042-052_PB SuppSpr03_Keller 4/22/03 7:34 PM Page 42

Key Words: paroxetine, paroxetine CR, controlled release, major depressive disorder, treatment

Paroxetine Treatment of Major Depressive Disorder

By Martin B. Keller, MD

ABSTRACT *~ Major depression is recognized as a common, often chronic and recurrent illness that is associated with significant disability and comorbidity. The treatment of patients with major depressive disorder has advanced tremendously in the past decade as a result of the availability of effective and well-tolerated antidepressants. Paroxetine is a widely studied selective serotonin reuptake inhibitor (SSRI) with evidence for efficacy and safety that is supported by a large body of published literature. Evidence for the efficacy and tolerability of a new controlled-release formulation of paroxetine also has been published. Findings from paroxetine clinical studies have added considerably to our knowledge and understanding of the treatment of major depressive disorder, particularly with regard to duration of treatment, the need for treating to full remission and with full doses, and treatment of patients with concurrent symptoms of anxiety.* Psychopharmacology Bulletin. *2003;37(Suppl 1): 42-52.*

INTRODUCTION

Depression is an illness that is characterized by both recurrence and a chronic course.[1,2] Individuals with depression are more likely than not to experience a relapse of their index episode or to experience another, new episode some time after they recover from the first episode. In others, depression becomes chronic, with residual or subsyndromal symptoms persisting between episodes of full syndromal depression.[3] As many as 70% of patients with major depressive disorder will recover within 1 year of their index episode, and 81% will recover by 2 years. However, 5 years after their first episode, 12% of patients will continue to be depressed.[2]

The National Comorbidity Survey found that nearly 1 in 5 adults in the United States (17.1%) will experience at least 1 episode of major depression in their lifetime.[4] Depression also is a global concern of great significance. The World Health Organization's Burden of Illness study[5] estimates that by the year 2020, depression will be second only to ischemic heart disease worldwide as a source of disability and economic burden. These observations underscore the importance of adequately treating major depression.

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042-052_PB SuppSpr03_Keller 4/22/03 7:34 PM Page 43

As recently as 20 years ago, depression was considered a neglected disorder. Improvements have been made since then in the awareness and treatment of patients with depression. The availability of effective and well-tolerated antidepressants, in particular the selective serotonin reuptake inhibitors (SSRIs), has in large part been responsible for turning the tide for patients with depression.

The purpose of this article is to overview the experience with paroxetine in the treatment of major depressive disorder and highlight contributions that studies of paroxetine have made to our understanding of this serious psychiatric illness. Because the number of published clinical studies of paroxetine treatment of major depressive disorder is beyond the scope of this review, the findings and contributions of larger, randomized, placebo- and active-comparator-controlled studies will be considered herein. In addition, there is a large and growing body of published literature on the use of paroxetine in the treatment of major depressive disorder in special populations, including the elderly and patients with cardiovascular disease, cancer, or HIV/AIDS. These studies are summarized elsewhere in this supplement.

ACUTE TREATMENT OF DEPRESSION WITH PAROXETINE

A large body of published literature reviews the efficacy of paroxetine in the short-term treatment of major depressive disorder.[6,7] The results of fixed-dose studies have determined that the usual effective dose of paroxetine is 20 mg per day.[8] The short-term studies of paroxetine treatment of patients with major depressive disorder are generally 6 weeks in duration and consist of direct comparisons with placebo or tricyclic antidepressants (TCAs), SSRIs, and other antidepressants. Several studies were designed to include an active comparator group plus a placebo treatment arm,[9-14] the latter of which is considered essential in determining true equivalence between 2 antidepressants.[15] The findings of those studies that included a placebo arm in addition to the 2 active comparator arms are summarized in Table 1. It is important to note that some studies of paroxetine, as is the case for all SSRIs and other antidepressants, including some of the studies that were submitted to the Food and Drug Administration (FDA) for initial approval, were failed studies (ie, active drug did not separate statistically from placebo). However, the predominance of randomized, placebo-controlled trials of paroxetine and other SSRIs in major depressive disorder is positive and demonstrates efficacy.[16]

Comparative Studies with the TCAs

Initial clinical studies of paroxetine treatment of major depressive disorder that were published in the early 1990s were designed to show efficacy compared with the TCAs. At the time, the TCAs were considered to be

