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PHARMACOTHERAPY OF DEPRESSION: PRACTICAL ASPECTS

- **Following a single episode of depression, antidepressants should be continued for at least 6 to 9 months after resolution of symptoms**
- **In patients with a history of recurrent depression, antidepressants should be continued for at least 2 years**
- **Patients should be warned and monitored about an increased risk of suicidal thoughts and acts associated with antidepressants, especially in those aged <25 years**
- **Antidepressants should not be discontinued abruptly due to a risk of discontinuation symptoms**

PRACTICAL ASPECTS OF PHARMACOLOGICAL THERAPY

Antidepressants are indicated for patients with moderate and severe depression.[1-5] Although not routinely indicated for patients with mild depression, antidepressants may be considered in those with 1) a past history of moderate or severe depression, 2) sub-threshold symptoms that have been present for ≥2 years or 3) have persistent sub-threshold depressive symptoms or mild depression after other interventions.[1-7]

There are a number of factors which should be discussed with the patient prior to commencing therapy as summarised in table 1.

Table 1: Factors to discuss with the patient prior to commencing antidepressants [1]

The patient should be informed of:

- the benefits and risks associated with the antidepressant
- the likely time for the antidepressant to reach the full therapeutic effect
- the potential adverse effects (especially those that only occur at the start of treatment e.g. nausea)
- the risks of potential drug interactions
- the possibility of worsening or emerging suicidal thoughts after commencing treatment
- the importance of adhering to treatment
- the duration of treatment
- the risk of discontinuation symptoms on stopping treatment abruptly (especially for those with a shorter half-life such as paroxetine and venlafaxine)

CHOICE OF ANTIDEPRESSANT DRUG

Factors to consider when choosing an antidepressant for an individual patient include the patient's previous response and tolerability to antidepressants, co-morbidities, concomitant medication, co-morbid psychiatric disorder, suicide risk, likely adverse effect profile and cost of the antidepressant (see table 2).[6,8-10]

Selective serotonin re-uptake inhibitors (SSRIs) are usually indicated as first-line antidepressants.[1,5,6,11,12] Other antidepressants such as serotonin and noradrenaline re-uptake inhibitors (SNRIs) and other re-uptake inhibitors may also be considered.[6,8] There is evidence for the safety of sertraline and mirtazapine in patients at risk of arrhythmia due to recent myocardial infarction.[6,12] The choice of antidepressant also depends on the patient's symptoms. For example, patients with co-existing anxiety are often treated with antidepressants associated with increased sedation (e.g. mirtazapine, paroxetine and trazodone), which are also helpful for patients with insomnia.[7,10] Tricyclic antidepressants (TCAs) such as lofepramine are generally reserved for patients who are unresponsive to other antidepressants. TCAs should be avoided in patients with coronary artery disease; lofepramine seems to be less cardiotoxic than other TCAs.[1] **Non-reversible MAOIs should only be used under specialist supervision.**[6]

Adverse effects occur in up to 63% of patients prescribed antidepressants; these include constipation, diarrhoea, dizziness, headache, insomnia, nausea, sexual dysfunction and somnolence.[10] There are differences in the adverse effect profiles of the different antidepressants, which may influence the choice of antidepressant for an individual patient; in addition there is marked inter-individual variation in tolerability to different antidepressants (see table 2).[1] Antidepressants associated with increased weight gain include paroxetine and mirtazapine.[1,6,10] Some adverse effects may only occur at the start of treatment e.g. nausea associated with SSRIs and SNRIs starts almost immediately and lasts on average for a week, while other side effects may persist for longer (e.g. sexual dysfunction).[6,10] This may impact on adherence to therapy in patients requiring long-term medication.[6,10] Epidemiological studies have reported an increased risk of falls and fractures associated with antidepressants (e.g. TCAs and SSRIs) in adults aged ≥50 years; the mechanism for this is unknown.[8,13-18]

Table 2 provides the relative adverse effects and monthly costs (December 2018) of antidepressants used in primary care.[1,8,19]

Table 2: Relative adverse effects and costs* of antidepressants[1,8,19]

