

Timely, independent information about new drugs

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NPS RADAR provides timely, independent, evidence-based information on new drugs, research and PBS listings. It's published three times per year, in line with the *Schedule of Pharmaceutical Benefits*, for general practitioners, specialists, pharmacists and other health professionals.

NPS RADAR explains the reasons behind the PBS listing: if a medicine requires an Authority before it can be prescribed, NPS RADAR describes the evidence and deliberations behind the restrictions. NPS RADAR also considers the medicine's place in therapy and safety and dosing issues of note, using comparative evidence where available.

Drugs reviewed by NPS RADAR are selected by the NPS New Drugs Working Group using criteria that relate to quality use of medicines and relevance to primary care. The group comprises GPs, clinical specialists, academics, the pharmaceutical industry, those involved in providing independent information, and government. Each NPS RADAR issue is independently reviewed by the New Drugs Working Group and clinical experts in relevant fields.

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Timely, independent information about new drugs

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National Prescribing Service Limited

An independent, Australian organisation for Quality Use of Medicines

Quinine (Quinate, Quinbisul, Quinsul) for muscle cramp

Summary

- Quinine tablets should not be used for muscle cramp.
- The efficacy of quinine in preventing cramp is limited and is outweighed by the risk of severe thrombocytopenia, which may be fatal.
- The PBS listing and approved indications for muscle cramp for all oral quinine products have been deleted.

PBS Listing

The PBS listing for quinine for muscle cramp has been deleted. Quinine is still PBS listed for the treatment of malaria.

Reason for PBS listing

The PBS listing was deleted because the indications for muscle cramp for all oral quinine products have been removed due to an unfavourable benefit–harm profile (see *Place in therapy*).

Place in therapy

Quinine should not be used for treating muscle cramp. The efficacy of quinine in preventing cramp is marginal at best, and is outweighed by the risk of severe thrombocytopenia. For more information about quinine-induced thrombocytopenia, see *Safety issues*.

The Adverse Drug Reactions Advisory Committee (ADRAC) recently reviewed the safety and efficacy of quinine for muscle cramp and decided that the risk of adverse effects outweighs the benefits.¹ Consequently, the musculoskeletal indications (muscle cramp, treatment of myotonia congenita and diagnosis of myasthenia gravis) for oral quinine preparations have been withdrawn by the Therapeutic Goods Administration. Quinine is now indicated only for the treatment of malaria.

Quinine has poor efficacy in preventing muscle cramp

The evidence for quinine in muscle cramp is limited because studies have produced conflicting results. A meta-analysis of seven crossover trials estimated that quinine prevented 3.6 cramps (95% confidence interval 2.15–5.05) per person during a four-week period—that is, less than one cramp per week.² Cramp severity was reduced only slightly, and there was no evidence of a reduction in cramp duration.²

Alternative therapies for muscle cramp

Consider underlying causes of cramp, such as electrolyte disturbances (particularly sodium deficiency due to heavy sweating), peripheral vascular disease or motor neurone disease. Possible drug causes of cramp include calcium-channel blockers, beta₂-agonists and diuretics.

No drugs are known to be effective for preventing muscle cramp. Verapamil, vitamin E and magnesium citrate have all been assessed for preventing muscle cramp but current evidence does not support their use.^{3–6}

Passive stretch and massage of the affected muscle may relieve cramp. Stretching the calf muscles daily has been recommended to prevent cramp.⁷ Although there is no clinical trial evidence to support these measures, anecdotal evidence suggests they may be effective and the risk of adverse effects is very low.

Safety issues

Quinine can cause severe thrombocytopenia, which is unpredictable and may be fatal.

Quinine-induced thrombocytopenia

Since 1972, ADRAC has received 214 reports of thrombocytopenia involving quinine, four of which resulted in death.¹ Quinine-induced thrombocytopenia is often severe (with bleeding, or risk of bleeding) and can require hospitalisation, monitoring and blood product support.⁸

Most cases occur within a few weeks of starting quinine, although thrombocytopenia has been reported months after initiation. Intermittent dosing may result in a longer time to onset.^{8,9}

Quinine-induced thrombocytopenia is mediated by an immune mechanism so patients who experience it should subsequently avoid all quinine-containing products, including drinks such as bitter lemon and tonic water.

Dosing issues

There are no specific dosing issues.

Information for patients

Advise patients that the benefit of quinine in muscle cramp is small and uncertain, but that there is a risk of serious adverse effects. Discuss other ways to manage muscle cramp, such as passive stretching and massage.

Advise patients who have had quinine-induced thrombocytopenia to avoid all quinine-containing products, including bitter lemon and tonic water.

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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.

