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REVIEW

Citalopram

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Citalopram is a selective serotonin (5-HT) reuptake inhibitor (SSRI) developed by H. Lundbeck A/S in Denmark. It is the most selective serotonin antidepressant with proven efficacy, a favourable pharmacokinetic profile and a low potential for interactions with other concomitant medication. The drug has a low incidence of side effects, even when compared to the other SSRIs and good patient compliance and satisfaction is a feature of this drug. These factors make the drug a good choice for depressed patients who require continuation and long-term treatment, as well as for elderly patients.

KEY WORDS — citalopram; depression; anxiety; panic; OCD; elderly depression

INTRODUCTION

The emphasis of this review will be on new information published since 1995, covering issues such as citalopram's pharmacology and pharmacokinetics, as well as new data concerning the treatment of depression, anxiety disorders and the elderly patient. New treatment areas will be addressed shortly.

PHARMACOLOGY

The pharmacology of citalopram has previously been reviewed (Hyttel, 1982; Milne and Goa, 1991; Hyttel *et al*., 1995). A huge number of citalopram publications have appeared over the last 5 years and the pharmacology section of the present paper will by no means account for this information.

Selectivity of serotonin reuptake inhibitors is defined relative to inhibition of noradrenaline (NA) reuptake. Citalopram is the most selective and fluoxetine is the least selective of the clinically used SSRIs; citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline (Hyttel, 1994). The *N*-demethylated metabolite, demethycitalopram, has about 10 times lower 5-HT reuptake inhibitory potency *in vitro* than citalopram, and has only very weak activity *in vivo* (Sánchez and Hyttel, 1999). In addition citalopram and demethylcitalopram are practically devoid of activity in more than 140 different receptor binding, functional reuptake and enzyme activity assays (Lundbeck screening data and Cereb and Panlab receptor screens). The highest affinity is found to sigma 1-binding sites (IC_{50} = 200 nM relative to IC_{50} = 1·8 nM for 5-HT reuptake inhibition, Sánchez and Meier, 1997) and histamine H1 receptors (IC_{50} = 350 nM, Hyttel, 1994). This suggests that the pharmacological activity of citalopram is likely to be ascribed exclusively to its 5-HT reuptake inhibitory potency (Figure 1).

Citalopram shows antidepressant- and anxiolytic-like activity in a number of animal models (Table 1). The potency of citalopram is comparable to imipramine in the mouse forced swim test, whereas the other SSRIs show less potent and partial effects (Sánchez and Meier, 1997). Citalopram is also active in the rat chronic mild stress model of depression (Przegalinski *et al*., 1995). This model mimics a depressive core symptom, anhedonia. Rats exposed to chronic mild stress display a reduced sensitivity to rewards, e.g. decreased consumption of sucrose solution (Willner *et al*., 1992). In addition, antidepressants are effective in the chronic mild stress model only after repeated administration. Thus, the chronic mild stress model

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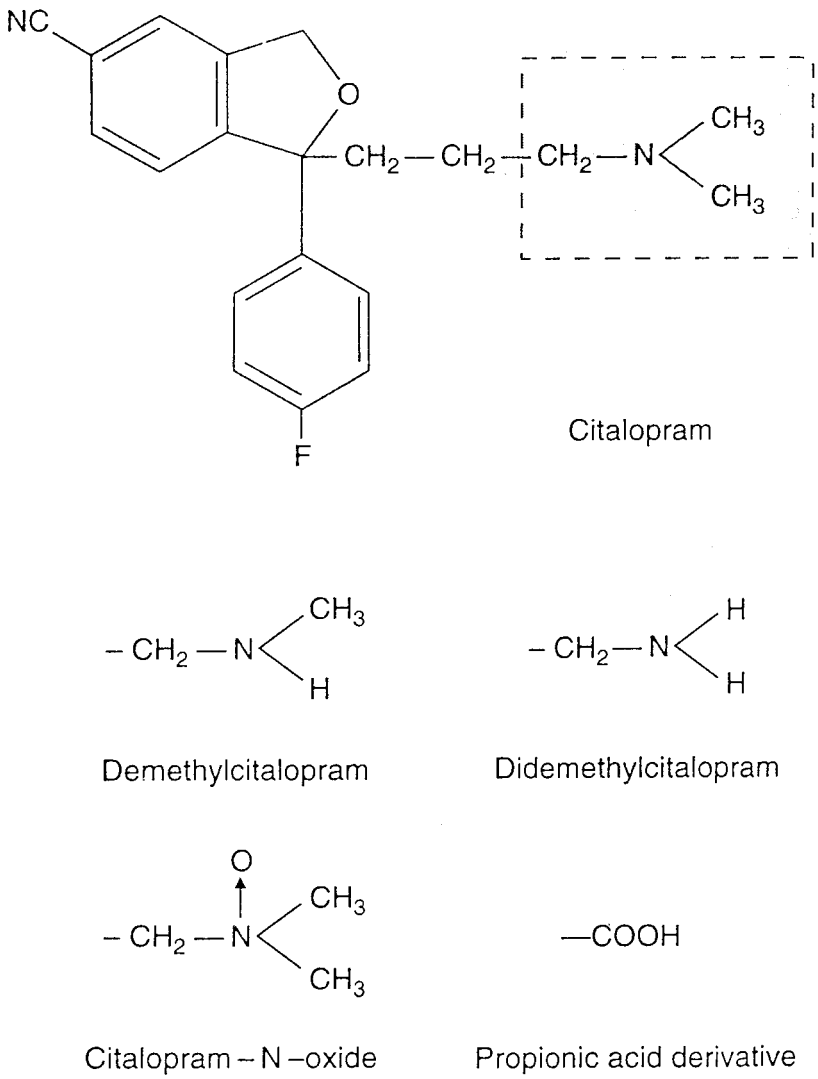

