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Raising the Bar From Response to Remission in the Therapy of Generalized Anxiety Disorder

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abstract

Worry is something that everybody experiences under the appropriate circumstances. In patients with generalized anxiety disorder (GAD), however, the worry that the affected individual experiences is virtually uncontrollable. GAD is a condition with xx victims in the United States. The lifetime risk of GAD for the general population is 5%. It is important to ask how we can do better in dealing with this disorder. How can we diagnosis GAD earlier and treat it more effectively, to remission? There are several questions that the clinician should ask when trying to judge whether treatment in GAD is complete: Are there any residual symptoms? Are there ongoing functional impairments? Is there any ongoing behavioral component? Among treatment responders, venlafaxine has shown particular efficacy in treating to remission. Adding a psychotherapeutic treatment to the medication regimen is also recommended.

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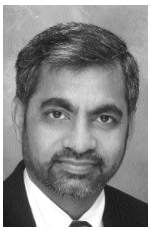

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Introductory Remarks

Response vs Remission in Generalized Anxiety Disorder

Patients with generalized anxiety disorder (GAD) often feel "better" when they initially respond to treatment. Response is transient however and, unfortunately, clinicians and patients sometimes believe that achieving a response is the best that they can do in GAD. However, a growing number of clinicians believe that we can better treat patients—and should do better—bringing them to complete remission of their symptoms. One of the major issues with GAD is that patients have a very high risk of developing depression. So, it is important when treating GAD to try to get the patient as symptom-free as possible.

Defining GAD

Worry is something that everybody experiences under the right circumstances. In patients with GAD, however, what happens is that the worry they experience is virtually uncontrollable. It is almost like their minds are spinning out of control, and they cannot engage in productive thinking. They are unable to relax emotionally because they are focusing on potential catastrophic events. As in obsessive-compulsive disorder, during the treatment process GAD patients sometimes have difficulty differentiating normal worry from pathological worry, and they experience difficulty in letting their clinician know that their excessive worry has been terminated.

One of the factors in anxiety which is not prominently mentioned in depression is the fact that there is a dimension of avoidance. When patients are anxious they will avoid situations that might trigger their anxiety. In GAD, patients might not challenge themselves because they have cognitive constructs of potential negative scenarios. This affects their peformance at work and their ability to develop healthy social relationships.

A Look at Remission

A Hamilton and Guidy scale score of greater than or equal to 7 has been proposed as the threshold for achieving remission in GAD. This score has been established not so much because it is the same score used in the Hamilton depression scale, but because, apparently, this score is 2 standard deviation points above the score for the general non-ill population. Most physicians do not use the Hamilton and Guidy scale in clinical practice, however, as it is more of a research tool. I teach my residents to use the Clinical Global Improvement scale. You can break the scale down into workable categories—no change, minimal improvement, much improvement, and very much improved. These indicants can be considered as quartiles, as follows: <25%, no significant change; 25% to 50%, minimally improved; 50% to 75%, much improved; and 75% very much improved.

In treatment, it is critically important to consider all of a GAD patient's symptoms. I tell my patients to think about all of their symptoms when they are doing a self assessment: psychic and somatic symptoms, functional capacity at work and in relationships, how they handle their daily responsibilities, etc. This kind of distinction allows the clinician to get a feel for where the patient stands. We can then use other reports and our own observations to confirm the patient's status and form a basis on which we can make treatment decisions.

Patients with GAD may isolate themselves from situations that bring about anxiety. As a result, they might subjectively describe symptomatic improvement in their condition, but their functional disability is still continuing because it is driven by avoidance.

The National Comorbidity Survey has looked at the societal costs of anxiety disorders, and the data is roughly similar to that of depression. But there is a fundamental difference: In depression, the major costs were related to lost productivity. In anxiety disorders, the majority of costs were related to medical treatments. We could argue that a large amount of those costs are related to tests and treatments provided on the basis of somatic manifestations of anxiety, and that clinicians are perhaps chasing symptoms when there is no end organ abnormality; GAD is not being considered in the differential diagnosis. Treating GAD to remission would have a much greater likelihood of dramatically reducing these treatment costs, compared to having patients with significant residual symptoms.

