Paroxetine and its uses in psychiatry

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Paroxetine is one of the specific serotonin-reuptake inhibitor antidepressants which is used in a variety of psychiatric disorders. It has recently gained considerable publicity because of its use in social anxiety disorder and its subsequent labelling by the media as a 'lifestyle drug'. This review summarizes current indications for paroxetine and outlines doses and duration of treatment for each condition.

Paroxetine (Seroxat, SmithKline Beecham, Welwyn Garden City, Herts) is one of the group of antidepressants called specific serotonin-reuptake inhibitors (SSRIs). It has recently received considerable publicity for its use in social anxiety disorder. The media has labelled it as another 'lifestyle drug' on a par with Viagra and the 'slimming pill' Xenical, implying that the conditions they treat are not really serious, do not really warrant medical intervention and are just a consequence of drug companies trying to find a market for their drugs. These kind of discussions are not particularly helpful and can obscure the real issues involved. As with the other drugs, correctly used in carefully diagnosed patients, paroxetine treats and alleviates considerable suffering.

Paroxetine is licensed for the treatment of a variety of disorders, i.e. depression, panic disorder, obsessive–compulsive disorder (OCD) and social anxiety disorder. Although it is the only SSRI licensed for all four conditions, the others all have similar indications — differences probably reflecting the fact that the other SSRIs have not yet fulfilled the licensing requirements rather than any specific pharmacological property of paroxetine.

This article will describe the current uses of paroxetine in psychiatry, emphasizing the key reference studies and giving a practical summary of its clinical use in each disorder.

THE DISORDERS

Major depression

The features of depression are well known and include low mood, inability to feel enjoyment, reduced interest in life with suicidal ideas, sleep disruption (typically early morning waking), reduced appetite with weight loss, reduced energy and reduced libido. Anxiety may also co-exist.

As with the other SSRIs, paroxetine is licensed for treatment of all types of depression. It has comparable efficacy to established antidepressants (Dunbar et al, 1991) with 60–70% response, and the typical clinical delay before improvements of 2–3 weeks. The dose required is usually 20 mg a day although some patients need a higher dose. Efficacy is maintained in long-term treatment and current guidelines recommend treating at the dose that gets the patient well for 6–9 months.

Paroxetine in the treatment of depression:

- Start at 20 mg a day
- Optimal dose 20 mg a day
- Duration of treatment 6–9 months.

Panic disorder

The essential feature of panic disorder is recurrent, unexpected panic attacks. These are sudden waves of intense fear accompanied by characteristic somatic symptoms which occur, at least initially, 'out of the blue'. Patients are terrified and often present in casualty departments convinced that they are having a heart attack or dying. Attacks typically become associated with specific situations, particularly those from which escape is difficult. This leads to marked anticipatory anxiety when these situations have to be encountered and their avoidance (agoraphobia) as far as possible.

Various drugs have been used to treat panic disorder: initially in the 1960s the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), then the high potency benzodiazepines, and since the 1990s the SSRIs. Serotonergic effects appear to be particularly important; noradrenergic agents are less effective than serotonergic ones (Johnson et al, 1995).

Of all the SSRIs, paroxetine has been the most comprehensively studied in panic disorder and was the first SSRI to be licensed for this in the UK.

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Studies have shown that paroxetine achieved similar results to the TCA clomipramine (the 'gold standard' comparator for panic disorder), with 65–76% of patients respectively reporting a >50% reduction in panic attack frequency. Paroxetine seemed to be better tolerated, with a more rapid onset of action (4–6 weeks) than clomipramine (10–12 weeks) (Lecrubier et al, 1997a).

The issue of duration of treatment is still only partially resolved. A long-term study, extending the 12-week study above by a further 36 weeks, showed that response was maintained over this time (Lecrubier et al, 1997b). In line with this and guidelines for treating depression, our current practice is to continue patients on the dose they have responded to for 9–12 months. This allows them to build on the benefits of drug treatment, put into practice psychological techniques, e.g. cognitive–behavioural therapy, and feel the benefits of successful exposure to feared situations.

Dose ranging studies have shown that the optimal dose for treating panic disorder is 40 mg daily (i.e. higher than for depression). The current recommendation is thus that patients should be gradually titrated up to this dose according to response, starting at 10 mg daily and increasing by 10 mg increments. This slow titration should reduce the likelihood of any exacerbation in anxiety which might occur if patients started at a dose of 20 mg a day. If anxiety exacerbation does occur it can be treated with a 2–3-week course of benzodiazepines to be used on an as-required basis.

Paroxetine in the treatment of panic disorder:

- Start 10 mg/day to prevent anxiety exacerbation (+ benzodiazepine for 2–3 weeks if required)
- Gradual titration according to response by 10 mg increments
- Optimal dose 40 mg a day
- Duration of treatment 9–12 months.

Obsessive–compulsive disorder

OCD is characterized by obsessions (recurrent ideas, thoughts or images) or compulsions (repetitive behaviours performed according to certain rules in a stereotyped fashion) which often revolve around the themes of contamination or checking. They cause considerable distress and significantly interfere with the patient's functioning — resulting in complex routines which take hours to perform and often involve the patient and their relatives.

