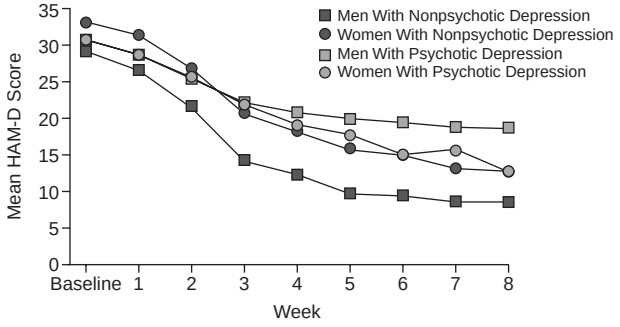
BPRS results at baseline and the end of the trial are shown in Figure 2. Overall, those with psychotic depres-

Figure 1A. Changes in Mean Hamilton Rating Scale for Depression (HAM-D) Scores for Sertraline-Treated Subjects With Psychotic and Nonpsychotic Depression[a]



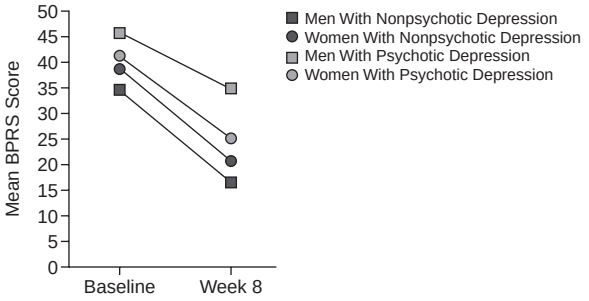
[a]N = 25 for each group. Between-group difference in HAM-D scores, p < .001.

Figure 1B. Changes in Mean HAM-D Scores for Sertraline-Treated Men and Women With Psychotic and Nonpsychotic Depression[a]



[a]Men: N = 13 for each group; women: N = 12 for each group. Absence of psychosis led to a significant difference in HAM-D total score (p = .016). Sex of the subjects did not lead to a significant difference (p = .257).

Figure 2. Changes in Mean Brief Psychiatric Rating Scale (BPRS) Scores for Sertraline-Treated Men and Women With Psychotic and Nonpsychotic Depression[a]



[a]Men: N = 13 for each group; women: N = 12 for each group. Psychotic depression was associated with higher BPRS scores compared with nonpsychotic depression $p < .001$. There was a significant sex-by–psychotic status interaction: $p = .009$ (BPRS scores for men with psychotic depression > scores for women with psychotic depression, and scores for women with nonpsychotic depression > scores for men with nonpsychotic depression).

sion had significantly higher BPRS scores than did those with nonpsychotic depression ($F = 19.505$, $df = 1,46$; $p < .001$), and their scores decreased significantly more slowly ($F = 4.197$, $df = 1,46$; $p = .046$), although BPRS scores did decrease significantly over all subjects ($F = 206.498$, $df = 1,46$; $p < .001$). However, all groups showed some improvement on the BPRS. For those without psychosis, the mean endpoint BPRS score was 49.3% of their baseline score (men, 46.6%; women, 52.1%), while for those with psychotic depression, the mean endpoint BPRS score was 68.0% of their baseline score (men, 73.8%; women, 61.7%). Overall, there was a significant sex-by–psychotic status interaction ($F = 7.413$, $df = 1,46$; $p = .009$), with psychotic women having lower BPRS scores than psychotic men, but nonpsychotic women having higher BPRS scores than nonpsychotic men. The interactions of sex over the 8-week trial ($F = 1.166$, $df = 1,46$; $p = .286$) and of sex and psychotic status over the 8-week trial ($F = 1.230$, $df = 1,46$; $p = .273$) were nonsignificant.

To examine predictors of response in another way, a stepwise multiple regression was performed with sex, psychotic status, baseline HAM-D total score, and baseline BPRS total score as predictors and HAM-D total score at the end of the 8-week trial as the dependent variable. Sex ($F = 4.302$, $df = 1$, $p = .044$), psychotic status ($F = 13.689$, $df = 1$, $p = .001$), and baseline HAM-D score ($F = 30.472$, $df = 1$, $p < .001$) were significant independent predictors, but baseline BPRS score was not ($F = 0.438$, $df = 1$, $p = .512$). To explore whether psychotic status was "controlling" the variance for the BPRS scores, the same regression analysis was run without psychotic status as a predictor variable, and BPRS baseline scores still did not significantly predict outcome ($F = 1.635$, $df = 1$, $p = .207$).

