New drug treatments in psychiatric disease

During the last 15 years, a number of new drugs for the treatment of psychiatric disorders have been marketed in the UK. Their rate of appearance has, however, become too fast for psychiatrists to accumulate personal experience with them. Furthermore, few of the new drugs have been adequately tested in subjects who develop psychiatric symptoms in the context of neurological or medical disease.

Depression

Depression is a condition that spans a spectrum of symptoms and is difficult to define because it lacks unique features: it is more a condition of ‘traits’ and ‘states’. The common characteristics of depression are sadness, apathy, lethargy, low self-esteem and a tendency to withdraw from others, with insomnia (especially early morning wakening) and loss of appetite and sexual drive. Depression may show bipolar characteristics with episodes of mania, a state characterised by euphoria, mental overactivity, delusions of grandeur, flights of ideas, and rapid changes in subjects and thoughts.

The main evidence in support of the neurochemical basis of depression comes from the effectiveness of the drugs used to treat it, although the advent of more sophisticated functional imaging and newer atypical drug therapies has led to some re-evaluation of these neurochemical theories.

Endogenous depression

The cause of endogenous depression is not known: there is clearly a genetic component to the disorder but its nature is unclear. Several different therapies, especially those employing serotonin (5-hydroxytryptamine (5HT)), are designed to work by enhancing the activity of central monoaminergic synapses — although this often takes several weeks to achieve. This serotonergic network has its cell bodies located within the raphe nucleus of the brainstem and projects to all central nervous system (CNS) structures. The drugs work by the combination of desensitisation of inhibitory receptors in the presynaptic nerve terminals (5HT₁₂) and of the cell bodies (5HT₁₂) in the dorsal raphe nucleus; this leads to increased synthesis, firing rate and release of 5HT at the terminal synapses throughout the CNS. Further evidence for a role of 5HT in depression comes from the observation of a reduction in the level of 5HT and its metabolite, 5-hydroxyindole acetic acid, in the brainstem and cerebrospinal fluid (CSF) of patients with depression and suicidal tendencies.

Evidence that underactive noradrenergic synapses contribute to depression has required some re-evaluation following the successful use of selective serotonin reuptake inhibitors (SSRIs), although the more recent introduction of noradrenergic and specific serotonergic antidepressants (NaSSAs) has re-opened the debate on the role of noradrenaline in the pathogenesis of depression. Tricyclic antidepressants appear to cause desensitisation of the presynaptic alpha₂ autoreceptor, which would allow for greater noradrenaline release as this receptor normally inhibits the further release of this neurotransmitter.

A more detailed discussion on the drug treatment of depression is given below.

Disorders of mood and emotions

Depression, pathological sadness, suicidal ideas, agitation, panic attacks and generalised anxiety (alone or combined) remain common in the context of general hospital medicine. Often enough, symptoms may not meet diagnostic criteria for DSM IV or ICD-10 diagnoses but are none the less severe enough to cause misery and/or interfere with medical treatment. In these cases, and when reassurance is not enough, the clinician may want to prescribe drugs from two groups: SSRIs and NaSSAs (see Table 1).

Selective serotonin reuptake inhibitors

The SSRIs include the older drugs, fluoxetine, fluvoxamine, sertraline and paroxetine and citalopram, nefazodone
Table 1. New antidepressants.

| Antidepressant | Mode of action | Main indication | Dosage (mg daily) | Interactions | Side effects |
|----------------|----------------|----------------|------------------|--------------|-------------|
| Fluoxetine     | 5HT reuptake inhibitor | Depression and OCD | 20–40 | Lithium, alcohol | Nausea, agitation, sexual dysfunction, headache, hepatotoxicity |
| Paroxetine     | 5HT reuptake inhibitor | Depression, anxiety disorders, OCD | 20–40 | Lithium, alcohol | Nausea, agitation, sexual dysfunction, headache, hepatotoxicity? |
| Citalopram     | 5HT reuptake inhibitor | Depression | 20–40 | MAOIs, neuroleptics, lithium | Prolongs Q-T interval, suicide |
| Fluvoxamine    | 5HT reuptake inhibitor | Depression, OCD | 150 | Propranolol, phentoyin, carbamazepine | Nausea, vomiting, diarrhoea, abdominal pain |
| Sertraline     | 5HT reuptake inhibitor | Depression | 50–150 | Lithium, alcohol, diazepam | Dry mouth, diarrhoea, sexual dysfunction, tremor |
| Venlafaxine    | NA and 5HT reuptake inhibitor | Depression | 150–225 | Alcohol | Dry mouth, asthma, headaches, nervousness, impotence |
| Nefazodone     | 5HT₂ receptor blockade | Depression | 300–600 | Haloperidol, alprazolam, triazolam | Dry mouth, nausea, sleepiness, chills, confusion |
| Reboxetine     | NA reuptake inhibitor | Depression | 4–12 | Antifungals, anti-arrhythmics, anti-psychotics | Dry mouth, constipation, insomnia |
| Moclobemide    | Reversible MAO type A inhibitor | Depression | 300–600 | Tyramine-containing foodstuffs, levodopa, catecholamine | Sleep disturbance, agitation, dry mouth, vomiting, confusion |
| Mirtazapine    | Pre-synaptic alpha₂ receptor blockade | Depression | 30 | Potentiates alcohol and diazepam | Drowsiness, somnolence, dry mouth, headache, weight gain |

