THE INCIDENCE AND IMPACT OF PARTIAL REMISSION

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Introduction

Despite many effective antidepressant strategies, depression continues to be a highly prevalent, disabling, and costly condition for both primary care and psychiatric populations.[1,2,3] Although most patients experiencing an episode of depression undergo some improvement with several months of treatment, it is the long-term outcome that remains problematical.[4,5] The optimal goal of treatment is a complete resolution of all symptoms of depression and the attainment of symptom-free status.[6] Patients may be much, or very much, improved after treatment, but many fail to achieve or maintain symptom-free states.[7] Many patients are left with what are referred to as residual symptoms, and evidence now suggests that these residual symptoms leave patients more susceptible to relapse. Therefore, more detailed analyses of suboptimal depression outcomes must be conducted to ensure that better predictors for relapse may be identified, ultimately improving both treatment choices and prognosis. This review will focus in the first instance on current conventional wisdom on the prevalence and characteristics of patients with residual symptoms of depression and their possible role in relapse in major unipolar depression and will subsequently point to inadequacies in the standard model.

Subsyndromal or residual depressive syndrome

Clinical depression with or without treatment can result in various negative outcomes including chronicity, relapse, and recurrence.[4] Chronicity has been defined as failure to achieve remission over a 2-year period.[8] Relapse is defined as an early return of the index episode, and recurrence as a new symptomatic episode that follows a sustained recovery.[9] Another important adverse outcome for major depression is partial remission with residual symptoms, also referred to as threshold depressive symptoms or subsyndromal depressive symptoms (SSD).[10,11,12] Subsyndromal depression is defined as two DSM-IV-defined symptoms of MDD with no complaint of decreased mood or lack of pleasure or interest. Partial remission is a period of sufficient improvement such that an individual no longer fulfills the criteria for major depression (HAM-D >18), but continues to evidence more than minimal symptoms (HAM-D <8).

Although partial remission has been widely recognized, its relevance in clinical practice has not been.[13] Clinical trials report rates of response (50% reduction in symptoms), nonresponse

and in a minority of studies, remission (HAM-D score <7). Partial remission and residual symptoms are not reported in most trials designed to look at the efficacy of antidepressant strategies. In most studies specifically designed to determine the nature and prevalence of partial remission, patients were considered to have residual symptoms if they had responded to therapy but had a HAM-D score of 8 or more.[4] However, it has now been suggested that patients who achieve full remission as defined by even the most conservative criteria may continue to have residual symptoms.[9,14] Estimating the impact of residual symptoms is further limited by the fact that there are few known baseline HAM-D scores for the general population, therefore accurate comparisons are not possible. Despite these limitations, studies to date have helped in establishing the importance of recognizing residual symptoms in potentially predicting relapse.

Prevalence of residual symptoms

Many studies have reported on the prevalence of symptomatic patients after various treatments both prospectively and naturalistically.[14,15,16,17,18,19] It should be noted that these studies each had their own method for reporting residual symptomatology, and patient populations, treatments and time periods varied.

Several studies have demonstrated that with treatment approximately one-third of patients are complete responders, partial responders and nonresponders, respectively.[15,17,18] Looking specifically at patients that had responded to therapy and no longer filled the criterion for major depression, several groups have described residual symptoms in about 35% of these patients.[4,19] The group of patients that respond to therapy, but fall between the definition of major depression and the definition of full remission are the most over looked patient group in clinical practice.

Many patients continue to have residual symptoms despite a robust response to antidepressants. In a study of subjects who were in full remission (HAM-D <8) after treatment with fluoxetine 20 mg for 8 weeks, more than 80% had one or more, and more than 30% had more than three residual symptoms of MDD.[14]

Several studies have also assessed the prevalence of subsyndromal depressive symptoms among the general population.[20,21] Epidemiological data on subjects with no prior history of MDD found that as many as 24% of the population has depressive symptoms.[21] Just 2-4 symptoms were associated with an increased risk of MDD within a year of follow-up.

Nature of residual symptoms

Residual symptom characteristics tend to show a pattern that is reflective of mild typical depressive symptoms without major biological symptoms. In Paykel's study of patients who had

responded to antidepressant therapy (HAM-D 8 to 18), depressed mood, impairment of work and activities, psychic anxiety and genital symptoms were reported in at least a moderate degree in 47% of patients.[4] Other symptoms were present to a mild degree with the exception of those typical of severe depression, including biological symptoms such as late insomnia, retardation, agitation, hypochondriasis, weight loss and loss of insight. A study in elderly patients (average 67 years) during the continuation phase of treatment found the most persistent residual symptoms were depressed mood, apathy, anxiety (both psychological and somatic), anergia, insomnia, feelings of guilt, and loss of libido.[22]

In patients who met the criteria for full remission (HAM-D <8), the three most common residual symptoms were sleep disturbances (44%), fatigue (38%), and diminished interest or pleasure (27%).[14] Depressed mood, and suicidal ideation were rarely seen. In an earlier study of patients in full remission after successful treatment, the most common residual symptoms were generalized and somatic anxiety, and irritability.[23] When depressed patients in remission were compared to a group of never-depressed volunteers, they demonstrated significantly more problems with social dysfunction, problem-solving abilities, and dysfunctional attitudes.[24] Overall, it appears that functional impairment and anxiety are the most common residual symptoms. While depressed mood may be present in patients who are responders, it is not usually present in patients in full remission.

