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## PHARMACOTHERAPY OF DEPRESSION IN ADULTS

- ☞ Depression is a major cause of disease burden with an estimated lifetime prevalence of 2 - 15%
- ☞ Antidepressants are effective for the treatment of moderate – severe depression
- ☞ Drug treatment should be continued for at least 6 - 9 months and should be closely monitored
- ☞ Switching to another antidepressant may be necessary to achieve individual optimal response

### INTRODUCTION

Depression is a common illness which can affect people of all ages.<sup>1</sup> It has an estimated lifetime prevalence ranging from 2 - 15%, is almost twice as common in females compared to males and is associated with substantial disability.<sup>2,3</sup> It is reported as the fourth leading cause of disease burden on society in terms of treatment costs, effect on families and carers, and impact on productivity in the workplace.<sup>4</sup> Following a first episode of depression up to 22% of people will continue to have symptoms after one year, and up to 85% of people diagnosed with depression will have two or more episodes despite active treatment.<sup>5</sup> Therefore depression is an important public health issue worldwide.<sup>2</sup> This bulletin, the first of two dealing with the pharmacological treatment of depression in adults, will outline the main agents used in the treatment of depression. The second bulletin will address frequently asked questions on antidepressants received by the National Medicines Information Centre. Other therapies (including psychological therapies and social supports) used to treat depression, either alone or in combination with antidepressants, are outside the remit of this bulletin.

### DIAGNOSIS AND CLASSIFICATION OF DEPRESSION

Depression is a clinical diagnosis, but the clinical presentation and severity varies between patients. Typical symptoms include a lowering of mood, loss of interest and enjoyment and a reduction of energy.<sup>1</sup> There are two main diagnostic criteria used to identify and classify depression (see Table 1). The International Classification of Diseases (ICD-10) is a WHO-sponsored classification of mental and behavioural disorders.<sup>6</sup> The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) is produced by the American Psychiatric Association.<sup>7</sup> Each classification lists typical symptoms which are associated with depression. **The extent to which these symptoms are present is important in determining the severity of the underlying depression**, which will in turn determine the appropriate treatment pathway for the patient.

**Table 1: Diagnostic Criteria for Depression<sup>6,7</sup>**

ICD-10 classification	DSM-IV criteria
<p><b>Individual usually suffers from:</b></p> <p>Depressed mood, loss of interest and enjoyment Reduced energy → to ↑ fatigability and ↓ activity Marked tiredness with only slight effort</p> <p><b>Other common symptoms:</b> ↓ concentration and attention ↓ self-esteem and self-confidence Ideas of guilt and unworthiness Bleak and pessimistic views of the future Ideas / acts of self-harm or suicide Disturbed sleep ↓ appetite</p>	<p><b>2 - 4 of the following symptoms must be present; at least one symptom must be (a) or (b)</b></p> <p>(a) depressed mood (b) markedly ↓ interest or pleasure in all or almost all activities (c) significant weight loss (when not dieting) or weight gain; ↓ or ↑ appetite (d) insomnia or hypersomnia (e) psychomotor agitation / retardation (f) fatigue or loss of energy (g) feelings of worthlessness or excessive or inappropriate guilt (h) ↓ ability to think or concentrate (i) recurrent thoughts of death; suicidal ideation or suicide attempt or specific suicide plan</p>

Diagnosis should take into account not just the presence of symptoms, as listed in Table 1, but also the degree of associated functional impairment and/or disability.<sup>8</sup> A diagnosis of **mild depression** requires the presence (every day for at least 2 consecutive weeks) of 2 - 3 of ICD-10 symptoms / at least 5 DSM-IV symptoms with mild functional impairment; a diagnosis of **moderate depression** requires >4 ICD-10 symptoms or >5 DSM-IV symptoms with the patient showing symptoms of functional impairment affecting the undertaking of ordinary activities, while a diagnosis of **severe depression** involves the presence of most of the symptoms listed, which markedly interfere with functioning, with/without psychotic symptoms. The DSM-IV also describes the following: **subthreshold/minor depression**, typically consisting of 2 - 4 DSM-IV symptoms and **dysthymia** which consists of subchronic minor depressive symptoms (i.e. that wax and wane but are present for at least 2 years).<sup>7,9</sup> These categories, although not meeting the minimum criteria for a formal clinical diagnosis of depression are important to recognise as each may cause considerable morbidity and human and economic costs as well as being a risk factor for future major depression.<sup>9,10</sup>

