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BRIEF COMMUNICATION

Three- to 5-year prospective follow-up of outcome in major depression

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ABSTRACT

Background. A Dutch cohort of predominantly out-patient DSM-III-R major depressive patients was followed for 3 to 5 years after start of treatment in a psycho-neuro-endocrinological prediction study. The study design permitted description of the course of remissions, relapses and recurrences.

Methods. Pharmacological treatment was standardized, psychotherapy was tailored to the needs of the patient, follow-ups were done monthly until 3 years or more after the initial recruitment.

Results. After 9 months 49% of the patients had reached full remission and 45% were in partial remission. During the following 3 to 5 years 82% of the patients had reached a period of full remission. Sixteen per cent of the patients needed 2 years or more before full remission. A relapse or recurrence rate of 41% within 5 years was found. Patients with residual symptoms relapsed particularly in the first 4 months after remission, while patients without residual symptoms recurred mainly after 12 months after remission. Previous depressive episodes and psychoticism predicted relapse. Psychomotor retardation at inception predicted a longer time to partial remission.

Conclusion. In most cases, major depression is a seriously impairing episodic disease. This is also true for a sample of predominantly out-patients treated at a university clinic.

INTRODUCTION

Recovery from major depression has become an important issue. Prospective follow-up studies that examine the lifetime prognosis of depression have shown that it can be a lifelong episodic condition requiring continued pharmacotherapy and psychotherapy in 75–80% of cases for both in-patients and out-patients (Angst *et al*. 1996). In a 2-year prospective follow-up study of a sample of depressed patients in Britain (Ramana *et al*. 1995) remission was reached by 70% within 6 months, but one-third of these patients had residual symptoms (Paykel *et al*. 1995) and 40% relapsed in the subsequent 15 months.

We started a 3 to 5 year longitudinal prospective study in 1990 to follow arginine vasopressin, oxytocin and cortisol plasma levels in a sample of depressed patients (Van Londen *et al*. 1997, 1998). Although the study aimed to follow neuropeptide concentrations in plasma prospectively, its design permitted description of the course of remissions, relapses and recurrences.

METHOD

Subjects

The 56 subjects initially participating in the study satisfied DSM-III-R criteria for major depression and had been diagnosed by a psychiatrist. They were recruited from the routine clinical care group of the Psychiatric Hospital Endegeest (Oegstgeest, The Netherlands) and included the in-patients depression unit and the out-patient clinic, from 1990 to 1994.

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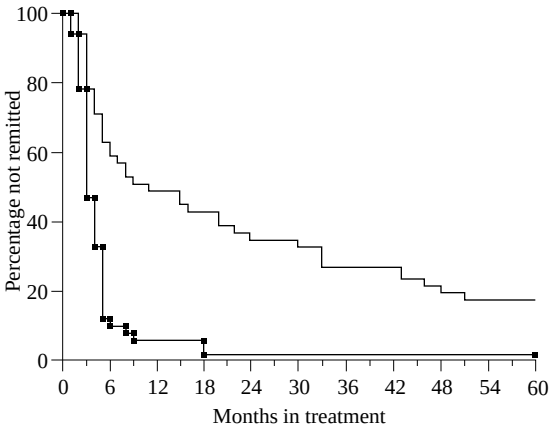

FIG. 1. Partial and full remission related to time from start of treatment. (-■-, Below major depression; —, no residual symptoms.)

Assessments

Initial interview and follow-up of all subjects were done by a psychiatrist (L. Van L.). The initial interview included the Comprehensive Psychopathological Rating Scale (CPRS, Åsberg *et al.* 1978), permitting the assessment of depression and anxiety by two subscales: the Montgomery & Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979) and the Brief Anxiety Scale (BAS) (Tyrer *et al.* 1984); the Salpêtrière Retardation Rating Scale (SRRS) (Widlöcher, 1983); and the Eysenck Personality Questionnaire (Eysenck & Eysenck, 1975). All of the assessments were done before treatment. Scores $\geqslant 20$ on the MADRS were required before entry. Follow-up interviews included all the above except the Eysenck Personality Questionnaire.

