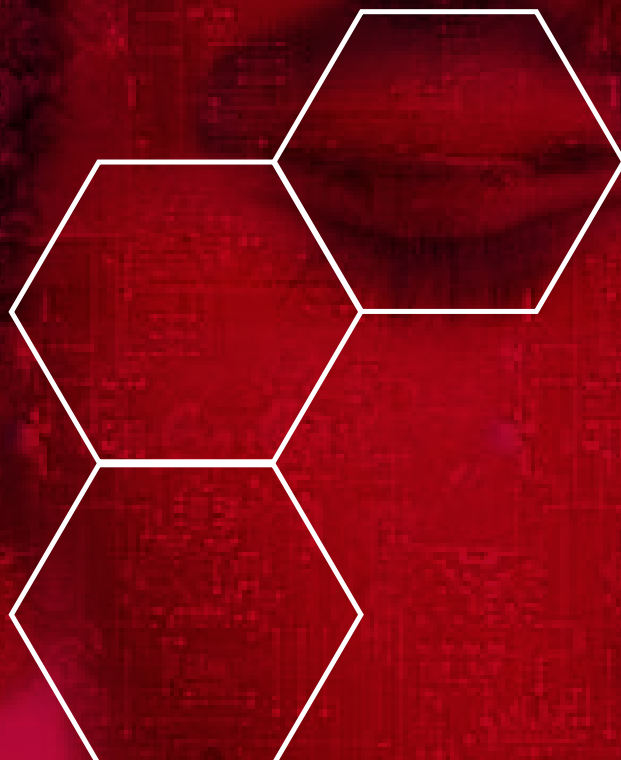


Western Australian
Psychotropic Drugs
Committee

Anxiety Disorders Drug Treatment Guidelines

August 2008



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Executive Summary

The purpose of these guidelines is to provide a summary of the current available information regarding the pharmacotherapy of anxiety disorders. They are intended as a non-prescriptive guide for all medical practitioners. The guidelines present recommended treatments based on current evidence and best-practice, however the treating clinician is responsible for patient management in each case.

Which anxiety disorder?

These guidelines consider pharmacological management of,

- generalised anxiety disorder (GAD)
- social anxiety disorder (SAnD)
- panic disorder (PD)
- specific phobia
- obsessive compulsive disorder (OCD)
- post-traumatic stress disorder (PTSD)

Patients may fall into more than one of these diagnostic groups as comorbidity between anxiety disorders is common, as is comorbidity with other physical and psychiatric illnesses, particularly depression. See *Figure 1* for a diagnostic algorithm.

When pharmacotherapy of anxiety is appropriate, SSRI drugs are recommended as the first-line option

SSRI drugs are preferred because of the strength of evidence indicating their use and because of their acceptable tolerability. Selection of a specific agent will depend on the disorder being treated and patient-related factors. See *Table 2* for selection of first-line SSRI drugs according to anxiety disorder. Drugs are listed in alphabetical order and in order of supporting evidence.

Points to consider when treating anxiety with an SSRI

- Start at a low dose and gradually titrate to a therapeutic dose
- Counsel the patient on expected onset of action (4-12 weeks) and potential side-effects of treatment (eg: initial jitteriness/anxiety¹, sexual dysfunction, discontinuation symptoms)
- Monitor patient's clinical condition for worsening of symptoms and suicidal ideation
- Allow up to 12 weeks of treatment to assess the patient's response
- When commencing treatment with an SSRI, consider supplementary treatment with benzodiazepine for a short period.

Psychological or pharmacological treatment?

Psychological treatment for anxiety disorders

Psychological therapies can be as effective as drug therapies in the treatment of anxiety disorders and should be considered first-line in the treatment of anxiety where accessible, acceptable to the patient and appropriate to the severity of impairment.

Psychological therapy may be used alone or in conjunction with pharmacological treatment, although there is limited evidence supporting its short-term efficacy. However, in the long-term there may be a reduction in the risk of relapse as a result of using psychotherapy.

