Incomplete remission in depression: role of psychiatric and somatic comorbidity

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Depression is one of the most pressing public health issues, because of its high lifetime prevalence and because it is associated with substantial disability. In depressed patients, psychiatric and medical comorbidity is the rule rather than the exception. About 60% to 70% of depressed patients have at least one, while 30% to 40% have two or more, concurrent psychiatric disorders. Among these, anxiety disorders and substance use disorders are the most common axis I comorbidities. Furthermore, two thirds of depressed patients have at least one comorbid medical illness. Among depressed patients, those with a current comorbid psychiatric condition (in particular an anxiety or substance use disorder) or medical illness seem to have an impaired response and remission rate during treatment compared with those patients without comorbidity. However, in depressed patients who all have the same comorbid condition, the relative benefit of an antidepressant compared with placebo appears to be equal to those effects achieved in depressed patients without comorbidity. These findings raise important research and treatment issues regarding the generalizability from randomized controlled trials that tend to exclude patients with comorbidity.

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Depression is one of the most pressing public health issues because of its high lifetime prevalence of about 15%, and because it is associated with substantial disability.[1] Depression was the fourth leading cause of disease burden in 2000 and accounted for 4.4% of total disability-adjusted life years (DALY).[1] Depression is projected to be the second leading cause of disease burden worldwide, and the leading cause in high-income countries for DALY in 2030.[2] Depression is also responsible for the greatest proportion of disease burden attributable to nonfatal health outcomes, accounting for almost 12% of total years lived with disability worldwide.[2] Often, depression assumes a chronic course, and over time is associated with increasing disability.[3,4] Furthermore, depression has been shown to be an independent predictor of the development of cardiovascular disease,[5] the leading cause of death worldwide.

For all of these reasons, it is important to treat depression aggressively. Remission, the virtual absence of symptoms, is the aim of depression treatment because remission is associated with better function and a better prognosis than is response without remission. However, in clinical trials only about one third of patients achieve remission.[6,7] There are several predictors of nonremission, among which somatic and psychiatric comorbidity have a prominent role. This article will shed some light on the role of somatic and psychiatric comorbidity in incomplete remission in depression.

Keywords: *depression; remission; response; predictor; comorbidity; clinical trial; antidepressant*

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Psychiatric comorbidity

In depressed patients, psychiatric comorbidity is the rule rather than the exception. In the National Comorbidity Survey replication (NCS-R), nearly three fourths (72%) of participants with lifetime major depressive disorder also met criteria for at least one of the other DSM-IV disorders assessed in the NCS-R, including about 60% with anxiety disorders and 24% with substance-use disorder.[8] Another large epidemiological study (The National Epidemiologic Survey on Alcoholism and Related Condition, NESARC) found that 40% of depressed patients had a comorbid anxiety disorder and 40% had comorbid alcohol abuse or dependence.[9] Furthermore, in a study of 479 depressed outpatients, 64% of the patients met criteria for at least one comorbid axis 1 disorder and 37% had two or more psychiatric disorders. Again, anxiety disorders were the most common comorbid condition and were present in 57% of those with any comorbid psychiatric disorder.[10] A European study from Finland (the Vantaa study) also demonstrated that the great majority (79%) of depressed patients suffered from one or more comorbid psychiatric disorder, including anxiety disorders (57%) and alcohol abuse (25%).[11]

These data have recently been confirmed by the Sequenced Alternatives to Relieve Depression (STAR*D) study which enrolled 2876 outpatients from 23 psychiatric and 18 primary care settings in the United States.[7] This highly representative clinical sample of depressed outpatients has revealed that depression is often chronic, severe, and associated with substantial general medical and psychiatric comorbidity.[12] Two thirds of patients had at least one other DSM-IV axis I psychiatric disorder, most often an anxiety disorder followed by drug or alcohol abuse. In fact, 40% of patients had more than one psychiatric comorbidity.

