# EDITORIALS

## 5-HT blockers and all that

One of the unsung medical heroes since the 1939–45 war has been the antidepressant. Properly described as a class, it can stand up to antibiotics, and all the medical "antis", in terms of efficacy. The illness it treats, "depression", is widespread, with data from the Epidemiologic Catchment Area projects in North America suggesting a lifetime prevalence for affective disorders of 10% and a period prevalence of 6·0%.[1]

So, depression is common and, frequently, horrendous. Patients often say that, in their experience, depression is worse than conditions such as cancer or a broken hip. (Anyone doubting the nature of the disorder should read *Memories* by Sir Julian Huxley.[2] Despite "protective factors" like good family background and high intelligence, depression runs in his family. Not until he was over 50 did a treatment—electroconvulsive therapy—emerge that shortened the natural history of his disease.) The illness varies in severity but medically is important in that it shortens life in terms of natural and unnatural causes.[3] It is an episodic illness, with definite seasonal and lifetime characteristics.[4]

Successful treatments of depression were ushered in by electroconvulsive therapy in the 1930s. Heterocyclic antidepressants and monoamine oxidase inhibitors followed in the 1950s, lithium in the 1960s, and carbamazepine, a mood-stabilising anticonvulsant, in the 1970s. The heterocyclic antidepressants have proved to be firm favourites. Amitriptyline has become the most popular antidepressant of all, which is extraordinary in view of the pronounced anticholinergic side-effects. Extensive drug trials have shown that the antidepressant drugs are better than placebo, work in at least 70% of well-defined cases, and are equally effective. Their mechanism remains a mystery since it is impossible to access living brain properly. Nevertheless, there are plausible ideas about neurotransmitters and the heterocyclic antidepressants have been deemed to block the re-uptake of noradrenaline or serotonin or both. Thus antidepressant treatment has had a focus and a rationale. Lately, however, the patient has become a consumer. With this in mind it has to be remembered that the atropine-like side-effects of the antidepressants cannot be dismissed lightly. They dry up the nasopharynx, constipate, may irritate the heart, may cause fainting, and frequently sedate. These features are not consumer friendly. Inevitably, the consumer has begun to weigh therapeutic effects against side-effects.

The pharmaceutical industry, which has long thought about this difficulty, two decades ago looked for a better side-effect profile and decided to concentrate on serotonin or 5-hydroxytryptamine (5-HT). This gamble entailed finding a drug that would prevent the re-uptake and, thereby, increase the concentration of 5-HT at the appropriate synapse. Eli Lilly in Indianapolis was the first to market in North America, although other 5-HT uptake blockers have been investigated. There had been some 5-HT uptake blockers among the heterocyclics, but the side-effect profiles were not satisfactory. Since its introduction 2 years ago, the Lilly product, fluoxetine ('Prozac'), has generated annual sales of US $500 million and is expected to realise a billion dollars. This financial success is spectacular and has aroused considerable interest in the media. Why all the attention?

Fluoxetine (N-methyl-3-phenyl-3-propylamine) is a bicyclic antidepressant, with a well-characterised activity profile.[5] To the public, it is plain and simple. A 20 mg dose is taken each morning and there are no increases in dose. Blood levels are not required. It is a marketing dream, like the contraceptive pill. Warding off depression is like preventing pregnancy—pop the pill and be happy. Side-effects are said to be mild and evanescent. No longer do patients have to cope with the exigencies of being dry mouthed, dizzy, constipated, and gaseous, or steadily getting fat. Instead they may be nauseous, headachy, overly stimulated, and sleep fitfully; there will, however, be no weight gain. There are more worrisome features. The drug has a long half-life and, as a potent inhibitor of mono-oxygenases, it may predispose to drug-drug interactions; it may also induce weight loss, which is not desirable in those who are already thin as a result of depression. Other side-effects include profound

hyponatraemia and the promotion of suicidal thoughts and behaviour.

In this postindustrial era people spend their time servicing each other's needs. Medicine is no exception. Depression is a horrid illness and it requires a kind and gentle treatment. Fluoxetine may be no more effective than other antidepressants but may be smoother. There are high hopes in the pharmaceutical industry that the 5-HT uptake blockers will become standard treatment for depression, and even for conditions such as anorexia nervosa and obsessive compulsive neurosis. However, should the drug fail, the long half-life of fluoxetine makes it difficult to switch immediately to other antidepressant treatment. Undoubtedly pharmaceutical companies will aim to produce drugs with shorter half-lives. Moreover, the 20 mg capsule is the smallest dose currently available, and this may be too large for many elderly patients.

