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# ANTIDEPRESSANTS IN USE IN CLINICAL PRACTICE

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## *SUMMARY*

*The object of this paper, rather than producing new information, is to produce a useful vademecum for doctors prescribing antidepressants, with the information useful for their being prescribed. Antidepressants need to be seen as part of a package of treatment for the patient with depression which also includes psychological treatments and social interventions. Here the main Antidepressant groups, including the Selective Serotonin uptake inhibiters, the tricyclics and other classes are described, together with their mode of action, side effects, dosages. Usually antidepressants should be prescribed for six months to treat a patient with depression. The efficacy of anti-depressants is similar between classes, despite their different mechanisms of action. The choice is therefore based on the side-effects to be avoided. There is no one ideal drug capable of exerting its therapeutic effects without any adverse effects. Increasing knowledge of what exactly causes depression will enable researchers not only to create more effective antidepressants rationally but also to understand the limitations of existing drugs.*

***Key words:*** *antidepressants – depression - psychological therapies - social therapies*

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## Introduction

Depression may be defined as a mood disorder that negatively and persistently affects the way a person feels, thinks and acts. Common signs include low mood, changes in appetite and sleep patterns and loss of interest in activities that were once enjoyable. Treating depression may involve single drugs or combinations of drugs, psychotherapy and electroconvulsive therapy, alongside medical and familial support. The route of treatment chosen is dependent on numerous factors including the type of depression, whether it is acute, chronic or recurrent, past positive responses to treatment, severity of the depression and so on (Azzopardi 2010).

The pathophysiology of depression mainly involves a reduction or functional deficiency of the brain neurotransmitters noradrenaline, serotonin and dopamine. Other factors that may contribute to depression include hormones, changes in circadian rhythm and neuropeptides. This article focuses on the anti-depressants that are available to doctors today (Fekadu 2016).

## Classes of Anti-Depressants

Anti-depressants may be divided into the following classes:

- **Monoamine uptake inhibitors**
  - Tricyclic Antidepressants (TCAs)
  - Tetracyclic Antidepressants
  - Selective Serotonin Reuptake Inhibitors (SSRIs)
  - Noradrenaline Reuptake Inhibitors (NARIs)
  - Serotonin-Noradrenaline Reuptake Inhibitors (SNRIs)
  - Noradrenaline - Dopamine Reuptake Inhibitors (NRDIs)
- **Monoamine oxidase (MAO) inhibitors**
  - Non-selective Monoamine Oxidase Inhibitors
  - Selective Monoamine Oxidase Type A inhibitors
- **Atypical Anti-Depressants and other classes**

### *Tricyclic and Tetracyclic Anti-Depressants*

#### *Mechanism of action*

Inhibit the neuronal re-uptake of noradrenaline and serotonin, thereby increasing their concentration within the synapses and enhancing neurotransmission. Their efficacy for the two types of neurotransmitter receptors varies and this results in different frequencies and intensities of side effects (BNF 2016).

**Table 1A.** Tricyclic anti-depressants and their dose ranges (BNF 2016)

| Examples | Adult daily dose range for depression (mg) |
|---|---|
| Amitriptyline | 75-200 |
| Clomipramine | 10-250 |
| Desipramine | 25-300 |
| Dosulepine | 75-225 |
| Doxepine | 75-300 |
| Imipramine | 75-200 |
| Lofepramine | 140-210 |
| Nortriptyline | 75-150 |
| Protriptyline | 10-60 |
| Trimipramine | 50-300 |
| Maprotiline | 25-225 |
| Mianserin | 30-90 |

Dosulepine is Considered to be less suitable for prescribing due to its relatively high toxicity in overdose without therapeutic advantages over other tricyclics (NHS Dorset Clinical Commissioning Group).