The optimal treatment for most patients with OCD is a combination of drug treatment and behaviour therapy. Behaviour therapy is aimed at exposing the patient to their feared situation, e.g. dirt, with response prevention, e.g. stopping them washing their hands. Serotonergic antidepressants are the most effective medications. Studies show marked superiority of serotonergic antidepressants over noradrenergic ones (Goodman et al, 1990).

Clomipramine is the most serotonergic of the TCAs, so has been most widely used in OCD. Paroxetine has been compared with both placebo and clomipramine (Zohar et al, 1996), and have shown that paroxetine and clomipramine have equal efficacy (about 60% of patients experience significant improvement) and both are superior to placebo. The effective dose is at least 40 mg a day (again higher than the antidepressant dose) with some patients needing 60 mg a day. The duration of treatment is unresolved. Studies have shown that efficacy is maintained over 12 months of treatment and current clinical recommendations are to continue at the dose that got the patient better for at least a year. Interestingly, unlike in panic disorder, patients do not report anxiety exacerbation with an initial starting dose of 20 mg a day.

Paroxetine in the treatment of OCD:

- Start at 20 mg a day
- Optimal dose 40 mg/day (some may need 60 mg)
- Duration of treatment 12 months.

Social anxiety disorder

Social anxiety disorder is characterized by fear of performance situations when the patient feels they are under scrutiny from other people and that they will do something embarrassing or humiliating. Particularly difficult situations include speaking, eating, drinking or writing in front of people, talking to people of the opposite sex or those in authority, going to parties or participating in small groups. When these have to be encountered patients have marked anticipatory anxiety and try to avoid them as much as possible (difficult when they are a major part of everyday life). If they have to endure these situations they experience marked anxiety, sometimes amounting to a panic attack. More typically they report specific symptoms of blushing, sweating, palpitations, tremor, difficulty passing urine in a public lavatory ('bashful bladder syndrome') and speech block. These are noticeable to other people, and set up and exacerbate a vicious cycle of cognitions and symptoms.

It is important to realize that patients with social anxiety are not just shy, they are often incapacitated by their anxiety. They are less likely to marry and to progress in their careers, suffer from secondary depression and frequently abuse alcohol. This alcohol abuse starts as an attempt at self medication of their anxiety but often leads to severe alcohol problems — figures being quoted of up to 25% of alcoholics suffering from an underlying social anxiety disorder (Schneier et al, 1992).

Drug treatment of social anxiety disorder is a relatively recent phenomenon dating from the mid

1980s. The MAOIs were the first to clearly show efficacy but since then similar benefits have been reported with the use of reversible and selective inhibitors of monoamine oxidase A (RIMAs) and over the last few years the SSRIs. As yet paroxetine is the only SSRI to be licensed for this condition, based on three large studies of 12 weeks duration. These showed that paroxetine at doses of 20–50 mg a day was significantly more effective than placebo at each dose (Stein et al, 1998).

The recommended dose of paroxetine to treat social anxiety disorder is 20 mg a day, increasing by 10 mg increments if there is no response up to a maximum of 50 mg a day. There does not appear to be any anxiety exacerbation on starting treatment, leading to a recommended initial dose of 20 mg a day. No long-term studies have been performed to allow formal assessment of the duration but, as with the other disorders, our practice is to treat patients who respond for 9–12 months.

Paroxetine in the treatment of social anxiety disorder:

- Start at 20 mg a day
- Dose may be increased to 50 mg a day
- Duration of treatment 9–12 months.

Mixed states

Many psychiatric presentations are of mixed anxiety and depressive states. While it is vital to take a careful history and establish a clear diagnosis, it is apparent that where conditions do co-exist, using a drug that treats both is sensible. As described above the serotonergic system is implicated in panic, OCD and social anxiety disorder. On the basis of this our clinical practice is to use an SSRI as the first-line antidepressant in cases of depression presenting with any combination of these.

Night terrors

Night terrors are episodes of autonomic and behavioural changes associated with intense fear which occur from slow wave sleep in the first third of the night. Typically sufferers have no recollection for the terror in the morning, but in the midst of one appear extremely frightened and distressed and in an attempt to defend themselves may lash out and hurt themselves or others. They appear to have a familial basis and are particularly common in children, although they also occur in adults.

Treatment of night terrors often proves difficult — successes have been reported with benzodiazepines and some TCAs, and psychological and psychotherapeutic approaches, but there is no really established treatment. There have been reported benefits with paroxetine in the treatment of six patients with disabling night terrors (Wilson et al, 1997). Doses used ranged from 20–40 mg a day and dramatic improvements were seen within a few days of starting treatment, clearly different from the antidepressant or anxiolytic effect.

ADVERSE EFFECTS

SSRIs are generally well tolerated and importantly are safe in overdose. The most common adverse effects are similar for all SSRIs, and include nausea and diarrhoea (usually occurs early in treatment and resolves over 1–2 weeks), headache, sleep disruption (both insomnia and marked sleepiness have been reported), anxiety and agitation (particularly in patients with pre-existing panic symptoms) and sexual dysfunction (delayed ejaculation, anorgasmia and reduced libido — often dose related and usually resolves on stopping paroxetine) (Boyer and Blumhardt, 1992). In some patients where premature ejaculation is a problem, a drug that delays this could be advantageous.

