CHAPTER 16.

ANTIDEPRESSANT DRUGS

"It is unlikely that we will see new medications with substantially greater effectiveness in the coming years." (Davey and Chanen, 2016)

Introduction

For more than half a century the pharmacological treatment of depression has focused on manipulating **synaptic monoamines** (particularly serotonin and noradrenalin, and to some extent, dopamine).

Recently, new approaches have been suggested, involving 1) the immune system, 2) melatonin receptor, 3) NMDA receptor, and 4) diet.

Current treatments of depression are only slightly more effective than placebo. This applies to both medications (Kirsch et al, 2008) and psychotherapies (Parker and Fletcher, 2007).

Parker (2009) makes the point that depression is generally conceptualized as a unitary entity – that is, all depressions are the same condition. He draws an analogy with dyspnoea – which may result from pneumonia, asthma, emphysema and pulmonary embolus – each of which requires a different treatment.

The current diagnostic systems in psychiatry (for all disorders) are descriptive. McHugh (2005) states the time has come to move to an etiological perspective. He proposes 4 clusters:
1) "brain disease", in which there is disruption of neural underpinnings,
2) "vulnerability because of psychological make-up",
3) adoption of behaviour "that has become a relatively fixed and warped way of life", and
4) "conditions provoked by events", that is, events that "thwart or threaten".

Applying the **McHugh approach to depression**, there are 4 clusters:
1. psychotic and melancholic depression, which should respond to medication,
2. low mood associated predisposed personality types
3. low mood associated alcoholism and anorexia nervosa, and
4. low mood associated with bereavement, situational anxiety and posttraumatic conditions.

All 4 clusters, but particularly 2-4, could be expected to respond to appropriate psychotherapy, and in some cases, the passage of time.

Legitimacy of the term: 'antidepressant'

Moncrief (2008) observes that the term "antidepressant" implies a drug that acts in a disease specific way to reverse the neuropathological basis of the symptoms of depression. She continues, "contrary to popular belief, it has not been demonstrated that depression is associated with an abnormality or imbalance of serotonin or any other brain problem, or that drugs act by reversing such a problem".

The antidepressants may not correct a "chemical imbalance" in all or any of the subtypes of depression, but they are clinically helpful, and the term will doubtless persist.

History of the antidepressants

The first antidepressant was discovered by chance. Mood improvement was observed in certain patients being treated for tuberculosis (Bloch et al, 1954). The antidepressant effects of the anti-tuberculosis drug, iproniazid, was attributed to the inhibition of monoamine oxidase. Soon, other monoamine oxidase inhibitors (MAOIs) were specifically developed for the treatment of depression.

Based on the success of chlorpromazine in the treatment of psychosis, new drugs with a similar structure were developed (for use in psychosis). One of these, **imipramine**, was found to have no antipsychotic action, but a strong antidepressant effect (Kuhn, 1958). It was the first tricyclic antidepressant (TCA).

Interestingly, in the 1950s, dexamphetamine was marketed for a time as "the specific antidepressant". The addictive and psychotogenic properties of the stimulants were soon recognized and their use in depression was largely abandoned.

