Treatment

Treatment recommendations differ between mild, moderate and severe depression

Severe depression is usually marked by agitation or retardation and the patient may be reluctant or unable to describe other features in detail. Both social functioning and work performance are likely to be disrupted. (PHQ scores of > 20)

Severe depression requires anti-depressant medication and consideration of Referral to Mental Health Specialists. Risk assessment is essential.

Reviewing Progress

Patients are more likely to implement advice if they know the GP will see them again soon to check whether the advice has been implemented or was helpful.
Contact at fortnightly intervals for moderate depression and initially weekly in severe depression should be considered, with contact remaining at 2-3 months intervals throughout treatment.

Referral to Mental Health Specialists

Psychiatry
Psychiatrists are happy and willing to see all patients with depression or any other psychiatric disorder if the general practitioner feels this necessary and outlines the reasons for requesting a psychiatric opinion in the referral letter. Guidelines for consideration as to what and when to refer include:

- Severe depression often with psychotic ideation where admission to hospital may be required
- Where there is suicidal ideation and you consider the patient to be at risk
- Failure to respond to treatment with at least one antidepressant drug despite adequate dosage and duration of treatment
- Chronic illness where the GP wishes advice as to continued management
- Where management is difficult or stressful and the GP feels in need of support or a break
- Where the GP wishes advice as to referral to other areas of the service
- At the patient's request if the GP feels this is appropriate

Community Mental Health Services

The structure of the Community Mental health Services varies throughout the Highlands and therefore there are local arrangements in place for referrals. Teams may compromise of Social Workers, Occupational Therapists and Community Psychiatric Nurses. They can offer a range of core skills such as assessment, treatment and care, outcome evaluation and health education. Some teams have specialists in Cognitive Behavioural Therapy. Community Mental Health Teams will consider referrals for any patient who is or is suspected to be suffering depression.

Consider referral to Community Mental Health if the patient:

- Is aged 16 or over and has left school
- Is isolated and vulnerable
- Has a previous history of mental health problems
- Has thoughts of self harm and/or feelings of hopelessness
- Abnormal grief reaction
- Presents with multiple psychosocial problems
- Has a history of poor coping skills

Referral to Cognitive Behaviour Therapists

CBT is particularly suitable for those who

- Can not or do not wish to take drugs
- Are frequent relapsers
- Are depressed about being depressed
- Experience hopelessness and feelings of helplessness
- Have chronic low self-esteem
- Complain of negative thoughts

Development plans for Psychological Therapies across Highlands include the establishment of Cognitive Behaviour Therapists posts for each area. These should be coming on stream during the lifetime of these Guidelines.

Referral to Psychology

Psychologists accept referrals of patients with all forms of depressive difficulties for assessment and treatment. Psychological therapy may be particularly relevant when one or more of the following apply:

1. Duration of six months in spite of adequate drug therapy
2. Refusal to use antidepressants/failure to respond to medication/other factors preventing drug treatment
3. History of relapses/recurrent episodes
4. Concurrent/alternative diagnosis or difficultly, particularly anxiety disorders, self injury
5. Depression is part of a pattern of difficulties arising out of adverse or traumatic early life experiences

In order for patients to see a psychologist they need to be able to attend a clinic during working hours.

Drug Therapy-

Which drug to use
Cost Effectiveness
The Elderly
Starting Treatment
Recommended Dosage
Failure to Respond
Anti depressant Swapping
Continuation
Maintenance
Compliance
Discontinuation
Antidepressants in Pregnancy and Breast-feeding
St John's Wort

Patients with low mood or loss of interest plus at least four of the other diagnostic features mentioned are most likely to respond to drug treatment. For these patients with moderate to severe depression, antidepressants should be considered the mainstay of treatment. Antidepressants are effective in the treatment of moderate to severe depression. However, antidepressants do not appear more efficacious than placebo in milder depression and are not recommended for the initial treatment of mild depression. In milder depressive states non-drug strategies are often preferable to drug treatment.

