



# THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

## Management of Anxiety Disorders in Primary Care

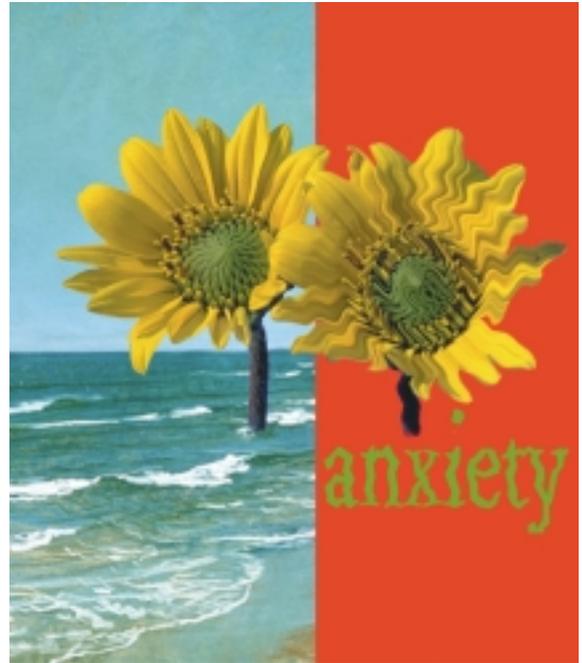
**A**nxiety disorders are characterized by symptoms of overriding apprehension or mental tension serious enough to disrupt daily activities. The most common forms are situational or stress-related anxiety, phobic disorders, generalized anxiety disorder, panic disorder, and obsessive-compulsive disorder. These are widely prevalent conditions predominantly managed in the primary care setting<sup>1</sup>. The present "best evidence" for treatment is based on several hundred trials, which unfortunately suffer from a number of methodological flaws that limit their usefulness. Our treatment recommendations are based on a critical review of the evidence-based literature<sup>1</sup> and a number of systematic reviews (meta-analyses) of controlled clinical trials.

### What is the initial approach to a patient who presents with anxiety?

- Establish diagnosis (rule out medical disorders, e.g. hyperthyroidism, substance abuse).
- Establish the timing and nature of symptoms, the extent of disability, and the presence of co-morbid conditions.
- Develop a plan of therapy.

### What non-drug therapies are strongly recommended in managing most patients?

- Decrease or discontinue caffeine and other CNS stimulants.
- Minimize use of alcohol and other sedatives or hypnotics.
- **Regular aerobic exercise lasting >20 min.** (This recommendation is based on a comprehensive meta-analysis of 104 studies with a total of 3048 subjects<sup>2</sup>).
- Anxiety management strategies- e.g. relaxation training and supportive psychotherapy.
- If appropriate involve a local Mental Health Program or other available support group.



### How does one manage the common uncomplicated cases?

#### • Situational or Stress-related Anxiety

Anxiety that results from an identifiable stress seldom requires treatment other than brief, supportive, problem focused psychotherapy. If the anxiety is severe and distressing a short course (2-3 weeks) of a long-acting benzodiazepine (eg. diazepam 5-15 mg qhs), with instructions as to gradual reduction of dosage, will provide some relief of the symptoms.

#### • Phobic Disorders

##### a) Social Phobia and Performance Anxiety

Social phobia is the persistent fear of a social activity where the individual fears being observed, such as speaking in public or voiding in a public lavatory. It is very prevalent and can severely limit an individual socially and occupationally. **There is a considerable amount of evidence demonstrating the effectiveness of cognitive-behavioral therapy<sup>1</sup> (CBT). CBT consists of various types of psychological treatment which attempt to alter the thought patterns or behaviour responsible for maintaining the disorder.** More research is required to establish the effectiveness of drugs.



Performance anxiety is milder and specific to certain activities. Although non-selective beta-blockers reduce anxiety and improve performance among musicians<sup>3</sup> and actors, their usefulness for patients with true social phobia has not been established.

