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DEPRESSION
POEMS



bpac nz
better medicine

Depression POEMs

Patient Oriented Evidence that Matters

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All information is intended for use by competent health care professionals and should be utilized in conjunction with pertinent clinical data.

Summary

1. For the majority of patients seen in general practice there is no evidence that any class of antidepressant is more efficacious than others or has a faster onset of action.
2. Explaining to patients that there is a wide range of antidepressant drugs to choose from with different side effect profiles will help maintain confidence if the patient experiences unacceptable side effects with the first drug tried.
3. Drug therapy should be accompanied by a suitable method for recording both benefits and side effects, such as a diary (a patient diary has been incorporated into a patient information leaflet available from bpac^{nz}).
4. Paroxetine and fluoxetine have nonlinear kinetics. Increasing the dose above 20mg will not increase the antidepressant effect but will increase the likelihood of side effects.
5. Low dose tricyclic antidepressants (TCAs) 100mg per day are effective in the treatment of depression. They may be as effective as standard dose TCAs and result in fewer side effects.
6. There seems to be little difference between selective serotonin reuptake inhibitors (SSRIs) with respect to frequency and severity of adverse effects. When selecting an SSRI factors to consider are drug interaction potential, severity of withdrawal syndrome, tendency to cause initial agitation and cost.
7. TCAs differ in their side effect profiles. Secondary amines such as nortriptyline and desipramine have less sedative and anticholinergic side effects than the other TCAs.
8. Anxiety is a core feature of depression. TCA and SSRI antidepressants are effective in reducing anxiety in depression.
9. SSRIs improve anxiety symptoms, although paradoxically they may increase anxiety in the short term. In patients where anxiety is a factor it is advisable to start with a low dose (about half the usual starting dose) and increase the dose slowly.
10. The proliferation of anxiety diagnoses has created niche licensing opportunities, in particular paroxetine is licensed for multiple anxiety diagnoses, while others such as fluoxetine are only licensed for selected indications. As a class SSRIs are effective in the management of anxiety disorders despite the fact that only certain ones are licensed for certain diagnoses.

Introduction

The treatment of depression is much wider than the use of antidepressant medication alone and includes psychological treatments and counselling. Current evidence suggests that in mild to moderate depression some psychological treatments such as cognitive behavioural therapy, are as effective as drug treatment, however access to these services can be a barrier. Referral to secondary services is appropriate when the depression is severe or safety is an issue, and if there is not improvement with initial treatment after an appropriate trial. The depression POEMs focus on the drug treatment of adults with mild to moderate depression managed in primary care.

Depression in primary care

The prevalence of major depression is between 5% and 10% of people seen in primary care settings. Two to three times as many people may have depressive symptoms but do not meet criteria for major depression. Women are affected twice as often as men. In older adults between 10% and 15% have depressive symptoms, although major depression is relatively rare (Geddes *et al* 2003).

Depressive symptoms are reported in up to 40% of patients in the primary care setting, although the majority do not meet the criteria for major depression

(Paulsen 2003).

A lot of depression that general practitioners treat is below, or only just reaches, the minimum diagnostic criteria for depression. General practitioners and their patients may see depressive symptoms much more in terms of fluctuating mood disturbances occurring in response to life situations, often against a background of chronic difficulties, physical illness, insecure relationships and deprivation. Treatment with an antidepressant seems sometimes to be given 'palliatively' in an attempt to ameliorate troubling symptoms, rather than to induce remission of an illness, and may be seen as subsidiary to supportive care given by the primary care team (Anon 2003).

Evidence suggests that many patients with depression would prefer psychological therapy to drug treatment (CEG 2002). For all patients, keeping a daily diary is an essential part of the behavioural approach. Whatever drug therapy may be required, lifestyle modifications are also needed such as stress management, reducing drug and alcohol use, improving sleep pattern, a balanced diet and physical exercise.

For many patients with depressive symptoms seen in general practice, a supportive 'watchful waiting' approach is reasonable (unless there is concern that the patient is suicidal). Patients should keep a diary charting their sleep, mood, appetite, and concentration difficulties. Medications should be considered especially where there are clear physiological changes (e.g. in sleep, appetite, concentration etc.).

Patients should keep a diary charting their sleep, mood, appetite, and concentration difficulties.

