The nature of remission

In the field of depression, some distinctions have been made between various aspects of outcome. An important paper published in 1991 by Frank et al. reviewed these, and assigned operational definitions. In the short-term outcome, the term remission has usually been applied to achievement of low or absent symptom levels, representing an end to the immediate episode. The term recovery has been used to reflect remission beyond this state, persistent for a longer time period and more complete. A further term, response, has sometimes been used, implying considerable improvement, variously defined, but not necessarily to remission. Even before recovery is fully achieved, relapse may occur. Conventionally, relapse in affective disorders has been used to describe an early return of the depressive episode after remission, up to approximately 9 months to a year following the acute episode. This has been assumed to be a return of the original illness. In part, this reflects views common in the early days of antidepressants that the disorder is merely suppressed, and that the underlying disturbance continues until spontaneous remission occurs. It is difficult to prove this theoretical
distinction, other than inferring it from the length of the symptom-free period. The term recurrence has been reserved for development of a subsequent episode, assumed to represent a new episode.

The Frank et al paper gave definitions by severity levels for presence of an episode, and for remission/recovery. A later paper from the US2 has updated the concepts and definitions. However, missing from the original schema was consideration of an intermediate state, where remission might be partial in degree or limited in some aspect, rather than complete. This has since received considerable attention, as it has become apparent that it is a key pointer to relapse and recurrence. This partial remission and its consequences are the topic of this paper.

Partial remission and residual symptoms

Our attention was first drawn to the importance of residual symptoms in a longitudinal follow-up of remission and relapse in depressed patients treated in Cambridge in the early 1990s.3,4 A sample of 64 depressed patients meeting the Research Diagnostic Criteria (RDC) for definite primary unipolar major depression was identified on presentation, and followed to remission, or for 15 months. Only 4 subjects in the sample of 64 failed to remit to the criterion of 2 months below definite major depression by this point. However, on examining the findings in more detail, although the majority of remitters scored in the lower ranges of the 17-item Hamilton Depression Rating Scale, an important proportion of 32% (19/60) scored 8 or more on the Hamilton scale, the criterion proposed by Frank et al1 as indicating full remission or recovery. They spanned a range from 8 to 18, although they did not satisfy the criteria for major depression.

We explored further the nature of these residual symptoms by examining individual symptom ratings. The residual symptoms were those typical of depression, with ratings at the level of moderate or greater on the Hamilton scale items of depression, impairment of work and activities, psychic anxiety, and genital symptoms. The remaining symptoms were present to at least a mild degree in most subjects, the exceptions being a group of symptoms typical of severe depression, such as the following: late insomnia, retardation, agitation, hypochondriasis, weight loss, and loss of insight. A parallel set of analyses carried out on the Clinical Interview for Depression,5 which has a wider range of symptom items, gave similar findings. Depressed mood, guilt, hopelessness, impaired work and interests, psychic anxiety, and anorexia were prominent. The remaining symptoms were present to at least a mild degree, except for delayed insomnia, retardation, agitation, panic attacks, increased appetite, and depressed appearance.

We also sought predictors of residual symptoms. Using an extensive set of ratings made at the initial assessment, we found very few significant predictors. Both reflected higher initial severity. Patients with residual symptoms had higher initial scores on the Clinical Interview for Depression anxiety total score and on the Hamilton scale 17-item total score. Life events, social support, and expressed emotion did not predict residual symptoms.

We also examined diagnoses made at initial interview on DSM-III-R criteria for dysthymia. Patients with residual symptoms were not predominantly previous dysthyms. Only 11% of those with residual symptoms satisfied DSM-III-R criteria for dysthymia, as opposed to 17% of those without residual symptoms. Residual major depression did not appear to represent return to dysthymia, but represented a different phenomenon: persistence of the episode in spite of treatment.

We also examined data which had been collected on drug treatment and care status, to determine whether deficient treatment might have been responsible for residual symptoms. This was not the case. In fact there was a general trend for patients with residual symptoms to be receiving more treatment and care, which would be expected by good treatment assignment in practice, based on the presence of symptoms. This does not mean that higher treatment levels would not be beneficial, but does indicate that the symptoms were not a consequence of failure to give standard treatment.

