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Generalized Anxiety Disorder

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Synonyms

Anxiety neurosis; Free-floating anxiety; GAD

Definition

Generalized anxiety disorder (GAD) is characterized by an excessive and inappropriate worrying that is persistent and not restricted to particular circumstances. Patients have physical anxiety symptoms (such as tachycardia and tremor) and key psychological symptoms, including restlessness, fatigue, difficulty in concentrating, irritability, and disturbed sleep. The disorder is common and disabling; a recent review of epidemiological studies in Europe suggests a 12-month prevalence of between 1.7 % and 3.75 % (being more common in old age), and the associated functional impairment is similar to that with major depression. However, many of those who might benefit from treatment are not recognized or treated, which is disappointing, as a broad range of evidence-based treatments is available.

Role of Pharmacotherapy

Efficacy in Acute Treatment

Current evidence-based guidelines for the pharmacological management of patients with GAD recommend initial treatment with either a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI), on the basis of proven efficacy and reasonable tolerability in randomized placebo-controlled trials (Baldwin et al. 2005; Bandelow et al. 2008). Approximately, 40–60 % of patients will "respond" to placebo and 60–75 % to the SSRIs escitalopram, paroxetine, or sertraline, when using global measures of improvement. Similar findings are seen for the SNRIs duloxetine or venlafaxine and for the anxiolytic drug pregabalin (Baldwin and Ajel 2007). Symptom severity on the primary outcome measure, traditionally the Hamilton Rating Scale for Anxiety (HAM-A), can be reduced markedly, but many patients remain troubled by distressing anxiety symptoms at study end point, despite seemingly making a good overall "response" to treatment.

Benzodiazepines are also efficacious in providing a rapid reduction in symptoms in many patients; they have similar overall efficacy rates to the best-established psychological treatment, cognitive therapy. However, they are usually ineffective in relieving comorbid depressive symptoms, and unwanted effects include sedation, disturbance of memory, and psychomotor function; other potential problems include development of tolerance, abuse and dependence, and distressing

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withdrawal symptoms. Because of these, it is advisable to restrict the use of benzodiazepines to short-term treatment (up to 4 weeks) or to reserve them for patients who have not responded to at least two previous treatments and who remain distressed by severe and impairing anxiety symptoms (Baldwin et al. 2005; Tyrer and Baldwin 2006).

Very few randomized controlled trials (RCTs) have directly assessed the relative efficacy of different drugs, when compared with placebo. An analysis of RCT findings found an overall mean effect size of 0.39, with pregabalin having the highest effect (0.50) and the azapirone anxiolytic buspirone the lowest effect (0.17) (Hidalgo et al. 2007). A systematic review and meta-analysis based on a mixed treatment comparison (Baldwin et al. 2011) suggests that, among licensed treatments for GAD, duloxetine had advantages in terms of response, escitalopram in terms of response, and pregabalin in terms of tolerability. There is much scope for developing pharmacological treatments with greater overall efficacy (Baldwin 2008).

Prediction of Response to Treatment

It is hard to predict reliably which patients will make a good response to treatment. Greater severity but shorter duration of symptoms, more pronounced impairment, and the presence of comorbid depressive disorders may predict a greater likelihood of response to antidepressant medications. Lower symptom severity, a history of benzodiazepine treatment, and the presence of comorbid personality disorders may be associated with a lesser chance of responding. Similar difficulties are seen when deciding how long the initial drug treatment in GAD should continue before it is reasonable to conclude that the chance of responding is too low to justify proceeding with the current approach. Nevertheless, some analyses show that an onset of efficacy (defined as a reduction in HAM-A score by 20 % or more) after 2 weeks of treatment is strongly predictive of response at the study end point for duloxetine (Pollack et al. 2008), escitalopram (Baldwin et al. 2009), pregabalin, alprazolam, and venlafaxine (Baldwin et al. 2012).

