Long-Term Goals in the Management of Acute and Chronic Anxiety Disorders

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Many anxiety disorders are not treated to remission (symptom-free state); however, this should be the minimum goal of therapy. Antidepressant therapies have shown significant beneficial effects in the management of anxiety disorders, with some variability in results in specific disorders. In social anxiety disorder, selective serotonin reuptake inhibitors and venlafaxine extended release (XR) have demonstrated efficacy, with response rates varying between 40% and 68%. Monoamine oxidase inhibitors and cognitive-behavioural therapies are also effective. In patients with generalized anxiety disorder, benzodiazepines, paroxetine, and venlafaxine XR have demonstrated remission rates that are 15% to 25% higher than placebo. In patients with posttraumatic stress disorder, about 60% to 70% of patients experienced a response with antidepressant therapy, compared with about 40% on placebo, while remission rates in one study were 30% with venlafaxine, 24% with sertraline, and 20% with placebo. In patients with obsessive–compulsive disorder, a 25% to 35% improvement in symptom scores was reported in 20% to 65% of patients. In the management of panic disorder, paroxetine and venlafaxine XR doubled the percentage of patients who were panic-free, compared with placebo. Ongoing antidepressant therapy further improved remission rates, and many patients with anxiety disorders required extended treatment trials before experiencing benefit. In most clinical trials, some benefits were seen within 3 to 4 weeks but continued to accrue throughout the 3- to 6-month duration of the trial. In the acute phase, patients with anxiety disorders should be treated aggressively with antidepressants for extended periods and may require long-term therapy to maintain benefits. Cognitive-behavioural therapy is another mainstay in the treatment of all anxiety disorders; exposure to feared situations is necessary to move beyond phobic avoidance and functional impairment to full recovery, the ultimate goal of therapy.

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Clinical Implications

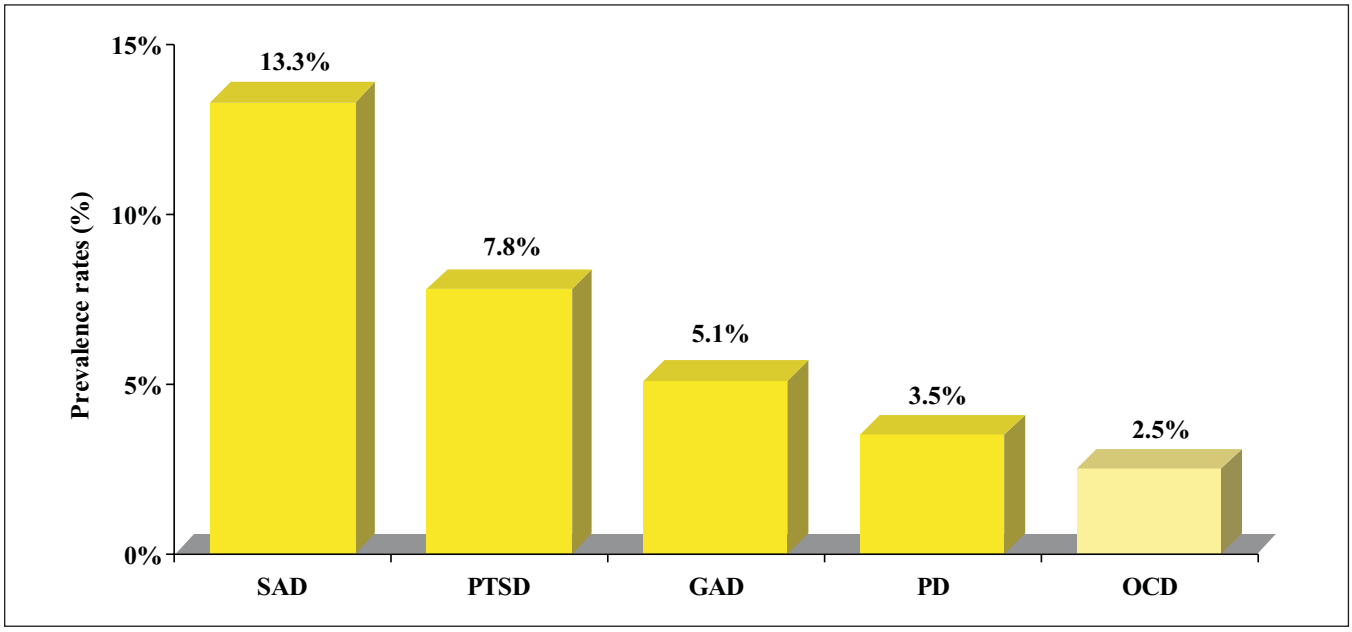
- Remission should be the ultimate goal of therapy in the treatment of anxiety disorders.
- Antidepressant therapies are effective in the management of anxiety disorders, with some variability in results in specific disorders.
- Ongoing antidepressant therapy further improves remission rates, and many patients with anxiety disorders required extended treatment before experiencing benefit.

Limitations

- This is a narrative review.
- Very few trials examined remission as an outcome of antidepressant therapy in anxiety disorders.
- Few data are available on combination and augmentation strategies to improve the rates of remission from anxiety disorders.

***Key Words*:** *anxiety, social anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder, obsessive–compulsive disorder, panic disorder, antidepressant therapy, remission, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors*

Figure 1 Prevalence of anxiety disorders in population studies: SAD, PTSD, GAD, and PD from the National Comorbidity Survey and OCD from the Epidemiological Catchment Area study



SAD = social anxiety disorder; PTSD = posttraumatic stress disorder; GAD = generalized anxiety disorder; PD = panic disorder; OCD = obsessive–compulsive disorder

As a diagnostic category, anxiety disorders are the most common psychiatric disorders, affecting an estimated 25% of the adult population at some point during their lifetimes (1). According to DSM-III-R criteria used in the National Comorbidity Survey (NCS), lifetime prevalence rates in the community are 13.3% for social anxiety disorder (SAD), 7.8% for posttraumatic stress disorder (PTSD), 5.1% for generalized anxiety disorder (GAD), and 3.5% for panic disorder (PD) (Figure 1) (1,2). Unfortunately, obsessive–compulsive disorder (OCD) was not studied in the NCS. Estimated 1-year prevalence for anxiety disorders in Canada is 12.2% (3). GAD and panic disorder are the anxiety disorders most commonly diagnosed in primary care (4). Anxiety disorders are highly comorbid, occurring in about 58% of patients with major depressive disorder (MDD) and 93% of patients with bipolar disorder (5,6).

