

Partial remission, residual symptoms, and relapse in depression

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Partial remission from depression, with residual symptoms, is an important problem in depression. This paper reviews the frequency and features of this outcome, and its association with relapse. Residual symptoms occur in many depressed patients after acute treatment. They span the typical symptoms of depression, except those characteristic of severe disorders. Other persistent abnormalities include social dysfunction, dysfunctional attitudes, hypothalamic-pituitary-adrenal axis overactivity, shortened REM sleep latency, and mood lowering after tryptophan depletion. Associations of some of these with residual symptoms are not clear. There is growing evidence for similar residual symptoms in bipolar disorder, particularly bipolar depression. The most important consequence of residual symptoms is a much-increased risk of relapse, particularly in the first year. Residual symptoms are a strong indication for vigorous and longer than usual continuation of antidepressant treatment, in order to prevent relapse. There is good evidence for the use of cognitive therapy as an adjunct.

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Dialogues Clin Neurosci. 2008;10:431-437.

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 al¹ 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

Keywords: *depression; remission; residual symptom; relapse*

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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, hopeless-

ness, 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 dysthymics. 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.⁷ Weissman et al⁸ 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,⁹ and in 38% of elderly depressives at 1 year, and 20% at 2 to 4 years.¹⁰ More recently, one or more residual symptoms have been found in 82% of elderly depression remitters below 8 on the Hamilton Depression scale.¹¹ 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.¹² They have been reported both after drug treatment and psychotherapy. Fava et al,¹³ 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,¹⁴ 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 study⁴ 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.³ Residual symptoms were a key indicator of subsequent relapse.

A number of other studies have drawn attention to high relapse rates in residual depressives.^{10,15-18} One study¹⁹ found that patients with residual symptoms of depression obtained greater benefit from maintenance antidepressant therapy than those who had completely recovered. Prien and Kupfer²⁰ 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.²¹ 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.²² Residual symptoms have been found to be a strong predictor of relapse in primary care depressives.²³ In Spanish outpatients,²⁴ a relapse rate of 67% was found in the 2 years following partial remission, as opposed to 14% after full remission. One study²⁵ 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. We²⁶⁻²⁸ 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.²⁹ In a similar trial in elderly patients, residual anxiety and residual sleep disturbance independently predicted early recurrence.³⁰

Social adjustment

Israel³¹ suggested that recovery from depression should be determined in three domains: symptoms, psychosocial function, and pathophysiological changes. Social dysfunction

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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.^{32,33} 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.^{12,34-42}

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,⁴³ 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 depres-

sives. These have been reviewed by Bhagwagar and Cowen.⁴⁴ Most prominent have been abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis, including waking salivary cortisol⁴⁵ 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.^{46-52,53} One study in outpatients⁵⁴ and two in patients treated with electroconvulsive therapy (ECT)^{55,56} have failed to find this. The enhanced dexamethasone-corticotropin-releasing hormone (CRH) test has also been found to predict relapse.⁵⁷

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.⁵⁸ A third group of abnormalities is sleep-related, specifically persistent shortened REM latency.⁵⁹

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.^{60,61}

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,^{62,63} as have a number of smaller studies.⁶⁴ Keller et al⁶⁵ 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 studies⁶⁶ 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 treat-

ment 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.⁶⁷ 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,⁶⁸ 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. □

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Remisión parcial, síntomas residuales y recaída 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 anomalías persistentes incluyen la disfunción social, actitudes disfuncionales, hiperactividad del eje hipotálamo-hipófisis-adrenal, reducción de la latencia del sueño REM y reducción del ánimo después de la depleción de triptófano. No está clara la asociación de algunos de estos síntomas con los de tipo residual. Hay una evidencia creciente para síntomas residuales 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 enérgico 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 récurrence 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 récurrence dépressive. Les symptômes résiduels s'observent chez beaucoup de patients déprimés après un traitement aigu. Ils recouvrent les symptômes typiques de la dépression à l'exclusion de ceux caractéristiques de la maladie sévère. D'autres anomalies persistantes sont retrouvées comme l'inadaptation sociale, les attitudes dysfonctionnelles, l'hyperactivité de l'axe hypothalamo-hypophyso-surrénalien, 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 récurrence dépressive, surtout au cours de la première année. Les symptômes résiduels sont une forte indication de poursuite du traitement antidepresseur de façon plus intensive et prolongée qu'habituellement afin de prévenir une récurrence. La thérapie cognitive s'est montré d'un apport efficace dans ce contexte.

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