Medicines Management Programme

Preferred Drugs

Selective serotonin reuptake inhibitors (SSRIs) & serotonin noradrenaline reuptake inhibitors (SNRIs) for the treatment of depression

Approved by	Professor Michael Barry, Clinical Lead, Medicines Management Programme (MMP)
Date approved	20/07/2021
Version	2.0

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List of abbreviations

ACP	American College of Physicians
ADR	Adverse drug reactions
ATC	Anatomical therapeutic chemical
BAP	British Association for Psychopharmacology
CANMAT	Canadian Network for Mood and Anxiety Treatments
CDS	Community drug schemes
CI	Confidence interval
CYP	Cytochrome P450
DDD	Defined daily dose
DP	Drugs Payment (scheme)
DOAC	Direct oral anticoagulant
5-HT	5-hydroxytryptamine (serotonin)
EMA	European Medicines Agency
GAD	Generalised anxiety disorder
GFR	Glomerular filtration rate
GI	Gastrointestinal

GMS	General Medical Services
HPRA	Health Products Regulatory Authority
HSE	Health Service Executive
IQR	Interquartile range
LTI	Long Term Illness
MDD	Max daily dose
MHRA	Medicines and Healthcare Products Regulatory Agency
MMP	Medicines Management Programme
MAOI	Monoamine oxidase inhibitor
NICE	National Institute for Health & Care Excellence
NNH	Number needed to harm
NSAID	Nonsteroidal anti-inflammatory drug
OCD	Obsessive-compulsive disorder
OR	Odds ratio
PCRS	Primary Care Reimbursement Service
PRAC	Pharmacovigilance Risk Assessment Committee
PTSD	Post-traumatic stress disorder
SmPC	Summary of product characteristics
RCT	Randomised controlled trial
RANZCP	Royal Australian and New Zealand College of Psychiatrists
SD	Standard deviation
SNRI	Serotonin noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
Va/DoD	(Department of) Veterans Affairs/Department of Defense
WHO	World Health Organisation

Acknowledgements

The MMP wishes to acknowledge the National Medicines Information Centre (NMIC) for their input and contributions to this document.

1. Purpose

Citalopram and venlafaxine have been the Health Service Executive's Medicines Management Programme (HSE-MMP) preferred selective serotonin reuptake inhibitor (SSRI) and serotonin noradrenaline reuptake inhibitor (SNRI) respectively, since March 2014.[1] The purpose of this report is to review the choice of preferred SSRI and SNRI considering current available evidence. This updated review in 2021 has now named **sertraline** and **venlafaxine** as the preferred SSRI and SNRI, respectively.

The MMP aims to promote safe, effective and cost-effective prescribing. The preferred drugs initiative identifies a single 'preferred drug' within a therapeutic drug class, and offers prescribers useful guidance on selecting, prescribing and monitoring this drug for a particular condition. In this case, the use of SSRIs and SNRIs for the treatment of depression in adults is reviewed.

Prescribers are encouraged to make the preferred drug their treatment of first choice, when initiating an SSRI or SNRI and when there is a need to change from one SSRI or SNRI to another in the treatment of depression.This report should be used in conjunction with clinical judgement and decision-making appropriate to an individual patient. Prescribers should refer to resources such as the summary of product characteristics (SmPC) to inform decisions concerning individual patients.

2. Scope

This evaluation considers SSRIs and SNRIs on the HSE-Primary Care Reimbursement Service (PCRS) list of reimbursable items. It is aimed at reviewing the choice of preferred SSRI and SNRI considering current available evidence for the treatment of adult patients with depression.

The following patient groups are outside of the scope of this document:

- Children
- Adolescents
- Pregnancy
- Adults with resistant depression, in which cases specialist advice may be sought.

Prescribers in these settings, however, should be mindful of the availability of preferred SSRIs and SNRIs.

3. Definitions

For the purpose of this report, the associated ingredient cost refers to the reimbursement price of the named SSRIs and SNRIs as listed on the HSE-PCRS website. Reimbursed SSRIs and SNRIs licensed for the treatment of depression are included in this review.

When two or more preparations of the same drug are listed, (e.g. where there are different manufacturers/suppliers), the least expensive preparation with all the relevant indications has been selected for the evaluation. Costs are correct as of 1st March 2021.

The community drug schemes (CDS) referred to throughout this document include Drugs Payment (DP), Long Term Illness (LTI) and the General Medical Services (GMS) schemes. The available data is limited by its inability to capture prescriptions that are solely funded by the patient, and therefore are not reimbursed under any of the state-funded CDS e.g. prescriptions that fall below the co-payment threshold on the DP scheme.

The defined daily dose (DDD) and max daily dose (MDD) are obtained for each drug using the anatomical therapeutic chemical (ATC) code. This code is a World Health Organisation (WHO) method for classifying drugs, based on the organ or system on which they act and their therapeutic, pharmacological and chemical properties.[2]

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

4. Preferred SSRI and SNRI

SSRI: Based on the current evidence sertraline is the MMP's preferred SSRI for the treatment of depression in adults.

SNRI: Based on the current evidence venlafaxine is the MMP's preferred SNRI for the treatment of depression in adults.

5. Background

SSRIs and 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.[3-11]

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

Expenditure on SSRIs and SNRIs has decreased in recent years due to the introduction of generic substitution and reference pricing. Total expenditure (inclusive of ingredient cost and pharmacy dispensing fees) in 2019 on SSRIs and SNRIs under the CDS was €29 million.[12]

SSRIs are potent and specific inhibitors of neuronal 5-hydroxytryptamine (5-HT) serotonin reuptake. They treat mental health disorders by increasing the levels of serotonin in the brain, making it readily available, to improve transmission of messages between neurons. SSRIs have very weak or no effects on noradrenaline and dopamine neuronal reuptake.[6-11] There are currently six SSRIs reimbursable in Ireland: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline.[13, 14] All six SSRIs have a similar mechanism of action.[6-11]

SNRIs are inhibitors of serotonin and noradrenaline reuptake and work by delaying their neuronal reuptake. They also are weak inhibitors of dopamine uptake.[3-5] There are currently two SNRIs reimbursable in Ireland, duloxetine and venlafaxine.[13, 14] Both SNRIs have a similar mechanism of action.[3-5]

SSRIs and SNRIs are frequently referred to as second generation antidepressants because of their improved side-effect profile and tolerability compared to the first generation antidepressants e.g. tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).

5.1 Pharmacokinetic properties of SSRIs and SNRIs

Although SSRIs, and separately SNRIs, share similar efficacy and safety profiles, they differ in terms of their chemical structures, pharmacokinetic profiles and receptor affinity. The chemical structures of SSRIs and SNRIs govern their lipophilicity and ability to cross the blood-brain barrier, which in turn influences their absorption, distribution, metabolism and excretion.[15] Some pharmacokinetic properties of SSRIs and SNRIs are compared in table 1.

SSRIs are well absorbed at their therapeutic dose and most have a plasma half-life of 13-35 hours [(fluoxetine has a longer half-life: 4-6 days (or 4-16 days for its active metabolite)]. A delay of 2-4 weeks before the therapeutic effect develops is consistent among SSRIs (fluoxetine reaches steady state after 4-5 weeks).[6-11]

The SNRIs, venlafaxine and duloxetine, have a half-life of 5±2 hours (or 11±2 for its active metabolite) and 8-17 hours respectively. Both SNRIs reach a steady state after about 3 days.[3-5] The therapeutic effect of duloxetine is usually seen after 2-4 weeks of treatment, while the therapeutic effect of venlafaxine is usually seen after 4-6 weeks of treatment.[3-5]

Table 1: Pharmacokinetic properties of SSRIs and SNRIs

	SSRI						SNRI	
	Citalopram	**Escitalopram**	**Fluoxetine**	**Fluvoxamine**	**Paroxetine**	**Sertraline**	**Duloxetine**	**Venlafaxine**
Bioavailability (%)[15]	80	80	60-80	53	50-90	80-95	30-80	45
Solubility (LogP)[15]	Lipophilic (3.76)	Lipophilic (3.5)	Lipophilic (4.05)	Lipophilic (2.89)	Lipophilic (3.6)	Lipophilic (5.1)	Lipophilic (4.72)	Lipophilic (3.2)
Volume of distribution (L/Kg)[15]	12	12	20-45	25	17	20	11-50	7.5
Absorption (Tmax in hours) [3-7, 9-11, 16]	3	4	6-8	3-8	6-10	4.5- 8.4	6	2-3Ω 5.5–9†
Protein binding (%)[15]	80	56	95	77	95	98	90	35
Active metabolites[3-11]	✓	✓	✓	x	x	✓	x	✓
Elimination half-life (hours)[3-11]	36	30	4-6 days (4-16 days¥)	13-15 (single dose) 17-22 (repeated dosing)	24	22-36 (62-104¥)	8-17	5 ± 2 11 ± 2¥
Major metabolic enzymes (additional)[15]	CYP2C19 CYP3A4 (CYP2D6)	CYP2C19 CYP3A4	CYP2D6 CYP2C9 (CYP2C19)	CYP2D6 (CYP1A2)	CYP2D6	CYP2B6 (CYP2C19, CYP3A4, CYP2D6)	CYP1A2 CYP2D6	CYP2D6 CYP3A4 (CYP2C19, CYP2C9)
Percentage of the dose excreted unchanged (%)[15]	12-23	8	12	<4	2	<0.2	<1	5
Steady state plasma levels[3-11]	Achieved in 1-2 weeks	Achieved in 1 week	Achieved at 4-5 weeks	Achieved in 10-14 days	Achieved in 7-14 days	Achieved in 1 week	Achieved within 3-5 days	Achieved within 3 days

Ω Immediate release preparation
† Prolonged release preparation
¥ Active metabolite
CYP: Cytochrome P450

6. Selection criteria

A number of key criteria were considered in the MMP preferred SSRI and SNRI selection process:

1. **Licensed therapeutic indications**
2. **Clinical outcome data**
3. **Clinical guidelines (for the treatment of depression)**
4. **Adverse drug reactions**
5. **Contraindications and cautions**
6. **Drug interactions**
7. **Patient factors**
8. **Cost**
9. **National prescribing trends**

6.1 Licensed therapeutic indications

The focus of this guidance is the use of SSRIs and SNRIs in the treatment of adults with depression.

6.1.1 Depression

Depression is a serious mental health diagnosis caused by complex interactions between social, psychological and biological factors.[17] It is characterised by a depressed mood, loss of pleasure in most activities, reduced energy, fatigue, difficulty thinking, concentrating or making decisions, changes in appetite, feeling of worthlessness or guilt, trouble sleeping and suicidal thoughts.[18] Severity of the disorder is determined by both the frequency and severity of symptoms in conjunction with the degree of functional impairment.[19]

Over 300 million people globally are estimated to suffer from major depression, which equates to 4.4% of the global population. It has been estimated that the prevalence of depression in Ireland is 4.8% of the total population.[20] Depression is most common among older adults and affects 7.5% of women and 5.5% of men aged 55 to 74 years.[21]

6.1.2 Anxiety disorders

There are many types of anxiety disorders where SSRIs are considered first-line; mixed anxiety-depression disorder, GAD, panic disorder, specific and generalised social phobias, OCD and PTSD.[22] The treatment of anxiety disorders is not the focus of this evaluation but co-existing GAD and depressive symptoms are common and many patients simultaneously fulfil the diagnostic criteria for anxiety and depressive disorders.[23]

Where anxiety symptoms are present within the context of a depressive disorder, drug treatment of the depression is effective at 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.[23] All SSRIs and SNRIs considered in this review are licensed to treat symptomatic depression in adults. The licensed indications for SSRIs and SNRIs are summarised in table 2.

Table 2: Licensed therapeutic indications for SSRIs and SNRIs[3-11]

	SSRI							SNRI	
	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline		Duloxetine*	Venlafaxine
Depression	✓	✓	✓	✓	✓	✓		✓	✓ Ω†
Panic disorder with or without agoraphobia	✓	✓			✓	✓			✓†
Social anxiety disorder (social phobia)		✓			✓	✓			✓†
Generalised anxiety disorder		✓			✓			✓	✓†
Obsessive compulsive disorder		✓	✓	✓	✓	✓			
Bulimia nervosa			✓						
Post-traumatic stress disorder					✓	✓			

*Duloxetine is also licensed for the treatment of diabetic peripheral neuropathic pain.
Ω Immediate release preparation
† Prolonged release preparation

Recommendation

SSRI: All SSRIs are licensed for the treatment of depression in adults.

SNRI: All SNRIs are licensed for the treatment of depression in adults.