Psychiatric disorders can be difficult to diagnose in a primary care practice (7). A large survey found that less than 14% of people with psychiatric disorders receive treatment (8). Only one-third of patients had seen a primary care physician for their mental health problems, and of those, less than 30% were receiving treatment. The burden of anxiety disorders is substantial, including not only direct costs of treatment but also the indirect costs of impaired functioning in all aspects of life (9–11).

This article reviews randomized controlled clinical trials published in the last 5 years, identified through Medline searches. Search terms included antidepressants, serotonin reuptake inhibitors (also specific agents), venlafaxine, nefazadone, mirtazapine, psychotherapy, remission, and anxiety disorders, as well as individual anxiety disorders (generalized anxiety, social anxiety, posttraumatic stress, obsessive–compulsive, and panic disorder).

Remission: The Minimum Goal of Therapy

Remission is the minimum goal in the treatment of anxiety disorders, which are often chronic. It is not uncommon for individuals to have suffered for 10 years or longer before their anxiety disorder is diagnosed. As with remission in depression (12), the remitted patient with anxiety is symptom-free. Conversely, response requires only a 25% to 50% reduction in symptoms (depending on which anxiety disorder is being treated) and does not take into consideration the severity of baseline illness; therefore, patients may have a response to treatment but remain symptomatically and functionally unwell. Recovery, the ultimate goal of therapy, requires full symptom resolution and a return to normal functioning. Table 1 reviews proposed definitions for remission of anxiety disorders (13).

Antidepressant Therapy to Achieve Remission

Comorbid Depression and Anxiety

Anxiety comorbid with depression worsens the clinical outcome and can complicate antidepressant treatment by necessitating higher dosages for a longer duration and, at times, additional or different pharmacotherapy (13). Patients should be treated to full remission of both the anxiety symptoms and depression (that is, Hamilton Anxiety Rating Scale [HARS] ≤ 7 and Hamilton Depression Rating Scale [HDRS] ≤ 7) (13).

Few studies have systematically assessed treatment of patients with comorbid MDD and anxiety disorders. Silverstone and Salinas assessed venlafaxine extended release

Table 1 Proposed objective remission goals in anxiety disorders

Anxiety disorder	Remission goals
SAD	No or minimal anxiety (HARS ≤ 7 to 10), no or minimal depression (HDRS ≤ 7), core symptoms of social anxiety have disappeared, and Liebowitz Social Anxiety Scale ≤ 30
GAD	No or minimal anxiety (HARS ≤ 7 to 10) and no or minimal depression (HDRS ≤ 7)
PTSD	No or minimal anxiety (HARS ≤ 7 to 10), no or minimal depression (HDRS ≤ 7), no or minimal PTSD symptoms, and Treatment Outcome PTSD Scale ≤ 5 or ≤ 6
PD	No or minimal anxiety (HARS ≤ 7 to 10), no or minimal depression (HDRS ≤ 7), essentially free of panic attacks, no or mild agoraphobic avoidance, and Panic Disorder Severity Scale ≤ 3 with no individual item score > 1
OCD	No or minimal anxiety (HARS ≤ 7 to 10), no or minimal depression (HDRS ≤ 7), no or minimal obsessions or compulsions, and Yale-Brown Obsessive Compulsive Scale ≤ 8

Adapted from Ballenger (26).

GAD = generalized anxiety disorder; HARS = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale; OCD = obsessive–compulsive disorder; PD = panic disorder; PTSD = posttraumatic stress disorder; SAD = social anxiety disorder

(XR) in the treatment of subjects with both MDD and GAD. Remission rates using HDRS criteria were significantly higher with venlafaxine XR (48%) and fluoxetine (48%), compared with placebo (25%), as were remission rates using HARS criteria (47%, 33%, and 28%, respectively) (14).

Data are available assessing the efficacy of selective serotonin reuptake inhibitors (SSRIs), venlafaxine XR, and other agents in patients with major depression and anxiety symptoms (Table 2). In patients with major depression, venlafaxine XR and fluoxetine significantly improved anxiety symptoms (15–17). In a pooled analysis of data from 1454 patients from 5 similar randomized controlled trials (RCTs), venlafaxine XR improved psychic anxiety as early as week 1 and demonstrated superior remission rates in patients with more severe anxiety, compared with fluoxetine (17). Remission rates in the severely anxious depression patients (HDRS psychic anxiety score > 2) were significantly higher with venlafaxine XR vs placebo starting from week 3. No difference in remission rates was seen between fluoxetine and placebo in this more anxious group. In another study, bupropion SR and sertraline had comparable antidepressant and anxiolytic effects and an equally rapid onset of clinically significant anxiolytic activity in depression patients with comorbid anxiety (18). A trial looking at the combination of nefazodone and the cognitive behavioural analysis system of psychotherapy (CBASP), which has been shown to be superior to either treatment alone for depressive symptoms, has also demonstrated greater improvements in HARS score response rates than either treatment alone (19,20). High baseline levels of anxiety did not reduce overall response in a study comparing sertraline and imipramine but did delay the onset of improvement somewhat (21). In a head-to-head trial, mirtazapine and citalopram were equally effective in reducing symptoms of depression and anxiety, but onset of improvement was faster with mirtazapine (22).

Social Anxiety Disorder

The lifetime prevalence of SAD has been estimated to be as high as 13.3% (1). People with social phobia are at increased risk for depression, suicidal ideation, increased medical utilization, and increased impairment in social, occupational, and school functioning (23,24). Remission in SAD has been defined as little or no anxiety and depression and a score of ≤ 30 on the Liebowitz Social Anxiety Scale (LSAS) (Table 1) (13,25,26). Although remission should be the goal of therapy, most recent studies report only response rates, with response defined as a Clinical Global Impression-Improvement (CGI-I) score of 1 ("very much improved") or 2 ("much improved") (Table 3).

Two recent metaanalyses reviewing studies of individuals with SAD reported effect sizes for the different SSRIs ranging from 0.3 to 1.8. It was concluded that SSRI treatment (primarily paroxetine, sertraline, and fluvoxamine) was effective, both in reducing total levels of social anxiety and in improving subjects' overall clinical condition (27,28). Response rates with SSRIs were twice those of placebo, and the odds of responding were 3 times higher with SSRIs, compared with placebo (27). Monamine oxidase inhibitors (MAOIs) demonstrated greater improvements than SSRIs in one metaanalysis but not another, while benzodiazepines were more effective in both analyses, although not significantly so (27,28).

