CHAPTER 16.

ANTIDEPRESSANT DRUGS

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, there have been suggestions of alternative approaches. Depression is associated with **immune** (and endocrine) **system** changes, but the addition of non-steroidal anti-inflammatory drugs to standard antidepressant treatment has yielded disappointing results (Andrade, 2014). Another new initiative - Agomelatine, a **melatonin receptor agonist** was suggested as an antidepressant – but again, results have been disappointing (Gahr, 2014). However, the experimental use of intravenous ketamine, an **NMDA receptor** blocker, has shown real promise (Monteggia and Zarate, 2015).]

Current treatments of depression are only slightly (if at all) more effective than placebo. This applies to both medications (Kirsch et al, 2009) and psychotherapies (Parker and Fletcher, 2007). The common antidepressants are inefficient, requiring to treat 7 patients to gain one positive outcome (Arroll et al, 2009).

On first reading, this is alarming. It is also inconsistent with the experience of clinicians who actually treat patients, who find that most of their patients improve.

In and editorial in the British Journal of Psychiatry, 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. To properly demonstrate effectiveness, a treatment should be tested on a specific type of depression. He observes that, until the unitary theory of depression is disassembled and treatments are tested on identified subtypes, “noise” will obscure our understanding of the best treatments.

The current diagnostic systems in psychiatry 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:
Cluster 1 (brain diseases) includes psychotic and melancholic depression, which could be expected to respond to medication,
Cluster 2 includes low mood associated predisposed personality types
Cluster 3 includes low mood associated alcoholism and anorexia nervosa, and

Cluster 4 includes 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, to 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".

She (Moncrief, 2008) points out that in earlier times, general stimulants were used in the treatment of depressed individuals, but were soon recognized as being "non-specific" and the cause of additional problems. When the first "antidepressants" were clearly not general stimulants, the idea emerged that they were "specific" to depression. This announcement was helpful to the status of psychiatry and the coffers of the drug companies. Instead of treating the pathophysiology of depression, she states these drugs mask the manifestation of the disorder and create the impression of improvement.

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

Many advances in psychiatric treatment have been the harvest of luck - people following up chance observations. Chlorpromazine, the first antipsychotic, was initially developed as an anaesthetic agent. In 1952, improvement was observed in people with schizophrenia who received chlorpromazine as an anaesthetic agent. New antipsychotic drugs quickly followed.

The first antidepressant was also a chance finding. Mood improvement was observed in certain patients who were being treated for tuberculosis (Bloch et al, 1954). Subsequently, the antidepressant effects of the anti-tuberculosis drug, iproniazid, were 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 was found to have no antipsychotic action, but treated patients became less depressed. This was imipramine, the first tricyclic antidepressant (TCA; Kuhn, 1958).

Interestingly, in the 1950s, dexamphetamine marketed for a time as "the specific antidepressant". [While marketing suggested a specificity for depression, clinicians

were well aware dexamphetamine was a general stimulant.] It was not long before the addictive and psychotogenic properties of the stimulants were recognized and their use in depression was largely abandoned.

