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THE MANAGEMENT OF DEPRESSION

- **It is estimated that 1 in 10 patients present with depressive symptoms in primary care**
- **Non-pharmacological therapy and symptom monitoring is usually recommended as first-line treatment for patients with mild depression**
- **Antidepressants are usually recommended as first-line treatment for patients with moderate and severe major depression**
- **The choice of antidepressant should be based on factors including tolerability, patient's previous experience with antidepressants, co-morbidities, concomitant medication, suicide risk and cost**

INTRODUCTION

Depression is a common and heterogeneous condition that globally affects more than 300 million people. It is the leading cause of disability worldwide.[1] **Depression is associated with increased morbidity and mortality. It has a major impact on quality of life for patients and their families.**[2] Depression can occur at any age, however most patients with depression present in their twenties, with a second peak occurring in patients in their fifties.[2,3] The lifetime prevalence of depression is approximately 15%.[4,5] It is twice as common in females as in males.[2,3,6] Depression is frequently associated with other chronic medical conditions including heart failure, hypertension, diabetes, coronary artery disease and chronic obstructive pulmonary disease.[2,6,7] Patients with depression may also have co-morbid psychiatric conditions including anxiety disorders and substance use disorders.[2,3,6] **The vast majority of patients with depression are treated in primary care, where it is estimated that 1 in 10 patients present with depressive symptoms.**[5,8] There is a high rate of under-diagnosis of depression (30 to 50%) in both primary care and other medical settings; reasons for this include lack of insight and motivation by patients to consult their doctor about the condition, fear of stigma associated with a psychiatric diagnosis and lack of time or training on the part of the doctor.[4,6] **Depression is a major risk factor for both attempted and completed suicide**; it is estimated that almost half of adults who complete suicide have had contact with primary care services in the month before death.[2] **Most patients will respond to treatment, however at least half will have a further episode of depression after the first and 10% will follow a persistent or chronic course.**[7]

There are two distinct types of depressive syndrome; unipolar depression in which the mood changes are always in the same direction, and bipolar disorder in which depressive symptoms alternate with mania.[9] **The lifetime prevalence of unipolar depression is 10 to 15 times higher than bipolar disorder.**[5] The majority of patients with bipolar disorder will experience several episodes of depression prior to developing mania.[5]

This, the first of 2 bulletins on the management of unipolar depression in adults, will review the diagnosis, non-pharmacological and pharmacological management of depression. The second bulletin will deal with some practical aspects of the pharmacological management of depression.

EPIDEMIOLOGY

The pathophysiology of depression remains incompletely understood. The monoamine hypothesis suggests that decreased functioning of neurotransmitters (e.g. serotonin, noradrenaline and dopamine) at key sites in the brain are implicated, however other mechanisms are also thought to be involved.[3,9,10] Risk factors for depression include a previous episode of depression, history of mental illness, history of substance abuse, family history of depression or suicide, chronic medical illness, unemployment, poor social support systems, a recent stressful life event and intimate partner's violence.[2,3] In addition, **certain medications (e.g. beta-blockers, glucocorticoids, statins, oral contraceptives, levodopa, opioids and some antibiotics) may contribute to depression.**[2,3]

DIAGNOSIS OF DEPRESSION

The use of self-reported questionnaires may help to identify patients who present with symptoms suggestive of depression or those at high risk of depression e.g. previous history of depression or those with significant physical illness.[2,11] The Patient Health Questionnaire [PHQ], is one of the most commonly used tools for screening depression in primary care.[12] The PHQ consists of a two item (PHQ-2) and a nine item (PHQ-9) questionnaire and a 2 step approach can be used; first screening with the PHQ-2 and then confirming with the PHQ-9 (see useful resources at the end of this bulletin).[2] Screening scores however should not be used in isolation; a positive screen for depressive symptoms should trigger additional assessment based on the criteria in the Diagnostic and Statistical Manual of Mental Disorder [5th Edition (DSM-V) (see table 1)].[2,13] Assessment should include a detailed history (e.g. current and past medical history, family history, social history, medication), physical examination and laboratory evaluation (e.g. full blood count, renal, hepatic and thyroid function).[2,14] It is useful to distinguish episodic depression which lasts <2 years, from persistent or chronic depression that lasts ≥2 years.[15]