**b) Simple or Specific Phobia**

Simple phobia is the fear and avoidance of specific objects or stimuli (e.g. dogs, airplane travel). Numerous trials have demonstrated the effectiveness of behavioural therapy; there are no controlled trials examining the use of drugs<sup>1</sup>.

**What therapies have been proven effective in the more difficult cases?**

**• Generalized anxiety disorder:**

This is a prevalent disorder, which is manifested by excessive worry (occurring more days than not), leading to significant distress or functional impairment. Effective therapies proven in placebo controlled trials include CBT, imipramine, and benzodiazepines<sup>1</sup> plus buspirone<sup>4</sup>. Benzodiazepines work more quickly than other therapies but are associated with potential dependency manifest by rebound and withdrawal symptoms.

**• Panic disorder +/- agoraphobia:**

Panic disorder is characterized by recurrent unexpected panic attacks without any obvious trigger,

plus significant worry and change in behavior as a result of the attacks. Agoraphobia is the substantive avoidance of activities because of the fear of a panic attack in a public place. **Treatment for panic disorder has been researched the most extensively.** In a meta-analysis of 27 drug trials with a total of 2348 patients, the order of effectiveness was clomipramine = fluvoxamine = paroxetine > imipramine = alprazolam<sup>5</sup>. **Thus clomipramine, fluvoxamine and paroxetine are the preferred drug treatments.** Various types of CBT are also effective, but there are no consistent differences between CBT, drugs and their combination<sup>1</sup>.

**• Obsessive-compulsive disorder:**

This disorder is defined by the presence of time-consuming or distressing recurrent intrusive thoughts and/or apparently meaningless repetitive behaviors. A meta-analysis of 47 studies with 2111 patients showed that in order of effectiveness: clomipramine > fluvoxamine = fluoxetine = sertraline > imipramine = nortriptyline<sup>6</sup>.

**Thus clomipramine, the serotonin selective tricyclic, and the selective serotonin reuptake inhibitors (SSRIs) are the preferred drug treatments.** In addition other controlled trials consistently showed CBT and combinations of CBT and drug to be effective<sup>1</sup>.

Table

Class	Generic Name	Trade Name	Daily Dose Range <sup>†</sup>	Average Daily Cost Range*
Benzodiazepines <sup>a</sup>	Alprazolam	Xanax <sup>®</sup>	0.25-2 mg BID	\$0.16-\$0.80
	Clonazepam	Rivotril <sup>®</sup>	0.5-4 mg	\$0.15-\$0.45
	Diazepam	Valium <sup>®</sup>	5-40 mg	\$0.01-\$0.04
Tricyclics	Clomipramine	Anafranil <sup>®</sup>	75-200 mg	\$0.75-\$1.84
	Imipramine	Tofranil <sup>®</sup>	75-200 mg	\$0.04-\$0.08
	Nortriptyline	Aventyl <sup>®</sup>	50-150 mg	\$0.88-\$2.64
SSRIs <sup>b</sup>	Fluoxetine	Prozac <sup>®</sup>	20-60 mg	\$1.18-\$3.54
	Fluvoxamine	Luvax <sup>®</sup>	100-300 mg <sup>c</sup>	\$1.54-\$4.62
	Paroxetine	Paxil <sup>®</sup>	20-50 mg	\$1.73-\$3.57
	Sertraline	Zoloft <sup>®</sup>	50-200 mg	\$1.75-\$3.68
Azapirone	Buspirone	Buspar <sup>®</sup>	5-15 mgTID	\$1.17-\$3.51

\*Pharmicare 1996 data.

<sup>†</sup> Dosing is once daily except where indicated.

<sup>a</sup> See Therapeutics Letter<sup>®</sup> issue 11, 1995, for half-life of all available benzodiazepines.

<sup>b</sup> Selective Serotonin Reuptaker Inhibitors.

<sup>c</sup> ≤ 150 mg give once daily, >150 mg give BID.

