

## To use, or not to use: an antidepressant for PMDD

Most women experience premenstrual symptoms, but only 3% to 8% meet the DSM-IV research criteria\*<sup>14</sup> for PMDD (also called severe premenstrual syndrome).<sup>4,15,16</sup> The cause is unknown, but it may be due to an interaction between normal cyclical ovarian activity and central nervous system transmitters, particularly serotonin.<sup>17,18</sup>

Antidepressants have not been directly compared with other drugs for PMDD (e.g. oral contraceptives). Uncertainties remain about the efficacy, tolerability and safety of long-term SSRI therapy because of a lack of long-term trials.

### Start with non-drug strategies and lifestyle changes

PMDD is a chronic condition, with symptoms lasting possibly until menopause. The efficacy, adverse effects and cost of treatment are important considerations.

Start with non-drug strategies (e.g. CBT, relaxation training) and lifestyle changes (e.g. exercise)<sup>17</sup>: see the *NPS RADAR* review for details.\*<sup>14</sup>

Consider adding an SSRI for women who still have symptoms after 2–3 months of non-drug strategies and

lifestyle changes.<sup>16,17</sup> Trials of oral contraceptives have conflicting results but they may be an option for women who have only physical symptoms.<sup>15-17</sup>

### Continuous vs cyclic dosing for PMDD

Both continuous and cyclic (also called intermittent or luteal) dosing of SSRIs have shown similar efficacy.<sup>18</sup> Cyclic dosing is possible because symptoms only occur during the luteal phase, SSRIs have a rapid onset of action (1–2 days)<sup>15</sup> and gradual discontinuation is unnecessary<sup>18</sup> (see Table 3). Cyclic dosing is less expensive, reduces drug exposure and may be suitable for women who have regular cycles or are considering pregnancy. However, it is unclear how cyclic dosing influences the severity and frequency of adverse effects or potential drug interactions, and women need to keep track of their cycle so they know when to start and stop therapy.<sup>19</sup>

**Table 3: Continuous and cyclic dosing of SSRIs for PMDD<sup>2</sup>**

Fluoxetine 20 mg or Sertraline 50 mg	<b>Continuous dosing</b> once daily	<b>Cyclic dosing</b> once daily Start 14 days before the expected start of menses, continue until the first full day of menses
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\* See the *NPS RADAR* review Sertraline (Zoloft), fluoxetine (Lovan, Prozac) for premenstrual dysphoric disorder (PMDD) for details.

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*The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.*



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## Which treatment for what anxiety disorder?

Up to 1 in 5 people presenting to primary care will experience symptoms of an anxiety disorder at some point in their life.<sup>1</sup> Psychological therapies should be the first choice for most anxiety disorders to control symptoms and improve functioning.<sup>2</sup> If these do not provide sufficient benefit and drug therapy is needed, an antidepressant may be added. In this *NPS News*, we discuss some general principles for managing anxiety disorders, including the role of psychological and drug therapies, with a focus on generalised anxiety disorder (GAD) and social anxiety disorder (also known as social phobia).

## Anxiety disorders: diagnosis and role of psychological therapies

Anxiety symptoms may be primary or secondary to other physical or psychiatric disorders. Anxiety disorders are usually chronic conditions and may coexist with other disorders (e.g. anxiety, mood or substance use). Characterise all anxiety symptoms against criteria to ensure accurate diagnosis and effective therapy (see insert Table).<sup>3,4</sup>

Psychological therapies such as cognitive behavioural therapy (CBT) and non-drug strategies are first-line for most anxiety disorders (see insert Box).<sup>2,3,5</sup> Many people prefer psychological therapies to drug therapy. Subsidised psychological therapy is available with a GP referral to

a psychologist\* and a GP Mental Health Care Plan.<sup>†,6,7</sup> However, the use of psychological therapies may be limited by the availability of qualified practitioners, their time-consuming nature and the motivation or preferences of some patients.<sup>2</sup>

The benefits of psychological therapies for both GAD and generalised social anxiety disorder are maintained for  $\geq 12$  months after stopping therapy<sup>1</sup>, and could be expected to continue for as long as people apply the skills learned. Up to 40% of patients relapse 6–12 months after stopping drug therapy.<sup>1</sup>

\* Up to a maximum of 12 sessions per calendar year (review by the referring GP is required after the initial 6 sessions).