6.2 Clinical outcome data

6.2.1 Meta-analyses and systematic reviews in the treatment of depression

Systematic reviews and meta-analyses, which utilise pooled data from clinical trials, provide a means of assessing the general and comparative efficacy of SSRIs and SNRIs, and were considered as part of the review process.

When the initial review, *Preferred Drugs: Selective serotonin reuptake inhibitors (SSRIs) and Serotonin noradrenaline reuptake inhibitors (SNRIs) for the treatment of depression* was undertaken in 2014, consideration was given to clinical evidence available at that point in time.

This review evaluates updated evidence since the publication of the initial review in 2014. A summary of recent systematic reviews and meta-analyses for SSRIs and SNRIs for the treatment of depression are illustrated in table 3.

Table 3: Summary of meta-analyses and systematic reviews for SSRIs and SNRIs in the treatment of depression (2015-present)

Review	Author	Year	Number of Patients	SSRIs/SNRIs evaluated	Conclusion
Application of antidepressants in depression: a systematic review and meta-analysis	Yuan et al.	2020	8,571	Duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine.	• Each of the seven antidepressants were effective. • By comparing the odds ratio (OR) values, the analysis found that when compared to placebo or the other antidepressants, venlafaxine and duloxetine had the greatest efficacy. • Sertraline had the greatest efficacy compared to other SSRIs. • On comparison between the seven drugs, fluvoxamine had the highest incidence of side-effects while fluoxetine had the lowest.[24]
Systematic review and meta-analysis of second-generation antidepressants for the treatment of older adults with depression: questionable benefit and considerations for frailty	Mallery et al.	2019	2,704	Citalopram, duloxetine, escitalopram, fluoxetine, venlafaxine.	• No statistically significant difference in response or remission to second-generation antidepressants compared to placebo. • More withdrawals due to adverse events with antidepressants. • Recommends using antidepressants judiciously, with awareness of the limited evidence for efficacy in adults aged ≥65 years and, by association, older adults with frailty. • Recommends considering the potential for adverse effects with frailty. Consider that, due to varied populations and heterogeneous response, antidepressants may be beneficial for some older adults who are frail.[25]
Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults	Cipriani et al.	2018	116,477	Citalopram, duloxetine, escitalopram, fluoxetine,	• All antidepressants were more effective than placebo.

Review	Author	Year	Number of Patients	SSRIs/SNRIs evaluated	Conclusion
with major depressive disorder: a systematic review and network meta-analysis				fluvoxamine, paroxetine, sertraline, venlafaxine.	• Escitalopram, paroxetine, and venlafaxine were more effective than other antidepressants whereas fluoxetine, and fluvoxamine, were the least efficacious drugs. • Citalopram, escitalopram, fluoxetine, and sertraline, were more tolerable than other antidepressants with fluoxetine being associated with fewer dropouts (for any reason) than placebo. Duloxetine, fluvoxamine, and venlafaxine had the highest dropout rates. • Some antidepressants, such as escitalopram, paroxetine, and sertraline had a relatively higher response and lower dropout then other antidepressants.[26]
Selective serotonin reuptake inhibitors and cardiovascular events: A systematic review	Nezafati et al.	2016	66,660	Citalopram, escitalopram, fluoxetine, paroxetine, sertraline.	• Both beneficial and adverse cardiovascular events can be discovered following the chronic use of SSRIs. • SSRIs, especially citalopram, can improve serotonin related platelet abnormalities. • SSRIs, especially sertraline, can improve endothelial function. • Some SSRIs, such as fluoxetine, could reduce the tonicity of arteriolar smooth muscle. • In rare cases, torsade de pointes and QT prolongation, can occur following the administration of fluoxetine, sertraline, and citalopram.[27]

The key findings from the meta-analyses and systematic reviews in table 3 were as follows:

Yuan et al. 2020[24]

A systematic review and meta-analysis of first-line and emerging antidepressants for the treatment of depression by Yuan et al. (2020), involved 27 trials [including double-blind randomised controlled trials (RCTs)], and 8,571 participants, aged 18 or older. It compared antidepressants versus placebo or comparators for adults with depression. The antidepressants included were duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and venlafaxine. The study also looked at ketamine and nonsteroidal anti-inflammatory drugs (NSAIDs). The primary outcomes were response and remission. Response was defined as a 50% improvement from baseline to endpoint on depression rating scales. Remission was defined as a relatively symptom-free period of no specific length. The review compared the efficacy of antidepressants by comparing the odds ratio (OR) values. For all studies that compared the antidepressant response and remission to a placebo, the participants were randomly assigned in a 1:1 ratio. In the trials that compared antidepressant response and remission to a comparator, the participants were randomly assigned in a 1:1 ratio with the exception of escitalopram, which was assigned in a 1:2 ratio. Age was represented as a range and no mean or median value was reported. Age ranged from 18–89 years across all trials. The baseline mean depression scores, duration of treatment and study duration were not reported in the review. The highest OR value in response for all antidepressants (SSRI and SNRI) was venlafaxine [OR=3.50 (95% confidence interval (CI): 1.83, 6.70)]. The highest OR value for antidepressants in remission was also venlafaxine (OR=2.55 (95% CI: 1.72, 3.78)). By comparing the OR value for both response and remission, duloxetine, venlafaxine and sertraline were the top three, suggesting that these three antidepressants are more effective at treating depression. Sertraline, when compared to a comparator for response had an OR=1.46 (95% CI: 1.06, 2.01). Paroxetine was the second most effective SSRI for response when compared to the comparator with an OR=1.25 (95% CI: 0.94, 1.66). Fluoxetine was the least effective SSRI for response when compared to the comparator with an OR=0.80 (95% CI: 0.61, 1.04). Fluvoxamine had the highest incidence of side-effects, while fluoxetine had the lowest. There were some limitations to this study. The data was derived from studies that had different study designs and the substantial heterogeneity among the studies remained largely unexplained. Many subgroup analyses relied on unpaired cross-sectional data collected at different hospitals, which may have introduced bias. The prescriber's preference for drug use and consideration of other co-existing diseases were unknown.[24]

Mallery et al. 2019[25]

A systematic review and meta-analysis of second-generation antidepressants for the treatment of older adults with depression by Mallery et al. (2019) involved nine trials including double-blind RCTs comprising of 2,704 participants that compared antidepressants versus placebo for adults aged 65 years or older with depression. The antidepressants that were included were buspirone, citalopram, duloxetine, escitalopram, fluoxetine, and venlafaxine. In total, 1,455 participants were randomly assigned to an active drug and 1,249 were randomly assigned to placebo. The primary and secondary outcomes were response and remission based on depression rating scales. The mean age of participants ranged from 71-82 years and only one study was limited to subjects who were 75 years of age or older. Based on mean depression scores, the study subjects had moderate to severe depression. Study duration ranged from eight to 12 weeks. In the meta-analysis of older adults with depression, there was no statistically significant response or remission for second-generation antidepressants compared to placebo. Frailty is associated with increased potential for adverse events. In this meta-analysis of older adults without frailty, 13% of subjects in the treatment arm withdrew because of adverse events compared to 5.8% with placebo [number needed to harm (NNH)=14], with nausea reported most frequently (NNH=11). The study considered the possibility that a frail patient may have limited response to an antidepressant and is more at risk for adverse events. It recommends the use of antidepressants judiciously in this population. The study warns of the limited evidence for efficacy in adults age 65 years or older and recommends to attentively consider the potential for adverse effects with frailty. The study also considers that, due to varied populations and heterogeneous response, antidepressants may be beneficial for some older adults who are frail and to routinely re-evaluate whether antidepressants should be continued when they are used for prolonged periods. There were some limitations to this study. The risks associated with under treating high-risk depression were not fully considered, as most studies excluded those at risk of suicide. The high degree of heterogeneity could indicate variable response to antidepressants based on duration of symptoms, severity, or number of recurrences. Several studies included older adults with dementia, which could negate the results for those without dementia. Antidepressants were compared to placebo. The exploration of how frail older adults might respond to antidepressants is theoretical and not based on study data.[25]

Cipriani et al. 2018[26]

A systematic review and network meta-analysis by Cipriani et al. (2018) involved 522 double-blind RCTs comprising of 116,477 participants including placebo-controlled and head-to-head trials of 21 antidepressants used for the acute treatment of adults (≥18 years old and of both sexes) with major depressive disorder. The antidepressants that were included were: agomelatine, amitriptyline,

bupropion, citalopram, clomipramine, desvenlafaxine (no marketing authorisation in Ireland), duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran (no marketing authorisation in Ireland), milnacipran (no marketing authorisation in Ireland), mirtazapine, nefazodone (no marketing authorization in Ireland), paroxetine, reboxetine, sertraline, trazodone, venlafaxine, vilazodone (no marketing authorisation in Ireland) and vortioxetine.[13] In total, 87,052 participants were randomly assigned to an active drug and 29,425 were randomly assigned to placebo. The primary outcomes were efficacy (response rate measured by the total number of patients who had a reduction of ≥50% of the total score on a standardised observer-rating scale for depression) and acceptability (treatment discontinuation measured by the proportion of patients who withdrew for any reason). All-cause discontinuation was used as a measure for the acceptability of treatments, because it encompasses efficacy and tolerability. The great majority of patients had moderate-to-severe major depressive disorder, with a mean reported baseline severity score on the Hamilton depression rating scale of 25.7 [standard deviation (SD)=3.97] among 464 (89%) of 522 studies. The median duration of the acute treatment was eight weeks [interquartile range (IQR)=6–8]. In terms of efficacy, all antidepressants were more effective than placebo. Of the eight antidepressants included in this review, escitalopram, paroxetine and venlafaxine were shown to be more effective, whereas fluoxetine and fluvoxamine were the least efficacious drugs. For acceptability, citalopram, escitalopram, fluoxetine and sertraline, were more tolerable than other antidepressants with fluoxetine being associated with fewer dropouts than placebo. Duloxetine, fluvoxamine and venlafaxine had the highest dropout rates. There were some limitations to this study including the considerable amount of unpublished data for some, but not all, antidepressants included in the analysis. This limitation in the primary trials might affect the validity of the findings for some antidepressants. Nine percent of the trials were rated as high risk of bias, 73% of trials as moderate risk, and 18% of trials as low risk.[26]

Nezafati et al. 2016[27]

A systematic review by Nezafati et al. (2016) comprising of 17 studies, aimed to systematically review the published evidence on the use of SSRIs and the risk associated with cardiac events. Key words such as “cardiovascular,” “event,” “outcome,” “side-effects,” and “selective serotonin reuptake inhibitor” were used to search databases for experimental studies that were in English and had full text availability. Among the 17 studies included, five of the articles had published follow up data for the effect of SSRIs on cardiovascular events, ranging in duration from 30 days to one year. Six of the 17 publications were review articles, comprising of 435 studies. Overall 66,660 patients were identified as being treated with various SSRIs, including fluoxetine, sertraline, citalopram, escitalopram, paroxetine, sibutramine (no marketing authorisation in Ireland), and benfluorex (no marketing authorisation in Ireland).[13] There was no obvious heterogeneity identified among the included studies.

The systematic review found that both beneficial and adverse cardiovascular events could be experienced following the 'chronic use' (undefined) of various types of SSRIs. Citalopram demonstrated inhibitory effects on platelet aggregation and the progression of atherosclerosis. Some SSRIs, such as sertraline, showed anti-inflammatory effects, as well as improving endothelial function. Sertraline also effectively reduced inflammatory markers, including C-reactive protein and interleukin 6 leading to the improvement of the endothelium-mediated dilation marker. A number of authors emphasised a similar role of some SSRIs, such as fluoxetine, to calcium channel blockers, in that fluoxetine could reduce intracellular calcium and the tonicity of arteriolar smooth muscle. Some SSRIs such as fluoxetine, sertraline and citalopram, were also reported to cause harmful effects such as torsade de pointes and QT prolongation. The review also reported the concern of increased myopathy and rhabdomyolysis in individuals co-prescribed escitalopram, citalopram, or paroxetine with a statin. In one clinical trial, after one month of treatment with paroxetine in patients with vasovagal syncope, spontaneous syncope was observed in 17.6% of the patients in the paroxetine group. Cardiac arrhythmias were the most frequent cardiovascular event, constituting one-third of the most commonly encountered adverse reactions following the consumption of SSRIs. The limitations of this systematic review were acknowledged as follows; a narrow range of keywords was used in the initial search, a lack of subgroup analysis and few studies had follow-up data.[27]

Recommendation

SSRI: Escitalopram, paroxetine and sertraline are the SSRIs of choice in terms of efficacy and tolerability.

SNRI: Venlafaxine is the SNRI of choice in terms of efficacy and tolerability.