Pharmacological treatment for anxiety disorders

Antidepressant and anxiolytic drugs are the two most commonly used pharmacological treatments for anxiety disorders. Newer anticonvulsant and sometimes antipsychotic drugs are also used in the treatment of some anxiety disorders. *Table 1* outlines some of the relative advantages and disadvantages of using these drug classes.

Positive and negative effects of drugs used to treat anxiety

Table 1

Agent	Positive	Negative
SSRI	<ul style="list-style-type: none"> ■ well tolerated ■ treats co-morbid depression ■ low risk of mortality in overdose when used as a single agent 	<ul style="list-style-type: none"> ■ slow onset of effect (4-12 weeks) ■ may worsen symptoms initially
Benzodiazepines	<ul style="list-style-type: none"> ■ quick onset of effect ■ well tolerated 	<ul style="list-style-type: none"> ■ sedation ■ rebound anxiety on withdrawal ■ risk of dependence
TCA	<ul style="list-style-type: none"> ■ treats co-morbid depression 	<ul style="list-style-type: none"> ■ cardiotoxicity ■ anticholinergic effects ■ risk in overdose
MAOI	<ul style="list-style-type: none"> ■ treats co-morbid depression 	<ul style="list-style-type: none"> ■ low tyramine dietary requirement ■ risk of hypertensive crisis
RIMA	<ul style="list-style-type: none"> ■ reduced dietary restrictions compared with MAOI 	<ul style="list-style-type: none"> ■ less effective than MAOI
Anticonvulsants	<ul style="list-style-type: none"> ■ quick onset of effect 	<ul style="list-style-type: none"> ■ low levels of evidence ■ sedation ■ there may be the potential for tolerance/dependence, but this has yet to be established ■ Pharmaceutical Benefits Scheme status issues

