THE PREVALENCE AND OUTCOME OF PARTIAL REMISSION IN DEPRESSION

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Abstract

Full remission is the goal of treatment, but many patients fail to achieve or maintain symptom free status. Residual symptoms are common even where there has been a robust response to antidepressant therapy. In clinical studies, one-third of patients achieve a full remission, one-third a response and one-third are non-responders. The substantial proportion of patients who only achieve partial remission have traditionally been a neglected subgroup in antidepressant trials.

Partial remission is characterised by the presence of residual depressive symptoms, although these have so far been poorly defined. Typical symptoms of mild depression such as depressed mood, psychic anxiety, sleep disturbance, fatigue, and diminished interest or pleasure are commonly reported, while major biological symptoms are typically absent.

It is currently unclear which factors predict partial remission. However, it is clear that residual symptoms are powerful predictors of relapse, with relapse rates that are 3 to 6 times higher than those seen in patients in full remission. They are also associated with more medical and psychiatric visits, increased public assistance, disability benefits, thoughts of, and attempts at suicide, and development of chronicity. The risk of stroke and coronary events is also increased in patients with residual depressive symptoms.

Residual symptoms may relate in part to an incompatibility between patient and treatment, and further research is needed to predict a better match. These symptoms are a clinically relevant state of illness activity and the choice of initial antidepressant medication should offer the greatest chance of achieving full remission.

Introduction

Despite many effective therapeutic strategies, depression continues to be a highly prevalent, disabling, and costly condition.[1,2,3] Although most patients experiencing an episode of depression undergo some acute improvement following treatment, long term outcomes remain disappointing.[4,5] While full remission is the goal of treatment,[6] many patients fail to achieve or maintain symptom-free states.[7] The exact nature and origin of residual symptoms is currently debated, but their tremendous impact on outcomes such as future relapse, morbidity, and mortality is clear. A greater understanding of residual symptoms may inform future treatment choices in depression and ultimately improve prognosis. As well as focusing on current theories regarding residual symptoms, this review will also point to inadequacies in the existing literature.

Partial remission

Full remission, the goal of therapy is the virtual elimination of symptoms with a return to premorbid levels of functioning. However, clinical depression with or without treatment can result in various negative outcomes including chronicity, relapse, and recurrence.[4,8] Definitions of response, remission, relapse, and recurrence are consistent with those described in the introductory article to this supplement.[9] Another important adverse outcome for major depression is partial remission with residual symptoms. Partial remission is a period of sufficient improvement such that an individual no longer fulfills the criteria for major depressive disorder (MDD) but continues to evidence more than minimal symptoms.[9] Subsyndromal or subthreshold depression, a related phenomenon (less than threshold symptoms for MDD), is much broader as it includes spontaneous depressive symptoms in community studies, prodromal symptoms, and residual symptoms.[10,11] Although the literature suggests a similarity (negative impact, increased episodes of depression), this concept is outside the scope of this review.

Residual symptoms have been defined in numerous ways in the literature, most commonly using the Hamilton Rating Scale for Depression (HAM-D) (table 1).[4,12,13,14,15,16] There are other tools that have been used to elicit residual symptoms such as the Clinical Interview for Depression (CID), however this review will focus on studies using the HAM-D to facilitate comparisons.

Table 1: Definition and nature of residual symptoms

Study	Definition of residual	Common Symptoms
Paykel et al 1995[4] (n=120) inpatients	$HRSD_{17}$ 8-18	Depressed mood Psychic anxiety, Genital Sx, Impaired work/activities
Opdyke et al. 1997[15] (n = 105) elderly (>67 yrs)	$HRSD_{17} \leq 10$ Duration 3 weeks	Depressed mood Psychic anxiety Somatic anxiety Genital Sx, Guilt, Anergia, Insomnia
Simon 2000[12] (n= 225)	$HRSD_{17} \geq 7$ Duration?	
Thase et al 1992[13] (n= 50) outpatients	$HRSD_{17}$ 6-10 Duration 2 weeks	
Ezquiaga et al 1998[16] (n= 90)	$HRSD_{17}$ 8-17 Duration?	
Nierenberg et al 1999[14] (n = 108) outpatients	$HRSD_{17}$ 0-6 (full responders)	Sleep disturbances, Fatigue Diminished interest/pleasure

NR, not reported

Although partial remission has been widely recognized, its relevance in clinical practice has not been.[17] Clinical trials report rates of response (50% reduction in symptoms), non-response and in a minority of studies, remission (HAM-D $\leq$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 usually considered to have residual symptoms if they had responded to therapy but had a HAM-D score of 8 or more (table 1).[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.[14,18] 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.

Prevalence of residual symptoms

Many studies have reported on the prevalence of symptomatic patients after various treatments including pharmacotherapy and psychotherapy, both prospectively and naturalistically, in psychiatric clinics and in primary care.[9,12,14,19,20,21,22] It should be noted that

these studies each had their own method for reporting residual symptomatology, and examined different patient populations, treatment modalities, and time periods. The majority demonstrated that with treatment approximately one-third of patients respond fully, one third show partial response, and one third show no response.[9,20] Other researchers have described residual symptoms in about 35% of patients that had responded to therapy and no longer fulfilled the criterion for major depression.[4,22] The paucity of information reporting on rates of partial remission suggests that this patient population is a relatively neglected group.