The fact that a patient's depression is "understandable" should not deter the GP from prescribing antidepressants since they are just as likely to be effective. 70% of patients are likely to respond to the first intervention offered.

Antidepressant Treatment – Which Drug to Use

All antidepressants have broadly similar efficacy (Song et al 1993) and therefore the choice of drug for a particular patient will depend on the nature of the symptoms, side-effect profile, concomitant therapy, concurrent illness, patient preference and safety in over-dose. Previous response to treatment is also a strong indication to repeat that treatment in future episodes.

The antidepressant whose profile best fits the ideal for an individual patient should be prescribed. In the absence of special factors, choose antidepressants which are better tolerated, safer in overdose, and more likely to be prescribed at effective doses. Since there is most evidence for SSRIs, they should be regarded as the preferred option for first line use.

When prescribing an SSRI, fluoxetine is a reasonable choice as it has efficacy similar to other SSRIs, but is available as a generic, and hence provides additional benefit in terms of cost effectiveness.

When considering toxicity in overdose, the evidence to date suggests that SSRIs, newer tricyclics, mirtazapine and reboxetine are safer than older tricyclics or venlafaxine.

The newer agents may have a place in treatment of patients for whom first choice drugs are poorly tolerated or ineffective.

Cost Effectiveness

The cost of these drugs should also be taken into account when a decision is made to prescribe, especially when choosing between drugs in the same class. Antidepressants account for a large proportion of the primary care drugs spend.

TCAs are by far the cheapest agents, especially compared to newer antidepressants, but they carry the risk that they may be prescribed in sub-therapeutic doses, e.g. to avoid adverse effects which are common with TCAs. Generic SSRI preparations such as fluoxetine offer a safer but relatively inexpensive alternative.

The Elderly

The same principals apply to the elderly as the adult population in the decision on which antidepressant to use. Concomitant therapy and concurrent illness are likely to be of greater relevance.

The main differences in the elderly regarding the use of antidepressant drugs relate to altered distribution, metabolism and excretion and their increased sensitivity to the effects of these drugs. This provides the reasoning behind the adage "start low and go slow" with antidepressant doses in this population. Psychomotor impairment and postural hypotension are particularly problematic in the elderly and there is therefore an argument for generally avoiding the older tricyclics (Lasser et al 1998).

Starting Treatment

SSRIs can usually be started at a therapeutic dose.

TCAs should be gradually increased to the therapeutic dose over 1-2 weeks, or as quickly as can be tolerated.

Patients should be advised of the likely early side effects, and the lag time before symptoms noticeably improve.

Increased anxiety/agitation can be problematic at the early stages of treatment with an SSRI. Judicious short-term use of a benzodiazepine may be helpful in such situations.

CSM Advice Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants and should be considered in the differential diagnosis of all patients who develop drowsiness, confusion or convulsion while taking an antidepressant.

Compliance Issues

Compliance with prescribed medication for all chronic conditions is estimated at 50%. There are a variety of reasons why patients cannot or will not comply with their prescribed medication, but there are particular reasons why compliance may be a problem with antidepressants.

- Lack of initial benefit
- High incidence of side effects, particularly occurring prior to the onset of antidepressant action
- Reluctance to accept the diagnosis of depression
- Fear that antidepressant medication is addictive
- Symptom improvement leading to patient stopping drugs, with subsequent relapse
- Difficulty obtaining relevant information

Before starting treatment compliance can be improved by

- Give positive advice regarding the benefits of treatment
- Reinforce that antidepressant are not addictive
- Inform patients about potential side effects
- Reinforce the importance of not discontinuing treatment before or during the continuation treatment phase
- Inform the patient about the possibility of discontinuation symptoms on missing doses, or stopping antidepressant medication
- Reassure regarding the low risk of discontinuation problems if reduced and stopped under supervision
- Advise on the timing of dosage
- That improvement may not be noticed until the patient has been on the medication for a week or more
- Advice that treatment is likely to be continued for at least 6 months from time of improvement

Community Pharmacists are usually pleased to offer advice to patients on antidepressants.