More recent RCTs confirm the benefits of SSRIs for generalized SAD. Response rates in the range of 43% to 53% over 8 to 20 weeks of acute therapy with fluvoxamine, sertraline, and paroxetine were generally twice as high as those seen with placebo (Table 3) (29–32). However, fluoxetine was not significantly superior to placebo in a 14-week trial (33). In a

Table 2 Controlled trials of antidepressant therapy in depression with comorbid anxiety

Study details	Treatment and dosage, mg	Number completed/ enrolled (%)	Anxiety scores change vs baseline (%)	HARS response or remission rate, %	HDRS total change vs baseline	HDRS response rate ≥ 50% decrease from baseline, %	HDRS remission rate $HDRS_{21}$ ≤7 or ≤ 8, %
Silverstone and others (15) *n* = 359; 12 weeks; $HDRS_{21}$ = 27.2; HARS = 25.2	VEN 75–225	91/128 (71.1)	–13.7 (54.4)**	64*[a]	–15.9***[a]	67***[a]	48***[a]
	FLX 20–60	89/121 (73.6)	–12.4 (49.2)*	53, ns[a]	–15.2***[a]	62***[a]	46***[a]
	PBO	71/119 (60.0)	–10.2 (40.5) HARS total	40 ≥ 50% decrease from baseline	–11.1	43	22
De Nayer and others (16) *n* = 146; 12 weeks; $HDRS_{21}$ = 23.1; CAS = 8.3	VEN 75–150	49/73 (67.1)	–5.7 (69.5)	NR	–14.4**[b]	75.0**[b]	59.4*[b]
	FLX 20–40	44/73 (60.3)	–3.9 (47.0) CAS		–10.4	50.7	40.3
Trivedi and others (18) *n* = 692; 8 weeks; $HDRS_{21}$ = 25.1; HARS = 18.7	BUP 150–400	—/234 (76)	–9.9 (52.7)**[a]	NR	–14.1	65	44
	SER 50–200	—/225 (69)	–9.4 (50.5), ns		–14.1	64	48
	PBO	—/233 (70)	–8.4 (45.2) HARS total		–11.8	50	33
Ninan and others (19,20) *n* = 681; 12 weeks; $HDRS_{24}$ = 26.9; HARS = 18.1	NEF	151/226 (66.8)	–7.7 (43.8)	43.4	–11.0	48	29
	CBASP	157/228 (68.9)	–6.8 (37.4)	38.5	–10.4	48	33
	NEF + CBASP	177/227 (78.0)	–11.1 (60.3)**[c] HARS total	56.4**[c] HARS ≤ 8	–16.6	73**[c]	48**[c]

[a]Asterisks indicate significant differences vs PBO: *$P \leq 0.06$; ***$P \leq 0.001$; ns = not significant ($P > 0.06$); [b]asterisks indicate significant differences vs FLX: *$P < 0.05$; **$P < 0.01$; [c]asterisks indicate significant differences vs NEF and CBASP alone: **$P <$ 0.01.

BUP = bupropion SR; CAS = Covi Anxiety Scale; CBASP = cognitive behavioural analysis system of psychotherapy; FLX = fluoxetine; HARS = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale; NEF = nefazodone; NR = not reported; PBO = placebo; SER = sertraline; VEN = venlafaxine XR

pooled analysis of 3 trials with paroxetine, only duration of therapy was a significant predictor of treatment response (32). Age, sex, baseline clinical severity of illness, and treatment dosage did not have an impact on response to therapy.

Venlafaxine XR has also demonstrated efficacy for generalized SAD in 2 large, 12-week, placebo-controlled comparisons with paroxetine. Both venlafaxine XR (63% to 68%) and paroxetine (58% to 65%) demonstrated significantly higher response rates, compared with placebo (33% to 35%) (34–36). Venlafaxine XR also demonstrated long-term efficacy in a 6-month study (37). Symptom improvements were seen as early as week 2 and continued throughout the study.

Patients with SAD suffer significant functional impairment. Pooled analysis of the two 12-week venlafaxine XR studies showed symptom improvement as early as week 2 and demonstrated significant improvements in work, family, and social functioning (11). Greater baseline impairment was associated with greater absolute improvement.

In a metaanalysis by Federoff and Taylor, data on pharmacologic and psychological therapies, including exposure therapy, cognitive restructuring, social skills training, and applied relaxation, were analyzed (28). Although pharmacotherapies were most consistently effective, the combination of cognitive restructuring and exposure therapy had a greater effect than SSRIs or MAOIs on observer-rated measures.

Generalized Anxiety Disorder

GAD is the most common anxiety disorder in primary care and is highly debilitating (4). During the first 5 years, GAD follows a chronic course with low rates of remission and moderate rates of relapse or recurrence following remission. Retrospective studies suggest that this chronic pattern may persist for 20 years or longer (38). Full remission, usually defined as a score of ≤ 7 on the HARS and HDRS, is essential for complete restoration of normal functioning (Table 1) (4). Benzodiazepines, tricyclics such as imipramine, the antihistamine hydroxyzine, the SSRI paroxetine, and venlafaxine XR have demonstrated significant efficacy in relieving GAD symptoms, including both psychic and somatic anxiety, in randomized, placebo-controlled trials (Table 4) (39–46). In general, remission rates were 30% to 50% higher with active treatment, compared with placebo.