## FACTORS IN THE DEVELOPMENT OF DEPRESSION

Several pathophysiological mechanisms have been proposed for the development of depression.<sup>11-13</sup> The original **monoamine hypothesis** suggested that depression was related to a deficiency in the amount or function of cortical and limbic serotonin (5-HT) noradrenaline (NA) and dopamine (DA); most of the commonly used antidepressants work by increasing levels or activity of these neurotransmitters. Depression is known to be associated with a number of **hormonal abnormalities**, including abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis, thyroid dysregulation and oestrogen deficiency. There is also substantial recent research evidence that depression adversely affects **nerve growth factors** (such as brain-derived neurotrophic factor (BDNF)) and that antidepressant therapies exert their action by counteracting these effects. It is likely that all of these different mechanisms are interrelated in the development of depression.<sup>11</sup>

**Genetic and environmental factors are recognised as important triggers in precipitating depression.**<sup>9,14</sup> Heritability of depression has been estimated to range from 30 - 40%; a family history of depressive illness accounts for around 39% of the variance of depression in both sexes. However, no one major gene has been identified. Environmental issues such as poor parent-child relationship, marital discord, physical and sexual abuse, poor social circumstances and the presence of chronic medical conditions have all been reported to increase a person's vulnerability to the development of depression.<sup>4,9</sup> In addition, factors such as ongoing social stresses or comorbidity, may increase the duration or severity of the depressive episode and need to be taken into account during the course of treatment; a combination of pharmacological and non-pharmacological therapies may be required.<sup>5,11</sup> A large variety of gender-specific social risk factors have been identified as predictors of depression in females (including role limitations associated with lack of education or lack of choice, role overload, competing social roles, or tendency for females to be undervalued).<sup>15</sup> Certain medicines (as well as substance misuse) have been implicated in the development of depression; these include corticosteroids, metoclopramide, propranolol, progestin-releasing implanted contraceptives and H-2 antagonists.<sup>1,16,17</sup>

## PHARMACOLOGICAL AGENTS USED IN THE MANAGEMENT OF DEPRESSION

Antidepressant agents make up a remarkable variety of chemical types.<sup>11</sup> However, they all work by enhancing neurotransmission via one or more mechanisms.<sup>9,11</sup> Currently available agents include (1) Selective Serotonin Reuptake Inhibitors (SSRIs), (2) those that inhibit the reuptake of more than one neurotransmitter (such as Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs) and Tricyclic Antidepressants (TCAs)) (3) Monoamine Oxidase Inhibitors (MAOIs) and (4) those with other effects on neurotransmission such as mirtazapine. Table 2 lists the most commonly prescribed antidepressants in Ireland.

**Table 2: "Top Ten" (most commonly prescribed) antidepressant agents in Ireland\***

Drug Name**	Number of Prescriptions	Total Ingredient Cost (€)
Escitalopram	435,927	12.5 million
Venlafaxine	314,329	7.3 million
Citalopram	278,338	3.9 million
Mirtazapine	210,789	3.2 million
Amitriptyline	187,470	245,000
Sertraline	151,196	3.3 million
Fluoxetine	139,034	2.4 million
Paroxetine	109,114	1.8 million
Duloxetine	100,335	3.6 million
Dosulepin/Dothiepin	89,069	351,000

\*figures relate to antidepressant agents dispensed for adults ( $\geq 16$  years of age) in HSE-PCRS database from Nov. 2009 to Oct. 2010.<sup>18</sup>

\*\*Please note diagnostic data are not available on the HSE-PCRS database, therefore these figures may include use of these agents for treatment of other conditions