Table 1: DSM-V criteria for major depressive disorder[16]

Criteria – five or more of the following symptoms during the same 2 week period, with the symptoms representing a change from previous functioning and with at least one of the symptoms being either depressed mood or loss of interest or pleasure in activities of daily life 1. Depressed mood for most of the day, nearly every day, as indicated by either the patient or an observation made by others. 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day. 3. Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day. 4. Insomnia or hypersomnia nearly every day. 5. Psychomotor agitation or retardation nearly every day. 6. Fatigue or loss of energy nearly every day. 7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day. 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day. 9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
Severity of depression • *Mild depression*: few, if any, symptoms in excess of those required to make the diagnosis are present, the intensity of the symptoms is distressing but manageable, and the symptoms result in minor impairment in social or occupational function • *Moderate depression*: the number of symptoms, intensity of symptoms, functional impairment, or all of these variables are between those specified for "mild" and "severe" • *Severe depression*: the number of symptoms is substantially in excess of that required to make the diagnosis, the intensity of the symptoms is seriously distressing and unmanageable, and the symptoms markedly interfere with social and occupational functioning

Distinguishing between bipolar disorder and unipolar depression is important, as **the use of antidepressants in bipolar disorder is associated with an increased risk of inducing mania.**[2,3]

As depression is associated with an increased risk of suicidal ideation and acts, **the risk of suicide needs to be assessed and monitored in patients treated for depression.**[2,17] Patients should be assessed for risk of suicide with a focus on 1) suicidal thoughts, 2) plans for suicide and 3) suicidal intent.[2]

MANAGEMENT

The management of depression should be individualised to the patient, who should be involved in the decision making process; a patient's previous response to treatment should be considered when deciding on the type of intervention.[13,18] The patient should be informed of the advantages and disadvantages of the available interventions and the expected outcomes.[8,13,18]

Psychological therapies are usually recommended as first-line treatment for patients with mild depression.[2,8,13,18,19] Pharmacological therapy is usually recommended first-line for patients with moderate and severe depression and may be considered for patients with mild depression who have a past history of moderate or severe depression, or who present with sub-threshold symptoms that have been present for ≥2 years or have persistent sub-threshold depressive symptoms or mild depression after other interventions.[3,6,7,8,11,13,19] The combination of psychotherapy and pharmacotherapy has been found to be more effective than either intervention alone and is usually recommended for patients with moderate and severe depression.[13,15,20-22]

Management of depression should include assessing the patient's response to treatment in terms of the effectiveness of the intervention, adverse effects and patient adherence. Response to treatment can be assessed by using rating scales such as the Hamilton Rating Scale for Depression (HAM-D) and the PHQ-9;[5,7,23] a clinical response can be defined as a 50% reduction on the scale while remission has a specific cut-off (e.g. ≤7 on the HAM-D and <5 on the PHQ-9).[23] However, reliance should not be placed only on rating scales; clinical assessment and judgement remains the cornerstone of management.

Guidelines recommend referral to specialist mental health services for patients including those where 1) there is a significant perceived risk of harm to the patient or others, 2) the patient has psychotic symptoms or bipolar disorder, and 3) those with treatment resistant depression (where there has been ≥2 interventions to treat depression).[6,8,11,18] There are a number of resources listed at the end of this bulletin which may be useful in managing depression.

NON-PHARMACOLOGICAL THERAPIES

Many non-pharmacological therapies are used in the treatment of depression. Psychological therapy (also known as psychoeducation) including cognitive behavioural therapy (CBT), behavioural activation (BA) and interpersonal psychotherapy (IPT) are effective for depression, and are recommended as first-line treatment for mild depression.[3,6,21,24-26] Evidence suggests that psychological (e.g. CBT, BA and IPT) and pharmacological interventions are of comparable efficacy for depression of mild to moderate severity.[5,6,20,21,24,27,28] The type of psychological therapy should be individualised to the patient. Access to psychological services may be limited. Low intensity treatments (e.g. guided self-help and internet CBT) require minimal input from a trained professional, while high intensity treatments (e.g. CBT, BA and IPT) should be administered by appropriately trained professionals.[6,8]

PHARMACOLOGICAL THERAPIES

Antidepressants are effective in the acute treatment of moderate and severe depression in adults;[4,6,19,23,29-32] **they have response rates of approximately 48 to 50% compared to 30 to 32% with placebo.**[6] The presumed primary mode of action for most antidepressants is to potentiate either directly or indirectly, the actions of noradrenaline and/or serotonin (5-HT).[9,10,19] While these changes occur relatively quickly, clinical improvement and therapeutic effects may take a few weeks;[19] patients need to be carefully educated about this.