Lofepramine is Particular in that it is the only tricyclic which is not cardiotoxic in overdose, thus safer albeit less potent than others within the same class (NHS Dorset Clinical Commissioning Group)

**Table 1B.** Tetracyclic anti-depressants and their dose ranges (BNF 2016)

| Examples | Adult daily dose range for depression (mg) |
|---|---|
| Amoxapine | 100-600 |
| Maprotiline | 25-225 |
| Mianserin | 30-90 |

Mianserin and Amoxapine are Often classed as Tricyclic Anti-depressants and grouped with secondary amines

- Their onset of action is delayed by seven to fourteen days. It is usual practice to start on low doses which are gradually increased until the patient is stable. Patients are advised not to stop taking suddenly due to the risk of withdrawal symptoms;
- They are more likely to be discontinued than SSRIs due to their side-effects. They are also fatal in over-dose;
- They are contra-indicated in patients with cardiac defects due to their quinidine-like effects and pro-longation of the QT interval. They also have a relatively high seizurogengenicity;
- May be preferred to SSRIs where sedation is required although this varies from one TCA to another (Feighner 1999).

**Table 2.** Tricyclic anti-depressant side effects (BNF 2016)

| Pathway | Effect |
|---|---|
| Adrenergic alpha-receptor antagonism | Orthostatic hypotension |
| Direct membrane effects | Arrhythmia, Tachycardia |
| Histamine H1 re ceptor antagonism | Sedation, Weight gain |
| Muscarinic M1 receptor antagonism | Anti-cholinergic symptoms - dry mouth, dry eyes, blurred vision, constipation, confusion, drowsiness, sedation, urinary retention |
| Serotonin 5-HT2 receptor antagonism | Weight gain |

**Serotonin Syndrome** - Involves excessive central and peripheral serotoninergic activity caused by a sudden dose increase, the addition of another serotoninergic drug or the replacement of one for another without an appropriate wash-out period in between. Risk of occurrence is more common with SSRIs than with TCAs and the combination of SSRIs with MAOIs is contraindicated (BNF 2016).

### *Selective Serotonin Reuptake Inhibitors (SSRIs)*

#### *Mechanism of action*

Inhibit the neuronal re-uptake of serotonin by specifically binding to 5-HT receptors within the synapses. Their effects on noradrenaline are minimal (BNF 2016).

**Table 3.** Selective Serotonin Reuptake Inhibitors and their dose ranges (BNF 2016)

| Common Examples | Adult daily dose range for depression (mg) |
|---|---|
| Citalopram | 20-40 |
| Escitalopram | 10-20 |
| Fluoxetine | 20-60 |
| Fluvoxamine | 50-300 |
| Paroxetine | 20-50 |
| Sertraline | 25-200 |

- Like the TCAs, their onset of action is also delayed by seven to fourteen days;
- In comparison to TCAs, they are better tolerated, safer in patients with cardiac defects, safe in overdosageand have low seizurogenicity;
- May be preferred to TCAs due to less frequent and less severe side-effects (less weight gain, no anti-cholinergic side-effects) (Feighner 1999).

**Discontinuation syndrome** is more common with SSRIs than TCAs – the most common symptoms manifest as headaches, electric shock sensations in the head, neck and spine, influenza-like symptoms, sweating, tinnitus, paraesthesia, fatigue, anxiety and dizziness. When stopping an SSRI, it is common practice to switch to a drug like Fluoxetine that has a long half-life and is metabolised to an active metabolite, in order to reduce the risk of this happening (BNF 2016).

**Table 4.** Selective Serotonin Reuptake Inhibitor side effects (BNF 2016)

| |
|---|
| Gastro-intestinal symptoms – abdominal pain, constipation, diarrhoea, dyspepsia, nausea, vomiting |
| Sexual dysfunction – anovulation, amenorrhoea, decreased libido and/or sexual arousal, galactorrhoea |
| Syndrome of Inappropriate Anti-Diuretic Hormone Secretion (SIADH) hyponatraemia manifesting as confusion, drowsiness, dizziness, seizures |

### *Noradrenaline Reuptake Inhibitors (NRIs or NERIs)*

#### *Mechanism of action*

Inhibit the re-uptake of the neurotransmitters norepinephrine (noradrenaline) and epinephrine (adrenaline) by blocking the action of the norepinephrine transporter, which leads to increased extracellular concentrations of the two neurotransmitters.(BNF 2016)

**Table 5.** Noradrenaline Reuptake Inhibitors and their dose ranges

| Common Examples | Adult daily dose range for depression (mg) |
|---|---|
| Atomoxetine[g] | / |
| Reboxetine | 8-12 |