Orlistat (Xenical) over-the-counter for obesity

Summary

- Lifestyle changes involving diet, exercise and behavioural therapy are first-line for the treatment of overweight and obese patients.
- Consider pharmacotherapy when lifestyle changes alone are unsuccessful and where BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² with co-existing morbidities.
- When added to lifestyle changes, orlistat produces additional mean weight loss of 4.5 kg by reducing the absorption of dietary fat.
- Lifestyle changes should be established as early as possible with orlistat therapy to ensure successful long-term weight maintenance.
- Orlistat will not help all patients achieve the weight loss required for significant health benefits.
- Gastrointestinal adverse reactions are common with orlistat and can be controlled by modifying dietary intake of fat.
- Orlistat may reduce absorption of fat-soluble vitamins and it is recommended that supplementary doses of multivitamins be taken.

PBS listing

Although orlistat is listed on the RPBS from 1 December, this document relates to the re-scheduling of orlistat from Schedule 4 (Prescription Only) to a Schedule 3 (Pharmacist Only) medicine.

The supply of Schedule 3 medicines is made directly by a pharmacist who must provide information on its safe and effective use; refer to the Pharmaceutical Society of Australia *Standards for the Provision of Pharmacist Only and Pharmacy Medicines in Community Pharmacy* (available at <http://www.psa.org.au/media/medicines.pdf>) and *Provision of orlistat as a Pharmacist Only medicine* (available at <http://www.psa.org.au/media/orlistatprotocol.pdf>).

Reason for PBS listing

This document relates to the re-scheduling of orlistat from Schedule 4 (Prescription Only) to a Schedule 3 (Pharmacist Only) medicine.

Place in therapy

Orlistat reduces the absorption of dietary fat by inhibiting gastrointestinal lipases. Orlistat has a modest additional effect on weight loss when used in conjunction with diet, exercise and behavioural modification to treat obese patients with a body mass index (BMI) ≥ 30 kg/m² or overweight patients with a BMI ≥ 27 kg/m² and co-existing morbidities.

The National Drugs and Poisons Schedule Committee (NDPSC) agreed to re-schedule orlistat from Schedule 4 (Prescription Only) to Schedule 3 (Pharmacist Only).^{1,2} The decision was partly based on the XENDOS Study³, where orlistat had reasonable efficacy for weight reduction and lacked serious adverse effects (including vitamin deficiency and bone disease). The NDPSC also acknowledged the ability of the patient to recognise obesity and of pharmacists to provide good advice on its management and treatment, to identify co-morbid conditions and monitor for adverse effects and misuse of orlistat.^{1,2}

Lifestyle changes are first-line for weight reduction

Diet, exercise and behavioural therapy are first-line treatments for overweight and obese patients.⁴ There is no single, effective treatment for weight reduction and a multifaceted approach is the key to successful long-term weight loss.

Use the BMI [weight (kg) divided by height squared (m²)] and waist circumference to assess obesity and the risk of co-morbidities such as diabetes, dyslipidaemia and cardiovascular disease. A BMI ≥ 30 kg/m² or waist circumference > 88 cm in women and > 102 cm in men indicates a high risk for morbidity.⁴

Table 1 outlines lifestyle changes that are effective for weight reduction.

Table 1: Lifestyle changes for weight reduction⁴

Diet
<ul style="list-style-type: none"> • Reduce daily energy intake by 2000 kilojoules (~500 to 600 calories). • Restrict the amount of fat and other energy-dense foods in the diet. • Increase the intake of high-fibre, high-water content foods (e.g. fruits, vegetables). • Maintain three balanced meals daily with low-fat, low-energy snacks in between. • Limit alcohol consumption.
Exercise
<ul style="list-style-type: none"> • Start with regular moderate-intensity exercise for at least 3 to 5 hours per week (e.g. brisk walking 30 to 60 minutes a day). • Increase the intensity of exercise only when cardiovascular fitness improves. • Maintain physical activity for at least 80 minutes a day to maintain weight loss.
Behaviour
<ul style="list-style-type: none"> • Behavioural therapy aids compliance to changes in diet and exercise and includes strategies such as counselling, hypnosis and stress management.

For more detailed information on lifestyle changes for weight reduction, refer to the National Health and Medical Research Council (NHMRC) *Clinical Practice Guidelines for the Management of Overweight and Obesity in Adults* (available at <http://www.obesityguidelines.gov.au/pdf/adults.pdf>).⁴

Set realistic goals for weight loss

A realistic goal is to reduce weight by 1–4 kg/month and achieve a weight loss of 5 to 10% of baseline body weight.⁴ This can provide substantial health benefits including reduced blood pressure and lipid levels.^{4,5}

Consider pharmacotherapy when lifestyle changes alone are unsuccessful

Consider adding pharmacotherapy when lifestyle changes do not produce a significant weight reduction after adequate trial(s) (e.g. 12 weeks).⁵ Orlistat must be used in conjunction with lifestyle changes to treat patients with a BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² with co-existing morbidities.

Orlistat produces modest weight loss in addition to lifestyle changes

Orlistat is used to assist patients with achieving a weight reduction of 5 to 10% of body weight:

- Cease orlistat if this weight reduction cannot be achieved.^{6,7}
- Use orlistat short-term to gain the greatest effect on weight loss and establish lifestyle changes as early as possible for successful long-term weight maintenance.