Drug	Relative adverse effects							Cost per month* (Dec 2018)
	Sedation	Postural hypotension	Cardiac conduction disturbance	Anticholinergic effects	Nausea/ vomiting	GI bleed	Sexual dysfunction	Defined daily dose
Citalopram	-	-	+	-	++	++	+++	€1.95
Escitalopram	-	-	+	-	++	++	+++	€3.36
Fluoxetine	-	-	-	-	++	++	+++	€3.08
Paroxetine	+	-	-	+	++	+++	+++	€6.16
Sertraline	-	-	-	-	++	+++	+++	€3.08
Fluvoxamine	+	-	-	-	+++	#	+++	€13.80
Venlafaxine	-	-	+	-	+++	+	+++	€3.36
Duloxetine	-	-	-	-	++	+	++	€5.61
Mirtazapine	+++	+	-	+	+	+	-	€4.48
Trazodone	+++	+	+	+	+	+++	+	€12.83
Reboxetine	+	-	-	+	+	#	+	€25.30
Agomelatine	+	-	-	-	-	#	-	€15.43
Vortioxetine	-	+	-	-	++	#	++	€17.09
Clomipramine	++	+++	+++	++	++	+++	+++	€3.53
Dosulepin	+++	+++	+++	++	+	#	+	€3.91
Lofepramine	+	+	+	++	+	#	+	€12.57
Trimipramine	+++	+++	++	++	+	#	+	€6.21

*-reimbursement cost per month (Defined daily dose) of the reference price or cheapest available preparation (PCRS data from December 2018); *+++- high incidence/severity; ++ moderate, + - low, - - very low/none; # – information not available*
GI – gastrointestinal

Risk of self-harm: Antidepressants have been associated with an **increased risk of suicidal thoughts and acts, especially in adolescents and young adults.[1,6]** This is a complex area and the explanation is unclear.[6,14,20] Overall the available evidence indicates the lack of a specific link between antidepressant use and suicide/suicidal behaviour however there is some evidence of a small increase in non-fatal suicidal ideation/self-harm behaviour in adolescents and adults <25 years.[6,14,20] It is important to note that the absolute risk is small and the most effective way to prevent suicidal thoughts and acts is to treat depression.[1] **The risk seems to be highest in the first month after starting and stopping treatment.[1,6]** Patients should be warned about the risk and patients (especially those <25 years) should be monitored.[1,14]

Toxicity in overdose: Antidepressants are involved in 10 to 20% of drug poisoning deaths in England and Wales.[6] In 2017 the Irish National Poisons Information Centre dealt with enquiries relating to antidepressants including sertraline, escitalopram, citalopram, mirtazapine, venlafaxine, fluoxetine and amitriptyline.[21] In patients with a significant risk of suicide, **the greatest risk of death from overdose is with TCAs (with the exception of lofepramine) and MAOIs;** venlafaxine has a greater risk of death from overdose than SSRIs.[5,6,13] Consideration should be given to limiting the amount of antidepressants available to patients, especially those at risk of suicide.[6,11]

QT prolongation: Antidepressants should be used with care in patients with prolonged QT or when combined with other agents known to prolong QT. Antidepressants such as TCAs, SSRIs (**especially citalopram and escitalopram**), venlafaxine, trazodone and moclobemide are associated with QT prolongation.[1,22-24] These adverse effects are dose-related and rarely occur at therapeutic doses; they may be seen when combined with other drugs known to prolong QT or in cases of overdose.[24] **ECG monitoring should be considered for patients prescribed doses at the higher end of the recommended range, who are prescribed other drugs that may increase the risk and who have other risk factors for prolonged QT** (e.g. bradycardia, hypokalaemia and hypomagnesaemia).[1,25]