Treatment Issues

It is difficult to treat to remission in GAD if a patient's stress level is not managed optimally. In patients with particularly high levels of stress and anxiety, adding a psychotherapeutic treatment to the medication regimen is recommended.

For GAD patients who do not show significant psychiatric/medical comorbidities, a unidimensional approach (pharmacotherapy) is often the most cost-effective treatment route. Among responders, venlafaxine extended-release (XR) has shown particular efficacy in treating to remission.

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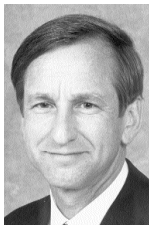


Response to Remission: Significance

GAD is a condition with tens of millions of victims in the United States. The lifetime risk of GAD for the general population has been listed at 5%. It is important to ask how we can do better in dealing with this condition. How can we diagnose GAD earlier and treat it more effectively, to remission? The earlier, more effectively, and more completely we treat GAD, the more we lessen the substantial burden of the condition, which stretches from personal to familial to financial. GAD is often chronic and persistent, and it takes a real effort on the part of clinicians to treat to remission.

When Is Treatment Complete?

There are several questions that the clinician should ask when trying to judge whether treatment in GAD is complete: Are there any residual symptoms? Are there ongoing functional impairments? Is there any ongoing behavioral component? If the answer to any of these questions is "yes," then the treating clinician should be aware that there is additional work to be done.

Psychotherapy for GAD

It is critical to keep in mind the importance of psychotherapy in the treatment of GAD, particularly in the primary care setting. With panic disorders, obsessive-compulsive disorders, and most probably social anxiety disorder and GAD, a patient's life circumstances or character patterns contribute to their symptoms. In these cases, pharmacotherapy alone is less likely to lead to a complete remission. Martie Keller and colleagues at xx completed a depression study showing how medication plus psychotherapy leads to significant treatment efficacy in patients. We simply should not forget about the importance of a psychosocial component in the treatment of anxiety-based disorders and GAD.

Pharmacotherapy for GAD

Meoni, Hackett, and Montgomery have show that venlafaxine XR can treat responders to remission in GAD. The longitudinal, 6-month study involved xx patients and compared venlafaxine to placebo. Remission in the study was defined as a 70% reduction in symptoms. The average venlafaxine dose in the study was 225 mg/day, which is somewhat high when looking at the primary care setting, but optimistic from the point of hanging in there with a treatment and giving it time to work.The study revealed that by month 6, the remission rate among patients on venlafaxine XR doubled over what it had been at week 6.

In the primary care setting, it seems that it is easy, when someone complains of nervousness or of being keyed up or tense, to administer a benzodiazepine and, without much effort, see what comorbidities are present. It is difficult to find a GAD patient without comorbidities. The rule is comorbidities, not the exception. If the thinking changed in the general medical arena, to where with anxiety the choice was not to treat directly with a benzodiazepine but with one of the newer antidepressants—venlafaxine, for example, now has a GAD indication—I think these are the much more appropriate mediations, suited to the condition and to long-term treatment.

It is important to be patient during the treatment process. Often, those who come in for the treatment of GAD have had the condition for decades. It is a major event when the pattern of decades of time begin to yield to any sort of therapy.

Failing to Achieve Remission: Consequences

If the clinician does not achieve remission in GAD, the patient faces a greater risk of relapse, worsened prognosis of comorbid conditions and Axis 3 disorders, and increased utilization of medical services. This point is particularly relevant to the primary care setting. Often, in the primary care environment GAD is present as somatic complaints. A partial response to medication would likely decrease complaints by some degree, but incompletely, at least theoretically. One of the more important aspects of achieving remission are the benefits to the primary care physician of not having to continue along with the somatic complaints that are often a part of GAD in the medical setting.