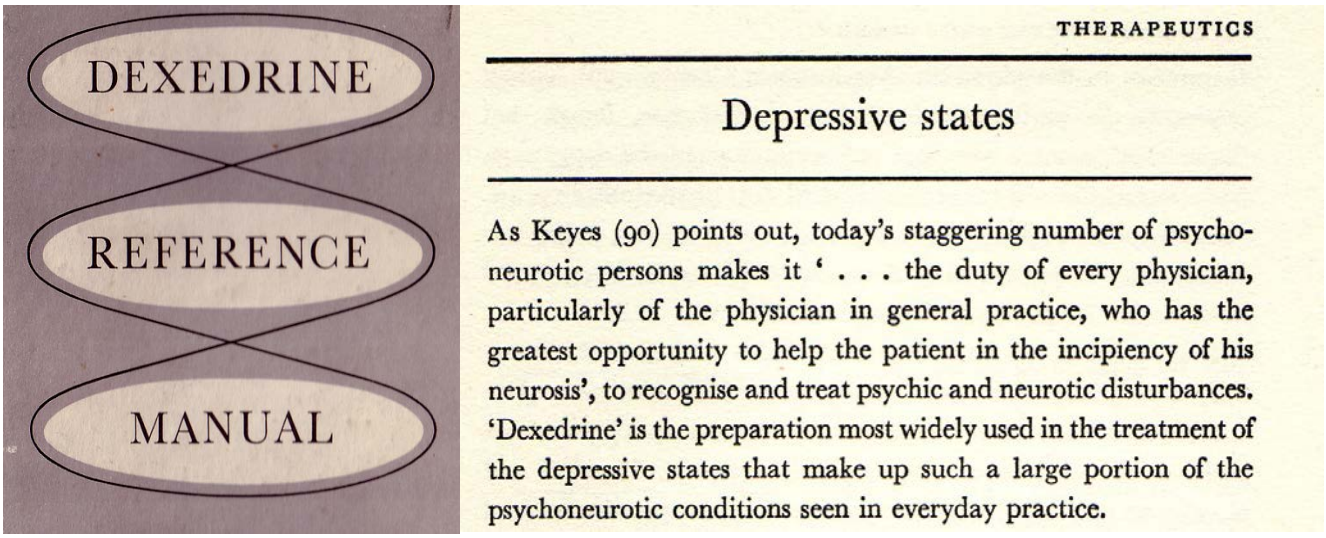

Illustration. The Dexedrine (dexamphetamine) Reference Manual was made available to practitioners by the manufacturer. "'Dexedrine' is the preparation most widely used in the treatment of the depressive states…" may or may not have been accurate. Either way, it was a brief, now long distant, era.

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.

More recently, antidepressants which have more than one pharmacological action have become available. These multiple action drugs are thus, similar in action to the old TCAs. However, they represent an advance insofar as they have fewer side-effect.

Unfortunately, current antidepressants take 2 weeks to have significant antidepressant effects. It may be the full antidepressant effect is not achieved for up to 6 weeks. This does not mean the antidepressants 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. The pharmacological effects at the synapse occur within hours to days; the longer time period required for the antidepressant effects is presumed to be because these depend to some extent on alterations to the "signal transduction cascade system" and gene expression (which are not immediate). A more rapid onset is a target for antidepressants of the future.

Non-pharmacological somatic treatments have included electroconvulsive therapy (ECT, Chapter 28). More recent non-pharmacological treatments [light therapy, transcranial magnetic stimulation (TMS, Chapter 29), vagal nerve stimulation (VNS; Bajbouj et al, 2010) and magnetic seizure therapy (MST)] may have a place in the future. Physical exercise as a treatment of depression has been recommended by

people who are not depressed, but does not appear to have a statistically significant benefit (Mead et al, 2008).

Side-effects of antidepressants

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

The **TCAs** and **MAOIs** shared some side effects with many of the older antipsychotic medications and also 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.

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 danger. A **discontinuation syndrome** can be troublesome with abrupt cessation (dizziness, headache and nausea) - 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. This syndrome is more likely when different classes of drugs which facilitate serotonin release are used concomitantly.

The newer **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 is associated with small for gestational age (SGA) babies (Jensen et al, 2013). This association is unrelated to underlying maternal depressive disorder. Other adverse outcomes have not yet been clearly identified.

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

The scientific literature is not very helpful on this topic. 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).

Monamine oxidase inhibitors (MAOIs)

MAOIs are of historical interest and should be used only by expert hands – 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. These include 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. In non-specialist hands the combination of MAOIs and other antidepressants (TCAs, SSRIs and stimulants) is discouraged. Nevertheless, in specialist hands, in resistant depression, combination with other antidepressants (Pridmore & Turnier-Shea, 2004) and even stimulants (Feinberg, 2004) has been reported.

These days, the early (irreversible) MAOIs are seldom used: **tranylcypromine** (somewhat stimulating) and **phenelzine** (somewhat sedating). In addition to refractory depression which has failed to respond to other treatment, the MAOIs have a place in the treatment of depression with marked hypochondriacal features, phobic disorders including agoraphobia, and OCD.