To further explore predictors of response, a logit analysis was performed with sex, psychotic status, baseline HAM-D total score, and baseline BPRS total score as predictors and recovery as the categorical dependent variable. Again, psychotic status ($t = 3.129$, $p = .003$) and baseline HAM-D scores ($t = –2.855$, $p = .004$) significantly predicted recovery, although sex ($t = –1.409$, $p = .159$) and baseline BPRS score ($t = 0.919$, $p = .358$) did not. Again, removing psychotic status from the list of predictor variables did not alter results. The results of both the regression and the logit analyses suggest that the presence of psychotic symptoms affects response independent of the general level of psychopathology.

DISCUSSION

In the present study, depressed patients without psychotic symptoms did significantly better than did depressed patients with psychotic symptoms when treated for 8 weeks with sertraline. Whether remission, response, referral for ECT, or ending HAM-D score was used, the results were the same. Further, the results of the regression and logit analyses suggest that presence of psychosis in depression is separate from either level of depression, which was an independent predictor, or level of general psychopathology, which was not.

To our knowledge, this is the first study to demonstrate that psychosis is an independent factor in response to medication and is separate from both degree of depression (at least as measured by the HAM-D) and degree of general psychopathology (at least as measured by the BPRS). Therefore, these results support viewing psychotic depression as a separate disorder.[5]

These obtained results were not only statistically significant, but they also appear nontrivial. For example, 64% of patients with nonpsychotic depression met the standard criterion for remission and 68% for response. In contrast, only 16% of patients with psychotic depression met the criterion for remission while 32% achieved a response. Although there was some therapeutic effect of sertraline in psychotic depression on both the HAM-D and the BPRS, this effect did not appear adequate.

On the basis of these results, sertraline cannot be recommended as the sole agent in the treatment of psychotic depression. The present findings are consistent with American Psychiatric Association guidelines for the treatment of depression, which recommend an antidepressant with an antipsychotic or ECT for psychotic depression.[20]

These results contrast with several studies that report high levels of remission with the SSRIs alone, including with sertraline.[11–16] Differences in design or treatment that would have led to the marked difference in results are not evident, since those studies also used the same criterion for remission as the present study and also did not have a placebo control group in their shorter 6-week trials.

Several of the studies showing efficacy with SSRIs alone included bipolar depressed patients along with unipolar depressed patients.[11–13] A switch of some of their bipolar patients to a hypomanic state could have falsely inflated their remission rates, although an analysis of just their unipolar depressed patients also showed extremely high rates of remission. Further, these other studies included more female than male patients, unlike our study in which the numbers of female and male patients were essentially the same. As shown both by our response rates for women versus men with psychotic depression (Table 2) and by changes in HAM-D scores over the 8-week trial (Figure 1B), the female patients with psychotic depression in our study did better than the men with psychotic depression. However, our female patients with psychotic depression showed a much lower rate of remission (Table 1) than did patients in these other studies.

Finally, unlike the present study, the other studies used no subjects with nonpsychotic depression as a contrast.[11–16] The response of the nonpsychotic subjects in the present study is in line with response rates expected for sertraline in major depression without psychotic features,[21,22] just as the response of subjects with psychotic depression is in line with studies using tricyclic antidepressants alone in the treatment of psychotic depression.[7–9]

Further, although serotonin does appear to interact with dopamine in certain tracts such as in the frontal lobe and the nigrostriatal area, it does not appear to exert appreciable influence in the limbic system to affect hallucinations or delusions, the positive symptoms of schizophrenia.[23,24] Therefore, since we found psychosis to be independent of depression, it is unclear how increased serotonin levels would impact psychosis in depression.

The meaning of the results showing interactions with the sex of the subjects is also unclear, although cultural factors are suspected. There is much poverty and a low rate of literacy in this geographic area, and cultural expectations for women may have affected who presented for help.

Limitations of this study include that it was not double blind. The rater's expectations could have affected the results. However, the pattern of results does have face validity. Although a placebo control group may have been helpful, the use of nonpsychotic depressed subjects allowed important comparisons, and the use of a placebo group in this case could be questioned on ethical grounds. However, it is not possible to definitively attribute any improvement of either group to the medication, since the milieu, time, or other factors could have been causative. On the basis of the obtained results, even a much larger sample would not have led to finding baseline BPRS scores significant in predicting response. Further, although side effects appeared to be mild and infrequent, a more systematic evaluation of the treatment tolerability would have been informative.

In summary, on the basis of these results, the use of SSRIs alone in the treatment of major depression with psychotic features does not appear warranted, and guidelines suggesting this should be revised.[6] Further, the presence of psychosis, independent of level of depression or level of general psychopathology, is predictive of poor response to an SSRI when used alone. This result may also be interpreted as supporting other research showing psychotic depression to be distinct from nonpsychotic depression.

Drug names: desipramine (Norpramin and others), fluvoxamine (Luvox and others), lorazepam (Ativan and others), paroxetine (Paxil), sertraline (Zoloft).

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