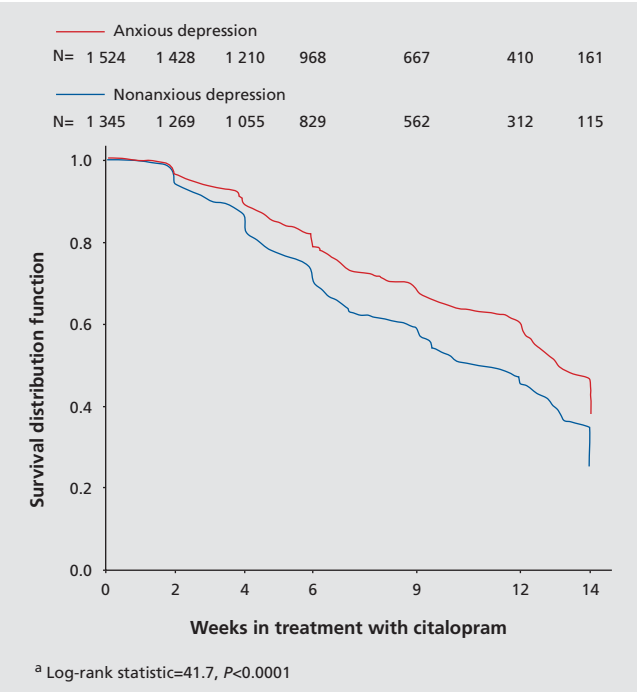
Of note, personality disorders have not been assessed in most studies. However, the NESARC study found a comorbid personality disorder in 30% of respondents with lifetime depression, while the Vantaa study found a comorbid personality disorder in 44% of depressed patients.[9,11] Therefore, psychiatric comorbidity in depression is even much higher if one considers personality disorders. The role of personality disorders in depression and its role in remission will be discussed elsewhere in this issue (see the article by Fava and Visani, p 461).

In summary, the available studies are remarkably consistent with regard to comorbid axis I psychiatric disorders in depressed patients. About 60% to 70% of depressed patients have at least one comorbid condition, about 30% to 40% have two or more comorbid psychiatric disorders. Among these, anxiety disorders and alcohol abuse are the most common comorbid conditions.

Anxiety disorders

Anxiety disorders are common among depressed patients, representing about 50% to 60% of all psychiatric comorbidity. There is now some evidence to suggest that the subtype of anxious depression or a comorbid anxiety disorder has a negative impact on remission rates in major depression.

In STAR*D, more than 50% fulfilled criteria of anxious depression defined at baseline. At treatment level 1 of STAR*D, which was monotherapy with citalopram, remission was significantly less likely (22% with anxious depression vs 33% with nonanxious depression) and took longer to occur in anxious patients than in those with nonanxious depression *(Figure 1)*.[13] Those patients who did not achieve



[a] Log-rank statistic=41.7, $P<0.0001$

Figure 1. Time to remission in 2876 patients in level 1 of STAR*D by anxious versus nonanxious depression.
Adapted from ref 13: Fava M, Rush AJ, Alpert JE, et al. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: A STAR*D report. *Am J Psychiatry*. 2008;165:342-351. Copyright © American Psychiatric Association 2008

remission could be switched to another antidepressant (sertralin, bupropion, venlafaxine) or citalopram could be augmented with bupropion or buspiron (treatment level 2). Again, those with anxious depression fared significantly worse on both the switching and augmentation options *(Figure 1)*.[13]

STAR*D is so far the largest sample to show that anxious depression is associated with a worse treatment outcome than nonanxious major depression. However, these results are corroborated by several other studies demonstrating worse outcome in anxious depression. As early as 35 years ago, Paykel described a worse response to treatment with amitryptiline in patients with anxious depression.[14] Furthermore, in 294 depressed outpatients, those with anxious depression improved significantly less on an 8-week treatment with fluoxetine compared with those with nonanxious depression.[15] Also, depressed patients with anxiety needed a longer time to recover than nonanxious patients in a sample of 327 consecutively evaluated in- and outpatients with unipolar depressive disorder.[16]

