Escitalopram: efficacy and tolerability in the treatment of depression

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Escitalopram is a new antidepressant drug, available for clinical use in many countries. This review describes the properties of escitalopram, summarizes the results of randomized controlled trials, and suggests that escitalopram has advantages over citalopram in the treatment of depression.

The antidepressant escitalopram is a single enantiomeric drug that is both more potent and selective than the parent compound, racemic citalopram. In randomized controlled trials and pooled analysis of data, escitalopram appears to have advantages over citalopram in terms of onset of action and greater overall efficacy, and is similarly tolerated. Do these features of escitalopram indicate that it will have advantages over citalopram in the treatment of depressed patients in wider clinical practice?

WHAT IS AN ENANTIOMER?

Many pharmacological compounds have a chiral centre (usually a carbon atom) and therefore exist as pairs of enantiomers (non-superimposable mirror images), which differ solely in terms of their three-dimensional characteristics. When a compound includes a pair of enantiomers it is known as a 'racemic mixture'. Although enantiomers have identical physicochemical properties, they can show major differences in their interaction with chiral drug targets in the body, leading to differences in pharmacodynamic and pharmacokinetic properties (Agranat et al, 2002).

In general, single enantiomeric drugs have certain advantages over racemic compounds, by allowing reduced variability in metabolism and response, simpler dose–response relationships, reduction in dosage and reduced toxicity (Wainer, 2001). This is the case with the local anaesthetic levobupivacaine, where safety has been improved without compromising efficacy. However, not all 'enantiomeric switches' have been successful: dexfenfluramine, the active enantiomer of fenfluramine, was withdrawn from use because of cardiac toxicity.

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PHARMACOLOGICAL PROFILE OF ESCITALOPRAM

The selective serotonin-reuptake inhibitor (SSRI) citalopram is a racemic mixture of an S-(+)-enantiomer, escitalopram and an R-(–)-enantiomer, R-citalopram. In-vitro and in-vivo studies demonstrate that escitalopram is a more potent SSRI than citalopram, whereas R-citalopram is practically devoid of serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitory effects. For example, in rat brain synaptosomes, escitalopram, citalopram and R-citalopram show IC50 (concentration at which that effect is seen in 50% of the experimental subjects; where smaller numbers indicate greater potency) values of 2.1, 3.9 and 280 nM respectively (Sanchez and Brennum, 2000).

Escitalopram is the most selective SSRI available for clinical use. The level of selectivity, expressed as the ratio between affinities for 5-HT and noradrenaline (NA) transporter proteins, is shown in *Table 1*. In addition, escitalopram has either no or minimal activity in more than 140 receptor binding, uptake and enzyme activity assays. As such the pharmacological effects of escitalopram are likely to arise exclusively from its 5-HT reuptake inhibitory effects (Owens et al, 2001).

TABLE 1.
Selectivity of different antidepressants

Antidepressant	Selectivity
Escitalopram	7100
Citalopram	3900
Sertraline	2700
Fluoxetine	540
Paroxetine	450

Selectivity is defined as the ratio between affinity for serotonin and noradrenaline transporter proteins

Animal models indicate that escitalopram possesses effects shared with other antidepressants. For example, the rat chronic mild stress model indicates that escitalopram and citalopram reverse the chronic mild stress-induced decrease in sucrose intake to a similar extent as tricyclic antidepressants. With escitalopram this effect is seen after only 1 week, compared to 4 weeks with the tricyclic antidepressant imipramine and 2 weeks with citalopram, suggesting that escitalopram may have an earlier onset of antidepressant-like action (Montgomery et al, 2001). In another animal model, known as the resident-intruder model, escitalopram-treated rats exhibited defensive behaviour from day 1, whereas previous studies show that venlafaxine and fluoxetine increase defensive behaviour from days 2 and 5 respectively (Mitchell and Hogg, 2001; Baumann et al, 2002).

EFFICACY OF ESCITALOPRAM IN RANDOMIZED CONTROLLED TRIALS

The clinical trial programme for escitalopram in the treatment of major depressive disorder included four placebo-controlled trials, three of which also included citalopram as an active comparator, to demonstrate the assay sensitivity of the trial (*Table 2*). Two of the studies used a fixed-dose design, two a flexible-dose design; two were conducted in the United States and two in Europe; two of the studies were conducted in primary settings, and two in psychiatric outpatient clinics. Two of the studies have already been published (Burke et al, 2002; Wade et al, 2002). These studies indicate that 10–20 mg daily doses of escitalopram are significantly more efficacious than placebo in the short-term treatment of patients with major depression.

None of the three studies that used citalopram as comparator were large enough to detect a significant difference between the active treatments, but some interesting findings were seen. For example, escitalopram separated from placebo as early as week one or two of treatment, and escitalopram 10 mg/day was as efficacious as citalopram 40 mg/day. For these reasons, a pooled analysis of all data arising from the three randomized trials with citalopram as comparator has been performed, to see whether the resultantly increased patient numbers can confirm whether these intriguing findings are detected more robustly in a larger data set (Gorman et al, 2002).