Serotonin syndrome or serotonin toxicity is an adverse drug reaction that is caused by excessive central and peripheral serotonergic activity.[12] Serotonin syndrome, which is potentially life-threatening may occur following the 1) initiation, dose escalation, or overdose of a serotonergic drug, 2) **the addition of a serotonergic drug (e.g. use of SSRI with drugs including tramadol, linezolid),** or 3) the replacement of one serotonergic drug by another without allowing a sufficient washout period in-between.[12] **Symptoms of serotonin syndrome** include tachycardia, hyperthermia, diaphoresis, diarrhoea, tremor, hyperreflexia, clonus, myoclonus, rigidity, agitation, confusion and mania.[12] Severe serotonin toxicity, which is a medical emergency, usually occurs with a combination of serotonergic drugs.[12]

Hyponatraemia is a potentially serious adverse effect that is reported with most antidepressants and is associated with increased mortality.[1,12] Hyponatraemia usually occurs within 30 days of commencing treatment; it is reported more frequently with SSRIs and SNRIs than with other antidepressants.[12] All patients prescribed antidepressants should be informed about and observed for signs of hyponatraemia (e.g. dizziness, nausea, lethargy, confusion, cramps, seizures).[1,12] Table 3 includes the most common risk factors for hyponatraemia.

Table 3: Common risk factors for hyponatraemia[1]

Risk factors for hyponatraemia include:

- Older age
- Female gender
- Major surgery
- History of hyponatraemia or a low baseline sodium concentration
- Co-administration with other drugs known to be associated with hyponatraemia e.g. diuretics, NSAIDs, antipsychotics, carbamazepine, cancer chemotherapy, calcium antagonists, ACE inhibitors and laxatives
- Reduced renal function (GFR <50mL/min)
- Medical co-morbidity (e.g. hypothyroidism, diabetes, chronic obstructive pulmonary disease, hypertension, head injury, congestive cardiac failure, cerebrovascular disease)
- Low body weight

The normal range of serum sodium is 136 to 145 mmol/L; **patients with serum sodium <125 mmol/L should be referred to specialist care as there is an increasing risk of life threatening symptoms such as seizures, coma and respiratory arrest**.[1] The antidepressant should be discontinued immediately. Patients with serum sodium >125 mmol/L require daily monitoring of their serum sodium, fluid restriction and possible discontinuation of the antidepressant

however be aware that the patient may experience discontinuation symptoms.[1]

Drug interactions involving antidepressants include pharmacokinetic and pharmacodynamic mechanisms. The individual Summary of Product Characteristics (SmPC) in particular the sections on contra-indications, special precautions and drug interactions should be consulted. It is important to note that the patient may already be on an antidepressant for a non-depression related indication (e.g. chronic pain). *Pharmacokinetic (PK) interactions* mainly involve antidepressants that inhibit or induce cytochrome P450 (CYP) enzymes (e.g. TCAs and SSRIs).[1] The clinical consequences of PK interactions in a patient can be difficult to predict and depends on factors including the degree of enzyme inhibition or induction, the PK properties, the dose of the affected drug, co-administered drugs and the presence of co-morbidities.[1] Some SSRIs are potent inhibitors of individual or multiple CYP pathways.[1] **Clinically relevant drug interactions are usually caused by agents that are potent CYP inhibitors including fluvoxamine (a potent inhibitor of CYP1A2 and CYP2C19), and paroxetine and fluoxetine (potent inhibitors of CYP2D6).**[1,5,6,14] Interactions involving drugs that are moderate CYP inhibitors (e.g. duloxetine and sertraline), are rarely clinically relevant except at higher doses.[6,14] *Pharmacodynamic (PD) interactions* involving SSRIs/SNRIs include increased risk of 1) **serotonin syndrome** with other serotonergic drugs (e.g. tramadol), 2) **bleeding** with other drugs (e.g. NSAIDs, aspirin, anticoagulants), 3) **hyponatraemia** with diuretics and 4) **QT prolongation** with other drugs.[1] Possible PD interactions involving TCAs include increased risk of 1) cardiotoxicity with drugs such as diuretics, 2) sedation with other sedating drugs, 3) anticholinergic effects with other anticholinergic drugs (e.g. antihistamines), 4) hypotension with antihypertensive drugs and 5) serotonin syndrome with other serotonergic drugs.[1] MAOIs can interact with serotonergic drugs causing serotonin syndrome and with sympathomimetic drugs causing hypertensive crisis.[1,6]