Figure 1. Chemical structure of citalopram and its metabolites

mimics the clinical situation, where efficacy is seen only after repeated dosing with antidepressants. Chronic treatment with citalopram normalises the sucrose intake to levels of unstressed controls (Przegalinski *et al*., 1995). Interestingly, the onset of antidepressant-like effect in this model appears to be faster for citalopram than for imipramine. Citalopram facilitates exploratory behaviour of mice and rats in a black and white test box, whereas the other SSRIs are practically devoid of activity (Sánchez, 1995; Sánchez and Meier, 1997). Citalopram and paroxetine are potent inhibitors of footshock-induced ultrasonic vocalisation in adult rats, while other SSRIs are moderately active in this anxiety model (Sánchez and Meier, 1997). Sertraline, fluoxetine and fluvoxamine exert moderate to weak inhibition of isolation-induced aggressive behaviour in male mice, while citalopram and paroxetine are inactive (Sánchez and Hyttel, 1994). However, the anti-aggressive effect of citalopram and paroxetine is dramatically increased if a sub-effective dose of the 5-HT precursor, 1-5-HTP, is co-administered. The response of the other SSRIs is potentiated to a minor extent. In conclusion, this differentiation of the antidepressant, anxiolytic and anti-aggressive effects between the SSRIs in animal

Table 1. Citalopram antidepressant- and anxiolytic-like activity in a number of animal models

	Forced swimming*	CMS†	Black/white box‡	USV§	Isolated aggressive mice¶	
					SSRI alone	SSRI + 1-5HTP
Citalopram	++	++	+++¶	++?	−	++
Fluoxetine	(+)	++	−	(+)	+	+
Fluvoxamine	(+)	nt	−	+	+	++
Paroxetine	(+)	nt	−	++	−	+++
Sertraline	(+)	nt	−	+	+	+

* Porsolt *et al*. (1977).
† Chronic mild stress model (Willner *et al*., 1992).
‡ Sánchez and Meier (1997).
§ Ultrasonic vocalisation, Sánchez and Meier (1997).
¶ Sánchez and Hyttel (1994).
? Biphasic.
−: no effect; +: weak; ++: moderately potent; +++: potent; 0: partial response; nt = not tested.

models could indicate differences in their clinical actions.

In conclusion, in animal models, citalopram appears to possess greater anxiolytic (Sánchez and Meier, 1997) and anti-aggressive effects (Sánchez and Hyttel, 1994) than other SSRIs. Citalopram also produces a more rapid onset of action in the chronic mild stress model in rats (Przegalinski *et al*., 1995). These preclinical features of citalopram could possibly be translated into the clinical setting.

PHARMACOKINETIC PROFILE

The pharmacokinetics of citalopram has previously been reviewed (e.g. Baumann and Larsen, 1995; Noble and Benfield, 1997). In brief, citalopram is well absorbed with an absolute bioavailability of about 80 per cent and peak concentrations observed 2–4 h post-dose. The protein binding and the apparent volume of distribution are about 80 per cent and 12–16 l/kg, respectively (Joffe *et al*., 1998; Kragh-Sørensen *et al*., 1981; Fredricson Overø, 1982, 1987). The single- and multiple-dose pharmacokinetics of citalopram are linear and dose-proportional in the dose range of 10–60 mg/day (Gutierrez *et al*., 1998; Baumann and Larsen, 1995).

