Pharmacological treatment of depression: the role of paroxetine

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Depression is reaching epidemic proportions in the western world. With each successive generation more people are becoming more severely depressed at a younger age.

Depression is the most frequently encountered mental illness in the UK, affecting approximately five million people at any one time. Overall, one in four people suffer a depressive illness at some point in their lives, with onset most often between the ages of 25 to 44. Women are twice as likely as men to be affected. The lifetime risk of suicide for people with affective disorders such as depression is estimated at 15% (Department of Health, 1994), and some 70% of the 4000 suicides experienced in Britain each year are attributed to depression. According to the National Depression Campaign, the cost of depressive illness to the UK alone, including days lost from work, has been estimated as being in excess of £8 billion per year. By the year 2020, the World Health Organization estimates clinical depression will be the second-most burdensome illness in the world (Department of Health, 1994).

Up until the early 1990s it was considered that a 'rule of halves' operated with respect to depression. Around one half of sufferers presented to their GP with symptoms, one half of those were recognized and half of those diagnosed or fewer were prescribed antidepressant therapy (Wade, 1999). Between 1994 and 1998, however, the UK consultation rate and prescriptions for depression doubled (4–9 million/year) (IMS Health, 1999a).

Most depressive illnesses are managed in general practice. However, around one in ten patients diagnosed with depression in general practice is subsequently referred to a specialist psychiatrist and one in a thousand will be admitted to hospital (Paykel and Priest, 1992).

GPs usually refer patients because they are unsure of the diagnosis, possibly because of overlapping symptoms from co-morbid mental illnesses such as anxiety, panic disorder, or obsessive compulsive disorder. Other reasons may be that the patient is either severely ill, suicidal or has not responded to treatment. Occasionally, organic brain disease may be suspected and require investigation or the depression may be a complication of another psychiatric disorder such as schizophrenia. It is also important not to forget that depression may be the presenting feature of a physical disorder such as hypothyroidism.

Some patients may initially be reluctant or refuse to be referred on account of a perceived stigma surrounding consultations with a psychiatrist.

ANTIDEPRESSANT THERAPIES

Until half a century ago there was no effective pharmacological treatment for depression of any kind. Lithium was discovered in 1949, the monoamine oxidase inhibitors (MAOIs) in 1952 and the tricyclic antidepressants (TCAs) in 1955. Lithium has a narrow therapeutic index and is reserved for bipolar depression or the augmentation of antidepressant therapy in cases of treatment resistance. The potential danger of MAOIs reacting with other drugs and some foods makes them second line treatment. The side-effect profile of TCAs, together with their risk of fatal cardiotoxicity in overdose, has led to them being superseded by newer, safer and better-tolerated agents.

The first selective serotonin-reuptake inhibitor (SSRI), fluoxetine, was launched in 1987 in the US and 1989 in the UK. This was followed by four more SSRIs — paroxetine, fluvoxamine, sertraline and citalopram. Other new drug classes have emerged, including reversible inhibitors of

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monoamine oxidase (RIMAs), noradrenaline reuptake inhibitors (NARIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), serotonin receptor modulators (SRMs), noradrenergic and specific serotonergic antidepressants (NaSSAs) and triple-action compounds regulating serotonin, noradrenaline and dopamine.

This article focuses on the SSRI paroxetine, one of the most widely used antidepressants in both general practice and hospital psychiatry. Over 70 million patient treatments worldwide have been made to date with paroxetine (unpublished data, SmithKline Beecham, 2000). Of all the SSRIs, paroxetine is one of the most studied in the common overlapping disorders often accompanying depression and it has the most licensed indications (Monthly Index of Medical Specialities, 2000).

USING PAROXETINE IN DEPRESSION

Paroxetine is a potent and selective inhibitor of the reuptake of serotonin (5-hydroxytryptamine), more potent in vitro than fluvoxamine and fluoxetine (Gunesekara et al, 1998). In depressive illness, the majority of patients (60–74%) treated with paroxetine 20–50 mg/day achieve a greater than 50% reduction in baseline symptom scores measured on the Hamilton Depression Rating Scale (HDRS) within 6–12 weeks of treatment (Gunesekara et al, 1998).

