Pharmacological Treatment of Generalized Anxiety Disorder

David S. Baldwin, Khalil I. Ajel, and Matthew Garner

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Abstract Generalized anxiety disorder (GAD) is common in community and clinical settings. The individual and societal burden associated with GAD is substantial, but many of those who could benefit from treatment are not recognized or treated. Recent evidence-based guidelines for the pharmacological management of patients with GAD have recommended initial treatment with either a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI), on the basis of their proven efficacy and reasonable tolerability in randomized placebo-controlled trials.

However, there is much room for improvement in both the efficacy and the tolerability of treatment. Response rates to first-line treatment can be disappointing and it is hard to predict reliably which patients will respond well and which will

D.S. Baldwin (✉)
Clinical Neuroscience Division, School of Medicine, University of Southampton, Southampton, UK; University Department of Mental Health, Royal South Hants Hospital, Brintons Terrace, Southampton, SO14 0YG, UK
e-mail: dsb1@soton.ac.uk

K.I. Ajel
Mood and Anxiety Disorders Service, Hampshire Partnership Trust, Southampton, UK

M. Garner
School of Psychology, University of Southampton, Southampton, UK

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have only a limited treatment response. Many patients worry about becoming dependent on medication, a substantial proportion experience troublesome adverse effects, and these problems limit the effectiveness of pharmacological treatments in clinical practice.

The relative lack of longitudinal studies of clinical outcomes in GAD, and the small number of placebo-controlled relapse prevention studies lead to uncertainty about the optimal duration of treatment after a satisfactory initial response. There have been few investigations of the further management of patients who have not responded to first-line treatment and there is a pressing need for further augmentation studies in patients who have not responded to an SSRI or SNRI, or to other initial pharmacological approaches.

Future treatment guidelines for GAD will be influenced by emerging data for established and novel pharmacological approaches, and possibly through the more accurate identification of certain patient subgroups who are likely to respond preferentially to particular interventions.

Keywords GAD · Treatment · SSRI · SNRI · Pregabalin

1 Clinical Features, Epidemiology and Burden of GAD

GAD is characterized by excessive and inappropriate worrying that is persistent (lasting some months in ICD-10, and 6 months or longer in DSM-IV) and not restricted to particular circumstances. Patients have physical anxiety symptoms (such as tachycardia and tremor) and key psychological symptoms, including restlessness, fatigue, difficulty concentrating, irritability, and disturbed sleep (Tyrer and Baldwin 2006).

The disorder is common in both community and clinical settings. A recent review of epidemiological studies in Europe suggests a 12-month prevalence of 1.2–1.9%, and a lifetime prevalence of 4.3–5.9%: "comorbidity" with major depression is seen in three out of five cases, and a similar proportion of individuals have other anxiety disorders (Wittchen and Jacobi 2005). The functional impairment associated with GAD is similar in severity to that with major depression (Kessler et al. 1999; Wittchen et al. 2000). Patients with comorbid major depression and GAD have a more severe and prolonged course of illness, and greater impairment of social and occupational function (Judd et al. 1998; Tyrer et al. 2004). The disorder is more common in women than in men, with a mean age of onset that is somewhat later than with other anxiety disorders: it is probably the most common anxiety disorder among the population aged 55–85 years (Beekman et al. 1998).

GAD is one of the most common mental disorders in primary care settings, and is associated with increased use of health services. However, only a minority of patients present with anxiety symptoms, and GAD often goes unrecognized as doctors

tend to overlook anxiety unless it is a presenting complaint. Patients with comorbid depression are more likely to be recognized as having a mental health problem, though not necessarily as having GAD (Weiller et al. 1998; Wittchen et al. 2002).