Drug Group	Description	Suggested Drug
Serotonin Selective Reuptake Inhibitors	Recommended for first line use, especially in older or physically ill patients, more susceptible to side effects. They are better tolerated than TCAs and are more likely to be prescribed at adequate doses for an adequate period. (Rosholm et al 1997). Fewer anticholinergic and cardiovascular side effects than TCAs. Are not without side effects. These are mainly gastrointestinal e.g. nausea, diarrhoea.	Fluoxetine
Tricyclic Antidepressants (TCA)	Use at adequate dosage often limited by side effects. Anticholinergic side effects e.g. constipation, blurred vision and dry mouth are common. Cardiovascular effects such as arrhythmias and hypotension can also occur. TCAs can prolong the QT interval. Sedation can be problematic but may also be useful in some patients. Tolerance to some side effects can develop but may necessitate gradual dosage increases. Amitriptyline is comparable in efficacy and safety to other TCAs but is recommended, as it is more cost effective.	Amitriptyline
Serotonin Norepinephrine Reuptake Inhibitor (SNRI)	Not for first line use. NICE recommend initiation and monitoring under specialist supervision only. May have greater efficacy than SSRIs at doses of 150mg or greater. Dose responsive so can titrate dose for further effect. Side effect profile similar to SSRIs but can lower/elevate blood pressure. Note requirement for pre-treatment ECG and B.P. check.	Venlafaxine
Norepinephrine and Serotonin Specific Antidepressants (NASSA)	Not for first line use. Weight gain can be a problem. Low incidence of sexual dysfunction. May potentiate other centrally acting sedatives. Suitable for patients who require sedation but for whom a TCA is not suitable.	Mirtazepine
Norepinephrine Reuptake Inhibitor (NARI)	Normally used after consultation with secondary care. Is not sedating but insomnia can be a problem, along with some anticholinergic side effects.	
Monoamine Oxidase Inhibitor (MAOI)	Normally used after consultation with secondary care.	Phenelzine

Recommended Dosage

Normal recommended dose range for the ten most frequently prescribed antidepressants in Highland in 2002-3 are shown below. Please see NHS Highland Joint Formulary for currently recommended antidepressants.

SSRIs	ADULTS	ELDERLY
Fluoxetine	20mg	20mg
Citalopram	20-60mg	20-40mg
Paroxetine	20-50mg*	20-40mg
Sertraline	100-200mg	50-200mg
NEWER ANTIDEPRESSANTS		
Venlafaxine**	75-375mg	75-375mg
Mirtazapine	15-45mg	15-45mg
OLDER TCAs		
Amitriptyline	150-200mg	
Clomiprammine	150-200mg	Not Recommended
Dosulepin	150-225mg	
NEWER TCAs		
Trazodone	200-300mg	150-300mg

*Note CSM 2004 advice. Recommended dose for depression is 20mg
**Applies only to the immediate release preparation

Failure to respond despite good compliance

Adult

• No response after 4 weeks
• Partial response after 4 weeks, continue for a further 2 weeks. Partial response converted to full response at 6 weeks?

Elderly

• No response after 6 weeks
• Partial response after 6 weeks, continue for a further 3 weeks. Partial response converted to full response at 9 weeks?

If a full response is not obtained within the time scales outlined above then:

• First increase the dose of the current antidepressant to the upper limit of the therapeutic range, provided the patient can tolerate any side effects.

• Switch to a drug of a different class. Different classes of antidepressant in addition to MAOIs, TCAs and SSRIs include SNRI, NARI, and NaSSAs. Call Pharmacy Department at New Craigs Hospital for advice if required (Tel: 01463 704663).