In clinical trials involving patients with major depressive illness, paroxetine has proved statistically superior to placebo, and comparable in efficacy to TCAs and related antidepressants (Dunner and Kumar, 1998). The chief advantage of paroxetine over TCAs is in its greater tolerability and safety with regard to both overdose and psychomotor profile. TCAs tend to be prescribed in subtherapeutic doses because of their poor tolerability in many cases and studies which show that they impair reaction times substantially (IMS Health, 1999b; Hindmarsh and Harrison, 1988).

Over both TCAs and some other SSRIs, paroxetine may also have the advantage of a faster speed of onset (Gunesekara et al, 1998; De Wilde et al, 1993). Feighner and colleagues compared paroxetine, imipramine and placebo in a study of 717 outpatients with major depression and found depressive symptoms improved after only 1 week with paroxetine compared with 2 weeks for imipramine. An earlier improvement in anxiety symptoms also occurred in paroxetine-treated patients (Feighner et al, 1993).

In a randomized, double-blind study of 100 patients with major depression, De Wilde and colleagues compared paroxetine 30–40 mg against fluoxetine 40–60 mg administered in divided doses, morning and midday. Both drugs showed comparable efficacy after 6 weeks but paroxetine achieved a statistically significantly greater number of responders at week 3, with a significantly greater reduction from baseline in HAM-D anxiety factor score. It was also associated with fewer adverse effects (De Wilde et al, 1993).

Although SSRIs are broadly similar with regard to efficacy in depression, they differ with regard to pharmacokinetics, speed of onset and agitatory side effects. For example, jitteriness, nervousness and anxiety have been reported with fluoxetine therapy (Kuzel, 1996). In a large Canadian multi-centre study comparing the two agents, paroxetine was found to be statistically superior to fluoxetine on measures of agitation and psychic anxiety after only 1 week of therapy (Chouinard et al, 1999). In a head to head of paroxetine *vs* fluvoxamine, the response rate at 6 weeks was similar but there was a significantly lower drop-out rate as a result of adverse effects for paroxetine (5% *vs* 17%) (Ansseau et al, 1994).

EFFICACY IN CO-MORBID DISORDERS

Another advantage of paroxetine from the clinician's point of view is its evidence base and licensed indications for the treatment of a broad range of symptomatic disorders frequently accompanying depression. These include anxiety, panic disorder, obsessive compulsive disorder, and social anxiety disorder.

Anxiety symptoms are experienced by 60–90% of people with depression, panic attacks by 30%, obsessional compulsive symptoms by 38% and 27% have social anxiety disorder (Nutt, 1997; Hamilton, 1998; Fawcett, 1990; den Boer, 1997; Kessler et al, 1996). Where these conditions are predominant, symptoms of depression are also common. For example, among patients with anxiety, 20–65% become depressed (Nutt, 1997). 30–90% of patients with panic disorder and 70% of patients with social phobia become depressed (Dubovsky, 1990; Van Amerigen et al, 1991). Furthermore, there is an almost three-fold increased risk of suicide when both depression and anxiety disorders are present (Kuzel, 1996).

Obsessive compulsive disorder

In a study of 348 patients with obsessive compulsive disorder (OCD) of 6 months or longer, paroxetine 40 mg and 60 mg were statistically significantly superior to placebo in reducing scores on the Yale-Brown obsessive compulsive scale (Wheadon et al, 1993). In a study of long-term treatment of 263 patients with OCD, parox-

etine demonstrated efficacy in maintaining a therapeutic response and preventing relapse over 1 year (Dunbar, 1995).

Panic disorder

In panic disorder, three studies have demonstrated efficacy for paroxetine in short term treatment (Ballenger et al, 1998; Lecrubier et al, 1997; Oehrberg et al, 1995). In a 10-week placebo-controlled study of 278 patients, 40 mg paroxetine was more effective than placebo in reducing the number of panic attacks. By the end of the study, 86% of paroxetine patients were completely free of panic attacks compared with 50% of the placebo group (Ballenger et al, 1998).

