DERBYSHIRE JOINT AREA PRESCRIBING COMMITTEE (JAPC)

Guidelines for choosing Antidepressants in Moderate and Severe Unipolar Depression in Adults and Older Adults
Antidepressants in Moderate and Severe Unipolar Depression
Guidelines for Choosing in Adults (≥ 18 years of age) and Older Adults***

STEP 1
Standard dose SSRI
(see Citalopram notes overleaf)
MI (in past 4 weeks), unstable angina, QT prolongation risk:
Consider Sertraline (or possibly Fluoxetine)
High risk of bleed (esp. GI) or concurrent NSAID, antplatelet, anticoagulant, corticosteroid:
Consider Mirtazapine
(avoid SSRI- see overleaf)

STEP 2
Switch to different SSRIs1,2 (standard dose) or to a ‘better tolerated’ different class e.g. Mirtazapine Lofepramine, Moclobemide
Sexual dysfunction: consider Mirtazapine

STEP 3
Re-evaluate diagnosis *** (see ref 5)
Specialist initiation only:
Dual combination other than in Step 3 e.g. Mirtazapine + Venlafaxine or Atypical antipsychotic augmentation or Classical MAOI alone or Liothyronine (T3) augmentation (see shared care) or Lamotrigine augmentation

STEP 4
Re-evaluate diagnosis *** (see ref 5)
Specialist initiation only:
Dual combination other than in Step 3 e.g. Mirtazapine + Venlafaxine or A typical antipsychotic augmentation or Classical MAOI alone or Liothyronine (T3) augmentation (see shared care) or Lamotrigine augmentation

* Risk of self harm is greatest around the time of presentation and may increase in early stages of treatment. In addition, young adults (≤ 30 years of age) are at a higher background risk of suicidal behaviour. Careful and frequent monitoring is important in the early stages of treatment and at dose increases, particularly in young adults and where a service user of any age experiences worsening of symptoms or new symptoms after starting treatment or around the time of a dose increase.

** Consider rating scale e.g. Patient Health Questionnaire PHQ-9, (local modified version for Learning Disability available here or via Gaynor Ward), Geriatric Depression Scale-15.

*** For children and young people under 18 contact your local CAMHS or for other special clinical situations such as pregnancy or possibility of bipolar depression seek specialist advice.
Citalopram Usage and Maximum Dose Recommendations

MHRA recommendations for citalopram due to a dose-dependent risk of QT prolongation:
- Maximum dose 40mg/d in adults and 20mg/d in the elderly and people with reduced hepatic function
- C/I with known QT prolongation, congenital long QT syndrome or taking other QT-prolonging medicines
- Caution with higher risk of developing Torsades de Pointes (see overleaf)

- Perform ECG and check U & Es to exclude electrolyte imbalance

**Existing citalopram user**

- A QTc interval beyond 500ms is generally considered to present an unacceptable level of risk necessitating prompt review and/or change of medicine regime.

**Continue citalopram**

- No

**Discuss MHRA contraindications with patient. Compelling evidence from patient history not to reduce dose within licence?**

- No

**Discuss with patient and reduce dose stepwise to within licensed maximum dose for user’s clinical condition**

- Review patient within 2-4 weeks

**Patient remains clinically stable?**

- No

**Perform ECG if new QT prolonging medicines are co-prescribed and considered essential**

**Citalopram above the maximum licensed dose?**

- Yes

**Known QTc prolongation, congenital long QT syndrome, higher risk of Torsades de Pointes or concomitant QT-prolonging medicines?**

- Yes

**Call patient for review. Check for further risk factors such as citalopram above licensed dose. Discuss MHRA contraindications, seek user view of switching to suitable alternative. Compelling patient history to remain on citalopram e.g. previous treatment resistant depression?**

- Yes

**Switch to an appropriate alternative for the given indication e.g. Sertraline licensed for both depression and panic disorder, Fluoxetine or Mirtazapine**

**No**

**Perform ECG and check U & Es to exclude electrolyte imbalance**

**QTc ≥ 500ms?**

- No

**Seek psychiatrist +/- cardiologist opinion**

**Yes**

**Having sought specialist opinion and considered other options, if it is felt to be in patient’s best interests to continue using citalopram outside of its product licence, this should be discussed fully with the patient. Patient consent should be clearly documented and the prescriber takes full responsibility for unlicensed dose or off-label use. Tell patient to report heart rhythm disturbance or fainting.**