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 $\leq$7) 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.[18] The prevalence of subsyndromal depressive symptoms has also been examined among the general population.[23,24] Epidemiological data on subjects with no prior history of MDD showed that as many as 24% of the population has depressive symptoms.[24] 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 (table 1). In a study of patients who remained partial responders to antidepressant therapy (HAM-D 8 to 18), depressed mood, impairment of work and activities, psychic anxiety and genital symptoms were reported to at least a moderate degree in 47% of patients.[4] Other symptoms were present to a mild degree with the exception of those associated with more severe depression, including late insomnia, retardation, agitation, hypochondriasis, weight loss and loss of insight. In a study of elderly patients (average 67 years) during the continuation phase of treatment, the most persistent residual symptoms were apathy, anxiety (both psychological and somatic), anergia, insomnia, feelings of guilt, and loss of libido.[15] Although genital symptoms were reported in some studies, drug side effects were not systematically excluded from residual symptom scores.[4,15]

In patients who met the criteria for full remission (HAM-D $\leq$7), the three most common residual symptoms were sleep disturbances (44%), fatigue (38%), and diminished interest or pleasure (27%).[18] 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.[25] When depressed patients in remission were

compared to a group of never-depressed volunteers, they demonstrated significantly more problems with social function, problem-solving abilities, and dysfunctional attitudes.[26]

Various models have been described in an attempt 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.[27] A number of studies have found that neuroticism-like personality factors appear to predispose to development of major depression,[28] while extroversion-like factors have been associated with a better response to therapy.[29,30] This suggests that in some patients, the presence of "residual symptoms" may represent 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]

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.[4,31] On the other hand, for patients in so-called "full remission" (HAM-$D_{17} \leq 6$), Nierenberg et al found that the presence of residual symptoms was not predicted by baseline severity of depression.[18]

In some studies, there was no relationship between residual symptoms and life events.[5,18] In contrast, residual symptoms during continuation treatment in elderly patients in full remission as defined by a HAM-D_{17} <10, were higher in subjects with depression associated with a severe life event or ongoing major stressors.[15] Similarly, personality traits have been associated with residual symptoms in some studies but not in others.[5,15]

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.[5,15,18] In addition, residual symptoms are prevalent both in patients who receive psychotherapy, as well as those treated with pharmacotherapy.[13]

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, unfortunately, 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 2).[4,13,32,33,34]

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

In a larger study, patients with (n = 82) or without (n = 155) residual depressive symptoms after treatment were followed naturalistically for 10 years or longer.[22] Patients with residual symptoms relapsed more than 3-5.5 times faster ($p<0.0001$) than patients who were asymptomatic.[22] A history of recurrent episodes has also been associated with higher relapse rates. However, in this study, the increased probability of relapse in patients with residual symptoms was 368% (Odds Ratio 3.68) compared to 64% (OR=1.64) for patients with a history of more than four depressive episodes.

In a 1-year follow-up of patients who had recovered from the index episode of unipolar depression, 50% of patients relapsed.[32] Those who relapsed showed higher levels of residual symptoms, with CGI scores that were significantly different between the groups, while the differences in HAM-D scores were not. Patients who received psychotherapy (n=20) to reduce residual symptoms had lower rates of relapse than those who did not (n=20) at both 2 years (15% vs. 35%, p=ns) and at 4 years (35% vs. 75%, $p<0.05$).[25,33]

A subset analysis of subjects with residual symptoms compared those with more severe symptoms (HAM-D >12) to those with milder symptoms (HAM-D 8-12). Surprisingly, the rate of relapse was higher among patients with milder symptoms (90%) compared to those with severe symptoms (57%).[4] It is unknown whether relapse is related to specific symptoms or to the number of symptoms.

Table 2: Prevalence of early relapse in patients with residual symptoms

Study	**Patients**	**Symptom level**	**Relapse rate (%)**
Thase et al. 1992[13] (n= 50) 1 year	Outpatients Responders (HRSD ≤10)	HRSD ≤6 HAM-D 7-10	9% 52% (p=0.004)
Paykel et al. 1995[4] (n=60) 12-15 months	Majority inpatients Responders (HRSD 8-18)	HRSD ≤7 HRSD >8	25% 76% (p<0.001)

The cost of residual symptomatology

In addition to a higher risk of relapse, residual symptoms are associated with a number of other negative outcomes. Residual symptoms after recovery from depression are associated with more medical and psychiatric visits, emergency room use, psychiatric hospitalization, increased public assistance, disability benefits, thoughts of suicide, and attempted suicide.[2,22] 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 (MDE) demonstrated that those with residual symptoms had more severe and chronic future courses.[35]

Residual depressive symptoms also predict future morbidity for cardiovascular disease and stroke. The Montreal Heart Studies clearly demonstrated that the risk of cardiovascular mortality after myocardial infarction was significantly increased in patients with mild to moderate symptoms of depression (odds ratios (OR) at 12 months was about 3.0 and at 18 months was 7.82).[36,37] In patients with unstable angina, depression was identified in over 40% of patients and was associated with a significantly increased risk of cardiac death or nonfatal myocardial infarction at one year, even after controlling for other significant prognostic factors (OR 6.73).[38] 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.[39] 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, recurrent acute myocardial infarction or cardiovascular death as compared to only 9% of the women who were free of depressive symptoms and had good social integration.