Orlistat in addition to lifestyle changes (e.g. hypocaloric diet containing 30% of calories from fat, exercise, behavioural intervention) had a modest additional effect on weight reduction in studies of men and women aged 18–76 years with a BMI 28–47 kg/m² and risk factors for morbidity (e.g. hypertriglyceridaemia) (see Table 2).

Table 2: Effect of orlistat on weight reduction in 1-year^{4,8-10}, 2-year^{4,11,12} and 4-year³ studies

Studies of orlistat with lifestyle changes versus lifestyle changes alone (placebo)	Mean weight reduction with lifestyle changes alone (placebo)	Mean weight reduction with orlistat (additional to placebo)
1-year studies	≤ 8.6 kg	≤ 4.5 kg
2-year studies	≤ 3.8 kg	≤ 3.4 kg
4-year XENDOS study	≤ 3.0 kg	≤ 2.8 kg

Despite long-term efficacy and safety data, the greatest benefit of orlistat is seen with shorter-term use. Results from studies may have been affected by non-compliance with lifestyle changes and possible unblinding of orlistat treatment due to adverse effects. However the available evidence suggests that the effectiveness of orlistat in weight reduction and weight maintenance is largely dependent on lifestyle changes, particularly diet.^{3,4,8-12}

In studies, orlistat plus lifestyle changes improved obesity-related risk factors (such as total cholesterol^{3,8-12}, LDL-cholesterol^{3,8-12}, LDL/HDL ratio³, triglycerides³, blood pressure^{3,8,12}, fasting blood glucose^{3,8,10,11} and insulin levels^{3,8,11,12}) more than lifestyle changes alone.

This is important for those with existing risk factors who have attained a weight loss of ≥ 5 to 10% of body weight.^{4,5,10}

Orlistat does not produce significant long-term weight loss in all patients

Orlistat will not help all patients achieve the weight loss required for significant health benefits, particularly if there is non-compliance with lifestyle changes. In the XENDOS Study³, more patients lost ≥ 5 to 10% of body weight after 1 year of orlistat plus lifestyle changes than after 4 years of treatment (see Table 3).

Studies have shown orlistat as effective for prevention of weight regain compared with placebo^{3,8-12} however weight regain may occur when a normal energy diet is resumed whilst taking orlistat or when orlistat is ceased.

Safety issues

For more information, refer to the Xenical Product Information.

Minimise gastrointestinal adverse effects by restricting fat intake

Gastrointestinal adverse effects are common with orlistat and they reinforce to patients the need to restrict fat in the diet. To minimise adverse effects, ensure that fat intake is restricted to < 20 g per meal.⁴

Gastrointestinal adverse effects in clinical trials included faecal urgency and incontinence, oily spotting, oily evacuation, fatty/oily stool, flatus with discharge, increased defecation and abdominal pain.^{8,9,11,12} In the XENDOS Study³, at least one gastrointestinal adverse effect occurred in 91% of orlistat-treated subjects (versus 65% placebo) during the first year of treatment.

Use fat-soluble vitamin supplements to prevent deficiencies

Orlistat decreased levels of fat-soluble vitamins (vitamin A, betacarotene, vitamin D, 25-hydroxyvitamin D, vitamin E and vitamin K) in studies^{3,8,9,11,12} however they remained within the reference range.

To prevent vitamin deficiencies, it is recommended that supplementary doses of fat-soluble vitamins be taken 2 hours before or after a dose of orlistat or at bedtime.^{2,13} Multivitamin supplements used in trials contained retinyl acetate 2000 IU, betacarotene up to 11,000 IU, vitamin D₃ 5 micrograms, vitamin E 14.9 mg and vitamin K₁ 36 micrograms.¹³

Table 3: Proportion of patients with $\geq 5\%$ or 10% weight loss in the XENDOS Study³

XENDOS Study duration of treatment (years)	Proportion of patients (%) with $\geq 5\%$ weight loss		Proportion of patients (%) with $\geq 10\%$ weight loss	
	Orlistat plus lifestyle changes	Lifestyle changes alone	Orlistat plus lifestyle changes	Lifestyle changes alone
1 year	73%	45%	41%	21%
4 years	53%	37%	26%	16%

A possible increased risk of age-related macular degeneration (ARMD) due to impaired absorption of lutein and zeaxanthin (deficient in the retinas in ARMD) has been proposed with orlistat.² Given the lack of evidence of association between orlistat and ARMD and the low incidence of vitamin deficiencies in the XENDOS study³, this risk with orlistat is considered low.²

Monitor patients on warfarin or cyclosporin

Orlistat may reduce absorption of vitamin K and an increased International Normalised Ratio (INR) may occur with warfarin.¹³⁻¹⁵ Monitor INR when initiating or ceasing orlistat with anticoagulant therapy.¹³⁻¹⁵

Orlistat may decrease cyclosporin absorption and it is recommended to monitor plasma cyclosporin concentrations. If practical take the dose at least 2 hours before or after orlistat.¹³⁻¹⁵

Avoid orlistat in pregnancy and lactation

Orlistat should be avoided during pregnancy and lactation.¹⁴

Dosing issues

The recommended dose of orlistat is one 120 mg capsule taken during, or up to one hour after, the three main meals.^{6,13} The daily intake of fat, carbohydrate and protein should be evenly distributed, however a dose of orlistat should be omitted if a meal is missed or contains no fat.^{6,13}

Information for patients

Patients should receive the Xenical Consumer Medicine Information from either their doctor or pharmacist.