Diaries available from bpac^{nz}

Choice of antidepressant

The major classes of drugs used to treat depression are the tricyclic antidepressants (TCAs) and related agents, selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase (MAO) inhibitors. Antidepressants prescribed in either the acute or maintenance phase of depression therapy are associated with a 50% to 60% response rate among patients with major depression in the primary care setting (Paulsen 2003). TCAs and SSRIs are suitable first choice agents for most patients.

The choice of antidepressant should be based upon the individual patient. In particular, the following factors should be considered:

- If a patient has previously responded to an agent then consider continuing with the same agent.
- If a patient has previously experienced troublesome side effects with an agent then avoid that agent.
- Potential for interaction with existing drug treatment.
- Side effects associated with a particular drug. Some patients will find the stimulatory effects associated with SSRIs unacceptable while others will be intolerant to the anticholinergic effects associated with the TCAs.
- Concomitant conditions can guide choice of agent e.g. TCAs are relatively contraindicated for patients with cardiac disease or epilepsy.
- If poor compliance is a concern then fluoxetine may be a good option due to its long half life.
- Suicide risk.
- Cost.

Side effect profile

Understanding the adverse effect profile is important if treatment is to be tailored to the individual patient. Some patients will find insomnia and agitation unbearable while others will be susceptible to urinary retention or sexual dysfunction.

TCAs

The major side effects of tricyclic antidepressants include anticholinergic effects such as dry mouth, blurred vision, constipation, nausea, urinary retention, and tachycardia. The elderly are particularly susceptible to memory impairment, confusion, and hallucinations. Drowsiness is also common. Sexual dysfunction may also be a problem. TCAs differ in their side effect profiles (table 1). Secondary amines such as nortriptyline and desipramine have less sedative and anticholinergic side effects than the other TCAs (Fenando & Chew 2003).

SSRIs

Jitteriness, restlessness, agitation, headache, gastrointestinal symptoms (diarrhoea and nausea), and insomnia are common side effects with SSRIs. A significant percentage of men and women develop sexual side effects after several weeks or months of SSRI therapy. SSRIs (in particular fluoxetine and paroxetine) may inhibit the activity of the cytochrome p450 isoenzymes and therefore interact with other drugs. Hyponatremia can occur with all SSRIs, particularly in the elderly (PreMeC 2002). The major advantages of SSRIs over TCAs are their less pronounced anticholinergic adverse effects and lack of severe cardiotoxicity (Dukes & Aronson 2000).

There seems to be little difference between SSRIs with respect to frequency and severity of adverse effects

(Dukes & Aronson 2000).

The side effects of SSRIs are generally mild and transient, and can often be dealt with by altering the time of administration (morning versus evening), decreasing the dose, or taking the drug with food (Peretti *et al* 2000).

Adverse events (% of people) with SSRIs versus TCAs (Geddes *et al* 2003).

Adverse effects	SSRI event rates (%)	TCA event rates (%)
Dry mouth	21	55
Constipation	10	22
Dizziness	13	23
Nausea	22	12
Diarrhoea	13	5
Anxiety	13	7
Agitation	14	8
Insomnia	12	7
Nervousness	15	11
Headache	17	14

Many of the side effects of antidepressants are dose dependent. Starting at low doses can minimise the side effects of antidepressants.

Dose dependent side effects (PreMeC 1997):

SSRIs	TCAs	
Anxiety & Agitation	Drowsiness	Drymouth
Anorexia	Nausea	Constipation
Insomnia	Blurred vision	Tachycardia
Lethargy, malaise, somnolence	Urinary retention	
Diarrhoea	Orthostatic hypotension	

A typical starting dose for the SSRIs; fluoxetine, paroxetine and citalopram, is 20mg daily but may be lower to minimise side effects, particularly in the elderly or anxious patient. It is reasonable to initially prescribe a 10mg dose for approximately one week, and then gradually titrate up to full doses. *Note: fluoxetine 20mg dispersible tablet can be halved to provide a 10mg dose.*

Fluoxetine and paroxetine have nonlinear pharmacokinetics. 20mg per day of fluoxetine or paroxetine is an effective dose for the majority of depressed patients. Increasing the dose above 20mg per day may not increase the antidepressant response but will increase the related adverse effects.

Recent evidence suggests a role for low dose TCAs (100mg per day or less) (Furukawa *et al* 2002). Low dose TCAs may be as effective as standard dose TCAs but result in fewer side effects.