Other studies of residual symptoms

Residual symptoms had received comparatively little attention prior to this, although they were clearly evident in the detail of studies, and some aspects had briefly been reviewed.6 Clinical experience had also long suggested that many patients treated initially improved only partially, leaving residual symptoms which persisted and fluctuated in the community, causing considerable disability and family burden. Because many studies treated these patients either as nonremitted or as relapsed, their proportion had not been very well documented. Among inpatients treated with amitriptyline, approximately one third had been found to be complete responders, partial responders, and...
nonresponders, respectively. Weissman et al reported a follow-up study to 4 years in a sample of female depressives who had responded to initial treatment with amitriptyline and had been included in a controlled trial of continuation antidepressant and psychotherapy. Many showed moderate or fluctuating symptoms, corresponding approximately to residual chronicity, but included some subjects who relapsed and then remitted. Occurrence of residual symptoms had been noted in general practice patients with depression and anxiety, and in 38% of elderly depressives at 1 year, and 20% at 2 to 4 years. More recently, one or more residual symptoms have been found in 82% of elderly depression remitters below 8 on the Hamilton Depression scale. At these levels the subjects would be below the usual threshold for partial remission, however.

More recent studies of residual symptoms have been reviewed by Fava et al. They have been reported both after drug treatment and psychotherapy. Fava et al, in a study of their own, reported a strong relationship between prodromal and residual symptoms. The most common symptoms were irritability and anxiety. The influential Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which has reported higher nonremission rates for depression than hitherto thought to occur, did not use a criterion for partial remission.

### Residual symptoms and relapse

Following remission, the patients in our original study were followed for another 15 months. As in other follow-up studies, there was a high rate of subsequent relapse, with 40% of subjects relapsing over the next 15 months. All the relapses occurred in the first 10 months, giving some support to the concept of relapse as an early phenomenon that is distinguished from recurrence later in time.

An important finding emerged when we separated out the subjects with residual symptoms at remission. Among these, 76% relapsed in the next 10 months, compared with 25% of subjects without residual symptoms. Residual symptoms were a key indicator of subsequent relapse. A number of other studies have drawn attention to high relapse rates in residual depressives. One study found that patients with residual symptoms of depression obtained greater benefit from maintenance antidepressant therapy than those who had completely recovered. Prien and Kupfer found that relapse was less common after full remission of at least 16 weeks, a finding on which they based a recommendation that continuation treatment should comprise at least 4 months of complete remission. After 9 months, 49% of a Dutch sample were found to be in full remission and 45% in partial remission. Patients with residual symptoms relapsed early, mainly in the 4 months after remission, while those without these symptoms had further episodes later than 1 year. Another study reported that major depressives with residual symptoms relapsed three times faster than those without. Residual symptoms have been found to be a strong predictor of relapse in primary care depressives. In Spanish outpatients, a relapse rate of 67% was found in the 2 years following partial remission, as opposed to 14% after full remission. One study attempted to find the best definition of rating scale scores at 3 or 6 months to predict later relapse. No precise cutoff score with good sensitivity and specificity was found, but the higher the score, the greater the likelihood of relapse.

There has been less study of the association between residual symptoms at remission and longer-term recurrence, although some of the above studies fused earlier relapse and later recurrence in reporting. We later extended our original follow-up study to 10 years. The subjects with previous residual symptoms spent more time with depressive symptoms over follow-up, but not more time at full criteria for major depression, and they showed greater impairment in social adjustment. No significant differences were found between the two groups in percentage recurring long-term, mean number of recurrences, readmissions, chronic episodes, or clinical global outcome criteria, although there were small differences towards worse outcome on these criteria. The effects of previous residual symptoms tended to decay over time, and more of the subjects achieved full remission in due course.

In a trial of maintenance imipramine and interpersonal therapy in patients who had achieved stable remission, the level of residual symptoms did not predict long-term outcome, but subjects with greater variability of residual symptoms had a higher risk of recurrence. In a similar trial in elderly patients, residual anxiety and residual sleep disturbance independently predicted early recurrence.