Advise patients that:

- lifestyle changes are necessary for weight loss and long-term weight maintenance.
- Orlistat has a modest additional effect on weight loss in conjunction with diet, exercise and behavioural modification and is used to achieve a weight loss of 5 to 10% of body weight that is beneficial to health.
- the diet must contain no more than 30% calories from fat (e.g. < 20 g fat per meal when the daily energy intake is 2000 calories).
- increased fat in the stools can be managed by reducing fat intake.
- it is recommended that supplementary doses of multivitamins containing fat soluble vitamins be taken 2 hours before or after a dose of orlistat or at bedtime.

For more information on obesity and lifestyle changes, refer to the Australasian Society for the Study of Obesity (ASSO) (available at <http://www.asso.org.au>), the National Heart Foundation of Australia (available at <http://www.heartfoundation.com.au>) and Nutrition Australia (available at <http://www.nutritionaustralia.org>).

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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.

Galantamine (Reminyl) prolonged-release capsules for dementia in Alzheimer's disease

Summary

- Prolonged-release galantamine has been PBS listed as an authority item for initial and continuing treatment of mild to moderate Alzheimer's disease. The listing was based on equivalence of the new formulation with the immediate-release formulation already listed on the PBS.
- There are no clinically relevant differences between prolonged-release and immediate-release galantamine.
- There is no reliable evidence of galantamine's long-term effectiveness. Short-term trials have found only modest improvements in scores on rating scales of cognitive, psychological and behavioural functioning.
- Galantamine has similar efficacy to other cholinesterase inhibitors.
- Increasing the dose of galantamine above 16 mg/day is not associated with greater benefit, and is likely to increase adverse effects.
- There is doubt about the place in therapy of cholinesterase inhibitors. Recent evidence with donepezil (Aricept) found no effect on long-term outcomes relevant to patients and carers such as delay in progression of disability or institutionalisation, behavioural and psychological symptoms and active carer time.

PBS Listing

The new PBS listing is for prolonged-release, once-daily formulations of galantamine (8 mg, 16 mg, 24 mg) for initial and continuing treatment of mild to moderately severe Alzheimer's disease. There is no change to the authority listing—see the *Schedule of Pharmaceutical Benefits* for the full authority requirements.

Reason for PBS listing

The PBAC considered the new once-daily capsules to be equivalent to the twice-daily tablets already listed on the PBS.¹

PBAC reviews found no benefit for higher doses of galantamine

An application for galantamine 12 mg immediate release tablets was rejected by PBAC in September 2003.² It was later recommended for listing in March 2004, but the PBAC stated that 'no evidence was presented that 12 mg twice daily provides any additional clinical benefits in terms of either effectiveness or toxicity over 8 mg twice daily'.³ Because there was no additional benefit, the PBAC recommended listing on the condition that should be no additional cost to the PBS for the prescribing of galantamine overall.

Place in therapy

- Guidelines suggest that patients who do not stabilise or improve in the first few months of anticholinesterase therapy are unlikely to have any subsequent benefit.⁴
- Patients should be reviewed regularly to assess the value of ongoing treatment.
- The clinical and cost-effectiveness of cholinesterase inhibitors is uncertain. While these drugs improve the quality of life of some people with Alzheimer's disease, clinical trials have found that, on average, improvements are modest.

The authority listing restricting the use of cholinesterase inhibitors to people with mild to moderate Alzheimer's disease improved by drug therapy reflects the evidence

- which is restricted to people with mild to moderate Alzheimer's disease
- that not all patients improve with cholinesterase inhibitors
- that it is not possible to predict which patients will respond to these drugs.⁴

Prolonged-release formulation no different to twice-daily tablet

The Reminyl Product Information states there are no clinically relevant differences between the prolonged-release once-daily formulation and the immediate release twice-daily tablets in terms of drug compliance, dose titration, dose reduction, discontinuation or dose compliance.⁵ It is of interest that there is no improvement in compliance in moving from a twice-daily preparation to a once-daily preparation.

Short-term effectiveness is modest

A Cochrane review⁶ of 3–6 month trials of galantamine found:

- cognitive function was improved marginally by galantamine compared to placebo (a change of between 2 to 4 points on the 70-point ADAS-Cog*)
- psychological and behavioural scores† were improved slightly in one six-month trial
- patients taking galantamine were between 1.3 and 3 times as likely as patients on placebo to be rated 'same' or 'improved' by physicians and carers (a subjective rating).