Drug therapy should be accompanied by a suitable method for recording both the benefits and side effects, such as a diary (a patient diary has been incorporated into a patient information leaflet available from bpac^{nz}).

Interaction potential

The capacity of individual SSRIs to cause interactions is influenced by their effects on cytochrome P450 enzymes. From the data available it would appear that the potential for individual SSRIs to interact with other drugs is greatest for fluoxetine and paroxetine and least for citalopram.

Important interactions with SSRIs (Edwards & Anderson 1999)

SSRIs	Interacting substance	Possible result <small>*indicates interactions that are potentially hazardous</small>
All	Alcohol	Possible enhanced effect
All	Anticoagulant e.g. warfarin	*Possible enhanced anticoagulant effect
All	MAOIs TCAs Tryptophan St. John's Wort	*CNS toxicity *Increased plasma level of some TCAs Agitation, nausea
Fluoxetine	Flecainide	Increased plasma concentration of flecainide
Fluoxetine	Carbamazepine Phenytoin	*Antagonism of anticonvulsant effect Increased plasma concentration of anticonvulsant
Paroxetine	Phenytoin and possibly other anticonvulsants	Decreased plasma concentration of paroxetine
All	Terfenadine	*Increased risk of arrhythmias
Fluoxetine	Clozapine Haloperidol	*Possible increased plasma concentration of clozapine *Increased plasma concentration of haloperidol
All	Ritonavir	*Possible increased plasma concentration of some SSRIs
Fluoxetine	Selegiline	*CNS excitation, hypertension
All	Tramadol	*Possible increased risk of convulsions
All	Lithium	*CNS toxicity (lithium is sometimes used to augment antidepressant response)
All	Sumatriptan	*CNS toxicity

CNS toxicity is characterised by excitation, restlessness, sweating, flushing, pyrexia, fluctuating vital signs, tremor, rigidity, myoclonus, delirium, and rarely coma and death.

Potential Interactions with TCAs (Tatroo 2003)

Major severity	Moderate Severity	Mild Severity	Limited Documentation <small>i.e. there is less confidence that the interaction can cause an altered clinical response (monitor)</small>	
Clonidine	Anticoagulants	Barbiturates	Antipsychotics	NSAIDs
MAO Inhibitors	Antiepileptics	Anorexiant	Azole antifungals	Levodopa
Quinolones	Sympathomimetics		Beta blockers	Lithium
	SSRIs		Bupropion	Oestrogens
	H2RA e.g. cimetidine		Benzodiazepines	Quinidine & quinine
	Antihypertensives		Contraceptives	Phenothiazines
			Diltiazem, verapamil	St. John's Wort
			Disulfiram	Sulphonylureas
			Haloperidol	Thyroid hormones

Notes: All interactions are not listed and all agents in a class of pharmaceuticals may not be associated with the interaction. Antihypertensives: in general the hypotensive effect is enhanced (but antagonism of effect occurs with clonidine).

The most important interactions are those with other drugs that affect serotonergic neurotransmission as these can lead to serotonin syndrome with the clinical features of CNS toxicity (table 4).

Duration of treatment

About 37% of patients in primary care relapse within a year of remission from depression (MeReC 2000). Therefore antidepressant medication should be continued for at least 6-12 months after the depression has lifted to minimise recurrence (CEG 2002, Ellis & Smith 2002). Patients who have had multiple episodes should be advised to continue with treatment for at least two years (NICE 2003).

At remission continue maintenance treatment:

- **first episode** for at least 6 to 12 months
- **recurrent** ongoing for 2-3 years (or longer)

Role for low dose TCAs

Recommended doses of TCAs are usually higher than the doses used to treat most people with depression. Many of the existing guidelines recommend dosages greater than 100mg or 125mg per day (Furukawa *et al* 2002).

A meta-analysis combined the results of 35 studies, all fairly small but adding up to a total of 2013 participants, comparing low dose TCAs (≤ 100 mg/day) with placebo in the treatment of adults with depression (Furukawa *et al* 2002). Also evaluated was the benefit of high dose versus low dose TCAs from 6 studies (551 participants). In this analysis, patients were significantly more likely to benefit from low dose therapy as compared with placebo at 4 weeks (relative risk = 1.65; 95% CI 1.36-2.00, **NNT = 6**) and at 6 weeks (relative risk = 1.47, 95% CI 1.12-1.94, **NNT = 5**). Standard dosage TCAs were not significantly more effective than low dose TCAs when evaluated at 4 or 8 weeks of therapy, but produced more dropouts due to side effects (Furukawa *et al* 2002).