Jack M. Gorman is professor of psychiatry and vice chair for research at Columbia University College of Physicians and Surgeons in New York City. He is also the editor of CNS Spectrums.

GAD: Psychosocial Interventions

Compared to the other anxiety disorders, there has been a lag in developing effective psychosocial interventions for GAD, mostly because we did not have that concept of the condition until more recently. Nevertheless, a number of manualized treatments for GAD have been studied in rigorous controlled trials, and the outcomes are very good. Cognitive behavioral therapy and stress management are viable treatment options. These therapies tend to focus, as most of the therapies for anxiety disorders do, on relaxation and cognitive restructuring, and primarily on helping the patient recognize cues in the environment that trigger their anxiety. One of the clear things about GAD patients is that they become inured to elements in the environment that make them anxious. They are so used to being anxious that they do not notice that there are actually environmental events that are responsible for their developing anxiety. By making those factors more obvious, you can help the patient control their anxieties better. Also of note, there is an advantage to getting patients into psychotherapy at the same time that they are on medication, because they then seem to better tolerate medication side effects.

The dropout rates for cognitive behavioral therapy tend to be much higher in randomized trials. In trials, we tend to apply much more rigorous criteria (who is a completer, who is not, etc). The field really needs head-to-head comparisons of psychosocial interventions, including an arm where there is a combination of medication and psychotherapy.

Longitudinal Management

GAD is a chronic illness and many patients require long-term therapy. Most clinicians will usually treat a patient for at least a year with medication after they have responded, and then they may discuss with the patient the possibility of a slow tapering of the medication, explaining that their medication may need to be started up again at a later date if symptoms redevelop Given the fact that GAD treatment is often long-term, it is very important to initially select an agent that the patient is going to be able to safely and comfortable use for an extended period of time.

Benzodiazepine Therapy

In a significant number of head-to-head studies comparing benzodiazepines to antidepressants, benzodiazepines are shown to work more quickly in a patient. However, by week 6 or 8 of the trial, antidepressants are shown to be working more effectively. The data thus suggests that benzodiazepines simply do not work as well in GAD as the antidepressants. In addition, benzodiazapines will not treat comorbid depressive symtoms or prevent the potential onset of depression.

We have to remember that long-term use of benzodizapines has side effects. Patients may complain about daytime sedation, memory problems, and motor impairment, especially in the elderly. A patient may also become physically dependent on the benzodiazepine, making it difficult to terminate treatment. In sum, there really is not a very good case to be made for benzodiazepines as monotherapy or long-term therapy for GAD.

Medication Options

Buspirone is a useful medication devoid of many of the risks seen with the benzodiazepines.

Buspirone is indicated for GAD, but it is not an antidepressant, so it will not treat comorbid depression or depressive symptoms. This is a very important issue in GAD treatment.

Buspirone and venlafaxine were compared in a study by xx. On many measures, the two medications showed equal efficacy. Venlafaxine, however, showed superior efficacy in xx. We can thus conclude that venlafaxine is probably more potent than buspirone for GAD, and certainly better for treating comorbid depressive symptoms, but buspirone is still certainly a useful medication to consider in treating the condition.

Q&A

Until recently, there have not been many studies on GAD treatment. Why has this been the case?

Daniel Christensen: GAD is a relatively new diagnosis. The first time we had this phrase was 1980. Even though that is 21 years, GAD was considered to be a residual category for patients who did not have panic disorder. Also, the criteria for GAD underwent several phases of change. When the National Comorbidity Survey came out, however, it was revealed that the rate of GAD is high—a 5% lifetime risk. And that surprised people.

As a clinician, do you think that GAD takes longer to achieve remission?

Jack Gorman: I think so, because it is hard to eradicate all of a patient's worries, and data shows that the more severe the illness is, the longer it takes to achieve remission. The clinician has to be persistent and willing to titrate to a high enough medication dosage, deal with adverse side effects, and encourage the patient to continue with treatment .

