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Lack of efficacy of fluoxetine in recurrent brief depression and suicidal attempts

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Abstract Recurrent brief depression (RBD) fulfills DSM-III-R symptom criteria for major depression but the episodes are of shorter duration than the 2 weeks required by DSM-III-R. The clinical importance of the disorder has been observed in prophylactic studies of suicidal behavior. The possibility that antidepressants with selective action on the reuptake of serotonin might be effective in preventing recurrences of brief depression has been investigated. Fluoxetine in a dose of 120 mg a week, administered biweekly, had no effect on the recurrence rate, which was maintained at approximately the same rate on fluoxetine (1 every 18.7 days) as with placebo (1 every 17.6 days). In a group of patients with two or more prior episodes of suicidal behavior, there were 18 attempted suicides in the 54 patients treated with fluoxetine and the same number in the 53 patients treated with placebo. Fluoxetine neither raised nor lowered the suicide attempt rate as compared with placebo, providing no evidence to support the drug's role in either suicide provocation or prevention. Since fluoxetine is clearly effective with recurrent major depression, it would appear that recurrent brief depression has a different pharmacology.

Key words Recurrent brief depression · Fluoxetine · Placebo · Suicide attempt · Prophylaxis

Introduction

Diagnostic classifications of depression currently in wide use define a syndrome of depression by requiring the presence of a minimum number of a specific list of symptoms, a defined duration of illness, and the exclusion of conflicting diagnoses. There has been general agreement among different classificatory systems concerning the defining symptoms of recurrent brief depression and the defining duration of illness has varied from 2 weeks according to DSM-III, DSM-III-R, Research Diagnostic Criteria of Spitzer et al. and ICD-10, to the longer 4-week period required in the criteria published by Feighner et al. (American Psychiatric Association 1987; American Psychiatric Association 1980; World Health Organization 1992; Spitzer et al. 1978; Feighner et al. 1972). These diagnostic criteria identify a group of patients suffering from major depression who have functional impairment and who are likely to respond to conventional antidepressant treatment. However, the criteria for major depression do not address the large number of cases that fulfill the syndromal definition of major depression but do not meet the requirement of at least 2 weeks' duration.

Until recently, there had been little systematic investigation of depressive states with a duration of less than 2 weeks, although their existence had been noted in the psychiatric literature (Paskind 1929; Gregory 1915). The early reports suggest that such episodes have a relatively high incidence; for example, 14% of one large sample of inpatients were reported to suffer from brief episodes of depression lasting from a few hours to a few days (Paskind, 1929). The Research Diagnostic Criteria of Spitzer et al. (1978) include a category that recognizes the existence of depressions that are intermittent but classifies them as minor depression in contrast to major depression, thus implying that it is a mild disorder of lesser importance.

More recently, brief episodes of depression have been recognized as being important in clinical populations because of their severity and associated impairment in functioning (Montgomery et al. 1989) and in epidemiological studies because of the high incidence. In the ongoing longitudinal studies of an enriched normal population sample by Angst and his colleagues, frequently recurring depressive episodes lasting less than 2 weeks were observed to

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have a prevalence at least as high as major depression (Angst and Dobler-Mikola 1985; Angst et al. 1990; Angst 1990). Similar rates of recurrent brief depression, i.e. brief episodes of depression lasting less than 2 weeks and occurring with a frequency of at least 12 episodes a year, have now also been reported in psychiatric and general practice populations (Maier et al. 1994; Lepine et al. 1994).

Clinical studies of recurrent brief depression

A mild but frequently occurring condition might not attract the attention of psychiatrists or focus investigation on the need for treatment. However, the clinical studies of recurrent brief depression show that it is not a mild disorder: most episodes are of moderate or severe intensity (Montgomery et al. 1989; Montgomery et al. 1990). The clinical importance of brief depressive episodes was noted in a series of studies designed to test the efficacy of treatment in reducing suicide attempts in a group of patients with a history of suicidal behavior (Montgomery et al. 1979; Montgomery et al 1983).

Patients with major depression were excluded from these studies, which used a prophylactic design, randomly assigning patients with a history of three or more suicide attempts to treatment for 6 months with placebo or a low-dose neuroleptic, flupenthixol given in a monthly i.m. dose of 20 mg, or, in a parallel study, with placebo or the antidepressant mianserin in a daily dose of 30 mg. The definition of preventing a suicide attempt was successful completion of the study period; a further suicide attempt was a treatment failure.