Prevention of Relapse

GAD is usually regarded as a chronic disorder, waxing and waning in severity over many years, although many patients have a more episodic course, with periods of anxiety symptoms and intervening improved health. Unlike the situation in recurrent unipolar depression, where continuation of antidepressant treatment beyond initial response substantially reduces the risk of early relapse and later recurrence of depressive symptoms, the value of long-term treatment in GAD is less well established due to the limited number of relapse prevention studies. Eight studies with this design demonstrate the value of continuing pharmacological treatment, with agomelatine, duloxetine, escitalopram, paroxetine, pregabalin, quetiapine, venlafaxine, and vortioxetine.

Further Management After Nonresponse to Initial Treatment

Much uncertainty continues about subsequent stages in patient management after a poor response to first-line treatment. Commonly employed interventions include an increase in dosage, a switch to another evidence-based drug treatment, an augmentation with an additional psychotropic agent, and the combination of medication with a psychological treatment. There is no published dosage escalation study in GAD, in which patients either continue with the initial low dose or are switched to a subsequent higher dose; the findings of fixed-dose randomized placebo-controlled studies do not provide consistent evidence that higher doses are more efficacious. Most guidelines recommend an SSRI for first-line pharmacological treatment; so, common second-line approaches include an SNRI, buspirone, the tricyclic antidepressant imipramine, pregabalin, or a benzodiazepine. Buspirone is more efficacious when GAD patients have not previously been treated with

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a benzodiazepine; so, it makes sense to consider the use of buspirone before prescribing a benzodiazepine anxiolytic (Chessick et al. 2006).

Some doctors recommend an antipsychotic drug after nonresponse to SSRI or SNRI treatment, perhaps fearing the development of tolerance or dependence with the use of benzodiazepines. The conventional neuroleptic drug trifluoperazine has proven efficacy in acute treatment, and more recently, the second-generation antipsychotic drug quetiapine has also been found efficacious in placebo- and comparator-controlled studies. However, the adverse effect profile and potential long-term risks of antipsychotics should usually lead them to be reserved for patients who have not responded to earlier SSRI treatment, perhaps followed by an SNRI treatment. Both risperidone and olanzapine can enhance the efficacy of SSRI treatment, on at least some measures, and other potential alternative augmentation approaches include the use of pregabalin (Rickels et al. 2012), or the novel antidepressant drug agomelatine, which has recently been found efficacious (Stein et al. 2008). Combining pharmacological interventions with psychological interventions is often advocated for patients with anxiety disorders, but in GAD, it is uncertain whether the combination treatment is superior to psychological or drug treatment given alone (Bandelow et al. 2007).

Tolerability of Current Treatments

The acceptability to patients of prescribed medication is an important consideration, particularly when recommending long-term treatment. The adverse effects of SSRIs and SNRIs, including headache, nausea, and increased nervousness, and the drowsiness associated with benzodiazepines and pregabalin, usually diminish after a few weeks, though other side effects can become more important over subsequent months. Common concerns during longer-term treatment with SSRIs or SNRIs include the development of sexual dysfunction, weight gain, persistent disturbed sleep, and the potential for experiencing discontinuation symptoms on stopping the treatment. Many prescribers regard the latter as meeting criteria for withdrawal syndromes.

Withdrawal syndromes are common with many classes of psychotropic drugs, including SSRIs, SNRIs, and benzodiazepines. Symptoms are typically mild and usually transient, but many patients report severe and distressing symptoms, despite gradual discontinuation by tapering the prescribed dose of medication. Compounds differ in their propensity to cause discontinuation symptoms (Baldwin et al. 2007), but it is hard to predict which patients will be the most affected. Gradual withdrawal ("tapering") is often advised in the hope of minimizing symptoms, but this is not fully established. Although it may minimize the symptoms, it may not obviate them entirely. There continues to be a need for withdrawal studies with a randomized double-blind staggered design, in which patients and doctors are unsure of whether treatment ends slowly or swiftly, or when the dosage reduction has actually occurred.

Cross-References

- ► Anticonvulsants
- ► Antidepressants
- ► Antipsychotics
- ► Benzodiazepines
- ► Randomized Controlled Trials
- ► SSRIs and Related Compounds
- ► Withdrawal Syndromes

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