042-052_PB SuppSpr03_Keller 4/22/03 7:34 PM Page 44

the gold-standard class of antidepressants against which newer agents were compared. These were flexible-dose studies in which patients generally started treatment with 10-mg or 20-mg doses of paroxetine with forced upward titration to a maximum tolerated dose of no more than 50 mg. Comparable doses of imipramine were used in the placebo-controlled comparator studies (Table 1). Patients had moderate to severe depression, with baseline Hamilton Rating Scale for Depression (HAM-D) total scores of approximately 25 and higher. After 6 weeks of treatment, both paroxetine and imipramine resulted in reduced HAM-D total scores that were statistically significantly lower than placebo. Mean HAM-D total scores for patients in the paroxetine and imipramine groups

TABLE 1

PLACEBO-CONTROLLED, COMPARATIVE DEPRESSION STUDIES BETWEEN PAROXETINE AND TCAS OR SSRIS

			MEAN HAM-D TOTAL SCORE	
Reference	*Treatment duration (weeks)*	*Dose (N)*	*Baseline*	*End point*
Paroxetine vs TCAs				
Cohn and Wilcox[9]	6	Par 10-50 mg (35)	24.9	15.9*
		Imi 80-275 mg (31)	24.5	14.3*
		Pbo (36)	25.6	20.1
Dunbar et al.[10]	6	Par 10-50 mg (240)	26.5	16.4*
		Imi 80-275 mg (237)	26.2	16.4*
		Pbo (240)	26.6	20.9
Fabre[11]	6	Par 10-50 mg (38)	29.7	20.6*
		Imi 65-275 mg (37)	27.8	20.2*
		Pbo (36)	28.8	25.7
Feighner et al.[13]	6	Par 10-50 mg (240)	26.4	16.4*
		Imi 65-275 mg (237)	26.2	17.0*
		Pbo (240)	26.6	20.8
Shrivastava et al.[14]	6	Par 10-50 mg (33)	27.6	15.6*,†
		Imi 65-275 mg (35)	26.3	19.6*
		Pbo (36)	26.7	19.6
Paroxetine vs SSRIs				
Fava et al.[12]	12	Par 20-50 mg (55)	23.1	12.1[NS]
		Flu 20-80 mg (54)	23.9	13.1[NS]
		Pbo (19)	23.7	12.1[NS]

Placebo-controlled, comparative studies between paroxetine and tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs).

Flu=fluoxetine; Imi=imipramine; Par=paroxetine; Pbo=placebo.
*$P \leq .05$ vs placebo; †$P < .05$ vs comparator antidepressant.
NS=no statistically significant differences between treatment groups.

Keller MB. *Psychopharmacology Bulletin.* Vol. 37. Suppl. 1. 2003.

042-052_PB SuppSpr03_Keller 4/22/03 7:34 PM Page 45

after 6 weeks of treatment ranged from 14 to 20, which in all cases were lower than the scores in the placebo groups, but did not represent a return to euthymia.

A large meta-analysis conducted by Montgomery[17] found paroxetine to be as effective as the TCAs, but better tolerated, during short-term treatment. This analysis considered 39 randomized, controlled studies of more than 3700 patients with major depressive disorder. Using a rigorous definition of response, 41% of patients treated with paroxetine, 48.1% of those treated with clomipramine, and 38.8% of patients treated with other TCAs achieved an end point HAM-D total score of 8 or less ($P>.05$ for between-group differences). Although not designed to be a direct, head-to-head comparison, the findings of another study, which is the largest study to date of adolescents with major depressive disorder, demonstrated significantly higher response rates for paroxetine, but not imipramine, compared with placebo. Of note was the observation that paroxetine was significantly better tolerated than imipramine in this population.[18]

Taken in the aggregate, the findings of the individual, placebo-controlled, comparative studies summarized in Table 1 and the Montgomery[17] meta-analysis demonstrate the effectiveness of paroxetine in the short-term treatment of depression and clinical equivalence to the TCAs in this patient population. Importantly, however, the findings from these early studies highlight that therapy should not end with a short-term, 6-week course of antidepressant treatment. Continued treatment beyond 6 weeks is clearly required to achieve robust therapeutic response and full remission.