### Social adjustment

Israel suggested that recovery from depression should be determined in three domains: symptoms, psychosocial function, and pathophysiological changes. Social dysfunc-
tion and disability are further additional important consequences of a depressive episode. Social function, or social adjustment, refers to the function of an individual within his or her usual environment, and is manifested in performance and interactions occurring in a variety of domains including work, leisure activities, or a variety of roles such as worker, spouse, or parent. Within the hospital setting, social function has reduced relevance, as the environment is abnormal and the expectations of role performance are less, but social function has increased importance in the outpatient clinic and the community. Social adjustment was evaluated longitudinally in a sample of depressed women in New Haven, Connecticut, USA, in the late 1960s, comparing them with a matched group of normal subjects in the general population. Widespread impairment was found in the depressed group compared with normal subjects, extending across all the domains studied, including work, social and leisure activities, relationships with extended family, marital relationships, and parental function. These deficits remitted more slowly than did depressive symptoms, and in the 2-month time period including response and remission, these deficits were still severe. Improvement in some aspects was incomplete even at 8 months. A particularly marked work impairment was noted. This translates to decreased productivity and absence from employment, producing some indirect economic costs of depression. The problems associated with parental roles are particularly important, since problems in parenting and parent-child relationships impact on development and later adaptation of the next generation.

Residual social dysfunction has since been reported by many other investigators and has been found to correlate with symptom outcome. Some of the many studies have been reviewed by Fava et al. Residual symptoms are associated with increased social dysfunction. In unpublished data derived from a recent controlled trial of cognitive therapy in patients with residual symptoms, mean total scores on the Social Adjustment Scale were examined at 20 weeks. Both subjects with residual symptoms at 20 weeks and subjects who had relapsed by 20 weeks showed worse social adjustment than those with neither adverse outcome at this point.

**Biological and neurocognitive measures**

A number of biological and neurocognitive measures have been found to be abnormal in recovered depressives. These have been reviewed by Bhagwagar and Cowen. Most prominent have been abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis, including waking salivary cortisol and dexamethasone nonsuppression. The latter has been found to predict relapse. Several studies that followed up patients treated with tricyclic antidepressants found that persistent dexamethasone nonsuppression at the time of discharge predicted a greater risk or early relapse. One study in outpatients and two in patients treated with electroconvulsive therapy (ECT) have failed to find this. The enhanced dexamethasone-corticotropin-releasing hormone (CRH) test has also been found to predict relapse. A second group of persistent biological abnormalities is related to serotonin. The most prominent of these is a return of depressive symptoms on depletion of tryptophan by a high amino-acid drink low in tryptophan. A third group of abnormalities is sleep-related, specifically persistent shortened REM latency.

A further group of abnormalities is neurocognitive. Particularly prominent are the dysfunctional attitudes and attributions which occur in depression and have also been found to persist after symptomatic recovery. The relation of these varied abnormalities to residual symptoms has not been well studied, although they do appear to occur with full remission. Neither is there good evidence that they predict relapse, other than for dexamethasone suppression, and REM sleep latency.

**Bipolar disorder**

This review primarily concerns unipolar disorder. However, there is a smaller but growing parallel literature regarding bipolar disorder. Two large prospective follow-up studies have found subthreshold symptoms present for substantial periods between episodes, as have a number of smaller studies. Keller et al had earlier described subsyndromal symptoms in about half of a sample of bipolar patients in a controlled trial of high- or low-dose maintenance lithium. Both the large studies found these to be present for much longer than the periods of major disorder, and found that depressive symptoms predominated over hypomanic. There has been less examination of the prediction of major relapse episodes by these symptoms, but one of the larger studies found that, when present, these subthreshold residual symptoms were strong predictors of relapse and recurrence.
The nature and treatment of residual symptoms

What can be concluded regarding the nature of residual symptoms? There are various possibilities. Residual symptoms might represent persistent illness—the original illness continuing in milder form. Alternatively, they might represent the phenomena preceding and underlying the depressive episode. Two possible aspects of the latter can substantially be discounted: subjects with residual symptoms are neither liable to be diagnosed as dysthymic nor, except to a minor degree, to show more personality abnormality than those who remit fully. A third possible underlying phenomenon is that the residual symptoms could reflect the cognitive vulnerability of dysfunctional attitudes. However, the symptoms shown by residual depressives, although they include negative cognitions, are not limited to these, but include core mood and functional symptoms of depression. These are too wide to be related easily to a single abnormality of low self-esteem.