5-HT = serotonin; MAO = monoamine oxidase inhibitor; NA = noradrenaline; OCD = obsessive compulsive disorder.

and venlafaxine. Their mechanism of action is shown schematically in Fig 1. There is evidence that the lung may function as a reservoir for antidepressants with high affinity for the serotonin transporter. All SSRIs also produce inappropriate antidiuretic hormone (vasopressin) secretion and can cause hyponatraemia. To some extent, all SSRIs cause headache, dizziness, nausea, restlessness, drowsiness, insomnia, extrapyramidal side effects, and sexual dysfunction. Occasional side effects include loss of hair (in particular, fluoxetine and sertraline), miscarriages (fluoxetine), weak anticholinergic and extrapyramidal side effects (paroxetine). Inhibition of hepatic cytochrome enzymes by SSRIs may increase the plasma level of concurrent medication such as chlorpromazine, warfarin, propranolol and some anti-convulsants. SSRIs should be used with caution in subjects with renal impairment.

As treatments for depression, there is little practical difference between the SSRIs. Paroxetine has not yet been shown to work like the others in hospitalised depressive patients, but its anti-anxiety and anti-obsessional properties have made it popular in the hospital environment. In overdose, SSRIs are safer than conventional tricyclic antidepressants, but are just as likely to predispose to hip fracture in the elderly. Evidence for a 'discontinuation syndrome' affecting all SSRIs is also accumulating, with paroxetine particularly implicated. Hence, withdrawal from SSRIs should be slow, over about three weeks.

The bicyclic phthaline citalopram is the most specific of SSRIs in inhibiting 5HT reuptake, although it is not clear how advantageous this might be clinically. In addition, it prolongs the QT interval and may not be safe in some cardiac patients. Six suicides have so far been recorded in relation to this drug. Nefazodone, a phenylpiperazine derivative related to the old trazodone, is said selectively to block 5HT₂ receptors and hence cause less sexual dysfunction, agitation and sleep disturbance. However, nefazodone increases the bioavailability of haloperidol, alprazolam and triazolam.

Venlafaxine is a potent inhibitor of both serotonin and noradrenaline reuptake, and has few cholinergic and alpha-adrenergic effects. It has the disadvantage of occasionally raising blood pressure, but interacts less with concurrent medication. Moclobemide is the only available reversible selective monoamine oxidase A inhibitor. Although useful in the context of psychiatric practice, this drug
ways, first-pass (typically symptoms affecting Schizophrenia Schizophrenia Mirtazapine antidepressants paranoia sedation effects of synaptic and prove in presynaptic mianserin, mirtazapine enhanced NaSSA drugs. It is not dissimilar to mianserin, and blocks both central presynaptic alpha2 receptors, resulting in enhanced release of noradrenaline and noradrenergic terminals, and postsynaptic 5HT2, and 5HT7 receptors. After first-pass metabolism, only about 50% of mirtazapine is absorbed, which may prove a disadvantage. Its anti-anxiety effects seem good, but it causes sedation and dry mouth13.

Schizophrenia

Schizophrenia is a common disease, affecting 1% of the population worldwide. It can present in several different ways, more typically with positive symptoms of auditory hallucinations (typically hearing voices), delusions with paranoia and thought disorder; the more negative presentation resembles depression. These two sets of symptoms of schizophrenia, like the two forms of depression, may have a different neurobiological basis.

Schizophrenia has a significant genetic component, with the 10% risk for a first-degree relative developing the disease rising to 40% for the offspring if both parents are afflicted.

Aetiology of schizophrenia

There have been several theories of the aetiology of schizophrenia, the early ones proposing that it was due to the production of some endogenous psychotogen, perhaps a transmethylated derivative of dopamine. Subsequently, it was proposed that schizophrenia was due to overactivity of the central dopaminergic pathways, especially the mesolimbic projections, with relative sparing of the dopaminergic nigrostriatal pathway. This has been further modified to a theory suggesting that the negative symptoms of schizophrenia may be due to hypodopaminergic activity in the mesocortical system, whilst the psychotic symptoms result from hyperdopaminergic activity in the mesolimbic system. Indeed, patients appear to have increased levels of the D2 dopamine receptors, but decreased numbers of D1 receptors in the frontal cortex, independent of any medication they may have received. In addition, schizophrenics show frontal hypoperfusion which, coupled to previous studies showing non-progressive cerebral ventricular dilatation without gliosis, led to the proposal that schizophrenia may be a neurodevelopmental disorder. It is not known which part of the brain fails to develop normally, although the amygdala, frontal and temporal lobes seem likely candidates. Alternatively, it may involve non-dopaminergic transmitter networks, contrary to the belief that any alterations seen in these pathways are secondary to the alterations in dopaminergic pathways.