DC: As much as with any other disorder, I think GAD simply becomes a lifestyle of the patient. So often we see the disease history tracing back into a patient's childhood years. They were always a worrier, they were always uncomfortable, and so forth. Regarding treatment, we simply have to be patient.

Philip Ninan: That is true. I saw a patient, a woman in her early fifties, who had GAD and a number of other conditions—depression, alcohol abuse. When she was on a selective serotonin reuptake inhibitor she showed a 50% reduction in symptoms. When I switched her to venlafaxine, she eventually achieved remission for GAD and her comorbid conditions. What was remarkable was that this was a woman who, all of her life, had been very symptomatic. She said that for the first time in her life she was able to focus on elements of her life other than worries—spirituality, etc.; she had been so preoccupied with symptoms before that such an effort had been impossible. When we control symptoms over time, it frees the patient and allows him or her to examine their potential. They are then much more likely to have a full pursuit of happiness.

Is there data on GAD and gender differences?

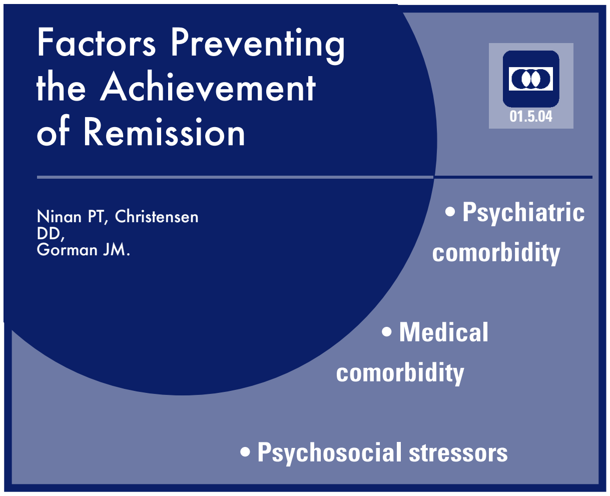
DC: I do not know of any data, but I can speculate. If you think of males as having more comorbidities—Wittchen and colleagues published a paper a while ago stating that in about two thirds of males, GAD is comorbid and in two thirds in females GAD is less comorbid, or "pure." I think that does complicate the issue. Any time we have comorbidities, it raises the bar a bit because we have the complication of, for example, depression, or substance abuse, or personality disorder, etc. My speculation would be that GAD in males would be more difficult to treat to remission.

In depression, we have a categorization of acute treatment, continuation treatment, and maintenance treatment, and relapse and recurrence are defined based on the treatment phase that one is looking at. Does this translate in GAD?

JG: It is a little harder in GAD than in depression. We don't have the data to tell us what the risk of relapse is in someone who has already remitted. So we don't have the concept of recurrent GAD in the same way that we have the concept of recurrent depression.

Is the superior efficacy of a dual action drug, such as we see in depression, going to be replicated in GAD, or are we going to see equivalent benefits among single and dual action drugs?