The results of the pooled analysis indicate that escitalopram has both an earlier onset of antidepressant effect and greater overall efficacy than citalopram, as measured by change in mean score on the Montgomery-Asberg Depression Rating Scale (MADRS, Montgomery and Asberg, 1979). Using last observation carried forward (LOCF) analysis, escitalopram was significantly more efficacious than placebo from week 1, whereas citalopram only separated from placebo at week 6; escitalopram was also significantly more efficacious than citalopram at week 1. Escitalopram was also significantly more efficacious than citalopram at week 6 in the LOCF analysis, and at study end-point (week 8) in the less rigorous but more clinically meaningful observed case analysis.

Similar findings were seen when comparing the overall response to treatment using a clinical global impression of improvement: in both the LOCF and observed case analyses, escitalopram was significantly more effective than placebo from week 1, whereas citalopram separated from placebo at week 4 (*Table 3*) (Gorman et al, 2002).

Typically, depression is a recurring episodic disorder and it is important to establish whether antidepressants that are efficacious in relieving symptoms in short-term treatment are also efficacious in maintaining remission in long-term

TABLE 2.
Randomized placebo-controlled treatment studies with escitalopram in patients with major depressive disorder

					Escitalopram daily dose (mg)			Citalopram daily dose (mg)	
Study	Design	Overall *n* (ITT)	Setting	Mean MADRS score at baseline	10	20	10–20	40	20–40
MD-01 (Burke et al, 2002)	Fixed dose	485	Outpatients	28	Yes (*n*=118)	Yes (*n*=123)	–	Yes (*n*=125)	–
99001 (Wade et al, 2002)	Fixed dose	377	Primary care	29	Yes (*n*=189)	–	–	–	–
99003	Flexible dose	468	Primary care	29	–	–	Yes (*n*=155)	–	Yes (*n*=160)
MD-02 *	Flexible dose	368	Outpatients	28	–	–	Yes	–	Yes

ITT= intention to treat population; MADRS= Montgomery-Asberg Depression Rating Scale. * escitalopram and citalopram did not differentiate from placebo on primary outcome measure in last observation carried forward analysis: not all data available to author

TABLE 3.
Efficacy of escitalopram in major depression: pooled analysis

Measure	Escitalopram more efficacious than placebo?	Citalopram more efficacious than placebo?	Escitalopram more efficacious than citalopram?
Change from baseline MADRS score	Yes, LOCF and OC, week 1 onwards	Yes, LOCF and OC, weeks 6 and 8	Yes, LOCF weeks 1 and 6, OC weeks 1 and 8
50% or more reduction in MADRS score from baseline	Yes, OC, week 8	Yes, OC, week 8	No
Clinical global impression of improvement	Yes, LOCF and OC, week 1 onwards	Yes, LOCF and OC, weeks 4–8	Yes, OC, weeks 4 and 6
MADRS inner tension item	Yes, OC, week 1 onwards	Yes, OC, weeks 4–8	Yes, OC, week 1
Change from baseline in patients with severe depression (baseline MADRS 30 or more)	Yes, LOCF, week 1 onwards	No	Yes, LOCF and OC, weeks 1, 6 and 8

From Gorman et al (2002). MADRS = Montgomery-Asberg Depression Rating Scale; LOCF = last observation carried forward analysis; OC = observed case analysis

treatment. An unpublished placebo-substitution relapse prevention trial with escitalopram indicates that it is significantly more efficacious than placebo in preventing a return of depressive symptoms (data on file, Lundbeck Ltd, 2002).

TOLERABILITY OF ESCITALOPRAM IN RANDOMIZED CONTROLLED TRIALS

In an analysis of tolerability data pooled from the four randomized placebo-controlled acute treatment trials with escitalopram, only one adverse event (nausea) was both significantly more common with escitalopram than with placebo, and occurred in more than 10% of treated patients (escitalopram 15.0%; placebo 7.4%). The other significant differences from placebo are shown in *Table 3*. Less than 6% of patients stopped treatment as a result of adverse events. There were no clinically significant changes in vital signs, electrocardiogram (ECG) or laboratory values. When compared to citalopram, a similar adverse event profile was seen, with no significant differences between drugs (*Table 4*).

TABLE 4.
Treatment-emergent adverse events with escitalopram and citalopram

Preferred term	Placebo *n* (%)	Escitalopram *n* (%)	Citalopram *n* (%)
Patients treated	592	715	408
Patients with TEAE	379 (64.0)	520 (72.7)	312 (76.5)
Headache	97 (16.4)	113 (15.8)	81 (19.9)
Nausea	44 (7.4)	107 (15.0)*	70 (17.2)*
Ejaculation disorder (gs)	–	21 (9.3)*	14 (8.8)*
Insomnia	23 (3.9)	66 (9.2)*	35 (8.6)*
Diarrhoea	31 (5.2)	57 (8.0)*	44 (10.8)*
Somnolence	13 (2.2)	49 (6.9)*	19 (4.7)
Dry mouth	27 (4.6)	44 (6.2)	33 (8.1)
Upper respiratory tract infection	41 (6.9)	44 (6.2)	16 (3.9)
Dizziness	21 (3.5)	43 (6.0)*	23 (5.6)
Influenza-like symptoms	24 (4.1)	36 (5.0)	25 (6.1)
Rhinitis	30 (5.1)	35 (4.9)	23 (5.6)
Sinusitis	13 (2.2)	31 (4.3)*	21 (5.1)*
Back pain	30 (5.1)	22 (3.1)	14 (3.4)