In spite of the exclusion of major depression at the start of the study, it was observed that during the study patients suffered short depressive episodes that lasted under 2 weeks. Patients were assessed at the start of the study and monthly using the Montgomery & Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979). The MADRS scores at the start of the study, which were low, as is consistent with periods of waiting for any present brief episode to resolve itself to ensure the exclusion of major depression, did not predict subsequent suicide attempts. However, at 4 weeks, the MADRS score representing the severity of the brief depression over the period, as well as individual items of the scale, were significant predictors of subsequent suicide attempts. The brief episodes of depression that were measured in the study were clearly associated with the suicide attempts; those patients with more severe brief depressions were at a greater risk. Furthermore the suicide attempts seemed to occur only during these brief depressions lasting less than 2 weeks.

The results of these placebo-controlled studies showed a significant advantage for the low-dose neuroleptic ($P < 0.01$) over placebo in reducing suicidal behavior. There was a reduction in suicide attempts in the group treated with the antidepressant compared with placebo but the difference was not statistically significant. These studies were designed to test the effect of pharmacological intervention on suicidal behavior and were not specifically directed at treatments that might affect brief depressive episodes. The apparent link between episodes of suicidal behavior and brief depressive episodes and the finding of an effective treatment that reduced suicidal behavior suggested that pharmacological treatment might be a possible strategy for both conditions.

Studies on the duration, recurrence and severity of RBD

A second stage of investigating the clinical nature of brief recurrent depression was carried out on a similar group of patients with a history of suicidal behavior during long-term follow-up. This was aimed at determining the frequency of the episodes and whether the episodes differed in an important way from major depression, apart from their brevity. Some patients with a history of suicide attempts but without major depression were followed up at intervals of approximately 2 weeks. Their history of depressive episodes was recorded and any episodes of depression of brief or longer duration occurring during follow-up were recorded and rated for length and severity. The results of this follow-up, reported elsewhere (Montgomery et al. 1989), confirmed that the episodes of brief depression occurred frequently, with a mean of approximately 20 episodes per year.

The episodes of brief depression were erratic in both their occurrence and the duration of the intervals between episodes. The intervals between the brief depression, measured from the beginning of one episode to the beginning of the next, varied substantially in duration, with a mean of 18 days. They lasted mostly between 1 and 5 weeks, with only 14% longer than 5 weeks.

The median duration of the individual episodes was 3 days. Two-thirds of episodes lasted between 2 and 4 days and 75% had a duration of 3 days or less. The mean severity of the episodes of depression measured by the MADRS score was 30.3, which is rather high, and 70% of the episodes could be categorized as moderate or severe. The episodes of recurrent brief depression appear to have the same symptoms as major depression and to be of similar or higher levels of severity. These findings contradicted the perception that brief depressions were largely mild.

Since the pattern of symptoms and the severity of the brief depression resembled major depression, it seemed possible that the use of an antidepressant might be an appropriate treatment approach. However, it seemed unlikely that currently available antidepressants with a delayed onset of action would be effective in the 2–4 days necessary to treat individual episodes. In the absence of rapidly acting antidepressants, efficacy needed to be tested in longer term prophylactic treatment where the treatments might reduce the rate of recurrence of episodes. The prophylacitc efficacy of a variety of antidepressants in major depression has been demonstrated in studies that have concentrated on measuring the recur-

rence rate in a group treated with an antidepressant compared to placebo (Montgomery and Montgomery 1992). This prophylactic design, similar to that used in the earlier study which showed the efficacy of flupenthixol in reducing suicidal behavior was adopted for the investigation of recurrent brief depression. Although it was apparent in the study that a high proportion of patients had brief episodes of depression, it had not been designed to specifically measure the duration. A preliminary analysis of a prophylactic study of fluoxetine is presented here.

Methods

Patients attending a psychiatric clinic with a history of 2 or more suicide attempts but who were not suffering from major depression according to the criteria of DSM-III-R were randomly allocated to double blind treatment for 6 months, given 60 mg fluoxetine or placebo twice weekly, and followed up at intervals of approximately 2–4 weeks. The length of any episode of depression occurring during follow-up was recorded. The severity of the episodes was rated using the MADRS. An episode of recurrent brief depression was defined as an episode of depression satisfying DSM-III-R criteria for major depression but which lasted less than 2 weeks. Suicide attempts occurring during the study were recorded. The preliminary results of the recurrence rate of the brief depressions and the suicide attempt rate are reported here.