Fluoxetine represents US know-how at its best and has been aired in the media at a time when biological psychiatry has become supreme in North America. However, we do not know whether the drug is better than earlier antidepressants, whether 5-HT is the main neurotransmitter in depression, and whether the 5-HT uptake blockers have acceptable side-effects. The cost of $1.50 daily may be prohibitive when individuals have to pay their own drug bills.

The possible gainsay of all this is that depressive illness is becoming more recognised, more admissible and, at least for those with the wherewithal, more treatable.

1. Bland RC, Newman SC, Orn H. Epidemiology of psychiatric disorders in Edmonton. *Acta Psychiatr Scand* 1988; **77** (suppl 338).
2. Huxley J. Memories. London: Allen and Unwin, 1970.
3. Murphy JM, Monson RR, Olivier DC, Sobol AM, Leighton AH. Affective disorders and mortality: a general population study. *Arch Gen Psychiatry* 1987; **44:** 473–80.
4. Thompson C, Silverstone T. Seasonal affective disorder. London: Clinical Neuroscience, 1989.
5. Freeman H. Progress in antidepressant therapy. Fluoxetine: a comprehensive overview. *Br J Psychiatry* 1988; **153** (suppl 3).

## Antenatal screening for toxoplasmosis in the UK

Toxoplasma infection, when acquired in pregnancy, can cause fetal infection with potentially serious consequences for the newborn infant, including chorioretinitis, cerebral calcifications, hydrocephalus, and neurological damage. Only infants of mothers who acquire a primary infection in pregnancy (which is usually symptomless) appear to be at risk;[1] on this basis serological screening has been adopted in some countries—notably, France and Austria. The French national screening programme was established in 1976 with the aim of reducing the number of infants born with congenital toxoplasmosis.[2,3] A toxoplasma IgG antibody screening test is carried out on serum collected at the first antenatal visit; if the test is positive an IgM test is done to determine whether the infection has been recently acquired; if the initial IgG test is negetive, repeat tests are carried out monthly throughout pregnancy to detect new infections. Identification of acute toxoplasma infection results in an offer of therapeutic abortion; treatment with spiramycin to reduce the likelihood of transmission of infection to the fetus; and/or further evaluation, which includes ultrasound scanning to detect fetal abnormalities, and amniocentesis, or fetal blood sampling by cordocentesis at 20–24 weeks of pregnancy, to confirm fetal infection.[3] In this issue (p 359), Dr Jeannel and colleagues discuss the French screening programme, which in their opinion is not as straightforward as had been thought.

In the UK, the possibility of screening in pregnancy for the prevention of congenital toxoplasmosis has received considerable media attention and several microbiologists have supported such a policy.[4-7] Not surprisingly, there has been an increasing public demand for antenatal tests for toxoplasmosis. However, the possible adverse effects of this expansion of ad hoc testing have not been adequately discussed. Before any screening programme is introduced, the benefits and risks of the programme must be assessed; this approach requires reliable epidemiological information, much of which is unavailable. One needs to know the prevalence of toxoplasmosis immunity in women of childbearing age, the incidence of infection in pregnancy, the risk of transmission to the fetus, and the likelihood of damage, both short term and long term. In addition, the sensitivity and specificity of the screening and diagnostic tests must be known, so that their predictive value in the UK population can be estimated. Finally, the efficacy of the intervention offered needs to be assessed.

In France, about 80% of pregnant women are reported to have evidence of past infection with toxoplasma,[8] but the figure in the UK is much lower. In London, the prevalence is about 20%.[9-11] In 1986, Desmonts assessed the seroprevalence of toxoplasma antibodies in prepregnancy sera from women in Paris, Padua, Stuttgart, and London and found rates of 75%, 56%, 36%, and 23%, respectively. Thus, only about 20–25% of French women will require repeated testing throughout pregnancy, whereas a similar programme in the UK would mean the monthly testing of nearly 80% of pregnant women.

Estimates of the rate of transmission of infection from mother to fetus vary, but are about 40%.[1] This rate of fetal infection is related to the time of acqusition of maternal infection and increases from about 15% in the first trimester to 60% in the third. However, if fetal infection occurs the risk of severe fetal damage is inversely related to the gestational age of acquisition.[12] Overall, about 90% of congenitally infected infants have no clinical manifestations at birth.[12,13] Although those advocating antenatal screening often emphasise the high incidence of subsequent sequelae in apparently healthy infants, few studies have adequately investigated this aspect and the results of such investigations are difficult to interpret because