Patient monitoring: Patients diagnosed with depression require monitoring for risks of suicide, response to treatment and adherence to therapy;[6] the monitoring interval depends on the individual patient. For patients who are considered to be at increased risk of suicide or aged <25 years, guidelines recommend that the patient ideally is seen 1 week after commencing treatment and then frequently until the risk is no longer clinically important.[4-6] For patients who are not considered to be at increased risk of suicide, some guidelines recommend review 2 weeks after diagnosis, then at regular intervals if the response is good.[5,6]

Response to treatment: The onset of improvement with antidepressants usually occurs in the first 2 weeks, however it may take up to 3 weeks;[1,6,9] remission usually requires 6 weeks of treatment.[9] In patients where no or minimal antidepressant effect is evident after 3 to 4 weeks of treatment, a change in dose or drug should be considered.[1,5,6] **Approximately one third of patients treated for depression do not achieve remission with first-line antidepressants.**[6,26,27] It is important to ensure that the antidepressant is given at the correct dose and to check for adherence, as remission rates decline with successive treatment failure.[6,26,27] Patients with co-morbid medical illness have a poorer response to antidepressants.[6] Interventions to improve adherence to antidepressants include patient education, prompt management of adverse effects and frequent monitoring of progress.[6,9]

Switching of antidepressants may be required if there are intolerable adverse effects (e.g. sexual dysfunction) and/or there has been no improvement in a patient's symptoms on the first antidepressant.[5,6] **Evidence suggests that approximately 50% of patients who do not respond to their first treatment are likely to respond to a second antidepressant irrespective of whether it is from the same class or a different one.**[27] In general, it is recommended to switch within an antidepressant class initially and then to consider a different antidepressant class after more than one failure in a specific class.[5,6]

There is limited data on regimens for switching antidepressants. Direct switching may be reasonable for some regimens e.g. when switching from one SSRI to another;[1,6] their effects are so similar that administration of the second drug is likely to ameliorate the discontinuation effects of the first.[1] Cross-tapering is preferred for other types of switches, for example if changing from an SSRI to mirtazapine, where the dose of the SSRI is slowly reduced while the mirtazapine dose is slowly increased.[1] **Cross tapering is absolutely contraindicated with co-administration of some antidepressants** (e.g. co-administration of a MAOI and an SSRI or a TCA);[1] there is a risk of serotonin syndrome and a washout period is advised.[1]

Duration of treatment: Depression is a relapsing-remitting illness in 50 to 85% of patients. Approximately half of all people who stop their antidepressants on remission will have a relapse within 3 to 6 months.[6,8] Risk factors for relapse include 1) the presence of residual symptoms, 2) the number of previous episodes of depression, 3) the severity and duration of the most recent episode, and 4) co-morbid conditions.[6] Evidence supports continuing treatment for at least 6 months after remission, as this has been shown to reduce the three year likelihood of relapse by 65%.[8] **Patients with a single episode of depression and low risk of relapse should be treated for at least 6 to 9 months after remission.**[1,6] Patients who are at a high risk of relapse (e.g. those who have had >5 lifetime episodes of depression or those who have had ≥2 episodes of depression in the recent past), should continue antidepressants for at least 2 years.[1,6] CBT in addition to medication should be considered for patients with residual symptoms or those at high risk of relapse.[6,26]

Discontinuation symptoms occur in at least a third of patients who stop antidepressants abruptly.[6,8] **Antidepressants which have been taken continuously for ≥6 weeks should not be stopped abruptly.**[1] Symptoms include restlessness, insomnia, unsteadiness, sweating, abdominal symptoms and altered sensations. They usually appear within 5 days of cessation; they may be mild and self-limiting however in some cases they can be severe.[6,8] Symptoms are most likely to occur with antidepressants that have short half-lives (e.g. paroxetine and venlafaxine), while fluoxetine the SSRI with the longest half-life has the lowest association with discontinuation symptoms of all the SSRIs.[3,5,6,8] Agomelatine and vortioxetine do not seem to be associated with discontinuation symptoms.[6,8] For many patients with mild symptoms, explanation and reassurance is often all that is required, however for those who experience more severe discontinuation symptoms, the antidepressant may need to be recommenced and withdrawn more gradually or another antidepressant started from the same class with a longer half-life (e.g. fluoxetine).[6,8] The incidence of discontinuation symptoms can be reduced by gradually withdrawing antidepressants over 4 weeks (not required with fluoxetine).[3,5,6,8] Patients should be informed that discontinuation symptoms may occur if the treatment is stopped suddenly or doses are missed.[5,6]