**Repeat regular ECG monitoring advisable e.g. 6 monthly or after any dose or relevant medicine changes**

**Perform ECG after dose stabilisation and after any relevant medicine or dose changes**

**QTc prolongation has also been reported with all SSRIs, mirtazapine, venlafaxine and tricyclic antidepressants. If switching to one of these agents, use the minimum effective dose and consider repeat ECG monitoring.**

**No**

**Yes**

**Tell patient to report heart rhythm disturbance or fainting.**

**Repeat regular ECG monitoring advisable e.g. 6 monthly or after any dose or relevant medicine changes**
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Cognitive Behavioural Therapy (CBT) and other intervention options
The use of antidepressants should be considered within the overall framework of managing depression where other intervention options may also be appropriate e.g. in moderate depression. CBT should also be considered for those service users who do not take, refuse or are unable to tolerate antidepressant treatments or have shown an inadequate response to them. In severe depression, a combination of antidepressants and individual CBT has been shown to be more cost effective than either treatment alone. Other options to consider are Interpersonal Psychotherapy (IPT), couple-focused therapy and occupational therapy.

Electro-Convulsive Therapy (ECT)
Should be considered as an emergency treatment in life-threatening situations. It may also be considered in severe depression where a trial of antidepressants up to and including Step 3 of the above algorithm (where feasible) has produced inadequate response or has been poorly tolerated, depending on the individual clinical situation.

Treatment Resistant Depression (TRD)
Usually denotes a failure to respond to 2 or more single antidepressants given at adequate dose for an adequate time sequentially. Level of service user concordance should be investigated in any apparent antidepressant failure. There is significant variation in the level of evidence supporting the options listed in Steps 3 and 4 and this evidence is being constantly added to. The options therefore represent a guide only and it is anticipated that the Specialist would consider seeking further opinion for individual service users e.g. for concordance and thorough medication history assessment, consideration for tertiary referral service, review of diagnosis (e.g. possibility of hitherto undiagnosed bipolar depression, co-morbid anxiety etc.)

Hyponatraemia – any antidepressant may be associated with this. Recommendation is for baseline serum sodium and repeat within first month. Risk is greater in older adults or those taking concurrent natriuretic medicines e.g. diuretics or with low body weight or in warm weather.

Serotonin syndrome and toxicity: predictable from serotonergic drug combinations (including single serotonergic agents in highly susceptible individuals, lithium and non-psychiatric medicines e.g. tramadol, sumatriptan). Level of severity ranges from milder chronic symptoms of akathisia, tremor, agitation, sweating and shivering to rapid onset of potentially fatal metabolic acidosis, seizures and rhabdomyolysis. Stopping serotonergic agent(s) is key as this usually results in rapid symptom resolution within 24 – 72 hours. Serotonergic antidepressant combination options (see Steps 3 and 4) are an obvious risk for developing toxicity, in particular the combination of a tricyclic and an MAOI. For this reason, the relatively safer combination of Mirtazapine with a SSRI is put forward as an option but, as a minimum, the service user is expected to be informed of possible symptoms to look out for and should ideally be monitored frequently over the first few days. Switching between antidepressants can also prove hazardous and useful tables with recommendations for method and speed of switch are available such as Maudsley handbook.

Antidepressant discontinuation syndrome – onset usually within 5 days of stopping (or sometimes tapering) antidepressant. Level of symptom severity varies and although often mild and self-limiting can be severe or prolonged. Evidence suggests symptom severity is worse if service user is not forewarned of possibility. Generally if an antidepressant has been taken for 8 weeks or more, a gradual taper over 4 weeks (not necessary with Fluoxetine) and represents unlicensed use.