2 Response Rates to Initial Treatment in GAD

The findings of randomized controlled trials show that 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, usually the Clinical Global Impression of Improvement Scale (CGI-I) (Guy 1976). Similar findings are seen in randomized controlled trials with the SNRIs duloxetine or venlafaxine, and with the novel anxiolytic drug pregabalin (Baldwin and Ajel 2007) (Table 1). There can be a striking reduction in symptom severity on the primary outcome measure, traditionally the Hamilton Rating Scale for Anxiety, HAMA (Hamilton 1959): for example, a decline from baseline in mean HAMA score of over 15 points with the optimal 10 mg/day dosage in a recent randomized controlled trial with escitalopram (Baldwin et al. 2006a). However, many patients remain troubled by significant symptoms at study end point, despite seemingly making a good overall "response" to treatment, according to the CGI-I score.

A systematic review of the findings of randomized controlled trials has established that benzodiazepines are an efficacious and rapid treatment for many patients with GAD, having similar overall efficacy to the psychological treatment cognitive therapy (Gould et al. 1997). However, benzodiazepines have limited efficacy in relieving comorbid depressive symptoms, and unwanted effects include sedation, disturbance of memory, and psychomotor function. These problems limit the overall effectiveness of benzodiazepines, as many patients discontinue treatment before the occurrence of optimal anxiolytic efficacy (Martin et al. 2007). Other potential problems include the development of tolerance, abuse or dependence, and distressing withdrawal symptoms on stopping the drug (Tyrer et al. 1983; Rickels et al. 1988). Because of these difficulties, general guidance is to use benzodiazepines only for short-term treatment (up to 4 weeks) (Baldwin et al. 2005), or in patients who have not responded to at least two previous treatments, and who remain troubled by severe, distressing, and disabling anxiety symptoms (Baldwin and Polkinghorn 2005; Nutt, 2005).

Unlike the situation in major depressive disorder, there is as yet no general consensus on what constitutes symptom remission in GAD (Ballenger et al. 1999). A post hoc analysis of randomized controlled trials with escitalopram (Bandelow et al. 2006) indicates that a HAMA score of 9 or less corresponds to the category of "borderline ill" on the CGI Severity scale (Guy 1976). Using this cut-off score, 56% of patients treated with the optimal dosage of escitalopram had remitted at the end of double-blind treatment (and 47.9% when using a lower HAMA cut-off score, of 7 or less) in the escitalopram study (Baldwin et al. 2006a). The post hoc analysis of data from the extensive clinical trial program for paroxetine using this more

Table 1 Generalized anxiety disorder: response rates in double-blind placebo-controlled studies of acute treatment with SSRIs, SNRIs or pregabalin

Study	Treatment	Dose (mg/day)	Length (Weeks)	Active response (%)	Placebo response (%)
SSRI treatment					
Pollack et al. (2001)	Paroxetine	20–50	8	62	56
Rickels et al. (2003)	Paroxetine	20, 40	8	61.7*, 68***	45.6
Rynn et al. (2001) (children)	Sertraline	≤50	9	90***	10
Allgulander et al. (2004)	Sertraline	50–150	12	63***	37
Brawman-Mintzer et al. (2006)	Sertraline	50–200	10	59.2*	48.2
Davidson et al. (2004)	Escitalopram	10–20	8	58**	38
Goodman et al. (2005)	Escitalopram	10–20	8	52***	37
Pooled analysis, three studies					
Baldwin et al. (2006a)	Escitalopram	5, 10, 20	12	70.9, 78.4**, 74.2*	63
	Paroxetine	20		66.2	
SNRI treatment					
Koponen et al. (2007)	Duloxetine	60, 120	9	63***, 65***	34
Rynn et al. (2008)	Duloxetine	60–120	10	40^{a,*}	32^{a}
Hartford et al. (2007)	Duloxetine	60–120	10	56**	42
	Venlafaxine	75–225	10	60***	
Davidson et al. (1999)	Venlafaxine	75, 150	8	62**, 49	39
	Buspirone	30		55*	
Gelenberg et al. (2000)	Venlafaxine	75–225	28	67***	33
Rickels et al. (2000)	Venlafaxine	75, 150, 225	8	NS, NS*	NR
Allgulander et al. (2001)	Venlafaxine	37.5, 75, 225	24	63**, 73***, 81^{***,b}	47^{a}
Lenox-Smith et al. (2003)	Venlafaxine	75–225	24	65**	46
Rynn et al. (2007)	Venlafaxine	Flexible dose in children 6–17 years	8	69*	48
Pregabalin treatment					
Pande et al. (2003)	Pregabalin	150, 600	4	NS, 47*	28
Pande et al. (2000)	Pregabalin	150, 600	4	No significant difference in efficacy for any treatment versus placebo	
	Lorazepam	6			

