BEHIND THE HEADLINES

Behind the Headlines reproduces selected clinical articles which have been published online in *The Bulletin* in the preceding quarter, in order to disseminate this topical clinical information to a wider audience (including those Fellows and Members without internet access).

The reproduced articles aim to educate and inform the wider College membership about specialist items that have been reported in the international medical and mainstream media: to the non-specialist it may not always be clear how accurately such stories – whether reporting results of scientific studies or issues of concern to health professionals – have been reported. To clarify such situations, expert clinical comments are commissioned on matters that are recurring in the international media, or about which different reports have caused conflicting messages for those practising in other specialties.

It is hoped that this section will, in time, become an invaluable source of independent and authoritative advice for Fellows and Members interested in updating their knowledge of new developments in other specialties.

IN THIS ISSUE

- The pros and cons of SSRI antidepressants;
- euthanasia today; and
- reports of a single-injection cure for diabetes are premature.

THE PROS AND CONS OF SSRI ANTIDEPRESSANTS

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BACKGROUND

During the last year public and media concern has increased in the UK regarding the prescribing of the selective serotonin reuptake inhibitor (SSRI) antidepressant 'Seroxat' (paroxetine). Concern has focused on claims that the drug could be addictive and that it has led to an increase in suicidal thoughts, and was heightened after an independent expert group, established to examine the long-term safety of paroxetine, had to be disbanded following revelations that two of the four member group had shareholdings in the company which manufactures the drug. In parallel to this, conflicting scientific studies have been published which have suggested both a decrease and an increase in the risk of suicide in patients prescribed SSRIs. To provide our general medical audience with much needed clarity on this topical situation, Dr George Masterton was commissioned to provide this expert commentary.

Recently the spotlight of medical investigative journalism has fallen on one of the new generation of selective serotonin reuptake inhibitor (SSRI) antidepressants, paroxetine, with two *Panorama* television programmes devoted to its alleged hazards,[1] notably discontinuation reactions and increased propensity to suicide. Where such journalism leads, medical litigation specialists follow, patients understandably become angry and worried – and doctors confused and uncertain. So it is timely to comment on the current standing of the SSRIs.

First, the clinical problem: depression is a common, distressing illness with appreciable mortality, principally because of suicide. When moderate or severe specific treatment is required antidepressant medication remains the mainstay of therapy.

- Effectiveness
  The SSRIs are equally effective. Of the newer antidepressants, venlafaxine may be slightly more effective. In meta-analyses the tricyclics (TCAs) also tend to emerge as more effective, especially when the illness is severe.[2]

- Tolerability
  The SSRIs are undoubtedly better tolerated than the TCAs, such that patients are less likely to drop out of treatment. There is not much difference between the SSRIs and most of the other newer antidepressants. Among the SSRIs, fluvoxamine is distinctly inferior, mainly because of more severe gastrointestinal side-effects.

- Toxicity
  While SSRIs are safer and better tolerated than the TCAs, they are not free from either potentially significant side-effects or hazards. Gastrointestinal (GI) symptoms, sweating and insomnia are well-known side-effects, but there are other important problems regularly encountered with this group of drugs, notably sexual dysfunction, weight change, agitation and vivid dreams or nightmares.

  The propensity for SSRIs to provoke upper GI bleeding through impairment of platelet aggregation has been confirmed, a risk that is clinically important when prescribing for the elderly and patients with a history of previous GI bleeding.[3]

- Discontinuation reactions
  This syndrome, and whether it does or does not define addiction, is the main battleground over paroxetine.

  Discontinuation reactions can occur with all classes of antidepressant – indeed they were first recognised with imipramine in the 1950s. The syndrome differs from one type of antidepressant to another, and may figure symptoms that seem unusual in drug withdrawal. For the SSRIs the commonest complaints are dizziness and light-headedness, while sensory disturbances – numbness, tingling and electric shock-like spasms – are characteristic. Several strands of evidence indicate these reactions occur more often with paroxetine among the SSRIs.[4] The disorder is usually mild, but the subheading to a *British Medical Journal* editorial that it is 'preventable and simple to treat' is an oversimplification.[5]

  While a drug withdrawal state leads to a commonsense inference of addiction to that drug, the clinical diagnosis of drug dependence is based on the presence of several diverse features being established, none of which are diagnostic alone – so in ICD-10, for instance, an abstinence syndrome is one of six cardinal features, three of which must be present to make the diagnosis. Hence drug dependence can occur without an abstinence syndrome, while a drug withdrawal state on its own is insufficient to diagnose dependence.