A **"reversible" inhibitor of MAO-A** (RIMA; **moclobemide**) is available. 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 – and 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. Nevertheless, moclobemide continues to be reported as a valuable antidepressant (Baume and Renger, 2014).

Tricyclic antidepressants (TCAs)

For decades, the TCAs were the most commonly used antidepressants, and they continue to have a place in the treatment of unresponsive depression. The first developed were imipramine and amitriptyline. **Imipramine** is the less sedating and is appropriate when the patient is already "slowed-down" by the disorder. **Amitriptyline** 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 to be especially effective in OCD. While the SSRIs are now also used in OCD, many experts still regard clomipramine as the most effective drug available. **Nortriptyline** (the N-demethylated metabolite of amitriptyline) has the most benign side-effect profile of the TCAs, and is quite often used in the elderly.

Selective serotonin reuptake inhibitors (SSRIs)

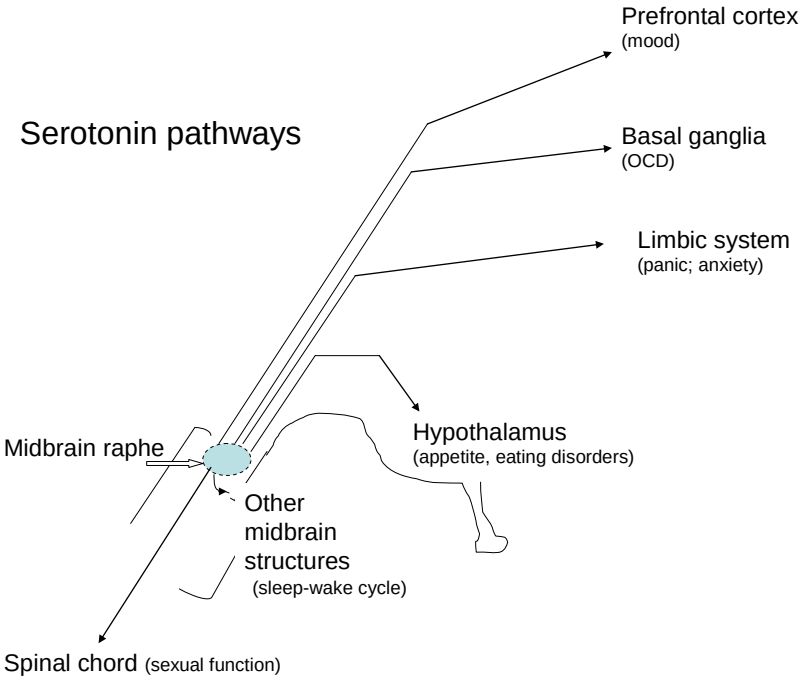

Illustration. 6 serotonin pathways of interest (see text).

Although generally characterized as antidepressants, the SSRIs have multiple uses in psychiatry. 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 (and may cause insomnia), and
2) spinal cord (and may cause sexual dysfunction)

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

Multiple action antidepressants

Venlafaxine 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.

The dual action antidepressants are 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). Mirtazapine has a more rapid onset of effects than many of the other newer antidepressants (Gartlehner et al, 2008).

Selective noradrenergic reuptake inhibitors (NARIs)

Reboxetine is the only NARI antidepressant currently available. A recent study criticised the manufacturer for not disclosing information and concluded, "Reboxetine is, overall, an ineffective and potentially harmful antidepressant" (Eyding et al, 2010). There are claims its reputation rests on "publication bias" (Gupta, 2014).

Atypical antipsychotics

Some atypical antipsychotics have been shown to be effective as monotherapy in the treatment of major depression.

Quetiapine is the most extensively studied (Cutler et al, 2009). It has D2 and 5HT2 antagonism. It appears 5HT2 blockade results in increased NA and DA release in the prefrontal lobe. It has been approved in many countries for the treatment of bipolar depression.

Agomelatine

A**gomelatine** was mentioned in the introduction to this chapter. It was recently released in Europe, Australia and some other countries. Agomelatine is an **agonist of melatonin receptors** (MT1 & 2) – and it is proposed that this action has antidepressant effects. [However, it is also a serotonin 2C receptor antagonist (which increases noradrenalin and dopamine release in the prefrontal cortex)].