Feltner et al. (2003)	Pregabalin	150, 600	4	47.8, 49.2	42.4
	Lorazepam	6		56.3	
Rickels et al. (2005)	Pregabalin	300	4	61***	31
	Alprazolam	450		44	
		600		51**	
		1.5		45*	
Montgomery et al. (2006)	Pregabalin	400, 600	6	56*,59*	42
	Venlafaxine	75		61**	
Pohl et al. (2005)	Pregabalin	200, 400, 450	6	56**, 55**, 59**	34
Momtgomery et al. (2008) (elderly patients)	Pregabalin	150–600 (mean maximal 270)	8	58.4	48.4
Kasper et al. (2009)	Pregabalin	300–600	8	59	46
	Venlafaxine	75–225		44	

*$p<0.05$; **$p<0.01$; ***$p<0.001$, advantage for active treatment over placebo

[a]response defined as $\geq$50% reduction in HAMA score; [b]estimates from published figure; NR, not reported; NS, not significantly different from placebo

stringent criterion found that only 36% of patients undergoing double-blind treatment with paroxetine had remitted at study end point (Rickels et al. 2006).

Only few randomized controlled trials permit assessment of the relative efficacy of different treatments when compared to placebo. However, a recent analysis of findings from randomized controlled trials found an overall mean effect size of 0.39, with some differences between medication class: pregabalin, 0.50; the antihistamine hydroxyzine, 0.45; SNRI, 0.42; benzodiazepines, 0.38; SSRI, 0.36; and the azapirone anxiolytic buspirone, 0.17 (Hidalgo et al. 2007). The overall effect size in this analysis is somewhat higher than that from a previous meta-analysis (0.33) (Mitte et al. 2005), which possibly reflects differences in publication selection criteria. Estimations such as these represent post hoc analyses of pooled data, derived from randomized controlled trials that differ in design and which were not powered for the demonstration of particular levels of effect size, so care must be taken when comparing relative effect sizes. Nevertheless, there is much scope for further improvement in developing pharmacological treatments with greater efficacy than is seen with currently available medications.

3 Prediction of Response to Pharmacological Treatment in GAD

Unfortunately it is not possible to predict accurately which patients will respond well and which will have only a limited response to treatment. A greater likelihood of response to venlafaxine or the SSRI fluoxetine is associated with a shorter duration of symptoms (Perugi et al. 2002; Simon et al. 2006) and the presence of comorbid dysthymia (to venlafaxine) (Perugi et al. 2002). Other predictors of response include psychiatric comorbidity (Rodriguez et al. 2006), a history of depression or panic disorder (to venlafaxine) (Pollack et al. 2003), and the severity of psychosocial impairment (Rodriguez et al. 2006). A lower likelihood of response to escitalopram treatment is seen with lower baseline symptom severity (Stein et al. 2006), and a history of benzodiazepine use is associated with lower response to treatment with venlafaxine (Pollack et al. 2003). The presence of comorbid depressive symptoms probably does not reduce the overall response to treatment in patients with primary GAD, for the reason that although comorbid depression may delay the response to venlafaxine (Pollack et al. 2003), it does not substantially reduce overall response rates with escitalopram (Stein et al. 2005) or pregabalin (Stein et al. 2008), or affect the degree of reduction in anxiety symptoms with fluoxetine treatment (Olatunji et al. 2008).