In subjects with GAD, hydroxyzine and bromazepam demonstrated significant improvements in HARS scores, with approximately twice as many subjects responding to active

Table 3 Controlled trials of antidepressant therapy in social anxiety disorder

Study details	Treatment and dosage, mg (trials)	Number completed/ enrolled (%)	LSAS score change from baseline (%)	Other social phobia scales change from baseline (%)	Response CGI-I:1 or 2 (or remission CGI-I: 1) rate, %
van der Linden and others (27) Metaanalysis of 17 RCTs		Drug PBO	LSAS ES	OR (95%CI) for CGI response	Drug PBO
	SSRI (8) vs PBO	—/701 —/471	0.3 to 1.8	3.3 (2.6, 4.2)	53 26
	RIMA (6) vs PBO	—/429 —432	0.3 to 0.9	2.1 (1.6, 2.8)	46 29
	MAOI (2) vs PBO	—/55 —/54	0.3 to 1.0	5.5 (2.4, 12.7)	64 24
	BZD (1) vs PBO	—/39 —/36	1.0	12.0 (4.0, 35.9)	74 19
Fedoroff and Taylor (28) Metaanalysis of 108 trials Pharmacotherapy trials ~12 weeks			LSAS/SPAI ES (95%CI)	NR	NR
	SSRIs (12)	(81.8)	1.540 (1.10, 1.98)		
	MAOIs (15)	(77.3)	1.235 (0.96, 1.51)		
	BZD (5)	(77.0)	3.150 (1.13, 5.17)		
	Pill PBO (17)	(84.0)	0.811 (0.66, 0.96)		
Stein and others (29)				BSPS	
12 weeks; *n* = 92; BSPS = 43.3	FLV	—/48	–22.0 (27.2)**[a]	–15.3 (35.5)**	42.9*
	PBO	—/44	–7.8 (9.6)	–8.1 (18.6)	22.7
van Ameringen and others (30)				BSPS	
20 weeks; *n* = 204; BSPS = 46.6	SER 50–200	104/135 (77)	NR	–16.30 (34.3)**	53 (30)**
	PBO	54/69 (78)		–8.49 (18.6)	29 (13)
Liebowitz and others (31)	PRX 20	66/97 (68)	–31.4 (39.3)*	NR	44.9 (19.1)
12 weeks, *n* = 384; LSAS = 76.9	PRX 40	55/95 (58)	–24.5 (31.6)		46.6** (20.5)
	PRX 60	54/97 (55.7)	–25.2 (32.8)		42.9 (22.0)
	PBO	67/95 (71.0)	–15.0 (20.5)		28.3 (7.6)
Stein and others (32)	PRX	—/499	NR	NR	52.7
12 weeks; *n* = 829; pooled 3 RCTs	PBO	—/330			28.8
Kobak and others (33)				BSPS	
14 weeks; *n* = 60; LSAS = 81.76; BSPS = 43.05	FLX 20–60	25/30 (83.3)	–22.60 (27.6) ns	–11.63 (26.6) ns	40 ns
	PBO	23/30 (76.7)	–23.37 (28.6)	–10.73 (25.3)	30
Leibowitz and Mangano (36)	VEN 75–225	122/129 (94.6)	–36* (43.3)	NR	68*
12 weeks, *n* = 863; 2 RCTs; LSAS = 85.5	PRX 20–50	122/128 (95.3)	–35* (41.7)		65*
	PBO	119/132 (90.1)	–18 (20.8)		33
	VEN 75–225	103/133 (77.4)	–36* (41.8)	NR	63*
	PRX 20–50	102/136 (75.0)	–40* (45.9)		58*
	PBO	113/128 (88.3)	–23 (26.7)		35

[a]Asterisks indicate a significant difference vs PBO: *$P \leq 0.05$; **$P \leq 0.01$; ns = not significant ($P > 0.05$).

BSPS = Brief Social Phobia Scale; BZD = benzodiazepine; CBASP = cognitive behavioural analysis system of psychotherapy; CGI = Clinical Global Impression Scale; ES = effect size; FLV = fluvoxamine; FLX = fluoxetine; LSAS = Leibowitz Social Anxiety Scale; MAOI = monoamine oxidase inhibitor; NEF = nefazodone; NR = not reported; OR = odds ratio; PBO = placebo; PRX = paroxetine; RCTs = randomized controlled trials; RIMA = reversible monoamine oxidase inhibitor; SER = sertraline; SPAI = Social Phobia and Anxiety Scale; SSRI = selective serotonin reuptake inhibitor; VEN = venlafaxine XR

treatment, compared with placebo (39). Paroxetine improved the core symptoms of GAD and was associated with significant reduction in disability after 8 weeks of treatment (40). Remission rates were significantly higher in trial participants treated with paroxetine, compared with placebo (42.5% and 26.3%, respectively). Similar results were seen in a recent fixed-dose study, where remission rates were higher with 20 mg and 40 mg paroxetine, compared with placebo (30%, 36%, and 20%, respectively) (41).

Venlafaxine XR is effective, safe, and well tolerated in patients with GAD (Table 4) (42,43). Pooled data from two 8-week studies demonstrated higher remission rates with venlafaxine XR over placebo (31% and 18%, respectively) (44). Long-term, 6-month studies demonstrated significantly greater improvements in HARS scores and higher response and remission rates (45,46). In a pooled analysis of these 6-month trials, remission rates were significantly higher with venlafaxine XR than with placebo (43% and 19%, respectively) (47). An analysis of dropouts for lack of efficacy revealed a dose–response relation among 3 dosages of venlafaxine XR (75 mg, 150 mg, and 225 mg), with the lowest rate of discontinuation at the higher venlafaxine XR dose (48). Venlafaxine XR was equally efficacious, safe, and well tolerated by younger and older patients and by men and women in

Table 4 Controlled trials of antidepressant therapy in generalized anxiety disorder