For low dose TCAs compared to placebo the number needed to harm to produce one dropout due to side effects was around 24 (**NNH = 24**) at 1-6 months. Standard dose TCAs cause more dropouts due to side effects than placebo (**NNH = 11**) (Furukawa *et al* 2002).

Subgroup analyses also showed that the overall results of the study could be applied to:

- Older people aged 65 years or more
- Patients in the primary care setting
- Patients in the psychiatric setting

In the treatment of depression TCAs at doses lower than the usually recommended range are more effective than placebo and may be as effective as standard dose TCAs but with fewer side effects.

Further studies are needed to definitively establish the role of various doses of TCAs. This meta-analysis questions our understanding that TCAs need to be used in doses above 100mg/day to achieve therapeutic effectiveness. Perhaps the main concern with adopting the use of low dose TCAs is that there could be patients that go on to have chronic symptoms if under treated with a low dose TCA. However, it is reasonable for patients who start on low dose TCAs and who have a clear clinical response to be maintained on that dose with careful monitoring (NICE 2003).

Are all SSRIs equally effective?

There are no compelling data that guide the choice of SSRI for first line therapy. This is supported by a randomised trial of 573 depressed patients treated in the primary care setting that compared use of three SSRIs, paroxetine, fluoxetine and sertraline (Kroenke *et al* 2001). There was no significant difference between the three drugs on any outcome measure, even when factoring in baseline characteristics such as age and anxiety level. Approximately 20% of patients switched medications one or more times and more than two-thirds showed an improvement in symptoms over 9 months of follow-up, suggesting that physicians should not be reluctant to change drugs if the first one chosen does not work.

There have been suggestions that fluoxetine causes more agitation than the other SSRIs. A meta-analysis quantified this difference and showed that 3% more patients on fluoxetine experienced anxiety or agitation compared with other SSRIs (Edwards & Anderson 1999). This is likely to be of minor importance clinically.

No single SSRI has a significantly better safety and efficacy profile than the others
(Edwards & Anderson 1999).

Although there may be some characteristics of any medication that distinguishes its use in a particular patient, it is reasonable to suggest that any of the available SSRIs can be recommended over another in terms of effectiveness.

SSRI	Advantages	Disadvantages
Fluoxetine	Long half-life which may allow for less frequent administration in poorly compliant patients and less troublesome discontinuation effects. Cost (currently fluoxetine is the least expensive SSRI).	Possible higher incidence of stimulant and dermatological effects, and of weight loss. Longer delay required before switching to MAOI. Potentially hazardous interactions.
Citalopram	Probable lower potential for drug interactions.	Relatively new, therefore less chance of rare adverse reactions having been identified. Case reports of lethality in overdose.
Paroxetine		Higher incidence of sedation, tremor, sweating, discontinuation reactions. Potentially hazardous interactions. Weight gain. Sexual dysfunction.

(Edwards & Anderson 1999, Fava *et al* 2000)

In the majority of patients it is reasonable to consider fluoxetine first line, as:

1. It is the least expensive SSRI (Pharmaceutical Schedule, October 2003).
2. It is fully funded (both paroxetine and citalopram require the prescription to be endorsed to exempt the patient from additional charges).
3. It is less likely to be associated with a discontinuation syndrome.
4. The long half life may allow for less frequent administration in poorly compliant patients.

But be aware that fluoxetine:

5. May have a higher incidence of stimulant effects (consider starting with a 10mg dose).
6. Requires a longer washout period before switching to another antidepressant.
7. Is associated with potentially hazardous interactions.

Depression & Anxiety

Anxiety is a core feature of depression. Between 60% and 90% of depressed patients manifest anxiety symptoms (Montgomery & Judge 2000). Studies have demonstrated that SSRIs are as efficacious as TCAs in reducing anxiety and agitation in depression (Fava *et al* 2000).

Anxiety is a recognised side effect of the SSRIs. There is a widespread belief that some SSRIs (in particular fluoxetine) may be too stimulating for effective treatment of depression with anxiety symptoms.

An analysis by Tollefson *et al* involving 4737 patients found no evidence that either fluoxetine or TCAs induced psychomotor agitation at rates exceeding the natural course of the disorder over time. On the contrary, therapy with either fluoxetine or TCAs was typically associated with diminished agitation, probably as part of the response to treatment of depression.