* ADAS-Cog: Alzheimer's disease assessment scale cognitive section

† Rated on the Neuropsychiatric Inventory

Additional benefit of long-term treatment is unclear

Three-year data exist only for a sub-group of patients who chose to stay on extended, open-label treatment after a randomised clinical trial—that is, those who probably responded well to treatment.⁷ Such results cannot be applied to previously untreated patients who might be eligible for treatment.

In a randomised year-long trial, most improvement in Mini-Mental State Examination (MMSE) scores occurred in the first 6 months of treatment, and declined gradually afterwards. After one year the score was similar to baseline.⁸

Galantamine has similar efficacy to other cholinesterase inhibitors

A meta-analysis reported similar effect sizes for donepezil, rivastigmine and galantamine.⁹ The maximum mean benefit achieved is similar across the class: for example, a 3-point improvement in the ADAS-Cog (a 70-point scale).¹⁰

Two trials comparing galantamine with donepezil do not show any consistent differences in efficacy.^{8,11} The longer of these, a 12 month comparison found no difference between the two drugs in the primary outcome of function in activities of daily living.⁸

Questions about effectiveness of cholinesterase inhibitors

The recent large AD2000 trial, which looked at long-term, real-life outcomes associated with **donepezil (Aricept)**¹², has raised doubts about the clinical relevance of statistically significant, but small, changes in rating scales seen in short-term studies. Although **galantamine was not studied** in the AD2000 trial, the questions raised apply to the whole class.

AD2000 found that donepezil improved scores on the MMSE and the Bristol Activities of Daily Living Scale (BADLS)* by about 1 point each over 2 years of treatment. Clinicians have indicated a change of 3 points as the minimally clinically relevant change in the MMSE for people with dementia.¹³ However in AD2000 there was

- no delay in progression of disability associated with Alzheimer's disease
- no delay in institutionalisation
- no change in behavioural and psychological symptoms
- no reduction in caregiver psychological morbidity (measured by the General Health Questionnaire—GHQ)
- minimal reduction in active carer time (reduced by 12 minutes per day, not statistically significant).¹²

It is possible the study was underpowered to detect differences in institutionalisation and progression of disability. Nonetheless changes on the MMSE and BADLS rating scales are consistent with those found in other trials.¹⁴

*BADLS: measures non-cognitive functioning and ability to perform tasks such as dressing, daily hygiene, mobility, communication.

Consider practical needs of patients and carers

After diagnosis, encourage patients and carers to make plans that take into account the patient's current functional state, as well as thinking broadly about what to do when deterioration occurs.

Changes to the person's environment, routines and tasks may help to reduce patient and carer distress in day-to-day activities. See the Alzheimer's Association website (www.alzheimers.org.au) for help sheets on daily care (hygiene, dressing, safety), behavioural issues (sundowning, wandering, aggression, agitation), and changes that can be made to the home and environment.

Consider the use of respite care. In Australia, the Commonwealth National Respite for Carers Program provides information and help to arrange access to respite care for carers of people with chronic conditions (www.health.gov.au/acc/carers/index.htm; phone 1800 059 059).

Some behavioural therapies (e.g. reorientation, reminiscence, music therapy) may be useful in some people with behavioural disturbance but clinical trials are small in size and few in number.^{15–17}

GP-initiated Care Plans for people with chronic illness who require a multidisciplinary approach can be reimbursed through Medicare (www.health.gov.au/epc/careplan.htm#careplan).

Safety issues

Adverse effects such as nausea, vomiting, diarrhoea and dizziness appear to be similar to those of other drugs in the class¹⁸ and are increased at doses higher than 16 mg per day.⁶

Dosing issues

Starting dose: 8 mg per day for 4 weeks.

Galantamine 8 mg per day is used for titration to minimise adverse effects but is not a therapeutic dose.

Maintenance dose: 16 mg per day

Doses of galantamine above 16 mg per day are not associated with greater clinical improvement.^{6,9,19}

The maximum dose recommended in the product information is 24 mg per day. If 24 mg per day is prescribed, minimise adverse effects by ensuring at least 4 weeks at 16 mg per day before increasing the dose.⁵

Information for patients

Patients and/or carers should receive the Reminyl Consumer Medicine Information (CMI) from either their doctor or pharmacist.