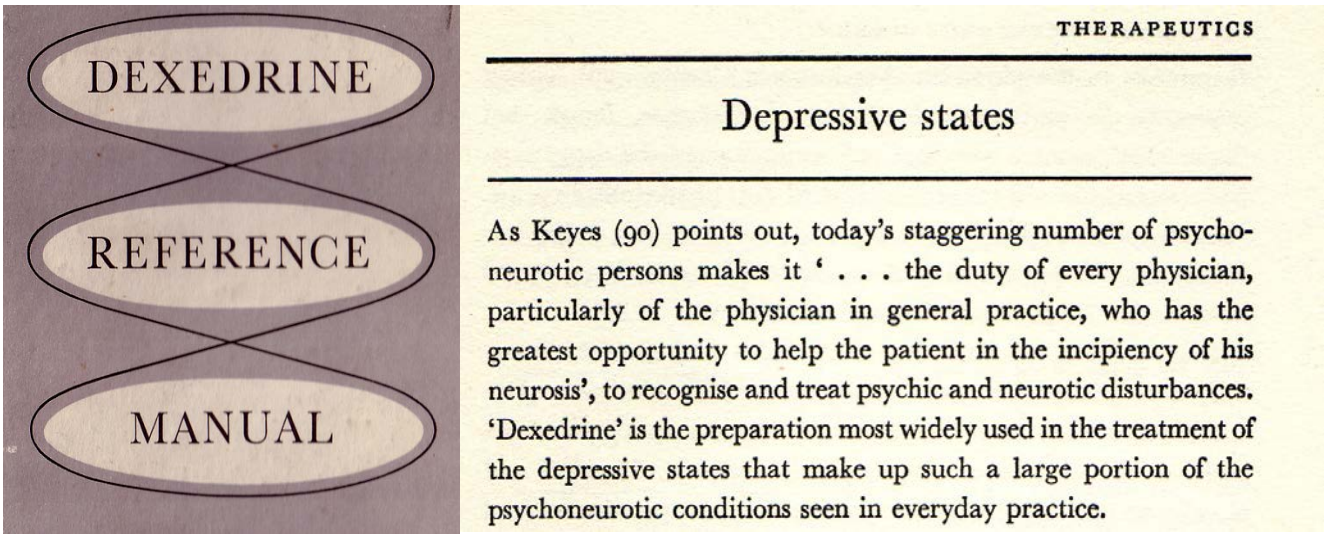

Illustration. The Dexedrine (dexamphetamine) Reference Manual was made available to practitioners by the manufacturer. "'Dexedrine' is the preparation most widely used in the treatment of the depressive states…" may or may not have been accurate. Either way, it was a brief, now long distant, era.

The MAOIs and TCAs are effective antidepressants, but they have troublesome side-effects. Both inhibit serotonin reuptake. Focusing on this feature, the selective serotonin reuptake inhibitors (SSRIs) were developed. These have an antidepressant action, and their more 'selective' action results in less troublesome side-effects.

Current antidepressants take 2 weeks to have significant antidepressant effects. The full antidepressant effect may not be achieved for up to 6 weeks. This does not mean they provide no relief in the short-term. Symptoms such as insomnia, lack of appetite and accompanying anxiety may respond within a day or so, and well ahead of the antidepressant effect.

Non-pharmacological somatic treatments have included electroconvulsive therapy (ECT, Chapter 28). More recent non-pharmacological treatments transcranial magnetic stimulation (TMS, Chapter 29), and vagal nerve stimulation (VNS; Muller et al, 2017) may have a place in the future.

SIDE (ADVERSE) EFFECTS

Each drug has a unique side-effect profile, but general comments are possible.

TCAs and MAOIs

The **TCAs** and **MAOIs** share some side effects with some of the newer antidepressants:

1. **Alpha-1 adrenergic** receptor blocking produces hypotension. In orthostatic hypotension there is a marked fall in blood pressure with change of position – most usually, on rising from lying or sitting to standing – there is dizziness and the risk of falls.
2. **Histamine** receptor blockade is associated with drowsiness and increased appetite (weight gain).
3. **Acetylcholine** receptor (muscarinic) is associated with dry mouth, constipation, blurred vision and difficulty initiating micturition.

More serious side effects include:
1) **TCA**s present the risk of cardiac conduction delays leading to heart block in patients with pre-existing conditions, and overdose can cause life-threatening arrhythmias
2) **MAOI**s make the use of certain other drugs problematic, and the ingestion of certain dietary substances (tyramine) dangerous (hypertensive crisis). See later.

SSRIs

The **SSRI**s, while largely free of dangerous side-effects (even in overdose), have some troublesome effects including agitation, sedation, anxiety, headache, tremor and sexual dysfunction (especially anorgasmia). They are more likely to cause GI symptoms (nausea, vomiting and diarrhoea) than other antidepressants. SSRI side-effects are more nuisance than dangerous. A **discontinuation syndrome** can be troublesome with abrupt cessation (dizziness, headache and nausea) – thus, a tapered withdrawal is recommended.

The **serotonin syndrome** (excessive release of serotonin) is characterized by sweating, diarrhoea, abdominal pain, tachycardia, elevated blood pressure, myoclonus, hyper-reflexia, pyrexia and agitation. Extreme cases may prove fatal. More likely when different classes of drugs which facilitate serotonin release are used concurrently.

Dual Action Antidepressants
The **dual action** (noradrenaline and serotonin) **antidepressants** have SSRI-type side-effects, and are also relatively free of dangerous side-effects. They may, of course, be associated with the serotonin syndrome. **Venlafaine** is sometimes associated with 'electric shock'-like pains in the limbs, and rebound agitation on cessation. **Mirtazapine** is sedating and increases appetite (weight gain).

