Medicines Management Programme: Preferred Drugs

Selective Serotonin Reuptake Inhibitors (SSRIs) & Serotonin Noradrenaline Reuptake Inhibitors (SNRIs) for the Treatment of Depression

Approved by
Prof. Michael Barry, Clinical Lead, MMP.

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List of abbreviations

ACP  American College of Physicians
APA  American Psychiatric Association
BAP  British Association of Psychopharmacology
CYP450 Cytochrome P450
DDD  Defined daily dose
DPS  Drug Payment Scheme
EMA  European Medicines Agency
GAD  Generalised Anxiety Disorder
GDP  Gross Domestic Product
GMS  General Medical Service
GP   General Practitioner
HAM-D Hamilton Rating Scale for Depression
HSE  Health Service Executive
ICGP Irish College of General Practitioners
IMB  Irish Medicines Board
MADRS Montgomery-Asberg Depression Rating Scale
MAOI Monoamine oxidase inhibitor
MCID Minimum Clinically Important Difference
MHRA Medicines and Healthcare products Regulatory Agency
MMP Medicines Management Programme
NICE National Institute for Health and Care Excellence
OCD Obsessive Compulsive Disorder
OECD Organisation for Economic Co-operation and Development
PCRS Primary Care Reimbursement Service
PTSD Post-traumatic stress disorder
RCT Randomised controlled trial
SNRI Serotonin noradrenaline reuptake inhibitor
SSRI Selective serotonin reuptake inhibitor
TCA Tricyclic antidepressant
TdP Torsade de pointes
1. Background

Selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) are routinely prescribed in the community to treat a range of mental health disorders including depression, generalised anxiety disorder (GAD), obsessive compulsive disorder (OCD), social anxiety disorder, panic disorder, post-traumatic stress disorder (PTSD) and bulimia nervosa.

These conditions vary considerably in complexity and severity but in many cases are managed in the community by general practitioners (GPs). Antidepressant drugs such as SSRIs and SNRIs are frequently prescribed as part of a broader treatment plan involving psychological therapy.

There are currently six SSRIs and two SNRIs authorised in Ireland. In 2013 there were in excess of 1.6 million prescriptions for SSRIs and approximately 700,000 prescriptions for SNRIs dispensed on the community drug schemes, the General Medical Service (GMS) and the Drug Payment Scheme (DPS). In any month, over 110,000 patients are expected to be treated with an SSRI and over 40,000 patients treated with an SNRI. These drug classes represent a considerable cost to the health system, in excess of €55 million in 2013.

2. Aim

The Medicines Management Programme (MMP) conducted a review of SSRIs and SNRIs as part of the Preferred Drugs initiative. The selection of a preferred SSRI and SNRI under the MMP is designed to support prescribers in choosing a medicine of proven safety, efficacy and cost effectiveness in the management of patients with depression.

As with previous MMP Preferred Drugs initiatives, prescribers are encouraged to consider these preferred drugs when initiating SSRI and SNRI therapy, and when switching from another antidepressant when a change in drug treatment is indicated.

This guidance is not applicable to all patient populations, e.g. adolescents or patients with resistant depression, in which cases specialist advice may be sought.


2.1 Definitions

For the purposes of this report, major depressive disorder, depressive disorder and unipolar depression are hence referred to as depression.

3. Preferred Drugs

3.1 Preferred SSRI

**Under the MMP, the preferred SSRI is CITALOPRAM.**

3.2 Preferred SNRI

**Under the MMP, the preferred SNRI is VENLAFAXINE.**

4. Therapeutic Indications

4.1 Depression

The focus of this guidance is the pharmacological treatment of depression, which is commonly treated in primary care. The six SSRIs and two SNRIs reviewed as part of this evaluation are licensed in the treatment of depression.4-11

The severity of depression at which antidepressants show consistent benefits over placebo is poorly defined.12 Antidepressants are generally recommended as first-line treatment in patients whose depression is of at least moderate severity.12, 13 Of this group, approximately 50% will respond to antidepressant drug treatment.12

SSRIs are well tolerated compared to older classes of antidepressants, i.e. tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), and are usually recommended as first-line pharmacological treatment for depression.12-14 There is evidence that SNRIs are less well tolerated than SSRIs but better tolerated than TCAs.12
4.2 Generalised Anxiety Disorder

SSRIs are considered the first line treatment for GAD,\textsuperscript{13, 15} however, the treatment of GAD is not the focus of this evaluation. In patients with GAD, co-existing depressive symptoms are common and many patients simultaneously fulfil diagnostic criteria for anxiety and depressive disorders.\textsuperscript{16}

Where anxiety symptoms are present within the context of a depressive disorder, drug treatment of the depression is effective in improving anxiety. Clinical practice has been to direct treatment towards the depressive disorder in the first instance, choosing treatments that also have action against the symptoms of the anxiety disorder.\textsuperscript{16}

Where GAD occurs without co-existing depression, prescribers should consider a suitable, licensed SSRI for its treatment.

