Business Trends Editor: Steve Carney
s.carney@elsevier.com

business trends

The future of antidepressants

Frances Learner, frances.learner@informa.com

In 2003, 40,000 children and teenagers across the UK were taking prescribed selective serotonin reuptake inhibitors (SSRIs) for the treatment of depression at any one time. Half of these prescriptions were for Lilly's Prozac® (fluoxetine). The same year, the UK Department of Health stated that the majority of SSRIs, the most commonly prescribed type of antidepressant, should not be administered to children. Coming in the wake of research linking some SSRIs to an increased rate of several adverse events, including insomnia, agitation, weight loss, headache, tremor, loss of appetite, self-harm and suicidal thoughts in under-18s, the announcement sparked controversy over the safety of these antidepressants in children. It also left the pharmaceutical industry with the challenge of finding new ways of combating depression in the young. Treatment of depression has historically been controversial (as electric shock therapy and the use of addictive drugs, such as benzodiazepines, exemplify); more recently, classes of drugs that were once thought safe treatments for depression have fallen by the wayside.

Feeling low

Depression is a mental state characterized by feelings of sadness and despair that occur in the absence of causative factors (depression is therefore distinct from, for example, the grief caused by the death of a loved one). There are several theories on the exact aetiology of depression, but the consensus subscribes to the biogenic amine hypothesis of affective disorders. This theory postulates that functional underactivity of brain monoamines [e.g. dopamine, noradrenaline (norepinephrine) and serotonin, also known as 5-hydroxytryptamine (5-HT)] causes depression, whereas functional overactivity is associated with mania – particularly that seen in bipolar disorder. The World Health Organization estimates that by 2020, depression will be the highest ranking cause of disability in developed countries, second only to ischaemic heart disease worldwide. In the UK, it is estimated that 70% of women and 40% of men will experience significant depressive symptoms by the age of 65. British general practitioners diagnose depression in 3% of the population every year. Of these patients, 10% will be referred to a psychiatrist, and a third of these will be admitted to hospital. The USA records 18.8 million new cases of depressive disorders per year. Worryingly, it is estimated that only 60–70% of patients worldwide respond to currently available antidepressants.

Prozac® nation

First-generation antidepressants include biogenic amine uptake blockers, known as tricyclics because of their three-ring structure, and monoamine oxidase inhibitors (MAOIs). MAOIs were the first type of antidepressant in use, dating back to the 1950s. Monoamine oxidase (MAO) is found intracellularly in nerve terminals, where it controls the free cytoplasmic pool of monoamines. Researchers believe MAOIs relieve depression by preventing MAO from catalysing the intracerebral degradation of extracellular noradrenaline, 5-HT and dopamine. As a result, levels of these compounds within the brain remain high, boosting mood. Classical MAOIs tend to be irreversible inhibitors and non-isoform selective.

Unfortunately, MAOIs can be responsible for a variety of adverse effects, which can include hypertension, changes in heart rate and rhythm and weight gain. One of the more famous side effects is the onset of dangerously high blood pressure if combined with food containing tyramine – this is colloquially known as the 'cheese effect'. Consequently, irreversible MAOIs are rarely used these days; however, there are several reversible MAOIs, with less potent side effects, such as Roche's Aurorix® (moclobemide) and Sanofi-Aventis's Lifril® (pirlindole) and Humoryl® (toloxatone), that are still available.

Tricyclic antidepressants inhibit the reuptake of 5-HT and noradrenaline and, to a lesser extent, dopamine. They hit the market in the 1960s and they remained the first line of treatment for depression through the 1980s. They are thought to be just as effective as SSRIs. However, their side effects included tachycardia, arrhythmias, orthostatic hypotension, tremor, seizures, weight gain and, more importantly, toxicity in overdose. This rendered them less popular than the less toxic alternatives that have entered the market.

Second-generation antidepressants include SSRIs, broad-spectrum antidepressants (drugs that inhibit the reuptake of a combination of 5-HT, noradrenaline and dopamine) and α_2-adrenoceptor inhibitors (AAIs) (Figure 1).