JG: We have evidence from the venlafaxine studies that higher doses of venlafaxine are better than lower doses. The higher the dose, the more recruitment we have of the norepinephrine effect. I think it is almost certainly the case that dual action makes a big difference in treating GAD.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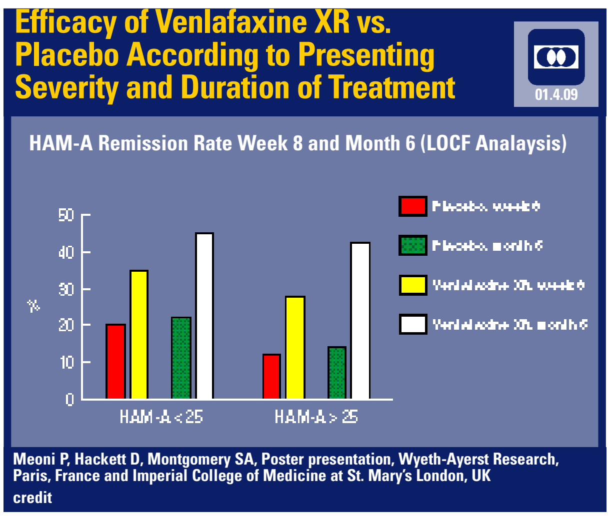
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HAM-A Remission Rate Week 8 and Month 6 (LOCF Analaysis)
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10
20
30
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50
HAM-A < 25
HAM-A > 25
Meoni P, Hackett D, Montgomery SA, Poster presentation, Wyeth-Ayerst Research, Paris, France and Imperial College of Medicine at St. Mary's London, UK