6.3 Clinical guidelines for the treatment of depression

When the initial review, *Preferred Drugs: Selective serotonin reuptake inhibitors (SSRIs) and Serotonin noradrenaline reuptake inhibitors (SNRIs) for the treatment of depression*, was undertaken in 2014 consideration was given to clinical guidelines for the treatment of depression available at that point in time. This review evaluates updated clinical guidelines since the publication of the review in 2014. The clinical guidelines for the treatment of depression are outlined in table 4.

Table 4: Clinical guidelines for the treatment of depression (2015-present)

Clinical Guidelines				
Review body	**Guideline**	**Year**	**Recommended drug**	**Excerpt/Comment**
National Institute for Health & Care Excellence (NICE) (UK)	**Depression in adults: recognition and management. Clinical guideline (2009)**[28] (Minor changes made since publication in 2016, 2019, 2020) **Depression in adults with a chronic physical health problem: recognition and management. Clinical guideline (2009)**[29] (Minor changes made since publication in 2016, 2019, 2020)	**2020**	**SSRI:** No general preference; citalopram and sertraline (chronic physical health problem) **SNRI:** No preference	**First episodes of depression:** • Consider a generic SSRI such as citalopram, fluoxetine, paroxetine or sertraline. **Chronic physical health problem**: • Consider using citalopram or sertraline as these have a lower propensity for interactions. **Safety:** • Do not use citalopram or escitalopram in people who are taking other medication that could prolong QT interval. • Fluoxetine, fluvoxamine and paroxetine have a higher propensity for drug interactions. • Venlafaxine is associated with a greater risk of death from overdose. **Tolerability:** • Paroxetine is associated with a higher incidence of discontinuation symptoms. • Increased likelihood of the person stopping treatment because of side-effects with venlafaxine and duloxetine.
American College of Physicians (ACP)	**Non-pharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: A clinical practice**	**2016**	**SSRI:** No preference **SNRI:** No preference	ACP recommends that clinicians select between cognitive behavioral therapy and second-generation antidepressants to treat patients with major depressive disorder after discussing treatment effects, adverse effect profiles, cost, accessibility, and preferences with the patient.

	guideline from the American College of Physicians (2016)[30]			
Canadian Psychiatric Association	**Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological treatments (2016)**[31]	**2016**	**SSRI:** No preference **SNRI:** No preference	Pharmacological treatments can be considered for mild depression in some situations, including patient preference, previous response to antidepressants, or lack of response to non-pharmacological interventions. **First episodes of depression:** • SSRIs, SNRIs and other (agomelatine, bupropion, and mirtazapine) antidepressants are first-line recommendations for pharmacotherapy for major depressive disorder.
British Association for Psychopharmacology (BAP)	**Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines (2015)**[23]	**2015**	**SSRI:** No preference **SNRI:** No preference	**Efficacy:** • There is most evidence for SSRIs, which, together with other newer antidepressants, are first line choices. • Venlafaxine, escitalopram and sertraline appear to be marginally more effective than other SSRIs in hospitalised patients.
Practice Guidelines				
Review body	**Guideline**	**Year**	**Recommended drug**	**Excerpt/Comment**
The Maudsley prescribing guidelines in psychiatry (UK)	**The Maudsley prescribing guidelines in psychiatry (13th edition)**[32]	**2018**	**SSRI:** No general preference; sertraline (post	• Sertraline is safe post myocardial infarction and in heart failure and is the drug of choice for myocardial infarction. • There is no ideal antidepressant in older people.

			myocardial infarction) **SNRI:** No preference	• Fluoxetine has been associated with improvement in HbA1c levels, reduced insulin requirements, weight loss and enhanced insulin sensitivity. • Sertraline may also reduce HbA1c. Escitalopram also seems to improve glycaemic control.
Department of Veterans Affairs Department of Defense (Va/DoD) (USA)	**Va/DoD clinical practice guideline for the management of major depressive disorder (2016)**[33]	**2016**	**SSRI**: No preference (not fluvoxamine) **SNRI:** No preference	**First episodes of depression:** • Department of Va/DoD recommends offering SSRIs (except fluvoxamine) or SNRIs.
Royal Australian and New Zealand College of Psychiatrists (RANZCP)	**Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders (2015)**[34]	**2015**	**SSRI:** No preference **SNRI:** No Preference	**Safety and tolerability:** • SSRIs are suitable first-line. • Many SSRIs (especially fluoxetine and paroxetine) cause significant cytochrome P450 (CYP) inhibition and care is needed when co-prescribed with other medications. • SNRIs appear to be more effective than SSRIs in treating severe depressive symptoms.

6.3.1 National Institute for Health & Care Excellence (NICE)

National Institute for Health & Care Excellence (NICE) has published two guidelines relevant to this review: *Depression in adults: recognition and management* (2009) and *Depression in adults with a chronic physical health problem: recognition and management* (2009). Both of these guidelines received minor changes since publication in 2016, 2019 and 2020. A full update on *Depression in adults: recognition and management* (2009) is expected by May 2022. NICE guidance recommends when initiating an antidepressant, it should normally be an SSRI in a generic form because SSRIs are equally as effective as other antidepressants and have a favourable risk–benefit ratio.[28] NICE clinical knowledge summary on depression suggests that these generic SSRIs should be one of citalopram, fluoxetine, paroxetine or sertraline.[35] For people with chronic physical health disorders such as cancer, heart disease or diabetes, citalopram or sertraline should be considered as these have a lower propensity for interactions.[29] Consideration should be given to the presence of additional physical health disorders, side-effects, lack of available evidence supporting the use of specific antidepressants for patients with particular chronic physical health problems and drug interactions.[29] The guidelines warn of the higher propensity for drug interactions with fluoxetine, fluvoxamine and paroxetine; they also warn prescribers to avoid citalopram or escitalopram in people who are taking other medications that could prolong the QT interval. As SSRIs are associated with an increased risk of bleeding, prescribers should consider prescribing a gastro-protective drug in older people who are taking a NSAID or aspirin.[29] NICE guidance also highlights that there is an increased likelihood of a person stopping treatment because of side-effects (and the consequent need to increase the dose gradually) with venlafaxine and duloxetine. Compared with other equally effective antidepressants, venlafaxine is associated with a greater risk of death from overdose.[28, 29, 35]

6.3.2 American College of Physicians (ACP)

The American College of Physicians (ACP) developed a guideline to present available evidence and to provide clinical recommendations on the comparative effectiveness of second-generation antidepressants versus non-pharmacological interventions for the treatment of depression in adults. ACP recommends that clinicians select between cognitive behavioral therapy and a second-generation antidepressant to treat patients with depression after discussing treatment effects, adverse effect profiles, cost, accessibility, and preferences with the patient. ACP makes no recommendation in relation to specific second-generation antidepressants, but notes that people on paroxetine experience higher rates of sexual dysfunction compared to fluoxetine, fluvoxamine, and sertraline.[30]

6.3.3 Canadian Psychiatric Association

The Canadian Network for Mood and Anxiety Treatments (CANMAT), on behalf of the Canadian Psychiatric Association, conducted a revision of the 2009 guidelines for the management of depression in adults in 2016. CANMAT outline that the process of selecting an antidepressant should involve both the expertise of the prescriber and the patient's perceptions and preferences. The first-line recommendations for depression were SSRIs, SNRIs, agomelatine, bupropion, and mirtazapine. CANMAT indicate that many clinical features and medication characteristics influence the choice of a first-line antidepressant and that there are no absolutes and relative differences between medications are small. Selecting an antidepressant therefore involves an individualised needs approach. CANMAT highlight the concerns of QT prolongation with the use of citalopram and escitalopram. CANMAT recommend that patients maintain treatment with antidepressants for 6 to 9 months after achieving symptomatic remission, while those with risk factors for recurrence extend antidepressant treatment to 2 years or more.[31]

6.3.4 British Association for Psychopharmacology (BAP)

The British Association for Psychopharmacology (BAP) published a revision of the 2008 evidence-based guidelines for treating depressive disorders with antidepressants in 2015 to incorporate new evidence and to update the recommendations where appropriate. The guidance recommends that prescribers match the choice of antidepressant drug to individual patient requirements where possible and consider likely short-term and long-term effects. Determination of the severity and duration of depression guides the choice of antidepressant. An antidepressant that is better tolerated and safer in overdose should be chosen. Citalopram, sertraline, fluoxetine, fluvoxamine, paroxetine and duloxetine were considered low lethality in overdose. Venlafaxine was considered a moderate lethality in overdose. BAP outline that there is most evidence for SSRIs, which together with other newer antidepressants are first-line choices. Venlafaxine (≥150 mg), escitalopram (20mg) and sertraline are preferred to other antidepressants in severely ill patients, as they appear to be marginally more effective than other SSRIs and SNRIs. BAP consider fluoxetine, fluvoxamine and paroxetine to be strong inhibitors of hepatic enzymes, and venlafaxine to be a moderate inhibitor of hepatic enzymes, which is a consideration for prescribing with concurrent medication. BAP also highlights that there is a lack of direct evidence for the efficacy of increasing the dose if no response is experienced after initial treatment. Indirect evidence suggests there is a dose response for venlafaxine and escitalopram but not for other SSRIs.[23]

6.3.5 The Maudsley prescribing guidelines in psychiatry (UK)

The Maudsley prescribing guidelines in psychiatry (13th edition) (2018) suggest an SSRI as first choice (or mirtazapine if sedation required) for the treatment of depression. The guideline look at some specialist groups such as post-stroke depression, treatment of depression in older people and the use of antidepressants in diabetes mellitus. Treatment of post-stroke depression is complicated by medical co-morbidity and by the potential for interaction with other co-prescribed drugs e.g. direct oral anticoagulants (DOACs) or warfarin. The guideline states that there is no ideal antidepressant for the treatment of depression in older people and that older people are particularly prone to develop hyponatraemia with SSRIs, as well as postural hypotension and falls. Fluvoxamine, fluoxetine and paroxetine are potent inhibitors of several hepatic cytochrome P450 (CYP) enzymes, which cause concern in polypharmacy. The guidance commented on the propensity of antidepressants in general to cause drug-drug interactions and states that sertraline is safer and citalopram, escitalopram (and vortioxetine) are safest. Sedation can be a problem with both paroxetine and fluvoxamine, in older people. Venlafaxine is more toxic in overdose compared to SSRIs. Venlafaxine can cause hypotension at lower doses, but it can increase blood pressure at higher doses, as can duloxetine. Sertraline is the antidepressant of choice post myocardial infarction and is safe in heart failure. The guidance references studies that demonstrate that SSRIs have a favorable effect on diabetic parameters in patients with type 2 diabetes. Fluoxetine has been associated with an improvement in HbA1c levels, reduced insulin requirements, weight loss and enhanced insulin sensitivity. Sertraline may also reduce HbA1c. Escitalopram also seems to improve glycaemic control. SNRIs do not appear to disrupt glycaemic control and have minimal impact on weight.[32]

6.3.6 Department of Veterans Affairs/Department of Defense (Va/DoD)

The American Department of Veterans Affairs and the Department of Defense (Va/DoD) *Clinical practice guideline for the management of major depressive disorder* (2016) recommends an SSRI (except fluvoxamine), an SNRI, mirtazapine or bupropion as a first-line treatment for uncomplicated depression. They state that their efficacies are comparable, and therefore selection should be based on the antidepressant's safety and side-effect profile. The long half-life of fluoxetine is highlighted as an issue and may not be suitable in certain patient groups, such as in pregnancy, breastfeeding mothers or in older people.[33]

6.3.7 Royal Australian and New Zealand College of Psychiatrists (RANZCP)

The Royal Australian and New Zealand College of Psychiatrists (RANZCP) published *Clinical practice guidelines for mood disorders* in 2015. RANZCP state that SSRIs are suitable first-line and are generally

better tolerated than other classes of antidepressants. They do not have a preference in SSRI but state that sexual dysfunction and GI symptoms are common across the class. They advise that fluoxetine and paroxetine cause significant CYP inhibition and care is needed when co-prescribing with other medications. RANZCP state that SNRIs appear to be more effective than SSRIs in treating severe depressive symptoms. In some cases, adverse effects may limit SNRIs to second-line treatment. However, if depression is severe, then SNRIs are a suitable first-line option. There was no preference of SNRI.[34]

Recommendation

SSRI: There is no preference within clinical guidelines for the treatment of depression in adults.

SSRI: Sertraline is a common preference within some clinical guidelines for the treatment of depression in adults with a co-existing chronic physical health problem.

SNRI: There is no preference within clinical guidelines for the treatment of depression in adults.

6.4 Adverse drug reactions

The common adverse drug reactions (ADRs) [incidence of ≥1 in 100 to 1 < 10] for SSRIs and SNRIs are listed in table 5. A full list of ADRs for each drug can be found in the individual SmPCs available at www.hpra.ie.