Citalopram is the predominant compound in serum (Priskorn *et al*., 1997a) and is metabolised in the liver to demethylcitalopram (DCT), didemethylcitalopram (DDCT), citalopram-*N*-oxide and a deaminated propionic acid derivative. The three former metabolites are less selective and less potent SSRIs *in vitro* (Hyttel and Larsen, 1985; Sánchez and Hyttel, 1999) than citalopram and are of minor clinical importance. Renal excretion is the major route of elimination and about 20 per cent of the dose is excreted unchanged in the urine. A considerable amount of citalopram is excreted as polar conjugates (Dalgaard and Larsen, 1999).

The serum half-lives of citalopram, DCT and DDCT are about 1·5, 2 and 4 days, respectively (Fredricson Overø, 1982; Kragh-Sørensen *et al*., 1981; Priskorn *et al*., 1997a; Sidhu *et al*., 1997), and steady-state conditions are normally attained in about 1–2 weeks. The systemic and oral clearance for citalopram is about 20 and 25 l/h, respectively (Joffe *et al*., 1998; Priskorn *et al*., 1997a).

Special-populations

In elderly patients longer half-lives, higher concentrations and lower oral clearances of citalopram have been observed (Fredricson Overø *et al*., 1985; Uehlinger *et al*., 1995). This supports the possibility of a decreased metabolic activity of citalopram in elderly patients. However, in a more recent multiple-dose study (40 mg/day), no significant difference between healthy young and elderly subjects was found, although the average concentrations were 23 per cent higher and the half-life 31 per cent longer in the elderly (Data on file, H. Lundbeck A/S). The general recommendation is to give elderly patients (>65 years) doses not exceeding 40 mg/day.

In patients with reduced hepatic function, longer half-lives and decreased oral clearance (to about 16 l/h) of citalopram was observed and a lower maxi-

mal dose in this population should be considered (Joffe *et al*., 1998).

Mild to moderate renal insufficiency has no major impact on citalopram pharmacokinetics (Joffe *et al*., 1998). However, no information is available for chronic treatment of patients with severely impaired renal function.

Interaction potential

In vitro models have shown that CYP3A4 and CYP2C19 mediate the formation DCT and DDCT with a minor contribution of CYP2D6. In therapeutic doses citalopram may produce weak inhibition of CYP1A2, 2C19, and CYP2D6, but a weak or negligible inhibition of CYP2C9, 2E1 and CYP3A (Greenblatt *et al*., 1998; von Moltke *et al*., 1999). Drug interaction studies including cimetidine, warfarin, neuroleptics, lithium, TCAs, triazolam and selegiline support this predicted relatively low propensity for interactions (Priskorn *et al*., 1997a, 1997b; Sylvälahti *et al*., 1997; Gram *et al*., 1993; Baettig *et al*., 1993; Baumann and Bertschy, 1993; Nolting and Abramovitz, 1999; Laine *et al*., 1997).

CITALOPRAM IN THE TREATMENT OF DEPRESSION

Citalopram has been proven to be effective in the treatment of depression in various studies (e.g. Feighner and Overø, 1999; Mendels *et al*., 1999; Frampton, 1997; Montgomery and Johnson, 1995).

Meta-analyses of the depression trials with citalopram have been undertaken (Bech, 1989; Milne and Goa, 1991). From these analyses, previous suggestions as to safety and efficacy are confirmed, as is the efficacy across the broader spectrum of anxiety disorders and depression. The dose should be 20–40 mg/day and should be continued for 6–9 months following remission of the depressive symptoms, to maintain the optimal therapeutic response and reduce the likelihood of relapse (Montgomery, 1989).

Conclusions from another meta-analysis, of nine clinical trials, were that the minimum effective dose for citalopram is 20 mg/day (Montgomery *et al*., 1994). Patients suffering from severe depression may require a higher dose of 40 mg/day, and due to the relatively safe adverse event profile, doses of 60 mg/day can be tolerated well.

In a short-term, placebo-controlled study, 650 patients with moderate to severe depression were randomised to either citalopram (10, 20, 40 and 60 mg/day) or placebo. Treatment discontinuation rates due to lack of efficacy were similar in the placebo (9 per cent) and citalopram 10 mg (7 per cent) groups, but significantly lower in the citalopram 20 mg (2 per cent), 40 mg (2 per cent), and 60 mg (3 per cent) groups (Feighner and Overø, 1999).