Antidepressants include selective serotonin re-uptake inhibitors (SSRIs), serotonin and noradrenaline re-uptake inhibitors (SNRIs), other re-uptake inhibitors and atypical antidepressants, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).

In terms of efficacy, there is little evidence to recommend the selection of one antidepressant over another for

depression.[3,6,17,23,29,33-42] **In general SSRIs are usually recommended as first-line antidepressants.**[6,8,11,13,18,43,44] They are better tolerated and safer in overdose than other antidepressants.[6,8,47] TCAs which have a greater adverse effect profile are generally reserved for patients when first-line antidepressants have failed.[6,23,33,43] **MAOIs should only be initiated by physicians with expertise in their use.**[6,23,33,43] The choice of antidepressant should consider 1) the individual patient, 2) the presence of concomitant disease and medication, 3) previous response to antidepressant therapy and 4) suicide risk.

Table 2 summarises the mode of action and special precautions to be considered for the antidepressants used in primary care in Ireland. Full prescribing information is available in the Summary of Product Characteristics (SmPC). Drug interactions will be discussed in more detail in the next bulletin (NMIC 2019; Vol 25: Number 3).

Table 2: Mode of action and special precautions associated with antidepressants used in primary care[10,37,45-61]

Drug	Mode of action	Special Precautions include*
Selective serotonin re-uptake inhibitors (SSRIs)		
Citalopram **Escitalopram** **Fluoxetine** **Paroxetine** **Sertraline** **Fluvoxamine**	Inhibits serotonin re-uptake	C/I with MAOIs, C/I or caution in patients with QT prolongation and drugs known to prolong QT interval. Monitor for: ↑ risks of suicidal thoughts, self-harm and suicide, serotonin syndrome, QT prolongation, hyponatraemia, haemorrhage, seizures, altered diabetes control, narrow-angle glaucoma, discontinuation symptoms, paradoxical anxiety (in first few weeks) **Pharmacokinetics*:** all SSRIs inhibit CYP P450 but to varying degrees; fluoxetine, paroxetine and fluvoxamine have the greatest potential to cause drug interactions
Serotonin and noradrenaline re-uptake inhibitors (SNRIs)		
Venlafaxine **Duloxetine**	Inhibits serotonin and noradrenaline re-uptake	C/I with MAOIs. Monitor for: ↑ risks of suicidal thoughts, self-harm and suicide, serotonin syndrome, QT prolongation, hyponatraemia, haemorrhage, seizures, altered diabetes control, narrow-angle glaucoma, increased blood pressure and heart rate, discontinuation symptoms, ↑ LFTs with duloxetine **Pharmacokinetics *:** venlafaxine metabolised by CYP2D6 and 3A4; however has lower potential for CYP2D6 and 3A4 inhibition. Duloxetine metabolised by CYP1A2 and 2D6
Other reuptake inhibitors and/or atypical antidepressants		
Mirtazapine	Presynaptic alpha$_2$-adrenoceptor antagonist which ↑ central noradrenergic and serotonergic neurotransmission	C/I with MAOIs. Monitor for: ↑ risks of suicidal thoughts, self-harm and suicide, serotonin syndrome, QT prolongation, hyponatraemia, seizures, narrow-angle glaucoma, altered diabetes control, discontinuation symptoms, bone marrow depression, monitor in hepatic and renal impairment **Pharmacokinetics*** – mainly metabolised by CYP2D6 and 1A2
Trazodone	Serotonin antagonist and re-uptake inhibitor	C/I with acute myocardial infarction, alcohol and hypnotic intoxication. Monitor for: ↑ risks of suicidal thoughts, self-harm and suicide, serotonin syndrome, QT prolongation, narrow-angle glaucoma, ↑ LFTs, bone marrow suppression, priapism, orthostatic hypotension and anticholinergic effects especially the elderly. Monitor patients with epilepsy, hepatic or renal impairment, cardiac disease, hyperthyroidism, micturition disorders **Pharmacokinetics*** –metabolised by CYP2D6 and inhibits 3A4
Reboxetine	Noradrenaline re-uptake inhibitor	Precautions with use of MAOIs. Monitor for: ↑ risk of suicidal thoughts, self-harm and suicide, close supervision in patients with urinary retention, prostatic hypertrophy, glaucoma and history of cardiac disease, risk of orthostatic hypotension at higher doses, narrow-angle glaucoma **Pharmacokinetics*** – metabolised by and inhibits CYP2D6 and 3A4
Agomelatine	Melatonin agonist (MT_1 and MT_2 receptors) and weak 5-HT_{2c} antagonist	C/I- concomitant use of potent CYP1A2 inhibitors, hepatic impairment. Monitor for : ↑ risk of suicidal thoughts, self-harm and suicide, ↑ risk of hepatic injury (monitoring of LFTs required) **Pharmacokinetics*** – metabolised by CYP1A2 and 2C9/19
Vortioxetine	Inhibits serotonin re-uptake and 5-HT transporter	C/I with MAOIs. Monitor for ↑ risks of suicidal thoughts, self-harm and suicide, serotonin syndrome, hyponatraemia, haemorrhage, seizures. Caution in patients with hepatic or renal impairment **Pharmacokinetics*** – metabolised by CYP2D6 and to a minor extent by 3A4/5 and 2C9
Tricyclic antidepressants (TCAs)		
Clomipramine **Dosulepin** **Lofepramine** **Trimipramine** **Amitriptyline**	Inhibit noradrenaline and serotonin re-uptake; also inhibits α-adrenergic, histaminic and muscarinic receptors	C/I after recent MI and in patients with arrhythmia, those on MAOIs, severe liver disease. Risk of arrhythmias and hypotension at high dose and in patients with pre-existing cardiac disease at normal dose, monitor for increased risk of suicidal thoughts, self-harm and suicide, altered glycaemic control in diabetics, hyperpyrexia, discontinuation symptoms, risks of QT prolongation, orthostatic hypotension (in the elderly), use with caution in patients with convulsive disorders, hyperthyroidism, urinary retention, prostatic hypertrophy, advanced hepatic or cardiovascular disease, pyloric stenosis, paralytic ileus, risk of narrow-angle glaucoma **Pharmacokinetics*** – TCAs are metabolised by a range of P450 enzymes e.g. CYP1A2, 2D6 and 3A4