Results

A total of 107 patients entered the study, 54 in the fluoxetine group and 53 in the placebo group. The proportion of patients who developed periods of brief depression during the 6-month study was high and the numbers of episodes of brief depression seen in each group were very similar. There were 153 episodes of brief depression lasting less than 2 weeks in the fluoxetine treated group compared with 157 in the placebo-treated group.

The length of exposure to treatment has to be taken into account in assessing differences between treatments (Table I). The recurrence rate, calculated as the number of episodes in relation to the length of exposure, was high in both groups. Expressed in terms of a 12-month period, there were 18 episodes per year in the fluoxetine-treated group compared with 17.6 in the placebo-treated group. There was no apparent significant difference between the groups.

The suicide attempt rate on placebo was high, with 18 attempts over the 6-month period. The suicide attempt rate in the fluoxetine-treated group was identical, with 18 attempts during the 6-month study period. The cumulative suicide attempt rate was 33.3% in the fluoxetine-treated group and 34% in the placebo treated group, with no apparent or significant difference between the groups (Table 2).

Table 1 Recurrence rate of brief episodes of depression in patients treated with fluoxetine 20 mg twice weekly or placebo. No significant difference

	Fluoxetine $n = 54$	Placebo $n = 53$
Number of episodes	159	157
One episode per	18.7 days	17.6 days

Table 2 Suicide attempts occurring during 6-month study in fluoxetine- or placebo-treated patients

	Fluoxetine $n = 54$	Placebo $n = 53$
Suicide attempts	18	18
Suicide attempt rate	33.3%	34.0%

Discussion

The rate of recurrence of brief depressive episodes in this study was very similar to the recurrence rate reported in our earlier studies. In the present study, there were 18 episodes per year compared with 20 reported in the earlier studies. The difference between 18 and 20 episodes is not large and may be accounted for by random variation in the population. The population studied here has a rather high recurrence rate when compared with the epidemiological samples. It is possible that those with a history of suicide attempts and recurrent brief depression have a higher recurrence rate than those who do not.

Fluoxetine has been found to be effective in treating major depression in a large number of placebo-controlled studies in acute treatment (Stark and Hardison 1985; Montgomery 1989). It has also been shown in two large studies to have prophylactic efficacy in reducing the risk of new episodes of depression (Montgomery et al. 1988; Rosenbaum et al. 1993). The failure of fluoxetine in this study in recurrent brief depression, despite the large number of episodes observed during the study, indicates that fluoxetine is not an effective agent in treating recurrences of brief depression.

Fluoxetine in this study apparently had no effect on the course of illness in those suffering from recurrent brief depression or on the recurrence rate of the brief depressions. The failure to detect any evidence of efficacy of fluoxetine in recurrent brief depression in a long-term study is in sharp contrast to the clearcut demonstration of efficacy of fluoxetine in recurrent major depression (Montgomery et al. 1988; Rosenbaum et al. 1993).

The failure of fluoxetine to affect the suicide attempt rate, either by reducing or even raising it, is an important finding. The consistent observation of an association between low levels of 5-hydroxyindoleacetic acid in the cerebrospinal fluid and suicide attempts pointing to a serotonergic involvement in suicidal behavior has led investigators to speculate that treatment with selective serotonin reuptake inhibitors might reduce suicidal thoughts or behav-

ior. There is some evidence in major depression that such a strategy is effective in reducing suicidal thoughts (Wakelin 1988; Montgomery et al. 1981) and possibly suicidal acts (Beasley et al. 1991; Montgomery 1992). The absence of any beneficial effect of fluoxetine on the suicide attempt rate in this study, which had high morbidity, suggests that this group of patients with a combination of recurrent brief depression and recurrent suicidal behavior differs from major depression in an important way.

It is clear that in this study, fluoxetine neither increased nor decreased the suicide attempt rate. The absence of provocation of suicidal behavior by fluoxetine in this group of high-risk patients contradicts the suggestions that have been made on the basis of anecdotal reports that fluoxetine provokes suicidal behavior (Teicher et al. 1990). A high suicide-attempt rate, in line with previous placebo-controlled studies, was seen during placebo treatment in this group of previous suicide attempters and there was no difference between the active antidepressant and placebo. The high suicide-attempt rate observed on placebo emphasises the danger of bias in interpreting open report of suicidal behavior in those with a history of suicide attempts and makes it clear that judgments that particular treatments are likely to cause suicide attempts should only properly be made on the basis of randomized, placebo-controlled studies.