Follow-up procedures

Clinical assessments were done: (*i*) at initial recruitment; (*ii*) between 2 and 6 weeks after treatment was started; (*iii*) monthly to 3 years or more after initial recruitment. We based the following definitions of remission, recovery relapse and recurrence on the concepts of Frank *et al.* (1991). A full remission was defined as at least 2 consecutive months, with symptoms below the threshold for definite DSM-III-R major depression without residual symptoms. The absence of residual symptoms was defined as a score of < 2 per symptom on the MADRS. Recovery was a full remission that lasted for at least 6 months. Partial remission was defined as at least 2 consecutive months with symptoms below the threshold for definite DSM-III-R major depression, but with residual symptoms. For a partial remission the cut-off sum-score for residual symptoms was < 10 on the MADRS and, additionally, the symptoms had to be 'minimal': one symptom with a maximum of 3 on the MADRS was allowed, any further symptoms had < 3 on the MADRS scale. Relapse was defined as at least 1 month with return to symptoms satisfying the full syndrome criteria of DSM-III-R major depression, before recovery. Relapse can represent a change from either partial or full remission. Recurrence was defined as appearance of a new episode, i.e. return of symptoms as described for relapse, during recovery, i.e. after at least 6 months after full remission.

Treatment

A response was defined as the beginning of a partial remission. If partial remission failed to become a full remission, the clinician altered the patient's regimen after 3 months, by increasing a higher dose of medication and/or the frequency of therapy sessions, or by adding additional treatments to the one associated with the partial response (Frank *et al.* 1991). All subjects used medication. We aimed at standardization of dosages, but on occasion these had to be reduced because of undesirable side-effects. In the acute phase pharmacological treatment consisted of a selective serotonin re-uptake inhibitor (paroxetine up to 40 mg dd, or fluvoxamine up to 300 mg dd, or fluoxetine up to 40 mg dd) during a period of 6–10 weeks. In the case of non-response the treatment was followed by a MAO-A inhibitor (moclobemide up to 600 mg dd) during a period of 8 weeks, after a wash-out period of 2 weeks (3 weeks in case of fluoxetine). In case of non-response to moclobemide, it was replaced by a tricyclic antidepressant (amitriptyline up to 150 mg dd) during 6 weeks. If this regimen was ineffective lithium was added. As maintenance therapy patients used the full dosage of antidepressant(s) for 1 year following full remission when the index episode was the first episode and for at least 2 years following full remission when the index episode was a recurrent episode. The choice and sequence of the antidepressants used was based largely on the

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influence the drug is known or suspected to have on vasopressin and oxytocin plasma levels. That is, drugs without orthostatic or diuretic properties were preferred. Psychotherapy differed among patients, and it included cognitive behavioural therapy, group therapy, supportive therapy and attendance at day-treatment. ECT was not used. Statistical analyses involved two-sample *t* tests, χ^2 tests, Kaplan–Meier curves and Cox regression analyses.

RESULTS

Fifty-six depressed patients entered the study. Of these, seven were lost to follow-up: one by suicide before remission, one through refusal, two for medical reasons (one was diagnosed with multiple sclerosis the year after the index episode, the other appeared to be alcohol dependent), one because of missing neuropeptide values and two by moving away. The remaining 49 were followed for 36 to 60 months: 47 patients were followed up for longer than 3 years. The sample consisted of 20 (40·8%) males and 29 (59·2%) females, age ranged between 20 and 77 years, mean 45·4 ± 14·1 years. They were 37 unipolar and 12 bipolar depressed patients, predominantly out-patients (65%); 26 had a recurrent episode, four patients were delusional and 27 were defined as melancholic subtype (DSM-III-R). The sample was ethnically homogenous, most of the subjects being Dutch-born, with two exceptions: one female patient was Turkish and one male patient was Moroccan, but both were adequately fluent in Dutch. There were no significant age ($t = 1{\cdot}30$, df = 47, $P = 0{\cdot}20$) or sex ($\chi^2 = 0{\cdot}37$, df = 1, $P = 0{\cdot}54$) differences between unipolar and bipolar depressive patients.

