Citalopram — a review of pharmacological and clinical effects

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Objective: To provide clinicians with a critical evaluation of citalopram, a selective serotonin reuptake inhibitor (SSRI) that has been available in Canada since March 1999. **Data sources:** Commercial searches (MEDLINE and BiblioTech) and an "in-house" search (InfoDrug) were used to find published English-language references for clinical and preclinical publications. There was no restriction of publication dates. Primary index terms used were: pharmacological properties, receptors, pharmacological selectivity, pharmacokinetics, age-related pharmacokinetics, sex-related pharmacokinetics, renal dysfunction, hepatic dysfunction, cytochrome activity, drug interactions, adverse reactions, antidepressant switching, precautions, overdose, drug discontinuation, children, geriatric, depression, combination therapy, placebo control, refractory depression, anxiety disorders and medical disorders. **Study selection:** A total of 74 studies were reviewed. Twenty-one of these studies specifically examined the clinical efficacy and tolerability of citalopram in depressive disorders as well as other disorders. In depressive disorders, clinical studies were required to have either placebo or active comparison controls for a minimum of 3 weeks. For other disorders, in the absence of double-blind trials, open-label studies were included. Pharmacological studies were limited to animal studies focusing on citalopram's selectivity and receptor specificity, and positron emission tomography studies were incorporated to include human pharmacological data. Pharmacokinetic studies focused on the metabolism, safety and tolerability of citalopram, specifically with reference to adverse reactions, drug interactions and overdose in addition to citalopram's effect on vulnerable populations, such as children, the elderly and patients with metabolic diseases. **Data extraction:** Data on clinical studies were summarized according to test measures, study duration and outcome of study. Pharmacokinetic and pharmacodynamic studies were summarized according to properties and interactions. Adverse reactions were extracted to outline citalopram's safety profile. **Data synthesis:** Citalopram is an SSRI antidepressant with a more specific and selective pharmacological profile than other antidepressants of its class. It is well tolerated, and drug interactions are not a significant concern. It is also reasonably safe for populations vulnerable to pharmacokinetic effects, such as the elderly and patients with metabolic diseases. In addition to its tolerability, citalopram is effective in the treatment of major depression, other

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depressive disorders and panic disorder. It has the potential to effectively treat other anxiety disorders and substance-use disorders; in addition, it may be useful in several medical conditions. **Conclusions:** There is evidence to support the role of citalopram as a well-tolerated and effective SSRI antidepressant. There is a need for further evaluation of its role in psychiatric disorders other than major depressive disorder.

Objectif : Fournir aux cliniciens une évaluation critique du citalopram, inhibiteur sélectif du recaptage de la sérotonine (ISRS), disponible au Canada depuis mars 1999. **Sources de données :** On a effectué des recherches commerciales (MEDLINE et BiblioTech) et des recherches «internes» (InfoDrug) pour trouver des références cliniques et précliniques publiées en anglais. Il n'y avait aucune restriction quant aux dates de publication. Les principaux termes d'indexation utilisés ont été les suivants (en anglais) : propriétés pharmacologiques, récepteurs, sélectivité pharmacologique, pharmacocinétique, pharmacocinétique liée à l'âge, pharmacocinétique liée au sexe, dysfonction rénale, dysfonction hépatique, activité cytochromique, interactions médicamenteuses, effets indésirables, changement d'antidépresseur, précautions, surdose, interruption du médicament, enfants, gériatrique, dépression, thérapie combinée, contrôle par placebo, dépression rebelle, troubles de l'anxiété et troubles médicaux. **Sélection des études :** On a passé en revue 74 études au total, dont 21 portaient spécifiquement sur l'efficacité clinique et la tolérabilité du citalopram dans des cas de troubles dépressifs et autres. Dans les cas de troubles dépressifs, les études cliniques devaient comporter des contrôles par placebo ou comparaison active pendant au moins trois semaines. Dans le cas d'autres troubles, comme il n'y avait pas d'étude à double insu, on a inclus des études ouvertes. Les études pharmacologiques ont été limitées aux études animales portant avant tout sur la sélectivité du citalopram et la spécificité des récepteurs, et l'on a incorporé des études de tomographie par émission de positrons afin d'inclure des données pharmacologiques portant sur les êtres humains. Les études pharmacocinétiques ont porté avant tout sur le métabolisme, l'innocuité et la tolérabilité du citalopram, spécifiquement en ce qui concerne les effets indésirables, les interactions médicamenteuses et les surdoses, outre l'effet du citalopram sur des populations vulnérables comme les enfants, les personnes âgées et les patients atteints de troubles du métabolisme. **Extraction des données :** On a résumé les données sur les études cliniques en fonction des mesures des épreuves, de la durée de l'étude et de son résultat. On a résumé les études pharmacocinétiques et pharmacodynamiques en fonction des propriétés et des interactions. On a extrait les effets indésirables pour tracer le profil d'innocuité du citalopram. **Synthèse des données :** Le citalopram est un antidépresseur ISRS qui a un profil pharmacologique plus spécifique et sélectif que celui d'autres antidépresseurs de sa catégorie. Il est bien toléré et les interactions médicamenteuses ne représentent pas un problème important. Il est aussi raisonnablement sûr pour les populations vulnérables aux effets pharmacocinétiques comme les personnes âgées et les patients atteints de troubles du métabolisme. Outre sa tolérabilité, le citalopram est efficace dans le traitement de dépressions majeures, d'autres troubles dépressifs et des troubles paniques. Il peut traiter efficacement d'autres troubles de l'anxiété ou liés à l'utilisation de substances et il peut aussi être utile pour traiter plusieurs problèmes médicaux. **Conclusions :** Des données probantes appuient le rôle du citalopram comme antidépresseur ISRS efficace et bien toléré. Il faut évaluer plus à fond son rôle dans le traitement de troubles psychiatriques autres que le trouble dépressif majeur.