1359-6446/05/$ – see front matter PII: S1359-6446(05)03553-1

business trends

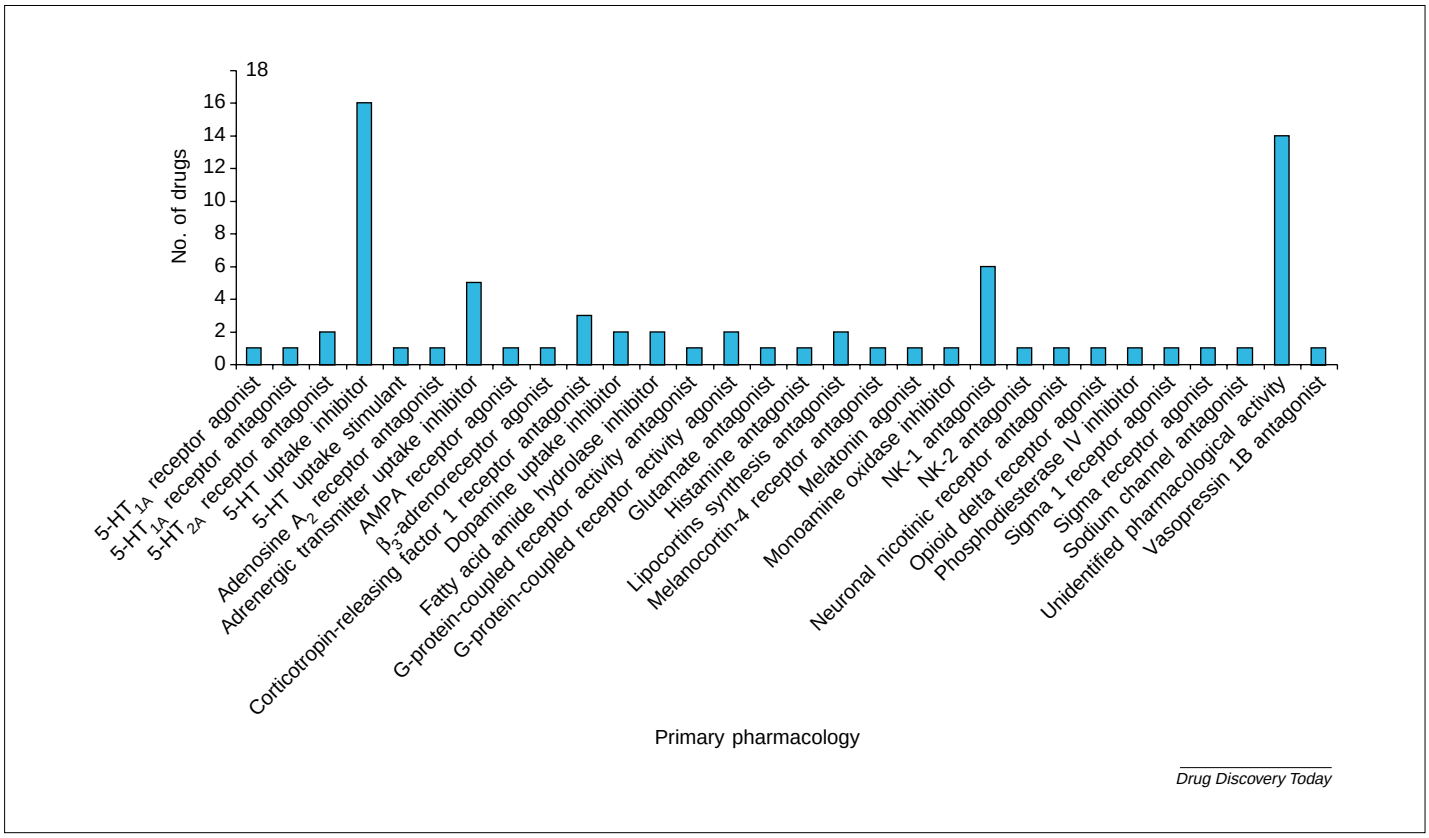

FIGURE 1

Pharmacology of antidepressants currently in development. Abbreviation: AMPA, aminohydroxymethylisoxazolyl propanoic acid.

