Prescribing Guidelines for the Management of Moderate to Severe Depression

Oxfordshire Clinical Commissioning Group

Assess severity of depression & suicide risk & exclude Bipolar Affective Disorder

Consider psychological therapies - antidepressant treatments are only appropriate for the management of moderate/severe depression

First line choices:

- **Retry previous successful antidepressant treatment**
- **Citalopram or fluoxetine** - long half life (Risk of interactions due to CYP2D6 interaction see Appendix 1 overleaf)

Second line choice – either fluoxetine or citalopram

Good response – continue for 6 to 9 months once better
Monitor for adverse effects

If no response within 2 weeks monitor patient closely and consider changing dose or drug at weeks 3 – 4. Consider another first choice or second choice below

Third line choices:
Sertraline – may need dose titration
Mirtazapine – if SSRI adverse effects are unacceptable (GI bleeding, hyponatraemia, sexual dysfunction, insomnia)
Venlafaxine – monitor BP. Prominent withdrawal symptoms. No evidence of greater efficacy than sertraline & mirtazapine
Paroxetine – risk of withdrawal symptoms & drug interactions.
Fluvoxamine – highest incidence of gastric adverse effects. Risk of drug interactions
Tricyclics

If no response or not tolerated switch to another class (above) or seek specialist advice (choice below or combination therapy)

Specialist Advice / Third line choices

	Traffic light classification
Moclobemide	***Need to classify as*** **Yellow continuation following specialist recommendation**
Duloxetine	**Yellow continuation following specialist recommendation**
Agomelatine	**Black no Prescribing.**
MAOI	***Need to classify as*** **Yellow continuation following specialist recommendation**

Special Populations

Elderly – SSRIs or mirtazapine; Watch for hyponatraemia (FAQ link), co-morbid illness and interactions with other medication. Gastro protection may be advised where concomitant administration of SSRIs with NSAIDs Healthcare professionals should be aware of a small increased risk of falls and fractures associated with the use of TCAs and SSRIs, and should take this risk into account in their discussions with patients and in prescribing decisions

Epilepsy – SSRIs; citalopram is less likely to interact with anticonvulsants. Also may need to review anticonvulsants as some have been reported to cause depression. (FAQ link)

Hepatic impairment – Paroxetine or agomelatine*. Use lower doses and monitor for adverse effects regularly. Watch out for hepatic drug interactions.

Renal impairment – SSRIs; choose one with short half life (sertraline, paroxetine) unless concerned about drug interactions (citalopram). Moclobemide, agomelatine* and tricyclics are also lower risk, although monitor for urinary retention.

Cardiovascular disease – SSRIs (esp. sertraline), mirtazapine. (FAQ link) Avoid tricyclics and venlafaxine if possible.

Parkinsons – SSRIs; monitor for movement disorders. Depression often difficult to treat. (FAQ link)

Diabetes – Sertraline is the drug of choice. SSRIs may decrease weight and glucose in the short term, but long term antidepressant use is associated with an increased incidence of diabetes (reason unclear).

Pregnancy and Lactation -Tricyclics are currently the drugs of choice in pregnancy. These should be considered in women of child-bearing age who plan to become pregnant in the near future. Sertraline, imipramine and nortriptyline are the drugs of choice in lactation.

For further advice see our MI bulletin Antidepressants in Pregnancy and Lactation June 2010 (link)

Suicide risk:

Antidepressant therapy has been associated with a short term increase in suicidal thoughts and acts, particularly in young adults and adolescents. It should be noted that although the relative risk might be elevated compared to placebo, the absolute risk remains very low. Secondly, the most effective way to reduce suicidality is to treat depression. Nevertheless, the risk of overdose should be considered when prescribing antidepressants. Drugs with lower toxicity (e.g. SSRIs) should be chosen and limiting tablet quantities may be necessary. Patients under 30 should be reviewed within 7 days. Depressed patients with insomnia have significantly higher suicidal ideation, so it is important to manage sleep disorders in the early stages of treatment (especially if the antidepressant can make insomnia worse).