Incidence of any worsening, development and improvement of psychomotor agitation

Incidence of:	Fluoxetine	Placebo		Fluoxetine	TCAs
Worsening agitation	29%	30.5% P=0.976		33.3%	28.8% P=0.149
Development of agitation	3.3%	4.0% P=0.699		6.9%	6.0% P=0.728
Improvement of agitation	58.4%	48.5% P<0.001		66.0%	60.8% P=0.091

(Tollefson & Saylor 1996)

Studies have confirmed that SSRIs, including fluoxetine and paroxetine, are not associated with an increase in treatment emergent anxiety compared to the TCAs (Montgomery & Judge 2000).

Dosing for both TCAs and SSRIs is usually slower for anxious patients as they appear more sensitive to side effects. It is not unusual for anxious patients to have more anxiety during the titration of SSRIs (Fernando 2000). Dosing can be as low as 10mg of fluoxetine, paroxetine or citalopram. After a week, if the patient tolerates the medication, the dose can be gradually increased.

In cases where the person presents with symptoms of both anxiety and depression, priority should be given to the treatment of the depression, particularly if it is severe. This is because the negative symptoms of depression (low motivation, apathy, poor concentration, low energy) may compromise the efficacy of cognitive therapy treatments for anxiety e.g. general stress management (including physical exercise), slow-breathing techniques, progressive muscle relaxation, and staged confrontation of feared situations (exposure therapy) (NHC 1998).

When depression and anxiety coexist, the depression should be treated first, enabling both conditions to improve (MeReC 2000).

Anxiety Disorders

Both TCA and SSRI antidepressants are effective in treating a wide variety of anxiety disorders (Zohar & Westenberg 2000). The proliferation of niche anxiety diagnoses since the 1980s has created niche licensing opportunities for drugs (Shorter & Tyrer 2003). The paroxetine (Aropax®) data sheet includes indications for obsessive compulsive disorder (OCD), panic disorder, social phobia, generalised anxiety disorder and post traumatic stress disorder, while that for fluoxetine (Fluox®) only includes OCD and the citalopram (Cipramil®) data sheet does not list any. However it is important to remember that SSRIs are a class and are all likely to be beneficial despite the fact that only certain ones are licensed for certain diagnoses.

Some SSRIs show a dose response for anxiety disorders, with higher doses required for efficacy compared to depression e.g. paroxetine 20mg/day is generally sufficient for the treatment of depression, while the minimum dose demonstrated to be effective in panic disorder is 40mg/day. Fluoxetine, on the other hand, is effective in panic disorder at the same dose that is recommended for depression (20mg/day) (Zohar & Westenberg 2000).

SSRIs may be associated with an initial increase in anxiety that peaks over the first week of treatment and then subsides as the treatment effect emerges. Counselling patients about this possibility is important to prevent withdrawal from treatment.

Combination therapy

Avoid using more than one antidepressant drug at any one time. There is not enough evidence to support combination antidepressant drug therapy, and serious adverse effects may occur because of pharmacokinetic and pharmacodynamic drug interactions (AMH 2002).

Despite the potential for adverse drug interaction a popular intervention in the United States for partial responders to antidepressants is augmentation. Augmentation is the addition of another pharmacologic agent to enhance the effects of the current antidepressant. Several medications from different classes have been used for augmentation including lithium, thyroid hormones and tricyclic antidepressants. In New Zealand augmentation may be considered following referral to a psychiatrist or initiated by doctors with special experience in the use of these combinations.

TCA's added to SSRIs

It is important to remember that SSRIs can raise TCA levels through their effects on the cytochrome P450 system. Fluoxetine and paroxetine are potent with their effects of raising TCA levels in the serum. The more common TCAs used as augmenting agents include desipramine and nortriptyline (e.g. 25mg of desipramine or 20mg nortriptyline). Desipramine is used for its mildly activating property and hence is dosed in the morning while the more sedating nortriptyline is dosed before sleep. Citalopram has the least ability to raise TCA levels and therefore is the safest. Ideally, serum levels should be monitored. The main adverse events to monitor are the anticholinergic signs including dry mouth, blurring of vision, urinary incontinence and constipation. Cardiac arrhythmia could also occur (Fernando & Chung 2000).