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Bleeding risk
SSRI-induced platelet dysfunction may manifest as bruising, nose bleeds, peri-operative bleeding, uterine bleeding, gastro-intestinal bleeding or possibly even as cerebral haemorrhage - stroke. There is some controversial evidence that SSRIs with less potency for inhibiting serotonin reuptake at the receptor level and avoiding the use of higher than standard SSRI doses may be associated with less risk. It is therefore recommended that SSRIs are avoided if at all possible in patients with high risk of bleed e.g. previous history of bleed (especially gastro-intestinal) or taking concurrent medicines known to increase bleeding risk e.g. anticoagulants, antiplatelets, NSAIDs or glucocorticoids. Additive factors may also include patients over 80 years of age, smokers and those liable to consume alcohol to excess - Mirtazapine may be considered in these high risk patients. Offering gastro-protection alongside an SSRI would seem advisable for those ≥ 65 years old where an alternative to an SSRI is less suitable and who either take anticoagulants, antiplatelets, NSAIDs or glucocorticoids or have other risk factors for bleeding. However there is no evidence that this will reduce haemorrhage risk and represents unlicensed use.
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Co-morbid conditions requiring careful consideration of the choice of antidepressant include:
- Diabetes, glaucoma, epilepsy, bleeding disorders (especially gastro-intestinal bleeding - see above) and cardiovascular disease (including hypertension, postural hypotension, arrhythmias, known QT prolongation, congenital QT syndrome and conditions that pose a risk of Torsade de Pointes including medication known to be associated with QT prolongation).

There is perhaps a greater association of QT prolongation with Citalopram than with other SSRIs and safeguards in terms of appropriate patient selection and consideration of concomitant medication should be taken as detailed below and in the Citalopram SPC.

Citalopram - MHRA Usage and Maximum Dose Recommendations
Whilst Citalopram remains a treatment option in Derbyshire, the MHRA has warned of dose-dependent QT prolongation associated with Citalopram. Therefore licensed prescribing recommendations changed in October 2011.

- Citalopram is contraindicated in people:
  - with a known QT prolongation or congenital long QT syndrome
  - taking other medicines known to prolong QT interval (see table below #)
- Citalopram should only be used with caution in people with higher risk of developing Torsades de Pointes e.g. CHF, recent MI, bradyarrhythmias, hypokalaemia or hypomagnesaemia
- Citalopram should not be used above 40mg/d in adults
- Citalopram should not be used above 20mg/d in older adults and people with reduced hepatic function
- Patients on Citalopram at high risk of QT prolongation should be offered ECG monitoring.
- Patients on Citalopram should be advised to contact a health care professional immediately if they experience signs or symptoms of an abnormal heart rate or rhythm, such as fast or irregular heartbeat, shortness of breath, fainting, collapse or dizziness.

In addition, Cimetidine may inhibit the metabolism of Citalopram and caution is therefore advised when co-administering (the FDA recommend not exceeding 20mg/day for such patients).

# Some medicines and substances associated with QT prolongation (list not exhaustive) include:

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Antiarrhythmics</th>
<th>Antipsychotics (examples, all have potential)</th>
<th>Antidepressants</th>
<th>Others</th>
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<tbody>
<tr>
<td>Azithromycin</td>
<td>Disopyramide</td>
<td>Risperidone</td>
<td>SSRIs</td>
<td>Methadone</td>
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<tr>
<td>Clarithromycin</td>
<td>Procanamide</td>
<td>Fluphenazine</td>
<td>Tricyclics</td>
<td>Substance misuse</td>
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<tr>
<td>Erythromycin IV</td>
<td>Quinidine</td>
<td>Haloperidol</td>
<td>Trazodone</td>
<td>e.g. ecstasy,</td>
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<tr>
<td>Roxithromycin</td>
<td>Amiodarone</td>
<td>Clozapine</td>
<td>Mirtazapine</td>
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<td>Sotalol</td>
<td>Pimozide</td>
<td>Venlafaxine</td>
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<td>Moxifloxacin</td>
<td>Flecaïnide</td>
<td>Chlorpromazine</td>
<td>Lithium</td>
<td>Domperidone</td>
</tr>
</tbody>
</table>

Antifungals

- Fluconazole
- Ketoconazole
- Itraconazole
- Posaconazole

- Nelfinavir

- Chloroquine
- Mefloquine
- Halofantrine

- Halothane

See also free regularly updated resource [https://www.crediblemeds.org/](https://www.crediblemeds.org/) (the user is required to register)

References
1. NICE Clinical Guidelines 90 Depression, 91 Depression in adults with chronic physical health problem Oct 2009
2. STAR*D (Sequenced Treatment Alternatives to Relieve depression) Level 2 Rush AJ, Trivedi MH et al Bupropion – SR, Sertraline or Venlafaxine XR after failure of SSRIs for depression. NEJM; Mar 2006; 354 (12): 1231 – 1242
9. Acknowledgement to Stephen Bazire, Principal Pharmacist, Norfolk and Waveney Mental Health NHS Trust for his work assembling main list of medicines associated with QT prolongation.

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