They effectively replaced the earlier forms of antidepressants as a result of their improved efficacy and safety profiles. Combination 5-HT and noradrenaline reuptake inhibitors block reuptake of both monoamines with little or no affinity for adrenoceptors or muscarinic or histamine receptors. Medications in this group are sometimes known as dual reuptake inhibitors and include venlafaxine, launched as Efexor® by Wyeth, and duloxetine, Lilly's Celexa®. The only combination noradrenaline and dopamine reuptake inhibitor approved by the US FDA specifically to treat depression is buproprion, launched by GlaxoSmithKline (GSK) as Wellbutrin®.

AAIs increase noradrenoceptor and serotonin receptor neurotransmission by blockade of α_2-autoreceptors and α_2-heteroreceptors. The increased amount of free noradrenaline and 5-HT improves and elevates mood. Mirtazapine (Remeron®) is the only AAI approved by the US FDA specifically to treat depression.

SSRIs inhibit 5-HT uptake more selectively than tricyclics and have weak interactions with nerve terminal receptors (they display virtually no noradrenaline or acetylcholine antagonism). SSRIs and related antidepressants have been used to treat depression for the past two decades. The first drug in this class was fluoxetine (Prozac®), which reached the US market in 1987, and was to become one of the greatest blockbusters of all time. As with all antidepressants, there are several adverse effects associated with the use of SSRIs (increase in agitation, anxiety, nervousness, sexual dysfunction, gastrointestinal discomfort, nausea and reduced appetite), but they are safer than tricyclics when the possibility of overdose is considered. As depressives are arguably the patient group most likely to attempt suicide, it is of paramount importance that they cannot use their medication to harm themselves. This is perhaps the greatest advantage the SSRIs had over the previous generations of antidepressants, and until recently it was thought that the therapeutic benefit of this class of drug outweighed the risks.

Risk versus benefit

In 2004, a review undertaken by the Royal College of Psychiatrists Research Unit (UK) analysed the results of five published and six unpublished studies on the effects of SSRIs on children. They found, to quote, 'instead of being safe and effective, the risk:benefit reversed'. Of the five SSRIs reviewed (fluoxetine, paroxetine, sertraline, citalopram and venlafaxine), only fluoxetine offered more benefits than risks in children. For example, unpublished studies of venlafaxine suggested that the drug increased suicide-related events, such as suicidal thoughts or attempts, 14-fold compared with placebo. The US FDA picked up the trail and asked all manufacturers of antidepressants to include in their labelling a boxed warning of the risks of suicidality in children and adolescents being treated with SSRIs. However, recently, the FDA modified its warning, stating that the drugs 'increased the risk of suicidal thinking in short-term studies of adolescents and children'. These findings could have potentially big implications for the