• Washout periods are required for switching between certain antidepressants (see below)

Antidepressant Swapping – General Guidelines

1. Fluoxetine, due to its long plasma half-life and active metabolite, may be stopped abruptly if the dose is 20mg/day.
2. When swapping from one antidepressant to another, abrupt withdrawal should usually be avoided. Cross tapering is preferred, where the dose of the ineffective or poorly tolerated drug is slowly reduced while the new drug is slowly introduced.
3. The speed of cross tapering is best judged by monitoring patient tolerability. No clear guidelines are available, so caution is required.
4. Note that the co-administration of some antidepressants is absolutely contra-indicated. See BNF Chapter 4.3.2 and Appendix 1. In other cases, theoretical risks or lack of experience preclude recommending cross tapering.
5. Withdrawal ideally involves a gradual reduction to a low dose of antidepressant before stopping.
6. Potential dangers of simultaneously administering two antidepressants include pharmacodynamic interactions (serotonin syndrome, hypotension and drowsiness) and pharmacokinetic interactions (e.g. elevation of tricyclic plasma levels by some SSRIs).

TO / FROM	Tricyclics	Citalopram	Fluoxetine	Paroxetine	Sertraline	Trazodone/ nefazodone	Venlafaxine	Mirtazapine	Reboxetine
Tricyclics	Cross taper cautiously	Halve dose and add citalopram then slow withdrawal. **	Halve dose and add fluoxetine then slow withdrawal. **	Halve dose and add paroxetine then slow withdrawal. **	Halve dose and add sertraline then slow withdrawal. **	Halve dose and add trazodone/ nefazodone then slow withdrawal. **	Cross taper cautiously starting with venlafaxine 37.5mg at night	Withdraw before starting mirtazapine cautiously	Cross taper cautiously
Citalopram	Cross taper cautiously. **	-	Withdraw then start fluoxetine.	Withdraw and start paroxetine at 10mg/day	Withdraw and start sertraline at 25mg/day	Withdraw before starting titration of trazodone/ nefazodone	Withdraw. Start venlafaxine 37.5mg/day. Increase very slowly	Withdraw before starting mirtazipine cautiously	Cross taper cautiously
Paroxetine	Cross taper cautiously with low dose of tricyclic.**	Withdraw and start citalopram	Withdraw then start fluoxetine	-	Withdraw and start sertraline at 25mg/day	Withdraw before starting titration of trazodone/ nefazodone	Withdraw paroxetine. Start venlafaxine 37.5mg/day and increase very slowly	Withdraw before starting mirtazipine cautiously	Cross taper cautiously
*Fluoxetine*1*	Stop fluoxetine. Start tricyclic at very low dose and increase very slowly	Stop fluoxetine. Wait 4-7 days. Start citalopram at 10mg/day and increase slowly	-	Withdraw fluoxetine. Wait 4-7 days, then start paroxetine 10mg/day	Stop fluoxetine. Wait 4-7 days. Start sertraline at 25mg/day	Stop fluoxetine. Wait 4-7 days. Start low dose trazodone/ nefazodone	Withdraw. Wait 4-7 days. Start Venlafaxine at 37.5mg/day. Increase very slowly.	Withdraw. Wait 4-7 days before starting mirtazapine cautiously	Withdraw. Start reboxetine at 2mg bd and increase cautiously
Sertraline	Cross taper cautiously with very low dose of tricyclic. **	Withdraw then start citalopram	Withdraw then start fluoxetine	Withdraw then start paroxetine	-	Withdraw before starting trazodone/ nefazodone	Withdraw. Start venlafaxine at 37.5mg/day	Withdraw before starting mirtazapine cautiously	Cross taper cautiously
Trazodone/ nefazodone	Cross taper cautiously with very low dose of tricyclic.	Withdraw then start citalopram	Withdraw then start fluoxetine	Withdraw then start paroxetine	Withdraw then start sertraline	-	Withdraw. Start venlafaxine at 37.5mg/day	Withdraw before starting mirtazapine cautiously	Withdraw, start reboxetine at 2mg BD and increase cautiously
Venlafaxine	Cross taper cautiously with very low dose of tricyclic. **	Cross taper cautiously. Start with 10mg/day	Cross taper cautiously. Start with 20mg every other day	Cross taper cautiously. Start with 10mg/day	Cross taper cautiously. Start with 25mg/day	Cross taper cautiously	-	Withdraw before starting mirtazapine cautiously	Cross taper cautiously
Mirtazapine	Withdraw then start tricyclic	Withdraw then start citalopram	Withdraw then start fluoxetine	Withdraw then start paroxetine	Withdraw then start sertraline	Withdraw then start trazodone/ nefazodone	Withdraw then start venlafaxine	-	Withdraw then start reboxetine
Reboxetine	Cross taper cautiously	Cross taper cautiously	Cross taper cautiously	Cross taper cautiously	Cross taper cautiously	Cross taper cautiously	Cross taper cautiously	Cross taper cautiously	-