Study details	Treatment and daily dosage, mg	Number completed/ enrolled (%)	HARS total change vs baseline	HARS response rate, ≥ 50% decrease, %	CGI-I response rate, 1 or 2,%	HARS remission rate, %
Llorca and others (39) 12 weeks; *n* = 334; HARS = 25.5	HYD 50	88/105 (83.8)	–12.16*[a]	57**	NR	44*
	BRO 6	99/116 (85.3)	–13.5**	60**		53**
	PBO	91/113 (80.5)	–9.64	31		28
						HARS ≤ 10
Pollack and others (40) 8 weeks; *n* = 324; HARS = 24.2	PRX 20–50	127/161 (78.9)	–12.2**	NR	62.1**	42.5**
	PBO	133/163 (81.6)	–10.1	NR	47.2	26.3
						HARS ≤ 7
Rickels and others (41) 8 weeks; *n* = 566; HARS = 24.1	PRX 20	143/188 (76.1)	–12.5***	NR	61.7***	30**
	PRX 40	143/197 (72.6)	–12.2***	NR	68.0***	36**
	PBO	140/180 (77.8)	–9.3	NR	45.6	20
Davidson and others (42) 8 weeks; *n* = 365; HARS = 23.5	VEN 75	64/87 (73.6)	–10.7	49	62**	Pooled 8-week data (44)
	VEN 150	55/87 (63.2)	–9.2	49	49	VEN: 31
	BUS 30	69/93 (74.2)	–9.7	45	55*	PBO: 18
	PBO	64/98 (65.3)	–8.1	36	39	HARS ≤ 8
Rickels and others (43) 8 weeks; *n* = 370; HARS = 24.2	VEN 75	60/86 (70)	–11.22	NR	NR	Pooled 8-week data (44)
	VEN 150	52/81 (64)	–12.36	NR	NR	VEN: 31
	VEN 225	58/86 (67)	–11.52*	NR	NR	PBO: 18
	PBO	77/96 (80)	–9.51	NR	NR	HARS ≤ 8
Gellenberg and others (45) 28 weeks; *n* = 251; HARS = 25.0			12 weeks / 28 weeks	12 weeks / 28 weeks		Pooled 6-month data (44,47)
	VEN 75,150,225	60/124	–13.4*** / –13.4***	74*** / 71***	NR	VEN: 43***
	PBO	44/127	–9.0 / –8.7	42 / 40	NR	PBO: 19
				≥ 40% decrease		HARS ≤ 8
Allgulander and others (46) 24 weeks; *n* = 541 HARS = 26.5			8 weeks / 24 weeks	8 weeks / 24 weeks	8 weeks / 24 weeks	Pooled 6-month data (44,47)
	VEN 37.5	102/140 (72.8)	–12.0 / –13.8	49 / 60[a]	59* / 67	VEN: 43***
	VEN 75	101/134 (75.4)	–13.8* / –15.5*	57* / 68[a]	70* / 75*	PBO: 19
	VEN 150	106/137 (77.4)	–14.5* / –16.4*	70* / 75[a]	79* / 81*	HARS ≤ 8
	PBO	85/130 (85.0)	–10.1 / –11.0	40 / 45	46 / 49	

[a]Asterisks indicate significant differences vs PBO: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

BRO = bromazepam; BUS = buspirone; BSPS = Brief Social Phobia Scale; BUP = bupropion; BZD = benzodiazepine; CBASP = cognitive behavioural analysis system of psychotherapy; CGI = Clinical Global Impression Scale-Improvement; FLV = fluvoxamine; FLX = fluoxetine; HARS = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale; HYD = hydroxyzine; LSAS = Leibowitz Social Anxiety Scale; MAOI = monoamine oxidase inhibitor; NEF = nefazodone; NR = not reported; PBO = placebo; PRX = paroxetine; RCTs = randomized controlled trials; RIMA = reversible monoamine oxidase inhibitor; SER = sertraline; SPAI = social phobia and anxiety scale; VEN = venlafaxine XR

the treatment of GAD (44,49). An analysis of HARS items found that improvements with venlafaxine XR were greatest for the core symptoms of GAD, specifically, anxious mood, tension, intellectual functioning, and behaviour (50).

Treatment in patients with GAD should be continued up to 8 weeks, even in patients who have not responded, and up to at least 6 months to optimize remission rates. Pooled data from the two 6-month trials of venlafaxine XR showed that 2.5 times as many patients treated with venlafaxine XR for up to 8 weeks went on to respond at 6-month follow-up, compared with those treated with placebo (51). The percentage of nonremitters who became remitters at month 6 was significantly greater with venlafaxine XR than with placebo (odds ratio [OR] 2.47, $P = 0.009$). Similarly, Stocchi found that 73% of patients with at least a partial response to paroxetine at week 8 of open-label treatment went on to achieve remission at week 24 (52). In the 3-month study of hydroxyzine and bromazepam, remission rates did not begin to differ from placebo until day 21 and continued to increase over the full 3-month period.

A metaanalysis of psychotherapy trials found significant benefits in patients with GAD, with a median effect size of 0.9 and an improvement rate of 44% (53).

Table 5 Controlled trials of antidepressant therapy in posttraumatic stress disorder

Study details	Treatment and daily dosage, mg (mean)	Number completed/ enrolled (%)	CAPS total Change vs baseline	Cluster B, Reexperiencing Change vs baseline	Cluster C, Avoidance Change vs baseline	Cluster D, Hyperarousal Change vs baseline	% Responders CGI	Additional results
Stein and others (54) metaanalysis 4 and 6 data sets	SSRIs/BZD/ TCA							Effect sizes
	PBO	170	NR	NR	NR	NR	71.2	0.1 to 0.9
		179					44.7	
Tucker and others (55) 12 weeks; *n* = 307; CAPS-2 = 75	PRX 20–50 (27.6)	93/151 (61.6)	–35.5***[a,b]	–10.5**	–15.0***	–10.0***	58.8***	Significant improvements in DTS, MADRS, SDS; 6-week responder rate: 48.6% vs 27.3%, $P < 0.001$
	PBO	94/156 (60.3)	–24.7	–7.9	–10.4	–6.3	38.0	
Marshall and others (56) 12 weeks; *n* = 551 CAPS-2 = 75	PRX 20	122/183 (67)	–39.6***	–11.6***	–16.9***	–11.1	62	
	PRX 40	113/182 (62)	–37.9***	–11.1***	–16.7***	–10.0	56	
	PBO	120/186 (65)	–25.3	–7.3	–11.1	–7.0	37	
Davidson and others (57) 12 weeks; *n* = 202 CAPS-2 = 74	SER 25–200 (146)	68/98 (69	–33.0*	–7.5	–14.7*	–10.8	60**[b]	Significant improvements in IES total, DTS
	PBO	73/104 (70)	–26.2	–6.5	–10.6	–8.9	38	
Davidson (58) 12 weeks; *n* = 531								Symptom-free days
	VEN 300	125/179 (70	–42*	13.0	17.1*	11.7*	31*[c]	27.8*
	SER 200	111/173 (64)	–39	8.2	16.7*	10.9	24	23.4
	PBO	114/179 (64)	–34	11.2	4.0	9.4	20	21.5

[a]Asterisks indicate significant differences vs PBO: *$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$; [b]≥ 30% reduction on CAPS-2; [c]remission ≤ 20 on CAPS-SX_{17}

BZD = benzodiazepine; CAPS = Clinician Administered Posttraumatic Stress Disorder Scale; DTS = Davidson Trauma Scale; IES = Impact of Events Scale; MADRS = Montgomery–Asberg Depression Rating Scale; MAOI = monoamine oxidase inhibitor; NEF = nefazodone; NR = not reported; PBO = placebo; PRX = paroxetine; SDS = Sheehan Disability Scale; SER = sertraline; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; VEN = venlafaxine XR

Posttraumatic Stress Disorder (PTSD)

One definition of remission in PTSD includes little or no anxiety and depression and few or no PTSD symptoms as measured by the Treatment Outcomes PTSD Scale (TOP-8) (Table 1) (26). The TOP-8 scale is a recently developed simplified version of the Clinician Administered PTSD Scale (CAPS-2), with the 8 items chosen for their particularly robust response during medication treatment. Although commonly used in clinical trials, the CAPS-2 is burdensome for use in clinical practice.