Table 5: Common adverse drug reactions of individual SSRIs and SNRIs[3-11]

System organ class	Adverse drug reaction	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Duloxetine	Venlafaxine
Metabolism and nutrition disorders	Appetite ↓ (anorexia)	✓	✓	✓	✓	✓	✓	✓	✓
	Appetite ↑		✓				✓		
	Weight ↑		✓			✓	✓		✓
	Weight ↓	✓		✓				✓	✓
	Cholesterol levels↑					✓			✓
Psychiatric disorders	Agitation	✓		✓**	✓	✓	✓	✓	✓
	Libido ↓	✓	✓	✓			✓	✓	✓
	Anxiety	✓	✓	✓	✓	✓ **	✓	✓	
	Depression						✓		
	Restlessness		✓	✓					
	Tension			✓					
	Bruxism						✓		
	Nervousness	✓		✓	✓		✓		✓
	Confusional state	✓							✓
	Depersonalisation						✓		✓

System organ class	Adverse drug reaction	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Duloxetine	Venlafaxine
	Abnormal orgasm (female)	✓						✓	
	Anorgasmia (female)		✓						✓
	Abnormal dreams (nightmare)	✓	✓	✓		✓	✓	✓	✓
	Suicidal ideation					✓*			
Nervous system disorders	Sleep disorder	✓**		✓		✓**		✓**	
	Insomnia		✓		✓	✓		✓	
	Somnolence		✓	✓	✓	✓		✓**	
	Headache	✓**		✓**	✓	✓		✓**	
	Tremor	✓	✓	✓	✓	✓	✓	✓	✓
	Paraesthesia	✓	✓				✓	✓	✓
	Dizziness	✓	✓	✓	✓	✓		✓	
	Disturbance in attention/ concentration impaired	✓		✓		✓	✓		
	Dysgeusia			✓			✓		✓
	Lethargy			✓				✓	
	Movement disorders						✓		
	Akathisia								✓
	Hypertonia						✓		✓
	Sensory disturbances	✓**		✓**		✓**		✓**	

System organ class	Adverse drug reaction	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Duloxetine	Venlafaxine
Ear and labyrinth disorders	Tinnitus	✓				✓*	✓	✓	✓
	Vertigo							✓**	
Respiratory, thoracic and mediastinal disorders	Yawning	✓	✓	✓		✓	✓	✓	✓
	Sinusitis		✓						
	Dyspnoea								✓
Gastrointestinal disorders	Diarrhoea	✓	✓		✓	✓		✓	✓
	Vomiting	✓	✓	✓	✓	✓	✓	✓	✓
	Constipation	✓	✓		✓	✓	✓	✓	
	Flatulence						✓	✓	
	Dry mouth		✓	✓	✓	✓			
	Dyspepsia			✓	✓		✓	✓	
	Abdominal pain				✓		✓	✓	
	Nausea	✓**		✓**	✓			✓**	
Renal and urinary disorders	Dysuria							✓	
	Pollakiuria							✓	✓
	Urinary retention								✓
	Frequent urination			✓					
Eye disorders	Vision blurred/disturbed	✓**		✓		✓	✓	✓	✓
	Accommodation disorder								✓

System organ class	Adverse drug reaction	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Duloxetine	Venlafaxine
	Mydriasis								✓
Vascular	Flushing (hot flushes)			✓			✓	✓	✓
Skin and subcutaneous tissue disorders	Sweating ↑ (Hyperhidrosis)	✓**	✓	✓	✓	✓	✓	✓	
	Rash			✓			✓	✓	✓
	Urticaria			✓					
	Pruritus	✓		✓					✓
General disorders	Asthenia	✓**			✓	✓	✓		✓
	Pyrexia	✓	✓				✓		
	Malaise				✓		✓		
	Chest Pain						✓		
	Feeling jittery			✓					
	Fatigue	✓	✓					✓	✓
	Chills			✓					✓
Musculoskeletal and connective tissue disorders	Back Pain						✓		
	Arthralgia	✓	✓	✓			✓		
	Myalgia	✓	✓				✓	✓**	
	Musculo-skeletal pain							✓	
	Muscle spasm							✓	
	Impotence (male)	✓	✓	✓			✓	✓	✓

System organ class	Adverse drug reaction	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Duloxetine	Venlafaxine
Reproductive system and breast disorders	Ejaculation disorder (male)	✓	✓	✓				✓	✓
	Ejaculation failure or delayed	✓						✓	
	Gynaecological bleeding			✓					✓
	Menorrhagia								✓
	Menstruation irregular						✓		
Cardiac disorders	Palpitations	✓**		✓	✓		✓	✓	✓
	Hypertension							✓	✓
	Tachycardia				✓				✓
	QT prolonged	✓*	✓*	✓					
Infections and infestations	Upper respiratory tract infection						✓		
	Pharyngitis						✓		
	Rhinitis						✓		
Injury, poisoning and procedural complications	Injury/falls						✓	✓	

*Frequency not known **Common side-effect on withdrawal

6.4.1 SSRI adverse effect profile

SSRIs share a number of common or very common side-effects, most notably changes in appetite, GI side-effects and psychiatric disorders such as anxiety and impaired concentration.[36] Overall, the SSRIs are broadly similar in terms of adverse effects, although these effects may occur to a lesser or greater extent with certain SSRIs.[6-11]

Escitalopram and citalopram have a susceptibility to dose-dependent QT-interval prolongation. These effects are predominantly in patients of female gender, with hypokalaemia, or with pre-existing QT interval prolongation or other cardiac diseases.[6, 9] Co-administration with other drugs known to prolong the QT-interval and in patients with a known QT-interval prolongation are therefore contraindicated. The maximum dose of both of these SSRIs is restricted in patients older than 65 years.[6, 9]

The tolerability of a particular drug is a subjective parameter and can depend very much on an individual patient's experiences. The systematic review and meta-analysis by Cipriani et al. (2018) reported dropouts due to side-effects. Their results showed that escitalopram, fluoxetine, citalopram and sertraline had fewer dropouts due to side-effects (ORs ranging between 1.72 and 2.01). Of the SSRIs, fluvoxamine and paroxetine had the highest dropout rates due to side-effects (ORs 2.83 and 2.95 respectively). Similarly the systematic review and meta-analysis by Yuan et al. (2020) showed fluvoxamine had the highest incidence of side-effects, while fluoxetine had the lowest.[24]

The NICE clinical guideline *Depression in adults: recognition and management* (2009) states that paroxetine is associated with a higher incidence of discontinuation symptoms.[28] The RANZCP clinical guideline *Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders* (2015) similarly states that paroxetine can cause withdrawal agitation.[34]

6.4.2 SNRI adverse effect profile

SNRIs share a number of common or very common side-effects, most notably changes in appetite and weight, GI side-effects, headache, sexual dysfunction and sweating. Venlafaxine has some common side-effects associated with it such as arrhythmias, confusion, depersonalisation, hypertension, menstrual cycle irregularities, movement disorders, muscle tone increase, mydriasis, sedation, urinary disorders and vision disorders. Duloxetine has some common side-effects associated with it such as drowsiness, falls, muscle complaints and pain.[36]

The systematic review and meta-analysis by Cipriani et al. (2018) reported that venlafaxine has the highest dropout rates (of all SSRIs and SNRIs) due to side-effects (OR=2.95). Duloxetine had the third highest dropout rates due to side-effects [(following fluvoxamine) (OR=2.48)][26] The NICE clinical guideline *Depression in adults: recognition and management* (2009) states that there is an increased likelihood of the person stopping treatment because of side-effects with venlafaxine and duloxetine.[28] The RANZCP clinical guideline *Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders* (2015) states that venlafaxine can also cause withdrawal agitation.[34]

6.4.3 Safety alerts relating to adverse drug reactions for SSRIs and SNRIs

The Pharmacovigilance Risk Assessment Committee (PRAC) reviewed available evidence from the European Medicines Agency's (EMA) database of adverse reactions, literature, social media and cumulative data reviews for SSRIs and SNRIs medicinal products in 2019.[37] They considered that the product information for SSRI and SRNI medicinal products should be amended to warn about the possibility of sexual dysfunction, which may persist following discontinuation of these medicinal products. The Health Products Regulatory Authority (HPRA) included this information in their drug safety newsletter in April 2020.[38]

In summary, under this criterion, ADRs as per SmPCs, QT-interval prolongation, dropouts due to side-effects in meta-analysis and systematic reviews, clinical guidance and safety alerts were considered. Escitalopram and citalopram have a susceptibility to QT-interval prolongation.[6, 9] Results from the meta-analysis and systematic reviews showed that fluvoxamine and paroxetine had more dropouts due to side-effects.[26] Clinical guidance in the UK and Australia/New Zealand published the concerns with prolonged withdrawal agitation associated with paroxetine.[34] The SNRIs, duloxetine and venlafaxine, have higher dropout rates due to side-effects compared to SSRIs (except fluvoxamine).[26]

Recommendation

SSRI: There is no preferred SSRI in terms of adverse drug reaction profiles.

SNRI: There is no preferred SNRI in terms of adverse drug reaction profiles.

6.5 Contraindications & cautions

SSRIs and SNRIs have a number of cautions and contraindications that are outlined below. For a full list and further information, it is advisable to consult the SmPCs of the individual SSRIs and SNRIs, available at www.hpra.ie.

6.5.1 Contraindications

All SSRIs are contraindicated in a manic phase of bipolar disorder and poorly controlled epilepsy.[6-11] Some SSRIs have additional contraindications and it is advisable to consult the SmPCs for individual guidance. As there is a potential for QT interval prolongation with citalopram and escitalopram, they are contraindicated in people with a known QT interval prolongation, a congenital long QT syndrome and in people taking other medicines that prolong the QT interval.[6, 9] Sertraline is contraindicated in severe hepatic impairment.[11] According to their SmPCs, escitalopram, fluoxetine and fluvoxamine are contraindicated in breastfeeding.[7, 9, 10]

Table 6: SmPC SSRI contraindications[6-11]

	Citalopram	Escitalopram	Fluoxetine	Fuvoxamine	Paroxetine	Sertraline
In manic phase of bipolar disorder	✓	✓	✓	✓	✓	✓
Poorly controlled epilepsy	✓	✓	✓	✓	✓	✓
With known QT interval prolongation/congenital long QT syndrome/taking other medicines which prolong QT interval	✓	✓				
Severe hepatic impairment						✓
Breastfeeding mothers		✓	✓	✓		

All SNRIs are contraindicated in those with uncontrolled blood pressure and in breastfeeding mothers.[3-5] It is advisable to consult the SmPCs for individual guidance, available at www.hpra.ie.

Table 7: SmPC SNRI contraindications[3-5]

	Duloxetine	Venlafaxine
Uncontrolled blood pressure	✓	✓
Hepatic impairment	✓	
Renal impairment	✓	
Breastfeeding mothers	✓	✓

6.5.2 Cautions

All SSRIs are cautioned in cardiac disease, concurrent electroconvulsive therapy, diabetes mellitus, epilepsy (discontinue if seizures develop), history of bleeding disorders (especially GI bleeding), older people with current or recent significant hyponatraemia, history of mania, hepatic impairment, pregnancy and susceptibility to angle-closure glaucoma.[6-11] A full list of cautions for each drug can be found in the individual SmPCs available at www.hpra.ie.

Escitalopram, sertraline, fluoxetine and citalopram are additionally cautioned in patients who have any risk factors for QT-interval prolongation, such as electrolyte disturbances, bradycardia, congenital long QT syndrome, concomitant use of more than one drug that prolongs the QT interval, cardiac disease, thyroid disease, female sex and aged over 65 years.[6, 7, 9, 11] Fluvoxamine and paroxetine carry this caution for concomitant use with other drugs that prolong QT-interval.[8, 10]

Table 8: SmPC SSRI cautions[6-11]

	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
History of bleeding disorders*	✓	✓	✓	✓	✓	✓
History of mania	✓	✓	✓	✓	✓	✓
Cardiac disease	✓	✓	✓	✓	✓	✓
Diabetes mellitus	✓	✓	✓	✓	✓	✓
Epilepsy	✓	✓	✓	✓	✓	✓
Hepatic impairment	✓	✓	✓	✓	✓	✓
Susceptible to angle-closure glaucoma	✓	✓	✓	✓	✓	✓
Undergoing concurrent electroconvulsive therapy	✓	✓	✓	✓	✓	✓
Pregnancy	✓	✓	✓	✓	✓	✓
Older people with current or recent significant hyponatraemia	✓	✓	✓	✓	✓	✓
Risk factors for QT-interval prolongation (including concomitant use with other drugs that prolong QT-interval)	✓	✓	✓	✓	✓	✓
Renal impairment**	✓	✓	✓	✓	✓	✓
Significant bradycardia	✓	✓				
Recent myocardial infarction	✓	✓				

*Gastrointestinal bleeding **Check individual SmPCs for further information on renal function and dose reductions

The Medicines and Healthcare Products Regulatory Agency (MHRA) published a drug safety update in January 2021 on SSRIs and SNRIs. The drug safety update outlined that SSRIs and SNRIs are known to increase bleeding risks due to their effect on platelet function and data from observational studies suggest that the use of SSRIs and SNRIs during the month before delivery may result in a small increased risk of postpartum haemorrhage.[39]

SNRIs are cautioned in cardiac disease, history of bleeding disorders, history of epilepsy, susceptibility to angle-closure glaucoma, and history of mania. It is advisable to consult the SmPCs for individual guidance, available at www.hpra.ie.