† GP Medicare items 2710, 2712, 2713.

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## Starting and continuing antidepressant therapy for GAD and generalised social anxiety disorder

If psychological and other non-drug therapies do not provide sufficient benefit or are unsuitable, an antidepressant may be added. Guidelines do not recommend starting with combined therapy (an antidepressant combined with psychological and other non-drug therapies) because there is no evidence that the combination is more effective than either an antidepressant or psychological and other non-drug therapies alone.<sup>1,5</sup> Not all antidepressants have been assessed for efficacy for all anxiety disorders, nor can efficacy be generalised across an antidepressant class (see Tables 1 and 2).<sup>5</sup> Consider the adverse effect profile and concomitant medicines before prescribing. Assess efficacy after at least 12 weeks therapy (in contrast to 6–8 weeks for major depression).

It appears that CBT or an antidepressant may be similarly effective for GAD or generalised social anxiety disorder.<sup>1,3,5</sup> Few trials have directly compared drug and psychological therapies (alone or in combination) and long-term comparative efficacy is unknown.<sup>5</sup> There is likely to be a significant placebo response: for example in a small (n = 265) 14 week trial, the response rate in generalised social anxiety disorder was 32% with placebo compared with 51% with fluoxetine, 52% with group CBT, 54% with group CBT + fluoxetine and 51% with group CBT + placebo.<sup>8</sup>

### Which antidepressant for GAD?

Antidepressants are more effective than benzodiazepines for treating the uncontrollable worry associated with GAD and they do not produce tolerance or dependence.<sup>1,3</sup>

Most people presenting to primary care with GAD have comorbidities such as major depression or a substance use related disorder. Trials may not give an accurate estimate of the 'real life' effect of antidepressants for GAD because such patients are excluded. A meta-analysis of imipramine, paroxetine and venlafaxine (which included trials excluding people with comorbidities) found that about 5 people need to be treated for 1 person to benefit clinically. It also showed that similar numbers of people taking these antidepressants or placebo therapy withdrew because of adverse effects.<sup>9</sup> In practice the use of imipramine is limited by the risk of death in overdose and adverse effects.<sup>1</sup>

### Antidepressants for social anxiety disorder: non-generalised and generalised

There is little evidence for antidepressants in non-generalised social anxiety disorder: beta-blockers (e.g. propranolol) can be used before the social event or performance.<sup>1,3</sup>

Short-term (12–24 weeks) trials in generalised social anxiety disorder show that escitalopram, fluvoxamine, paroxetine, sertraline and venlafaxine appear to be similarly effective but differ in their adverse effects.<sup>10</sup>

Long-term therapy with escitalopram, paroxetine or sertraline has been shown to prevent relapse in generalised social anxiety disorder.<sup>5</sup> Phenzelzine (a non-selective MAOI) is effective but use is limited by its adverse effect profile (e.g. sedation, weight gain), significant interactions with many other drugs, and the need to avoid all foods containing tyramine (e.g. matured cheese).<sup>3</sup>

**Table 1: Guideline recommendations for drug therapy for GAD and generalised social anxiety disorder\*<sup>1,3,5,11</sup>**

Anxiety disorder	If adding drug therapy, start with a 12 week trial of:	After 12 weeks of therapy	
GAD	<ul style="list-style-type: none"> <li>an SSRI (escitalopram, paroxetine, sertraline)</li> <li>mipramine</li> <li>venlafaxine</li> </ul>	If there is improvement, continue for at least 6 months, then slowly taper the dose and stop.	If there is no improvement or the first antidepressant is not suitable, switch to another antidepressant
Generalised social anxiety disorder	<ul style="list-style-type: none"> <li>an SSRI (escitalopram, fluvoxamine, paroxetine, sertraline)</li> <li>venlafaxine</li> </ul>	If there is improvement, continue for at least 6 months (up to 12–24 months), then slowly taper the dose and stop.	