Treatment of schizophrenia

The mainstay of therapy in schizophrenia remains the use of drugs that block the dopaminergic receptors, of which there are least 5 subtypes (D1–D5 receptors).

Disorders characterised by delusions and hallucinations

General hospital patients may exhibit delusions and hallucinations in a variety of clinical contexts. These symptoms, together with temporo-spatial disorientation, are characteristic of the acute confusional and toxic states not uncommonly induced by therapeutic drugs14. Acute psychotic states may also occur in clear consciousness in the wake of brain surgery, steroid medication, and traumatic stress.

Management of delusional disorders and hallucinations

The golden rule in the management of all these cases is to avoid medication, but the clinician may be forced to prescribe chlorpromazine, haloperidol
or droperidol when symptoms interfere with medical management. However, their side effects (particularly important, for example, in the management of subjects with basal ganglia disorders) have led some to consider using ‘atypical’ neuroleptics in these cases. (‘Atypical’ means anti-psychotics which, because of their novel chemical structure, produce far less extrapyramidal side effects.) Their role in general hospital practice has not yet been investigated, but it is predicted that their delayed action will limit usage in acute hospital psychiatry.

Among the atypical neuroleptics, the physician is more likely to have come across clozapine and risperidone (now called ‘old’ atypical) than olanzapine and sertindole (Table 2). All four are expensive (£100 per patient per month), and their prescription is subject to financial control in some health regions. The primary indication for all of them (particularly clozapine) is schizophrenia characterised by cognitive, emotional and volitional deficits, and social dysfunction. Because clozapine causes hypotension, tachycardia, drowsiness and agranulocytosis, it requires monitoring (in the UK, undertaken by a national patient monitoring service run by the manufacturers). This also means that coprescription with drugs known to cause agranulocytosis (e.g., carbamazepine) is particularly contraindicated.

Risperidone is a benzisoxazole derivative with high binding affinity to both 5HT and dopamine receptors. In spite of its high occupancy of striatal D2 receptors, it does not appear to cause many extrapyramidal side effects. Meta-analysis of 11 double-blind randomised control trials has shown that the short term efficacy of risperidone is com-

| Table 2. Main atypical anti-psychotics. |
|--------------------------------------|
| Anti-psychotic | Mode of action | Main indication | Dosage (mg daily) | Cost (£) (for 28 days treatment) | Interactions | Side effects |
| Clozapine | Affinity for D1, alpha, & alpha, 8 receptors, H, and M, receptors | Positive & negative symptoms of schizophrenia, Refractory illness | 300–900 | 75–150 | Not to be combined with lithium (danger of neuroleptic malignant syndrome). In combination with benzodiazepines may cause respiratory arrest. | Weight gain, seizures, myoclonus, severe hypotension, tachycardia, drowsiness, agranulocytosis. Monitoring required |
| Risperidone | Affinity for 5HT2, alpha, 8 receptors, adrenergic receptors, symptoms of schizophrenia | Positive & negative symptoms of schizophrenia | 2–8 | 70–145 | Not suitable for treatment of psychosis of Parkinson’s disease. | Weight gain, hypotension, hyperprolactinaemia, neuroleptic malignant syndrome. Sudden cardiac death, cardiac arrhythmia. |
| Sertindole | Suspension of availability on 2nd December 1998 | | | | | |
| Olanzapine | Affinity for D1, D2, 5HT2, 5HT1, and M, receptors | Positive & negative symptoms of schizophrenia | 7.5–20 | 55–210 | Little effect on P450 cytochrome enzymes (hence low potential for interaction with drugs handled by these enzymes). | Weight gain, hypotension, drowsiness, dry mouth, nausea. |
parable to other neuroleptics in the treatment of schizophrenia and that this drug is associated with fewer extrapyramidal symptoms than conventional neuroleptics.

Olanzapine seems to cause less agranulocytosis and lowering of seizure threshold than risperidone and clozapine because it does not antagonise alpha2 adrenergic receptor function. It is more effective than haloperidol in the treatment of deficit symptoms in subjects with schizophrenia. Olanzapine has been used with some benefit in the management of psychotic symptoms in the context of neurological disease (e.g. hallucinations in Parkinson’s disease).

Sertindole will not be discussed here; it has been withdrawn from the formula because of its serious cardiac effects.

Miscellanea

Two other new drugs are worth mentioning. For a long time, and after the withdrawal from the market of mazindol, methylphenidate remained the only drug available for the treatment of narcolepsy and some hypersomnia syndromes. Recently, modafinil has become available. A putative central post-synaptic alpha2 adrenergic receptor agonist, this drug may act on cells of the anterior hypothalamic nucleus and it has little effect on dopaminergic transmission. Drug trials have shown that modafinil has positive effects on excessive daytime sleepiness but not on cataplexy. At a dosage of 400mg, however, it tends to produce nausea and nervousness.

Sildenafil citrate is now too well known to require description. It works particularly well in psychogenic impotence syndromes (not necessarily related to ‘stress’). It is unfortunate that these do not figure in the list of central indications recently provided by the Department of Health.

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