Remission

Fig. 1 shows percentages of patients in partial and in full remission related to time from start of treatment. After 9 months 49% had reached full remission and 45% had reached partial remission (*v.* respectively 67% and 17% in Ramana *et al.* 1995). For the remaining 6% the first response came after 18 months. The number reaching a period of full remission increased steadily: from 65% after 2 years to 82% after 5 years. Sixteen per cent of the patients reaching full remission did so in the period between 2 to 5 years. All of these patients had reached partial remission within the first 2 years. After 5 years 2% had failed to reach partial remission and 18% had no full remission. Bipolar patients did not differ significantly from unipolar patients for time to partial remission ($t = 1{\cdot}41$, df = 44, $P = 0{\cdot}17$), for time to full remission ($t = 0{\cdot}94$, df = 35, $P = 0{\cdot}35$), or for the number of patients reaching full remission.

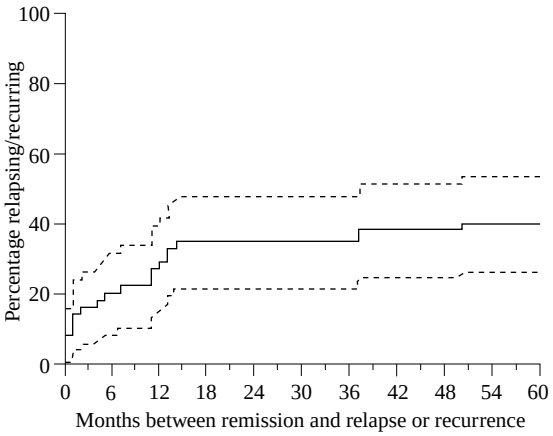

FIG. 2. Relapse and recurrence related to time after partial or full remission. Dotted lines indicate 95% confidence limits.

Relapse

Fig. 2 shows the number of relapses and recurrences related to time after partial or full remission. Most relapses and recurrences came forward in the first 15 months after partial or full remission, despite continuing pharmacotherapy in the majority of cases. The relapse rate was 33% within 15 months after remission (*v.* 40% in Ramana *et al.* 1995). Relapses or recurrences after 15 months were rare: only three patients recurred in subsequent months. A 41% relapse or recurrence rate was found after 5 years. Fig. 3 shows the series of relapses and recurrences in time. A series of relapses occurred within 12 months after partial remission, with a mean time of 3·7 ± 3·5 months to relapse. A series of, mainly, recurrences started after 12 months after remission, with a mean time of 24·4 ± 15·4 months to recurrence. Patients in partial remission were at significantly greater risk of relapse in the subsequent 12 months than patients in full remission (Fig. 3: $\chi^2 = 6{\cdot}75$, df = 1, $P = 0{\cdot}009$), despite continuing therapy. Change of antidepressant medication did not

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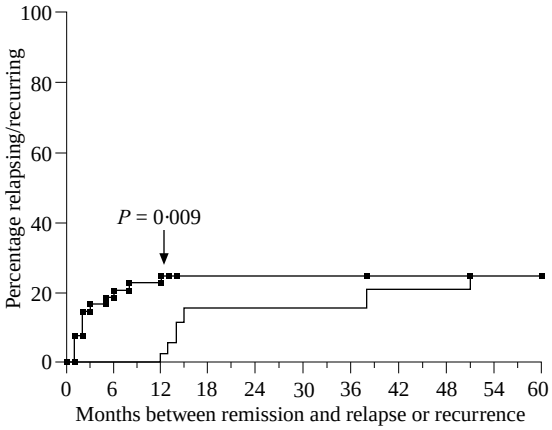

FIG. 3. Relapse and recurrence related to time after partial and full remission. Patients in partial remission were at significantly greater risk of relapse in the subsequent 12 months than patients in full remission ($P = 0{\cdot}009$). (-■-, Below major depression; —, no residual symptoms.)

occur in the month before relapse. No significant differences in the number of relapses were found between bipolar and unipolar patients.