The long-term efficacy of citalopram has been established in preventing relapse and recurrence of depression (Montgomery *et al*., 1993; Robert and Montgomery, 1995; Wade *et al*., 1999a). Relapse rates for citalopram were 10·5 per cent and 13·8 per cent, respectively, in the two relapse prevention studies, compared with 31 per cent and 24·3 per cent for the placebo-treated patients.

Wade *et al*. (1999a) studied the prevention of possible recurrence of depression and found that patients who were to suffer a relapse of the depressive illness had a longer period to recurrence when treated with citalopram in comparison to those receiving placebo.

CITALOPRAM VERSUS OTHER ANTIDEPRESSANTS IN THE TREATMENT OF DEPRESSION

Citalopram has been compared to amitriptyline (Shaw *et al*., 1986), and mianserin (de Wilde *et al*., 1985) in depression. In these studies, citalopram proved to be as effective as the comparative agents but with far fewer side effects (Frampton, 1997). In a meta-analysis of five controlled studies, there was no difference in efficacy between citalopram and the TCAs (imipramine, amitriptyline, clomipramine and nortriptyline). However, the side effects of the TCAs were more pronounced than those of SSRIs.

In a comparative study of citalopram and fluoxetine in the treatment of major depression, the clinical efficacy of the two drugs was the same. In the subgroup of patients who were severely depressed, there was a more rapid therapeutic onset in the patients using citalopram. After two weeks, 16 per cent of these patients showed a complete response compared with none in the fluoxetine group (Bougerol *et al*., 1997).

Another comparison study between citalopram and fluoxetine found that most outcome measures were similar. However, response rates at 2 weeks favoured citalopram significantly over fluoxetine ($p = 0{\cdot}048$; 35 per cent versus 24 per cent), as did the proportion of treatment responders ($p = 0{\cdot}034$; 27 per cent versus 16 per cent). When evaluating the

patients not receiving benzodiazepines, citalopram was superior to fluoxetine at all evaluation points in the study (Patris *et al*., 1996; Bougerol *et al*., 1997).

In a study comparing citalopram to sertraline (Ekselius *et al*., 1997) response rates were similar. However, a greater proportion of patients in the sertraline group discontinued treatment prematurely (26 per cent versus 18 per cent) and/or required concomitant hypnotic or anxiolytic medication (55 per cent versus 44·5 per cent).

Citalopram has been compared with fluvoxamine in outpatients with major depression (Haffmans *et al*., 1996). The two drugs were equally effective, but citalopram was better tolerated than fluvoxamine.

A comparison study between citalopram (20–60 mg) and sertraline (50–150 mg) (Stahl, 1999), reports significantly improved response for citalopram, specifically where anxiety symptoms are seen in association with depression. After two weeks of treatment there was a significantly better response for citalopram, possibly indicating a more rapid onset of action.

CITALOPRAM IN ANXIETY DISORDERS

Although citalopram is primarily indicated as an antidepressant agent, there have been animal and clinical studies reporting that it is an active anti-anxiety and anti-aggression agent as well (Hyttel *et al*., 1995; Sánchez and Meier, 1997; Boyer, 1992; Inoue *et al*., 1996), with proven efficacy within several of the anxiety disorders (Joubert and Stein, 1999).

A recent placebo-controlled study comparing citalopram (20–60 mg) and sertraline (50–150 mg) (Stahl, 1999) found that citalopram resulted in a significantly greater improvement in the Hamilton Anxiety Rating Scale total score as well as the Hamilton Depression Rating Scale's anxiety subscale. The improved response shown for citalopram suggests that citalopram may be the favoured drug in the treatment of anxiety disorders.

PANIC DISORDERS

Humble and Wistedt (1992) first suggested the therapeutic efficacy of citalopram in panic disorder, with or without agoraphobia, from a small open trial. Likewise Lepola *et al*. (1994b) found that citalopram brought relief of generalised anxiety and phobic avoidance behaviour in the first week of treatment of PD.

In the first double-blind placebo-controlled study of citalopram and clomipramine, Wade *et al*. (1997) report on an 8-week trial evaluating panic disorder patients, with or without agoraphobia. A total of 475 patients were randomised to treatment with placebo, clomipramine 60 or 90 mg/day, or citalopram 10 or 15 mg/day, or 20 or 30 mg/day, or 40 or 60 mg/day, as part of a comparative efficacy and dose-finding protocol (Figure 2).

The results showed that citalopram at 20–30 mg and 40–60 mg, and clomipramine at 60–90 mg/day, were significantly superior to placebo, evaluated by the number of patients free of panic attacks in the week prior to the final assessment. Rating scales used suggest that citalopram 20–30 mg is more effective than citalopram 40–60 mg (Wade *et al*., 1997).