In elderly patients, anxious depression was associated with lower response rates to nortriptyline and was also associated with greater treatment discontinuation rates.[17] Furthermore, in a study of 157 depressed primary care patients, patients with a comorbid anxiety disorder tended to prematurely terminate treatment more frequently than patients with major depression alone.[18] Depression-specific pharmacological and psychotherapeutic treatments were effective for depressed patients with and without a comorbid generalized anxiety disorder, although time to recovery was longer for the former. Patients with lifetime panic disorder showed poor recovery in response to psychotherapy or pharmacotherapy.[18] This was corroborated by another primary care study, in which depressed patients with comorbid anxiety disorder had a 44% increased risk of persistent depression after 12 months.[19] Comorbid anxiety was also a strong predictor of nonresponse in a psychotherapy trial of 134 female depressed outpatients treated with interpersonal therapy. Higher levels of baseline somatic anxiety and social functioning were the most consistent predictors of nonresponse.[20] In the Vantaa study, severity of depression and current comorbidity were the two most important predictors of longer episode duration.[21] In that study, comorbidity, especially social phobia, also predicted probability of, shorter time to, and number of recurrences in patients with recurrent depression.[22] Finally, panic attacks were associated with longer depressive episodes in a population-based study of major depressive disorder in more than 5000 participants followed over 13 years, also consistent with the hypothesis that comorbid anxiety impairs remission in depression.[23]

A slightly different research question was asked in two meta-analyses and one pooled analysis with venlafaxine, fluoxetine, and mirtazapine, respectively. These studies did not assess the impact of anxiety on remission in depressed patients with or without anxiety. Instead, these studies examined the efficacy of antidepressants vs placebo in depressed patients who also had a comorbid anxiety disorder or anxious depression.

In a pooled analysis of 19 randomized controlled trials with 3183 patients, fluoxetine was significantly more effective than placebo in treating anxious major depression.[24] Venlafaxine was shown to be more efficacious than placebo in a meta-analysis of six trials with 1398 patients with anxious depression.[25] Finally, a meta-analysis of eight randomized controlled trials in 293 patients found that mirtazapine was superior to placebo and comparable to amitriptyline for the treatment of patients with major depression with symptoms of anxiety/agitation or anxiety/somatization.[26]

There are also some studies that failed to identify anxious depression as a predictor of nonremission in depression. In the first study, all patients suffered from chronic or double depression. Surprisingly, this study even found a better response in those patients with high baseline anxiety (66% response in those with anxiety vs 54% response in those without anxiety).[27] A second study found that in a group of 134 outpatients with major depression, those patients with anxious depression were only slightly less likely to respond to their first tricyclic antidepressant than patients with nonanxious depression. When functional severity or symptom severity was controlled for, this differential treatment response did not hold.[28]

In summary, the available data suggest that comorbid anxiety disorders and the subtype of anxious depression are associated with a slower response and lower rates of remission in depressed patients. However, antidepressants do not appear to differ in their relative effects compared with placebo in depressed patients with and without anxiety.

Substance use disorders

While there are many studies examining the impact of comorbid anxiety on treatment response in depressed patients with and without anxiety, only a few studies looked at the impact of comorbid substance use disorders

on outcome in patients with major depression. Virtually all large, placebo-controlled trials of antidepressants for major depression exclude persons who have current substance use disorders. Instead, studies examining comorbid depression and substance use disorders rather determined the effects of depression on outcome in substance use.

The best way to treat patients with these concurrent disorders has not been well established. One of the most basic questions is whether to treat depression in the setting of ongoing substance abuse. There are many published reports of the treatment of depression in patients who have substance-use disorders. A systematic review and meta-analysis of antidepressant treatment of depressed patients who have a concurrent alcohol or substance use disorder found that antidepressant treatment had an overall modest effect on depression and a small effect in decreasing drug or alcohol use in these patients.[29] The likelihood of finding an antidepressant effect was higher in studies with low placebo response, consistent with findings in antidepressant trials in depressed patients without substance use disorders. The authors concluded that antidepressants can be useful in these patients if used in adequate doses and for an adequate length of time (at least 6 weeks). The overall effect size they found was 0.38, which is comparable with the effect size, 0.43, found in a meta-analysis of antidepressant trials in depressed outpatients.[30]

Only a few studies examined depressed patients with and without comorbid substance-use disorder. One older study found alcohol use to be a predictor of nonresponse in depressed patients.[31] In STAR*D, about 20% of depressed patients fulfilled criteria of drug or alcohol abuse or dependence and presence of these disorders impaired remission during monotherapy with citalopram.[7]

In summary, there is some evidence to suggest that a comorbid substance use disorder impairs remission in depressed patients. With regard to treatment recommendations in patients with substance abuse and comorbid depression, a recent, thorough review[32] concluded that there is a clear pattern of benefit in favor of antidepressant drug treatment for patients who have co-occurring major depression and substance use disorders.