The Alzheimer's Association of Australia offers support and information to people with Alzheimer's disease and their carers and families.

website: www.alzheimers.org.au

Phone (toll-free): 1800 639 331

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Sertraline (Zoloft), fluoxetine (Lovan, Prozac,) for premenstrual dysphoric disorder (PMDD)

Summary

- Sertraline and fluoxetine are TGA-approved for premenstrual dysphoric disorder (PMDD). However they cannot be prescribed on the PBS for this indication.
- Premenstrual dysphoric disorder (PMDD) is a recently characterised diagnosis, provisionally listed in the appendix of DSM-IV while being better defined. It is **not** the same as premenstrual syndrome (PMS), but is a more severe manifestation.
- There is debate over the validity and usefulness of the diagnosis.
- Before considering fluoxetine or sertraline:
 - Confirm the diagnosis and assess severity with prospective monitoring
 - Consider behavioural treatment including information, coping skills training, relaxation and/or cognitive behavioural therapy.
- Dosing may be either continuous daily or intermittent in the premenstrual, luteal phase only. It is unclear whether intermittent dosing reduces common adverse effects, but it does limit drug exposure.

PBS listing

Sertraline and fluoxetine cannot be prescribed on the PBS for premenstrual dysphoric disorder (PMDD).

Reason for PBS listing

This indication is not PBS listed.

Place in therapy

Sertraline has **TGA approval** for the treatment of premenstrual dysphoric disorder (PMDD), as defined by the DSM-IV criterion in adults (18 years and above).¹ The other selective serotonin re-uptake inhibitor (SSRI) approved for this indication in Australia is fluoxetine.²

PMDD is a recently characterised diagnosis, provisionally listed in the appendix of DSM-IV while being better defined (see Figure 1).

Diagnosis: PMDD *is not* the same as PMS

PMDD is an extreme manifestation of premenstrual syndrome (PMS). While PMS is experienced by many women, the more severe disorder is experienced by relatively few.³ It is characterised by:

- severe mood changes premenstrually, which abate after menstruation
- significant functional impairment disrupting work, social activities, and/or relationships.⁴

Diagnosis requires patients to record symptoms daily for 2 months.

This diary is used to check that symptoms are cyclical as well as recurring, and to exclude an ongoing problem. Diagnosis may be complicated by the fact that some disorders (e.g. depression, anxiety) can be exacerbated premenstrually⁴, although this has not been well researched.³

Figure 1: Provisional DSM-IV criteria for diagnosis of PMDD⁴

- a. Symptoms begin 1 week before menses and resolve in the first few days after menses (over most menstrual cycles during the past 12 months).
- b. Five of the symptoms below, one of which must be a mood symptom.
- | | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Mood symptoms (at least one must be present)</p> <ul style="list-style-type: none"> • Depressed mood with feelings of hopelessness • Anxiety/tension • Mood swings • Irritability/anger | <p>Other symptoms</p> <ul style="list-style-type: none"> • Decreased interest in usual activities and social withdrawal • Difficulty concentrating • Lack of energy (fatigue) • Appetite changes (overeating/undereating) • Hypersomnia/insomnia • Feeling out of control or overwhelmed • Somatic symptoms such as bloating, mastalgia or headaches |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
- c. Symptoms must be severe enough to interfere with work, school, usual activities or interpersonal relationships.
- d. Symptoms may be superimposed on an underlying psychiatric disorder, although they should not be an exacerbation of another condition.
- e. Criteria a, b, c and d must be confirmed by prospective daily charting for a minimum of two consecutive symptomatic menstrual cycles.

Is PMDD a real disorder?

There are debates about the validity of the disorder. Supporters of the PMDD classification argue that better recognition will allow treatment of distressing and disruptive symptoms.^{5,6} Others argue that inclusion of menstruation-related mood changes in DSM-IV stigmatises women and encourages drug treatment of a normal experience.⁷

The definition of PMDD (Figure 1) was derived primarily to allow a common definition for research, and is provisionally listed in the appendix of the DSM-IV. It is not listed in the International Classification of Disease, although PMS is included under gynaecological disorders. The UK recently revoked the PMDD indication for fluoxetine, as not all European countries recognise PMDD as a disorder.⁸

These debates aside, in practice ensure that:

- women presenting with severe or disabling premenstrual symptoms are assessed
- other possible causes are excluded, including a primary diagnosis of major depression (see Table 1: Differential diagnosis)
- a clear distinction is made between PMS and the more extreme manifestation of PMDD.

There may be consumer demand for inappropriate use of these medicines in PMS.

Table 1: Differential diagnoses for women with symptoms of PMS or PMDD³

Psychiatric	Physical
Major depression	Endometriosis
Dysthymia	Thyroid disorders
Bipolar disorder	Seizure disorders
Generalised anxiety	Autoimmune disorders
Panic disorder	Dysmenorrhoea
Perimenopausal mood symptoms	Allergy

Behavioural measures appear beneficial and may have sustained benefit

Behavioural changes such as limiting salt, caffeine and alcohol in the diet are often suggested for PMS and PMDD, but these have not been evaluated.⁹

Regular moderate exercise may help relieve physical symptoms.⁹

Consider psychological therapies such as cognitive behavioural therapy (CBT). CBT and coping skills training have shown promise in the treatment of PMDD and unlike drug therapy, changes may be sustained when treatment stops.¹⁰⁻¹³ A three-armed trial comparing fluoxetine, CBT and fluoxetine+CBT found similar improvements in all groups. Fluoxetine users improved more rapidly, but the ultimate outcome was similar for all treatment types.¹⁰

Psychological therapies in trials have included

- information about PMDD
- an emphasis on coping skills
- behavioural strategies to manage stress in the premenstrual phase
- relaxation training
- assertiveness training.