- Loss of effect
  Loss of effect is a problem with longer term use of the SSRIs. Although less well-known than the discontinuation reaction, it is clinically significant, and difficult to recognize and treat. The phenomenon is thought to be due to down-regulation of the neuro-receptors, and may occur more often with the SSRIs than with other antidepressants. Its importance has not yet been fully realised.

- Suicide
  A major benefit of the SSRIs is the much-reduced toxicity in overdose compared with the TCAs (and probably venlafaxine too[6]), such that their use in depressed patients has been advocated as a key suicide-prevention measure. This proposition has generated a lot of studies with diverse methodologies, yet the position is still unclear. To illustrate this, over the past three months a study found suicide rates fell in Australia as exposure to SSRI antidepressant prescribing rose;[7] an analysis of US Food and Drug Administration (FDA) data on suicides in antidepressant clinical trials found no difference in risk between SSRIs, other antidepressants and placebo;[8] and a selective review of trials and meta-analyses found an increased risk of self harm and suicide in patients and volunteers prescribed SSRIs.[9]

The second major concern about paroxetine is that it may stimulate suicidal ideation and behaviour in vulnerable patients, a charge that was previously levelled at fluoxetine.

- Drug interactions
  With the SSRIs, the key to this aspect is their metabolism via cytochrome P450 enzymes: the interactions are with other drugs that compete for this metabolic pathway. Sertraline and citalopram have the lowest potential for drug interactions among the SSRIs, and are to be preferred, along with other classes of antidepressants, in patients taking competitor drugs. Finally, there are potentially hazardous interactions with dopaminergic and serotonergic drugs, resulting in a serotonin syndrome, or crisis in extreme cases.

So what is the advice for a physician whose patient has expressed concern about taking paroxetine? First, discuss the issues with the patient; switch to an alternative if the patient has lost confidence in the drug and needs to continue on an antidepressant – stop the drug if they do not; in all cases, explain the risk of a discontinuation syndrome, its likely content and generally short duration, and agree a management plan, emphasising the need to phase out the drug rather than stop abruptly.

And what about paroxetine? A few years ago the media focused on fluoxetine because of an alleged association with suicides and homicides, an effect that generated a class action and medical debate. The same process seems to be occurring now with paroxetine. At present, paroxetine remains a suitable option for adult patients who are depressed, but it would be sensible to discuss these recent concerns with the patient before prescribing it.

POSTSCRIPT (30 JUNE 2003)

- Children and adolescents
  Within the past fortnight the Committee on the Safety of Medicines (CSM) in the UK has concluded that the evidence is sufficiently strong to recommend that paroxetine should not be prescribed to treat depression in children and adolescents. A review has indicated paroxetine is not an effective antidepressant in patients under 18 years of age while the risk of episodes of self harm and potentially suicidal behaviour is 1·5–3·2 greater with paroxetine compared with placebo. The CSM's prescribing and discontinuation recommendations for paroxetine[10] in adults accords with this review. The CSM is monitoring the situation closely.

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GENERAL READING

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EUTHANASIA TODAY

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'To please no one will I prescribe a deadly drug, nor give advice which may cause his death.' These words from the Hippocratic oath date from a time (third to sixth centuries BC) when medical practice was not regulated and suicide might be approved if it was committed for 'noble' reasons. The physicians who originally took the oath are now thought to have been a reforming minority, influenced by religious respect for life, but also anxious to dissociate themselves from those who misused pharmacological knowledge for nefarious purposes. Later, the oath was adopted by physicians in the Jewish, Christian and Islamic traditions, all of which prohibited suicide because the time of death was for God to decide, and because suffering might be an opportunity for spiritual growth. But compassionate relief of suffering, by medical means where available, was also central to these traditions. In Judaism and Christianity today, drugs may be used to relieve terminal suffering, even if they incidentally hasten death, provided that the intention is to relieve and not to kill.