It thus seems likely, given these findings, and the relative lack of association of residual symptoms with anything else except subsequent relapse, that the explanation is the first of those given above, persistence of the original disorder and its underlying neurobiological substrates. The most likely conclusion is that residual symptoms are a manifestation of a disorder which, in spite of improvement, is still present—they are the evidence that the disorder continues. This is also supported by the tendency of relapses following residual symptoms to occur early. The most important implications of our findings concern future prognosis and treatment. The association with relapse argues strongly that residual symptoms should be treated vigorously, in order to abolish them. Their treatment is dealt with in other papers in this journal issue, and therefore will not be discussed here.

There are also implications for continuation and maintenance treatment. It is mainly on the basis of the continuation drug trials cited above that a recommendation was made that continuation treatment should not be withdrawn until the patient had experienced 4 months free of all symptoms.20 This may in fact be too early, in the light of later evidence that the risk of relapse extends longer than previously thought.21 The presence of residual symptoms sufficient to indicate incomplete remission should be a strong indicator for continued treatment until they have become of minor degree or completely subsided, for about 9 months. Such treatment may include not only antidepressants and possibly lithium augmentation, but also cognitive therapy, which has been shown to reduce relapse rates,66 including in one study which specifically targeted relapse-prone subjects with residual symptoms. In this study,43,69 we found that adding cognitive therapy to full doses of antidepressant continuation and maintenance lowered relapse rates, and the effect lasted for 3 and a half years after the end of the cognitive therapy. Residual symptoms at remission also suggest that maintenance antidepressant may be required, at least for 2 to 3 years. Such symptoms also indicate that, when treatment is withdrawn, withdrawal should be slow.

Conclusion

Partial remission with residual symptoms is an important outcome of major depression. It probably reflects persistence of the original disorder, in a milder form. It is a key indicator of much-increased risk of relapse, and the need for continuing treatment, including antidepressants, and, in some cases, cognitive therapy.

REFERENCES

1. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Arch Gen Psychiatry. 1991;48:851-855.
2. Rush AJ, Kraemer HC, Sackeim HA, et al. Report by the ACNP Task Force on Response and Remission in Major Depressive Disorder. Neuropsychopharmacol. 2006;31:1841-1853.
3. Paykel, E.S., Ramana R, Cooper Z, Hayhurst, H, Kerr J, Barocka A. Residual symptoms after partial remission: an important outcome in depression. Psychol Med. 1995;25:1171-1180.
4. Ramana R, Paykel ES, Cooper Z, Hayhurst, H., Saxty, M. Surtees PG. Remission and relapse in major depression: a two-year prospective follow-up study. Psychol Med. 1995;25:1161-1170.
5. Paykel ES. The Clinical Interview for Depression: development, reliability and validity. J Affect Disord. 1985;9:85-96.
6. Fawcett J. Antidepressants: Partial response in chronic depression. Br J Psychiatry. 1994;165:37-41.
7. Kupfer DJ, Spiker DG. Refractory depression: prediction of nonresponse by clinical indicators. J Clin Psychiatry. 1981;42:307-312.
8. Weissman MM, Prusoff WA, Klerman GL. Personality in the prediction of long term outcome of depression. Am J Psychiatry. 1978;135:797-800.
Remisión parcial, síntomas residuales y recaida en la depresión

La remisión parcial con síntomas residuales es un importante problema en la depresión. Este artículo revisa la frecuencia y las características de esta evolución y su asociación con la recaída. Los síntomas residuales se presentan en muchos pacientes depresivos después del tratamiento agudo. Ellos abarcan los síntomas típicos de la depresión, excepto aquellos característicos del trastorno grave. Otras anormalidades persistentes incluyen la disfunción social, actitudes disfuncionales, hiperactividad del eje hipotálamo-hipofís-adrenal, reducción de la latencia del sueño REM y reducción del anímico después de la depresión de triptófano. No está clara la asociación de algunos de estos síntomas con los de tipo residual. Hay una evidencia creciente para síntomas similares en el trastorno bipolar, particularmente en la depresión bipolar. La consecuencia más importante de los síntomas residuales es un gran aumento en el riesgo de recaída, especialmente en el primer año. Los síntomas residuales constituyen una potente indicación para un tratamiento antidepresivo de continuación energico y más prolongado que lo habitual, orientado a prevenir recaídas. También existe importante evidencia para el empleo de terapia cognitiva como tratamiento adyuvante.