Results of a 1-year extension phase of the 8-week study support the short-term evidence that citalopram (20–60 mg/day) and also clomipramine (60–90 mg/day) are effective in the treatment of PD with or without agoraphobia and indicate that the response rate improves further beyond 2 months' treatment. The dose-range of 20–30 mg/day was clearly the optimal range. All three dose levels of citalopram and clomipramine were well-tolerated over the year of treatment (Lepola *et al*., 1998).

Available evidence suggests that, with respect to efficacy, tolerability and relative safety, the SSRIs are the most favourable treatment choice for patients with panic disorder (Sheehan and Harnett-Sheehan, 1996; Baldwin and Birtwistle, 1998; DeVane, 1997). The evidence presented here shows that citalopram is a good choice for the treatment of panic disorder.

OBSESSIVE-COMPULSIVE DISORDER

The use of citalopram in obsessive-compulsive disorder (OCD) was first documented in the mid-1980s (White *et al*., 1986), whereafter another early study of six OCD patients supported the use of citalopram in OCD (Bejerot and Humble, 1991). Koponen *et al*. (1995) reported on two cases of OCD responding well to citalopram.

Stein *et al*. (1996b) describe the use of citalopram for OCD in a naturalistic open-label trial in 12 patients. After 12 weeks of treatment, 66·7 per cent of patients were judged responders with a mean citalopram dose of 44·2 mg. Side effects during this study were few and their severity was described as minimal. While the need for concomitant medication, such as a benzodiazepine, was not an

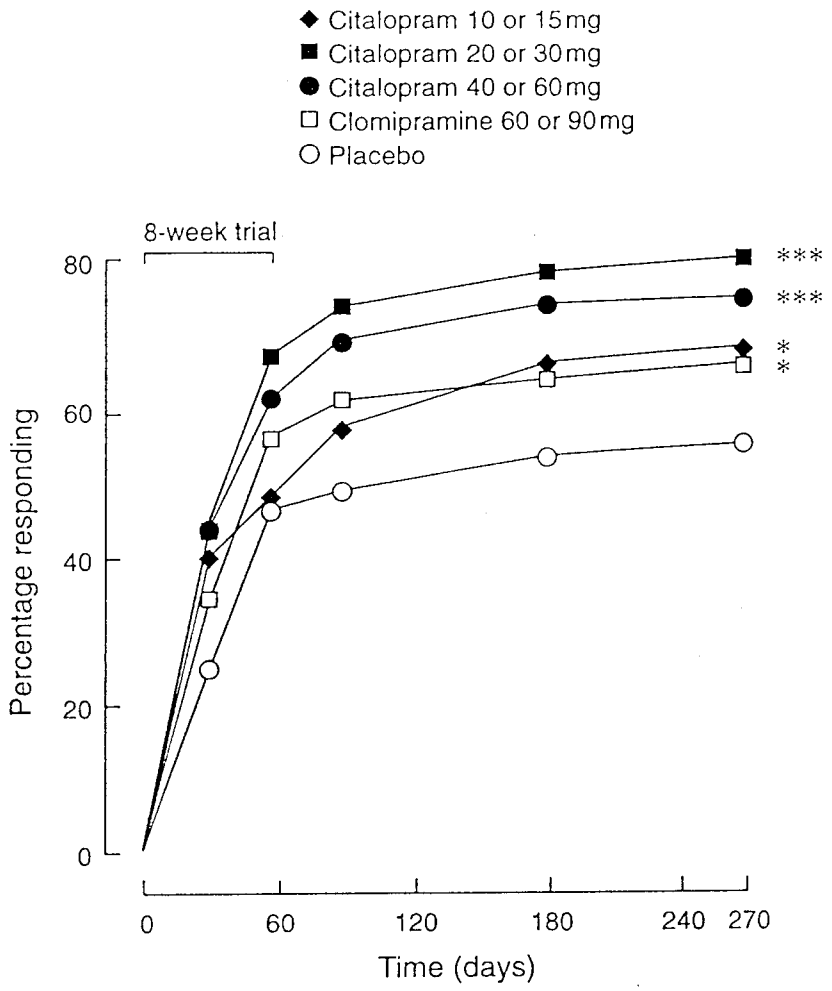

Figure 2. Three doses of citalopram, clomipramine and placebo in the treatment of panic disorder

exclusion criterion, it turned out that none of the patients required additional medication during the trial.