ANTIDEPRESSANTS IN PREGNANCY

Antidepressant use during pregnancy has been associated with small for gestational age babies (Jensen et al, 2013). Other adverse outcomes have not yet been clearly identified.

A Danish study found that 5.3% of mothers were taking an antidepressant at conception, and 1/3 of these were still taking them at 3 months (Huybrechts et al, 2013).

The management of mood disorder in pregnancy is a difficult issue. Some adverse outcomes have been reported with antidepressant medication. However, adverse outcomes for both mother and foetus/baby may also accompany inadequately treatment of serious mood disorder pregnancy. In each case, the risks and benefits need to be carefully weighed.

ANTIDEPRESSANTS IN CARDIAC DISEASE

The TCAs are highly cardiotoxic in overdose, and may worsen outcome in established cardiovascular disease. Fluoxetine, citalopram and mirtazapine appear to be safe after MI, and paroxetine and citalopram appear to be safe in established coronary artery disease.

Duloxetine and venlafaxine are known to increase blood pressure and should be used only with great caution in established hypertension (Taylor, 2008).

CATEGORIES

MONOAMINE OXIDASE INHIBITORS (MAOIs)

MAOIs are of historical importance. Use requires expert experience – they are of little interest to medical students.

Monoamine oxidase is an enzyme located on the outer mitochondrial membrane - it degrades monoamines, including noradrenaline, serotonin, dopamine, adrenaline, and tyramine. There are two types. MAO-A predominantly metabolises noradrenaline, serotonin and adrenaline. Both MAO-A and MAO-B metabolize dopamine and tyramine. MAOIs operate in the nervous system, the liver and the GI tract. When the usual metabolism of dietary tyramine by GI MAOs is inactivated by irreversible MAOIs, intact tyramine can enter the circulation and cause hypertensive crisis.

Tyramine containing foods must therefore be avoided (cheese, meat and yeast extract, aged meat and fish, and alcohol, particularly red wine). First aid in hypertensive crisis includes alpha-1 blockers (chlorpromazine) and sublingual glycerol trinitrate spray (Pridmore, 2003).

Caution is also required when combining MAOIs with certain other drugs. The metabolism of some is greatly slowed, and L-Dopa and pethidine for example, are best avoided. Drugs with direct and indirect pressor actions such as adrenaline, ephedrine and stimulants carry the risk of hypertensive crisis.

The combination of MAOIs and other antidepressants (TCAs, SSRIs and stimulants) demands caution. Nevertheless, in resistant depression, combination with other antidepressants and even stimulants may be helpful, in expert hands (Feinberg, 2004).

These days, the early (irreversible) MAOIs are seldom used.

A **"reversible" inhibitor of MAO-A** (RIMA) is available (**moclobemide**). RIMAs have relatively little effect on MAO-B, they can be displaced by other substances such as tyramine, and their inhibitory effects are lost within hours of the last dose. Thus, dietary restrictions are not necessary. **Moclobemide** has a benign side-effect profile and has the advantage of not interfering with sexual function – it has a place in modern therapy.

Moclobemide is not available in the USA, which may explain a relative lack of interest in the scientific literature.

TRICYCLIC ANTIDEPRESSANTS (TCAs)

For decades, the TCAs were the most commonly used antidepressants. They continue to have a place in unresponsive depression. **Imipramine** (first developed) is the less sedating and is appropriate when the patient is already "slowed-down" by the disorder.

Amitriptyline (second developed) is the more sedating and is appropriate when the patient is anxious (agitated) or suffering insomnia. **Clomipramine** is a more active serotonin reuptake inhibitor than the other TCAs and was found especially effective in OCD. While the SSRIs are now also used in OCD, many experts still regard clomipramine as the most effective drug. **Nortriptyline** (the N-demethylated metabolite of amitriptyline) has the most benign side-effect profile of the TCAs, and is often used in the elderly.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