Comparative Studies with the SSRIs

The efficacy of paroxetine has also been compared with that of the other SSRIs in a number of head-to-head comparative trials. As seen with the TCAs, most of the studies comparing paroxetine with other SSRIs do not include a placebo treatment arm. Nonetheless, the findings of non-placebo-controlled comparative studies suggest equivalent efficacy in the treatment of major depressive disorder for paroxetine compared with fluoxetine,[12,19-23] sertraline,[12,24,25] and fluvoxamine.[26,27] Notably, mean end point HAM-D total scores of 7 to 12 that were achieved by patients treated for 10 weeks to 4 months[12,19] demonstrated that more robust clinical responses are possible when treatment continues beyond 6 weeks. In the 1 placebo-controlled comparison of SSRIs (Table 1), end point HAM-D total scores for patients in the paroxetine, sertraline, and fluoxetine groups were not statistically significantly different from each other or from placebo.[12]

042-052_PB SuppSpr03_Keller 4/22/03 7:34 PM Page 46

Paroxetine CR

The efficacy of the controlled-release formulation of paroxetine (ie, paroxetine CR) in the treatment of patients with major depressive disorder also has been demonstrated in flexible-dose[28] and fixed-dose[29] studies and is reviewed extensively by Golden and Dubé[30] elsewhere in this supplement. In the pooled analysis of the 12-week, flexible-dose studies of more than 600 patients, paroxetine CR (mean dose, 48.2 mg) and paroxetine immediate-release (IR) (mean dose, 38.2 mg) resulted in statistically significantly lower mean end point HAM-D total scores (8.5 and 9.2, respectively) compared with placebo ($P<.05$). Remission, which was defined as end point HAM-D total scores of 7 or less, was achieved by 56% of patients who completed treatment in the paroxetine CR group ($P<.05$ vs placebo), 53% of paroxetine IR patients, and 44% of placebo patients.[28] When a 12.5-mg dose of paroxetine CR was compared with a 25-mg dose of paroxetine CR in a placebo-controlled, 8-week study of nearly 500 patients with major depressive disorder, both doses of paroxetine CR resulted in statistically significant improvements in end point HAM-D scores ($P<.05$ versus placebo).[29]

LONG-TERM TREATMENT WITH PAROXETINE

As many as 50% to 85% of persons with major depressive disorder will experience at least one other, new episode of depression in their lifetime. Although the time between episodes is variable, the risk for recurrence increases with each subsequent depression. More than 50% of patients who experience a first episode of depression will likely have a second episode. The risk for subsequent depression increases up to 90% in patients with a history of 2 episodes. Patients with 3 or more episodes are virtually assured of having a recurrence, with recurrence rates in excess of 90%.[31,32]

The natural course of major depressive disorder and the risk of recurrence have important implications for treatment planning.[33] Patients who do not fully respond to acute treatment are at increased risk of relapse.[34] To sustain remission and relapse, full-dose antidepressant therapy should be continued for at least 4 to 9 months after the initial response (ie, continuation therapy).[35] Treatment for at least 1 year is warranted for a second episode of recurrent depression (ie, maintenance therapy). Long-term and possibly life-long maintenance therapy may be warranted for patients with 3 or more episodes of depression and for patients with 2 prior episodes and risk factors for recurrence.[36]

The long-term studies of paroxetine[37-39] and other SSRIs[40,41] were among the first to demonstrate that recurrent episodes of major depressive disorder may be prevented. Montgomery and Dunbar[38] showed that, in patients with a history of 3 or more recurrent episodes of major depressive

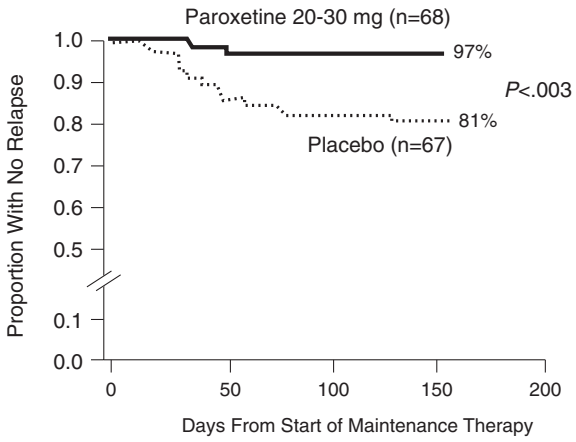
042-052_PB SuppSpr03_Keller 4/22/03 7:34 PM Page 47