4.3 Additional anxiety-related disorders

While SSRIs are considered the first line pharmacological treatment for a range of other related illnesses, e.g. OCD, social anxiety disorder and PTSD, these conditions are not the focus of this guidance.
5. Selection Criteria

Six key criteria were considered in the selection process:

1. Efficacy
2. Adverse Effect Profile
3. Drug Interactions
4. Cost
5. Prescribing trends
6. Clinical guidelines

Submissions from relevant stakeholders, including the pharmaceutical industry and clinician groups, were sought and considered in the evaluation process.

5.1 Efficacy

All licensed SSRIs and SNRIs have been shown to be effective in relieving the symptoms of depression in placebo-controlled clinical trials of varying duration. However, the selective nature of the study populations, differences in clinical trial design, including patient characteristics, make meaningful comparisons between clinical trial results difficult. Systematic reviews and meta-analyses utilise pooled data from clinical trials and provide an additional means of assessing the general and comparative efficacy of SSRIs and SNRIs.

Randomised controlled trials (RCTs) in depression generally use a 50% reduction in depression rating scale scores, e.g. the Montgomery-Asberg Depression Rating Scale (MADRS), the Hamilton Rating Scale for Depression (HAM-D), as the primary outcome measure. When discussing the results of clinical trials in depression, the issue of clinically meaningful differences becomes essential: a statistically significant difference in outcome does not necessarily correspond to a clinically important difference in outcome.

The issue of clinically important differences was addressed by Duro et al (2008), who sought to determine the clinical relevance of changes in the MADRS using the Minimum Clinically Important Difference (MCID) approach.
The MCID of the MADRS was estimated using data from three RCTs, and cross-validated using data from an observational study. From these analyses, estimates of the MCID threshold for MADRS were found to range from 1.6 to 1.9. The MMP considered the MCID threshold of 1.6 to 1.9 when reviewing comparative studies of SSRIs and SNRIs that used a change in the MADRS as the primary outcome measure. Similarly, where a change in the HAM-D scale is used as the primary outcome measure, it has been proposed that a 2-point difference on this scale represents a clinically meaningful difference in short-term clinical trials.

Where available, the less frequently used outcome measures response rate and remission rate were also considered in the context of clinical efficacy. Response rate refers to the proportion of patients achieving a $\geq 50\%$ reduction in depression rating score from baseline. Remission rate refers to the proportion of patients experiencing minimal or an absence of major depressive symptoms, or a depression score within normal, ‘non-depressed’ range, e.g. MADRS 11-13.

### 5.1.1 Comparative efficacy - SSRIs

A meta-analysis of 234 studies of 2nd generation antidepressants (including the SSRIs and SNRIs) conducted on behalf of the Agency for Healthcare Research and Quality in the USA, determined that overall, treatment effects were similar among the SSRIs and SNRIs. Meta-analyses of head-to-head trials showed statistically greater response rates for escitalopram than citalopram, and sertraline than fluoxetine. However, the report concluded that absolute differences were modest and probably not clinically relevant. For example, the pooled difference between escitalopram and citalopram in the reduction of points on the MADRS was 1.52 in favour of escitalopram, which is below that which the MMP considers to be the lower limit of clinical importance in depression, i.e. 1.6-1.9 MADRS points. These findings support the results of an earlier review of 46 RCTs which evaluated the efficacy, effectiveness and tolerability of commonly prescribed 2nd generation antidepressants and concluded that overall, these antidepressants do not differ substantially for the treatment of depression.
The MANGA study, a meta-analysis of 117 comparative RCTs of antidepressants for the acute treatment of depression in adults, concluded that escitalopram and sertraline are statistically more efficacious than fluoxetine, fluvoxamine and paroxetine.\textsuperscript{22} The main outcome measures were the proportion of patients who responded to or withdrew from treatment. Reductions in MADRS/HAM-D for individual drugs are not reported.\textsuperscript{22} It assumed that a response on the HAM-D equals a response on MADRS.\textsuperscript{20, 23}

The MANGA study has been criticised in some quarters on the basis that it included studies with a high risk for bias and open-label designs, and excluded placebo-controlled trials.\textsuperscript{20, 24} It has been advised that these results should be interpreted with caution.\textsuperscript{12}

A number of analyses of escitalopram versus other SSRIs for the treatment of depression were reviewed.

- An analysis of the comparative efficacy of escitalopram and citalopram showed a difference in favour of escitalopram.\textsuperscript{25} The difference was modest, however, with weighted mean differences ranging from 1.13 to 1.73 MADRS points. The MMP’s view is that this difference is, at most, borderline for clinical importance in the treatment of depression.