* see full prescribing information available in the Summary of Product Characteristics (SmPC);
C/I - contraindicated; MAOIs - monoamine oxidase inhibitors; SSRI- selective serotonin reuptake inhibitor; CYP – cytochrome P450; LFTs – liver function tests; TCAs – tricyclic antidepressants

Selective serotonin re-uptake inhibitors (SSRIs) have similar efficacy in treating depression as other types of antidepressants.[35,40,41,62-65] **SSRIs are usually recommended as first choice for treatment of depression**; they are associated with less anticholinergic side effects, are safer in overdose and are less cardiotoxic than TCAs.[8,10,44] Adverse effects include headache, anxiety, gastrointestinal (GI) effects, fatigue, sexual dysfunction, sleep disturbances and bleeding.[7,8,10] Risk factors for bleeding associated with SSRIs include those aged >65 years, hypertension, alcohol misuse, coronary artery disease, history of stroke, GI bleeding, renal disease and co-administration of medications such as aspirin, NSAIDs and anticoagulants.[7,66]

Serotonin and noradrenaline re-uptake inhibitors (SNRIs) may be an option in patients in whom SSRIs are ineffective.[10,42] Adverse effects are similar to the SSRIs. The SNRIs tend to be less well tolerated than SSRIs but are better tolerated than TCAs.[6,7]