Adverse event terminology used: World Health Organization Adverse Reaction Terminology (preferred term); gs = gender specific preferred term; * = significantly different from placebo, $P<0.05$. TEAE = treatment emergent adverse event

The long-term tolerability of escitalopram has been examined in an open-label 12-month safety study, conducted in outpatients who had satisfactorily completed one of two placebo-controlled acute treatment studies. As might be expected, the incidence of adverse events was lower than in the short-term studies: again there were no untoward changes in vital signs, ECG or laboratory findings.

There have been no deaths after escitalopram overdose, nor are there any cases of switch into mania in the clinical trial database; furthermore there is no evidence of a discontinuation syndrome on stopping the drug (data on file, Lundbeck Ltd, 2002).

POSSIBLE EFFICACY OF ESCITALOPRAM IN TREATMENT OF ANXIETY DISORDERS

Escitalopram may have advantages over citalopram in relieving anxiety symptoms within depression. In the pooled analysis of randomized controlled trials, escitalopram and citalopram both significantly improved anxiety symptoms compared with placebo. However, escitalopram was more efficacious than placebo at week 1, whereas citalopram could only be discriminated from placebo at week 4: escitalopram was superior to citalopram in improving anxiety symptoms at week 1 (Gorman et al, 2002).

Other SSRIs have proven efficacy in the treatment of a range of anxiety disorders, including panic disorder, social anxiety disorder and generalized anxiety disorder (Baldwin and

Birtwistle, 2000). The preliminary findings of randomized controlled trials indicate that escitalopram is efficacious in the treatment of generalized anxiety disorder (data on file, Lundbeck Ltd, 2002; data on file, Forest Laboratories, Inc., 2002), social anxiety disorder (Kasper, 2002) and panic disorder (Stahl, 2002).

AREAS OF UNCERTAINTY

A substantial clinical trial programme is underway, one component being to compare the efficacy and tolerability of escitalopram to antidepressants other than citalopram. The indication that escitalopram has greater overall efficacy and an earlier onset of action than citalopram are intriguing findings, given conclusions that dual-acting less selective antidepressant drugs (e.g. venlafaxine or mirtazapine) are somewhat more efficacious than single-acting antidepressants such as the SSRIs in the treatment of depression (Anderson et al, 2000). The earlier relief of anxiety symptoms in depression with escitalopram than with citalopram suggests that it should be compared to other antidepressants that have well-documented anxiolytic properties, including paroxetine and mirtazapine.

As escitalopram enters wider use in routine clinical practice it will be possible to establish whether the apparent advantages seen in randomized controlled trials are confirmed. Wider exposure of patients to escitalopram will allow a more detailed evaluation of its side-effect profile in groups such as the elderly or the physically ill, and also further evaluation of its safety after overdose, and risk of causing a switch to hypomania or mania when used in treatment of patients with bipolar depression.

CONCLUSIONS

Escitalopram is the active enantiomer of racemic citalopram. Pre-clinical studies with escitalopram indicate not only that it is the most selective SSRI, and more potent than citalopram, but also that it has an earlier onset of antidepressant-like action. Randomized controlled trials in patients with major depression show that it has certain advantages over citalopram in measures of efficacy, while maintaining the satisfactory tolerability profile. Current treatment studies will establish the relative efficacy and tolerability of escitalopram and other antidepressants, and the effects of escitalopram in the treatment of anxiety disorders. HM

Conflict of interest: The School of Medicine at the University of Southampton has received support from Lundbeck Ltd, the manufacturers of escitalopram, to conduct research. Dr Baldwin has spoken at satellite symposia supported by Lundbeck Ltd, and is a member of an international advisory board for Lundbeck Ltd. This paper is based upon a talk given during the 2002 annual meeting of the British Association for Psychopharmacology in Harrogate: the opinions are those of Dr Baldwin, and not necessarily those of the manufacturers.

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KEY POINTS

- Escitalopram is the single active enantiomer of citalopram, an antidepressant that has proven efficacy in depression, panic disorder and obsessive-compulsive disorder.
- Preclinical studies with escitalopram show that is both more potent and selective than citalopram; it may have an earlier onset of antidepressant-like action than citalopram or imipramine.
- Randomized controlled trials show that escitalopram is an efficacious antidepressant drug, with some advantages over citalopram in terms of earlier antidepressant effects and greater overall efficacy.
- The tolerability profile of escitalopram is similar to that with citalopram.
- More research is needed to compare the efficacy and tolerability of escitalopram to that seen with other antidepressant drugs in the treatment of depressive and anxiety disorders.