Somatic comorbidity

Clinical trials of antidepressants usually exclude patients with medical comorbidity; however, depression with medical comorbidity is the norm rather than the exception among patients who are seen in most clinical settings. Recently, the WHO World Health Survey with 245 404 participants from 60 countries from all regions of the world, showed that an average of between 9% and 23% of participants with one or more chronic physical disease had comorbid depression.[1] This result was significantly higher than the likelihood of having depression in the absence of a chronic physical disease.[1] Depression produced the greatest decrement in health compared with the chronic diseases angina, arthritis, asthma, and diabetes.

Before the introduction of selective serotonin reuptake inhibitors (SSRIs), treatment of depression in the medically ill was difficult due to many contraindications for the use of tricyclic antidepressants in medically ill depressed patients. One study trying to recruit medically ill patients with depression to a study with nortriptyline was halted at the midpoint because of inadequate patient recruitment, primarily a consequence of medical illnesses that prevented more than 80% of eligible patients from participating in or completing the clinical trial. Major or minor medical contraindications to the use of antidepressants were present in over 90% of depressed patients.[33] Another study reported that only 40% of patients with medical illnesses responded to treatment with different antidepressants. At the time, the authors concluded that trials of antidepressants in medical inpatients did not achieve the pattern of therapeutic responses routinely characterizing comparable interventions in psychiatric patients with depression.[34] However, there are now many studies demonstrating not only good tolerability of the newer antidepressants in the medically ill but also response and remission rates comparable to depressed patients without medical illness. This was confirmed in a recent meta-analysis including 18 studies, covering 838 patients with a range of physical diseases (cancer 2, diabetes 1, head injury 1, heart 1, HIV 5, lung 1, multiple sclerosis 1, renal 1, stroke 3, mixed 2).[35] The results of the meta-analysis were corroborated by newer randomized controlled trials in patients with coronary heart disease,[36-38] diabetes,[39] and stroke.[40]

The studies above were conducted in patients who all had a medical illness. Clinical trials of antidepressants usually exclude patients with medical comorbidity. However, some studies also addressed the issue of response and remission in depressed patients with and without medical comorbidity. The STAR*D study, which was designed to reflect "real-world" conditions, confirmed that two thirds of depressed patients had at least one concurrent general medical condition.[12] Generally, the remission rates in

STAR*D (about 30%) were similar to rates found in uncomplicated, nonchronic symptomatic volunteers enrolled in placebo-controlled, 8-week, randomized controlled trials with selective serotonin reuptake inhibitors.[7] Nevertheless, more general medical disorders were associated with lower remission scores. Furthermore, in a study with 370 depressed patients, a comorbid medical condition was one of six risk factors for sustained nonremission of depression over 4 years.[41] These findings are consistent with another study in 384 depressed outpatients that were enrolled in a 8-week open treatment with fluoxetine. Compared with patients who achieved remission with antidepressant treatment, those who did not achieve remission had significantly greater medical illness. Importantly, the final Hamilton depression rating Scale score directly correlated with the total burden of medical illness.[42] However, among those patients for whom the first antidepressant treatment with fluoxetine failed to achieve remission and who were randomized either to increased doses of fluoxetine or to augmentation with lithium or desipramine, medical illness was not associated with likelihood of remission or premature study discontinuation.[43]

There also exist studies in primary care. Among 601 depressed patients treated in primary care settings with an SSRI and followed over 9 months, physical impairment was one of four independent predictors of nonresponse.[44] In a study of 1356 patients with major depression or dysthymia from 46 primary care clinics, the likelihood of having a depressive disorder during 6- and 12-month follow-up was higher for depressed patients with comorbid medical disorders than for depressed patients who did not have comorbid medical disorders. The authors concluded that depressed patients with comorbid medical disorders tend to have similar rates of treatment but worse depression outcomes than depressed patients without comorbid medical illness.[45] Of note, two studies have demonstrated that greater body weight[46] and obesity[47] predicted nonrepsonse and slower response to antidepressants.