Other re-uptake inhibitors and/or atypical antidepressants have actions at several different sites (see table 2), with similar efficacy to other antidepressants.[6,36,38,67-69] *Mirtazapine* has a faster onset of action than other antidepressants;

it may be an option in patients where a more prompt onset of action is required.[10,67] It is not associated with the anticholinergic side effects of the TCAs or sexual dysfunction seen with SSRIs, however mirtazapine is associated with sedation and weight gain (which may be useful therapeutically).[10,53] *Trazodone* is sedating and has been associated with priapism.[10,54] *Reboxetine* is associated with dizziness, hypotension, GI effects, tachycardia, urinary retention, and narrow angle glaucoma.[55] *Agomelatine* is not associated with discontinuation symptoms but it is associated with hepatotoxicity; **liver function needs to be monitored at baseline, at 3 weeks, 6 weeks, 3 months and 6 months**.[6,89] Adverse effects include headache, dizziness, somnolence, fatigue and nausea.[56] Vortioxetine which has a long half-life is not associated with discontinuation symptoms.[6,68] Adverse effects include nausea, constipation and headache.[68] Vortioxetine is recommended as an option for treating major depressive episodes in adults whose condition has responded inadequately to 2 antidepressants within the current episode.[43]

Tricyclic antidepressants (TCAs) are effective in the treatment of depression,[70] however they are generally not used first-line due to the risk of adverse effects associated with their use.[7,13] TCAs may exacerbate certain medical conditions such as benign prostatic hyperplasia, epilepsy, and pre-existing arrhythmias.[10] **TCAs may affect cardiac conduction and precipitate life threatening arrhythmias in an overdose situation.**[8,10] Adverse effects include blurred vision, dry mouth, urinary retention, sinus tachycardia, constipation, sedation and aggravation of narrow-angle glaucoma.[10] Lofepramine appears to cause fewer adverse effects than other TCAs.[6]

Monoamine oxidase inhibitors (MAOIs) are effective for the treatment of depression however, they are **usually used under specialist supervision,** due to the dangers of dietary and drug interactions. They are **reserved for patients with depression who are unresponsive to other treatments**.[10,44,71] *Tranylcypromine* is an irreversible non-selective long-acting MAOI that can interact with a wide range of medications and tyramine-containing foods (e.g. cheese) resulting in hypertensive crisis.[6,10] Patients prescribed MAOIs must be educated to avoid tyramine-containing foods.[10] Adverse effects of MAOIs include anticholinergic side effects, hypotension, nausea and insomnia.[9] **The use of MAOIs, such as tranylcypromine with other antidepressants is contraindicated, due to an increased risk of serotonin syndrome.**[10,44] *Moclobemide* is a reversible selective short-acting MAOI with less severe drug and food interactions, which are unlikely to occur under normal conditions.[9,37] Caution is advised when prescribing moclobemide with drugs that enhance serotonin (e.g. SSRIs and TCAs).[72]

SUMMARY

In summary, depression is a condition that is commonly seen in primary care. Psychoeducation is a key first step in the management of depression. **Non-pharmacological therapy and symptom monitoring is recommended as first-line treatment for patients with mild depression**. Antidepressants are usually recommended as first-line treatment for patients with moderate and severe major depression. A combination of non-pharmacological and pharmacotherapy has been found to be more effective than either intervention alone and is usually recommended for patients with moderate and severe depression.

The practical aspects of pharmacological therapy will be dealt with in the next bulletin. The use of antidepressants in pregnancy, was covered in a previous NMIC bulletin on "Prescribing in Pregnancy (2): Frequently Asked Questions" (NMIC 2018;Vol 24: Number 3) available on our website www.nmic.ie.

Useful resources

- Patient Health Questionnaire (PHQ) – tool for screening and assessing response to treatment available on www.icgp-education.ie/depression/PHQ-9-scoring-pearse.pdf
- Aware is a voluntary organisation which provides information, education and support for patients with depression www.aware.ie
- Computerised CBT available on www.getselfhelp.co.uk/
- Counselling in primary care (CIPC) – HSE National Counselling Service information available on ww.hse.ie/eng/services/list/4/mental-health-services/counsellingpc/
- The British Association for Psychopharmacology has evidence-based guidelines for treating depressive disorders with antidepressants (2015) available on https://www.bap.org.uk/pdfs/BAP_Guidelines-Antidepressants.pdf
- Choice and Medication website for HSE Mental Health Services - patient information service on www.choiceandmedication.org/ireland
- The Summary of Product Characteristics (SmPC) for individual medicines is available on www.hpra.ie and www.medicines.ie
- National Framework for Recovery in Mental Health – information available on www.hse.ie
- The NMIC clinical enquiry answering service is available to deal with specific enquiries on use of antidepressants: e-mail nmic@stjames.ie or telephone 01 4730589

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