**Table 2: Prescribing antidepressants in Australia for GAD, generalised social anxiety disorder and premenstrual dysphoric disorder (PMDD)<sup>2,12</sup>**

Drug (Brand)	TGA approved indication*	PBS listing restrictions
<b>Selective serotonin reuptake inhibitors</b>		
Escitalopram (Esipram, Lexapro)	GAD, Social anxiety disorder	Restricted benefit for: <ul style="list-style-type: none"> <li>• major depression</li> <li>• moderate to severe GAD (see PBS for full details)</li> <li>• moderate to severe social anxiety disorder (see PBS for full details)</li> </ul>
Fluoxetine (Auscap, Fluohexal, Fluoxebell, Fluoxetine, Lovan, Prozac, Zactin)	PMDD	Restricted benefit for: <ul style="list-style-type: none"> <li>• major depression</li> <li>• obsessive–compulsive disorder</li> </ul>
Fluvoxamine (Faverin, Luvox, Movox, Voxam)	Not TGA approved for GAD, social anxiety disorder or PMDD	Restricted benefit for: <ul style="list-style-type: none"> <li>• major depression</li> <li>• obsessive–compulsive disorder</li> </ul>
Paroxetine (Aropax, Extine, Paxtine, Paroxetine)	GAD, Social anxiety disorder	Restricted benefit for: <ul style="list-style-type: none"> <li>• major depression</li> <li>• obsessive–compulsive disorder</li> <li>• panic disorder</li> </ul>
Sertraline (Concorz, Eleva, Sertra, Setrona, Sertraline, Xydep, Zoloft)	Social anxiety disorder, PMDD	Restricted benefit for: <ul style="list-style-type: none"> <li>• major depression</li> <li>• obsessive–compulsive disorder</li> <li>• panic disorder where other treatments have failed or are inappropriate</li> </ul>
<b>Other</b>		
Imipramine (Tofranil, Tolerade)	Not TGA approved for GAD, social anxiety disorder or PMDD	Unrestricted
Moclobemide (Amira, Aurorix, Clobemix, Mohexal, Moclobemide)	Social anxiety disorder	Restricted benefit for major depression
Phenelzine (Nardil)	Not TGA approved for GAD, social anxiety disorder or PMDD	Depression where all other antidepressants have failed or are inappropriate
Venlafaxine (Efexor-XR)	GAD, Social anxiety disorder	Restricted benefit for major depression

\* TGA-approved indications for GAD, social anxiety disorder and PMDD are listed; refer to approved product information and the *Schedule of Pharmaceutical Benefits* ([www.pbs.gov.au](http://www.pbs.gov.au)) for information about other indications.

## Reserve benzodiazepine use to limited circumstances

In general, **reserve benzodiazepine use to the short-term** for people who have not responded to at least 2 therapies (e.g. psychological therapy, antidepressant).<sup>1,5</sup> Benzodiazepines may cause dependence — particularly in those with a history of dependence on alcohol and/or other drugs — and a withdrawal syndrome. Up to a third of people taking a benzodiazepine long-term have difficulty withdrawing or stopping.<sup>1,3,5,13</sup>

However, a benzodiazepine may be useful:

- For an acute exacerbation of GAD refractory to non-drug strategies and psychological therapies. Gradually reduce the benzodiazepine dose to zero within 6 weeks.<sup>3</sup>
- Before the social event or performance for people with **non-generalised** social anxiety disorder who cannot

use propranolol (e.g. those with asthma).<sup>3</sup> However, adverse effects (e.g. sedation) may limit their use.<sup>3</sup>

The long-term use of benzodiazepines for GAD is controversial.<sup>1,3,11</sup> Consider only for people for whom non-drug strategies, psychological therapies and alternative drug therapies (e.g. SSRI) have failed to provide significant improvement.<sup>3</sup> Try to wean every 6–12 months by gradual dose reduction and increased focus on psychological therapy (to manage symptom exacerbation).<sup>3</sup>

For generalised social anxiety disorder, limit long-term benzodiazepines to people who have unsuccessfully trialled at least 2 antidepressants, and only for those with no history of alcohol and/or other drug abuse or depression (common co-morbidities).<sup>1,3</sup>