Introduction

Despite the availability in Canada of 8 first-choice antidepressant agents for the treatment of major depression,[1] reports of underdetection and undertreatment of depression, as well as poor compliance with treatment, are prevalent. According to reports from epidemiological studies in Ontario[2] and in 5 European countries,[3] only 20% to 25% of identified individuals who were experiencing a depressive episode received any form of antidepressant therapy. In addition, more than 50% of patients with depression who were followed up after 12 weeks of antidepressant therapy in family practice settings had discontinued treatment.[4]

The availability in Canada of citalopram as an alternative antidepressant agent within the selective serotonin reuptake inhibitor (SSRI) class provides the clinician with an additional choice in the pharmacological management of depression. The purpose of this review is to provide clinicians with the information needed to compare citalopram with existing antidepressant agents. Although in Canada citalopram is indicated only for the treatment of patients with major depression, evidence of its efficacy in other disorders, includ-

ing anxiety disorders, disorders of substance use and other medical disorders, will also be summarized.

Pharmacodynamic properties

Effect on receptors

Citalopram and its metabolites are racemic compounds with both S–(+) and R–(–) enantiomers. The S–(+) enantiomer of citalopram is pharmacologically active in relation to inhibition of serotonin (5-HT) reuptake, and it accounts for 24% to 49% of the total plasma citalopram level,[5,6] whereas the R–(–) enantiomer of citalopram appears to be pharmacologically inactive. The S/R ratio varies from 0.32 to 1.25.[7]

There is an acute increase in extracellular 5-HT levels in animals following citalopram 10 mg/kg twice daily, which in turn results in activation of somatodendritic 5-HT_{1A} autoreceptors.[8] The result of this acute activation is a feedback inhibition in the raphe nucleus, with down-regulation of autoreceptors and a subsequent increase in serotonergic neurotransmission.[9,10] This delay in autoreceptor down-regulation coincides with the usual "therapeutic lag" of 2 to 3 weeks. In vitro studies have also confirmed that citalopram has very low affinity and selectivity for post-synaptic 5-HT receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A} and 5-HT_{2C}) and also for adrenergic, histaminergic, muscarinic and dopaminergic receptors.[6,11–13]

In vitro studies indicate that citalopram has additional selectivity and affinity for 5-HT_{1C} receptors, and may function as an antagonist at this receptor; however, definitive in vivo evidence is unavailable.[14] Theoretically, this could hasten the time to antidepressant clinical response, but there is no clinical evidence to substantiate this claim. Additional in vivo studies have suggested that co-administration of a 5-HT_{1A} receptor antagonist such as (S)-5-fluoro-8-hydroxy-2-(dipropylamino)-tetralin [(S)-UH-301] or [(+)-WAY100135] can augment both acute and chronic effects of citalopram on central serotonergic neurotransmission.[15,16] It is as yet uncertain whether co-administration of 5-HT_{1A} antagonists in clinical populations would hasten citalopram's antidepressant effect.