- In a meta-analysis of 16 RCTs the mean treatment difference was 0.9 MADRS points for patients treated with escitalopram compared to other SSRIs.\textsuperscript{26} This is below that which the MMP considers clinically important. With regard to specific SSRIs, the difference was statistically significant only versus citalopram (1.2 MADRS points) but was below that which the MMP considers to be the limit of clinical importance.
A series of Cochrane reviews explored the efficacy and tolerability of several SSRIs vs. other antidepressants.27-31 Efficacy was measured in terms of acute response and remission. While there were differences between SSRIs in terms of clinical outcomes/benefit, these differences were modest and in most cases, were only statistically significant during specific phases of treatment, e.g. in the period from 6 to 12 weeks of treatment. As the treatment of a first episode of depression with an SSRI is recommended to continue for at least 6 months, 12, 14, 32 the MMP takes the view that these differences are of little importance clinically.

Following a comprehensive review of the literature and submissions from stakeholders, the MMP has concluded that the clinical efficacy of individual SSRIs in treating adults with depression does not differ substantially. Therefore, recommending a particular SSRI on the basis of clinical efficacy is not warranted.

**Favoured SSRI - Clinical Efficacy: No preference**

### 5.1.2 Comparative efficacy – SNRIs

The balance of evidence suggests that venlafaxine and duloxetine have similar efficacy in the treatment of depression, though information is limited. Pooled data from two virtually identical head-to-head RCTs (n=667) found similar response and remission rates between the two treatments.33

A systematic review and meta-analysis to explore the general and comparative efficacy and safety of duloxetine in depression determined that the only available evidence is that which is referred to above.34

A Cochrane review found no difference between venlafaxine and duloxetine in terms of clinical efficacy.35

**Favoured SNRI - Clinical Efficacy: No preference**
5.2 Adverse Effect Profile

5.2.1 Adverse Effect Profile – SSRIs

SSRIs share a number of common side-effects, most notably gastrointestinal (GI) and sleep disturbances. Overall, the SSRIs are broadly similar in terms of adverse effects though these effects may occur to a lesser or greater extent with certain SSRIs. Differences may arise between individual drugs, e.g. diarrhoea, nausea. A large meta-analysis found that paroxetine was less well tolerated than escitalopram and sertraline and there is evidence that paroxetine may be associated with more weight gain and sexual side effects compared to other SSRIs.

Some SSRIs are associated with particular side effects that may not arise as frequently with others, e.g. escitalopram/citalopram and a dose-dependent risk of QT interval prolongation. A recent review of QT interval prolongation potential among the SSRIs points to numerous limitations in interpreting available data, not least that most trials are not designed to examine QT interval changes. However, it concludes that current evidence indicates that QT interval prolongation or the cardiac arrhythmia Torsade de Pointes (TdP) is reported more frequently with citalopram and escitalopram. Where the other SSRIs are concerned, QT prolongation and TdP are largely limited to case reports, though there is evidence that paroxetine has the lowest risk for QT prolongation of the SSRIs.

The tolerability of a particular drug is a subjective parameter and can depend very much on individual patients’ experiences. Furthermore, the inter-individual variation in tolerability is not easily predicted by knowledge of a drug’s adverse effect profile. In order to determine the tolerability of individual drugs, the MMP considered rates of withdrawal from clinical trials due to adverse effects, while recognising that such outcomes are a ‘crude measure of tolerability’. Published evidence suggests that rates of discontinuation due to adverse effects are broadly similar among the SSRIs. Furthermore, analysis of the GMS database confirms little difference in the discontinuation rate for currently marketed SSRIs in the Irish healthcare setting.
Discontinuation symptoms were also considered in the review process. Where possible, SSRIs and SNRIs should be not stopped abruptly but should be withdrawn following a gradual dose reduction over a period of at least 4 weeks.\textsuperscript{32, 27} Paroxetine is associated with a greater risk of discontinuation effects relative to other SSRIs.\textsuperscript{12, 32}

**5.2.2 Adverse Effect Profile – SNRIs**

The evidence suggests that SNRIs are less well tolerated than SSRIs.\textsuperscript{12, 32, 38} In clinical trials, more patients withdrew from duloxetine than venlafaxine because of adverse effects.\textsuperscript{39} A Cochrane review comparing duloxetine to other antidepressants for the treatment of depression found that duloxetine was less acceptable and less well tolerated than venlafaxine.\textsuperscript{35}

Evidence comparing venlafaxine and duloxetine in terms of discontinuation symptoms is limited. However, venlafaxine is generally regarded as having a higher relative risk of discontinuation symptoms.\textsuperscript{12, 32}

**5.2.3 Safety**

The use of antidepressants has been linked with suicidal thoughts and behaviour. Younger adults (<25 years) with a history of suicidal behaviour are at particular risk. Where necessary, patients should be monitored for suicidal behaviour, self-harm or hostility, particularly in the early stages of treatment and following dose changes.\textsuperscript{32}

Over the last number of years the Irish Medicines Board (IMB), the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medicines Agency (EMA) have issued warnings about the safety of some antidepressants, including SSRIs and SNRIs.\textsuperscript{40-42} While undertaking this review, we remained cognisant of these safety warnings.
5.2.3.1 Citalopram & Escitalopram and risk of QT interval prolongation (IMB, 2011):
- Dose dependent prolongation of the QT interval.
- Co-administration with other drugs known to prolong the QT interval is contraindicated.
- Contraindicated in patients with known QT interval prolongation.
- Maximum daily dosages now apply to patients > 65 years.