disorder who fully remitted after an 8-week course of paroxetine, continued treatment with the same dose of paroxetine prevented relapse during continuation therapy (Figure 1). Relapse during the next 4 months was prevented in 66 of 68 paroxetine-treated patients (97%) compared with 54 of the 67 patients (81%) who were randomized to placebo ($P<.003$). In patients who had sustained remission through the 4-month continuation treatment phase and were randomized to receive full-dose therapy for up to 1 year, paroxetine prevented recurrent episodes in 86% of patients compared with 70% of those who were randomized to placebo ($P<.05$; Figure 2).

In a landmark series of studies, investigators at the University of Pittsburgh demonstrated the importance of full-dose treatment with imipramine in preventing recurrent episodes of depression.[42] Franchini and colleagues[43] furthered our understanding of maintenance antidepressant therapy by comparing the efficacy of 2 different doses of paroxetine in preventing recurrent depression. Patients who were hospitalized for recurrent depression were treated with a 6-week course of open-label paroxetine in doses that were titrated to 40 mg per day. Those patients who achieved sustained remission for at least 4 months (ie, HAM-D total score of 7 or less) were randomized to a 28-month course of either the same dose of paroxetine (ie, 40 mg; 34 patients) or a 50% lower dose (ie, 20 mg; 34 patients). After 2.3 years of maintenance therapy, the

FIGURE 1

RELAPSE PREVENTION IN PATIENTS WITH RECURRENT MDD TREATED WITH PAROXETINE



MDD=major depressive disorder.
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Keller MB. *Psychopharmacology Bulletin.* Vol. 37. Suppl. 1. 2003.

042-052_PB SuppSpr03_Keller 4/22/03 7:34 PM Page 48

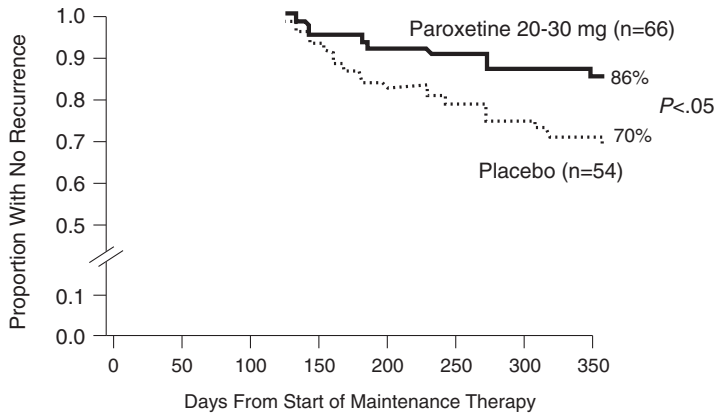
cumulative probability of remaining well (ie, no recurrence) was 76.5% for patients in the 40-mg group and 48.5% for patients in the 20-mg group (*P*=.018; Figure 3). These findings are important and speak to the need for higher doses of antidepressants in patients with severe, recurrent depression. Moreover, for optimal clinical outcome, the same antidepressant dose that resulted in acute remission should be administered without reduction during long-term maintenance therapy.

DEPRESSION AND SYMPTOMS OF ANXIETY

Although the SSRIs are effective treatments for anxiety disorders as well as for depression with predominant symptoms of anxiety, emergent symptoms of arousal may occur during treatment with some agents.[44] Paroxetine and paroxetine CR are particularly useful antidepressants in this regard, with demonstrated anxiolytic properties.[28,45,46] In an analysis of the paroxetine short-term clinical trials database, paroxetine was not associated with exacerbation of existing anxiety symptoms or with treatment-emergent anxiety.[46] Data from 2,963 paroxetine-treated patients, 1,151 patients treated with comparator antidepressants (usually a TCA), and 554 placebo-treated patients were assessed. In this population, approximately 65% of patients scored 7 or higher on the anxiety item of the HAM-D at baseline. At 6-week end point, paroxetine resulted in statistically significant improvements in the psychic anxiety, somatic

FIGURE 2

RECURRENCE PREVENTION IN PATIENTS WITH MDD TREATED WITH PAROXETINE



MDD=major depressive disorder.
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042-052_PB SuppSpr03_Keller 4/22/03 7:34 PM Page 49