Rémission partielle, symptômes résiduels et récidive dans la dépression

La rémission partielle avec symptômes résiduels est un problème important dans la dépression. Cette article se propose d’en présenter la fréquence, les caractéristiques ainsi que son association avec la récidive dépressive. Les symptômes résiduels s’observent chez beaucoup de patients déprimés après un traitement agu de la dépression à l’exclusion de ceux aux caractéristiques de la maladie sévère. D’autres anomalies persistantes sont retrouvées comme l’adaptation sociale, les attitudes dysfonctionnelles, l’hyperactivité de l’axe hypothalamo-hypophysosurrénalien, la diminution de latence du sommeil paradoxal et le fléchissement de l’humeur après déplétion en tryptophane. L’association de certaines de ces anomalies avec des symptômes résiduels n’est pas claire. Il existe de plus en plus d’arguments en faveur de la présence de ces symptômes dans les troubles bipolaires, en particulier la dépression bipolaire. La conséquence majeure est le risque augmenté de récidive dépressive, surtout au cours de la première année. Les symptômes résiduels sont une forte indication de poursuite du traitement ant dépresseur de façon plus intensive et prolongée qu’habituellement afin de prévenir une récidive. La thérapie cognitive s’est montré d’un apport efficace dans ce contexte.

9. Ormel J, Oldenhinkel T, Brilman E, van den Brink W. Outcome of depression and anxiety in primary care: a three wave 3½ year study of psychopathology and disability. Arch Gen Psychiatry. 1993;50:759-766.
10. Brodaty H, Harris L, Peters K, et al. Prognosis of depression in the elderly: A comparison with younger patients. Br J Psychiatry. 1993;163:589-596.
11. Gasto C, Navarro V, Catalán R, Portella MJ, Marcos T. Residual symptoms in elderly major depression remitters. Acta Psychiatr Scand. 2003;108:15-19.
12. Fava GA, Ruini C, Belaise C. The concept of recovery in major depression Psychol Med. 2007;37:307-317.
13. Fava, GA, Grandi S, Zielezny M, Canestri R, Morphy MA. Cognitive behavioral treatment of residual symptoms in primary major depressive disorder. Am J Psychiatry. 1994;151:1295-1299.
14. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163:1905-1917.
15. Faravelli C, Ambonetti A, Pallanti S, Pazzaglia A. Depressive relapses and incomplete recovery from index episode. Am J Psychiatry. 1986;143:888-891.
16. Georgotas A, McCue RE, Cooper TB, Nagachandran N, Chang I. How effective and safe is continuation therapy in elderly depressed patients? Factors affecting relapse rate. Arch Gen Psychiatry. 1988;45:929-932.
17. Simons AD, Murphy GE, Levine JL, Wetzell RD. Cognitive therapy and pharmacotherapy for depression. Sustained improvement over one year. Arch Gen Psychiatry. 1986;43:43-48.
18. Evans MD, Hollon SD, Derubeis RJ, et al. Differential relapse following cognitive therapy and pharmacotherapy for depression. Arch Gen Psychiatry. 1992;49:802-808.
19. Mindham RH, Howland C, Shepherd M. An evaluation of continuation therapy with tricyclic antidepressants in depressive illness. Psychol Med. 1973;3:5-17.
20. Prieur RF, Kupper DJ. Continuation drug therapy for major depressive episodes: how long should it be maintained? Am J Psychiatry. 1986;143:18-23.
21. Van Londen L, Molenaar RP, Goekoop JG, Zwinderman AH, Rooijmans HG. Three- to 5-year prospective follow-up of outcome in major depression. Psychol Med. 1998;28:731-735.
22. Judd LL, Akiskal HS, Maser JD, et al. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictors of rapid relapse. J Affect Disord. 1998;50:97-108.