There may be therapeutic value in recognising that the symptoms are distressing and affect women's lives. The fact that trials provide ongoing follow-up and discussion of symptoms may account for high placebo effects in both drug and non-drug trials.

Evidence base for SSRIs in PMDD

From the 30–40 trials available, it seems likely that sertraline and fluoxetine reduce the mood symptoms of PMDD. Both intermittent (luteal phase, between ovulation and menses)^{5,14–16} and continuous daily dosing^{5,17–19} regimens have shown similar effects. (See *Dosing issues*)

However questions remain about:

- to what extent function is improved (clinical impact)
- whether effects are sustained with prolonged use (most trials of three months duration)
- the safety and suitability of these drugs for long-term use.

Questions about the evidence

There have been large placebo effects in PMDD trials of SSRIs. In most trials, patients on placebo also improved over time—but to a lesser extent than drug treatment groups.^{14,15,20} For example, PMDD symptom scores after active treatment were reduced by 30–40%, while placebo scores were reduced by about 20%.^{14,20}

Although a recent study (n=167) found differences in average symptom scores, placebo-treated and sertraline-treated patients were not significantly different by the third month.²⁰

Further, the validity of a Cochrane review¹⁹ which described SSRIs as 'highly effective in treating premenstrual symptoms' has been questioned, and should be treated with caution as the methodology may have overestimated the treatment effect.^{21,22}

Compared to existing therapy

Other treatments focusing on ovulation suppression (e.g. danazol, gonadotrophin-releasing hormone agonists) have had significant adverse effects. Use of oral contraceptives to suppress ovulation has been proposed but not well investigated.⁹

Safety issues

If SSRIs are chosen as the primary treatment for PMDD, this is potentially long-term treatment for women in their reproductive years. The safety of such prolonged use is unknown.

While SSRIs do not appear to be teratogenic²³, they have been associated with withdrawal effects in neonates (e.g. jitteriness, agitation).^{24,25} An increased risk of preterm birth and other adverse effects in neonates has been associated with use of SSRIs in the third trimester.²⁴

Discuss these risks and contraception needs with the woman when prescribing. However PMDD symptoms are likely to resolve in pregnancy.⁹

Adverse drug reactions

- PMDD trials report the common known adverse effects of SSRIs (insomnia, gastrointestinal disturbances, fatigue and decreased libido).
- Adverse effects are dose-related.
- Intermittent dosing appears to be effective and limits drug exposure. However it is not clear how intermittent dosing influences the severity and frequency of adverse effects—including possible withdrawal symptoms with sertraline. While one study found adverse effects (nausea, headache, insomnia) reduced over three months of intermittent use¹⁴, another found that adverse effects persisted with intermittent dosing compared to continuous use.²⁰ Clinical drug interactions might be more difficult to manage with intermittent dosing.

Dosing issues

Fluoxetine:

- Continuous dosing: 20 mg per day
 Intermittent dosing: 20 mg per day for 14 days prior, until first day of menses.

A trial of a higher (60 mg) dose showed significant increase in adverse effects with no additional benefit.¹⁷

Sertraline:

- Continuous dosing: 50–150 mg per day (depending on response)
 Intermittent dosing: 50–100 mg for 14 days prior, until first day of menses. (If 100 mg, start at 50 mg for 3 days each month)

In sertraline trials, average doses after 3 months have been between 70–100 mg.^{5,14,18,27} Prescribers and consumers need to judge whether adverse effects of higher doses are justified by treatment benefits. (See *Adverse drug reactions*)

Some consumers may find intermittent dosing schedules more difficult to manage, however they may be worth using initially to limit drug exposure.

Information for patients

Talking about the impact of premenstrual symptoms on women's lives and supportive and/or problem-solving therapy may have a therapeutic effect. If symptoms are related to menstruation, women may be able to plan to limit stressors at the time when they are less able to cope. The symptom diary may be helpful in unravelling timing of symptoms, stressors and management strategies.

Patients should receive the Consumer Medicine Information (CMI) for the drug prescribed from either their doctor or pharmacist.

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In Brief

In Brief is a digest of news items about NPS RADAR, new drugs and changes to PBS listings.

PBS changes simplify glitazone prescribing

In response to prescribers' concerns regarding the complexity of the PBS listing of pioglitazone (Actos) and rosiglitazone (Avandia), the conditions under which glitazone therapy can be continued have been simplified.

For patients who have been prescribed glitazone therapy on the PBS, HbA_{1c} measurements are no longer required by the Health Insurance Commission (HIC) to continue glitazone therapy. Patients who had glitazone therapy interrupted because they did not fulfil the previous continuation criteria around HbA_{1c} readings can have their glitazone therapy re-commenced.