A recent metaanalysis found few controlled studies for SSRIs in PTSD but showed that the OR for response, defined as CGI-I score of 1 ("much improved") or 2 ("very much improved") or CAPS-2 reduction of ≥ 30%, with drug vs placebo ranged from 2.2 to 5.6 for various SSRIs (Table 5) (54). Two recent placebo-controlled trials of paroxetine demonstrated significant efficacy in the treatment of chronic PTSD, with improvements in all 3 symptom clusters (reexperiencing, avoidance or numbing, and hyperarousal) and a significant reduction in disability with 12 weeks of treatment (55,56). Sertraline has also demonstrated efficacy in subjects with PTSD; however, benefits were significant only for the CAPS total score and the Avoidance subscale (57). Responder rates in the metaanalysis and in these 3 trials were similar at about 60% to 70% for SSRI treatment, compared with 40% for placebo (54–57).

In a recent RCT, venlafaxine XR was compared with sertraline and placebo in 531 patients with PTSD (58). After 12 weeks of therapy, mean change on a 17-item version of the CAPS with venlafaxine XR, but not sertraline, was significantly greater than with placebo. Remission rates with venlafaxine XR were significantly greater than with placebo (31% vs 20%; $P < 0.05$), while those with sertraline were not (24%). Venlafaxine XR resulted in a significantly greater number of symptom-free days, compared with placebo (27.8 and 21.5 days, respectively; $P = 0.05$).

Table 6 Controlled trials of antidepressant therapy in obsessive–compulsive disorder

Study details[a]	Treatment and daily dosage, mg (mean)	Number completed/ enrolled (%)	Y-BOCS total change vs baseline (%)	Y-BOCS total change vs PBO (95%CI)	% Responders
Ackerman and Greenland (68) 8–13 weeks; *n* = 26 trials; Y-BOCS = 24–27; metaanalysis of 26 RCTs	All vs PBO	20 trials		–2.57 (–3.5, –1.6)	na
	CLM vs PBO	7 trials	—	–8.19 (–10.5, –5.9)	
	FLV vs PBO	4 trials	–8.0 to –16.8	–4.84 (–7.8, –1.8)	
	FLX vs PBO	3 trials	–3.8 to –7.0	–1.61 (–2.2, –1.0)	
	SER vs PBO	4 trials	–2.8 to –6.8	–2.47 (–6.1, 1.2)	
	CLM vs SSRI	6 trials	–2.2 to –9.0	0.15 (–8.9, 9.2)	
Montgomery and others (69) 12 weeks; *n* = 401; Y-BOCS = 25–26	CIT 20	86/102 (84)	–8.4**[b]		57.4*[b]
	CIT 40	83/98 (85)	–8.9**[b]		52*[b]
	CIT 60	85/100 (85)	–10.4**[b]		65*[b]
	PBO	84/101 (83)	–5.6		36.6
					≥ 25% decrease in Y-BOCS
Mundo and others (70) 10 weeks; *n* = 227; Y-BOCS = 26	FLV 150–300	96/115 (83.5)	–12.2		62
	CLM 150–300	86/112 (76.8)	–12.0		65
					≥ 35% decrease in Y-BOCS
Albert and others (71) single-blind 12 weeks; *n* = 73; Y-BOCS =25.35	VEN 225–350	25/26 (96.2)	–6.64 (26.6)		34.6
	CLM 150–225	40/47 (85.1)	–8.4 (32.7)		42.6
					≥ 35% decrease in Y-BOCS
Bergeron and others (72) 24 weeks; *n* = 150; Y-BOCS = 26			12 weeks / 24 weeks		12 weeks / 24 weeks
	SER 50–200	55/77 (71)	–8.4**[c] / –9.6 ns[c]		20*[c] / 36 ns[c]
	FLX 20–80	51/73 (70)	–6.1 / –9.7		8 / 22
					CGI-I ≤ 2 + Y-BOCS ≤ 11
Denys and others (74) 12 weeks; *n* = 150	VEN 300	—/74	–7.2 (30)		40
	PRX 60	—/76	–7.9 (30)		40
					≥ 35% decrease in Y-BOCS

[a]All trials were double-blind except where noted. [B]Significantly different vs PBO: *$P \leq 0.05$; **$P \leq 0.01$. [c]Significantly different vs FLX: *$P \leq 0.05$; **$P \leq 0.01$; ns = not signitficant ($P > 0.05$).

CIT = citalopram; CGI = Clinical Global Impression Scale; CLM = clomipramine; FLV = fluvoxamine; FLX = fluoxetine; na = not applicable; PBO = placebo; PRX = paroxetine; RCTs = randomized controlled trials; SER = sertraline; VEN = venlafaxine XR; Y-BOCS = Yale-Brown Obsessive Compulsive Scale

For some patients with PTSD, monotherapy is inadequate. The atypical antipsychotics risperidone, olanzapine, and quetiapine have demonstrated benefit as adjunctive therapy in patients with PTSD who were refractory to treatment with SSRIs (59–61). In small double-blind trials, improvements in global psychosis, hallucinations, and delusions were seen with risperidone augmentation (60), together with a significant reduction in the CAPS-2 and improvement in sleep with olanzapine augmentation, compared with placebo augmentation (61).

Panic Disorder

Remission in PD is defined as a HDRS score of < 7, a HARS score of < 7 to 10, and the near absence of panic attacks, with nearly complete resolution of agoraphobia (Table 1) (13,26). An alternative definition of remission is a score of≤ 3 with no individual item score > 1 on the Panic Disorder Severity Scale (PDSS). A metaanalysis of 43 studies including 2367 patients concluded that the efficacy of SSRIs and TCAs in the treatment of PD were comparable but that SSRIs were better tolerated (62). Both therapies reduced panic symptoms, agoraphobic avoidance, depressive symptomatology, and general anxiety, and there were no differences in the percentage of patients free of panic attacks. However, there were significantly fewer dropouts in the SSRI group, compared with the TCA group (18% vs 31%; $P < 0.001$).