However, there are also studies failing to demonstrate an impact of medical illness on remission in depression. One study enrolled 259 depressed subjects >60 years. After adjusting for age, remission rates did not differ between depressed patients with and without medical illness.[48] Another study examining the effects of duloxetine 60 mg in 311 elderly patients with major depression with and without medical comorbidity also failed to find an impact of medical comorbidity on response and remission rates.[49] Another very small study with limited power (n = 31) also demonstrated that response rates to a 12-week treatment with bupropion did not differ statistically among those with high and low medical comorbidity.[50] Furthermore, in a 6-week, randomized, double-blind, placebo-controlled trial of fluoxetine, 20 mg daily in 671 outpatients older than 60 years, the number of chronic illnesses did not influence treatment response but historical physical illness was associated with greater fluoxetine response and lower placebo response.[51] Another study examined 92 patients with treatment-resistant depression who entered a 6-week open-label trial with nortriptyline. Medical comorbidity did not predict treatment response.[52]

One study in depressed patients >70 years examined the effects of paroxetine and interpersonal psychotherapy in maintenance therapy of depression once remission was achieved.[53] The impact of medical illness on recurrence was also assessed. The study found that paroxetine was superior to placebo and psychotherapy in the maintenance therapy of major depression in old age. Importantly, patients with fewer and less severe coexisting medical illness received greater benefit from paroxetine as indicated by a significant interaction between treatment with paroxetine and baseline severity of medical illness *(Figure 2)*.[53] These results indicate that medical illness might not only affect remission during acute treatment with antidepressants, but that it might also lead to a greater rate of recurrence during maintenance treatment of depression in old age.

Patients with a greater number of and more severe con-

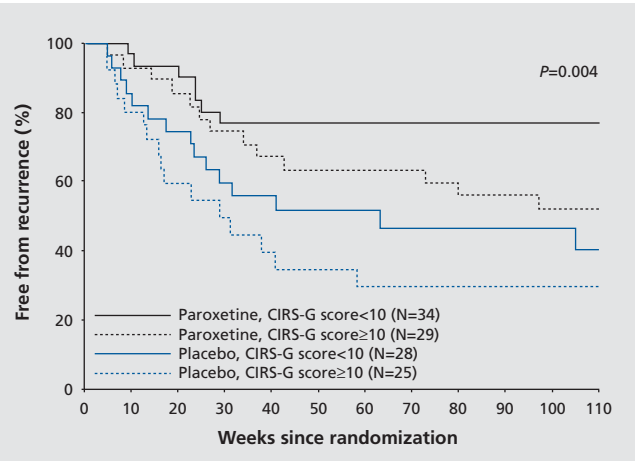


Figure 2. Effect of the number and severity of concomitant medical illnesses on the efficacy of maintenance therapy with paroxetine. Reproduced from ref 53: Reynolds CF, III, Dew MA, Pollock BG, et al. Maintenance treatment of major depression in old age. *N Engl J Med*. 2006;354:1130-1138. Copyright © Massachusetts Medical Society 2006

comitant medical illnesses, as indicated by scores of 10 or more on the Cumulative Illness Rating Scale for Geriatrics (CIRS-G), had higher rates of recurrent depression and did not fare as well during treatment with paroxetine as those with fewer and less severe concomitant medical illnesses. Although both paroxetine use and the score on the CIRS-G affected risk—main or direct effect, P=0.004—paroxetine was more effective in preventing recurrence in patients with fewer and less severe concomitant medical illnesses—interaction effect, P=0.03.

A direct comparison of the results of the above studies is difficult because of the differences among studies. However, most studies reported lower treatment response in patients who had depression and comorbid medical illness. Of those studies reporting no difference in treatment outcome in patients with and without medical comorbidity, two studies included only patients who had treatment-resistant depression and had small numbers, thus having small power to detect a difference. In conclusion, most studies suggest that depressed medically ill individuals may be more treatment-refractory and may respond slower or less well to antidepressant treatment and have higher rates of depressive relapse in the maintenance phase.[54]

Conclusion

In depressed patients, psychiatric and medical comorbidity is the rule rather than exception. About 60% to 70% of depressed patients have at least one comorbid psychiatric condition, about 30% to 40% have two or more comorbid psychiatric disorders. Furthermore, two thirds of depressed patients have at least one concurrent general medical condition.