Various models have been described to try to explain the cause of residual symptoms. A "vulnerability" model suggests that preexisting personality traits are a risk factor in the development of depression and persist after recovery. In contrast, the "scar" model proposes that depressive episodes cause lasting changes in personality.[25] A number of studies have found that neuroticism-like personality factors appear to predispose to development of major depression,[26] while extroversion-like factors have been associated with a better response to therapy.[27,28] This suggests that residual symptoms may be a return to the baseline personality characteristics, which are also those that predispose to depressive illness. Alternatively, residual symptoms may represent persistent illness; that is, the original illness continuing in a milder form.[4] The fact that the presence of residual symptoms is associated with rapid episode relapse supports either of these theories.[19]

Predictors of residual symptoms

Paykel's group investigated a number of patient characteristics and found that only severity of illness was a predictor of residual symptoms.[4,29] On the other hand, in patients in full

remission, Nierenberg et al found that the presence of residual symptoms was not predicted by baseline severity of depression.[14]

In some studies, no relationship was found between residual symptoms and life events.[5,14] In contrast, residual symptoms during continuation treatment in elderly patients in full remission were higher in subjects with depression associated with a severe life event or ongoing major stressors.[22] Similarly, personality traits have been associated with residual symptoms in some studies but not in others.[5,22] Patients in remission showed a weak trend for more personality abnormalities in those patients with residual symptoms. Only avoidant personality and passive dependent personality were significantly more common.

No relationships were found between residual symptoms and sociodemographic factors, family and personal history, follow-up care, comorbid conditions, chronic medical burden, social support, and past and present illness history.[5,14,22] Undertreatment also does not appear to explain the presence of residual symptoms, in fact patients with residual symptoms tended to receive higher doses of antidepressant medication.[4,5]

Overall, which patients will develop residual symptoms cannot be accurately predicted by age, gender, marital status, number of prior episodes, duration of current episode, treatment courses, or comorbid conditions. There is some conflict in the literature concerning initial severity of depression, life stressors, and personality.

Residual symptoms and relapse

Relapse and recurrence are important and too frequent long-term outcomes in the management of patients with depression. The presence of residual symptoms has been associated with a significantly increased risk of relapse after treatment with either pharmacotherapy or psychotherapy (table 1).[4,30,31,32,33] In a 1-year follow-up of patients who had recovered from primary depression, 50% of patients relapsed.[30] Only the presence of residual symptoms at the time of remission was significantly different between the group that relapsed and those who did not.

Thase et al found that relapse occurred in 52% of the patients who responded to treatment with HAM-D scores of 10 or lower for 2 consecutive weeks, whereas relapse occurred in only 9% of those who responded to treatment with HAM-D scores of 6 or lower for two consecutive months.[33] In Paykel's study in subjects who had responded to treatment (HAM-D 8-18), 76% (13/17) of those with residual symptoms as opposed to 25% (10/40) of those without, relapsed over the 12-15 month follow-up period ($p < 0.001$).[4]

In a larger study, patients with that had residual depressive symptoms (n = 82) or were asymptomatic (n = 155) after treatment were followed naturalistically for 10 years or longer.[19] Patients with residual symptoms relapsed more than 3-5.5 times faster ($p < 0.0001$) than patients who were asymptomatic.[19] A history of recurrence has also been associated with higher relapse rates. However, in this study the increased probability for relapse in patients with residual symptoms was 368%, compared to 64% for patients with a history of more than four depressive episodes.

A subset analysis of subjects with residual symptoms compared those with more severe (HAM-D >12) to those with milder symptoms (HAM-D 8-12). The relapse rate was higher among patients in the milder group at 90% compared to 57% in the severe group.[4] This suggests that the majority of cases relapse did not represent a minor fluctuation, but a clear worsening from mild residual symptoms.