Atomoxetine is Licensed for use in Attention Deficit Hyperactivity Disorder (ADHD). It is not efficacious in clinically significant depression, however may improve global cognitive performance and daytime sleepiness (Weintraub 2010)

**Table 6.** Noradrenaline Reuptake Inhibitor side effects (BNF 2016)

| Drug | Effect |
|---|---|
| Atomoxetine | Abdominal pain, anorexia, dry mouth, dyspepsia, constipation, flatulence, nausea, taste disturbances, vomiting |
| | Increased blood pressure, palpitations, tachycardia |
| Reboxetine | Constipation, dizziness, dry mouth, impaired visual accommodation, urinary retention |
| | Tachycardia, postural hypotension, vasodilation |

### *Serotonin-Noradrenaline Reuptake Inhibitors (SNRIs)*

#### *Mechanism of action*

Inhibit the neuronal re-uptake of serotonin and noradrenaline at neuronal ends, thereby increasing both levels within the synapse.

**Table 7.** Serotonin-Noradrenaline Reuptake Inhibitors and their dose ranges.(BNF 2016)

| Common Examples | Adult daily dose range for depression (mg) |
|---|---|
| Duloxetine | 30-120 |
| Venlafaxine | 75-375 |

**Table 8.** Serotonin-Noradrenaline Reuptake Inhibitor side effects (BNF 2016)

| Drug | Effect |
|---|---|
| Duloxetine | Constipation, Decreased appetite, Diarrhoea, Dry mouth, Nausea, Vomiting, |
| | Somnolence, Headache, Dizziness, Insomnia, Fatigue, Sweating, Erectile dysfunction |
| Venlafaxine | hypertension, headache, dizziness, nausea, dry mouth, constipation, abnormal ejaculation, impotence, insomnia, somnolence, nervousness, sweating |

Duloxetine is also commonly used to control diabetic neuropathy and stress urinary incontinence

Due to higher noradrenaline activity, hypertension is more common with Venlafaxine than with TCAs and SSRIs

- Venlafaxine's effects are initiated quicker than other anti-depressants. This may be due to its acute onset of down-regulation of beta-adrenergic receptors (Feighner 1999).

### *Noradrenaline – Dopamine Reuptake Inhibitors (NDRIs)*

#### *Mechanism of action*

Inhibit the re-uptake of the neurotransmitters norepinephrine anddopamine by blocking the action of the norepinephrine transporter and the dopamine transporter, respectively (BNF 2016).

**Table 9.** Noradrenaline-Dopamine Reuptake Inhibitor Bupropion

| Common Examples | Adult daily dose range for depression (mg) |
|---|---|
| Bupropion | / |

Bupropion is Marketed as an aid to smoking cessation, however use in depression may be considered instead of SSRIs where Syndrome of inappropriate antidiuretic hormone secretion is a problem (BNF 2016)

**Table 10.** Noradrenaline-Dopamine Reuptake Inhibitor side effects (BNF 2016)

| |
|---|
| agitation, anxiety, dizziness, dry mouth, gastro-intestinal disturbances, insomnia, sweating, taste disturbances, tremor |

### *Monoamine Oxidase Inhibitors (MAOIs)*

#### *Mechanism of action*

Inhibit the enzyme monoamine oxidase from removing the neurotransmitters norepinephrine, serotonin and dopamine from the brain, resulting in their accumulation.

They are in turn divided into selective and non-selective MAOIs.

**Table 11.** Monoamine Oxidase Inhibitors and their dose ranges (BNF 2016)

| Common Examples | Adult daily dose range for depression (mg) |
|---|---|
| Non-Selective Irreversible MAOIs | |
| Phenelezine | 15-90 |
| Tranylcypromine | 10-30 |
| Isocarboxazid | 30-60 |
| Selective Reversible MAOIs (Type A) | |
| Moclobemide | 150-600 |
| Selective MAOIs (Type B) | |
| Rasagaline | / |
| Selegiline | / |

Selegiline and Rasagaline are used for the treatment of Parkinson's Disease rather than depression, due to their selective effect on dopaminergic neurotransmission