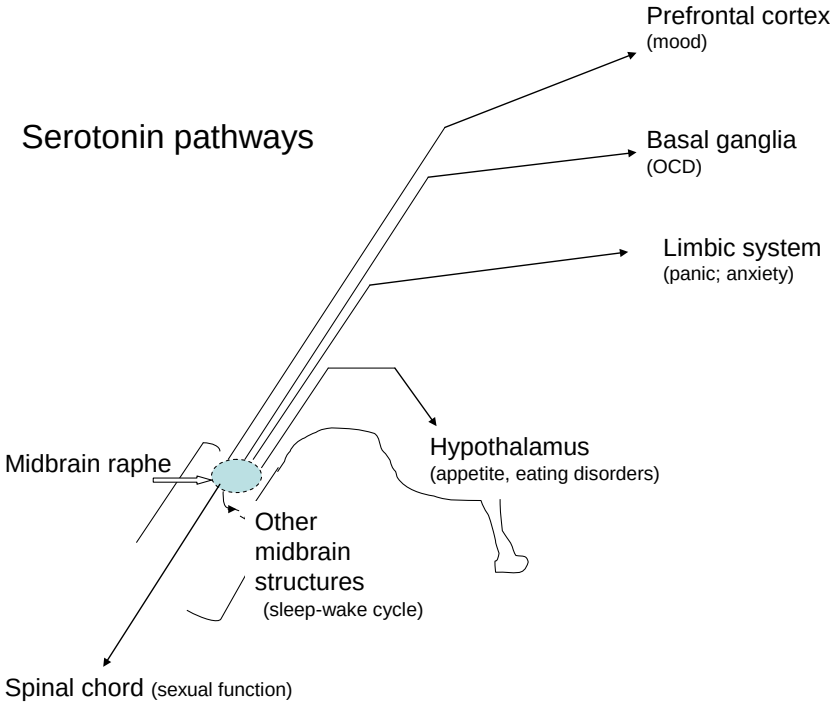

Illustration. 6 serotonin pathways of interest (see text).

Generally characterized as antidepressants, the SSRIs have multiple uses. Serotonin pathways commence at the mid-brain raphe.

SSRI actions are helpful:
1) prefrontal cortex (low mood),
2) basal ganglia (OCD),
3) limbic system (panic and anxiety), and
4) hypothalamus (eating disorders).

SSRI actions are unhelpful in
1) mid-brain structures (may cause insomnia), and
2) spinal cord (may cause sexual dysfunction)

The SSRIs are the most widely used antidepressants (at present) - **fluoxetine**, **sertraline**, **fluvoxamine**, **paroxetine**, **citalopram** and **escitalopram.**

Vortioxetin was recently released in Australia, Canada and the UK. It inhibits the reuptake of serotonin and acts as an agonist or antagonist at various 5-HT receptors. Five to 20 mg daily may lower depression scores, and provide some relapse prevention (Boulenger et al, 2012). Nausea is the most common side-effect, and abrupt discontinuation is well tolerated (McIntyre, 2017).

A**gomelatine** is an **agonist of melatonin receptors** (MT1 & 2) – and it was proposed that this action had antidepressant effects. There is some evidence of antidepressant action, however, this is now attributed to SSRI effects.

Agomelatine carries risk of liver injury and monitoring of liver function throughout treatment is recommended (Freiesleben and Furczyk, 2015). It suffers extensive first-pass metabolism - an intranasal administration method has recently been devised which enhances both absolute bioavailability and brain delivery (Fatouh et al, 2017). This compound is not yet available in clinical practice.

SELECTIVE NORADRENERGIC REUPTAKE INHIBITOR (NARI)

Reboxetine is a selective noradrenergic reuptake inhibitor (NARI). In 2010, the German Institute for Quality and Efficiency in Health Care (IQEHC) published results of a meta-analysis which found that reboxetine was not more effective than placebo. Nevertheless, sales continue.

MULTIPLE/DUAL ACTION ANTIDEPRESSANTS

The dual action antidepressants may be more effective antidepressant than the SSRIs; remission is achieved by **venlafaxine** in 45% of cases, and by SSRIs in 35% of cases (Thase et al, 2001). And, **mirtazapine** may have a more rapid onset than many of the newer antidepressants (Gartlehner et al, 2008).

Venlafaxine (and **desvenlafaxine**) is described as a selective noradrenalin and serotonin reuptake inhibitor.

M**irtazapine** has a range of actions, central is alpha-2 antagonism which disinhibits 5HT and NA neurons causing release of these transmitters. In addition, mirtazapine blocks most 5HT receptors, which results in the release of DA.

Duloxetine has a range of actions impacting on synaptic 5HT, NA and DA.

AUGMENTATION OF ANTIDEPRESSANTS

The response rate to antidepressants is poor. Unresponsive depression may be managed by combining antidepressants.

