Is Once Weekly Administration of Antidepressants Feasible?
Experience with Fluoxetine

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Summary

Antidepressant medications are taken daily or more frequently based on both tradition and pharmacokinetics of the drugs. However, weekly administration may be a feasible option for drugs with a long elimination half-life and flat dose-response curve. In addition to providing effective control of symptoms, it is possible that weekly administration could also benefit patients by reducing costs and minimising drug interactions and adverse effects. The selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor fluoxetine appears to be a candidate for once weekly administration.

Most physicians prescribe antidepressants to be taken on a daily or more frequent basis. This strategy reflects not only the pharmacokinetics of the drugs involved, but also the clinical tradition of dispensing these drugs. In this review, alternative dosage strategies for these medications are considered, in particular weekly administration of the commonly prescribed antidepressant fluoxetine. We will first explore the feasibility of weekly administration during acute treatment, followed by similar use in longer term treatment.

1. Why are Antidepressants Given on a Daily Basis?

The reasons for daily administration of antidepressants are both scientific and traditional. However, the scientific rationale for daily administration is limited by our incomplete understanding of the mechanism of action of antidepressant drugs. We assume that a certain amount of an antidepressant, or its metabolite, is required in the CNS for some period of time before an effect is elicited. Further, we have tended to classify drugs by their presumed action, such as selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs). However, the acute effects that these agents have on amines and serotonin do not correspond with the time course of clinical response. Furthermore, for many of these drugs, a substantive dose-response relationship has not been demonstrated. These facts point to a fundamental lack of understanding, which leaves us with little scientific rationale for establishing an optimal dosage regimen for either short or long term antidepressant treatment.

Daily use of antidepressants also has strong cultural roots. As Sir William Osler stated, 'The desire to take medication is perhaps the greatest feature which distinguishes man from animals'. Taking medication daily (or more frequently) is such a potent cultural practice that it may be difficult for patients with moderate to severe depression to ac-
cept less frequent treatment. Although untested, it seems likely that patient compliance might be negatively affected if daily administration is not recommended. Whereas intermittent therapy is not without precedent in medicine, e.g. weekly or monthly cancer chemotherapy, the vast majority of medical conditions are treated with daily medication. A change in this strategy would require a substantial mind-shift for both physician and patient.

After the initial treatment period has ended and the patient has responded favourably to an antidepressant, different problems arise. Obstacles present themselves which tend to diminish the patient’s willingness to take daily medication. Once patients feel better, they commonly stop taking their medication (a familiar example is the low level of compliance with 10-day courses of antibiotics). Patients may see the need to take long term medication as evidence that they have not really recovered. Non-compliance may also represent a rejection of the ‘sick role’, or a refutation of the biological underpinnings of the condition. In spite of these common reasons for treatment discontinuation, patients with recurrent depression need long term antidepressant treatment, and those experiencing multiple episodes of depression may require life-long antidepressant treatment.

Clinical experience tells us that patients with depression who are treated with antidepressants do best when medications are taken routinely and daily. Patients who do not conform to this ritual may be subject to treatment relapse or inadequate treatment response. There are compelling data suggesting that patients with major depression and dysthymia can be successfully treated over a long period, providing they comply strictly with their treatment. Frank et al.\textsuperscript{2} have shown that the cycle of recurrent depression can be interrupted by careful attention to ongoing pharmacotherapy. This finding has been extended recently to those with dysthymia.\textsuperscript{3} This implies that many patients with recurrent depression or dysthymia might be best treated intensively, for long periods of time. The success of long term treatment has been demonstrated by Kupfer et al.\textsuperscript{4} with imipramine and by Montgomery et al.\textsuperscript{5} with fluoxetine.

2. An Alternative Approach: Focus on Fluoxetine

We believe that patients who require long term antidepressant therapy would show greater compliance if their medication was more convenient to take, less expensive and could be taken on a less frequent, though regular, basis. We have been evaluating a weekly administration regimen for fluoxetine in the treatment of patients who, in response to fluoxetine treatment, have recovered from an episode of major depression. This work is based on 2 observations. The first is the report, from Montgomery et al.,\textsuperscript{6} that patients treated for acute episodes of depression with fluoxetine 80 mg/week were as likely to recover as patients receiving daily amitriptyline. The second is that fluoxetine has a pharmacological profile that is uniquely suited for use on an intermittent basis. The elimination half-life of fluoxetine ranges from 1.9 to 5.7 days, while that of norfluoxetine, the primary metabolite of fluoxetine, ranges from 7 to 15 days.\textsuperscript{7} These variations in half-life are attributable to the inhibition of the hepatic microsomal cytochrome P450 (CYP) 2D6 system by fluoxetine, resulting in a gradual increase in the time necessary for elimination of the drug.\textsuperscript{8} While this inhibition and long half-life may increase the likelihood of unwanted drug interactions, more importantly it suggests the possibility that fluoxetine could be administered less frequently than every 24 hours.

Another factor that makes fluoxetine an intriguing potential agent for intermittent use is its ‘flat’ dose-response curve. As a class of drugs, the SSRIs show little correlation between dosage and clinical response. In fixed-dosage studies of fluoxetine, 5 mg/day was as effective as the more commonly used 20 mg/day dosage.\textsuperscript{9,10} Conceivably, some graduated effect might have been seen if lower dosages were used. However, because the half-life of fluoxetine is relatively long and the dose-response curve is quite flat, it is uniquely qualified as a candidate for intermittent administration.