## INDIVIDUAL ANTIDEPRESSANT DRUG CLASSES

**Selective Serotonin Reuptake Inhibitors (SSRIs)** are the most widely used antidepressant agents in Ireland.<sup>18</sup> As a class they are associated with less anticholinergic side effects, are less likely to cause postural hypotension or sedation, are safer in overdose and are less cardiotoxic than the older TCAs.<sup>9,19</sup> In general they are well absorbed, undergo hepatic metabolism and are cleared via the kidneys. However, there are differences in the pharmacological profile between the various SSRIs, which impact on their clinical use (Table 3). **In terms of their potential for drug-drug interaction, fluoxetine, paroxetine and fluvoxamine have the greatest potential, citalopram and escitalopram have minimal potential and sertraline has a dose-related potential** (see Table 3).<sup>20-25</sup> In addition, fluoxetine is known to have a much longer half-life (4 - 6 plus days) compared with the others in the class; this must be taken into account when switching from one antidepressant to another.<sup>11,19</sup>

**Adverse drug reactions (ADRs)** most commonly associated with SSRIs include GI problems (nausea, vomiting, diarrhoea) and sleep disturbances.<sup>20-26</sup> These are typically worse in the first few weeks of treatment. Sexual dysfunction has been reported in up to 70% of patients. More recently, an **increased risk of GI bleeding** (particularly upper GI) has been reported with use of SSRIs and this is further increased with concomitant NSAID (including aspirin) use.<sup>1,20-26</sup> As with other antidepressants, hyponatraemia has been reported rarely with SSRIs. Underweight, female gender and increasing age are associated with increased risk of **hyponatraemia**. There are variations in the toxicity profile between SSRIs: e.g. paroxetine is associated with a greater risk of sweating, dry mouth, sedation and weight gain (thought to be due to its anticholinergic effects), sertraline with an increased risk of diarrhoea, and fluvoxamine with increased nausea.<sup>1,9,26</sup> Discontinuation of most SSRIs (particularly when abrupt) commonly leads to **withdrawal symptoms**. Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. Symptoms most commonly reported include dizziness, sensory and visual disturbances, CNS symptoms (including agitation, irritability and emotional lability, sleep disturbances), gastrointestinal effects, sweating, headache and palpitations. It is advised that gradual discontinuation by dose tapering is undertaken (generally  $\geq 4$  weeks);<sup>26</sup> the SmPC for each SSRI may give more specific advice regarding the tapering.<sup>20-25</sup> Because of the long half-life of fluoxetine, withdrawal symptoms are thought less likely to occur, while such symptoms may be more problematic for agents with a short half-life e.g. paroxetine.<sup>9</sup>

**Table 3: Pharmacological properties of the most commonly prescribed\* antidepressant agents<sup>20,34</sup>**

Drug Class** (Mode of Action)	Drug Name***	Effect on Cytochrome P (CYP) 450 system (potential for drug-drug interaction)	Half-life
<b>SSRI</b> ↓reuptake of 5HT (minimal effects on other neurotransmitters)	Citalopram Escitalopram Fluoxetine Paroxetine Sertraline	minimal effect minimal effect inhibitor of CYP 2D6, 3A4++ inhibitor of CYP 2D6++ dose-related inhibitor of CYP 2D6	36 hrs 30 hrs 4-6 days 24 hrs 22-36 hrs
<b>SNRI</b> ↓reuptake of 5HT + NA (minimal effects on other neurotransmitters)	Venlafaxine Duloxetine	metabolised by CYP 2D6, 3A4+ moderate inhibitor of CYP 2D6++ (also metabolised by CYP1A2)+	5-11 hrs 8-17 hrs
<b>TCA</b> ↓reuptake of 5HT + NA (plus effects on many other neurotransmitters)	Amitriptyline Doxepin/dothiepin Trimipramine	metabolised by CYP 2D6, 2C19++ metabolised by CYP 2D6++ metabolised by CYP 2D6++	9-25 hrs 14-45 hrs 7-23 hrs
<b>Other agents</b> ↑5HT + NA neurotransmitter activity (plus antagonist effects at histamine receptors)	Mirtazapine	minimal effect	20-24 hrs
↑NA activity (not by reuptake)	Trazodone	minimal effect	5-13 hrs