Social anxiety disorder

Two double-blind randomized studies demonstrate paroxetine's efficacy in controlling social anxiety disorder. In a mainly European, multicentre trial, Baldwin and colleagues studied 290 patients with social phobia randomized to either paroxetine (20–50 mg/day) or placebo for 12 weeks. Results were assessed primarily in terms of Liebowitz Social Anxiety Scale (LSAS) and Clinical Global Impression (CGI) total scores. There was a highly statistically significant difference in scores favouring paroxetine (-29.4 *vs* -15.6, $P<0.001$) and in the number of responders (65.7% *vs* 32.4%, $P<0.001$) from week 4 onwards (Baldwin et al, 1999).

In an earlier North American study, Stein et al (1998) investigated paroxetine *vs* placebo in 187 patients with social phobia using the same dosages and principal outcome measures as above. Again, results show statistically significant superiority for paroxetine over placebo. LSAS scores were reduced by 39.1% *vs* 17.4%.

TOLERABILITY

Unlike TCAs, paroxetine has only a weak affinity for the muscarinic cholinergic receptor, the 5-HT_2 receptor, histamine and other central neurotransmitter receptors. For this reason, it avoids much of the anticholinergic adverse event profile (dry mouth, constipation) associated with TCAs (Gunesekara et al, 1998). More than 6000 patients have received paroxetine in clinical trials and post-marketing surveillance/prescription event-monitoring data is available for a further 17 000.

Overall, paroxetine is very well tolerated and adverse events reported tend to be mild. The most common side effect is nausea, occurring in 22% of patients in the clinical trial database and 14% in post-marketing surveillance, tending to decrease within a few weeks of treatment (Gunesekara et al, 1998, Stein et al, 1998). In a placebo-controlled study, side effect profiles for the two patient groups after 1 year were indistinguishable (Dunner and Kumar, 1998; Claghorn and Feighner, 1993).

Male sexual dysfunction (ejaculatory disturbance) has been reported and appears to be dose-related. In depression the incidence was 13%, while in OCD and panic disorder, where doses tend to be higher, the incidence was 23% and 21% respectively (Gunesekara et al, 1998). Among the elderly, a similar picture emerges with regard to side effects and, overall, paroxetine's tolerability profile resembles those of the other SSRIs (Gunesekara et al, 1998).

SAFETY

With the arrival of the first four SSRIs, major advantages over TCAs soon emerged with regard to cardiac safety and survival in overdose. Patients who overdose on TCAs frequently die from either heart block or arrhythmias. Relatively small overdosing of three to four times the daily therapeutic dose of TCAs is associated with considerable symptoms and even therapeutic doses can impact adversely on patients already suffering from cardiovascular disease (Barbey and Roose, 1998).

Roose et al (1998) compared the cardiovascular effects of paroxetine 20–30 mg/day with nortriptyline (25–125 mg/day) in 81 depressed patients with pre-existing ischaemic heart disease over 6 weeks in a double-blind randomized trial. One patient on paroxetine suffered a cardiac event during this time compared with seven receiving nortriptyline. No significant changes in blood pressure, heart rate or electrocardiogram (ECG) were observed in paroxetine-treated patients, whereas nortriptyline patients experienced increases in heart rate of around 7 beats per minute and prolongation of the PR and QTc intervals.

Before the advent of SSRIs, thousands of deaths per year were attributed to TCA overdoses. Over the 12-year period following the introduction of the first SSRIs, only six deaths from overdose had been verified in the US as attributable to either fluoxetine, sertraline, paroxetine or fluvoxamine alone. A further 51 cases were reported, but not verified — the majority occurring in fluoxetine, the first and most widely prescribed SSRI in the USA (Barbey and Roose, 1998). Six fatalities have been reported to the USA Food and Drugs Administration where paroxetine was allegedly the only substance ingested (Barbey and Roose,

1998). However, experience during clinical trials with paroxetine overdoses alone or in combination with other drugs revealed effects of nausea, vomiting, drowsiness, dizziness, sinus tachycardia, sweating and dilated pupils but no ECG abnormalities, coma or convulsions, even at doses of up to 2000 mg (maximum recommended daily dose of 50 mg) (Barbey and Roose, 1998).