- MAOIs are used much less frequently than SSRIs and TCAs due to their significant effect on the digestive system and their tendency to interact with other drugs;
- In inhibiting the enzyme monoamine oxidase, the non-selective MAOIs inhibit the breakdown of tyramine which is an amino acid responsible for the regulation of blood pressure; the higher the levels, the greater the blood pressure. The consumption of tyramine-containing foods like yeast, red wine and aged cheese thereby result in its accumulation and a possible dangerous rise in blood pressure. Monoamine oxidase takes several weeks to be replaced thereby the danger of such an interaction persists for up to two weeks following discontinuation of the MAOI;

- They are contra-indicated for use alongside SSRIs due to the risk of triggering the Serotonin-Syndrome
- Phobic patients and depressed patients with atypical, hypochondriacal or hysterical features are said to respond best to MAOIs. They may also be used in the treatment of panic disorder with agoraphobia, social phobia, Post Traumatic Stress Disorder, borderline personality disorder and bipolar depression (BNF 2016)

**Table 12.** Monoamine Oxidase Inhibitor side effects (BNF 2016)

| |
|---|
| Dizziness, Headache, Postural Hypotension, weight gain, sleep disturbances, sexual dysfunction |

***Atypical anti-depressants and other classes***

See Table 13.

**Table 13.** Atypical anti-depressants and other classes

| Drug | Classification | Mechanism of action | Dose range (mg) | Common side effects | Notes |
|---|---|---|---|---|---|
| Mirtazapine (BNF 2016, Feighner 1999) | Noradrenergic and specific Serotoninergic Anti-Depressant (NaSSA) | Antagonises the presynaptic alpha$_2$-adrenoreceptor and serotonin receptor subtypes 5-HT$_{2A}$, 5-HT$_{2C}$ and 5-HT$_3$to increase central noradrenergic and serotoninergic neurotransmission | 15-45 | constipation, dizziness, drowsiness, dry mouth, increased appetite, somnolence, weight gain | May act more rapidly than other anti-depressants and causes less of the side-effects that are common to TCAs and SSRIs. It however has a significant anti-histaminic effect |
| Trazodone (BNF 2016, Feighner 1999, Fagiolini 2010) | Serotonin Antagonist and Re-uptake Inhibitor (SARI) | Antagonises all 5-HT receptor sites except 5-HT$_{1A}$, where it acts as a partial agonist. It also simultaneously (weakly) inhibits serotonin transporters (SERT) | 150-600 | Blurred vision, drowsiness, dizziness, dry mouth, fatigue, headache, nausea, nervousness, priapism | It is used particularly where sedation is required due to its hypnotic and anxiolytic effects |
| Nefazodone (BNF 2016m, Feighner 1999) | SARI | | | Sedation, impaired concentration, lethargy | Its lack of antihistaminic and anticholinergic activity improves tolerance and safety |
| Tianeptine (BNF 2016) | Selective Serotonin Reuptake Enhancer (SSRE) | Increases the uptake of serotonin within synapses. It is not known how this results in relieving depression but theories include modulation of glutamatergic transmission and its agonist effects on mu-opiate receptors | 12-36 | Dizziness, drowsiness, dry mouth, constipation, headache, insomnia | Lacks cardiovascular, anti-cholinergic and sedativeadverse effects and has a quicker onset of action to traditional anti-depressants |
| Tryptophan (BNF 2016) | Essential Amino Acid | Converted into serotonin itself following reactions of condensation, reductive decarboxylation and catalysis | 6000-12,000 | Dizziness, drowsiness, dry mouth, headache, loss of appetite, nausea | May be obtained from protein-based dietary sources or as a synthetic supplement |
| Agomelatine (BNF 2016, Manikandan 2010) | Melatonergic Anti-Depressant | Agonises melatonergic MT$_1$ and MT$_2$ receptors and antagonises the serotonin 5HT$_{2C}$ receptor | 25-50 | Abdominal pain, constipation, diarrhoea, nausea, vomiting Raised liver enzymes | No dosage tapering required on treatment discontinuation |

## Conclusion

The efficacy of anti-depressants is similar between classes, despite their different mechanisms of action. The choice is therefore based on the side-effects to be avoided. There is no one ideal drug capable of exerting its therapeutic effects without any adverse effects. Increasing knowledge of what exactly causes depression will enable researchers not only to create more effective antidepressants rationally but also to understand the limitations of existing drugs (Feighner 1999).

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Mark Agius devised the project and supervised it.
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