Table 9: SmPC SNRI cautions[3-5]

	Duloxetine	Venlafaxine
Recent myocardial infarction		✓
Cardiac disease; monitor blood pressure	✓	✓
High risk of cardiac arrhythmia/QT prolongation		✓
History of bleeding disorders	✓	✓
History of epilepsy	✓	✓
Susceptibility to angle-closure glaucoma	✓	✓
History or family history of mania	✓	✓
Diabetes mellitus		✓
Hepatic impairment		✓
Renal impairment		✓
Older people	✓	✓

6.5.2.1 Risk of suicide and overdose

Depression can be associated with an increased risk of suicidal thoughts and suicide-related events and this risk persists until significant remission occurs. Consideration should therefore be given to the risk of suicide and the fatalities in overdose of SSRIs and SNRIs. The increased frequency of suicidal thoughts and behaviour is listed as an uncommon [incidence of ≥1/1,000 to1/100] side-effect with the use of duloxetine, sertraline and fluoxetine.[5, 7, 11] The increased frequency of suicidal thoughts and behaviour is unknown for citalopram, escitalopram, fluvoxamine, paroxetine and venlafaxine.[4, 6, 8-10] Paroxetine showed a higher frequency of suicidal behaviour in young adults (aged 18-24 years) with psychiatric disorders compared with placebo.[8] Fatal cases of overdose have been reported with citalopram alone. The majority of fatal cases have involved overdose with concomitant medications.[6]

The same risk is associated with escitalopram.[9] Cases of overdose of fluoxetine alone usually have a mild course and fatality attributed to overdose of fluoxetine alone has been extremely rare.[7] Fluvoxamine also has a wide margin of safety in overdose and reports of deaths attributed to overdose of fluvoxamine alone are extremely rare.[10] A wide margin of safety is evident from available overdose information on paroxetine.[8] Sertraline has a margin of safety dependent on patient population and/or concomitant medication. Deaths have been reported involving overdoses of sertraline, alone or in combination with other drugs and/or alcohol.[11] Some fatalities have occurred, with duloxetine alone or with concomitant medicines.[5] Overdose with venlafaxine was reported predominantly in combination with alcohol and/or other medicinal products. Published retrospective studies report that venlafaxine overdose may be associated with an increased risk of fatal outcomes compared to that observed with SSRIs, but lower than that for TCAs.[3, 4]

6.5.2.2 Older people

Aging is associated with a progressive decline in liver and kidney functions and with polypharmacy. Consideration should therefore be given to the pharmacokinetics of SSRIs and SNRIs in this subpopulation. The mean age of the population taking SSRIs and SNRIs on CDS in Ireland between the years 2015-2020 was 57.66 years (SD=18.42).[12] Fluoxetine may not be appropriate for use in older people because of its long half-life and prolonged side-effects. Paroxetine and fluvoxamine may not be appropriate for the use in older people because of the higher risk of drug-drug interactions.[26] Sedation can be a problem in older people with paroxetine and fluvoxamine. Venlafaxine can cause hypotension at lower doses, but it can increase blood pressure at higher doses, as can duloxetine.[32]

6.5.2.3 Renal impairment

The manufacturers' dosing information for SSRIs and SNRIs in people with impaired renal function is outlined in table 10. Citalopram, sertraline and escitalopram, although still cautioned, are the only SSRIs that do not require a dose adjustment in people with mild–to-moderate renal impairment.[6-11] Neither SNRI requires a dose adjustment in mild-to-moderate renal impairment, however they should still be used with caution.[3-5]

Table 10: Use of SSRIs and SNRIs in renal impairment[3-11]

	Manufacturers' information
Citalopram	Dosage adjustment is not required if the patient has mild to moderate renal impairment. Caution is advised in patients with severe renal impairment.
Escitalopram	Dosage adjustment is not necessary in patients with mild or moderate renal impairment. Caution is advised in patients with severely reduced renal function.
Fluoxetine	Dose reduction or alternate day dosing is recommended for patients with mild to moderate renal failure.
Fluvoxamine	Patients suffering from renal insufficiency should start on a low dose and be carefully monitored.
Paroxetine	Increased plasma concentrations of paroxetine occur in patients with severe renal impairment. Therefore, dosage should be restricted to the lower end of the dosage range.
Sertraline	Dosing does not have to be adjusted based on the degree of renal impairment.
Duloxetine	No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). Duloxetine must not be used in patients with severe renal impairment.
Venlafaxine	Although no change in dosage is necessary for patients with glomerular filtration rate (GFR) between 30-70 ml/minute, caution is advised. For patients that require hemodialysis and in patients with severe renal impairment (GFR < 30 ml/min), the dose should be reduced by 50%.

6.5.2.4 Breastfeeding mothers

Depression and anxiety affects 15% to 20% of women in the first year after childbirth.[40] *The Maudsley prescribing guidelines in psychiatry* (13th edition) (2018) state that it usually advisable to continue the antidepressant prescribed during pregnancy and switching antidepressant post-partum is not usually advised.[32] This evaluation therefore considers the use of antidepressants for new onset depression in breastfeeding mothers. According to the SmPCs, the SSRIs escitalopram, fluoxetine and fluvoxamine are contraindicated in breastfeeding mothers and citalopram is to be used with caution.[7, 9, 10] Similarly, both SNRIs, venlafaxine and duloxetine, are contraindicated in breastfeeding mothers.[3-5] Traces of paroxetine are present in breastmilk but amounts are too small to be harmful.[8] Sertraline is not known to be harmful.[11] According to the US Drugs and Lactation Database (Lactmed), levels of paroxetine and sertraline in breastmilk are low and they are usually not detected in the serum of an infant.[41, 42] Lactmed reports that infants receive citalopram in breastmilk and it is detectable in low levels in the

serum of some.[43] They report that there is limited information indicating that maternal doses of escitalopram up to 20mg daily produce low levels in milk and would not be expected to cause any adverse effects in breastfed infants, especially if the infant is older than 2 months.[44] The same evidence has been shown for fluvoxamine at doses of up to 300 mg daily.[45] Lactmed report that the average amount of drug in breastmilk is higher with fluoxetine than with most other SSRIs and the long-acting, active metabolite, norfluoxetine, is detectable in the serum of most breastfed infants during the first two months postpartum and in a few thereafter.[46] Little published information is available on the use of duloxetine during breastfeeding; however, the dose in milk is low and serum levels were low in two breastfed infants.[47] Infants receive venlafaxine and its active metabolite in breastmilk, and the metabolite of the drug can be found in the plasma of most breastfed infants; however, concurrent side-effects have rarely been reported.[47] Lactmed reports that sertraline is considered the preferred antidepressant in breastfeeding mothers by most authoritative reviewers.[42] The Va/DoD *Clinical practice guideline for the management of major depressive disorder* (2016) refers to the use of sertraline in postpartum women who intend to breastfeed, and suggests it as the drug of choice in this group due to the lower levels of medication transferred to infants via breastmilk.[33]

Recommendation

SSRI: There is no significant difference between SSRIs in terms of contraindications and cautions.

SSRI: Sertraline is a common preference for the treatment of new onset depression in breastfeeding mothers.

SNRI: There is no significant difference between SNRIs in terms of contraindications and cautions.

6.6 Drug interactions

SSRIs and SNRIs share the risk of developing potentially life-threatening syndromes such as serotonin syndrome or neuroleptic malignant syndrome with concomitant use of other serotonergic drugs, with drugs which impair metabolism of serotonin (including MAOIs), antipsychotics and other dopamine antagonists and opioid drugs.[36]

All SSRIs and SNRIs are inhibitors of CYP. There are differences in the isoenzymes inhibited and the degree of inhibition, resulting in different propensities of individual antidepressants to cause interactions.[3-11]

Of the SSRIs, fluoxetine, fluvoxamine and paroxetine are all potent inhibitors of CYP2D6, which will affect the oxidative metabolism of other drugs.[7, 8, 10] Sertraline is a mild-moderate inhibitor of CYP2D6, so it will have a lesser effect on the oxidative metabolism of other drugs.[11]

Although citalopram and escitalopram have minimal effect on CYP, their metabolism can be inhibited by other drugs via CYP, thereby increasing the potential risk for QT prolongation.[6, 9] Of the SNRIs, duloxetine and venlafaxine are both metabolised by CYP2D6. Duloxetine is a moderate inhibitor of CYP2D6 and venlafaxine has low potential to inhibit the metabolism of substrates for CYP2D6.[3-5]

Citalopram and escitalopram are drugs that evidentially have some risk associated with causing QT prolongation and torsade de pointes and they may have an additive effect to other drugs that prolong the QT interval. Co-administration of citalopram and escitalopram with medicines that prolong the QT interval is therefore contraindicated. These medicines include; class IA and III antiarrhythmics, antipsychotics, TCAs, some antimicrobial agents, some antihistamines and some anti-retrovirals.[48]

In a recent publication by Das. B et al. (2020), escitalopram co-prescribed with an antipsychotic, ciprofloxacin or domperidone; and fluoxetine co-prescribed with an antipsychotic; accounted for the majority of the top 20 QT-prolonging drug-drug interaction pairs in older people.[49]

6.6.1 Drug interactions as outlined by manufacturers

An overview of potential drug-drug interactions that may occur with SSRIs and SNRIs and commonly prescribed drugs in Ireland is summarised below. This list is not exhaustive and it is advisable to consult the SmPCs of individual SSRIs and SNRIs for a comprehensive list of drug interactions, available at www.hpra.ie.

Serotonergic agents: Serotonin syndrome, a potentially life-threatening condition, may occur with all SSRIs and SNRIs, particularly with concomitant use of other serotonergic agents, e.g. other SSRIs or SNRIs, TCAs (e.g. amitriptyline), triptans, lithium, MAOIs, opioids (e.g. tramadol), antipsychotics and St John's wort. Refer to the SmPCs of individual products for information on starting and stopping an SSRI or SNRI.[3-11]

Drugs that prolong the QT interval: Co-administration of citalopram, escitalopram, fluoxetine, or venlafaxine with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, antipsychotics (e.g. chlorpromazine**,** promethazine and haloperidol), TCAs, certain antimicrobial agents (e.g. moxifloxacin, intravenous erythromycin) and certain antihistamines is contraindicated.[3, 4, 6, 7, 9] This is a precaution with the use of sertraline.[11]

Proton pump inhibitors: Co-administration of escitalopram or citalopram with omeprazole 30 mg once daily (a CYP2C19 inhibitor) results in a moderate (approximately 50%) increase in the plasma concentrations of escitalopram and should be co-prescribed with caution. The same interaction cannot be excluded for the use of sertraline.[6, 9, 11]

Metoprolol: Caution is recommended when citalopram, duloxetine, escitalopram, fluoxetine or venlafaxine is co-administered with metoprolol as it is mainly metabolised by CYP2D6 and has a narrow therapeutic index.[3-7, 9]

Anticoagulants: All SSRIs and SNRIs should be used cautiously in patients predisposed to bleeding, including patients co-prescribed anticoagulants and platelet inhibitors. The manufacturers of citalopram, escitalopram, fluoxetine, paroxetine and sertraline also report a pharmacodynamic interaction with NSAIDs/aspirin, leading to an increased haemorrhagic risk, in their SmPCs.[6-9, 11]

Increased risk of hyponatremia: There is an increased risk of hyponatremia when SSRIs and SNRI are used in combination with other agents associated with hyponatremia (e.g. diuretics, desmopressin, carbamazepine and oxcarbazepine). The manufacturers of duloxetine, fluoxetine, sertraline and venlafaxine, report this interaction in their SmPCs.[3-5, 7, 11]

Long half-life: The long elimination half-lives of both fluoxetine and norfluoxetine should be borne in mind when considering pharmacodynamic or pharmacokinetic drug interactions (e.g. when switching from fluoxetine to other antidepressants).[7]

Centrally acting medicinal products: Most manufacturers advise caution when SSRIs and SNRIs are taken in combination with other centrally acting medicinal products or substances, including alcohol and sedative medicinal products (e.g. benzodiazepines, antipsychotics, phenobarbital, sedative antihistamines).[3-11]

Statins: An interaction between paroxetine and pravastatin has been observed in studies suggesting that co-administration of paroxetine and pravastatin may lead to an increase in blood glucose levels.[8]

Grapefruit juice: Intake of grapefruit juice daily increased the sertraline plasma levels and should therefore be avoided during treatment with sertraline.[11]

Recommendation

SSRI: Sertraline has a favourable drug interaction profile.