Sadly, recent evidence indicates agomelatine is a weak antidepressant with a serious (hepatotoxicity) potential side-effect (Koesters et al, 2013; Gahr, 2014).

Circadian rhythm and depression

The mention of agomelatine forces us to consider circadian rhythm and depression. Circadian rhythm ('circa', around; 'diem', day), is a 24 hour (roughly) cycle which is important in the physiology and behaviour of most living entities. These cycles are endogenous (come from within), but are adjusted (entrained) by external cues, of which daylight is most important. They operate at many levels, from the cellular to the total organism.

The circadian rhythm has survival value, ensuring coordination of the metabolism of the organism with the environmental events: the physiology of animals which are active during daylight is clearly different to those which are active at night.

A gene which encodes proteins regulating the circadian rhythm of mice has been described (Vitaterna et al, 1994).

Melatonin levels are undetectable during the day. Release commences in dim light (about 9 pm) and reaches a peak at about 4 am. It then drops and is low to unmeasurable at about 8 am.

Core body temperature is important in the human circadian rhythm, being almost the inverse of the melatonin level, reaching a minimum (about 36.6 C) at about 4 am and rising to 37 C at about 8 am. Whether melatonin has a direct effect on the core temperature are unclear.

Behavioural features of the circadian rhythm/sleep-wake cycle are important. With the absence of light, sleepiness arrives – related to the rise in melatonin levels (and melatonin has been used, with uncertain success, as an hypnotic, particularly in a setting of 'jet lag'). Subjective alertness and performance reaction time are lower at night than during the day.

Major depressive disorder has some symptoms in common with disturbance of the circadian rhythm: sleep disturbance, slowness and weakness during the day. There is little to suggest that disturbance of circadian rhythm is a root cause of major depressive disorder. However, some researchers suggest there is a particular mood disorder (seasonal affective disorder) which deserves such consideration.

Seasonal affective disorder (SAD) does not appear in the **DSM-5** (by this name). However, the specifier 'With seasonal pattern' can be applied to Major Depressive Disorder and Bipolar Disorder, when depressive episodes occur at characteristic times of the year. In most cases the onset is in autumn or winter, and the remission is in spring.

Circadian rhythm related treatments

Various treatments have been suggested

1. **Sleep deprivation** and partial sleep deprivation produces a significant antidepressant response in 40-60% of depressed patients. Unfortunately, more than 80% of responders relapse after they sleep next. Should it prove possible to prevent this relapse (Hemmeter et al, 2010) sleep deprivation would be a valuable therapy.
2. **Bright light therapy** applied during the day has been found effective in the treatment of SAD. Bright light therapy may also influence the course of depression in bipolar disorder (Sit et al, 2007).
3. **Melatonin** is available from health food shops. It has been used in the treatment of insomnia (with modest benefit) and depression (with little benefit).
4. **Agomelatine** – discussed above.

Choice

The issue raised by Parker (2009) of the heterogeneity of depression is important.

A recent review (Gartlehner et al, 2008) concluded that current evidence of effectiveness does not warrant the choice of one second-generation antidepressant [SSRI, or multiple action drug] over another. This is not consistent with Thase et al (2001) who found the dual action medications to be more effective than the selective medications. However, the difference is not great.

When one antidepressant is ineffective at recommended dosage, it is appropriate to re-evaluate the diagnosis, try higher doses of the chosen antidepressant and then try another (as necessary). Specialist advice is recommended before combining antidepressants or augmenting them with other agents.

For established depression, when remission is achieved, there is evidence to support long-term maintenance treatment (Hansen et al, 2008).

Augmentation of antidepressants

The response rate to antidepressants is poor, and unresponsive depression may be managed by specialists 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. Recently the atypical antipsychotics (particularly quetiapine; Bauer et al, 2009) have been found to be effective augmenters.

Bipolar depression

Until recently, episodes of unipolar depression and episodes of 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.

Manic episodes are features of the natural course of bipolar disorder, of course, but some evidence indicates that antidepressants may trigger manic swings. [Recent evidence suggests this danger may have been overstated (Grunze, 2008).]