Practice notes

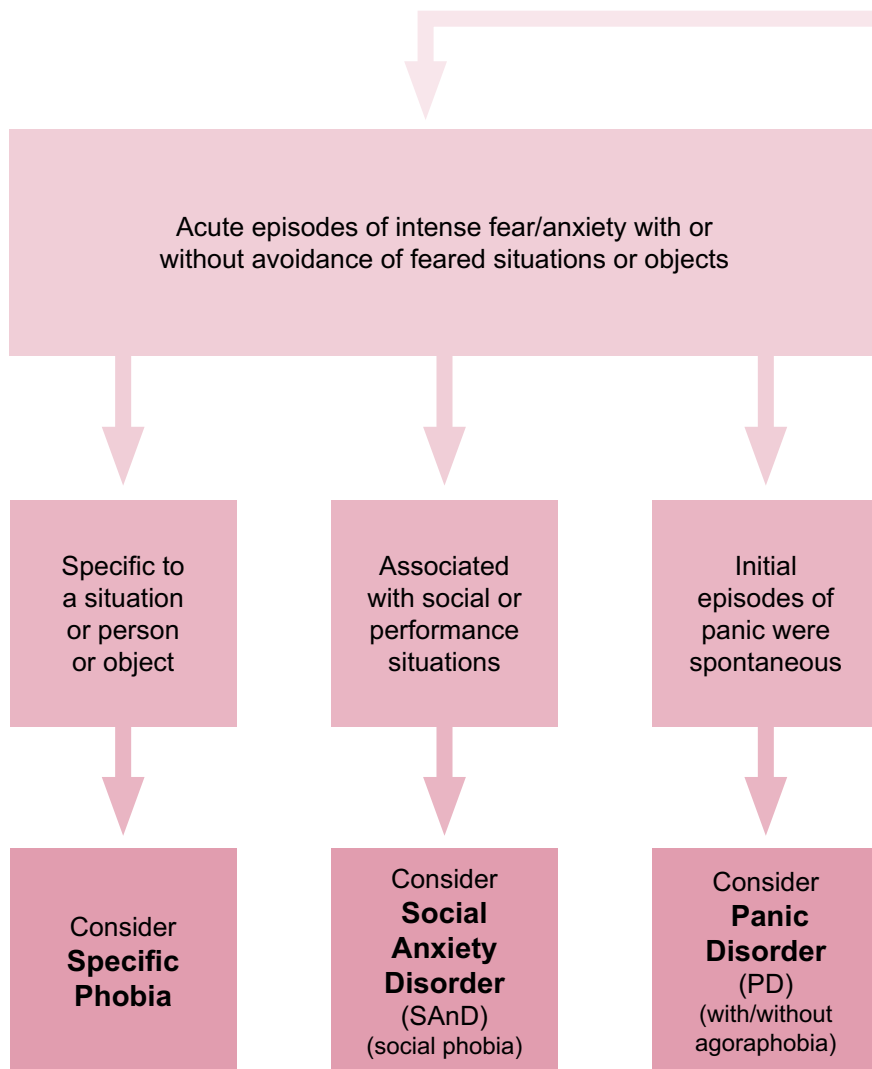
- Antidepressants, particularly SSRI, may be associated with an initial worsening of anxiety symptoms in some patients. Start patients on low doses and slowly titrate up to a therapeutic dose to reduce these “activation” symptoms¹. Patients should be advised of the potential for initial increase/worsening of symptoms and the likely delay of clinical effect (some response often seen by 4 weeks). Patient awareness of these factors when commencing SSRI treatment assists in reducing early discontinuation of treatment. Concomitant use of benzodiazepines during early treatment with SSRI may be useful in moderating these “activation effects” of SSRI early in treatment, although the potential for dependence must be considered.
- SSRI need to be taken for up to 12 weeks in order to assess a patient’s response to treatment. Dosing requirements for antidepressants differ to that needed in the treatment of depression. Start patients on low doses of SSRI and slowly titrate up. Higher therapeutic SSRI doses are often required, particularly for OCD and PTSD. When using TCA to treat anxiety, start at very low doses.
- The risks and benefits of using benzodiazepines should be carefully considered in each patient. Benzodiazepines have rapid onset, relatively low toxicity, and anxiolytic potency but these benefits should be weighed against potential for motor impairment, dependence and withdrawal symptoms.
- All patients being treated with antidepressants (irrespective of diagnosis) should be monitored for worsening of their clinical condition and the emergence of suicidal ideation.
- There is little systematic evidence to aid in the decision of what to do when the initial (or subsequent) therapies do not work. The options are to:
 - 1) **INCREASE** the dose
 - 2) **SWITCH** to an alternative drug - within the same class, another drug class or psychotherapy
 - 3) **ADD ON** another drug treatment or psychotherapy

The evidence for dealing with incomplete response or treatment resistance is outlined in *Table 4*.

Which anxiety disorder?

Figure 1.

Figure 1 presents a schematic representation of DSM-IV defined anxiety disorders. Note that patients may fall into more than one diagnostic category since anxiety disorders have a high co-morbid association with other anxiety disorders and other psychiatric illnesses, particularly depression.



Anxiety disorder suspected

Uncontrollable
worry or
tension

Consider
**Generalised
Anxiety
Disorder**
(GAD)

Obsessions
and/or
compulsions

Consider
**Obsessive
Compulsive
Disorder**
(OCD)

Previous
trauma
flashbacks

Consider
**Post-traumatic
Stress
Disorder**
(PTSD)

First-line drug treatment of anxiety disorders

Table 2.

SSRI are the recommended first-line drugs for treatment of anxiety based on strength of evidence and acceptable tolerability. In this, and the following tables, the level of evidence is shown in parentheses.