Lepola *et al.* (1996) reported on a pilot study of citalopram in the treatment of OCD. Subsequently, Koponen *et al.* (1997) reported on an open study of citalopram in OCD in which 76 per cent of the patients showed 'marked' improvement, mostly using doses of 40–60 mg of citalopram. Side effects were mild in severity and included nausea and vomiting which subsided during the study (Figure 3).

The first controlled study of citalopram in OCD (Montgomery, 1998) compared 400 patients' response to placebo-response. At all three doses (20, 40 and 60 mg/day) citalopram had significantly superiority over placebo. The drop-out rates from adverse events were similar in the citalopram and the placebo groups (2–6 per cent versus 4 per cent, respectively).

In the first comparative study of three SSRIs in OCD, fluvoxamine, paroxetine and citalopram, 30 patients were treated for 10 weeks under single blind conditions; only the patients knew which drugs they were receiving (Mundo *et al.*, 1997). All patients completed the study with mean doses of: 290 mg $\pm$ 31 mg for fluvoxamine; 53·3 mg $\pm$ 10 mg for paroxetine; and 50·9 mg $\pm$ 10·4 mg for citalopram. The response rates were similar with no significant differences between the different drugs and all three drugs were well tolerated.

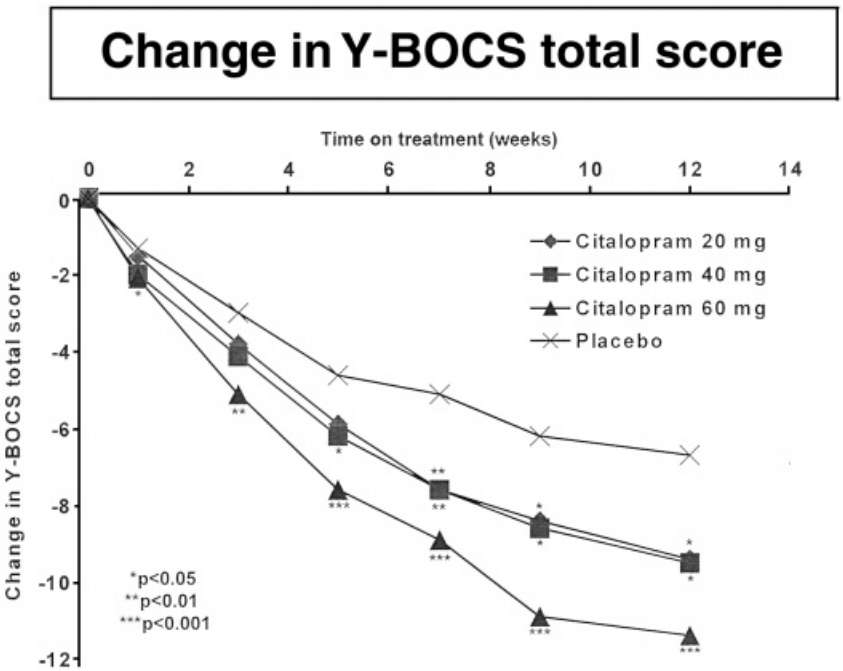

Figure 3. Citalopram in the treatment of obsessive-compulsive disorder

Citalopram appears to be both effective and well-tolerated in the treatment of OCD over the short-term. Citalopram has also been used successfully in the treatment of children with OCD where over 75 per cent of the patients showed a marked or moderate improvement in OCD symptoms. None of the 23 patients dropped out of the study or had the medication discontinued because of side effects (Thomsen, 1997).

OTHER ANXIETY DISORDERS

The use of citalopram has been reported in the treatment of several other anxiety disorders: social phobia, mixed anxiety-depression (MAD) and post-traumatic stress disorder (PTSD).

Social phobia

Lepola *et al*. (1994a) report on three patients with social phobia treated effectively with citalopram 20 mg/day.

Bouwer and Stein (1998) report on the use of citalopram (22 patients on 40 mg daily) in a naturalistic open-label treatment of generalised social phobia. Citalopram was initiated at 20 mg daily and increased to 40 mg. After 12 weeks of treatment, with a CGI change score of 2 or less used to indicate a positive response, 86 per cent of patients were responders.

As naturalistic open studies, these reports have the inherit limitations related to such study settings, yet these results indicate that citalopram may be effective in the treatment of social phobia.

MAD

There is evidence that citalopram works for anxiety in depressed patients (Stahl, 1999; Flicker and Tsay, 1998).