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### Practical Prescribing Tips

The tricyclic antidepressants and SSRIs are used in the same doses as those for depression. **On average, lower doses are required and side effects are more prevalent in the elderly.** Antidepressants must be started in low dosage and gradually increased; the onset of effect is gradual and it takes at least 3 weeks for the drugs to be effective.

Bupirone is an azapirone. It produces less drowsiness and psychomotor impairment than benzodiazepines, does not exacerbate underlying depressive symptoms, does not potentiate effects of alcohol, and does not result in tolerance, dependence, or withdrawal symptoms. Major disadvantages of bupirone include the slow onset of action, requiring 3-5 weeks for maximal effectiveness, and the relatively low response rate (54% of patients receiving bupirone were classified as responders in the meta-analysis<sup>4</sup>).

### Why discourage long-term benzodiazepine therapy?

Most anxiety disorders tend to run a long course and require long-term treatment, including supportive or intensive psychotherapy. Although benzodiazepine therapy has the advantage of rapid onset of action, it has the potential to interfere with the patient's ability to respond to psychotherapy and deal with the underlying problem. Benzodiazepines also interfere with driving ability<sup>7</sup>, and increase the risk of motor vehicle accidents<sup>8</sup> and falls<sup>9</sup>. These risks are not acceptable in the long term. In addition, once started, patients are reluctant to give up their benzodiazepine support. It is more difficult to stop with shorter acting benzodiazepines ( $t_{1/2} < 15\text{hr}$ )<sup>10</sup>, and with higher doses and longer duration of therapy. Problems with discontinuing are primarily the result of frequent occurrence of withdrawal anxiety and recurrence of the original symptoms.

**Treatment with other drugs or psychotherapy takes longer to have effect, but is equal or more effective than benzodiazepine therapy, and more likely to be effective in the long term.**

### How does one manage patients who are already receiving long-term drug therapy?

As with any drug treatment the need for continuing the treatment needs to be reassessed on at least an annual basis. The only way to establish the need is to stop the treatment for 1-3 months and thereby re-evaluate whether it is continuing to provide a benefit. **It is important to continue to provide support and/or psychotherapy during and after the withdrawal of medication.** The tricyclics, SSRIs and bupirone can be easily tapered over 2-4 weeks and stopped. With benzodiazepines tapering must be carried out over a longer period of time, because withdrawal symptoms are common and often difficult to differentiate from the anxiety symptoms which led to the treatment in the first place.

### Tips for the management of Benzodiazepine withdrawal

- Involve the patient and make sure he/she understands the benefits of stopping.
- If the benzodiazepine has a short half-life (<15 h) substitute with an equivalent dose of diazepam.
- Use a gradually tapering schedule (6-12 weeks).
- Offer regular support sessions.
- **Be certain that the patient is not substituting alcohol for the benzodiazepine.**
- If this approach is unsuccessful, continue to provide medication and supportive therapy with the option of another attempt at withdrawal in the future.

### Conclusion

More and better clinical trials are needed to identify the best possible ways to treat anxiety disorders. **Current evidence suggests that non-benzodiazepine treatment, particularly psychotherapy, is safer and as effective for most patients with anxiety disorders.** Primary care physicians need to be trained and given the financial support to provide psychotherapy.

*We would like to acknowledge the psychiatrists and others whose thoughtful suggestions have greatly assisted in the preparation of the final version of this Letter.*

**References:**

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**For individuals who require more information we recommend :**

- Antony, MM, and Swinson, RP, (Reference 1)  
**Anxiety Disorders and their Treatment: A critical review of the evidence-based literature.**  
Health Canada. 1996. 1-101.

**and the companion document:**

- Antony, MM, and Swinson, RP,  
**Anxiety Disorders: Future Directions for Research and Treatment.**  
Health Canada. 1996. 1-37.

**These can be obtained (free of charge) from:**

**Publications  
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