** Do not co-administer clomipramine and SSRIs or venlafaxine. Withdraw clomipramine before starting

*1 Beware interactions with fluoxetine may still occur for five weeks after stopping fluoxetine because of long half-life.

Serotonin Syndrome – Symptoms

Restlessness
Sweating
Tremor
Shivering
Myoclonus
Confusion
Convulsions
Death

Duration of Treatment

Inadequate or no treatment for six months after the illness has resolved can result in relapse rates as high as 50%.

Continue antidepressant drug treatment for a minimum of 6 months after remission of symptoms in adults, and for a minimum of 12 months in the elderly.

Continue the same dose of antidepressant used that produced a response to treatment.

Patients with residual depressive symptoms and other factors increasing risk of relapse should continue treatment for longer with the duration taking into account the persistence of these factors.

Maintenance Therapy

The risk of recurrence of depressive illness is high and increases with each episode.

Maintenance therapy should be at the same dose of antidepressant that produced a response to treatment.

The decision to go on to maintenance therapy, rather than stop treatment at the end of the continuation phase, must be made on clinical grounds in discussion with the patient. Maintenance treatment with antidepressants is indicated for patients with:

- 3 or more episodes of depression in the last 5 years.
- More than 5 episodes altogether.
- Fewer recurrent depressive episodes but with persistent risk factors for relapse/recurrence

Re-evaluate patients on maintenance treatment, taking into account age, co morbid conditions and other risk factors in the decision to continue the treatment beyond 2 years.

For the elderly, with two or more relapses, life long therapy is indicated.

Discontinuation

Discontinuation symptoms can occur with all the major classes of antidepressant

Symptoms start abruptly within a few days of stopping the antidepressant

Symptoms usually resolve with days to 3 weeks

Risk factors: longer duration of treatment, short half life drugs such as paroxetine and venlafaxine

If administered for 8 weeks or more, antidepressants should be reduced gradually over a minimum of 4 weeks. Fluoxetine may be an exception to this rule. Rapid discontinuation may be required for severe adverse reactions or if the patient switches into a manic state

Ideally taper the dose over 6 months in patients who have been on longer-term maintenance treatment

If discontinuation symptoms are mild then explanation and reassurance are often all that is required

If severe symptoms are experienced consider the re-introduction of the original antidepressant (or another from the same class with a longer half life e.g. fluoxetine for paroxetine) and reduce gradually.

Discontinuation symptoms are varied and differ depending on the class of antidepressant. Symptoms common to all classes include gastro-intestinal disturbance (nausea, abdominal pain, diarrhoea), general somatic distress (sweating, lethargy, and headache), sleep disturbance (insomnia, vivid dreams, nightmares) and affective symptoms (low mood, anxiety, irritability). With the SNRI/SSRIs the commonest symptoms appear to be dizziness and sensory abnormalities such as numbness or electric shock like sensations. Discontinuation symptoms may be a useful clue to convert non-compliance.