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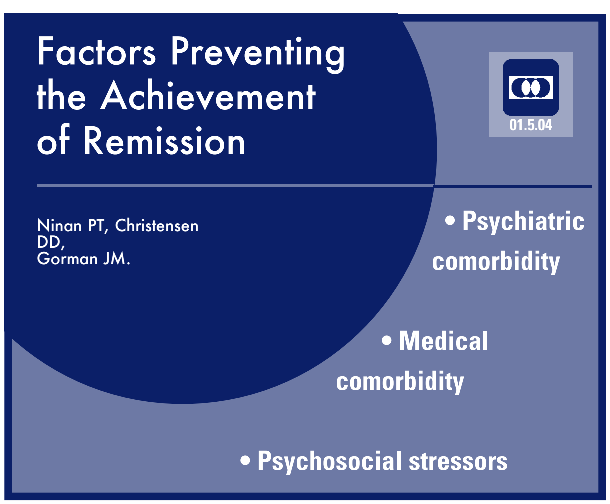
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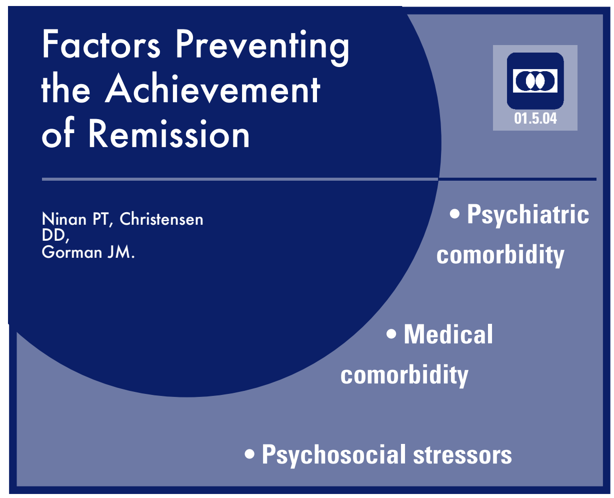
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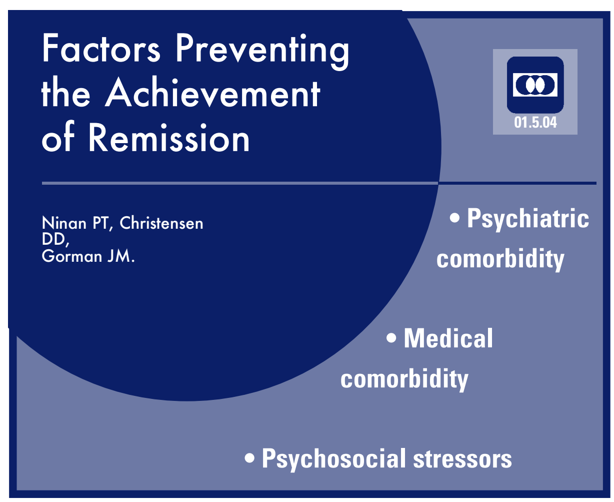
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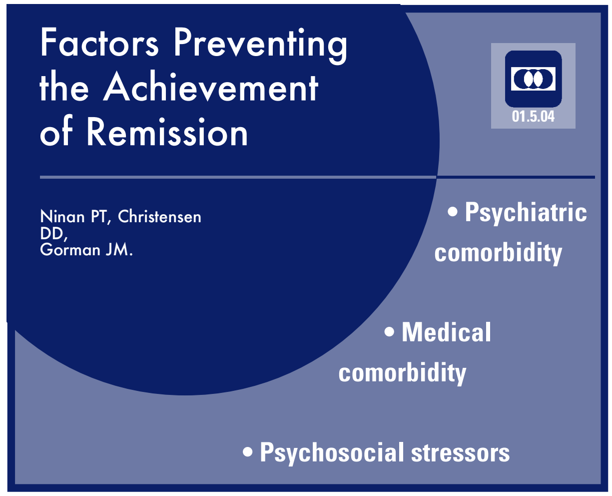
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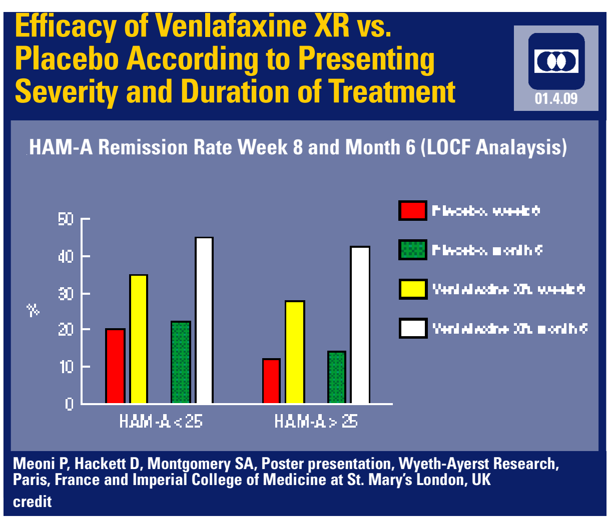
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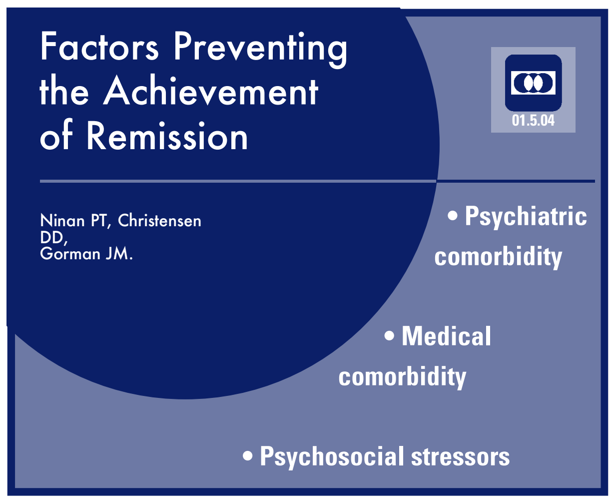
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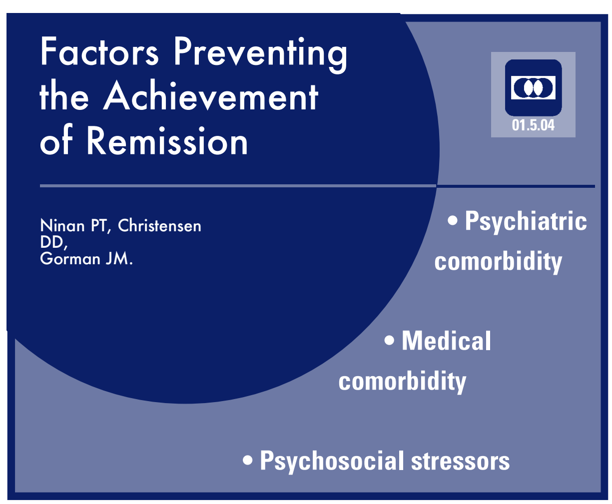
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