In the treatment of PD ($n = 328$), venlafaxine XR resulted in higher response and remission rates (response, 68.1% vs 55.4%, $P < 0.05$; remission, 35.6% vs 24.4%, $P < 0.05$), compared with placebo, and greater reduction in panic attack frequency (–5.0 vs –3.7, respectively; $P < 0.05$) (63). A recent trial compared treatment with venlafaxine XR and paroxetine

for 12 weeks in 634 patients with panic disorder (64). About 60% of patients became panic-free on venlafaxine XR 150 mg daily or paroxetine 40 mg daily, compared with only 34% on placebo ($P < 0.002$). Venlafaxine XR and paroxetine were effective in ameliorating the physiological symptoms and improving quality of life in the acute treatment of panic disorder (65,66). Both therapies were associated with greater improvement vs placebo on the Physical Health–Activities subscale, and on most of the 9 other subscales of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (venlafaxine XR 8/9; paroxetine 5/9) (65). Venlafaxine XR 150 mg, venlafaxine XR 75 mg, and paroxetine were associated with greater improvement, vs placebo, on the work, social activities, and family life items of the Sheehan Disability Inventory (66).

A metaanalysis of psychotherapy trials found significant benefits in patients with PD, with a median effect size of 0.8 and an improvement rate of 54% (53).

Obsessive–Compulsive Disorder

Remission in OCD has been defined as a HDRS score of < 7, a HARS score of < 7 to 10, a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) ≤ 8, and the near absence of obsessions and compulsions (Table 1) (26). However, this very often is not an attainable goal, and even percentage improvements on the main outcome measure (Y-BOCS) for response are low, compared with the usual 50% improvement on HDRS or Montgomery–Asberg Depression Rating Scale required for response in major depression trials. In the recent trials comparing 2 active medications, response rates have been defined as improvements in Y-BOCS scores of 25% to 35%, with or without an attendant response on the CGI-I scale.

An early metaanalysis of pharmacotherapy trials for the treatment of OCD found a significant beneficial effect for SSRIs and suggested that clomipramine was more effective than fluoxetine (67). However, this analysis was based on a very limited number of studies. A more recent metaanalysis of 26 randomized trials reported comparable benefits with SSRIs and the TCA clomipramine (Table 6) (68). Effect sizes for improvement in Y-BOCS were significantly greater with clomipramine, compared with SSRIs, in 6 placebo-controlled trials. However, an analysis of data from 6 head-to-head trials revealed no significant differences between clomipramine and SSRI therapy. Desipramine was compared with fluoxetine in one study and sertraline in another. Fluoxetine had significantly more effect than desipramine in one study, and sertraline demonstrated a trend to better results in the other; however, the difference was not significant. In a more recent study, citalopram demonstrated significant improvement, compared with placebo, in treating OCD (69).

Because the definitions of response rates vary, this makes comparisons of different trial results difficult (Table 6). However, data from recent trials suggest that clomipramine does not possess significantly superior effects. In separate comparisons with fluvoxamine or venlafaxine, no significant differences in changes in Y-BOCS scores or response rates were seen between agents, but fluvoxamine and venlafaxine were better tolerated than clomipramine (70,71). In another study, sertraline showed a greater likelihood of remission as well as an earlier improvement on some (obsessions), but not all, efficacy measures, compared with fluoxetine at 12 weeks of treatment, but there were no significant differences at 24 weeks (72). Venlafaxine XR and paroxetine demonstrated equal efficacy in treating subjects with OCD (73,74).

Clomipramine, the SSRIs, and venlafaxine all appear to have beneficial effects on both obsessions and compulsions with no differences between treatment groups (70–74). In these trials, response rates were 20% to 65%, and patients were considered responders with as little as a 25% improvement in OCD symptoms. Switching between SSRIs or to a serotonin norepinephrine reuptake inhibitor (SNRI) after an adequate SSRI trial with an optimized dosage for at least 12 weeks can bring about an improved response rate for some patients. A small study found that a second medication trial with a different serotonergic agent could significantly improve outcomes in nonresponders, boosting the responder rate to 70% (75). Nonresponders to either venlafaxine or paroxetine were switched to 12 additional weeks of double-blind treatment with the alternate medication, and more than 40% responded. More recently, the atypical antipsychotics risperidone, olanzapine, and quetiapine have been investigated in hopes of improving outcomes for patients with OCD. These agents have demonstrated some benefit as adjunctive therapy in patients with OCD who were refractory to treatment with SSRIs (76–79). In small open-label and double-blind trials, about 45% to 70% of SSRI-refractory patients responded when an atypical antipsychotic was added (76–79).

Antidepressant Therapy to Sustain Remission and Prevent Relapse

Outcomes in short-term pharmacotherapy trials with anxiety disorders can be less than optimal. However, several studies have shown improved long-term remission rates and reduced relapse rates with ongoing antidepressant therapy.

In SAD, both paroxetine and sertraline have demonstrated significant reductions in relapse rates in separate 24-week placebo-controlled maintenance trials (80,81). Paroxetine treatment resulted in significantly fewer relapses than placebo (14% vs 39%; $P < 0.001$) (80). Similarly, only 4% of sertraline-treated patients, compared with 36% of those receiving placebo, relapsed ($P = 0.01$). Switching to placebo

was associated with 10 times the risk of relapse (81). Venlafaxine XR for 6 months was associated with continued improvement in symptoms from 2 weeks through to the end of the study at 6 months (37).