5.2.3.2 Dose related toxicity of venlafaxine (UK MHRA, 2006):
- Retrospective analysis of UK data found that the rate of overdose-related death for venlafaxine is higher than that for SSRIs.
- Caution is advised in patients with pre-existing cardiac abnormalities that may increase the risk of ventricular arrhythmias.
- The SmPCs of venlafaxine preparations authorised in Ireland contain warnings in relation to cardiac arrhythmias and suicidal behaviour.

5.2.3.3 Paroxetine & increased risk of suicide in children/adolescents & risk of withdrawal symptoms (EMA, 2004):
- Paroxetine is not to be used in children/adolescents
- Monitoring required for patients at risk of suicide
- Withdrawal effects are usually mild-moderate and self-limiting but in some cases can be severe and/or prolonged.

**Favoured SSRI – Adverse Effect Profile: No preference**

**Favoured SNRI – Adverse Effect Profile: Venlafaxine**
5.3 Drug Interactions

There is a reciprocal relationship between physical and mental health. Chronic or numerous physical illnesses have an increased association with poor mental health. Patients with conditions requiring drug treatment, e.g. diabetes and heart failure, are more likely to suffer chronic depression compared to their healthier counterparts. Consequently, the potential for drug-drug interactions must be borne in mind when selecting a preferred drug. Antidepressant drugs with less potential for drug-drug interactions are preferred.

Particular focus was placed on the potential for pharmacokinetic interaction with other drugs. Drugs with cytochrome P450 (CYP450)-inhibiting or inducing properties have greater potential for drug interactions and are, therefore, less favoured with regard to drug interactions (Table 1).

5.3.1 Drug Interactions - SSRIs

SSRIs have a common mechanism of action and generally, therefore, pharmacodynamic interactions with other drugs are likely to occur with all SSRIs, e.g. all SSRIs are contraindicated in combination with monoamine oxidase inhibitors (MAOIs) due to a risk of serotonin syndrome, and there is an increased risk of upper GI bleeding when aspirin is administered with SSRIs. However, fluoxetine, fluvoxamine, and paroxetine have a higher propensity for pharmacokinetic drug interactions than other SSRIs (Table 1).

There is potential for QT interval prolongation when citalopram or escitalopram is administered with drugs that prolong the QT interval. While this potential exists for the other SSRIs, cases of QT interval prolongation and TdP are largely limited to case reports, as discussed in section 5.2.1.
An analysis of all citalopram and escitalopram prescriptions reimbursed on the GMS and DPS for a 12-month period determined that the rate of co-prescribing of citalopram or escitalopram with drugs that have potential to prolong the QT interval\(^{(a)}\) is currently low.\(^{2}\)

- Approximately 6% of patients on citalopram received at least one prescription for a QT-interacting drug.
- Approximately 5% of patients on escitalopram received at least one prescription for a QT-interacting drug.

In both cases, tricyclic antidepressants (TCAs) accounted for the majority (3-3.5% overall) of these prescriptions. Quinine accounted for 1% overall in both cases.\(^{2}\)

### 5.3.2 Drug Interactions - SNRIs

Available evidence suggests that there is little difference between venlafaxine and duloxetine in terms of potential for drug interactions.
Table 1. Pharmacokinetic properties of SSRIs & SNRIs

<table>
<thead>
<tr>
<th>SSRI</th>
<th>Effect on cytochrome P450 (potential for drug-drug interactions)</th>
<th>Elimination half-life (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Minimal effect[^4]</td>
<td>36</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Minimal effect[^5]</td>
<td>30</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Potent inhibitor of CYP2D6[^6]</td>
<td>4-6 days.</td>
</tr>
<tr>
<td></td>
<td><em>Norfluoxetine</em> (active metabolite)</td>
<td><em>Norfluoxetine</em>: 4-16 days.</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Potent inhibitor of CYP1A2; lesser inhibitor of CYP2C2 &amp; 3A4[^7]</td>
<td>17-22</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Potent inhibitor of CYP2D6[^8]</td>
<td>24</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Mild-moderate inhibitor of CYP2D6[^9]</td>
<td>26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SNRI</th>
<th>Effect on cytochrome P450 (potential for drug-drug interactions)</th>
<th>Elimination half-life (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>Moderate inhibitor of CYP2D6; metabolised by CYP1A2[^10]</td>
<td>12</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Metabolised by CYP2D6 &amp; 3A4[^11]</td>
<td>5-11</td>
</tr>
</tbody>
</table>