SNRI: There is no preference in SNRIs in terms of drug interaction profiles.

6.7 Patient factors

The effects of food on the administration of SSRI and SNRIs are summarised in table 11. Dosing independent of food intake is preferential. Paroxetine is the only SSRI recommended to be taken with food while all other SSRIs are independent of food intake.[6-11] In the case of SNRIs, venlafaxine is recommended to be taken with food and duloxetine dosing is independent of food intake.[3-5]

Some people may have preference for a prolonged-release preparation over an immediate-release preparation or vice versa. This is not relevant to the use of SSRIs as all preparations are immediate-release.[6-11] In the case of SNRIs, venlafaxine is available in both an immediate-release and prolonged-release preparation. Duloxetine is only available in an immediate-release preparation.[3-5]

Some people may have preference to a tablet over a capsule or vice versa. This is not relevant to the use of SSRIs as the majority of SSRIs are available in either a capsule or a tablet form.[6-11] In the case of SNRIs, venlafaxine is available in both tablet (non-film coated) and capsule formulations. Duloxetine is available as a capsule.[3-5]

Table 11: Effects of food on the administration of SSRIs and SNRIs[3-11]

	Effect of food
Citalopram	Independent of food intake
Escitalopram	Independent of food intake
Fluoxetine	Independent of food intake
Fluvoxamine	Independent of food intake
Paroxetine	Recommended to be taken with food
Sertraline	Independent of food intake (grapefruit juice to be avoided)
Duloxetine	Independent of food intake
Venlafaxine	Recommended to be taken with food†Ω

Ω Immediate release preparation † Prolonged release preparation

Recommendation

SSRI: There is no difference between SSRIs in terms of patient factors in the treatment of depression.

SNRI: There is no difference between SNRIs in terms of patient factors in the treatment of depression.

6.8 Cost

Value for money is a consideration when choosing a preferred SSRI and SNRI. It is also a consideration for patients who pay for their medicines. A drug of lower acquisition cost is preferred unless the more expensive drug has a proven advantage in terms of either efficacy or safety.

6.8.1 Expenditure and utilisation of SSRIs and SNRIs on community drug schemes

Total annual expenditure (inclusive of ingredient cost and pharmacy dispensing fees) in 2019 on SSRIs and SNRIs under the CDS was €29.2million.[12] Expenditure on SSRIs and SNRIs has decreased in recent years due to the introduction of generic substitution and reference pricing. These total trends are illustrated in figure 1. Figure 2 illustrates that there has been an increase in the total number of prescriptions for SSRIs and SNRIs under CDS between the years 2015 and 2019.[12] Figure 3 illustrates the expenditure on individual SSRIs and SNRIs between 2015 and 2020 and changes in expenditure due to generic substitution and reference pricing.[12]

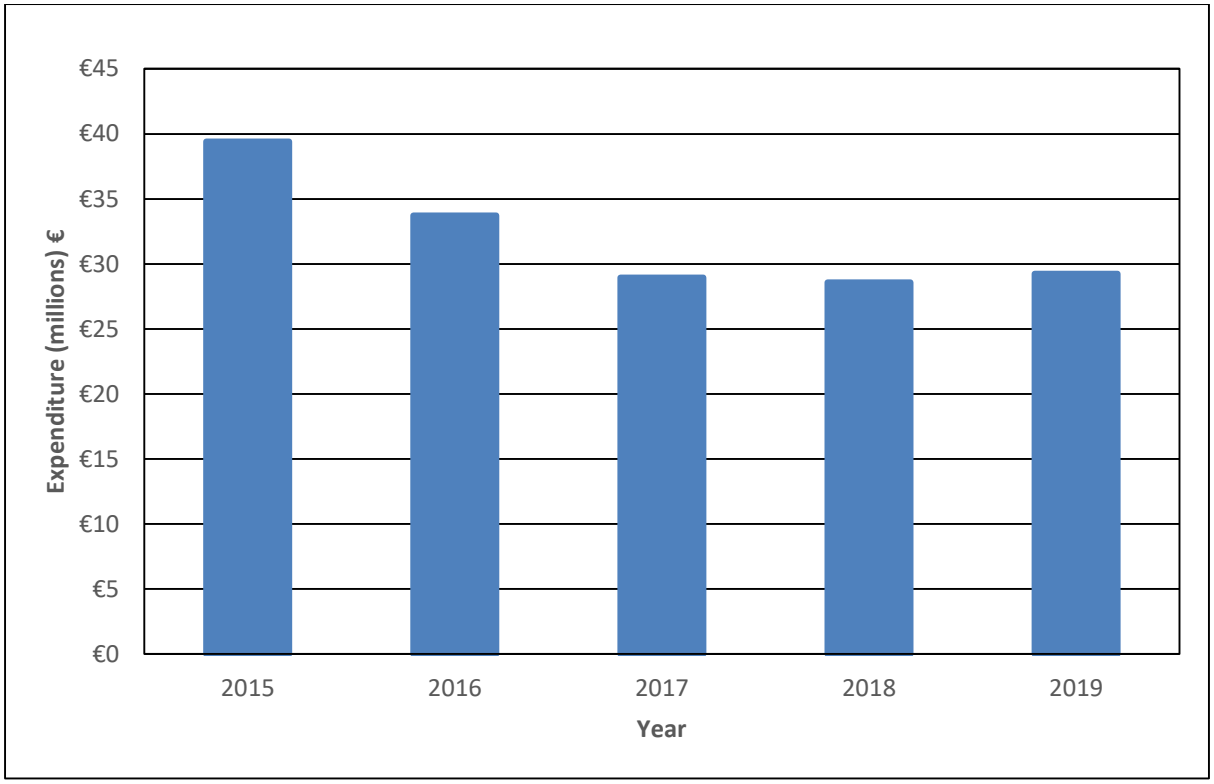

Figure 1: Total annual expenditure for SSRIs and SNRIs on community drug schemes (2015-2019)[12]

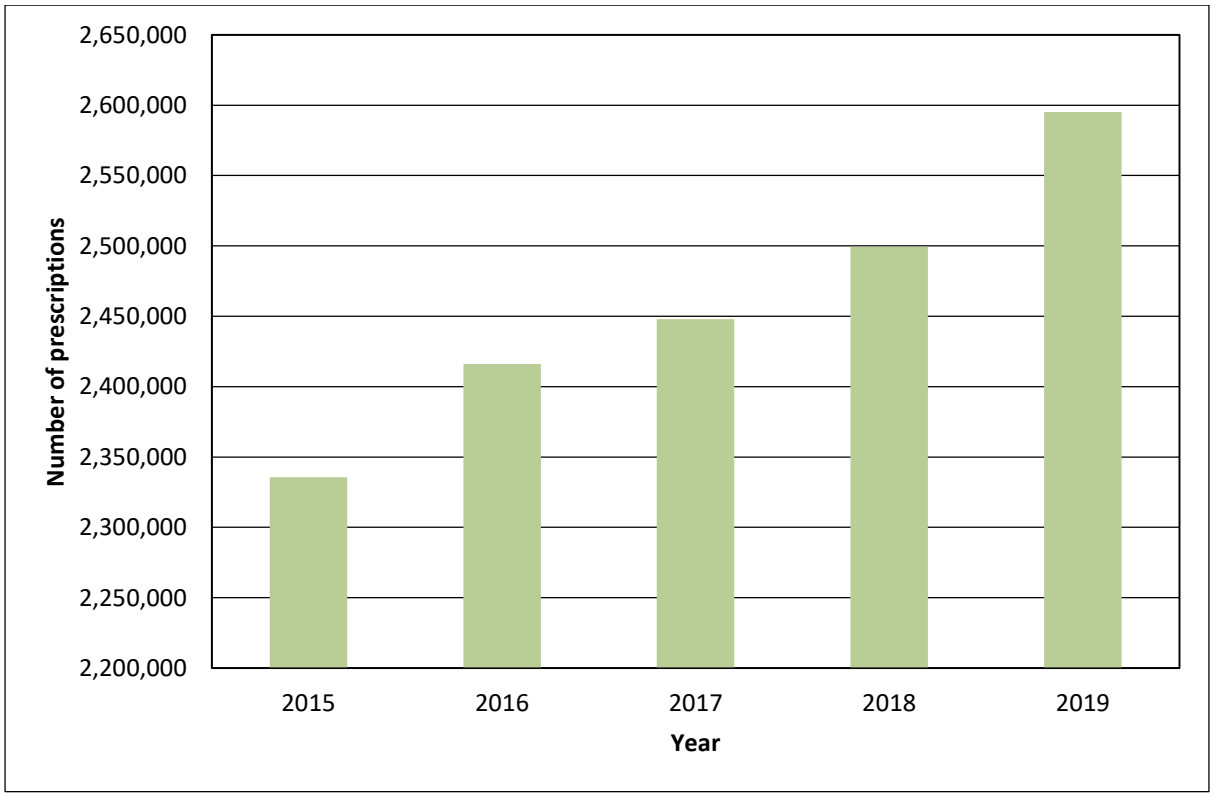

Figure 2: Total number of prescriptions for SSRIs and SNRIs on community drug schemes (2015-2019)[12]

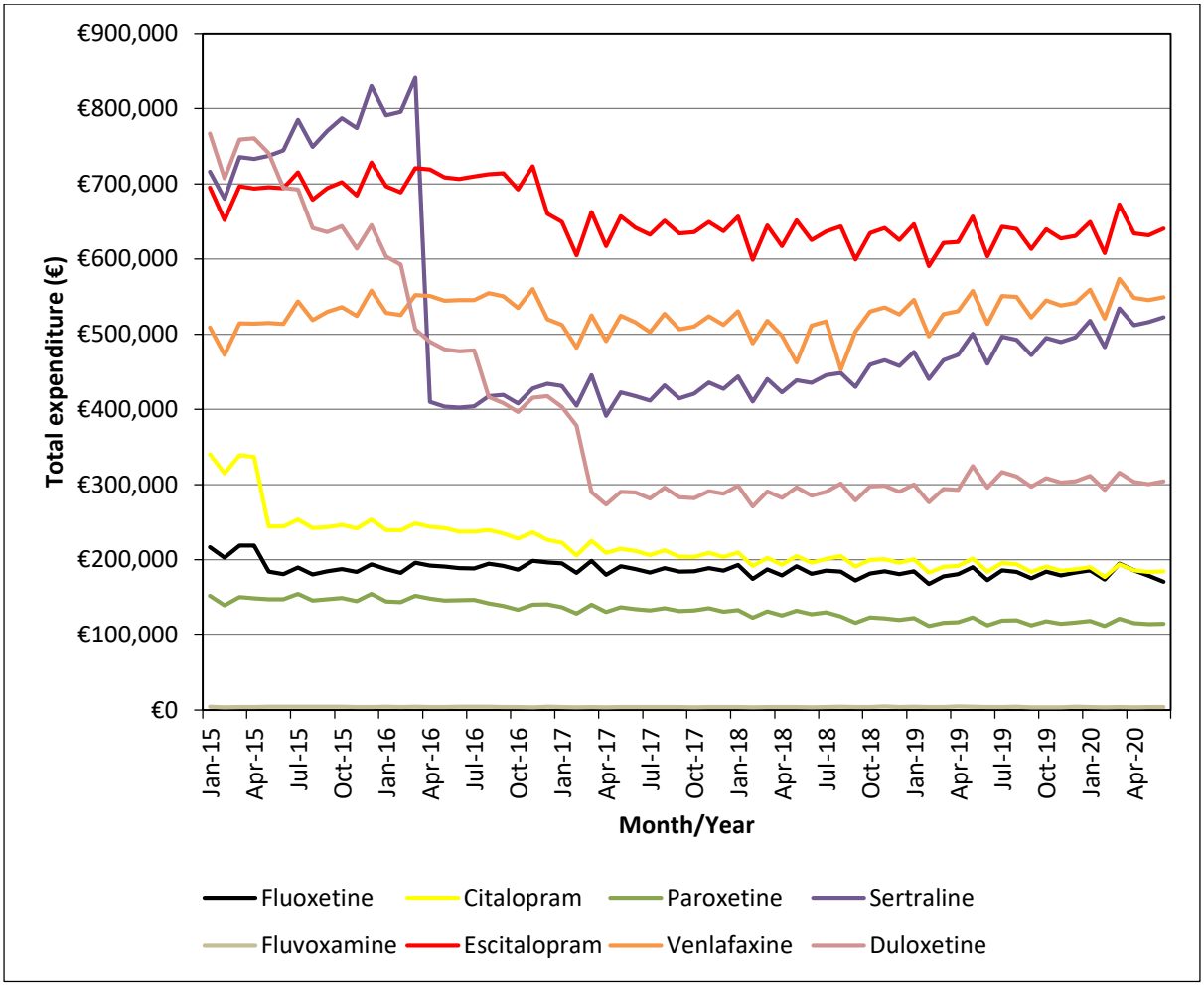

Figure 3: Total expenditure for individual SSRIs and SNRIs on community drug schemes (January 2015-May 2020)[12]

Sertraline had the highest expenditure of all SSRI/SNRIs from July 2015 up until April 2016. Following reference pricing the cost of a number of antidepressants reduced and total expenditure for sertraline dropped below escitalopram and venlafaxine. Expenditure on escitalopram remains the highest of all SSRI/SNRIs, followed by venlafaxine.