Similarly, poison control centre experience of paroxetine overdoses up to 1000 mg show effects ranging from either no symptoms at all to vomiting, drowsiness and tremor. Of 28 children who swallowed between 10–800 mg paroxetine, all recovered fully with no long-term sequelae (Barbey and Roose, 1998).

Most antidepressants, including paroxetine, have been associated with discontinuation reactions, although SSRIs as a class are not known to cause dependency (Committee for Proprietary Medicinal Products, 2000). The British National Formulary recommends gradual dose reduction, generally over 4 weeks, at the end of treatment for all antidepressants (British National Formulary, 2000).

PHARMACOKINETICS AND DRUG INTERACTIONS

Paroxetine is almost completely absorbed from the gastrointestinal tract and peak plasma concentration is reached on average after 5 hours (Gunesekara et al, 1998). The recommended starting dose for adults with depression is 20 mg daily, ideally taken in the morning with breakfast. The dose may be titrated up, after 2–3 weeks, in weekly 10 mg increments up to a maximum of 50 mg/day. For elderly patients a starting dose of 20 mg is advocated, rising, if necessary, to a ceiling of 40 mg/day (Gunesekara et al, 1998). For those with severe renal or hepatic impairment 20 mg/day is recommended, and dosing should be kept to the lower end of the range (SmithKline Beecham, 1997).

Paroxetine is metabolized in the liver to glucuronide and sulphate metabolites by enzymes in the cytochrome P450 system, primarily CYP 2D6. Inhibition of this enzyme, which also occurs with sertraline and fluoxetine, means there is a potential for interaction with other drugs that induce or inhibit this enzyme, e.g. phenytoin, cimetidine and certain TCAs, antipsychotics and antiarrhythmics (Gunesekara et al, 1998). In practice, no significant clinical effects have been reported in patients in whom these drugs have been co-administered. As is the case with any SSRI, paroxetine should not be administered with MAOIs because of the potential for excessive serotonergic activity leading to serotonin syndrome and the risk of fatality (Gunesekara et al, 1998).

In view of the potential for drug interactions, wherever possible, use of a single antidepressant drug with broad coverage, addressing all overlapping symptoms, is preferable to combining two or more agents. However, serotonin syndrome may also develop to a degree with co-administration of some other unrelated drug classes (e.g. paracetamol and dextromethorphan) (Gunesekara et al, 1998).

Only 1–2% of paroxetine is excreted unchanged in the urine. The remainder is excreted as metabolites, approximately two-thirds in urine and the rest in faeces. The mean half-life is approximately 21 hours after single doses of 20 or 30 mg, but there is considerable variation among individuals (Gunesekara et al, 1998).

Although a discontinuation syndrome has been described in association with paroxetine following abrupt withdrawal of the drug, it is likely that other SSRIs have similar effects. In one study, a higher number of withdrawal symptoms in paroxetine-treated patients were attributed to its comparatively shorter half-life compared with the other SSRIs (Young et al, 1997). All SSRIs should be withdrawn gradually, especially after prolonged use. Some authorities suggest tapering the dose, following a decision to stop long-term treatment (Lader et al, 1998).

CONCLUSION

Paroxetine, like other SSRIs, has proved a major advance in antidepressant therapy. It is effective in both the short-term and long-term management of depression and has demonstrable efficacy in controlling symptoms of anxiety, panic disorder, OCD and social anxiety disorder. It is well tolerated, has a good cardiovascular safety profile and is safe in overdose.

As such it represents a useful first line treatment for a broad range of depressive illnesses especially those with overlapping symptoms. The cost of one month's treatment with paroxetine 20 mg/day is currently £17.76 (approximately the cost of a single cognitive therapy session) against £19.84 for the standard recommended dose of branded fluoxetine (Monthly Index of Medical Specialities, 2000).