**Favoured SSRIs – Drug Interactions: citalopram, escitalopram, sertraline**

**Favoured SNRI – Drug Interactions: No preference**

[^4]: Drugs included in the analysis of citalopram and escitalopram prescriptions over a 12-month period[^4, 5, 32]. Lidocaine, flecainide, quinidine (class IA antiarrhythmics); amiodarone, dronedarone, sotalol (class III antiarrhythmics); pimozide, haloperidol (antipsychotics); amitriptyline, clomipramine, dosulepin, doxepin, imipramine, lofepramine, nortriptyline, trimipramine (tricyclic antidepressants); moxifloxacin (quinolone); halofantrine (anti-malarial); astemizole, mizolastine (antihistamines); amisulpiride, sertindole (antipsychotics, atypical); quinine (anti-malarial/leg cramps).
5.4 Cost

The direct and indirect costs associated with depression are high. In 2008, the OECD reported that 21 million people in 28 European countries had depression, with an associated cost of more than €118 billion, 1% of the region’s GDP.45

Antidepressants are just one of the many direct costs associated with depression. The cost of direct healthcare provision, e.g. hospitalisation, for those who require it represents another direct cost.45

The personal cost of depression is significant and can severely impact on home and family life, interpersonal relationships and employment. Indirect costs arising from lost work productivity, absenteeism and disability allowances account for much of the economic burden of depression.45

The MMP recognises the complex and multi-faceted nature of the costs associated with depression. However, in the absence of a mixed treatment cost-effectiveness analysis specific to the Irish healthcare setting, the MMP compared the drug acquisition cost of individual agents.46 The position of the MMP is that in general, the cheaper of two drugs is preferred unless the more expensive drug has a clear and proven advantage in terms of clinical efficacy, adverse effect profile and potential for drug interactions.

5.4.1 Cost - SSRIs

There is a considerable cost differential between individual SSRIs (Figure 1, Figure 2). The most expensive SSRI, escitalopram, is more than twice the price of the cheapest SSRI, fluoxetine, based on the cost per item dispensed(b) 2.47 and the reimbursement price of the defined daily dose (DDD) 47 (February 2014 prices). With the exception of escitalopram (Lexapro®), all SSRIs are now off patent and available in generic form. The patent for Lexapro® will expire in 2014.2

(b): Cost per item dispensed: the average drug cost paid by the HSE per item per month, taking into account dose range, dispensing fees and, where applicable, mark-up.
A number of studies in depression have focused on the cost-effectiveness of escitalopram relative to other antidepressants. A UK cost-effectiveness study in which escitalopram was compared to generic SSRIs for the treatment of severe depression found no significant difference between the total annual healthcare costs with escitalopram and generic SSRIs. A pharmacoeconomic study conducted in France which found escitalopram to be a more cost-effective treatment for severe depression than citalopram (MADRS >30) assumed parity between drug treatment costs, i.e. the cost of escitalopram was assumed to be the same as that of citalopram. As this is not the case in Ireland, this conclusion cannot be applied to the Irish healthcare setting.

(c): A preparation containing the DDD of venlafaxine (100 mg) is not available on the Irish market. The above figure relates to the cheapest available venlafaxine 150 mg XL preparation.
5.4.2 Cost - SNRIs

Duloxetine (Cymbalta®) is still under patent protection whereas venlafaxine is available in generic form. Therefore, a significant price difference exists. Duloxetine is generally €15-20 more expensive per month than venlafaxine.

5.4.3 Cost - Summary

In the case of SSRIs and SNRIs, the MMP takes the view that where one drug is more expensive than another, the increased cost should be justified in terms of clinical efficacy and tolerability. Significantly increased cost should correspond to significantly better clinical outcomes for more patients.

As discussed in section 5.1, the view of the MMP is that the evidence does not support the existence of meaningful differences between the SSRIs in terms of clinical efficacy. Therefore, choosing a medication of considerably higher acquisition cost, e.g. sertraline and escitalopram, for the MMP Preferred Drugs initiative is not justified.

Equally, the superiority of duloxetine over venlafaxine has not been demonstrated in clinical trials and consequently, choosing an SNRI with a relatively high acquisition cost is not justified.