If a patient fails to fully respond to an antidepressant agent:

- Optimise therapy maximising the dose and duration of the antidepressant trial (12 weeks)
- Switch to another agent or class of antidepressant
- Refer to a psychiatrist

Combination of two antidepressants can be dangerous and is rarely justified except under specialist supervision

(BNF 46, Sept 2003).

Discontinuation syndrome

Antidepressants that have been taken regularly for at least six weeks must not be discontinued abruptly, unless a serious adverse effect has occurred. Stopping treatment quickly can sometimes cause a withdrawal reaction. It is best to reduce the dose gradually over at least two to four weeks, but slower withdrawal may be necessary after longer periods (e.g. over six weeks after a six month course) (MeReC 2000).

Features of antidepressant discontinuation syndromes (AMH 2002)

Class	Discontinuation effects	Comments
TCA's	Cholinergic rebound - hypersalivation, runny nose, abdominal cramping, diarrhoea, sleep disturbance.	Possibly most common with amitriptyline, doxepin, trimipramine.
SSRIs	Dizziness, nausea, paraesthesia, anxiety, agitation, tremor, sweating, confusion, electric shock-like sensations.	More common with paroxetine and least likely with fluoxetine.

SSRIs with shorter half-lives, such as paroxetine, have a higher incidence of withdrawal symptoms. Fluoxetine is the SSRI least likely to be associated with a discontinuation syndrome due to its long half life.

Discontinuation symptoms usually begin within 1 to 3 days after abrupt cessation of the SSRI. A patient who has a discontinuation syndrome can be reassured that the symptoms are likely to be mild and short lived. If symptoms are acute, relief is usually achieved within 24 hours by restarting the SSRI at the same dose the patient was taking when the medication was discontinued. A slow taper can then be instituted over several weeks. If the patient continues to have difficulty cross tapering with an agent that has an extended half life (e.g. fluoxetine) may prevent discontinuation symptoms during the taper (Ditto 2003).

It is important that patients understand how these discontinuation symptoms might be avoided. A continuous supply of medication and good compliance is necessary. When the decision is made to stop therapy, a gradual withdrawal regimen may be advisable.

Venlafaxine

Like the SSRIs, venlafaxine has acute pharmacological effects on the reuptake of serotonin by presynaptic nerve terminals. It has a simultaneous effect on noradrenaline reuptake and some weak effects on dopamine reuptake. The combination of the effects on the reuptake mechanisms appears to be responsible for the antidepressant action of the drug.

The reuptake effects of venlafaxine are dose dependent. At low doses (<150 mg/day), the drug acts like the SSRIs. At intermediate to high doses, the additional effects on noradrenaline reuptake become important (Norman 1999).

Nausea, agitation, sexual dysfunction and insomnia at low doses of venlafaxine are probably mediated by effects on postsynaptic serotonergic receptors. At intermediate to high doses, additional adverse effects such as raised blood pressure and headache are observed in some patients, these effects are probably due to an action on adrenergic receptors (Norman 1999).

Venlafaxine should not be initiated routinely in primary care because of its high cost, increased adverse effects compared to TCAs and SSRIs and high propensity to cause discontinuation symptoms (NICE 2003).

Non-drug therapy

There is no reliable direct evidence that one type of treatment (drug or non-drug) is superior to another in improving symptoms of depression. However, there is strong evidence that some treatments are effective, whereas the effectiveness of others remains uncertain (Geddes *et al* 2003).

Effects of non-drug therapies:

Beneficial	
Cognitive therapy	In mild to moderate depression
Interpersonal psychotherapy	In mild to moderate depression
Electroconvulsive therapy	In severe depression
Likely to be beneficial	
Care pathways	In mild to moderate depression
Combining antidepressant medication with psychological treatment	In mild to moderate and severe depression
Non-directive counselling	In mild to moderate depression
Problem solving treatment	In mild to moderate depression
Unknown effectiveness	
Befriending	In mild to moderate depression
Bibliotherapy	In mild to moderate depression
Cognitive therapy versus antidepressants for long term outcomes	In mild to moderate depression
Exercise	In mild to moderate depression
Psychological treatments (cognitive therapy, interpersonal psychotherapy, problem solving treatment)	In severe depression

(Geddes *et al* 2003).