The first opportunity for cheaper generic SSRI treatment has presented itself with the patent expiry of Prozac (fluoxetine) this year. But while it will be fair enough for generic fluoxetine to be substituted for the branded product, it should not be assumed that substitution for all other SSRIs is justified on grounds of cost.

It is important to bear in mind that, although all the SSRIs have proven similar in antidepressant activity, there are differences among them in pharmacokinetics and side-effect profiles. In particular, success rates where overlapping symptoms are concerned may be very variable. Drugs which have a licensed indication supported by a strong evidence-base, are likely to offer a better chance of treatment success first time round. **HM**

Conflict of interest: Dr M Deahl acts as a consultant to a number of pharmaceutical companies including SmithKline Beecham.

Ansseau M, Gabriëls A, Loyens J et al (1994) Controlled comparison of paroxetine and fluvoxamine in major depression. *Hum Psychopharmacol* **9:** 329–36

Baldwin D, Bobes J, Stein D, Scharwächter I, Faure M (1999) Paroxetine in social phobia/social anxiety disorder: randomised, double-blind, placebo-controlled study. *Br J Psychiatry* **175:** 120–6

Ballenger J, Wheadon D, Steiner M, Bushnell W, Gergel I (1998) Double-blind, fixed dose, placebo-controlled study of paroxetine in the treatment of panic disorder. *Am J Psychiatry* **155**(1): 36–42

Barbey JT, Roose SP (1998) SSRI safety in overdose. *J Clin Psychiatry* **59**(suppl 15): 42–8

British National Formulary (2000) *British National Formulary,* No 40. British Medical Association, London

Chouinard G, Saxena B, Bélanger M et al (1999) A Canadian multi-center, double-blind study of paroxetine and fluoxetine in major depressive disorder. *J Affect Disord* **54**: 39–48

Claghorn J, Feighner J (1993) A double-blind comparison of paroxetine with imipramine in the long term treatment of depression. *J Clin Psychopharmacol* **13**(6)(suppl 2): S23–7

Committee for Proprietary Medicinal Products (2000) *CPMP Position Paper on SSRIs and Dependency/Withdrawal Reactions.* European Agency for the Evaluation of Medicinal Products, London

den Boer JA (1997) Psychopharmacology of comorbid obsessive-compulsive disorder and depression. *J Clin Psychiatry* **58**(8)(suppl): 17–19

De Wilde J, Spiers R, Mertens C, Bartholomé F, Schotte G, Leyman S (1993) A double-blind, comparative, multi-centre study comparing paroxetine with fluoxetine in depressed patients. *Acta Psychiat Scand* **87**: 141–5

Department of Health (1994) *Suicide Prevention — the Challenge Confronted.* HMSO, London

Dubovsky SL (1990) Understanding and treating depression in anxious patients. *J Clin Psychiatry* **51**(10)(suppl): 3–8

Dunbar G (1995) Long term treatment and prevention of relapse of obsessive compulsive disorder with paroxetine (abstract). *Eur Neuropsychopharmacol* **5 September**: 372

Dunner D, Kumar R (1998) Paroxetine: a review of clinical experience. *Pharmacopsychiatry* **31**: 89–101

Fawcett J (1990) Targeting treatment in patients with mixed symptoms of anxiety and depression. *J Clin Psychiatry* **51**(11)(suppl): 40–3

Feighner JP, Cohn JB, Fabre LF, Fieve RR, Mendels J, Shrivastava RK, Dunbar GC (1993) A study comparing paroxetine, placebo and imipramine in depressed patients. *J Affect Dis* **28**(2): 71–9

Grundemar L, Wohlfart B, Lagerstedt C, Bengtsson F, Eklundh G (1997) Symptoms and signs of severe citalopram overdose. *Lancet* **349**: 1602

Gunesekara N, Noble S, Benfield P (1998) Paroxetine: an update of its pharmacology and therapeutic use in depression and a review of its use in other disorders. *Drugs* **55**(1): 85–120

Hamilton M (1998) Distinguishing between anxiety and depressive disorders. In: Last C, Hersen M eds. *Handbook of Anxiety Disorders.* Pergamon Press, New York: 143–55