BACKGROUND

On 20 January 2003 a UK citizen, who had been terminally ill with motor neurone disease, died in an assisted-suicide clinic in Switzerland. The patient, Mr Reginald Crew, travelled to Switzerland to end his life, as assisted suicide is illegal in the UK. Prior to this incident a high-profile legal challenge was underway in the European Court of Human Rights in which another UK citizen, Diane Pretty, who was also terminally ill with motor neurone disease, was claiming that the British courts' refusal to allow her husband to help her to die was an infringement of her human rights. Mrs Pretty subsequently lost her legal challenge in April 2002, before dying naturally on 11 May 2002.

Against this, a more recent secular view of life and death argues that since modern medical means of prolonging life may also prolong dying, medical means of assisting death should not be denied to a competent terminally ill patient who sincerely wishes this. Many religious authorities agree that there is no duty to prolong life at all costs, and that when the burdens of treatment outweigh its benefits it may be withdrawn. But they remain opposed to active and intentional killing.

The word 'euthanasia', hitherto meaning a calm and peaceful death, was first used to advocate physician-assisted suicide in the late nineteenth century, when developments in pain relief meant not only that suffering could be managed much more effectively, but also that death could be accelerated by administering sufficiently large doses of chloroform. In Britain a voluntary euthanasia movement, around one quarter of whose original members were doctors, was founded in 1935. Before and after the Second World War a number of attempts were made to legalise voluntary euthanasia for adult patients suffering from fatal, incurable illness characterised by severe pain. None of these were successful. The Nazi atrocities clearly had an impact on post-war debates on the subject, with concerns being expressed about the possibility of ending vulnerable patients' lives without their express consent.

During the 1960s, the emergence of the hospice movement provided greatly improved pain relief and care for terminally ill patients, and this, it was argued, rendered calls for legalised euthanasia redundant. The British Medical Association (BMA), for example, now states that 'whilst there are many cases where a doctor should accede to a request not to prolong the patient's life, a doctor should not actively intervene to end that life'; and it goes on to 'recognise the vital contribution the hospice movement has made'. Since under 5% of deaths occur in a hospice setting, the official medical view is to seek a transference of hospice practices to hospital wards and patients' homes.

Euthanasia remains illegal in Britain. But both the Netherlands and Belgium have passed laws permitting doctors to help terminally ill patients to end their lives; in a recent case the Dutch Supreme Court has ruled that the strict medical guidelines for this do not include simply being 'tired of living'. Assisted suicide has been legal in Switzerland since 1942, provided that those helping dying patients can show that they are acting from altruistic motives. In the US, only Oregon has legalised euthanasia, but other states are considering similar changes. The federal government in Australia has reversed a law permitting assisted suicide in the Northern Territories, but the Australian right-to-die lobby remains vocal and powerful.

In Britain, public opinion on legalising euthanasia has been swayed by a number of recent events. In 2002, the European Court of Human Rights rejected the request of Mrs Diane Pretty, a patient in the terminal stages of motor neurone disease, to grant her husband legal immunity if he were to help her to die. The Court ruled that the European Convention on Human Rights did not confer a right to die, and that English law against assisting suicide should be upheld. But in another case occurring at the same time, the English High Court ruled that Ms B, a patient like Mrs Pretty in her forties and paralysed, but unlike Mrs Pretty not terminally ill, should be granted her competent request to have artificial ventilation withdrawn, even though this meant that she would die. These legal rulings were criticised by both advocates and opponents of euthanasia. The advocates argued that the inconsistent outcomes depended on an indefensible distinction between acts and omissions while the opponents argued that since Ms B's clear intention was to die, the judgement in her case undermined the law's prohibition of suicide. Mrs Pretty's case attracted much public sympathy, but this again was tempered by fears about vulnerable patients being killed without their consent. Harold Shipman, an English general practitioner, had recently taken the law into his own hands and murdered a large number of his elderly patients.