6.8.2 Individual cost of SSRIs and SNRIs

The WHO collaborating centre for drug statistics methodology lists the DDD and MDD for each SSRI and SNRI for the treatment of depression. These were utilised to compare the reimbursement cost of each SSRI and SNRI.[2] Figure 4 and 5 illustrate the PCRS reimbursement price comparison as DDD and MDD. Citalopram (€0.10 per day), fluoxetine (€0.11 per day), sertraline (€0.11 per day) and escitalopram (€0.12 per day) are similar in cost at the DDD. The most expensive SSRI in both the DDD and MDD is fluvoxamine (€0.45 per day and €1.34 per day respectively). Citalopram is the cheapest SSRI at both the DDD and MDD (€0.10 per day and €0.20 per day respectively). Venlafaxine is the cheaper of the two SNRIs for both the DDD and MDD.

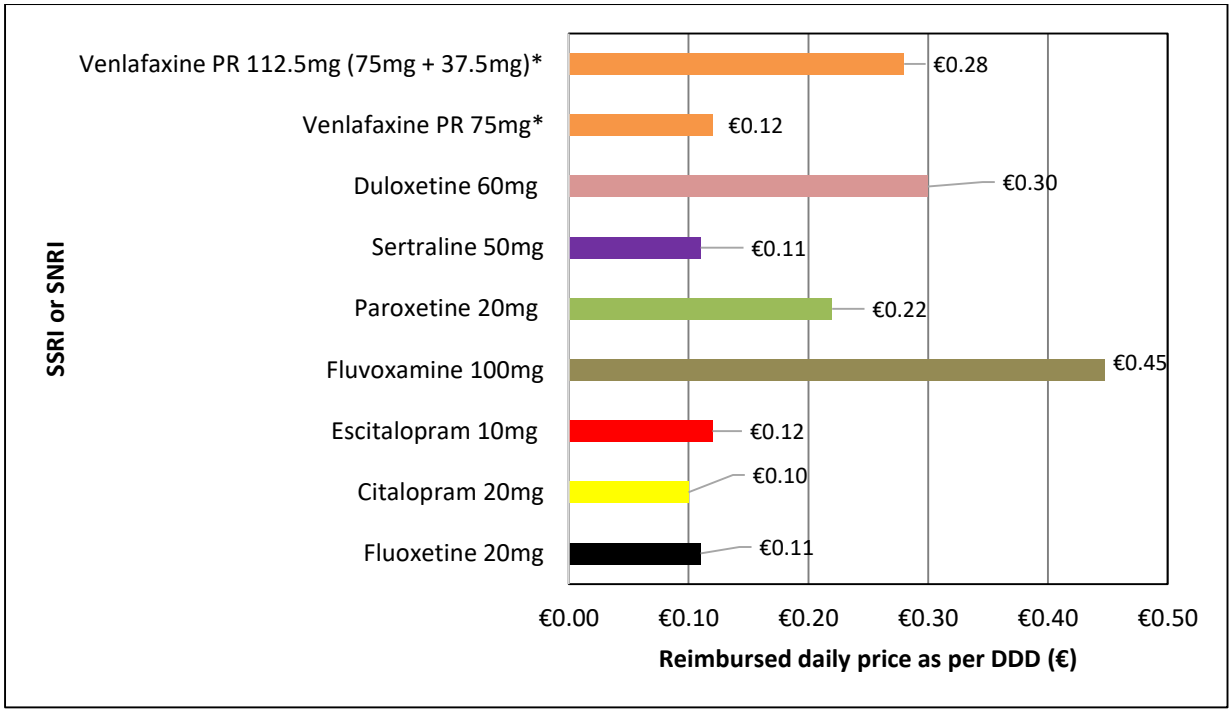

Figure 4: PCRS reimbursement price of SSRI/SRNI per day (defined daily dose)[14]
DDD: Defined daily dose *The DDD of venlafaxine is 100mg. The PCRS list of reimbursable items lists venlafaxine in three strengths: 37.5mg, 75mg and 150mg. The price of venlafaxine is represented in the above figure as 75mg daily and 112.5mg daily (the closest variations of the DDD).

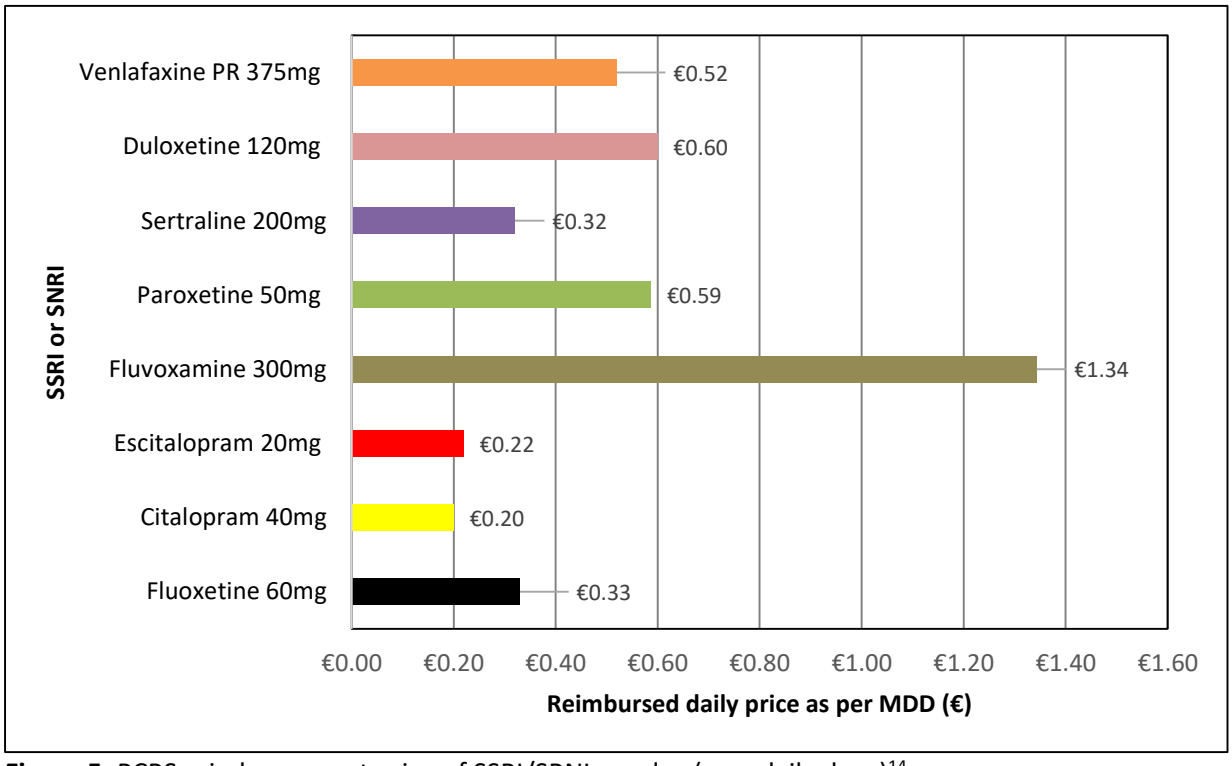

Figure 5: PCRS reimbursement price of SSRI/SRNI per day (max daily dose)[14]
MDD: Max daily dose

Recommendation

SSRI: Citalopram, fluoxetine and sertraline are the preferred SSRIs in terms of cost at their DDD.

SSRI: Citalopram is the preferred SSRI in terms of cost at its MDD.

SNRI: Venlafaxine is the preferred SNRI in terms of cost at DDD and MDD.

6.9 National prescribing trends

The MMP recognises that clinical experience is a factor for prescribers when choosing a medication. In order to determine prescribing trends for the SSRIs and SNRIs under review, the MMP performed an analysis of the PCRS pharmacy claims. Escitalopram was the most commonly prescribed SSRI in the years 2019-2020 and it reflects utilisation by approximately 60,000 patients in Ireland. Sertraline was the second most commonly prescribed SSRI in the years 2019-2020 and it reflects utilisation by approximately 48,000-50,000 patients in Ireland (Figure 6 &7). Venlafaxine was the most common SNRI prescribed in the years 2019-2020 reflecting utilisation by approximately 48,000 patients in Ireland (Figure 8 & 9).[12]

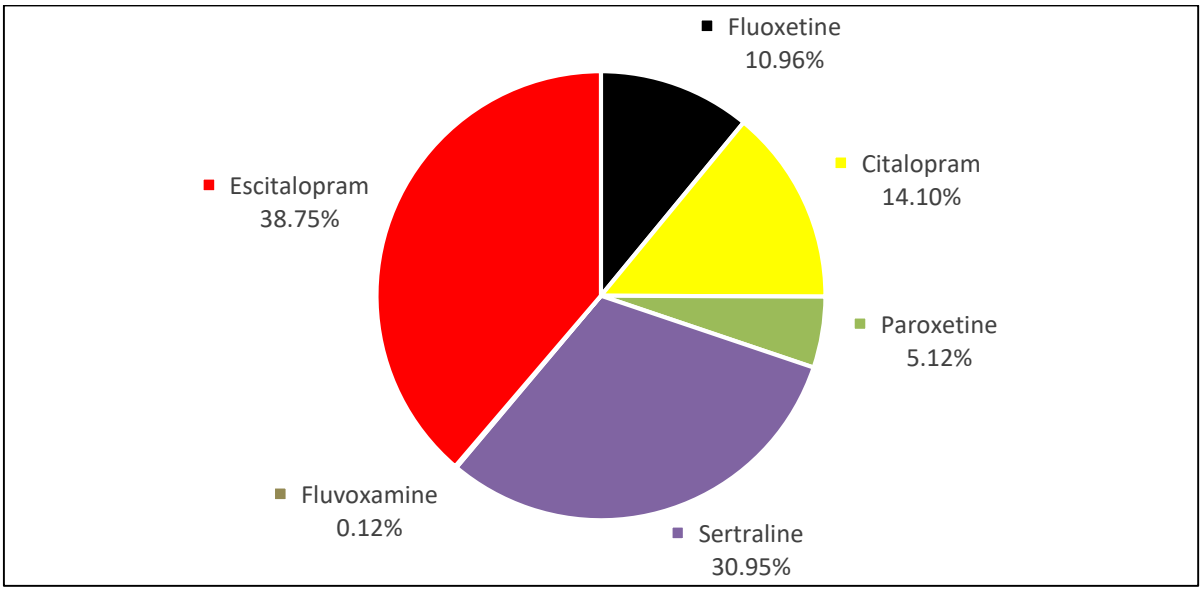

Figure 6: Proportion of individual SSRIs reimbursed on the community drug schemes (July 2019 – June 2020)[12]