Favoured SSRIs - Cost: Fluoxetine, citalopram

Favoured SNRI - Cost: Venlafaxine

5.5 Prescribing trends in Ireland

Prescribing trends are an important criterion. The MMP recognises that clinical experience is an important factor for prescribers when choosing a medication to prescribe. A drug that is rarely prescribed is at a disadvantage as clinical experience among prescribers may be lacking.
5.5.1 Market share

Escitalopram and venlafaxine are the most frequently prescribed SSRI and SNRI in Ireland, respectively (figure 5). Citalopram is the second most frequently prescribed SSRI.²

![Market share (SSRIs)](image)

**Figure 3** SSRI market share (percent) (GMS 2012)

Figure 3 and Figure 4 depict the overall prescribing figures for SSRIs and SNRIs on the GMS in 2012.² At the time of publication, complete 2013 data were not yet available to the MMP. As indication-specific data are not recorded by PCRS, a proportion of these prescriptions may relate to the treatment of other licensed indications, e.g. GAD in the cases of escitalopram, paroxetine and venlafaxine, and diabetic neuropathy in the case of duloxetine.

![Number of Prescriptions Dispensed](image)

**Figure 4** Number of prescriptions dispensed for SSRIs and SNRIs on the GMS in 2012
5.5.2 Dose

Adequate doses are needed for clinical effect in depression. However, antidepressant therapy is dosed according to clinical response and the patient’s ability to tolerate a drug rather than to target. It is not necessary to increase doses maximally in order to achieve maximal therapeutic benefit, as may be the case with other drug classes. The lowest effective dose of an SSRI is recommended. For these reasons, the MMP’s view is that prescribed doses of SSRIs and SNRIs are not an indicator of prescribing quality.

**Favoured SSRIs – Prescribing Trends:** Escitalopram & citalopram

**Favoured SNRI – Prescribing Trends:** Venlafaxine
### Table 2. Clinical Guidelines/Recommendations

<table>
<thead>
<tr>
<th>Clinical Guidelines</th>
<th>Guideline</th>
<th>Recommended Drug (if applicable)</th>
<th>Excerpt/Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irish College of General Practitioners (in collaboration with the HSE)</td>
<td>Guidelines for the Management of Depression and Anxiety Disorders in Primary Care (2006)</td>
<td>SSRI: No preference SNRI: No preference</td>
<td>‘Consider generic form of SSRI’. ‘Sertraline is the treatment of choice when initiating treatment in a patient with ischaemic heart disease’.</td>
</tr>
<tr>
<td>National Institute for Health &amp; Care Excellence (NICE) (UK)</td>
<td>Clinical Guideline No. 90: Treatment and Management of Depression in Adults (2009)</td>
<td>SSRI: No preference SNRI: No preference</td>
<td>‘While escitalopram has been found to be more effective than citalopram, the difference, though statistically significant, is unlikely to be clinically important’.</td>
</tr>
<tr>
<td>British Association for Psychopharmacology</td>
<td>Treating Depressive Disorders with Antidepressants (2008)</td>
<td>SSRI: No preference SNRI: No preference</td>
<td>‘Systematic reviews and meta-analyses suggest that the commonly available antidepressants have comparable efficacy in the majority of patients seen in primary care’. ‘……at a dose of 20 mg escitalopram appears to be [marginally more effective] for severely ill patients’.</td>
</tr>
<tr>
<td>American College of Physicians</td>
<td>Using 2nd-Generation Antidepressants to Treat Depressive Disorders (2008)</td>
<td>SSRI: No preference SNRI: No preference</td>
<td>‘The available evidence does not support clinically significant differences in efficacy, effectiveness, or quality of life among SSRIs, SNRIs for the treatment of acute-phase major depressive disorder’.</td>
</tr>
<tr>
<td>American Psychiatric Association</td>
<td>Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition (2011)</td>
<td>SSRI: No preference SNRI: No preference</td>
<td>‘For most patients, the effectiveness of antidepressant medications is generally comparable between classes and within classes of medications”’.</td>
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</tbody>
</table>

| Practice Guidelines | | | |
|---------------------|-----------------|-----------------|
| NICE Clinical Knowledge Summaries (CKS) | Depression (August 2013) | SSRI: Citalopram, fluoxetine, paroxetine, sertraline. SNRI: No preference | If it is the first episode, prescribe one of listed the SSRIs. In the case of a recurrent episode consider what worked/did not work in the past. |
6. Summary

The following summaries are based on the evidence reviewed and represent the views of the MMP. Further details and references may be found in the relevant sections of the evaluation.

✔ **Citalopram**

Citalopram has comparable efficacy to the other SSRIs. Citalopram is well tolerated and has a favourable pharmacokinetic profile, with limited potential for drug-drug interactions. Citalopram is the second least expensive SSRI on the Irish market, but is marginally more expensive than fluoxetine.

The MMP Preferred Drugs Initiative takes the view that of the available SSRIs, citalopram achieves the best balance between efficacy, adverse effect profile, potential for drug interactions, cost, and other important criteria considered as part of the evaluation.