\*includes only those agents with > 20,000 prescriptions recorded in the HSE-PCRS database from Nov 2009 – Oct 2010\*

\*\* SSRI = selective serotonin reuptake inhibitors; SNRI = serotonin and noradrenaline reuptake inhibitors; TCA = tricyclic antidepressants; 5HT = serotonin; NA = noradrenaline

\*\*\* Check the individual Summary of Product Characteristics (SmPC) for full information on each medicine at [www.imb.ie](http://www.imb.ie) or [www.medicines.ie](http://www.medicines.ie)

+ caution recommended if prescribing with another drug using the same CYP enzyme

++ moderate - strong potential for drug-drug interactions with other drugs using the same CYP enzyme

**Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)** are known to inhibit the reuptake of both 5HT and NA.<sup>27,28</sup> However, they differ from TCAs in that they have limited effect on other neurotransmitter systems, which reduces their toxicity.<sup>9,11</sup> Like the SSRIs, they are readily absorbed, are metabolised via the cytochrome P450 system and are excreted via the kidney. The currently available agents in this class have low-moderate potential for drug-drug interaction (see Table 3) and each has a much shorter half-life compared with SSRIs.

The **adverse drug reaction** profile of SNRIs has many similarities to that seen with SSRIs including GI problems (nausea, reduced appetite, constipation but not bleeding), headache and sexual dysfunction.<sup>27,28</sup> As with SSRIs, many of the ADRs appear early on in treatment and resolve spontaneously. In addition, **hyponatraemia** and **withdrawal symptoms** have also been reported. **Venlafaxine has been associated with dose-related increased blood pressure and increased heart rate**, especially at higher doses and it should be prescribed with caution in patients at risk of cardiac arrhythmias.<sup>27</sup>

**Tricyclic Antidepressants (TCAs)** were the antidepressants of first choice before the arrival of the more selective SSRI and SNRI agents.<sup>9</sup> In addition to inhibiting the reuptake of 5HT and NA they also have effects on other neurotransmitter systems which result in toxicity. They are well absorbed, metabolised by the cytochrome P450 system, and have varying half-lives (see Table 3). Pharmacokinetic **drug interactions with other drugs using the same cytochrome isoenzyme system are common** and may result in unexpected levels of TCA.<sup>29,31</sup>

**Adverse drug reactions** include dry mouth, blurred vision, constipation, urinary retention, sweating and weight gain (**anticholinergic effects**), sedation (**antihistamine effects**) and orthostatic hypotension (**alpha-adrenergic antagonistic effects**). Their effects on multiple neurotransmitters may result in **cardiac toxicity** and they are reported to be **arrhythmogenic at high doses**.<sup>11</sup> Patients should be considered for ECG examination before starting a TCA and use should be avoided in those with an underlying cardiac disorder or those considered at risk of an overdose. TCAs are also associated with an **increased risk of seizures**, therefore use should be avoided in patients with epilepsy.<sup>1,26</sup> They also have a prominent **withdrawal syndrome** characterised by cholinergic rebound and flu-like symptoms.<sup>11,26</sup> Therefore, these agents are now viewed as second-line treatment options for most patients. Care must be taken to start treatment at the lowest dose and titrate upwards according to response and development of ADRs.

**Other Agents.** These chemically-distinct agents appear to exert their antidepressant effect via differing effects on neurotransmission. They are all readily absorbed after administration. **Mirtazapine** (see Table 3) is not usually associated with pharmacokinetic interactions and it is less likely to be associated with GI effects and sexual dysfunction compared with SSRIs and SNRIs; however it is associated with sedation and weight gain.<sup>1,32</sup> **Trazodone** is also associated with sedation (antihistamine effects); other common ADRs reported include postural hypotension, tachycardia and GI upset.<sup>33</sup> Less frequently used agents include reboxetine, mianserin and agomelatine; all are reported to increase NA neurotransmission via different mechanisms. [Full prescribing information available in the individual SmPCs at [www.imb.ie](http://www.imb.ie); [www.medicines.ie](http://www.medicines.ie)].<sup>35-37</sup>