Similar difficulties are seen in deciding how long initial treatment in GAD should continue, before it is reasonable to conclude that the chance of responding is too low to justify continuing with the current approach. An early study showed that a greater reduction in HAMA score after 1 week of diazepam treatment predicted a higher likelihood of response at 6 weeks (Downing and Rickels 1985). A limited reduction in symptom severity (i.e., a reduction in total HAMA

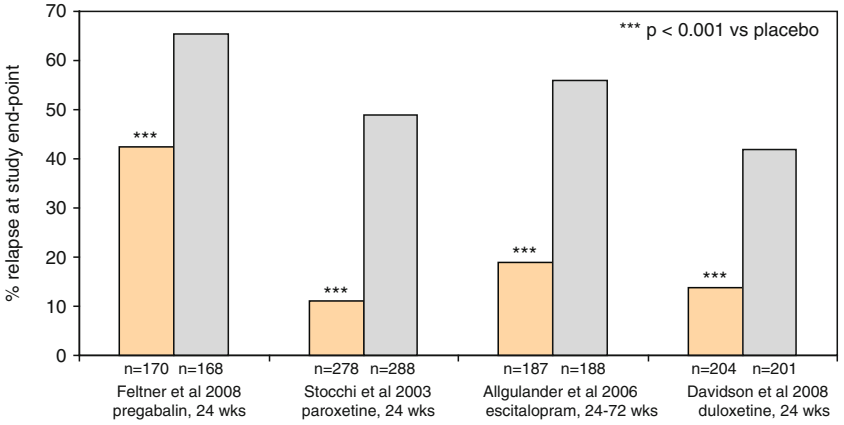

Fig. 1 Published placebo-controlled relapse prevention studies in generalized anxiety disorder

score by 25% or less) at 2 weeks of treatment predicts nonresponse to buspirone or lorazepam at 6 weeks (Laakmann et al. 1998); and the degree of response after one or 2 weeks was found to be strongly predictive of response to benzodiazepines or azapirones (or placebo) at 8 weeks (Rynn et al. 2006). Recent analyses show that the onset of efficacy (defined as a reduction in HAMA score of 20% or more) after 2 weeks of treatment is strongly predictive of response at study end point for duloxetine (Pollack et al. 2008) and escitalopram (Baldwin et al. 2009); and suggest that the likelihood of eventual response is low, if an onset of efficacy is not seen after 4 weeks of treatment (Fig. 1).

4 Optimal Duration of Treatment in GAD

Traditionally, GAD is regarded as a chronic disorder that waxes and wanes in severity over many years. In a prospective, naturalistic, longitudinal study, the probability of recovering from the index "episode" was only 58% at the end of 12 years, and over 40% of those who had recovered experienced subsequent recurrence of symptoms (Bruce et al. 2005). However, recent findings from the Zurich Study suggest there is rather more longitudinal fluidity in the diagnosis, than was previously thought (Angst et al. 2009). Continuation of antidepressant treatment beyond initial response substantially reduces the risk of early relapse and later recurrence of depressive symptoms (Geddes et al. 2003), but the value of long-term treatment in GAD is less established, due to the limited number of relapse prevention studies. Recent guidelines recommend at least 6 months of continuation treatment after initial response (Baldwin et al. 2005, Canadian Psychiatric Association 2006), but emerging data suggest that longer periods of continuation treatment may be advisable.

The value of continuation treatment in mood and anxiety disorders is usually ascertained through double-blind placebo-controlled relapse prevention studies, in