*On this basis, citalopram has been selected as the preferred SSRI.*

✔ **Escitalopram**

Escitalopram has comparable efficacy to the other SSRIs. While limited evidence suggests that it may be marginally more effective than some SSRIs, differences in efficacy are modest and below that which the MMP considers clinically relevant. Furthermore, statistically superior efficacy was demonstrated for the most part in RCTs of short duration, usually 8 weeks. Antidepressant treatment is generally recommended to continue for at least 6 months. The clinical superiority of escitalopram over these longer treatment periods has not been demonstrated.

Escitalopram is well tolerated and has a favourable pharmacokinetic profile, with limited potential for drug interactions.

Escitalopram is the most expensive SSRI in Ireland. The MMP takes the view that the increased cost of escitalopram relative to other SSRIs is not justified in terms of increased clinical efficacy, more favourable adverse effect profile or potential for drug interactions.

*On this basis, escitalopram has not been selected as the preferred SSRI.*
Franxetine

Fluoxetine has comparable efficacy to the other SSRIs in the treatment of depression. It is the least expensive SSRI & the 4th most frequently prescribed SSRI. Its CYP2D6-inhibiting effect makes drug interactions more likely and its long half-life (and the long half-life of its active metabolite, norfluoxetine) may necessitate longer ‘wash out’ periods when changing antidepressant treatments, due to the continued potential for drug interactions following fluoxetine withdrawal.

On this basis, fluoxetine has not been selected as the preferred SSRI.

Franvuxamine

Despite evidence of comparable efficacy to other SSRIs, there is limited clinical experience with fluvoxamine in Ireland and it is rarely prescribed. It is among the more expensive SSRIs. Like fluoxetine, fluvoxamine has considerable potential for drug interactions due to its CYP2D6-inhibiting effect.

On this basis, fluvoxamine has not been selected as the preferred SSRI.

Paroxetine

Paroxetine has comparable efficacy to the other SSRIs and compares favourably to escitalopram, fluvoxamine and sertraline on the basis of cost. Paroxetine is prescribed less frequently than the other SSRIs with the exception of fluvoxamine.

Its pharmacokinetic profile makes it more likely to interact with co-prescribed medications and its short half-life increases the risk of discontinuation effects.

On this basis, paroxetine has not been selected as the preferred SSRI.

Sertraline

Sertraline is the 3rd most frequently prescribed SSRI in Ireland, and has comparable efficacy to the other SSRIs. Though limited evidence suggests that sertraline may be more effective than some SSRIs, the MMP takes the view that this increased efficacy is unlikely to be important clinically.

Sertraline has a favourable drug interaction profile and safety in cardiac disease. However, the acquisition cost of sertraline is considerably higher than most other SSRIs, e.g. fluoxetine, citalopram. It is the view of the MMP that this increased cost is not justified in terms of clinical efficacy, adverse effect profile or potential for drug interactions.

On this basis, sertraline has not been selected as the preferred SSRI.
Venlafaxine

Venlafaxine has comparable efficacy to duloxetine. Venlafaxine is well tolerated though there is evidence that, in general, the SNRIs are less well tolerated than the SSRIs. Venlafaxine is less expensive than duloxetine, which remains under patent protection.

**On this basis, venlafaxine has been selected by the MMP as the preferred SNRI.**

Duloxetine

The evidence suggests duloxetine has comparable efficacy to venlafaxine in the treatment of depression. However, in RCTs and subsequent meta-analyses, duloxetine was found to be less well tolerated than venlafaxine. Duloxetine remains under patent protection and consequently, is considerably more expensive than venlafaxine.

**On this basis, duloxetine has not been selected as the preferred SNRI.**
7. Conclusion

**Preferred SSRI: CITALOPRAM**

- Citalopram has comparable efficacy to other SSRIs.
- Citalopram has a comparable or favourable adverse effect profile compared to other SSRIs.
- Citalopram has a favourable drug interaction profile and pharmacokinetic drug interactions are unlikely.
- Citalopram has a favourable cost profile relative to most SSRIs.
- Citalopram is the second most frequently prescribed SSRI, suggesting considerable clinical experience with its use among prescribers.

**Preferred SNRI: VENLAFAXINE**

- Venlafaxine has comparable efficacy to duloxetine.
- Venlafaxine has a favourable adverse effect profile relative to duloxetine, based on the evidence reviewed.
- Venlafaxine and duloxetine have similar potential for drug interactions.
- Venlafaxine is considerably cheaper than duloxetine.
- Venlafaxine is prescribed more frequently than duloxetine suggesting greater clinical experience with its use.
8. References

2. Health Service Executive (HSE) Primary Care Reimbursement Service (PCRS).
13. Copty M on behalf of the Irish College of General Practitioners (ICGP) in collaboration with the Health Service Executive (HSE). Guidelines for the Management of Depression and Anxiety in Primary Care, 2006.