British public opinion was again swayed in both directions by two further cases. Sympathy was expressed for Mr Reginald Crew, another patient with motor neurone disease, who in 2003 travelled to Switzerland for assisted suicide. His wife, who accompanied him, was not subsequently prosecuted because the authorities saw 'no public interest' in doing so. But then concerns were expressed when Mr and Mrs Stokes, a couple in their fifties and neither terminally ill, were both assisted to die by the same Swiss organisation. Following Mr Crew's case, but before that of the Stokes, a survey of 1,000 British doctors found that over half agreed that terminally ill patients should be allowed to seek physician-assisted death, but only one third agreed that the law should be changed to facilitate this. These views may seem inconsistent. But that may be because these doctors fear that current arrangements fail patients like Mrs Pretty and Mr Crew, but also feared the alternative – as one doctor told the BMA, 'We shall start by putting patients away because they are in intolerable pain and have not long to live anyway; and we shall end up by putting them away because it's Friday night and we want to get away for the weekend'. Euthanasia, in other words, may be a moral question to which no legislative answer, either way, will ever be ethically satisfactory.

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REPORTS OF A SINGLE-INJECTION CURE FOR DIABETES ARE PREMATURE

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BACKGROUND

Earlier this year an article was published in *The Scotsman*, a national newspaper in Scotland, which reported that a new injection could provide a single injection cure for diabetes. While reports of potential new treatments for a variety of diseases appear in the media around the world on a daily basis, it was decided to commission an expert clinical commentary on this matter given the increase in the incidence of diabetes in Scotland (and worldwide).

The Holy Grail in Type 1 diabetes is the development of a treatment (or even range of treatments) which will obviate the need for insulin administration by either injection or infusion. To achieve this goal, researchers aim to produce cells with the ability to synthesise insulin and then inject or implant these to provide the insulin which the patient's own pancreas is unable to produce. While this is an attractive concept, success so far has been limited, largely because the demands on such a bioengineered system are substantial.

Actual human ß-cells from cadaver donor pancreases have been used and are currently the subject of research in Canada and the UK. Present harvesting techniques are relatively inefficient and two to three donor pancreases are required to collect enough islets of Langerhans to render one patient independent of exogenous insulin. Potent immunosuppressive cocktails are also required to prevent rejection. The shortage of donor organs and the side-effects of the immunosuppression mean that this option is only ever going to be available for a tiny minority of diabetic patients.

Efforts have been made to encourage whole islets, or ß-cells alone, to grow *in vitro*, potentially providing limitless supplies of insulin producing cells. So far progress has been slow and limited.

Molecular biology techniques have been utilised to cause non-ß-cells to synthesise insulin. This has been achieved, with varying degrees of success, in a number of cell lines. These cell lines, however, lack the ability to measure ambient plasma glucose and therefore the ability to match insulin synthesis and secretion to the prevailing blood glucose. Uncontrolled insulin release would be unlikely to lead to acceptable glycaemic control and could produce potentially severe hypoglycaemia.

The hexokinase gene, responsible for glucose measurement by ß-cells, has been expressed in other cell lines. There remains, however, the substantial challenge of not only expressing the hexokinase gene and insulin gene in the same cell line but of establishing the, as yet poorly understood, intracellular signalling systems which link glucose sensing to insulin secretion. This ultimate 'bio-engineered ß-cell' is some way off at present.

An alternative solution is the use of stem cells, which could perhaps be grown *in vitro* and then persuaded to differentiate as B-cells. This is an attractive option but is, at present, many years away from reality.

Whatever techniques eventually succeed in producing artificial ß-cells, it is highly unlikely that a single 'dose' of such cells will provide a complete cure for Type 1 diabetes. The paracrine and other interactions which take place within the islet of Langerhans appear to be important for ß-cell longevity and function and these interactions will be absent where artificial ß-cells are being used in isolation. In addition, Type 1 diabetes is an auto-immune disease with cell-mediated immunity turned against the patient's own ß-cells. Any treatment which involves cells similar to real human ß-cells risks re-igniting the immune processes which led to the original disease; the use of immunosuppressive therapies to prevent this would carry the substantial long-term risks of such therapies.

In summary, much research effort is presently directed at the quest for a bioengineered solution to Type 1 diabetes and progress is being made. The recent report in *The Scotsman* is of another small, and not entirely novel, step along

a very long road.

At present we have the means, using insulin therapies, to achieve good glycaemic control in the great majority of people with Type 1 diabetes who receive adequate education and support. Until innovative therapies are much further advanced, care for people with diabetes should concentrate on maximising the efficacy of existing proven interventions rather than holding out the prospect of miracles to come.

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