**Monoamine Oxidase Inhibitors (MAOIs)** irreversibly bind to monoamine oxidase which reduces the breakdown of 5HT and NA, thereby increasing neurotransmission. Strict dietary restrictions were required with the original agents in the class (such as tranylcypromine)<sup>38</sup> because patients were unable to metabolise any tyramine-containing foods such as cheese etc, due to the potential for a hypertensive crisis with concomitant use. These are rarely prescribed in current practice and ideally should be under specialist supervision; moclobemide (a reversible inhibitor of MAO-A, which doesn't require dietary restrictions) may be useful for atypical depression.<sup>9,39</sup> **Care must be taken when switching between use of an MAOI and other antidepressants because of the risk of serotonin syndrome.**

### EFFICACY OF ANTIDEPRESSANT AGENTS

Currently available antidepressants have been shown to be significantly more effective than placebo in reducing the symptoms of depression (as measured by standard tools such as the Hamilton Depression Scale (HDRS) or Montgomery-Asberg Depression Scale (MADRS)) in randomised controlled trials (RCTs) of varying duration (6-24 weeks).<sup>9</sup> Longer term efficacy has been shown in open studies for periods of up to one year for some antidepressants.<sup>9</sup>

Several reviews have compared the efficacy of the different classes of antidepressants. There are methodological problems with many of these reviews, as they include studies of different duration and not all source data are available. In addition several papers have highlighted the issue of publication bias whereby studies of antidepressants with positive findings are more likely to be published while negative studies are rarely published.<sup>34,40,41</sup> A **review of head-to-head RCTs comparing SSRIs with SNRIs** reported a 6% additional efficacy for SNRIs but with a higher rate of drop-outs due to ADRs.<sup>42</sup> A meta-analysis (comparing the efficacy of SSRIs, SNRIs, mirtazapine and reboxetine) showed some additional clinical benefit for escitalopram, sertraline, venlafaxine and mirtazapine compared with the rest of the agents studied;<sup>43</sup> reboxetine was noted to be significantly less efficacious than the rest of the group. An extensive comparative review of the safety and efficacy of the currently available antidepressants undertaken by the UK National Institute for Health and Clinical Excellence (NICE) **has concluded that antidepressants are more effective than placebo on efficacy outcomes but produce more side effects.**<sup>9</sup> In particular TCAs were noted to be less well tolerated than other antidepressants in the outpatient setting. The NICE review also suggested **there is some evidence that antidepressants are less effective in people with less severe symptoms.**

### USE OF ANTIDEPRESSANTS IN PRIMARY CARE

Guidelines on the management of depression in adults recommend use of antidepressants for those with levels of depression greater than “mild” (as defined by the diagnostic criteria listed in Table 1). **A Cochrane review reported significant improvement for both SSRIs and TCAs, compared with placebo, for the treatment of depression greater than minor depression in primary care,**<sup>44</sup> but could not comment on the appropriate duration of treatment. Patients in the TCA group were more likely to suffer ADRs. When deciding on the drug of first choice the prescriber should take into account the patient’s concomitant diseases and medications (with respect to contraindications for use and risk of pharmacodynamic / pharmacokinetic interactions).<sup>26</sup> **Some guidelines currently recommend the use of SSRIs as first-line pharmacotherapy for depression.**<sup>9,26</sup> However, there is marked inter-individual variation in tolerability, which is not easily predicted by knowledge of a drug’s likely adverse effect profile;<sup>26</sup> therefore **patients should be closely monitored during the first weeks of treatment** in order to look for evidence of benefit (which should be present 1-2 weeks after starting treatment) or the emergence of toxicity (especially with respect to suicidal ideation in those <25 years old). At least 20% of patients do not respond to the first treatment regimen; therefore if no improvement has occurred after 4 weeks the dose should be increased gradually to the maximal tolerated dose (if applicable) and if this is not effective, a switch to an alternative therapy should be considered.<sup>19,26</sup> It is reported that up to 50% of patients will respond to a second treatment, irrespective of whether it is from the same class as the first drug or comes from another class of antidepressant.<sup>9,19,45</sup> Most guidelines recommend that once the patient is on optimal antidepressant therapy, treatment should be continued for 6-9 months (this is to cover the assumed duration of most single untreated episodes).<sup>26,46</sup> Patients who have responded to treatment should be encouraged and supported to continue treatment for the full prescribed period.<sup>4</sup> In patients who have had multiple episodes, there is evidence of benefit from maintenance treatment for at least 2 years.<sup>19,46</sup>

