

## Introduction

# The Role of Enteric-Coated Fluoxetine Once-Weekly in Achieving Optimal Outcomes in the Long-Term Treatment of Depression

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Long-term treatment with antidepressants is essential if optimal outcomes are to be achieved for patients suffering from depression. Despite the considerable advance in recent years in our understanding of the course and treatment of major depressive disorder, psychiatry remains challenged by significant gaps in the adequacy of our therapeutics. One gap, in spite of the public health burden presented by depression and the availability of medications with well-demonstrated efficacy, is that patients commonly do not take antidepressants for an adequate length of time. One factor contributing to undertreatment is nonadherence to the recommended treatment regimen, including both missed doses and early discontinuation of medication. Reluctance of patients to continue treatment requiring daily doses of antidepressant medications may stem from objectionable side effects, fear of stigmatization, and uncertainty about continued benefits of treatment, especially when they are feeling well. Simple once-weekly dosing may provide an alternative strategy for enhancing tolerability and psychological well-being, and hence, adherence with long-term treatment.

A panel of experts met recently to present and discuss the current knowledge regarding the epidemiology of depression, treatment recommendations versus realities, relapse prevention, the role of adherence, and the evidence supporting the long-term efficacy and tolerability of fluoxetine, given either daily or once-weekly, in the treatment of depression. Strategies for developing an alliance model for wellness between patients and physicians were discussed. In particular, the possible advantages and impact on achieving treatment goals that the new, enteric-coated formulation of fluoxetine, 90 mg given once weekly, in the

continuation treatment of depression may provide patients and physicians in the development of this alliance model were considered.

John F. Greden, M.D., in a review of the literature, noted that depression is a prevalent disorder that, due largely to its undertreatment and inadequate length of treatment, is associated with a lifetime recurrent course and a high public health burden. Onset is often earlier than believed and, if not treated adequately, can lead to gradually worsening limbic pathophysiology. He recommended aggressive diagnosis of depression in adolescents and use of maintenance treatment, which has been shown to be safe and effective, to reduce the rate of depressive recurrences.

Ellen Frank, Ph.D., in a review of the literature, presented the current treatment recommendations versus the treatment realities in the community setting. She pointed out data from naturalistic studies that showed that 6-month treatment completion rates for 3 selective serotonin reuptake inhibitors (SSRIs) were only 22% to 45%. She noted that nearly ideal prophylaxis can be achieved in a clinical trial setting due to the focus on patient education, visit frequency, and defined targets. She encouraged physicians to incorporate these features of clinical trials into their community treatment strategy.

Rajinder Judge, M.D., presented 2 naturalistic studies that highlighted the importance of stable continuation treatment, consistent with recommended depression treatment guidelines in the prevention of relapse and recurrence. She noted in one SSRI study that the majority of patients (73%) discontinued therapy prior to 120 days of treatment, thus achieving suboptimal continuation therapy.

Frederick W. Reimherr, M.D., discussed the prevention of relapse and presented several studies that demonstrated the safety and efficacy of fluoxetine in the prophylaxis of new depressive episodes. In particular, he discussed a recent study that examined the return of depressive symptoms and their interaction with social factors on long-term outcome. This study indicated that treatment refusal occurs as often as treatment failure and poorer outcomes are

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*The roundtable discussion "The Role of Enteric-Coated Fluoxetine Once-Weekly in Achieving Optimal Outcomes in the Long-Term Treatment of Depression" was held October 20, 2000, in Los Angeles, Calif., and supported by an unrestricted educational grant from Eli Lilly and Company.*

closely linked to psychosocial factors such as marital problems. These factors lead him to suggest that there continues to be a need for better-tolerated medications that are easier to administer, as well as a need for psychotherapy following successful antidepressant treatment, particularly when dealing with significant life stresses.

Helena M. Calil, M.D., Ph.D., presented a review of fluoxetine's safety profile, concluding that it is suitable for long-term administration. Key safety advantages she noted for fluoxetine were the reduction in discontinuation side effects due to fluoxetine's half-life, lower adverse event and dropout rates for fluoxetine versus tricyclic antidepressants and other SSRIs, safety in overdose, and established safety in special populations such as the cardiovascular compromised, suicidal, geriatric, pregnant/lactating, and children and adolescents.

Koen Demyttenaere, M.D., Ph.D., presented new research aimed at understanding the complexity of non-adherence. His recent naturalistic study of patients receiving antidepressant therapy found that only 50% of patients take their antidepressant medication for at least 6 months. He also found that men are more likely than women to prematurely discontinue antidepressant treatment as soon as their depressive symptoms no longer cause functional impairment. Dr. Demyttenaere stressed that the attitude of the physician plays an important role in patient adherence, as do patients' beliefs about antidepressants.

William J. Burke, M.D., reviewed the rationale and results of 2 studies which supported the hypothesis that the antidepressant effect of fluoxetine might be maintained during weekly dosing and could be comparable to that observed during continuation treatment with fluoxetine taken daily.

Erik de Klerk, M.D., M.Sc., presented the results of a study to determine if adherence with a new dosing regimen of enteric-coated 90-mg fluoxetine once-weekly was different from adherence with the standard regimen of 20 mg of fluoxetine once daily for up to 3 months of continuation treatment. He noted adherence to once-weekly fluoxetine was higher than adherence to once-daily fluoxetine, and adherence to 20 mg daily, unlike 90 mg once weekly, actually declined after randomization. He concluded that this study should help alleviate the concern that patients will be more likely to forget weekly antidepressant doses.

Timothy G. Dinan, M.D., Ph.D., presented the results from the primary efficacy and safety study of the new once-weekly 90-mg enteric-coated fluoxetine formulation given during continuation treatment of depression. He concluded that fluoxetine once-weekly was effective in preventing relapse during long-term treatment of depression, effective in maintaining remission in patients with high baseline levels of anxiety, and well-tolerated with a safety profile similar to fluoxetine 20 mg daily.

Rajinder Judge, M.D., discussed the results of 2 surveys, conducted in Europe and the United States, assessing physician and patient response to weekly fluoxetine. These surveys indicate a generally positive attitude toward weekly fluoxetine although there were some questions. Dr. Judge noted that, at least in the United States, physicians tend to overestimate how compliant their patients are with their daily antidepressant medication and to underestimate the interests of their patients in learning about new antidepressants.

The recurrent nature of depression and the resulting need for long-term treatment with antidepressants were emphasized. The panel repeatedly demonstrated that, despite the efficacy and tolerability of fluoxetine and other SSRIs in the long-term treatment of depression, many patients do not receive antidepressive therapy for an adequate length of time. The factors influencing adherence were shown to be complex and included both patients' and physicians' attitudes. The panel felt that the choice and convenience the new 90-mg once-weekly fluoxetine formulation may provide patients during long-term treatment of depression had the potential to improve adherence and ultimately outcomes. Linkage of the product introduction with more thorough physician and patient education regarding adherence issues and the need for long-term treatment of this highly recurrent disease was thought to be key to building an alliance model for wellness between the physician and patient.

Although an amount of this information has been previously disseminated, our intent for this roundtable was to review the collective current knowledge and to provide focus for future needs in a manner that would well serve the psychiatric community. We hope that this supplement will be a convenient and important reference in your clinical practice.