In a population-based cohort of 6,095 adults, depressive symptoms were found to be predictive of stroke.[40] After adjustment for other risk factors, the presence of self-reported depressive symptomatology was associated with a relative risk of stroke of 1.73.

An association between depression and cancer has also been suggested.[41,42] A 13-year follow-up of 2,017 individuals did not find an association between major depression and an increased risk of cancer overall.[41] However, among women the risk of breast cancer was increased (adjusted RR = 3.8) in those with MDD.

Management of residual symptoms

Residual symptoms are a tremendous economic burden to the health care system and are a clinically relevant state of illness activity following unipolar MDD. Therefore, it is important to identify treatment 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 amitriptyline and venlafaxine may offer higher rates of full remission.[43,44,45] Unfortunately, a relatively high incidence of adverse events limit the routine use of the tricyclic antidepressants.

A modified version of cognitive therapy (CT) designed to address the remaining symptoms after antidepressant treatment, can also lower the level of residual symptoms and the rate of relapse.[25] Cognitive therapy showed a benefit in patients who had only a partial remission with antidepressant treatment.[46] Patients randomized to continue therapy with the addition of CT had significantly reduced relapse rates compared to those who continued with pharmacotherapy alone (29% vs. 47%, $p=0.02$). In a long-term prospective 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.[25,33,47] After four years of follow-up, the difference in rates of relapse was significant for the CT group versus for the clinical management group (35% vs. 70%, $p<0.05$).[33] 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%).[48]

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 model may be misleading, if only for the reason that bacterial infections are "sui generis" conditions in medicine.

A study comparing mirtazapine and fluoxetine illustrates the failings of the conventional model.[49] In this study, the superior results with mirtazapine compared to fluoxetine might be accounted for by a better response in those who respond (i.e., fewer residual symptoms) or by a greater number of responders. In fact, the latter interpretation is the correct one, suggesting that antidepressants that act 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.[50]

In a recent study, the findings of Joyce and colleagues[50] regarding personality were replicated in a population of healthy volunteers.[51] 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 he or she is unable to achieve significant well-being on the primary therapeutic agent, the implications for residual symptoms becomes clear. This has to be interpreted in the context of the prima non nocere principle.[52,53]

Summary

Despite the inconsistencies in the research concerning partial remission, not least with regards its definition, it is clear that residual depressive symptoms are associated with a range of clinically significant negative outcomes. Even patients with minimal levels of residual symptoms are at greater risk of early relapse of their depression, they are burdened with greater levels of social dysfunction and experience higher rates of physical morbidity and ultimately mortality than those patients who have achieved full remission. Residual symptomatology may relate in part to an incompatibility between the treatment and the patient (personality factors) and further research is needed to allow a better prediction of the best match. Treatment strategies need to be directed towards residual symptoms. Current data suggests that venlafaxine and amitriptyline may induce full remission in a greater number of patients, and that cognitive therapy may be of particular value if residual symptoms do occur.

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Table 1: Definition and nature of residual symptoms

Study	**Definition of residual**	**Common symptoms**
Paykel et al 1995[4] (n=120) inpatients	HAM-D_{17} 8-18 Duration: NR	Depressed mood, Psychic anxiety, Genital Sx, Impaired work/activities
Simon 2000[12] (n= 225)	HAM-D_{17} ≥7 Duration: NR	NR
Thase et al 1992[13] (n= 50) outpatients	HAM-D_{17} 7-10 Duration: 2 weeks	NR
Ezquiaga et al 1998[16] (n= 90)	HAM-D_{17} 8-17 Duration: NR	NR
Patients in so-called "full remission"		
Study	**Definition of remission**	**Common symptoms**
Opdyke et al 1997[15] (n = 105) elderly (>67 yrs)	HAM-D_{17}≤ 10 Duration: 3 weeks	Depressed mood, Psychic anxiety, Somatic anxiety, Genital Sx, Guilt, Anergia, Insomnia
Nierenberg et al 1999[14] (n = 108) outpatients	HAM-D_{17} 0-6 (full responders)	Sleep disturbances, Fatigue, Diminished interest/pleasure

NR, not reported.

Table 2: Prevalence of early relapse in patients with residual symptoms

Study	**Patients**	**Symptom level**	**Relapse rate (%)**
Thase et al. 1992[13] (n= 50) 1 year	Outpatients Responders (HAM-D ≤10)	HAM-D ≤6 HAM-D 7-10	9% 52% (p=0.004)
Paykel et al. 1995[4] (n=60) 12-15 months	Majority inpatients Responders (HAM-D 8-18)	HAM-D ≤7 HAM-D >8	25% 76% (p<0.001)