### SWITCHING AND/OR STOPPING ANTIDEPRESSANT THERAPY

Switching between antidepressants can be problematic and should be done with caution.<sup>5</sup> **Risks include withdrawal symptoms, serotonin syndrome and pharmacokinetic or pharmacodynamic interactions.** Abrupt withdrawal should usually be avoided. Instead “cross-tapering” is preferred, in which the dose of the ineffective or poorly tolerated drug is slowly reduced while the new drug is slowly introduced. The speed of cross-tapering is best judged on an individual patient tolerability basis (typically over 2-4 weeks) but there are no clear guidelines available.<sup>5,26</sup> **If switching from one SSRI to another,** cross-tapering may not be considered necessary; immediate switching from one SSRI to another in the class may not only be well tolerated but may also reduce the risk of withdrawal symptoms.<sup>26</sup> However, in the case of an **SSRI with a long half-life** (for example fluoxetine) a wash-out period may be recommended (see Table 3).<sup>26</sup> Conversely, co-administration of some antidepressants is absolutely contra-indicated even if cross-tapering is taken into account (e.g. when one of the antidepressants is an MAOI). [The NMIC can often provide information on switching between specific antidepressants]

**Serotonin syndrome** is a potentially life-threatening adverse reaction that may result from the therapeutic use of a serotonin-enhancing antidepressant, after an interaction between two or more serotonin-enhancing medicines (e.g. use of **SSRI with a MAOI, tramadol or a triptan**), or **following an overdose** of a serotonin-enhancing medicine.<sup>5,11</sup> **Concomitant use of a medicine that inhibits the metabolism of a serotonin-enhancing antidepressant** (e.g. SSRI) may also precipitate the serotonin syndrome. Signs and symptoms range from mild diarrhoea and tremor to restlessness, myoclonus, confusion, convulsions and death.<sup>5,26</sup> Onset is usually quick (within hours in the majority of cases). Treatment involves removing the putative medicine(s) immediately and giving supportive care. Recovery should be complete within 24 hours after discontinuation of the medicine(s).

**Stopping therapy.** As noted previously, all antidepressants have the potential to cause withdrawal phenomena. Therefore it is recommended that, when taken continuously for  $\geq 6$  weeks, an **antidepressant should not be stopped abruptly unless a serious adverse event has occurred.** Slow tapering (over  $\geq 4$  weeks) is recommended to reduce the incidence and/or severity of such phenomena.<sup>19,26</sup>

### TREATMENT STRATEGY FOR DEPRESSION IN PRIMARY CARE: SUMMARY

- Clinical diagnosis should take into account both the symptoms of depression and their impact on the patient’s normal functioning. The prescriber should also ensure that the patient is not taking a medicine potentially associated with depression
- Antidepressants are indicated for moderate - severe depressive conditions or for mild depression in those with a past history of depression or with depressive symptoms for a long time
- Choice of antidepressant should be individualised according to the patient’s existing medical status and concomitant medications (because of the risk of drug-drug interactions, see Table 3)
- Once initiated, treatment should be closely monitored; benefit should be evident after 1 - 2 weeks
- If no effect is seen by 4 weeks, gradually increase dosage to maximal tolerated recommended dose. If still not effective, switch to another drug in same class or to another class; “cross-tapering” is recommended especially when switching to a drug of another class or to a drug with a long half-life within the same class (see Table 3)
- Specialist referral is indicated for refractory depression or for a patient with multiple co-morbidities
- Treatment should be continued for 6 - 9 months for a single episode and up to 2 years for recurrent depression / multiple episodes of depression
- All antidepressants have the potential to cause withdrawal phenomena therefore withdrawal should be tapered, typically over  $\geq 4$  weeks
- The NMIC can provide information in response to specific queries on antidepressants for individual patients.

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