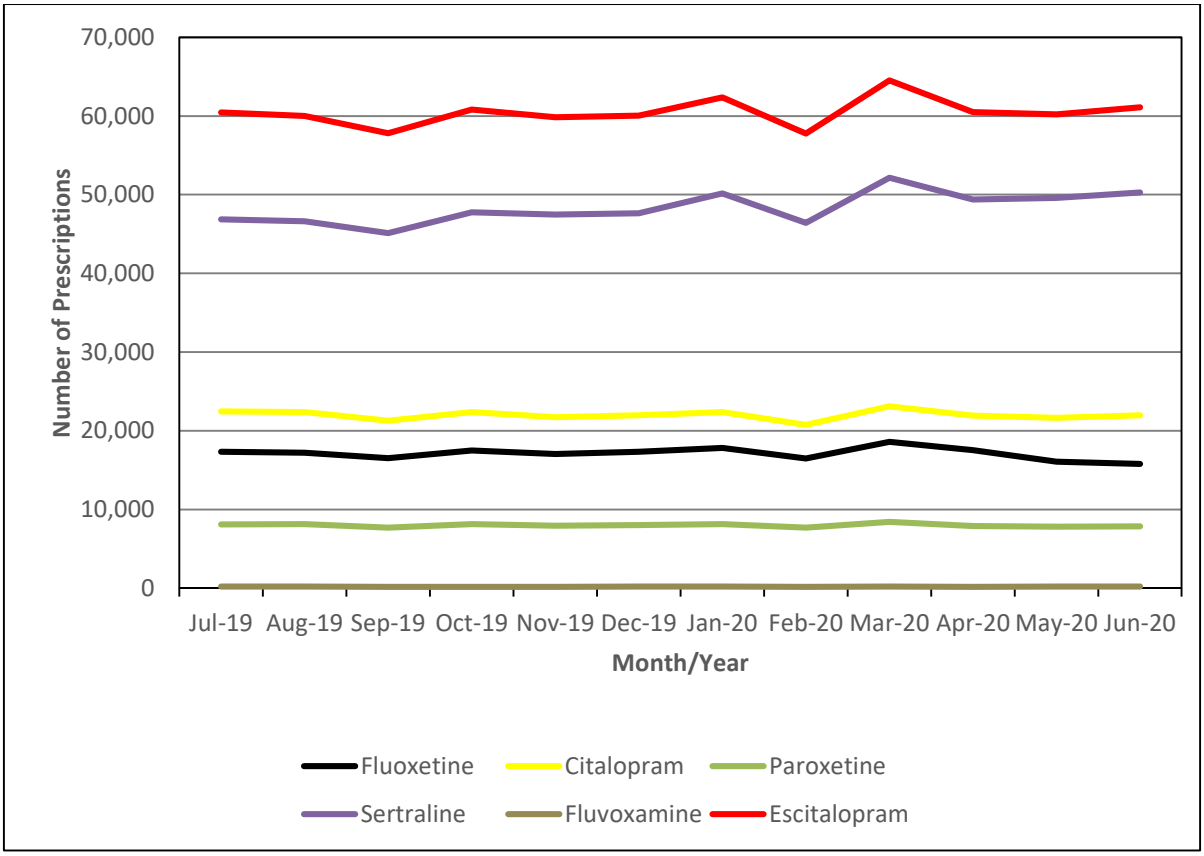

Figure 7: Number of prescriptions for SSRIs on community drug schemes (July 2019-June 2020)[12]

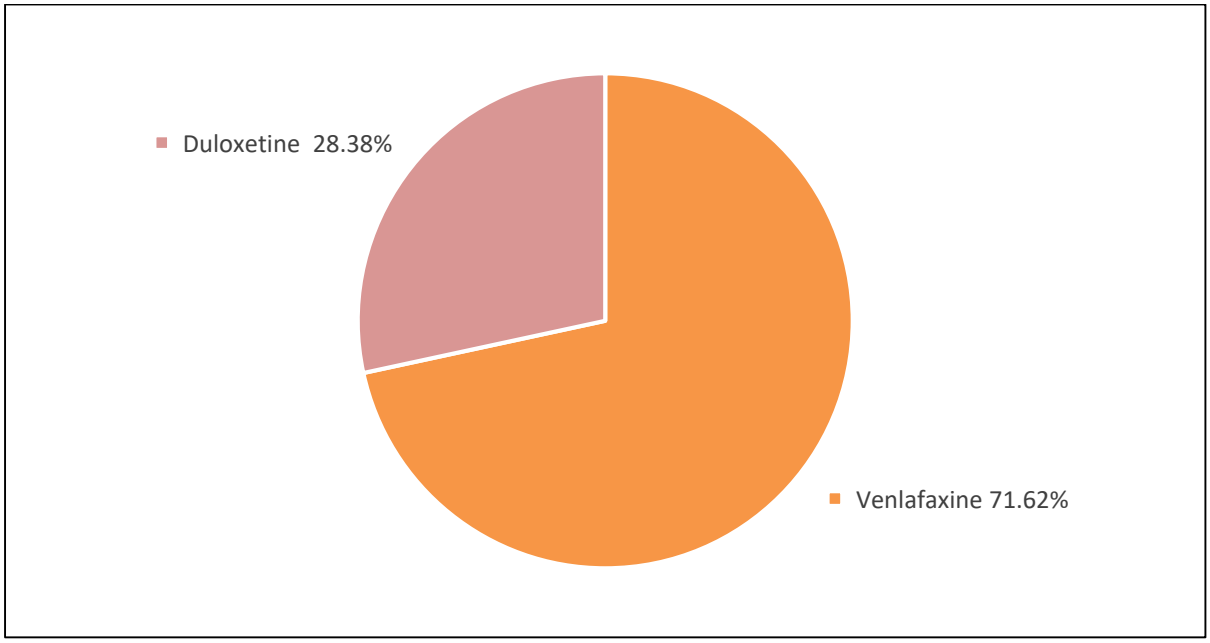

Figure 8: Proportion of individual SNRIs reimbursed on the community drug schemes (July 2019-June 2020)[12]

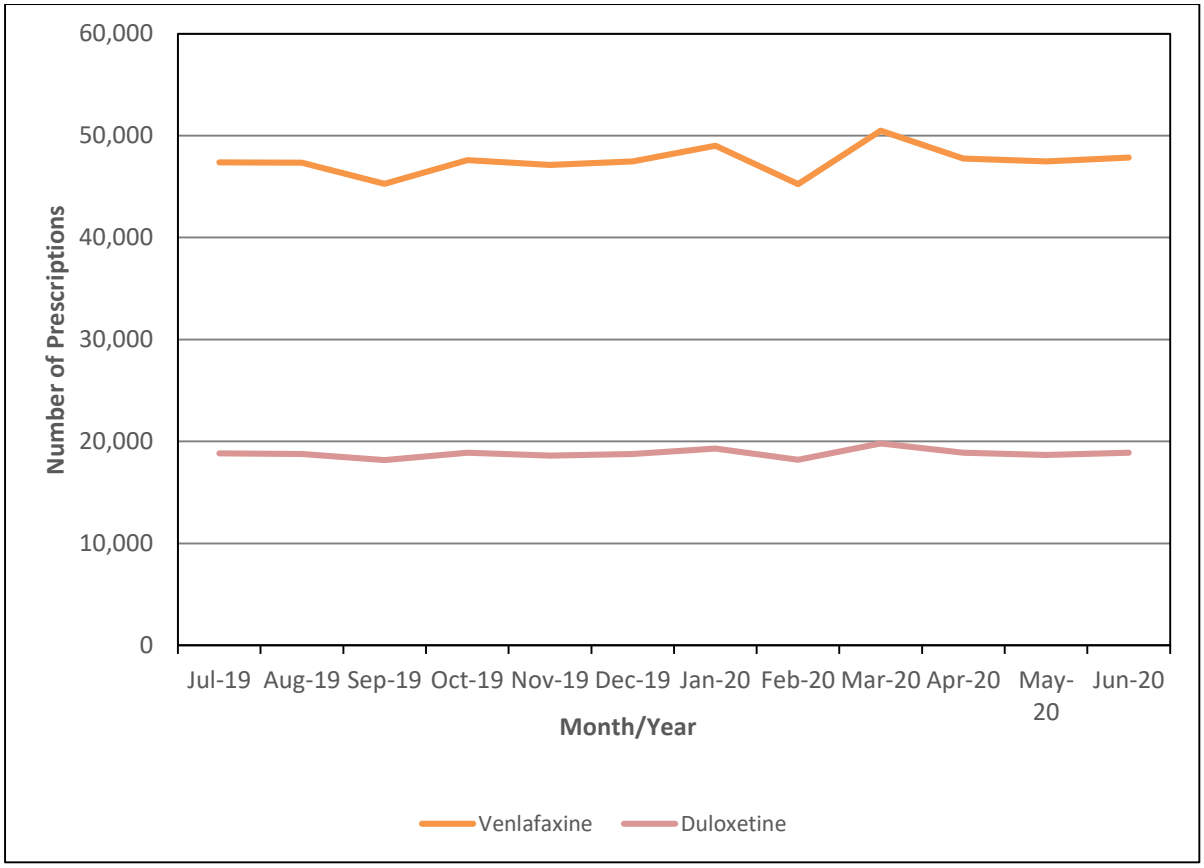

Figure 9: Number of prescriptions for SNRIs on community drug schemes (July 2019-June 2020)[12]

An analysis of dispensed data evaluated the different strengths of SSRI and SNRIs in use under the community drug schemes in Ireland. The analysis examined the strengths of SSRI and SNRI most commonly prescribed and cross-referenced them to the DDD.

Table 12 shows that the majority of prescriptions dispensed for all SSRIs in 2019 were for the DDD. This same conclusion can be drawn for duloxetine in the SNRI class. As there is no corresponding strength to the DDD of venlafaxine (100 mg) available on the PCRS reimbursement list, this analysis could not be performed for venlafaxine; 46.12% of the prescriptions of venlafaxine were for 75mg dose, 38.64% were for the 150mg dose (prolonged release and immediate release combined) and 15.24% were for the 37.5mg dose.[12]

Table 12: Breakdown of total number of prescriptions for different strengths of SSRIs on the community drug schemes in 2019[12]

SSRI/SNRI	No. of prescriptions	% of prescriptions
Citalopram 10mg	89,851	34.08%
Citalopram 20mg*	161,629	61.30%
Citalopram 30mg	4,366	1.66%
Citalopram 40mg	7,803	2.96%
Total	263,649	
Duloxetine 30mg	79,894	38.75%
Duloxetine 60mg*	126,282	61.25%
Total	206,176	
Escitalopram 5mg	121,105	17.10%
Escitalopram 10mg*	317,066	44.76%
Escitalopram 15mg	108,731	15.35%
Escitalopram 20mg	161,511	22.80%
Total	708,413	
Fluoxetine 10mg	68	0.03%
Fluoxetine 20mg*	201,510	99.02%
Fluoxetine 60mg	1,924	0.95%
Total	203,502	
Fluvoxamine 50mg	1,033	46.01%
Fluvoxamine 100mg*	1,212	53.99%
Total	2,245	
Paroxetine 10mg	11,202	11.69%
Paroxetine 20mg*	59,031	61.60%
Paroxetine 30mg	25,589	26.70%
Total	95,822	
Sertraline 20mg	61	0.01%
Sertraline 50mg*	300,048	54.87%
Sertraline 100mg	246,754	45.12%
Total	546,863	
Venlafaxine 37.5mg	84,118	15.24%
Venlafaxine 75mg	254,559	46.12%
Venlafaxine 150mg	213,249	38.64%
Total	551,926	

*DDD: Defined daily dose Note: The DDD of venlafaxine is 100mg

Recommendation

SSRI: Escitalopram and sertraline command the greatest share of SSRIs on the community drug schemes.

SNRI: Venlafaxine commands the greatest share of SNRIs on the community drug schemes.

7. Conclusion

The MMP have conducted a review of SSRI and SNRI treatments for depression. All available evidence and the following criteria: licensed therapeutic indications, clinical outcome data, clinical guidelines, adverse drug reaction profiles, cautions and contraindications, drug interaction profiles, patient factors, cost and national prescribing trends were considered. **Sertraline** and **venlafaxine** are recommended by the MMP as the preferred SSRI and SNRI respectively, for the treatment of depression.

Based on the current evidence sertraline is the MMP's preferred SSRI for the treatment of depression.

- ✓ **Sertraline is licensed for the treatment of depression in adults.**
- ✓ **Sertraline is among the preferred SSRIs in terms of efficacy and tolerability.**
- ✓ **Sertraline is a common preference within clinical guidelines for the treatment of depression in adults with a co-existing chronic physical health problem.**
- ✓ **Sertraline is a common preference for the treatment of new onset depression in breastfeeding mothers.**
- ✓ **Sertraline has a favourable drug interaction profile.**
- ✓ **Sertraline is among the preferred SSRIs in terms of cost per DDD.**
- ✓ **Sertraline is among the SSRIs commanding the greatest share of SSRIs on the community drug schemes.**

Based on the current evidence venlafaxine is the MMP's preferred SNRI for the treatment of depression.

- ✓ **Venlafaxine is licensed for the treatment of depression in adults.**
- ✓ **Venlafaxine is the SNRI of choice in terms of efficacy and tolerability.**
- ✓ **Venlafaxine is the preferred SNRI in terms of cost per DDD and MDD.**
- ✓ **Venlafaxine commands the greatest share of SNRIs on the community drug schemes.**

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