23. Lin EH, Katon WJ, Von Korff M, et al. Relapse of depression in primary care. Rate and clinical predictors. Arch Fam Med. 1998;7:443-449.
24. Pintor L, Gasto C, Navarro V, Torres X, Fañanas L. Relapse of major depression after complete and partial remission during a 2-year follow-up. J Affect Disord. 2003;73:237-244.
25. Taylor WD, McQuoid DR, Steffens DC, Krishnan KR. Is there a definition of remission in late-life depression that predicts later relapse? Neuropsychopharmacol. 2004;29:2272-2277.
26. Kennedy N, Abbott R, Paykel ES. Remission and recurrence of depression in the maintenance era: long-term outcome in a Cambridge cohort. Psychol Med. 1999;29:1179-1186.
27. Kennedy N, Abbott R, Paykel ES. Longitudinal syndromal and sub-syndromal symptoms after severe depression: 10-year follow-up study. Br J Psychiatry. 2004;184:330-336.
28. Kennedy N, Paykel ES. Residual symptoms at remission from depression: impact on long-term outcome. J Affect Disord. 2004;80:135-144.
29. Karp LF, Buyse DJ, Houck PR, Cherry C, Kupfer DJ, Frank E. Relationship of variability in residual symptoms with recurrence of major depressive disorder during maintenance treatment. Am J Psychiatry. 2004;161:1877-1884.
30. Dombrovski AY, Mulsant BH, Houck PR, et al. Residual symptoms and recurrence during maintenance treatment of late-life depression. J Affect Disord. 2007;103:77-82.
31. Israel JA. Remission in depression: definition and initial treatment approaches. J Psychopharmacol. 2006;20(3 suppl):S1-10.
32. Paykel ES, Weissman MM. Social adjustment and depression: a longitudinal study. Arch Gen Psychiatry. 1973;28:659-663.
33. Weissman MM, Paykel ES. The Depressed Woman: A study of Social Relationships. Chicago, Ill: University of Chicago Press; 1974.
34. Bauwens F, Tray A, Pardoen D, Van der Els M, Mendlewicz J. Social adjustment of remitted bipolar and unipolar outpatients. Br J Psychiatry. 1991;159:239-244.
35. Goering PN, Lancej WJ, Freeman SJJ. Marital support and recovery from depression. Br J Psychiatry. 1992;160:76-82.
36. Coryell W, McQuoid DR, Steffens DC, Krishnan KR. Is there a definition of remission in late-life depression that predicts later relapse? Neuropsychopharmacol. 2004;29:2272-2277.
37. Shapira B, Zislin J, Gelfin Y, et al. Social adjustment and self-esteem in remitted patients with unipolar and bipolar affective disorder. Comp Psychiatry. 1999;40:24-30.
38. Kudd LL, Akiskal HS, Zeller PJ, et al. Psychosocial functioning during the treatment of major depressive disorder with fluoxetine. J Clin Psychopharmacol. 2004;24:507-511.
39. Nasser EH, Overholser J, J. Recovery from major depression. Acta Psychiatr Scand. 2005;111:125-132.
40. Agosti V. Predictors of persistent social impairment among recovered depressed outpatients. J Affect Disord. 1999;55:215-219.
41. Furukawa TA, Takenchi H, Hiroe T, et al. Symptomatic recovery and social functioning in major depression. Acta Psychiatr Scand. 2001;103:257-261.
42. Paykel ES, Scott J, Teasdale JD, et al. Prevention of relapse in residual depression by cognitive therapy. A controlled trial. Arch Gen Psychiatry. 1999;56:829-835.
43. Bhagwagar Z, Cowen PJ. ‘It’s not over when it’s over’: persistent neurobiological abnormalities in recovered depressed patients. Psychol Med. 2008;38:307-313.
44. Bhagwagar Z, Hafizi S, Cowen PJ. Increase in concentration of wakening salivary cortisol in recovered patients with depression. Am J Psychiatry. 2003;160:1890-1891.
45. Goldberg IK. Dexamethasone suppression test as indicator of safe withdrawal of antidepressant therapy. Lancet. 1980;1:376.