While there is increasing evidence that some psychological treatments are as effective as antidepressants in many depressive illnesses, not all therapists are equally experienced or effective. Research studies of these therapies adhere strictly to versions of these therapies that follow treatment manuals and may not reflect usual practice. Cognitive behaviour therapy and interpersonal psychotherapy should be considered only if a competent and experienced practitioner is available. There are too few studies of other forms of psychological therapies to make evidence based recommendations, but clinical experience indicates that they can be valuable for those with major interpersonal difficulties and severe past trauma (Ellis *et al* 2003).

Box 1

Screening questions for depression

Two verbally asked questions for screening for depression will detect most cases of depression in general practice. Additional questions are required to confirm the diagnosis.

Screening questions about depressed mood (Arroll *et al* 2003):

1. During the past month have you often been bothered by feeling down, depressed, or hopeless?
 2. During the past month have you often been bothered by little interest or pleasure in doing things?
- If either question is associated with a positive response then screening is considered positive and can be followed by further questions from the diagnostic criteria.

Box 2

Diagnostic and Statistic Manual (DSM) Criteria

Major depression, as defined by DSM-IV, consists of either a depressed mood or a loss of interest and/or pleasure for at least 2 weeks, as well as at least 5 core symptoms.

Diagnostic criteria for major depression:

Pervasive depressed mood **AND/OR** marked loss of interest or pleasure

PLUS any of the following to a total of 5 or more

1. Marked weight loss/gain or increase/decrease in appetite
2. Insomnia/hypersomnia nearly every day
3. Psychomotor agitation/retardation nearly every day
4. Fatigue/loss of energy nearly every day
5. Feelings of worthlessness, excessive/inappropriate guilt
6. Indecisiveness or diminished concentration
7. Feelings of hopelessness
8. Thoughts of death, suicidal ideation/attempt
9. The core symptoms are not due to a physical/organic factor (e.g. substance abuse) or illness and are not better explained by bereavement.

Box 3

Prescribing points

1. Side effects may be experienced immediately but will often reduce after 2 weeks.
2. It may take 2 weeks on antidepressant medication before any improvement in symptoms (e.g. mood, sleep, anxiety) is experienced.
3. All antidepressants require at least 2-3 weeks to begin to work. SSRIs are no faster than TCAs and the onset of action is not related to the initial dose. Increasing the dose of an SSRI in the first 2 weeks of treatment will not speed up this process (PreMeC 2002).
4. Ideally, an antidepressant should be taken for at least 6 weeks before a judgement is made that it is ineffective.
5. A different medication often works even if first line treatment is unsuccessful.
6. The full effect of antidepressant medication may take 3 months at full dose.
7. Antidepressant medication should be continued for at least 6-12 months after the depression has lifted to minimise recurrence (preferably longer, 2-3 years, in patients with a prior history of depression).
8. Timing of dosage e.g. take TCAs at night because they may be sedative, most SSRIs should be taken in the morning due to the risk of insomnia.
9. When using TCAs in major depression start with a low dose (e.g. 25mg amitriptyline) and increase slowly.
10. Aim for the minimum effective dose.
11. Agree to a follow up plan with the patient.
12. Regular symptom review and monitoring of suicide risk are essential adjuncts to drug treatment.
13. Encourage concordance with medication.

Table 1: Relative incidence of some common adverse effects for older antidepressants

	Daily dose range (mg)	Sedation	Postural hypotension	Anticholinergic effects	Weight gain
TCAs					
Amitriptyline	75-150	+++	++	+++	+++
Clomipramine	75-150	+	++	+++	++
Desipramine	75-150	+	+	++	+
Dothiepin	75-150	+++	++	++	+
Doxepin	75-150	+++	++	+++	++
Imipramine	75-150	++	+++	+++	++
Nortriptyline	75-150	+	+	++	+
Trimipramine	75-150	+++	++	++	++
Others					
Mianserin	30-90	+++	+	+	0
Phenelzine	45-60	++	++	++	++
Tranlycypromine	30-40	++	++	++	+

0 = negligible or absent; + = mild; ++ = moderate; +++ = marked.
 NPS News, Issue 11, August 2000. <http://www.nps.org.au/index.html>

Table 2: Relative incidence of some common adverse effects for newer antidepressants

	Daily dose range (mg)	Insomnia	Sexual dysfunction	Agitation	Gastro-intestinal	Weight gain
SSRIs						
Citalopram	20-40	++	+++	+	++	0
Fluoxetine	20-40	++	+++	++	++	0
Paroxetine	20-40	++	+++	+	++	+
Others						
Moclobemide	300-600	++	0	++	++	0
Nefazodone	300-600	+	0	+	++	0