Another strategy is augmentation of an antidepressant with a non-antidepressant. Lithium is the most extensively reported antidepressant augmenter (Bauer et al, 2010). Thyroxine has also been widely used, even in the presence of normal thyroid function (Kaira and Balhara, 2014).

Atypical antipsychotics have been widely used as augmenters. However, a recent study found no clear evidence to support antipsychotic augmentation (Simons, 2017). We look forward to further work on this issue.

BIPOLAR DEPRESSION

Unipolar depression and the depressed phase of bipolar depression were considered to be much the same condition. However, they are now believed to be different. There

are at least two differences: 1) bipolar disorder depressive episodes are less responsive to medication, and 2) bipolar depression is frequently followed by a swing into mania.

Because of concern that antidepressants may trigger manic swings, they are usually only used in bipolar depression when a mood stabilizer is in place (Harel and Levkovitz, 2008). And, they are often withdrawn as soon as the depression has remitted.

Lamotrigine (an anticonvulsant: sodium channel blocker and inhibitor of glutamate release) is an effective mood stabilizer - it prevents relapse into bipolar depression (but not manic swings). It has also been suggested as an acute treatment of bipolar depression (Solmi et al, 2016).

Quetiapine (an atypical antipsychotic) has been approved in some countries for the treatment of bipolar depression (Avery and Drayton, 2016).

If bipolar depression is not resolving, and the decision is made to avoid antidepressant medication, ECT and TMS are treatment options.

PSYCHOTHERAPY

Psychotherapy [cognitive behavioural therapy (CBT) and interpersonal psychotherapy (IPT)] are effective in depression. Strangely, there appears to be a reduction in the efficacy of psychotherapy, just as has been observed with medication (Johnsen and Friborg, 2015).

The best outcome is obtained when the patient receives both psychotherapy and pharmacotherapy (Davey and Chanen, 2016). (The effects of psychotherapy and psychotherapy appear to operate independently of each other.)

THE FUTURE

Davey and Chanen, (2016) worry us a little - "It is unlikely that we will see new medications with substantially greater effectiveness in the coming years."

But, the current author agrees – it is clear that "depression" refers to a heterogeneous bunch of conditions associated with a range of etiological factors. This observation, but no progress, has been made (McHugh 2005; Parker 2009).

Davey and Chanen, (2016) argue the current antidepressants have not fulfilled the promise, but they have some value, and we must cope with what we have.

'Hope springs eternal in the human breast' (Alexander Pope, 1688-1744) – theories and therapies continue to appear. It is hoped some of the following will blossom (rather than fade like 'light therapy').

Depression is associated with **immune** (and endocrine) **system** changes. A systematic review and meta-analysis explored the association between two inflammatory markers (C-reactive protein, and Interleukin-6) and depression in older people (Smith et al, 2017). The authors found a cross-sectional and longitudinal association between these markers and depression, with inflammation leading to depression (rather than the reverse).

However, the addition of non-steroidal anti-inflammatory drugs to standard antidepressant treatment has yielded disappointing results (Husain et al, 2017a&b).

Omega-3 polyunsaturated fatty acids (PUFAs) can modulate key pathways in inflammation, and the nervous and other systems. Some work has indicated that omega-3 fatty acids have therapeutic benefits in the treatment of depression, both as monotherapy and adjunct therapy (Rutkofsky et al, 2017).

However, somewhat surprisingly, randomized placebo-controlled trials, omega-3 fatty acids did not prevent depressive symptoms during pregnancy and post-partum (Mozurkewich et al, 2013; Vas et al, 2017).

Agomelatine, a **melatonin receptor agonist** was suggested as a unique approach to the treatment of depression. Further research indicates it has small (if any) antidepressant effects, which are due to an SSRI action.

Attention has been directed to the **glutamate system**. Rapid remissions (within a couple of hours) have been claimed for intravenous administration of **ketamine** (**NMDA receptor antagonist/blocker**) in acute depression (Monteggia and Zarate 2015). A recent review (Swartz et al, 2017) found it premature to recommend ketamine in clinical practice – however, there was cautious optimism this drug will become an important tool in the treatment of severe mood and anxiety disorders.

Back to the future. Extracts of **Hypericum perforatum** L (popularly called **St. John's wort**) have been used for the treatment of depression for longer than living memory. A recent meta-analysis (Ng et al, 2017) – along with a previous Cochrane

review – report that these extracts have antidepressant effects superior to placebo, and similar to the SSRIs. To this point, however, follow-up studies are lacking.

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