Antidepressants in pregnancy and breast-feeding

Updated advice in these areas can be obtained locally from the Area Medicines Information Service (Tel. 01463 704288) or New Craigs Pharmacy Department (01463 704663).

Carefully consider the benefit/risk ratio of prescribing antidepressants during pregnancy and breastfeeding for both mother and baby/foetus. Taking into account:

a. Antidepressants are not licensed for use in pregnancy & breastfeeding.
b. There should be a clear indication for drug treatment
c. Lowest effective dose should be given for the shortest period necessary
d. Drugs with a better evidence base (generally more established drugs) are preferable.

Antidepressants in the first trimester

Evidence indicates no increased risk of major malformation or spontaneous abortion following exposure to TCAs or SSRIs in early pregnancy. There is most evidence for amitriptyline and imipramine in the TCA class, and most evidence for Fluoxetine in the SSRI class.

- Carefully assess the risks of stopping TCAs or SSRIs in relation to the mother's mental state & previous history
- There is no indication to stop TCAs or SSRIs as a matter of routine in early pregnancy
- If a woman becomes depressed during pregnancy, antidepressants should be prescribed with caution and specialist advice sought

Antidepressants after the first trimester

In later pregnancy there is evidence of neonatal toxicity and withdrawal at birth in infants exposed to antidepressants. There are also concerns about the possible effects on infant neurodevelopment.

- Neonates exposed to antidepressants during pregnancy should be monitored for withdrawal following delivery
- Consider dose reduction and/or discontinuation 2 to 4 weeks before expected delivery date then recommence after delivery.

Antidepressants during breast-feeding

Manufactures advise avoiding antidepressants during breast-feeding due to their excretion in breastmilk and the evidence base is very limited. However there is no clinical indication for women treated with TCAs (except doxepin) or the SSRIs paroxetine, sertraline or fluoxetine to stop breast-feeding provided the infant is healthy and progress is monitored.

- Breast-feeding should take place immediately prior to taking medication, ideally as a single daily dose just before the infant's longest sleep period
- Ideally avoid breast feeding when maternal plasma levels are highest, usually 1 to 2 hours after taking the medication
- Paroxetine or Sertaline may be the preferred SSRIs.

A patient information leaflet concerning antidepressants and breastfeeding has been produced by NHS Highland. This is written in plain English and is designed to assist the GP in enabling the patient to come to an informed decision.

Antidepressants in cardiovascular disease
When initiating treatment in patient with ischaemic heart disease, sertraline is the treatment of choice.

ST JOHN'S WORT

When a patient has declined a number of offers of treatment for depression or expressed a preference for St John's Wort they should be informed that St John's Wort may be of benefit in mild and moderate depression. They should also be informed, as should those taking St John's Wort, of the interactions of St John's Wort with other drugs, of the lack of information on longer term efficacy and side effects and of the different strengths of the preparation available and the uncertainty that arises from this

Always check if a patient is taking St John's Wort if considering prescribing an antidepressant.

Suicide Screening Questions

When a diagnosis of Depression is made, suicide risk requires assessment. For all depressed patients the following questions may be asked:

- Have these symptoms/feelings we've been talking about led you to think you might be better off dead?
- This past week, have you had any thoughts that life is not worth living or that you'd be better off dead?
- What about thoughts about hurting or even killing yourself? If **YES**, what have you thought about?
  Have you actually done anything to hurt yourself?

Risk Factors

- Previous attempt
- Older age
- Living alone/no social support
- Substance misuse/ alcohol,
- Chronic disease
- Helplessness

ASSESSMENT OF SUICIDE RISK

Risk	Description	Action
Low Risk	No current thoughts, no major risk factors * See risk factors above	Continue follow-up visits and monitoring
Intermediate Risk	Current thoughts, but no plans, with or without risk factors	Assess suicide risk carefully at each visit and contract with patient to call you if suicide thoughts become more prominent; consult with an expert as needed.
High Risk	Current thoughts with plans	Emergency assessment by qualified expert