Withdrawal symptoms:

All antidepressants have been associated with discontinuation symptoms - although patients should be informed they are not addictive. These include flu-like symptoms, nausea, irritability, neurosensory disturbances, etc. The onset is usually within 5 days of stopping treatment, depending on the half life of the drug. The risk is increased if patients miss or reduce doses and also with drugs that have a short half life e.g. paroxetine, venlafaxine, with children and adolescents and in those taking other psychotropic medication. Gradual withdrawal (over at least 4 weeks) is recommended to reduce this risk

Withdraw gradually to avoid discontinuation symptoms

Risk of relapse is highest in the first 2 – 3 months after withdrawal regardless of length of treatment.

Referral to secondary care

Refer all patients with a history of mania or manic symptoms that might be suggestive of bipolar disorder. Refer patients who have a poor response to treatment, co-morbid substance misuse, intolerable side effects, non-adherence to treatment or other significant risk factors

Appendix 1 interactions of fluoxetine

Fluoxetine does not appear to interact with alcohol - it does not raise blood alcohol levels nor does it potentiate the effects of alcohol.
The following are some of the potential drug interactions with fluoxetine:

Drug	Interaction
Acetylcholinesterase Inhibitors	Fluoxetine may increase levels of donepezil and galantamine
Antidepressants	Concomitant administration of MAOIs is a contraindication. Serious and potentially life-threatening reactions can occur. Following discontinuation of an MAOI, at least 14 days should elapse and following discontinuation of the reversible-MAOI, moclobemide, at least 1 day should elapse before fluoxetine is started. Concomitant administration of TCAs, SSRIs, or other related antidepressants should also be avoided due to the increased risks of side effects, particularly serotonin syndrome. Plasma levels of amitriptyline, clomipramine, desipramine, imipramine, nortriptyline and venlafaxine may all be increased by concomitant use of fluoxetine – levels may be increased by 20% to ten fold Concomitant administration of St John's Wort should be avoided due to the increased risks of side effects, particularly serotonin syndrome.
Anticonvulsants	Carbamazepine levels may rarely and unpredictably be increased by fluoxetine. Ideally carbamazepine levels should be monitored and the dose may need to be reduced accordingly. Phenytoin levels may unpredictably be increased by fluoxetine. Ideally phenytoin levels should be monitored and the dose may need to be reduced accordingly. Valproate levels may be increased or decreased with concurrent fluoxetine use. Concurrent use should be closely monitored
Antiplatelet agents (including clopidogrel)	The SSRIs have been reported rarely to cause cutaneous bleeding abnormalities therefore extra caution is advised in patients taking drugs that affect platelet function such as aspirin and NSAIDs.
Antipsychotics	Aripiprazole, clozapine, haloperidol, olanzapine, risperidone levels have been increased when fluoxetine is used concurrently
Atomoxetine	Fluoxetine may increase levels and side effects
Lithium	Increases and decreases of lithium levels have been seen with fluoxetine
5HT1 agonists (triptans)	Concurrent use is usually uneventful, however the combination of an SSRI with a triptan has occasionally resulted in adverse reactions. Concurrent use should be used cautiously with close monitoring, especially because of the increased risk of serotonergic side effects. Use with triptans carries the additional risk of coronary vasoconstriction and hypertension
Tamoxifen	A 65-75% reduction in plasma levels of one of the more active forms of tamoxifen, i.e. endoxifen,has been reported in the literature when co-administered with potent CYP2D6 inhibitors. Fluoxetine should therefore be avoided if possible
Tramadol	The combination of fluoxetine and tramadol should be used cautiously with close monitoring because of the increased risk of seizures and serotonergic side effects.
Warfarin	Fluoxetine may interact with warfarin, although this appears to be uncommon and unpredictable. There have been a few reports of INR changes, bruising and bleeding, therefore careful coagulation monitoring is advised during initiation of fluoxetine or following dose increases, decreases or discontinuation.

References:

Eli Lilly and Company Limited. Prozac 20mg capsules. Summary of Product Characteristics. Date of revision of the text: April 2011 (accessed via the Electronic Medicines Compendium)
Stockley I H. Stockley's Drug Interactions. Accessed from medicines complete online 1st October 2011

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