business trends

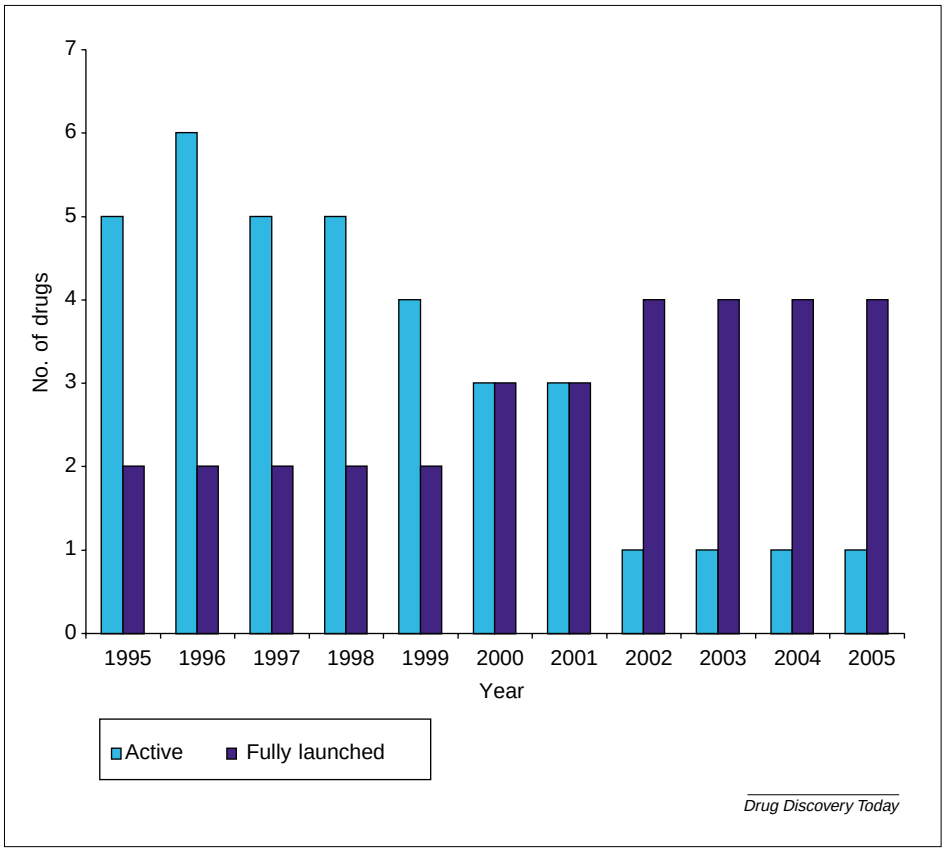

FIGURE 2

Trends in the marketing and development of monoamine oxidase inhibitor antidepressants.

industry. *The Lancet* reported that GSK sold almost US$5 billion-worth of paroxetine in 2003, and so would have inevitably felt the blow when, from November to December 2004, the number of children and adolescents taking antidepressants decreased by 16% compared with the same period the previous year.

Paroxetine, better known by its trade name Seroxat®, was intended to pick up where Prozac® left off. The list of the companies with a stake in it reads like a roll call of 'big pharma' – Novo Nordisk, Mitsubishi Pharma, Abbott, Johnson & Johnson, Gedeon Richter and Novartis are also involved, not forgetting GSK. Seroxat® has been the subject of newspaper articles and television documentaries alleging that patients attempting to come off the drug experience a psychological disorder similar to withdrawal and could attempt self-harm, or even suicide. Internet support groups appear to agree with the allegations.

Earlier this year, an article by the *British Medical Journal* concluded that the routine prescription of antidepressants to children should be discouraged because of the increased risk of suicidal thoughts and behaviour. The article was based on three recent studies. The first, a review of published trials, found an almost twofold increase in suicide and suicide attempts in users of SSRIs compared with placebo or other therapies. The second, a review of published and unpublished trials, found no evidence for an increased risk of completed suicide, only weak evidence of increased self-harm and inconclusive evidence of an increased risk of suicidal thoughts. Lastly, a nested case-control study based on information from the UK General Practice Research Database (a computerized database of anonymous longitudinal patient records from general practice) found that SSRI users were not at an increased risk of suicide or non-fatal self-harm compared with tricyclic users. However, in patients 18 years old or younger, evidence indicated a higher risk of non-fatal self-harm in those prescribed SSRIs. Previously, the UK government's Committee on Safety of Medicines banned the use of all SSRIs, except Prozac®, in children. However, recent recommendation by the European Medicines Agency for a Europe-wide, under-18s ban of Prozac® and other antidepressants for standard depression is to be considered by the European commission.

These findings might not be as detrimental as they first appear. The developmental trends of MAOIs – a first-generation class of drugs that has effectively had its day – show what might be expected: a steady increase of drugs moving to fully launched, stabilizing over the past few years, and a steady decline in drugs in active development, also stabilizing in the past few years (Figure 2). The SSRIs do not conform to this pattern. The number of drugs launched in all major markets initially increased but appears to have reached a plateau, and SSRIs in active development seems to be back on the increase after their turbulent recent history (Figure 3). Advocates for the use of antidepressants point out that the rate of teen suicide increased from 5.9 to 11.1 per 100,000 between 1970 and 1994, but decreased to 7.4 per 100,000 in 2002, around the time SSRI prescriptions for children were increasing. In other new directions of research into this area, researchers from Duke University Medical Centre (Durham, NC, USA) have found a mutation in a gene with a protein product that is involved in the synthesis of serotonin. People with depression that carry this abnormal gene also show resistance to treatment with SSRIs. In another report in the *American Journal of Psychiatry*, researchers from the University of Pittsburgh (PA, USA) found that blood platelets have serotonin reuptake transporters that are identical to those found in the brain. Analysis of the blood of 23 depressed adolescents before and after SSRI treatment showed that those who responded well to drug treatment had platelets that were much less sensitive to serotonin. The future of the SSRI as a main player in the antidepressant market remains opaque.