9. Bibliography


Appendix 1 Prescribing tips

Prescribing tips for Citalopram

There is a range of citalopram preparations available, including tablets and oral drops. An up-to-date listing is freely available on the Irish Medicines Board website at www.imb.ie

Depression: Dosing & Administration

Full prescribing information is available in the Summary of Product Characteristics (SmPC), which may be accessed freely online at www.imb.ie and www.medicines.ie Please consult individual SmPCs for guidance on prescribing for other indications and in special patient populations, e.g. hepatic failure.

Table 1a. Dosing and administration of citalopram

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Starting Dose</th>
<th>Maximum Daily Dose</th>
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<tbody>
<tr>
<td>Adults (18-65 years)</td>
<td>20 mg daily</td>
<td>40 mg</td>
</tr>
<tr>
<td>Elderly (&gt;65 years)</td>
<td>10 mg daily</td>
<td>20 mg</td>
</tr>
</tbody>
</table>

Comment: May be taken at any time of the day with or without food.

Important Prescribing Information

Onset of Action In clinical practice, an antidepressant effect in an individual is usually seen by 2 weeks. In individuals in whom no antidepressant effect is evident after 3-4 weeks, a change in dose or drug is indicated.

Duration of Treatment A single episode of depression should be treated for a minimum of 6 months after recovery. If antidepressant therapy is stopped immediately on recovery, 50% of patients may experience a return of their depressive symptoms.

QT Interval prolongation

- Citalopram is contraindicated in patients with known QT interval prolongation or congenital long QT syndrome.
- Citalopram is contraindicated with medicinal products that are known to prolong the QT interval.
- Caution is advised in patients at higher risk of developing Torsade de Pointes, e.g. patients with congestive heart failure, myocardial infarction, bradyarrhythmias or a predisposition to hypokalaemia or hypomagnesaemia.

Medicines that prolong the QT interval – avoid with citalopram

- Antihistamines: Astemizole, mizolastine.
- Anti-malarials: Halofantrine, quinine.
- Atypical antipsychotics: Amisulpiride, sertindole.
- Antipsychotics: Pimozide, haloperidol.
- Class IA antiarrhythmics: Flecainide, lidocaine, quinidine.
- Class III antiarrhythmics: Amiodarone, dronedarone, sotalol.
- Tricyclic antidepressants: Amitriptyline, clomipramine, dosulepin, doxepin, imipramine, lofepramine, nortriptyline, trimipramine.
- Quinolone: Moxifloxacin.

This list is not exhaustive and is intended to serve as guidance only. Prescribers should consult appropriate prescribing and drug interaction information for further guidance.
Prescribing tips for Venlafaxine
There is a range of venlafaxine preparations available, including modified-release capsules and immediate-release tablets. An up-to-date listing is freely available on the Irish Medicines Board website at www.imb.ie

Depression: Dosing & Administration
Full prescribing information is available in the Summary of Product Characteristics (SmPC) which may be accessed freely online at www.imb.ie and www.medicines.ie.

Please consult the individual SmPCs for guidance on prescribing for other indications and in special patient populations, e.g. renal impairment.

Table 2a. Dosing and administration of venlafaxine

<table>
<thead>
<tr>
<th>Adults (≥18 years)</th>
<th>Starting Dose</th>
<th>Maximum Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Release (XL)</td>
<td>75 mg once daily</td>
<td>375 mg once daily</td>
</tr>
<tr>
<td>Immediate-release tablets</td>
<td>75 mg in 2 divided doses</td>
<td>375 mg in 2 divided doses</td>
</tr>
</tbody>
</table>

**Comment** Should be taken with food at approximately the same time(s) each day.

Important Prescribing Information

**Onset of Action** In clinical practice, an antidepressant effect in an individual is usually seen by 2 weeks. In individuals in whom no antidepressant effect is evident after 3-4 weeks, a change in dose or drug is indicated.

**Duration of Treatment** A single episode of depression should be treated for a minimum of 6 months after recovery. If antidepressant therapy is stopped immediately on recovery, 50% of patients may experience a return of their depressive symptoms.

**Elderly Patients** No specific dose adjustments required. However, elderly patients are at increased risk of renal impairment and sensitivity to drug effects. Use the lowest effective dose.

**Dose Titration** The dose may be increased at intervals of 2 weeks. In some instances, faster dose titration may be necessary. A minimum of 4 days should be allowed between dose increases.

**Withdrawal symptoms**
- Abrupt discontinuation of venlafaxine should be avoided.
- When stopping treatment, reduce the dose gradually over a period of several weeks (minimum 2 weeks, longer if possible)
- If intolerable symptoms occur on dose reduction or withdrawal, consider restarting venlafaxine at the previously prescribed dose. Subsequent attempts to withdraw venlafaxine should be made at a more gradual rate.