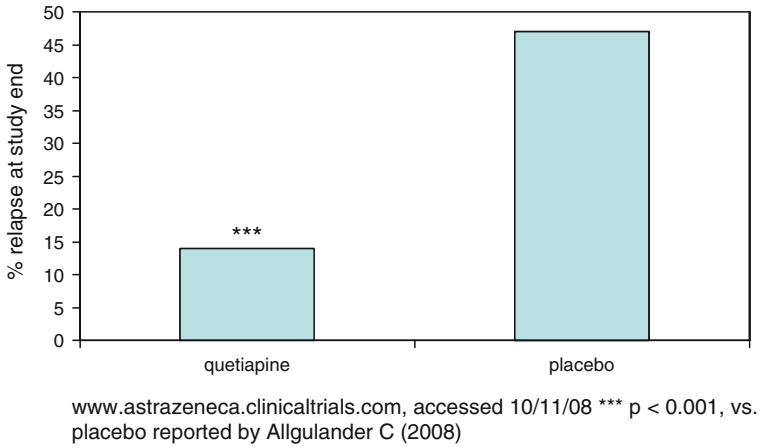

Fig. 2 Placebo-controlled relapse prevention study of quetiapine in GAD

which patients who have responded well to initial open acute treatment are randomized to either continue with active treatment, or switched to placebo. Of the five relapse prevention studies in GAD which have been published, four demonstrate the value of continuing pharmacological treatment, with escitalopram, paroxetine, pregabalin, or duloxetine (Allgulander et al. 2006; Stocchi et al. 2003; Feltner et al. 2008; Davidson et al. 2008). A formal relapse prevention study with venlafaxine did not reveal efficacy, although significantly fewer patients relapsed during venlafaxine treatment in a separate prolonged randomized double-blind placebo-controlled trial (Montgomery et al. 2002). An as yet unpublished relapse prevention study with the second generation antipsychotic drug quetiapine suggests it has some efficacy in relapse prevention (Allgulander, 2008) (Fig. 2).

The duration of double-blind treatment in the placebo-controlled relapse prevention study with escitalopram (Allgulander et al. 2006) could last for up to 18 months, so it is reasonable to recommend that treatment should continue for up to 18 months, after an initial response. The United States Federal Drug Administration has recently recommended that the double-blind relapse prevention phase in GAD studies should be preceded by 6 months of unblinded treatment (Food and Drug Administration 2006). Post hoc analyses of previously published randomized controlled trials will be able to establish whether patients with differing durations of response prior to randomization also differ in their relapse rates, and these analyses could strengthen the evidence regarding the duration of long-term treatment in GAD.

5 Management after Nonresponse to Initial Treatment in GAD

There is little consensus on the optimal next stage in patient management after a poor response to first-line treatment. Potential interventions include an increase in dosage, a switch to another evidence-based pharmacological treatment, augmentation

with an additional psychotropic drug, and the combination of medication with 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 much evidence to suggest that higher doses may be preferable. By illustration, the relative efficacy of paroxetine when compared to placebo is similar for daily dosages of 20 or 40 mg (Rickels et al. 2003), and the optimal daily dosage of escitalopram is probably 10 mg rather than 20 mg (Baldwin et al. 2006a). Furthermore, fixed-dose studies with venlafaxine have produced inconsistent findings, with evidence both for (Rickels et al. 2000) and against (Allgulander et al. 2001) a dose-response relationship. However, a recent post hoc analysis of pooled data from randomized controlled trials with pregabalin suggests that higher doses (200–450 mg/day) have greater efficacy than lower doses (150 mg/day), when both are compared to placebo (Bech 2007).

Most guidelines recommend an SSRI for first-line pharmacological treatment of GAD, on the balance of efficacy and tolerability, so common second-line drug treatments include an SNRI, buspirone, the tricyclic antidepressant imipramine, pregabalin, or a benzodiazepine. The azapirone anxiolytic drug buspirone is efficacious in GAD, more so when patients have not previously been treated with a benzodiazepine: as such, it is advisable to consider use of buspirone before prescribing a benzodiazepine anxiolytic (Chessick et al. 2006).

Despite reservations about potential adverse effects (such as weight gain and metabolic syndrome) some doctors recommend an antipsychotic drug after non-response to SSRI or SNRI treatment, perhaps fearing the development of tolerance or dependence with use of benzodiazepines. The conventional neuroleptic drug trifluoperazine has proven efficacy (Mendels et al. 1986) and more recently the second-generation antipsychotic drug quetiapine has also been found efficacious, in placebo- and comparator-controlled studies (Bandelow et al. 2007a; Meredith et al. 2008). Most probably, the adverse event profile and potential long-term risks of antipsychotics will result in their usually being reserved for patients who have not responded to earlier SSRI treatment, perhaps followed by SNRI treatment. Both risperidone and olanzapine can enhance the efficacy of SSRI treatment (Brawman-Mintzer et al. 2005; Pollack et al. 2006), but currently the evidence for augmentation with quetiapine is only limited (Katzman et al. 2008; Simon et al. 2008). Potential alternative augmentation approaches include the use of pregabalin, which can enhance the effectiveness of SSRI or SNRI antidepressants (Miceli et al. 2009), the novel antidepressant drug agomelatine, which has recently been found efficacious (Stein et al. 2008), and the novel anticonvulsant drug zonisamide (Kinrys et al. 2007). Combining pharmacological and psychological approaches is often advocated in the overall management of patients with anxiety disorders, although in GAD it is uncertain whether combination treatment is superior to psychological or drug treatment given alone (Bandelow et al. 2007a, b).