0 = negligible or absent; + = mild; ++ = moderate; +++ = marked.
 NPS News, Issue 11, August 2000. <http://www.nps.org.au/index.html>

Table 3: Inhibition of cytochrome P450 isoenzymes by SSRIs

SSRI	Cytochrome P450 isoenzyme				
	1A2	2C9	2C19	2D6	3A4
Citalopram	0	0	0	+	0
Fluoxetine	+	++	+ to ++	+++	+ to ++
Paroxetine	+	+	+	+ to ++	+

0 = minimal or no inhibition; + = mild inhibition; ++ = moderate inhibition; +++ = potent inhibition
 (Spina & Scordo 2002).

Table 4: Features of serotonin syndrome (AMH 2002)

Mental state changes (e.g. confusion, hypomania)	Shivering
Agitation	Tremor
Myoclonus	Diarrhoea
Hyperreflexia	Incoordination
Sweating	Fever
The serotonin syndrome may occur with antidepressant monotherapy, or when two serotonergic agents are used concurrently or without adequate washout period.	

Table 5: Drugs that may contribute to the development of serotonin syndrome (AMH 2002)

All antidepressants	Illicit drugs	Selegiline
Amphetamines	Lithium	St John's Wort
Bupirone	Pentazocine	Sumatriptan
Carbamazepine	Pethidine	Tramadol
Dextromethorphan	Phentermine	Tryptophan
Diethylpropion		

Table 6: Washout and Switching (Fernando & Chew 2003)

MAOI	Switching to MAOI from fluoxetine needs a five-week interval. Switching to MAOI from SSRIs (other than fluoxetine) needs a two-week interval. Switching to MAOI from another MAOI needs a two-week interval.
Moclobemide	Wait for 1 to 2 days before introducing the next antidepressant, depending on clinical urgency
SSRIs	Paroxetine is implicated the most in having a "discontinuation syndrome". If possible, the dose should be tapered to as low as 5mg/day over several weeks. If a patient develops a severe discontinuation syndrome, fluoxetine 10mg once daily for two weeks can help. Fluoxetine is effectively self-tapering due to its long half life. Fluoxetine requires a two-week washout period when switching to other drugs. Citalopram can be stopped a day before starting another SSRI or TCA.
TCAs	TCAs should be tapered when switching, particularly if used for a long time (i.e. many months). Occasionally, a cholinergic rebound can occur an uncomfortable situation but not life threatening. Tapering is also suggested when switching from TCA to SSRI, as the SSRI can raise the TCA to toxic levels.

Note: Elimination half life for most TCAs and SSRIs (except fluoxetine) is in the order of 20-30 hours; thus, after 3-4 days the majority of the drug will be cleared from the body (AMH 2000).

Box 4

<p>Information for patients (MeReC 2000)</p> <ul style="list-style-type: none"> • A response is unlikely within the first two weeks (full effect may take up to six weeks). • Treatment should be continued for at least 6-12 months after recovery. • Most side effects are minor and often improve with time. • Treatment should not be stopped abruptly. • St John's Wort (<i>Hypericum perforatum</i>) must not be taken as well as antidepressants because it interacts with many drugs e.g. SSRIs. • A cautious approach to driving is suggested when taking antidepressants.
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Box 5

<p>Pregnancy It is generally agreed that drugs of any type should be taken during pregnancy only when the risks to the mother and foetus of no treatment outweigh the risks of taking the drug involved. There is more experience with the use of tricyclic antidepressants.</p> <p>Breast feeding Tricyclics and SSRIs pass freely into breast milk. However, the dose taken in by infants seems to be minimal and reports of harm are rare. If medication was taken during pregnancy, continue with the same medication postpartum. There is more experience with the use of tricyclic antidepressants although doxepin should be avoided. There is less experience with SSRIs and the preferred options are sertraline or paroxetine. Adverse effects have been reported with fluoxetine (CEG 2002).</p> <p>Post natal depression A rapid antidepressant effect is important in women with post-partum depression, in whom we have to consider the safety of the newborn infant. However, an SSRI (or any other antidepressant) should only be administered to a nursing mother if there are compelling reasons to do so, with the benefits thought to outweigh the risks (Edwards & Anderson 1999).</p>
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