Panic disorder (with/without agoraphobia)²⁻⁵		
SSRI (I)	citalopram (II) fluoxetine (II) paroxetine (II)	escitalopram(II) fluvoxamine (II) sertraline (II)
Social anxiety disorder^{2-4,6}		
SSRI (I)^{9,10}	citalopram (II) fluoxetine (II) paroxetine (II)	escitalopram (II) fluvoxamine (II) sertraline (II)
Obsessive compulsive disorder^{2-4,7,8}		
SSRI (I)	escitalopram (II) ¹¹ fluvoxamine (II) sertraline (II)	fluoxetine (II) paroxetine (II)
Generalised anxiety disorder²⁻⁴		
SSRI (I)¹²	paroxetine (I) ¹³ sertraline (II)	escitalopram (II)
SNRI	venlafaxine (II) ²⁰	
Post-traumatic stress disorder²⁻⁴		
SSRI (I)¹⁴	fluoxetine (II) ^{a15} sertraline (II) ^{a16} escitalopram (IV) ¹⁷	paroxetine (II) citalopram (IV) ¹⁷

Second-line and other treatment options

Table 3.

Strength of evidence is sometimes very high for alternative treatments, but tolerability/ side-effects/concerns regarding abuse potential preclude them from first line.

Panic disorder (with/without agoraphobia)²⁻⁵	
TCA (I)	clomipramine (II), imipramine (II)
SNRI	venlafaxine (II)
NRI	reboxetine (II)
MAOI and RIMA	phenelzine (II) , moclobemide (II) ^a
NaSSA	mirtazapine (II)
BZD (I)	alprazolam (II), clonazepam (II), diazepam (II), lorazepam (II)
AC²	valproate (IV)
Social anxiety disorder^{2-4,6}	
SNRI	venlafaxine (II)
MAOI	phenelzine (II)
RIMA	moclobemide (II) ^a (<i>note 1 meta-analysis found moclobemide effective over 5 studies (I)</i>) ¹⁰
AC	gabapentin (II) pregabalin (II) topiramate (IV)tiagabine (IV) ¹⁸
BZD	clonazepam (I) bromazepam (IV)
AP	olanzapine (II) ^a quetiapine (IV)
NRI	reboxetine (IV)
Obsessive compulsive disorder^{2-4,7,8}	
TCA	clomipramine(I)
SNRI	venlafaxine (II)
Generalised anxiety disorder²⁻⁴	
AC	pregabalin (I) ¹⁹
SNRI	duloxetine (I/II)* ²¹
TCA	imipramine (II)
NaSSA	mirtazapine (IV)
Other anxiolytics	bupropion (II) ²²
BZD	alprazolam (II), diazepam (II), lorazepam (II), bromazepam (II)
Post-traumatic stress disorder²⁻⁴	
SNRI	venlafaxine (II)
TCA	amitriptyline (II), imipramine (II)
MAOI	phenelzine (II)
NaSSA	mirtazapine (II)
AC	lamotrigine (II) ^{23e}
RIMA	moclobemide (IV)
Other antidepressants	bupropion (IV), <i>but see Ref.24 (II) for no response cf placebo</i>
AP	quetiapine (IV) ^{25d}

What to do for incomplete responders?

Table 4.

These recommendations are based on studies that have either directly tested efficacy in partial or non-responders, or have demonstrated a particular effect for severely ill patients, under the presumption the more severely ill may be more treatment resistant.