In their analysis of pooled data from eight double-blind, placebo-controlled studies of almost 2000 depressed patients, Flicker and Tsay (1998) report on the mean change from baseline on the Hamilton Depression (HAMD) anxiety subscale in depressed patients. The patients treated with citalopram showed significantly greater improvement than patients treated with placebo after 3 weeks. After two weeks of treatment, the patients treated with citalopram experienced significantly fewer psychic anxiety symptoms than those receiving placebo.

From this study it is concluded that citalopram significantly improves anxiety in depressed patients,

depression symptoms in patients with anxious depression and does not cause activation side effects.

PTSD

Citalopram has been found to be useful in the treatment of PTSD (Seedat and Stein, unpublished data). The patients were treated with 40 mg/day of citalopram.

Blaha *et al*. (1999) report on the use of citalopram in severely burnt patients. In their study, the patients receiving citalopram responded better to the overall treatment of the burns and developed less scarring. Also none of the patients developed PTSD.

SIDE EFFECTS

Citalopram, as with the other SSRIs, has side effects, which seem to be of a transient nature and rarely continue for longer than the initial first two weeks of treatment (Table 2).

Using data from two large long-term studies, Wade *et al*. (1999b) found that there was no overall change in weight during citalopram treatment.

The cardiac safety of citalopram has been studied (Rasmussen *et al*., 1999). The sole effect, as noticed with other SSRIs, was a small reduction in heart rate (4–8 beats/min). Citalopram had no effect on PQ, QRS or QT_C intervals.

Citalopram appears to be safe in overdose. Reports of plasma levels three to four times higher than the patient's usual steady state have been found to cause tiredness, dizziness, tremor and nausea. No ECG abnormalities were observed. Citalopram seems to be less toxic than TCAs when taken in overdose during suicide attempts (Noble and Benfield, 1997).

A review of the safety of SSRIs in overdose (Barbey and Roose, 1998), note that, when taken alone, these agents are rarely fatal. They were not able to identify a difference between the various SSRIs.

Personne *et al*. (1997) reported an uneventful clinical course after citalopram overdose. Convulsions were seen at doses in excess of 600 mg. Clinically significant arrhythmias were not seen.

REDUCED ANXIETY AT ONSET OF TREATMENT

Citalopram has been studied extensively and the incidence of activating adverse events is of particular importance for the treatment of anxiety disorders. In a pooled analysis of safety and efficacy data from almost 2000 patients with depression who have participated in double-blind placebo-controlled citalopram studies, the incidence of activating symptoms was assessed (Flicker and Tsay, 1998). There were no significant differences as compared to placebo. In contrast, somnolence was the most frequently reported psychiatric event; not an activating symptom (Table 3).

CITALOPRAM IN THE ELDERLY

The metabolism of many antidepressants is altered in the elderly (von Moltke *et al*., 1993) and therefore their treatment warrants special consideration. In the elderly, the main drawback to using TCAs is that they have a number of troublesome side effects that are primarily of an anticholinergic nature. Elderly patients are more prone to suffer tachycardia, dry mouth, constipation, urinary retention and decrements in memory that could even progress to an acute delirium.

Citalopram is well-tolerated in the elderly (Noble

Table 2. Citalopram versus placebo: significant adverse events

Symptoms	Citalopram	Placebo
Nausea/vomiting	21·4	13·2
Diarrhoea	7·9	4·7
Dry mouth	20·0	12·6
Increased perspiration	11·3	7·4
Tremor	8·8	5·8
Somnolence	17·9	10·3
Delayed ejaculation	3·3	0·0

Table 3. Activating effects of citalopram versus placebo (%)

Symptoms	Citalopram	Placebo
Insomnia	13·8	12·8
Nervousness	4·1	3·7
Anxiety	4·2	3·1
Agitation	2·9	1·3
Tremor	7·6	6·1
Somnolence	17·9*	10·3

* Statistical significance, $p < 0{\cdot}05$.
Data from Flicker and Tsay (1998).

and Benfield, 1997) due to the low propensity for cardiovascular and anticholinergic adverse events. As citalopram has a low potency for inhibition of drug-metabolising enzymes, the risk of drug–drug interactions is considerably lower than with many other agents. This makes citalopram particularly suitable for elderly patients as they are more likely than younger patients to be using additional medication (Baumann and Larsen, 1995).

In a Scandinavian trial of citalopram versus placebo in the treatment of 149 elderly depressed patients (mean age of 77 years), citalopram had a superior efficacy compared with placebo for depression and cognitive functioning (Nyth *et al*., 1992).

In a Nordic study, elderly depressed patients were treated with citalopram and after 6-weeks there was a significant improvement in these patients compared to those who had received placebo. There was a good clinical antidepressant effect in the elderly both with core symptoms and other symptoms of emotional disturbance (Frampton, 1997) (Table 4).