The future of antidepressants

With the possibility of established antidepressants losing favour, the

business trends

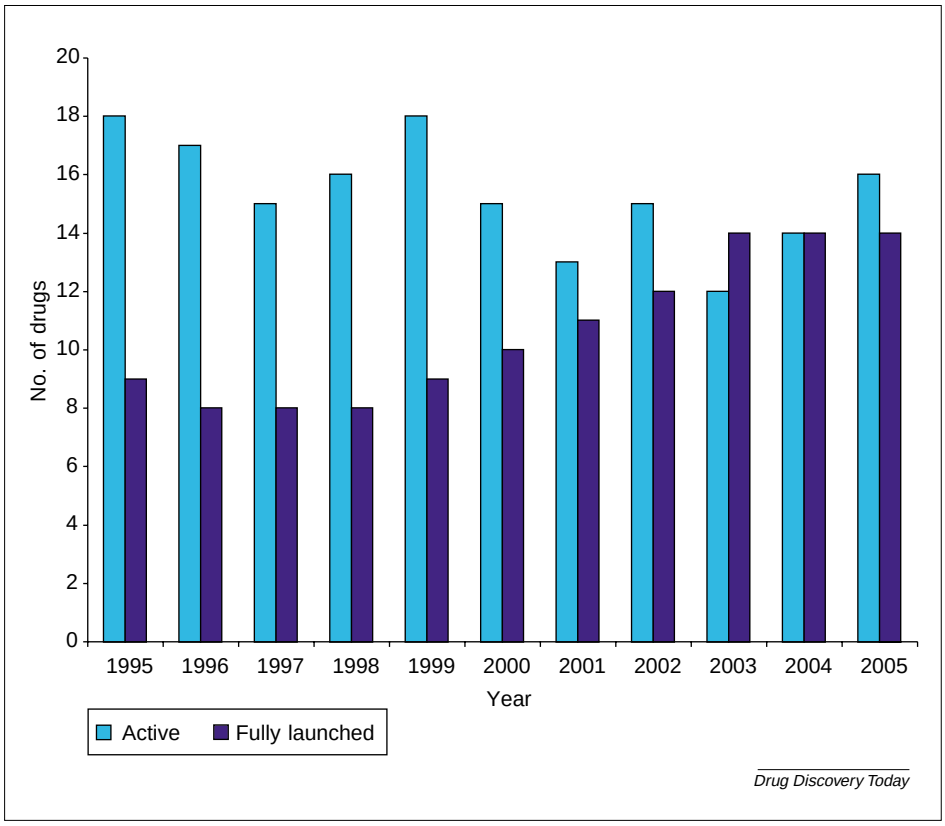

FIGURE 3

Trends in the marketing and development of selective serotonin reuptake inhibitor antidepressants.

pharmaceutical industry is rising to the challenge of producing depression therapeutics with novel mechanisms of action. Antagonists of neurokinin-1 (NK-1; also known as substance P) are among the promising new types of antidepressants to undergo investigation. GSK, Roche and Merck have all reached Phase II with this new class of drug, which, thankfully, appears to have a better safety profile than its predecessors. Another new area of investigation focuses on corticotropin-releasing factor 1 receptor antagonists. Bristol-Myers Squibb currently has a product in Phase II development, whereas Sanofi-Aventis's product is at the preclinical stage. Another direction of development includes γ-aminobutryic acid agonists for the treatment of bipolar depression, such as the recently launched pregabalin (Pfizer's Lyrica™).

Analyses show that 5-HT uptake inhibitors are still leading the field in terms of antidepressants under development. But with other classes of drugs, such as NK-1 inhibitors, poised to carve a niche in this market, the future of antidepressant development is hard to predict.

Frances Learner
Pharmaprojects,
PJB Publications,
69–77 Paul Street,
London,
UK, EC2A 4LQ
e-mail: frances.learner@informa.com
www.pharmaprojects.com