Panic disorder (with/without agoraphobia)²⁻⁵	
Switch	Moclobemide may be beneficial in more severely ill patients (II) ²⁶ ; Gabapentin improved symptoms in moderately to severely ill patients (II) ²⁷
Augment with medication or psychotherapy	Fluoxetine plus pindolol for treatment resistant patients (II) ²⁸ ; SSRI plus olanzapine (IV) ²⁹ ; Adjunct risperidone (IV) ³⁰ ; Adjunct phenelzine (IV) ³¹ ; Pharmacotherapy non-responders + group CBT (IV) ³²⁻³⁴
Increase dose	(EC)
Social anxiety disorder^{2-4;6}	
Switch	Phenelzine may be best option for treatment resistant patients (II) ⁶
Augment with medication or psychotherapy	SSRI non-responders may respond to venlafaxine (IV) ^{35;36} ; Adjunct risperidone (IV) ³⁰ ; SSRI + buspirone (IV) ³⁷ ; SSRI + aripiprazole (IV) ³⁶
Increase dose	(EC)
Obsessive compulsive disorder^{2-4;7;8}	
Switch	SRI resistant patients may respond to venlafaxine (IV) ⁴⁸ ; 42% response when non-responders to paroxetine or venlafaxine switched to the other (III-1) ⁴⁹
Augment with medication or psychotherapy	Antipsychotics (including risperidone, olanzapine and quetiapine) as adjunct to serotonergic antidepressants in treatment resistant OCD (I) ³⁸⁻⁴⁰ ; Adjunctive topiramate (IV) ^{41;42} ; Citalopram plus reboxetine (IV) ⁴³ ; CBT in conjunction with fluoxetine to fluoxetine-alone non-responders (IV) ^{44;45} ; CBT added to SRI non-responders in naturalistic fashion (IV) ⁴⁶
Increase dose	High dose sertraline (up to 400 mg/d) (caution serotonin syndrome) may improve response in people not responding to 200 mg/d (II) ⁴⁷
Generalised anxiety disorder²⁻⁴	
Switch	(EC)
Augment with medication or psychotherapy	Adjunct olanzapine (II) ^{50c} ; Adjunct risperidone (II) ⁵¹ ; Adjunct aripiprazole (IV) ⁵²
Increase dose	(EC)
Post-traumatic stress disorder²⁻⁴	
Switch	(EC)
Augment with medication or psychotherapy	SSRI (non responder) plus olanzapine (II) ⁵³ ; SSRI (non responder and aggression/psychotic symptoms) plus risperidone (II) ⁵⁴ ; SSRI plus quetiapine (IV) ⁵⁵ ; SSRI (non responder) plus tiagabine (IV) ⁵⁶ ; Monotherapy with antipsychotics (IV) ⁵⁷ ; Addition of psychotherapy (IV) ^{8;58}
Increase dose	(EC)

Serotonin syndrome

Serotonin syndrome can occur when prescribing high doses of a single serotonergic agent, after adding a second serotonergic drug, during switching of antidepressants or when drugs with different mechanisms of increasing serotonin are used together. Symptoms may include: confusion and agitation, hyperreflexia and clonus, flushing, shivering, sweating and hyperthermia.

NOTE: The early features of serotonin syndrome can mimic anxiety before other features develop.

Combinations of antidepressants

There is limited evidence on the efficacy of combinations of antidepressants. All combinations increase the risk of adverse effects, in particular serotonin syndrome. Patients receiving combinations should provide their informed consent. Psychiatrists may trial combinations for very treatment-resistant anxiety disorders when other options have failed.

There may be a theoretical advantage to the combination of:

SSRI plus (reboxetine or mirtazapine)

OR

SNRI plus mirtazapine

There is no evidence supporting an advantage in combining SSRI medications. Combinations of SSRI/TCA plus MAOI should be avoided and prescribed only under strict monitoring. Although a low dose of TCA may be combined with an SSRI to enhance sleep, clomipramine should never be used.

Drugs that are NOT recommended

Table 5.

The following drugs are NOT recommended in the treatment of anxiety disorders

Panic disorder (with/without agoraphobia)²⁻⁵
buspirone (-II); carbamazepine (-II); propranolol (-II)
Social anxiety disorder^{2-4;6}
acute alcohol (-II); adjunct pindolol (-II); adjunct clonazepam (-II); atenolol (-II) [†] ; buspirone (-II); imipramine (-II) [‡] ; propranolol (-II) [†] ; St John's wort (-II)
Obsessive compulsive disorder^{2-4;7;8}
buspirone (-IV); clonazepam (-II); clonidine (-II); lithium (-II); bupropion (-IV); naltrexone (-IV)
Generalised anxiety disorder²⁻⁴
propranolol (-II)
Post-traumatic stress disorder²⁻⁴
alprazolam (-II); cyproheptadine (-II); olanzapine (-II); clonazepam (-IV)

[†] Propranolol/Atenolol have evidence supporting use in performance anxiety but not social anxiety disorder.