Predictors of relapse and recurrence

The following variables were used in the predictor analysis: age, sex, previous episodes of major depression, DSM-III-R subtype melancholia, in- or out-patient status, time to partial remission, CPRS, MADRS, BAS, SRRS (Widlöcher, 1983) and EPQ scores. Previous episodes, psychotism (EPQ) scores and the time to partial remission gave significant results. The relative risk of relapse or recurrence was 2·76 times greater (95% CI: 1·06–7·21) in patients with a previous episode, 1·26 times greater (95% CI: 1·01–1·58) in patients with a high psychoticism score and 0·74 times greater (95% CI: 0·56–0·99) in patients with a short time to reach partial remission. Longer times to partial remission were predicted by psychomotor retardation at inception (multiple $R = 0{\cdot}34$, df = 1,35, $P = 0{\cdot}030$).

DISCUSSION

Our findings confirm the unsatisfactory longer-term outcome of major depression, this time in a sample of predominantly out-patients, who had failed primary care treatment. Although our sample was smaller and included unipolar and bipolar depressed patients, the initial response rates were good and were comparable to those obtained by Ramana *et al.* (1995). With the more demanding criterion of full remission, the Dutch rates were lower than these British rates, but we could not measure significance due to lack of data from the British study. After 5 years of treatment the number of Dutch patients in full remission reached the same level in the British study. Factors contributing to a bad outcome, e.g. insufficient dosages of antidepressants and insufficient psychotherapy are not likely to have played a role here. A history of previous episodes increased the risk of relapse and recurrence, which is in agreement with the factors identified by Kupfer & Frank (1992). Additionally, high levels of psychoticism predicted higher rates of relapse and recurrence. We are aware that these figures could have been influenced by the acute depressive state, because all of the questionnaires were filled out before treatment. We did not find that neuroticism at index contributed significantly to poorer outcome, in contrast to Surtees & Barkley (1994).

Sixteen per cent of the patients reaching full remission needed more than 2 years of treatment to do so, showing the importance of active and continuous treatment of residual symptoms. Some of these patients passed through years of residual symptoms before reaching full remission. While the data for months to full remission may differ between the British and the Dutch samples, the relapse rates are similar, the Dutch sample showing somewhat lower figures. The relapses occurred largely in the 15-months interval after partial remission and clustered in the first 4 months. This clustering was not found in the British study (Paykel *et al.* 1995). As in our study, residual symptoms were excellent predictors of subsequent early relapse. The finding that relapses clustered in the first 4 months in patients with residual symptoms and that recurrences started after 12 months in patients with full remission seems to support the concept of a distinction between relapse and recurrence. We have no explanation for the clustering of relapses in the first 4 months: we could not find a relationship with the change-over regimen of the medication. A possible explanation for the start of recurrences after 12 months could be that pharmacotherapy was diminished or stopped 1 year after full remission in patients with first episodes, maybe hereby

evoking a recurrence. The first 15 months after remission appear to be vulnerable times for relapse and recurrence and call for special clinical care in treatment protocols. Close monitoring and continued adequate treatment are essential during these months.

Summarizing, major depression has been found to be a seriously impairing disease, often with residual symptoms and with an episodic remitting character (Ramana *et al*. 1995; Angst *et al*. 1996). This description is also valid for a sample of predominantly out-patients treated in recent years at a university clinic. The findings call for continuing active and adequate treatment for residual symptoms after remission. Patients should be monitored closely in the vulnerable periods after remission: during the first 4 months after partial remission and starting from 12 months after full remission.

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