6 Tolerability of Current Treatments for GAD

The tolerability profile of prescribed medication is an important consideration, particularly when recommending long-term treatment, as is the case in GAD. Adverse effects of SSRIs and SNRIs such as increased nervousness, headache and nausea, and the drowsiness associated with benzodiazepines and pregabalin, usually resolve after a few weeks of treatment, but other side effects become more important factors in the overall acceptability of treatment for patients over subsequent months. The adverse event profile of different SSRIs and SNRI is generally rather similar, although significantly fewer patients drop out due to adverse events in short-term and medium-term randomized controlled trials with escitalopram, than with paroxetine or venlafaxine (Baldwin et al. 2007a). 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 treatment.

Treatment-emergent sexual dysfunction is probably the most common complication of SSRI treatment in depressed patients (Baldwin 2004), although some aspects of sexual function usually improve, as depressive symptoms resolve (Baldwin et al. 2006b; Baldwin et al. 2008). It is uncertain whether the same applies in the treatment of patients with GAD, in whom the complaint of loss of sexual desire is less common. Weight gain may be less troublesome with SSRIs than with many other psychotropic drugs, but the potential for gaining weight can cause concern in many patients, and there is reasonable evidence that some SSRIs can cause increases in weight of 6–10 kg after 6–12 months of treatment (Ferguson 2001). Finally, SSRIs and related drugs can have only limited benefit, or even deleterious effects, on sleep disturbance, despite beneficial effects on other depressive and anxiety symptoms (Carney et al. 2007; Cervena et al. 2005).

Discontinuation symptoms on stopping treatment are common with many classes of psychotropic drug, including SSRIs and SNRIs, as well as with benzodiazepines (Rickels et al. 1988; Baldwin et al. 2007b). Symptoms are typically mild and only transient, but many patients report severe and distressing symptoms, despite gradual discontinuation through tapering the prescribed dose of medication. Compounds differ in their propensity to cause discontinuation symptoms, but it is hard to predict which patients will be most affected. Recent research suggests that influences of diagnosis, longer duration of treatment, higher dosage, and the abrupt withdrawal of treatment are less established than previously thought (Baldwin et al. 2007b). Slow stepped withdrawal ("tapering") is often advised, in the desire to minimize the appearance of distressing discontinuation symptoms, but the value of this is not established fully and there is a need for withdrawal studies that adopt a randomized double-blind staggered design, in which both patients and doctors are unsure of whether treatment ends slowly or swiftly, or when dosage reduction occurs.

7 Conclusions

There are many psychotropic drugs and psychotherapies available for the treatment of patients with GAD, but despite this, overall clinical outcomes for many patients are often poor. The "ideal" treatment for GAD does not yet exist, as existing treatments have insufficient overall efficacy in short-term and long-term treatment and can have troublesome adverse effects when prescribed for long periods. The particular choice of treatment should be determined by the clinical features of the patient (such as the presence of comorbid depression and a history of a good response to previous treatment), patients' preferences for one approach over another and the availability of services. Doctors should counsel patients that they will not respond immediately, that sometimes symptoms can worsen in the early stage of treatment, and that long-term treatment is often needed to maintain an initial response. However, there is clearly much room for improvement, in the development of more efficacious and more acceptable pharmacological approaches in the management of this common, distressing, typically disabling, and often persistent anxiety disorder.

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