Table 1: Prevalence of early relapse in patients with residual symptoms

Study	**Patients**	**Symptom level**	**Relapse rate (%)**
Thase et al. 1992[33] (n=)		HAM-D ≤6 HAM-D ≤10	9% 52%
Paykel et al. 1995[4] (n=60) 12-15 months	Majority inpatients Responders (HAM-D 8 to 18)	HAM-D ≤7 HAM-D >8	25% 76% ($p<0.001$)
Judd et al. 1998[19] (n=237) 10 years	MDD/naturalistic study "Well interval"	PSR-MDD 1* PSR-MDD 2*	65.8% 86.6% ($p<0.001$)

* Psychiatric status rating scale for RDC MDD, score of 1 = asymptomatic, 2 = residual/mild symptoms

Impact of residual symptomatology

In addition to a higher risk of relapse, residual symptoms have been associated with a number of other negative outcomes. Subsyndromal depression and residual symptoms after recovery are associated with more medical and psychiatric visits, emergency room use, psychiatric hospitalization, increased public assistance, disability benefits, thoughts of suicide, and attempted suicide.[2,10,11,12,19] The development of chronicity is also increased in patients with residual symptoms. A 12-year follow-up of patients after their first major depressive episode, demonstrated that those with residual symptoms had more severe and chronic future courses.[34]

Increased cardiovascular risk has also been suggested. The Stockholm Female Coronary Risk Study, included 292 women patients aged 30 to 65 years, admitted for an acute coronary event between 1991 and 1994.[35]. After five years of follow-up, 35% of the women who lacked social integration and had two or more depressive symptoms had a relapse of their coronary disease (cardiovascular death, recurrent acute myocardial infarction or revascularization), as compared to only 9% of the women who were free of poor social integration and depressive symptoms.

Management of residual symptoms

Residual symptoms are a tremendous economic burden to the health care system and clearly are a clinically relevant state of illness activity in unipolar MDD. Therefore, it is important to identify antidepressant strategies that may minimize the incidence of residual depressive symptoms. The drug selected for initial treatment should offer the best chance to induce a full remission. Data suggest that antidepressants with more than one mechanism of action including the tricyclics may offer higher rates of full remission.[36,37] Unfortunately, a narrow therapeutic window and a relatively high incidence of adverse events limit the routine use of the tricyclic antidepressants. Newer agents that engage more than one neurotransmitter as their primary mechanism of action including venlafaxine, nefazodone, and mirtazapine also appear to offer a greater potential for achieving full remission compared to single action drugs.[38,39,40,41]

For patients that achieve a partial remission strategies include optimizing the dose, ensuring an adequate duration of therapy, switching drugs, or using augmenting or combination strategies. Psychotherapy and electroconvulsive therapy are also options.

Substantial evidence has demonstrated the need for continuation therapy in order to prevent relapse. Cognitive therapy (CT) designed to address residual symptoms after antidepressant treatment can lower the level of residual symptoms and the rate of relapse.[23] Cognitive therapy showed a benefit in patients who had only a partial remission with antidepressant treatment.[42] Patients randomized to continue therapy with the addition of CT had significantly reduced relapse rates (29%) compared to those who continued with pharmacotherapy alone (47%, p=0.02). In a long-term follow-up study, patients receiving continuation therapy with CT after treatment with antidepressants had a significantly lower level of residual symptoms, and a lower rate of relapse over six years of follow up.[23,43,44] At the four-year follow-up the difference was significant at 35% for the CT group versus 70% for the clinical management group. Similar results were reported in patients with recurrent depression, where

those receiving continuation therapy with CT had a significantly lower level of residual symptoms, and at the two year follow up had a much lower rate of relapse (25%) compared to the clinical management group (80%).[45]

Distinctions between categories and dimensions of residual symptoms

The conventional model outlined above is predicated on the assumption that depression is a categorical disorder akin to a bacterial infection, with the aim of treatment being to eradicate all traces of prior infection. This is almost certainly misleading if only for the reason that bacterial infections are sui generis conditions in medicine.

The mirtazapine data cited earlier illustrate the failings of the conventional model.[40] In this study the superior results with mirtazapine compared to fluoxetine might be accounted for by a better response in those who respond – fewer residual symptoms – or by a greater number of responders. In fact, the latter interpretation is the correct one, suggesting that antidepressants active on different neural systems can recruit responses from individuals of different constitutional types. This finding is consistent with a body of research indicating that the prior personality of the individual predicts outcome with selective antidepressants.[46]

In a recent study of this issue, we replicated the findings of Joyce and colleagues in a population of healthy volunteers.[47] The relevance of a healthy volunteer population to the issue of residual symptoms is as follows. If current treatment guidelines are followed, then the greatest amount of time any patient will spend on treatment will be in a remitted rather than a symptomatic state. If the patient's constitutional type is such that they are unable to achieve significant well-being on the primary agent they are being treated with, the implications for residual symptoms becomes clear. This is precisely the scenario that data from our and other healthy volunteer studies point to,[48,49] with the additional complication that the deleterious effects of treatment may extend beyond minor decrements in levels of well-being to full-blown active suicidality.

Summary

Significant data indicate that subsyndromal depression and residual symptoms lead to an increased risk of relapse, continuing functional impairment, and an increased use of health services. The risks appear to increase with increasing levels of residual symptoms. Residual symptomatology may also relate in part to an incompatibility between the treatment and the patient. On both these accounts, the choice of initial antidepressant strategy should be that which provides the greatest chance of full remission and the lowest chance of residual symptoms.

Further research is needed to allow a better prediction of the best match between available treatments and the individual patient.

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