Note the criteria for initiating glitazone therapy in patients are unchanged.

This means that patients must be taking either metformin or a sulfonylurea (or, in the case of pioglitazone, be using insulin) to be eligible for a glitazone on a PBS-subsidised prescription.

Measuring HbA_{1c} remains a valuable way of monitoring your patient's diabetes control and the effectiveness of drug therapy.

The PBS changes are effective from 17 November 2004. However, the changes have occurred too late to appear in the December *Schedule of Pharmaceutical Benefits*. The amendments will be made online in early 2005 and then in the April *Schedule*.

The NPS RADAR reviews for pioglitazone and rosiglitazone have been updated to reflect these changes and are available at www.npsradar.org.au.

Rofecoxib withdrawal — NPS factsheet

Rofecoxib (Vioxx) was withdrawn in October after it was found to increase the risk of heart attacks and strokes. Read NPS's factsheet, 'Switching patients from Vioxx' for information about alternatives. The December 2004 issue of *NPS News*, available from mid-December, discusses the evidence leading to the rofecoxib withdrawal. Both the factsheet and *NPS News* are available from the NPS website (www.nps.org.au, go to Health Professionals).

NPS RADAR to review antidepressants for children

ADRAC has recently updated its advice regarding use of SSRIs in children and adolescents with depression. The ADRAC advice (available at www.tga.gov.au/adr/adrac_ssri.htm) states that there is evidence of an increased risk of suicidality with each of the SSRIs. Appropriate warnings are to be added to each of the SSRI Consumer Medicine Information leaflets.

Early in 2005, NPS RADAR will provide advice to prescribers that will include a discussion of the evidence behind recent warnings, and the strengths and weaknesses of that evidence.

NPS News looks at the gaps in the evidence for new drugs

Drug marketing focuses on what we know about new drugs. An important part of deciding whether to use a new drug is being aware of what we don't know. Read a discussion of the limitations of the evidence for new drugs and practical steps to decide whether to use a new drug in the December 2004 issue of *NPS News*, available mid-December on the NPS website (www.nps.org.au).

Easier navigation through NPS RADAR reviews on the web

The December issue of NPS RADAR on the web (www.npsradar.org.au) includes a new navigation menu on the right-hand side of each review. The easy-to-use menu moves as you scroll and allows you to click through the contents of each RADAR review. We hope you find this new feature helpful—we look forward to your feedback at info@nps.org.au.



National Prescribing Service Limited

The Leading Edge: New Drugs Seminars

Due to the success of previous The Leading Edge: New Drugs Seminars, National Prescribing Service Ltd will be conducting approximately 50 of these events across Australia between February and June 2005. The seminars will be co-hosted with Divisions of General Practice for GPs and with State Branches of the Pharmaceutical Society of Australia for pharmacists.

These seminars, using clinical examples, provide GPs and pharmacists with generic principles in considering new drugs, and also give GPs and pharmacists the opportunity to:

- Discuss how new drugs can fit into general practice
- Debate new roles for older drugs
- Hear independent information about new drugs prior to patient requests
- Help sift the facts from the hype about new drugs
- Meet with and chat to other experts

Upcoming seminars will be advertised in medical and pharmaceutical magazines and be listed on www.nps.org.au.

Keep track of what's out there

If you or someone you know would like to receive free NPS RADAR reviews, simply complete the details below and fax a copy back to (02) 9211 7578. You can also register online for email updates at www.npsradar.org.au.

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The following NPS RADAR reviews are available at www.npsradar.org.au.
Look for the NPS RADAR index in Quick Links.

Adrenaline (EpiPen) auto-injector for acute allergic anaphylaxis	December 2003
Aripiprazole (Abilify) for schizophrenia	May 2004
Carvedilol (Dilatrend) titration pack for heart failure	August 2004
Deferiprone (Ferriprox) for thalassaemia major	February 2004
Escitalopram (Lexapro) for major depressive disorders	February 2004
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Ezetimibe (Ezetrol) for dyslipidaemia	August 2004
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Galantamine (Reminyl) prolonged-release capsules for dementia in Alzheimer's disease	December 2004
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Moxifloxacin (Avelox) for community-acquired pneumonia	November 2003
Oral inactivated cholera vaccine (Dukoral)	May 2004
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Quinine (Quinate, Quinbisul, Quinsul) for muscle cramp	December 2004
Ramipril (Tritace) titration pack	November 2003
Rosiglitazone (Avandia) for type 2 diabetes mellitus	May 2004
Sertraline (Zoloft), fluoxetine (Lovan, Prozac) for premenstrual dysphoric disorder	December 2004
Triptans for migraine	February 2004

Visit www.npsradar.org.au to view all NPS RADAR reviews or register for email updates. NPS RADAR reviews are also available in GP prescribing software (Genie, IBA Spectrum Plexus, Locum and Medical Director) for one year after publication.