GAD tends to run a chronic waxing and waning course. In a review by Yonkers and colleagues, the rate of remission was only 38% after 5 years in patients with chronic GAD (82). Comorbidity was high, and the likelihood of remission for GAD and any other comorbid condition after 1 year was one-half the annual remission rate for GAD that was non-comorbid (83). Venlafaxine XR demonstrated efficacy in the prevention of relapse in GAD (47,48). Pooled data from 2 placebo-controlled, 6-month trials demonstrated a significantly lower relapse rate among patients who had responded to venlafaxine, compared with placebo (6% vs 15%; $P < 0.01$) (47). In addition, the incidence of sustained remission in the venlafaxine XR group was twice that in the placebo group (43% vs 19%; $P < 0.001$). Placebo-treated patients discontinued treatment owing to lack of efficacy more frequently and earlier than those receiving venlafaxine XR ($P < 0.001$) (48). The long-term efficacy of paroxetine was demonstrated in a double-blind continuation trial in which 566 subjects with initially at least a partial response to 8 weeks of open-label paroxetine therapy were randomized to paroxetine or placebo. Over 24 weeks of therapy, significantly fewer subjects treated with paroxetine relapsed, compared with those treated with placebo (10.9% vs 39.9%; $P < 0.001$) (52). At the end of double-blind treatment, remission rates were significantly higher in patients who had continued on paroxetine, compared with those switched to placebo (73.0% and 34.4%, respectively; $P < 0.001$). There are substantial differences between this patient population (52) and those included in the venlafaxine XR trials (47). In the paroxetine study, only about 20% of patients had previously used medication. In addition, study designs varied. Patients were required to be responders to 8-week, open-label paroxetine, with at least a 2-point decrease to 3 or less on the CGI-S scale, before their inclusion and randomization in the 24-week extension (52).

Both sertraline and fluoxetine have demonstrated significantly reduced relapse rates in patients with PTSD during 6 months of maintenance therapy (84,85). In a randomized, placebo-controlled trial, rates of relapse were only 5% in the sertraline group, compared with 26% in the placebo group ($P < 0.02$) (84). In a 6-month randomized trial, fluoxetine patients were less likely to relapse than placebo patients (5.8% and 16.1%, respectively; $P = 0.027$) (85).

PD with or without agoraphobia has a chronic relapsing course. Over a 5-year period, rates of remission were only 39%, and 80% of patients with PD who discontinued medication relapsed with at least 1 full-blown attack (86,87). In a small open trial, 10 patients were successfully maintained free of panic attacks on weekly fluoxetine therapy over a 6-month period (88). Data suggest that psychotherapy may be highly effective in maintaining the benefits of treatment. About 75% of patients treated with cognitive-behavioural therapy (CBT) were able to discontinue any type of pharmacotherapy for PD during a 2- to 5-year follow-up period (89). Similarly, a cohort analysis found that patients who received a combination of medication and CBT had a 12.6 times lower risk of relapse, compared with patients who received medication alone (90). Despite the fact that CBT is very effective when given from a state-of-the-art facility, Barlow and colleagues report that the likelihood of receiving an empirically supported treatment outside a research facility is disappointing (91). Another study examining the benefits of CBT for PD with a comorbid condition suggests that the therapeutic effect may become weaker over time (92). If the comorbid condition is not treated properly, both the PD and the comorbid condition may return at their pretreatment intensity.

In OCD, patients randomized to fluoxetine had numerically, but not significantly, lower relapse rates, compared with placebo (20.6% and 31.9%, respectively) (93). However, a high dosage of fluoxetine (60 mg daily) did significantly reduce the relapse rate by one-half, compared with placebo.

Table 7 provides an overview of the doses and duration of treatment we recommend for select antidepressants used to manage anxiety disorders.

Summary

Anxiety disorders are highly prevalent psychiatric disorders and tend to have a chronic course if untreated. Remission is the minimum treatment goal in chronic anxiety disorders, but outcomes in short-term pharmacotherapy trials generally fall short of this goal. Anxiety disorders are highly comorbid, especially with MDD and bipolar disorder, which further complicates their management. Antidepressant therapy has demonstrated significant beneficial effects on both depression and anxiety symptoms in patients with comorbid depression and GAD or depression with high anxiety symptoms. Venlafaxine XR has demonstrated higher remission rates than placebo and fluoxetine for these patients. In SAD, SSRIs and venlafaxine XR have demonstrated efficacy, with response rates varying between 40% and 68%. The combination of cognitive restructuring and exposure therapy also demonstrated good results. In recent trials in patients with GAD, hydroxyzine, bromazepam, paroxetine, and venlafaxine XR have demonstrated remission rates that are 30% to 50% higher than achieved with placebo. In patients with PTSD, response rates were about 60% to 70% with antidepressant therapy, compared with about 40% on placebo, while remission rates in one study were 30% with venlafaxine, 24% with sertraline, and 20% with placebo. In patients with OCD, a 25% to 35% improvement was reported in

Table 7 Dosing strategies for selected antidepressants in the treatment of anxiety disorders (based on the authors' clinical experience)

Anxiety disorder	Antidepressant	Starting dosage, mg	Usual dosage, mg	Duration of Initial treatment
SAD	Fluvoxamine	25.0	200–300	2 years
	Paroxetine	10.0	40–60	
	Sertraline	25.0	150–200	
	Venlafaxine XR	37.5	150–375	
GAD	Paroxetine	10.0	40–60	2 years
	Venlafaxine XR	37.5	150–375	
PTSD	Paroxetine	10.0	40–80	2 years
	Sertraline	25.0	150–250	
	Venlafaxine XR	37.5	150–375	
PD	Clomipramine	25.0	100–250	2 years
	Imipramine	25.0	150–300	
	Fluoxetine	10.0	40–60	
	Fluvoxamine	25.0	150–200	
	Paroxetine	10.0	40–60	
	Sertraline	25.0	150–200	
	Venlafaxine XR	37.5	150–375	
OCD	Citalopram	10.0	40–80	2 years
	Clomipramine	25.0	150–250	
	Fluoxetine	10.0	40–80	
	Fluvoxamine	25.0	150–300	
	Paroxetine	10.0	40–80	
	Sertraline	25.0	150–250	
	Venlafaxine XR	37.5	225–375	

GAD = generalized anxiety disorder; OCD = obsessive–compulsive disorder; PD = panic disorder; PTSD = posttraumatic stress disorder; SAD = social anxiety disorder

20% to 65% of patients. When used to manage PD, paroxetine and venlafaxine XR doubled the percentage of patients who were panic-free, compared with placebo. In clinical practice, CBT offers significant benefits when used alone or in combination with medication in both the acute and maintenance treatment of anxiety disorders.

Despite sometimes suboptimal short-term results, several studies have shown improved long-term remission rates of anxiety disorders with ongoing antidepressant therapy. It appears that longer antidepressant treatment may be required before many patients with anxiety disorders experience benefit. This is in keeping with clinical experience. In most trials, some benefits are seen within 3 to 4 weeks but continue to accrue throughout the 3- to 6-month duration of the trial. CBT, specifically exposure to feared situations, is necessary to move beyond phobic avoidance and functional impairment to full recovery, the ultimate goal of therapy.

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