[‡] TCA are useful treatments of panic disorder, but are not effective in social anxiety disorder.

Practice points

Table 6.

The following practice points may be useful when treating anxiety disorders

Panic disorder (with/without agoraphobia)²⁻⁵

Severe agoraphobia is a negative prognostic factor. Medication should not be discontinued until avoidance behaviour has stopped, even if panic has remitted (EC). Adjunctive clonazepam on initiating SSRI treatment (paroxetine⁶⁰ or sertraline⁶¹) may improve the time to therapeutic effect (II).

CBT may decrease relapse rates in people discontinuing medication ^{62,63}.

Social anxiety disorder^{2-4,6}

Alcohol and other drug misuse/abuse is relatively common in SANd.

Paroxetine is effective in treating SANd with co-morbid alcohol abuse/ dependence⁶⁴.

Obsessive compulsive disorder^{2-4,7,8}

Therapeutic doses are higher than that used for depression.

OCD can be difficult to treat. Consideration may be given to augmenting (see *Table 4*) at an earlier stage of treatment in order to maintain small improvements gained with monotherapy³ (EC).

Generalised anxiety disorder²⁻⁴

Continue therapy for GAD for 12 months.

Ensure sufficient duration for trial of treatment.

[Meta-analysis for venlafaxine in GAD found improvement in partial responders with maintenance of treatment for 3-6 months (I)⁶⁵]

Post-traumatic stress disorder²⁻⁴

PTSD can be difficult to treat. Consideration may be given to augmenting (see *Table 4*) at an earlier stage of treatment in order to maintain small improvements gained with monotherapy³ (EC).

Treatment of anxiety in the elderly

Table 7.

Refer to the WAPDC Therapeutic Algorithm: Antidepressants for other issues relating to the use of antidepressants.

Special Group	Recommend	Avoid
Elderly	SSRI starting at lower doses.	fluoxetine; TCA; MAOI; BZD.

Comment

All potentially contributing factors, primary medical cause, medication, dementia etc should be identified.

SSRI (except fluoxetine) and moclobemide are preferred first-line antidepressants for the elderly. Paroxetine is associated with more anticholinergic side-effects than other SSRI.

Tricyclics, venlafaxine AND mirtazapine have all been associated with hypotension and may be an additional risk factor for falls (SSRI have been associated with falls also⁶⁶); anticholinergic side effects of TCA must be considered.

Venlafaxine, fluvoxamine, moclobemide, sertraline pharmacokinetics are not notably affected by age. All other antidepressants should be commenced at half the normal adult dose.

Caution should be exercised in patients treated with NSAID or aspirin due to increased risk of gastrointestinal haemorrhage.

Benzodiazepines must be prescribed judiciously due to increased risk of falls, and may accumulate in elderly patients.

Treatment of anxiety in children and adolescents

Table 8.

Special Group	Recommend	Avoid
Children and adolescents	Psychological interventions should always be tried first. Limited number of SSRI can be used starting at lower doses.	Most medication are not indicated.
Comment		
<p>Psychological treatments for anxiety should be used first-line in children and adolescents, and these are generally effective. Regardless of the condition, the management of anxiety should be multimodal (not medication alone).</p> <p>There is little evidence for the use of any medication for anxiety in the child and adolescent population other than fluvoxamine and sertraline for OCD and fluvoxamine for some other anxiety disorders. With the exception of SSRI, the use of medications in pre-adolescent patients is unlikely to be effective. However, SSRI may induce or exacerbate suicidal ideation in younger populations and this should be discussed with patient/parents and follow-up provided.</p> <p>Venlafaxine has been associated with a high incidence of suicidal ideation and it is not advisable to use this routinely in a paediatric population.</p> <p>TCA are generally used with extreme caution in children and adolescents given the potential for cardiovascular side-effects including sudden death.</p> <p>Benzodiazepines may cause confusion, paradoxical reactions as well as have an impact on learning.</p> <p>Antipsychotics (even in low dose) are associated with sensitivity to extra-pyramidal side-effects (EPSE).</p>		