Hindmarsh I, Harrison C (1988) The effects of paroxetine and other antidepressants in combination with alcohol on psychomotor activity related to car driving. *Hum Psychopharmacol* **3**: 13–20

IMS Health (1999a) *Medical Data Index.* IMS Health, London

IMS Health (1999b) *UK MediPlus Primary Care Database.* IMS Health, London

Kessler C, Nelson C, McGonagle K, Liu J, Swartz M, Blazer D (1996) Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US national comorbidity survey. *Br J Psychiatry* 168(suppl 30): 17–30

Kuzel RJ (1996) Treating comorbid depression and anxiety. *J Family Pract* **43**(6)(suppl): 45–53

Lader M, Taylor D, Wade A (1998) *Modern Antidepressants: Similarities and Differences. Formulary focus.* A&M Publishing Ltd, Guildford

Lecrubier Y, Bakker A, Dunbar G, Judge R (1997) A comparison of paroxetine, clomipramine, and placebo in the treatment of panic disorder. *Acta Psychiatr Scand* **95:** 145–52

Monthly Index of Medical Specialities (MIMS) (2000) Haymarket Medical Ltd, London: October

Nutt, D (1997) Management of patients with depression associated with anxiety symptoms. *J Clin Psychiatry* **58**(suppl 8): 11–16

Oehrberg S, Christiansen P, Behnke K et al (1995) Paroxetine in the treatment of panic disorder: a randomised, double-blind, placebo-controlled study. *Br J Psychiatry* **167:** 374–9

Paykel E, Priest R (1992) Recognition and management of depression in general practice: consensus statement. *Br Med J* **305**: 1198–202

Personne M, Sjöberg G, Persson H et al (1997) Citalopram overdose — review of cases treated in Swedish hospitals. *Clin Toxicol* **35:** 237–40

Roose S, Laghrissi-Thode F, Kennedy J et al (1998) Comparison of paroxetine and nortriptyline in depressed patients with ischaemic heart disease. *JAMA* **279**: 287–91

Rothenhäusler H, Haberl C, Ehrentrout S et al (2000) Suicide attempt by pure citalopram overdose causing long-lasting severe sinus bradycardia, hypotension and syncopes: successful therapy with a temporary pacemaker. *Pharmacopsychiat* **33**: 150–2

SmithKline Beecham (1997) *Paroxetine Product Monograph.* SmithKline Beecham, Harlow

Stein M, Liebowitz M, Lydiard R, Pitts C, Bushnell W, Gergel I (1998) Paroxetine treatment of generalised social phobia (social anxiety disorder): a randomised controlled trial. *JAMA* **280**: 708–13

Van Ameringen M, Mancini C, Styan G, Donison D (1991) Relationship of social phobia with other psychiatric illness. *J Affect Disord* **21**: 93–9

Wade A (1999) Diagnosis in Primary Care. In: Lader M, Wade A, eds. *The Many Faces of Depression.* Royal Society of Medicine, London

Wheadon D, Bushnell W, Steiner M (1993) *A fixed dose comparison of 20, 40 or 60mg Paroxetine to Placebo in the Treatment of Obsessive Compulsive Disorder.* SmithKline Beecham Pharmaceuticals, Conshohocken, PA 19428

Young A, Currie A, Ashton C (1997) Antidepressant withdrawal syndrome. *Br J Psychiatry* **170**: 288–91

KEY POINTS

- Modern antidepressant therapy with selective serotonin-reuptake inhibitors is a safe and effective means of controlling symptoms in patients who adhere to treatment.
- Depressive illness effects one in four people at some point in their lives, but is under-diagnosed and under-treated.
- Among antidepressants, paroxetine has the most licensed indications.
- Paroxetine has a weak affinity for the 5-HT_2 receptor, histamine and other central neurotransmitter receptors, avoiding much of the anticholinergic adverse event profile associated with tricyclic antidepressants.
- Paroxetine treatment causes no clinically significant changes in blood pressure, heart rate or electrocardiogram and has a wide safety margin in overdose.
- Paroxetine is well tolerated and is effective in both the short-term and long-term management of depression.