The differences between the SSRIs are quite minor — paroxetine tends to cause the least sleep disruption and agitation and so has advantages when these symptoms are already present.

PHARMACOKINETICS AND DRUG INTERACTIONS

Paroxetine is well absorbed and is extensively bound to plasma proteins. As with other SSRIs it is predominantly eliminated by cytochrome p450-catalysed oxidation in the liver. Drugs that inhibit this enzyme may increase plasma paroxetine levels. It is important to note that paroxetine itself inhibits cytochrome 2D6 within this enzyme system, which means that it could cause important interactions (i.e. higher plasma levels) with drugs that are metabolized by this route, e.g. TCAs, other SSRIs, opiates, neuroleptics, β-blockers and antiarrhythmics. The half-life of paroxetine is about 24 hours, allowing once a day dosing. The metabolites are inactive and are excreted via the kidneys; there are no active metabolites.

A combination of paroxetine or any SSRI with lithium could cause a serotonergic syndrome, although there have been few reports of this occurring (Rao, 1998). Again as with other SSRIs combination with MAOIs is contraindicated and SSRIs should not be started until 2 weeks after stopping treatment with an MAOI. There is a pharmacokinetic interaction with warfarin and the two drugs should be co-administered with caution.

DISCONTINUATION EFFECTS

Discontinuation effects have been reported with abrupt cessation of all the SSRIs but appear to be significantly more common with paroxetine, particularly in comparison with those of longer half-life, e.g. fluoxetine (Coupland et al, 1995).

The symptoms include dizziness, visual disturbance, anxiety, nausea, sleep disruption and confusion. These usually appear 3–5 days after stopping treatment and resolve over 1–2 weeks.

In view of this it is recommended that paroxetine be withdrawn gradually by tapering the dose for 1–2 weeks and then stopping.

DIFFERENT DISORDERS TREATED WITH THE SAME DRUG

Although we have emphasized that an accurate diagnosis is vital to choosing an effective drug, it is clear that paroxetine treats a variety of conditions. This does not mean that they are all the same disorder. There are important differences in the way therapeutic effects are achieved in each condition. First, the response to treatment is faster in depression than in the anxiety disorders, with OCD typically being the slowest to respond to treatment (up to 12 weeks). Second, there are differences in the dose of SSRI required; depression responds to lower doses than panic disorder or OCD. Finally, in the treatment of panic disorder there may be an initial worsening of anxiety symptoms during the first few weeks of treatment, a phenomenon that does not occur in the treatment of depression, OCD or social anxiety disorder.

All the SSRIs inhibit the reuptake of serotonin into nerve terminals which raises the question how one mode of action can explain the improvement seen in such a wide variety of conditions. As yet there is no definitive answer, although recent work using challenge responses to serotonergic agents and the technique of tryptophan depletion has tried to look at this (Bell and Nutt, 1998). Tryptophan is an essential amino acid (mainly available from the diet) which is the precursor of serotonin.

In tryptophan depletion studies, patients undergo a 24-hour low-tryptophan diet followed by ingestion of a tryptophan-free amino acid drink, a combination which dramatically lowers plasma tryptophan levels. In studies of depression this results in patients taking SSRIs who have responded to treatment becoming acutely depressed again; this is reversed within hours of starting back on a normal diet (Delgado et al, 1990). In OCD tryptophan depletion does not result in symptom relapse and studies with panic disorder patients are underway. It appears that SSRIs act by increasing the availability of serotonin in the synapse in depression. In OCD this does not seem to be the case; postsynaptic receptor adaptation may possibly be more important.

KEY POINTS

- Paroxetine is a specific serotonin-reuptake inhibitor (SSRI) which is licensed for use in depression, panic disorder, obsessive–compulsive disorder and social anxiety disorder.
- The doses required and duration of treatment are specific to the disorder but tend to be higher in the anxiety disorders than in depression.
- Anxiety exacerbation at the start of treatment occurs in panic disorder but not typically in the other disorders.
- Paroxetine is generally well tolerated, the side-effect profile being similar to that seen with the other SSRIs.
- Discontinuation effects can occur on abrupt cessation of treatment, therefore doses should be gradually tapered.

CONCLUSIONS

Paroxetine is an effective antidepressant which has also demonstrated efficacy in panic disorder, OCD and social anxiety disorder. Effectively treating patients suffering from these conditions alleviates considerable morbidity. Paroxetine is not a lifestyle drug and it is not a wonder drug. Patients need to be carefully diagnosed, and treated according to their specific disorder. They also need a clear explanation for their symptoms and management, including possible side effects and the likelihood of any anxiety exacerbation. They need to be reviewed regularly and quite frequently at first, and encouraged to take part in and use psychological approaches where required. HM

Conflict of interest: Professor Daivd Nutt has received grants for research projects and support for lectures from SmithKline Beecham

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