Treatment of anxiety in pregnancy

Table 9.

Special Group	Recommend	Avoid
Pregnancy	If clinically indicated, antidepressants may be prescribed, but the risk/ benefit should always be assessed & discussed with the patient.	MAOI; paroxetine (small but significant increase risk of cardiac septal defects); high-dose BZD; anticonvulsants.

Comment

Paroxetine is an Australian Drug Evaluation Committee (ADEC) category D agent. Recent studies have shown a small but significant risk of cardiac septal defects with first trimester exposure of the foetus to paroxetine. The tricyclics, fluoxetine, es/citalopram and sertraline are all in category C, corresponding to no malformations but with the possibility of reversible adverse effects. Neonates may show withdrawal or serotonergic symptoms where there has been maternal therapy with the tricyclics or SSRI. Nortriptyline is the preferred TCA because of low incidence of hypotension⁶⁶.

A significant association between the use of SSRI after the 20th week of pregnancy and Persistent Pulmonary Hypertension in the Newborn (PPHN) has been noted⁷² and should be considered when prescribing these medications⁷³.

Reboxetine (B1), fluvoxamine (B2), venlafaxine (B2), mianserin (B2), moclobemide (B3), and mirtazapine (B3) are in varying category B classifications. Data on use in pregnancy for these drugs is limited and while no malformations have been found in humans, there are animal data showing teratogenesis for some. Insufficient data exists at present to recommend reboxetine or mirtazapine.

A limited number of studies of longer term neurobehavioural sequelae of infants exposed to SSRI or TCA in pregnancy do not indicate any adverse effects at present, however data are still limited⁶⁷⁻⁷¹.

Exposure to benzodiazepines during the first trimester of pregnancy increases risk of major malformations or cleft lip or palate⁷⁴.

The anticonvulsants, sodium valproate, carbamazepine and lamotrigine are all Category D as they are known teratogenic drugs.

Guide to interpreting ADEC Categories

For drugs in the B1, B2 and B3 categories, human data are lacking or inadequate and subcategorisation is therefore based on available animal data. The allocation of a B category does NOT imply greater safety than the C category.

Drugs in category D are not absolutely contraindicated in pregnancy (e.g. anticonvulsants). Moreover, in some cases the 'D' category has been assigned on the basis of 'suspicion'.

Due to legal considerations in this country, sponsor companies have, in some cases, applied a more restrictive category than can be justified on the basis of the available data. In some cases there may be discrepancies between the published Product Information and the information in this booklet due to the process of ongoing document revision.

See over for ADEC Classifications.

ADEC Classification of drugs during pregnancy

- Category A*** Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.
- Category C*** Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.
- Category B1*** Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.
- Category B2*** Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.
- Category B3*** Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
- Category D*** Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialised texts should be consulted for further details.
- Category X*** Drugs which have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

Treatment of anxiety during lactation

Table 10.

