Volume 3 • Number 2 • 2007

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Treatment of generalized anxiety disorder

Anxiety disorders—generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder (PD), post-traumatic stress disorder (PTSD), and social anxiety disorder (SAD)—are common, persistent, and cause substantial impairment. With lifetime prevalence estimates of over 25%, they constitute a group that is the most frequently occurring of psychiatric disorders (Kessler et al 1994). They are also expensive, with the annual cost of anxiety disorders in the US estimated to be US$42.3 billion in 1990 and US$65 billion in 1994 (Greenberg et al 1999), representing a substantial burden in the direct costs of medication and psychotherapy as well as indirect costs associated with impaired functioning in social, educational, and employment aspects of life. Traditionally, anxiety disorders were treated with benzodiazepines, and despite the shortcomings of these agents in terms of long-term use and habituation, they are still widely prescribed, especially diazepam and lorazepam. Newer variations like clonazepam and alprazolam have also found their place. The 5-HT1A partial agonist buspirone has proven efficacy in anxiety disorders, as do some psychological treatments, especially cognitive behavior therapy (CBT). However, treatment of all anxiety disorders has largely been taken over by the selective serotonin reuptake inhibitors (SSRI) group of antidepressants to the extent that the anxiety disorders have become known as the 'serotonergic disorders' (Aouizerate et al 2005). Indeed many national guidelines for the management of anxiety disorders recommend the use of SSRIs as first-line treatment (Baldwin et al 2005; CADTGI 2007).

Neuropsychiatric Disease and Treatment has previously published several articles on anxiety disorders, including adult (Aouizerate et al 2005) and pediatric OCD (Lewin et al 2006) as well as a review of the use of one SSRI, fluvoxamine, in the treatment of anxiety disorders particularly OCD (Irons 2005). Efficacy in anxiety disorders is not confined to SSRIs, however, and most antidepressants, particularly but not exclusively those with a serotonergic arm to their pharmacology, are in fact anxiolytic – in the previous issue of the journal, the efficacy of the SNRI venlafaxine in panic disorder was reviewed (Katzman and Jacobs 2007). In this issue the focus is on the treatment of generalized anxiety disorder (GAD).

Generalized anxiety disorder is among the most common of mental disorders in primary care, with a reported 12-month and lifetime prevalence in Europe of 1.5% and 5.1%, respectively (Lieb et al 2005). It is characterized by excessive and inappropriate worrying that persists for 6 months or more and is not restricted to particular circumstances. Six key symptoms include restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and disturbed sleep, 3 of which must be present for the diagnosis (APA 2000). It is associated with increased use of mental health services, especially for patients with significant co-existing depressive symptoms who show a more severe and persistent course and greater functional impairment. Effective acute treatments include CBT, alprazolam, and benzodiazepines like diazepam and lorazepam, some SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs), buspirone, the antipsychotic trifluorperazine and the antihistamine hydroxyzine (Baldwin et al 2005; Baldwin and Polkinghorn 2005). Psychological symptoms of anxiety may respond better to antidepressants than to benzodiazepines. Continuation

of CBT or an SSRI or SNRI for longer periods is associated with an increase in overall response and helps to prevent relapse (Baldwin et al 2005).

There is a need for improvement in the treatment of GAD because the ideal anxiolytic drug does not exist, while CBT is not universally available especially in primary care where the majority of GAD patients first present. In this issue, two views from either side of the Atlantic are presented on the potential role of pregabalin in the treatment of GAD (Baldwin and Ajel 2007; Strawn and Geracioti 2007). Pregabalin is already approved in many countries for the treatment of chronic neuropathic pain and some forms of epilepsy. Its mechanism of action differs from that of known past treatments for GAD – although structurally related to GABA, pregabalin neither binds to benzodiazepine, $GABA_A$ or $GABA_B$ receptors, nor affects GABA currents in the brain. It seems to bind to the $\alpha_2\delta$ sub-unit of brain voltage-gated N-type calcium channels, thereby decreasing presynaptic calcium currents and consequently lowering the release of a number of neurotransmitters which have been shown to be involved in the pathophysiology of GAD such as glutamate, substance P, and noradrenaline.

The efficacy of pregabalin in the acute treatment of GAD and prevention of relapse is well established in a series of randomized, placebo-controlled trials. When compared with existing treatments, it may offer an earlier onset of action than venlafaxine and better efficacy across the range of psychological and somatic symptoms of anxiety than alprazolam or lorazepam. No specific antidepressant effects have yet been demonstrated and there is no study comparing pregabalin with either CBT or a SSRI in GAD, which is problematical since most GAD patients in clinical settings have significant co-existing depressive symptoms. The major side effects are dizziness and somnolence, while weight gain may be a problem, but in acute treatment studies pregabalin was generally better tolerated than benzodiazepines and venlafaxine. All-in-all, pregabalin is a promising newcomer for the treatment of GAD which may ultimately prove to be a viable alternative to current therapies. However, more (clinical) research is needed!

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