46. Greden IF, Albala AA, Haskell RF, et al. Normalization of dexamethasone suppression test: a laboratory index of recovery from endogenous depression. Biol Psychiatry. 1980;15:449-458.
47. Holsboer F, Liebl, R, Hofschusler E. Repeated dexamethasone suppression test during depressive illness: normalisation of test result compared with clinical improvement. J Affect Disord., 1982;49:103-109.
48. Nemeroff CB, Evans DL. Correlation between the dexamethasone suppression test in depressed patients and clinical response. Am J Psychiatry. 1988;145:247-249.
49. Schweitzer I, Maguire KP, Gee AI, et al. Prediction of outcome in depressed patients by weekly monitoring with the dexamethasone suppression test. Br J Psychiatry. 1987;151:780-784.
50. Charles GA, Schittecate M, Rush AL, Panzer M, Wilmotte J. Persistent cortisol non-suppression after clinical recovery predicts symptomatic relapse in unipolar depression. J Affect Disord. 1989;17:271-278.
51. Targum SD. Persistent neuroendocrine dysregulation in major depressive disorder: a marker for early relapse. Biol Psychiatry. 1984;19:305-317.
52. Yerevanian B, Privitera M, Milanese E, Sagi I, Russotto J. The dexamethasone test during major depressive episodes. Biol Psychiatry. 1984;19:407-412.
53. Peselow ED, Baxter N, Rieve RR, Baroureche F. The dexamethasone suppression test as a monitor of clinical recovery. Am J Psychiatry. 1987;144:30-35.
54. Coryell W. DST abnormality as a predictor of course in major depression. J Affect Disord. 1990;19:103-109.
55. Katona, CLE, Aldridge, CR, Roth M, et al. The dexamethasone suppression test and prediction of outcome in patients receiving ECT. Br J Psychiatry. 1987;150:315-318.
56. Zobel AW, Nickel T, Sonntag A, Uhr M, Holsboer F, Ising M. Cortisol response in the combined dexamethasone/CRH test as predictor of relapse in patients with remitted depression. A prospective study. J Psychiatr Res. 2004;38:93-94.
57. Ruhé HG, Mason NS, Schene AH. Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. Mol Psychiatry. 2007;12:331-359.
58. Giles DE, Jarrett RB, Rush AJ, Biggs MM, Roffwarg HP. Prospective assessment of electroencephalographic sleep in remitted major depression. Psychiatry Res. 1993;46:289-294.
59. Eaves G, Rush AJ. Cognitive patterns in symptomatic and remitted unipolar major depression. J Abnorm Psychol. 1984;93:31-40.
60. Timbremont B, Braet C. Cognitive vulnerability in remitted depressed children and adolescents. Behav Res Ther. 2004;42:423-437.
61. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry. 2002;59:530-537.
62. Paykel, ES Ackland R, Morris R, Hayhurst H, Scott J. Sub-syndromal and syndromal symptoms in the longitudinal course of bipolar disorder. Br J Psychiatry. 2006;189:118-123.
63. Morriss R. Clinical importance of inter-episode symptoms in patients with bipolar affective disorder. J Affect Disord. 2002;72:3-13.
64. Keller MB, Lavori PW, Kane JM, et al. Subsyndromal symptoms in bipolar disorder. A comparison of standard and low serum levels of lithium. Arch Gen Psychiatry. 1992;49:371-376.
65. Judd LL, Schettler PJ, Akiskal HS, et al. Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence. Arch Gen Psychiatry. 2008;65:386-394.
66. Reimherr FW, Amsterdam JD, Quitkin FM, et al. Optimal length of continuation therapy in depression. Arch Gen Psychiatry. 2008;65:386-394.
67. Paykel ES. Cognitive therapy in relapse prevention in depression. Int J Neuropsychopharmacol. 2007;10:131-136.
68. Paykel ES, Scott J, Cornwall PL, et al. Duration of relapse prevention after cognitive therapy in residual depression: follow-up of controlled trial. Psychol Med. 2005;35:59-68.