CNS Drugs 1997 Sep; 8 (3): 199-202
1172-7047/97/0009-0199/$02.00/0

Is Once Weekly Administration of Antidepressants Feasible?

Experience with Fluoxetine

William J. Burke, Shelton E. Hendricks and *Delores McArthur-Campbell*

Psychopharmacology Research Center, Creighton-Nebraska Department of Psychiatry, University of Nebraska Medical Center, Omaha, Nebraska, USA

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'.[1] 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. Noncompliance 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.[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.[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.[4] with imipramine and by Montgomery et al.[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.,[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.[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.[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.[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.

Our preliminary efforts to explore this potential application of fluoxetine have yielded promising clinical and pharmacokinetic data.[11,12] Patients who had responded to fluoxetine treatment were enrolled in a double-blind randomised trial of continued treatment with fluoxetine 20 mg/day, fluoxetine 60 mg/week or placebo (10 patients per treatment group). Of the 30 individuals randomised, 17 completed the 11-week double-blind trial (placebo = 4, 20 mg/day = 7, 60 mg/week = 6). Considering only data from the patients who completed 11 weeks of treatment, we found less depressive symptomatology in both fluoxetine groups compared with the placebo group, although statistically the groups did not differ. Because of the limited number of patients completing the study, we are currently enrolling additional patients to increase the sample size. These results suggest that patients may benefit from *weekly* treatment with fluoxetine, and that this regimen could be useful in the long term.

3. Clinical Implications of Weekly *vs* Daily Administration

3.1 Cost

The implications of long term treatment are rarely discussed, but at a minimum involve numerous direct and indirect costs and inconveniences for the patient. As in the treatment of other long-standing medical conditions, such as hypertension or diabetes mellitus, patients must bear not only the costs of medication, but also the monetary and temporal costs involved in close clinical monitoring of the illness and the accompanying pharmacotherapy. Long term treatment may also involve psychological or emotional costs, as the patient must deal with the reality of an ever present illness as well as the necessity of 'lifetime' of drug therapy. Other issues involved the difficulty in predicting relapse, the increased risk of adverse drug effects in elderly patients, and the masking of the possibility that drug therapy is no longer necessary.

In 1996, based on the 'patient cost' as determined by the UNMC Pharmacy Department Prescription Services, a 30-day supply of 20mg fluoxetine capsules cost approximately $US60.00. A single weekly dose of 60mg would cost about $US24.00 for 4 weeks. Annualised, the cost of 20 mg/day is approximately $US725.00 and for 60 mg/week about $US310.00. For a patient staying on the 60 mg/week regimen for 5 years, the saving would be over $US2000.00.

3.2 Drug Interactions and Adverse Effects

Weekly administration also has the potential to minimise drug interactions. The SSRIs have a number of effects on hepatic isoenzyme systems, including inhibition of the CYP2D6 isoenzymes by fluoxetine and paroxetine.[8] This enzyme system is responsible for metabolising a number of drugs, most notably the tricyclic antidepressants. Inhibition of this metabolic process may lead to elevations in the blood concentrations of concomitantly administered tricyclic antidepressants as well as other drugs. This inhibition is dose related and, in the case of fluoxetine, with its long half life, can cause drug interactions weeks after the drug has been stopped. The smaller dose of fluoxetine taken in a weekly administration strategy could reduce the magnitude of potential interactions or the risk of a clinically serious interaction.

Weekly administration may also minimise adverse effects. Nausea seems to be dose related and, in theory, a weekly dose could minimise its occurrence.[10]

3.3 Patient Compliance

The question of compliance with a weekly administration strategy must also be raised. No data presently address this issue. One could plausibly argue that weekly administration might lead to either better or worse compliance. In order to protect the double-blind in our study, all patients were given, on a daily basis, what appeared to be a capsule containing fluoxetine. Thus, we cannot estimate any difference in the rate of compliance. Once weekly administration may be very easy for some individuals yet problematic for others. Systemic study of this issue will be required.

4. Conclusion

It should be acknowledged that investigation of weekly administration of antidepressants is the first step in the study of alternative administration strategies. Whereas daily administration is the currently accepted standard, a well-established practice already exists for beginning antidepressants on an every-other-day basis in elderly patients. Our research suggests that daily administration of fluoxetine may be unnecessary in stabilised patients. However, it is unclear at this time what the optimum regimen might be for those patients who face long term treatment. To meet the needs of these patients, further exploration into treatment options must be undertaken. If other strategies are proven to be effective, the choice may be merely a matter of preference for patients and their physicians.

Acknowledgements

We wish to thank the Psychiatric Foundation of Nebraska at the University of Nebraska Medical Center for supporting this research.

References

1. Cushing H. Life of Sir William Osler. Vol. 1. Oxford: Clarendon Press, 1925
2. Frank E, Kupfer DJ, Perel JM, et al. Three-year outcomes for maintenance therapies in recurrent depression. Arch Gen Psychiatry 1990; 47: 1093-9
3. Thase ME, Fava M, Halbreich U, et al. A placebo-controlled, randomized clinical trial comparing sertraline and imipramine for the treatment of dysthymia. Arch Gen Psychiatry 1996; 53: 777-84
4. Kupfer DJ, Frank E, Perel JM, et al. Five-year outcome for maintenance therapies in recurrent depression. Arch Gen Psychiatry 1992; 49: 769-73
5. Montgomery SA, Dufour H, Brion S, et al. The prophylactic efficacy of fluoxetine in unipolar depression. Br J Psychiatry 1988; 153 (3 Suppl.): 69-76
6. Montgomery SA, James D, De Ruiter M, et al. Weekly oral fluoxetine treatment of major depressive disorder. Presented at the 15th Collegium Internationale Neuro-Psychopharmacologicum Congress; 1986 Dec 14-17; Puerto Rico
7. Van Harten J. Clinical pharmacokinetics of selective serotonin reuptake inhibitors. Clin Pharmacokinet 1993; 24 (3): 203-20
8. Preskorn SH, Magnus RD. Inhibition of hepatic P-450 isoenzymes by serotonin selective reuptake inhibitors: *in vitro* and *in vivo* findings and their implications for patient care. Psychopharmacol Bull 1994; 30 (2): 251-9
9. Wernicke JF, Dunlop SR, Dornseif BE, et al. Low-dose fluoxetine therapy for depression. Psychopharmacol Bull 1988; 24 (1): 183-8
10. Beasley CM, Bosomworth JC, Wernicke JF. Fluoxetine: relationships among dose, response, adverse events, and plasma concentrations in the treatment of depression. Psychopharmacol Bull 1990; 26 (1): 18-24
11. Burke WJ, Hendricks SE, McArthur-Campbell DA, et al. Weekly fluoxetine controls symptoms of depression [abstract no. NR169]. American Psychiatric Association: 1995 Annual Meeting New Research Program and Abstracts. American Psychiatric Association 148th Annual Meeting; 1995 May 20-25; Miami
12. Burke WJ, Hendricks SE, McArthur-Campbell DA, et al. Fluoxetine and norfluoxetine serum concentrations and clinical response in weekly versus daily dosing. Psychopharmacol Bull 1996; 32 (1): 27-32

Correspondence and reprints: Dr *William J. Burke*, Psychopharmacology Research Center, Creighton-Nebraska Department of Psychiatry, University of Nebraska Medical Center, 600 South 42nd Street, Omaha, NE 68198-5575, USA.
E-mail: wjburke@mail.unmc.edu