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. Some authorities take a more extreme position and do not use antidepressants at all in the management of bipolar disorder. In these circumstances the depressed patient will be placed on a mood stabilizer, or if already on one, another will be added, and natural remission is awaited.

Lamotrigine (an anticonvulsant: sodium channel blocker and inhibitor of glutamate release) is an effective mood stabilizer in so far as it prevents relapse into bipolar depression, but not manic swings). It has been suggested as an acute treatment of bipolar depression – but this acute action is now challenged (Trankner et al, 2013).

Quetiapine (an atypical antipsychotic) has been approved in some countries for the treatment of bipolar depression.

If bipolar depression is not resolving, and the decision is made to avoid antidepressant medication, ECT is an option.

Medicate or/and talk?

Various types of psychotherapy (CBT being the most commonly provided) may be effective in the treatment of mild to moderate depression. A combination of psychotherapy and medication is recommended in depression not responding to psychotherapy, or server depression.

All interactions with patients present opportunities for psychotherapeutic elements, including support, non-possessive warmth, respect, encouragement, and assistance with unhelpful/illogical thinking such as, “I’m only a worthy person if other people like me”.

There has been criticism of the medical profession for prescribing medication rather than spending time talking with patients and helping them work through problems.

There may appear to be excessive prescribing of antidepressants because these medications have a place in the management of personality disorder and various forms of distress which have not responded to psychotherapy. For example, a patient with some personality vulnerabilities and mild depressive or anxious symptoms (but not satisfying the criteria of major depressive disorder), who does not respond adequately to verbal therapy, may obtain benefits (less irritability, tension and unhappiness) from a trial of antidepressants.

Depressive symptoms may be associated with personality vulnerabilities, and it would be reasonable to expect that people with such vulnerabilities would respond better to psychotherapy, while major depressive disorder (conceptualized as a brain disease) would respond better to antidepressant medication. However, work by Fournier et al (2008) appears to turn this on its head. They compared people with depression and comorbid personality disorder, to people with depression and no comorbid personality disorder after 16 weeks of treatment. They found that when there was comorbid personality disorder, people responded better to antidepressants (66%) than to cognitive therapy (44%), while when there was no personality disorder, patients responded better to cognitive therapy (70%) than to antidepressants (44%). The answer may be to do with the nature of personality disorder, the difficulty of modifying underlying personality disorder, and short term versus long term outcomes.

In the case of people with personality disorder, antidepressants will help some symptoms such as anxiety and irritability. But, the modification of personality

disorder is very difficult and may require extended treatment. On the other hand, people without personality disorder are well able to co-operate and benefit from psychotherapy, and reap great benefit from psychotherapy, especially when the depression is mild to moderate, while (as Moncrief (2008) points out) antidepressants may not actually treat the core symptoms of depression.

The future

Recently, 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 agonist) in acute depression (Catena-Dell'osso et al, 2013; Monteggia and Zarate 2015). This is particularly exciting because a great deficiency of current pharmacological therapy is the delay in onset of action. The mechanism of action remains unclear, but there is enormous interest in the development of an oral agent with similar effects.

Recently, there have been claims that in addition to neural changes, depression is associated with **immune** (and endocrine) **system** changes, suggesting new pathophysiological and therapeutic pathways (Leonard, 2013) – but, do date, the

addition of non-steroidal anti-inflammatory drugs to standard antidepressant treatment has not been encouraging (Andrade, 2014).

New, potential targets include mechanisms connected with substance P, corticotropin releasing factor (CRF), neurotrophins and the excitatory and inhibitory amino acid systems.

A nerutrophin receiving much attention is brain derived neurotrphic factor (BDNF), which sustains the viability of brain neurons. Stress suppresses the gene for BDNF, which may be the key to the reduction in size of the hippocampus in depression.

A little further away, but in development, are CRH receptor antagonists (Millan, 2009) and TRH analogues.

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 Cochrane review (Linde et al, 2008) found these to be superior to placebo, as effective as standard antidepressants, and to have fewer side-effects than standard antidepressants. Whether they enter routine clinical practice remains to be seen.

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