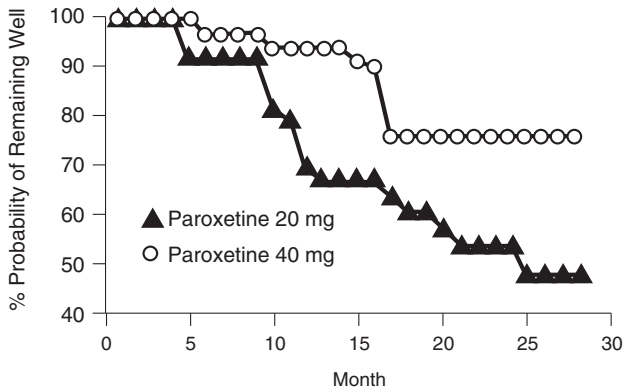
anxiety, and agitation items of the HAM-D compared with placebo ($P \leq .05$). Paroxetine also was not associated with emergence of new anxiety symptoms, and was associated with statistically significantly lower rates of emergent agitation compared with placebo ($P \leq .05$).

DETERMINANTS OF POSITIVE OUTCOME

The addition of pindolol to SSRI therapy in patients with major depressive disorder has been suggested, but not proven definitively, to hasten the onset of therapeutic response.[47,48] Currently the augmentation of SSRI treatment with pindolol to reduce latency of response is rarely used in clinical practice. Nonetheless, the findings from studies of pindolol augmentation of paroxetine therapy shed light on potential determinants of optimal clinical outcome. Tome and Isaac[49] conducted a naturalistic follow-up study of 63 patients with major depressive disorder who completed a double-blind, 6-week course of paroxetine 20 mg plus either pindolol 7.5 mg per day or placebo. By week 2 of the 6-week acute-treatment course, 42% of patients in the augmentation group versus 13% of patients in the paroxetine-only group were considered clinical responders based on reduction in baseline depression scores. At the conclusion of the 6-week trial, pindolol was discontinued, and patients continued open-label paroxetine for another 18 weeks. Paroxetine was discontinued at 6 months, and patients completed a survey 1 year from the initiation of acute-phase treatment.

FIGURE 3

RISK OF RECURRENCE OF MDD WHEN DECREASING THE DOSE OF PAROXETINE DURING LONG-TERM MAINTENANCE THERAPY



MDD=major depressive disorder.
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042-052_PB SuppSpr03_Keller 4/22/03 7:34 PM Page 50

Of patients who demonstrated early therapeutic response (ie, 50% reduction in the Montgomery Asberg Depression Rating Scale [MADRS] score within the first 2 weeks of acute treatment), 42% in the pindolol augmentation group compared with 13% of patients in the paroxetine-only group remained well at 1-year follow-up. Moreover, early responders, regardless of treatment assignment, tended to be more adherent to antidepressant therapy during the 6-month continuation phase. Although interpretation of these results is difficult because of the small sample size and open-label design, the findings suggest that patients who do well early in the course of treatment may be more adherent to antidepressants and may have a more positive outcome.

CONCLUSIONS

The goals of antidepressant treatment of major depressive disorder are to achieve full remission during short-term therapy, to consolidate remission and prevent relapse during continuation therapy, and to prevent recurrence during maintenance therapy. The findings of published studies of paroxetine and paroxetine CR treatment of patients with depression have contributed significantly to our understanding of and ability to achieve these treatment goals. Paroxetine is as effective as the TCAs and the other SSRI antidepressants and is distinguished by its clinically significant anxiolytic properties. Short-term studies of 6 weeks' duration have shown that paroxetine and comparator agents significantly improve depression rating scale scores compared with placebo, but longer courses of treatment result in more clinically relevant responses. Studies of paroxetine and other SSRIs in long-term maintenance treatment demonstrate that recurrence of depression can be significantly reduced, especially when the full therapeutic doses that resulted in initial response are employed. The results of paroxetine and paroxetine CR studies suggest that patients who do well early in the course of treatment, as judged either by early improvement in depression scores or by retention because of lack of adverse events, may achieve better treatment response and more favorable long-term outcomes. ✤

DISCLOSURE

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042-052_PB SuppSpr03_Keller 4/22/03 7:34 PM Page 51

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