Among depressed patients, those with a current comorbid psychiatric condition (in particular an anxiety or substance use disorder) or medical illness seem to have an impaired response and remission rate during treatment compared with those patients without comorbidity. However, in depressed patients who all have the same comorbid condition, the relative benefit of an antidepressant compared with placebo seems to be equal to those effects achieved in depressed patients without comorbidity.

These findings raise important research and treatment issues. Currently, several studies have demonstrated that 65% to 90% of treatment-seeking depressed patients would be excluded from a randomized controlled efficacy trial.[55-58] A comorbid psychiatric or medical condition was among the most prominent reasons for excluding patients while at the same time present in the vast majority of depressed patients in clinical practice. Therefore, efficacy trial findings may not generalize to actual practice. A recent editorial summarizing the STAR*D results[12] suggested that more broadly representative patients should be enrolled in efficacy trials while ensuring patient safety and internal validity. This would result in a better generalizability of the results achieved in efficacy trials, and could also reduce placebo response rates in these trials that have risen during the past years.[30] ❑

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Remisión incompleta en la depresión: papel de la comorbilidad psiquiátrica y somática

La depresión, por su alta prevalencia de vida y porque está asociada con una importante incapacidad, es uno de los temas de salud pública más urgente. En los pacientes depresivos la comorbilidad médica y psiquiátrica es más la regla que la excepción. Cerca del 60% al 70% de los pacientes depresivos tiene simultáneamente a lo menos un trastorno psiquiátrico y un 30% a 40% tiene dos o más trastornos. Entre estos, los trastornos de ansiedad y los trastornos por uso de sustancias son las comorbilidades más comunes del eje I. Además, dos tercios de los pacientes depresivos tienen a lo menos una enfermedad médica comórbida. Entre los pacientes depresivos, aquellos con una condición psiquiátrica comórbida actual (en particular un trastorno de ansiedad o uno por uso de sustancias) o con una enfermedad médica parecen tener porcentajes de respuesta y de remisión menores durante el tratamiento en comparación con los pacientes sin comorbilidad. Sin embargo, en todos los pacientes depresivos que tienen la misma condición comórbida, el beneficio relativo de un antidepresivo en comparación con placebo parece ser igual a los efectos logrados en los pacientes depresivos sin comorbilidad. Estos hallazgos promueven importantes temas de investigación y terapéutica en relación con la generalización de los ensayos randomizados y controlados que tienden a excluir pacientes con comorbilidad.

Rémission incomplète dans la dépression : rôle de la comorbidité psychiatrique et somatique

La dépression est l'un des problèmes de santé publique les plus urgents en raison de sa prévalence élevée au cours de la vie et du handicap important qui lui est associé. Chez les patients déprimés, la comorbidité psychiatrique et médicale est la règle plutôt que l'exception. Environ 60 % à 70 % des patients déprimés en ont au moins une et 30 % à 40 % ont au moins deux troubles psychiatriques concomitants. Parmi ceux-ci, l'anxiété et l'addiction sont les troubles de l'axe I les plus souvent rencontrés. De plus, 2/3 des patients déprimés ont au moins une maladie somatique comorbide. Pour les patients déprimés qui souffrent d'une comorbidité psychiatrique (en particulier un trouble anxieux ou addictif) ou médicale, les taux de réponse et de rémission au cours du traitement semblent diminués comparés aux taux des patients sans comorbidité. Cependant, chez les patients qui ont tous la même comorbidité, le bénéfice relatif d'un antidépresseur comparé au placebo semble équivalent à celui obtenu chez les patients déprimés sans comorbidité. Ces résultats soulèvent des questions thérapeutiques et de recherche importantes, les études randomisées contrôlées ayant tendance à exclure les patients atteints d'une pathologie comorbide.

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