Special Group	Recommend	Avoid
Lactation ⁷⁶⁻⁷⁸	If clinically indicated, antidepressants may be prescribed, but the risk/ benefit should always be assessed & discussed with the patient.	fluoxetine; doxepin; BZ.
Comment		
<p>The relative infant dose for a drug (infant daily dose/kg, as a percent of mother's weight adjusted dose) is often used to quantify the dose in mother's milk and a relative infant dose of <10% of mother's weight-adjusted dose is generally considered to be safe. Reports of adverse effects in exposed infants can also be used in assessing drug suitability. Drugs which have been used successfully in a previous episode in an individual patient should be considered first. If not suitable, other drugs with more favourable relative infant doses are then considered. Note that premature neonates have significantly lower capacity to clear drugs received via breast milk. Neonates may also have been exposed to these drugs in utero at levels that are an order of magnitude higher than that delivered via breast milk. A neonatal discontinuation syndrome with symptoms of serotonin toxicity may occur in the first 1-2 weeks of life particularly from pregnancy-related exposure to SSRI. Symptoms should be treated and are NOT an indication for discontinuation of breastfeeding.</p> <p>The SSRI es/citalopram, fluvoxamine, paroxetine, and sertraline have low relative infant doses, and few reports of adverse effects in breastfed infants. Fluoxetine and its metabolite norfluoxetine, have moderate relative infant doses, and there are some reports of short- and medium-term adverse effects in breastfed infants. The SNRI venlafaxine has a moderate relative infant dose and low likelihood of adverse effects, while the NRI reboxetine has a low relative infant dose and no reported adverse effects. There are also limited data showing low relative infant dose and no reported adverse effects available for mirtazapine. Moclobemide and the tricyclics have low relative infant doses and few adverse effects in exposed infants. However, doxepin should be avoided because there have been isolated case reports of sedation and respiratory depression. Mianserin and the irreversible nonselective MAOI have not been adequately studied in lactation.</p> <p>Floppy infant syndrome has been reported with the long-acting benzodiazepines, and diazepam should be avoided. Short-acting benzodiazepines are usually acceptable. There are very limited data relating to zopiclone and zolpidem, suggesting that both may be safe for short-term use.</p> <p>Benzodiazepine use in breastfeeding mothers is associated with sedation, lethargy, impaired respiration and withdrawal in the infant⁷⁹.</p>		

Description of levels of evidence

The levels of supporting evidence referred to throughout these guidelines are graded using the NHMRC guidelines. In general, the information considered and/or used was sourced from published guidelines, systematic and narrative reviews that are referenced in the heading of each column.

Level I	Evidence obtained from a systematic review of all relevant randomised trials
Level II	Evidence obtained from at least one properly designed randomised controlled trial
Level III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (i.e. non-random allocation to treatment)
Level III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised, cohort studies, case-control studies or interrupted time series with a control group
Level III-3	Evidence obtained from comparative studies with historical control two or more single arm studies or interrupted time series without parallel control group
Level IV	Evidence obtained from case series, either post-test or pre-test/post-test
EC	Expert Consensus. Not part of the NHMRC guidelines, an additional level of Expert Consensus has been used for those recommendations that are part of accepted clinical practice but as yet have no specific evidence for or against

To be recommended as first-line treatment, a drug needs to have at least level II evidence. Some treatments with strong evidence are demoted to second-line due to potential adverse effects and poorer tolerability compared to preferred first-line treatments.

Abbreviations used in this document

AC = anticonvulsant

ADEC = Australian Drug Evaluation Committee

AP = antipsychotics

BZD = benzodiazepines

CBT = cognitive behaviour therapy

EC = expert consensus

MAOI = monoamine oxidase inhibitors

NRI = noradrenaline reuptake inhibitors

NSRI = noradrenaline and serotonin reuptake inhibitors

NaSSA = noradrenergic and specific serotonergic antidepressants

RIMA = reversible inhibitors of monoamine oxidase type-A

SRI = serotonin reuptake inhibitors

SSRI = selective serotonin re-uptake inhibitors

TCA = tricyclic antidepressants

* = pooled analysis of all trials, not meta-analysis

a = positive and negative trials exist or conflicting results

b = severely ill patients in particular

c = authors noted substantial weight gain

d = PTSD with psychotic features

e = very small number

References

References cited in these guidelines are listed on the WATAG website at <http://www.watag.org.au/wapdc/guidelines.cfm>



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