The long-term safety, tolerability and efficacy of citalopram in the treatment of elderly people with emotional disturbances (76 per cent had dementia) have been studied in 123 elderly patients with symptoms of depression–anxiety. Irritability, depressed mood, anxiety, restlessness and fear–panic were significantly reduced during the one-year of treatment. The side effects reported were infrequent and mostly mild (Ragneskog *et al*., 1996).

A comparative study between citalopram and amitriptyline in elderly patients with major depression found similar efficacy, but there was a significantly higher discontinuation rate due to adverse events in the amitriptyline group (26 per cent) than in the citalopram group (17 per cent) (Kyle *et al*., 1998). More patients reported dry mouth, somnolence and constipation in the amitriptyline-treated patients.

Table 4. Adverse events of citalopram versus placebo in the elderly (age $\geqslant$ 65 years)

Symptoms	Citalopram	Placebo
Nausea/vomiting	9·6	9·0
Constipation	8·0	11·9
Dry mouth	16·0	9·0
Increased perspiration	4·8	0·0
Tremor	12·0	6·0
Palpitations	4·0	4·5
Blurred vision	1·6	1·5
Headache	5·6	7·5
Dizziness	5·6	4·5
Insomnia	12·8	7·5
Somnolence	15·2	11·9
Asthenia	20·0	10·4

Data from Lundbeck (1995).

CITALOPRAM IN ALCOHOL ABUSE

Animal studies have shown that alcohol consumption is reduced when serotonin levels are increased in the central nervous system. Similarly, studies of alcohol-dependent subjects have shown that treatment with SSRIs decreases the desire to drink alcohol and improves symptoms of alcohol-related anxiety and depression in patients who have undergone detoxification (Naranjo *et al*., 1997). Citalopram also has no specific interaction with alcohol (Lader *et al*., 1986).

Citalopram has been proven to reduce ethanol drinking by reducing the numbers of drinks consumed and increasing the number of abstinent days in non-depressed heavy drinkers (Naranjo *et al*., 1987). In another study of the treatment of severe alcoholism, citalopram was shown to be more effective than placebo (Tiihonen *et al*., 1996).

In a controlled study with citalopram to test the hypothesis that citalopram changes the desire to drink and mediates the effect of alcohol, daily alcohol-intake (decrease of 17·5 per cent) and number of drinks significantly decreased during citalopram treatment compared with placebo. The total number of days of abstinence increased significantly; by 28 per cent for the citalopram treated patients and 16 per cent for placebo treated patients. Citalopram significantly decreased the interest, desire and craving for alcohol (Naranjo *et al*., 1992). The findings indicate that citalopram acts by decreasing the urge to drink and the re-enforcing effects of alcohol.

A 16-week, randomised study to test the efficacy of fluvoxamine and citalopram showed a statistically higher rate of continuous abstinence (63·6 per cent and 60·7 per cent, respectively) compared to the group without pharmacological treatment (30·4 per cent). Only citalopram showed a significant effect on craving throughout the study period (Angelone *et al*., 1998).

OTHER TREATMENT AREAS

Citalopram (20–60 mg) has been reported to successfully treat post-stroke depression and it also

relieves post-stroke pathological crying (Andersen *et al*., 1993, 1994). The use of citalopram in patients who had suffered strokes led to a significant improvement in their HAMD and MADRS scores. Crying frequency was reduced by citalopram within 1–3 days.

In patients with depression and traits of personality disorders it was found that citalopram and sertraline could modulate personality. Significant decreases occurred in anxiety and aggression levels in this population (Ekselius and von Knorring, 1999).

The anti-aggression effects of citalopram are reported in a study of 15 chronically violent schizophrenia patients. The frequency of the aggressive incidents was significantly lower without deterioration in mental functioning or sedation (Vartiainen *et al*., 1995).

Citalopram has also shown efficacy in the treatment of premenopausal dysphoric disorder (PMDD), showing a significant advantage over placebo in the reduction of self-rated irritability and global improvement in the luteal phase of the menstrual cycle (Wikander *et al*., 1998).

SUMMARY

Citalopram is effective in the treatment of major depression in a wide variety of patients and is particularly suited to the treatment of elderly subjects and where depression has associated anxiety. In addition, the drug has proven efficacy in the treatment of panic disorder and obsessive-compulsive disorder. There is also promising potential for the use of the drug in the treatment of other anxiety disorders, such as social phobia and post-traumatic stress disorder.

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