Table 4 summarises the pharmacological treatment of depression.

Table 4: Summary of pharmacological treatment of depression[1]

Discuss choice of drug with the patient and include: Potential therapeutic effects, including likely time to effect Possible adverse effects Likelihood of discontinuation symptoms Suggest SSRI as first choice		
↓	↓	↓
Start antidepressant Titrate if necessary to therapeutic dose Assess efficacy after 2 weeks (after 1 week if increased risk of suicide)		
↓	↓	↓
No effect	Effective	Poorly tolerated
↓	↓	↓
Assess weekly for further 1 to 2 weeks If still no response consider increasing dose	**Continue for 6 to 9 months at full treatment dose** Consider longer-term treatment in recurrent depression	**Switch to a different antidepressant** Titrate to therapeutic dose Assess efficacy over 3 to 4 weeks
↓	↑	↓
No effect	Effective	Poorly tolerated or no effect
↓	↑	↓
Switch to a different antidepressant Titrate if necessary to therapeutic dose. Assess over 3 to 4 weeks, increase dose if necessary		
↓		
No effect		
↓		
Consider third-choice options Mirtazapine (if not already used) or vortioxetine or agomelatine		
↓		
No effect		
↓		
Refer for specialist advice		

Special considerations

Use of antidepressants in older patients: Depression occurring in older patients should be considered, as it is associated with increased morbidity and mortality.[1,28] It is estimated that approximately 20% of completed suicides occur in older people.[1] **There is no ideal antidepressant in older people as all are associated with increased adverse effects in this population**; they should be prescribed at an appropriate dose taking into account co-morbidities, concomitant medication and risk of falls, and the patient should be monitored for adverse effects.[5] The SSRIs are better tolerated in older people than the TCAs.[5] SSRIs however are associated with an increased risk of hyponatraemia and of gastrointestinal bleeds in older people, who may also be on concomitant medications (e.g. NSAIDs or anticoagulants) which further increase the risk of bleeds.[1] **Dose reductions are required for some antidepressants in this population e.g. citalopram, escitalopram.**[29,30]

Treatment-resistant depression (TRD) is usually defined as the failure to respond to 2 different antidepressant drugs of different classes taken at adequate doses for at least 4 weeks.[8] Non-adherence to antidepressants is estimated to be as high as 50% in the community; there is evidence to suggest that some patients thought to have TRD have been non-adherent or been receiving inadequate doses for too short a duration of therapy.[8] **Many of the strategies used to manage TRD require specialist input e.g. combination of antidepressants and augmentation with lithium or second generation antipsychotics.**[5,8]

Other types of treatment used in specialist care: Electroconvulsive therapy should be considered as a first-line treatment for major depression in urgent and emergency situations such as depressive stupor, high risk of suicide, extreme levels of distress and poor fluid intake.[6] Vagus nerve stimulation may be considered for patients with chronic depression not responding to other available treatments.[6]

Emerging treatments: Drug therapies are emerging that are not routinely used in primary care.[8] For example, ketamine, which is under assessment, reduces depressive symptoms rapidly (within hours). It requires repeated treatments and is associated with significant adverse effects including confusion, emotional blunting and a potential for abuse.[8,31]

Summary

Antidepressants are recommended for the treatment of patients with moderate and severe depression. Pharmacological management should consider a number of issues including the patient's previous response and tolerability to antidepressants, suicide risk, potential adverse effects, risk of drug interactions, duration of treatment, risk of discontinuation symptoms and cost of the antidepressant.

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