Concern about providing large numbers of capsules to a suicidally prone population prompted the adoption of a twice-weekly dosing regime. Fluoxetine, which has a half-life of 2–3 days, has an active metabolite with a very long half-life of around 7–10 days. This pharmacokinetic property of the drug was used to justify a safer intermittent dosage regime. An earlier study has shown that fluoxetine given in a dose of 60 mg once a week appears to be as effective as both fluoxetine given in a 60 mg daily dose and amitriptyline 150 mg. In that study, the plasma concentrations of norfluoxetine achieved during once weekly treatment were within therapeutic range. The decision to adopt a twice-weekly dosage regime of fluoxetine was taken in order to bring the dosage to within 120 mg per week, which would be in line with the recommended dose of 20 mg per day. The advantage of this regime was that the medication could be given under supervision in the clinic, thus providing less opportunity to overdose on the trial medication with obvious ethical advantages. A further advantage was the improved compliance with treatment.

The failure of fluoxetine in this study to affect either suicidal behavior or the recurrence rate of recurrent brief depression applies to this population and the dose studied. Nevertheless the failure to find any alteration in recurrence rate with a dosage regime which, from the results of earlier trials in major depression, is likely to be effective makes it unlikely that fluoxetine in the standard dose of 20 mg per day will prove effective in other samples.

It is of course possible that the failure to find efficacy might be due to chance factors. This is unlikely in this study, however, because of the very large number of episodes of brief depression seen in both the fluoxetine and placebo groups, and the absence of any detectable treatment effect. Another explanation might be the unusual dose used or that a dose equivalent to 20 mg a day was too low. However, in view of the demonstration of efficacy of fluoxetine in a wide range of doses from 5 mg to 80 mg a day in placebo-controlled studies in the acute treatment of major depression this seems unlikely.

The conclusion from this study is hard to escape. Fluoxetine, which is an effective treatment in major depression, does not seem to be effective in recurrent brief depression. The results are in accord with a study in a population with better defined recurrent brief depression. A preliminary analysis of a similar study of paroxetine in a dose of 20 mg a day is reported to show no evidence of efficacy compared with placebo in a 6-month prophylactic study (Montgomery et al. 1993).

The result have important clinical implications. They suggest that SSRIs are probably not effective, a conclusion that raises uncomfortable questions as to the efficacy of other antidepressants. The results of these studies are supported by the reported failure of these patients to find any effective treatment for their disorder and the generally negative reports of efficacy with traditional antidepressants. Without positive evidence of efficacy of an antidepressant in recurrent brief depression, it is inappropriate to recommend their use in the treatment of the condition.

The results remind one of the basis of the recommendation that major depression be defined by the persistence of the symptoms for 2–4 weeks. This criterion was developed to help define the population of depressions that were found to respond to conventional antidepressants and to exclude those who were thought not to respond. To some extent, these present findings suggest that this proposition was correct and recurrent brief depression has a different pharmacology and therefore probably a different biological basis.

For the clinician, it is now clearly important to distinguish between those with recurrent brief depression and those with major depression, since there are no grounds to expect an antidepressant response in the former group. In deciding whether antidepressant treatment is appropriate, careful attention should be paid to the duration criterion so that those with brief episodes are not given inappropriate treatment. A question that remains to be addressed is the problem of how to treat those with combined depression, that is, brief depression coexisting with major depression. We cannot assume response and it is possible that presence of brief depression identifies a population that is not responsive to antidepressants.

One is reminded by the results of this study of the poor response in another category of depressed patients, namely those with rapid-cycling bipolar illness. Antidepressants are reported to be ineffective in this group and in some cases to provoke ultra-rapid cycling. One perception of recurrent brief depressions could be the unipolar version of bipolar ultra-rapid cyclers. In that population, there are suggestions that mood stabilizers such as lithium and sodium valproate may be effective and these drugs may therefore be considered as candidate

treatments that meed to be investigated in recurrent brief depression.

There is currently little evidence of efficacy for any antidepressant in recurrent brief depression, which leaves the clinician with the dilemma of what advice to provide. In view of the associated substantial risk of suicide attempts, it would seem wise to avoid any toxic treatments since the likelihood of benefit is low. Recurrent brief depression is now recognized in the international classification of disease ICD-10, and sufferers, who report that they may have been considered malingerers or as personality disorders, experience relief from the realization that this a common disorder and not a figment of their imagination. Even so, with the present state of knowledge, there is no treatment. At the moment it seems that the best we can do is to provide common-sense advice on life style, including advice to avoid difficult decisions or confrontations during the episodes of depression.

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