Selectivity of 5-HT uptake sites

Citalopram is the most selective inhibitor of 5-HT uptake currently available. In vitro studies have corroborated this claim and confirmed that it inhibits norepinephrine and dopamine uptake minimally.[11,17] Its ratio inhibition constant (IC_{50} NA/IC_{50} 5-HT) for 5-HT uptake is over 3000 times lower than that for norepinephrine uptake; this is significantly higher than the IC_{50} of other SSRI antidepressant agents such as paroxetine (IC_{50} = 280), sertraline (IC_{50} = 840), fluvoxamine (IC_{50} = 160) and fluoxetine (IC_{50} = 54).[11] Because of its selectivity for 5-HT uptake sites, citalopram has been used in in vitro autoradiographic techniques in the rhesus monkey to label 5-HT uptake sites in the frontal, parietal and occipital cortices.[18]

Citalopram's specificity for 5-HT uptake sites is also supported by in vivo studies. [^{3}H] citalopram is the most selective 5-HT uptake inhibitor available; however, it is less potent than [^{3}H] paroxetine, which is the most potent inhibitor of 5-HT uptake sites among the SSRI antidepressant medications.[19] Consequently, because of the greater affinity of [^{3}H] paroxetine for the 5-HT uptake site, it is considered a preferred radioligand in positron emission tomography (PET) research.[19] Nonetheless, when citalopram was administered parenterally and McNeil 5652 (McN5652) was used as a PET radioligand, results indicated that 50% to 80% occupancy was achieved in regions of high 5-HT transporter density.[20] This finding not only confirms that citalopram is an effective inhibitor of 5-HT uptake sites but also supports the use of McN5652 as an effective radioligand in PET research.

Pharmacokinetics

Pharmacokinetic properties

Absorption and distribution

The absorption of citalopram is not affected by food, and its oral bioavailability is reported to be approximately 80%. Peak plasma levels occur 2 to 4 hours after single or multiple doses, and the mean peak plasma concentration (C_{max}) following dosages of 40 mg per day at steady state is 311 nmol/L.[21] Citalopram is 80% protein bound, somewhat less than other SSRIs; therefore, it is less likely to be involved in drug interactions that occur secondary to drug displacement from protein binding. It is widely distributed among peripheral tissues, with the volume of distribution (V_d) estimated to be between 12 and 16 L/kg.[7] (Table 1)

At clinically relevant doses, citalopram displays linear pharmacokinetics.[24] There is a linear correlation between dose and steady-state concentration of citalopram and its metabolites.[7] However, no clear correlation has been

established between plasma concentration and clinical response. Inter-individual variation in plasma levels is about 7-fold and appears to be independent of sex or age (up to age 65).[7,25] Intra-individual variability is estimated at 15%.[7] Steady-state plasma levels are reached within 1 to 2 weeks at each dose level. With 20 to 60 mg per day, steady-state plasma levels, measured at trough, were reported to be 130 (standard deviation 70) nmol/L at 20 mg, to 400 (SD 200) nmol/L at 60 mg.[7]

Metabolism

Citalopram is metabolized in the liver by 2 *N*-demethylation steps, to demethylcitalopram (DCT) via CYP2C19 and 3A4, and to didemethylcitalopram (DDCT) via CYP2D6. Oxidation occurs by monoamine oxidases A and B and aldehyde oxidase, to form a propionic acid derivative and citalopram-*N*-oxide.[7,22,23]

At single doses, as well as at steady-state plasma concentrations, the amount of metabolites, in relation to the parent drug citalopram, are 30% to 50% for DCT and 5% to 10% for DDCT.[7] In vitro studies suggest that citalopram is at least 4 times more potent than DCT and 13 times more potent than DDCT in inhibiting the reuptake of 5-HT. Since these metabolites enter the brain less readily and are present in lower concentrations, they do not appear to play a major role in the clinical action of citalopram.[26] The *N*-oxide and propionic acid derivative are present in low concentrations in plasma. The impact of metabolizer status (poor or extensive) on citalopram metabolism is considered to be clinically insignificant.

Table 1: Pharmacokinetic properties of citalopram*

Property	Value
Bioavailability	80%
Protein binding	80%
Time to peak plasma level (T_{max})	2 to 4 h
Mean peak plasma concentration (C_{max})	311 nmol/L (40 mg per d)
Volume of distribution (V_d)	12 to 16 L/kg
Distribution half-life	10 h
Metabolizing enzymes	CYP2C19, 3A4, 2D6
Metabolites	Demethylcitalopram (DCT), didemethylcitalopram (DDCT), propionic acid derivatives, citalopram-*N*-oxide
Elimination half-life ($T_{1/2}$)	30 to 35 h for citalopram; 50 h for DCT; 100 h for DDCT
Renal clearance	2.8 to 3.3 L per h
Systemic clearance	26 to 28 L per h
Urinary excretion	6% to 23% of dose

*Adapted from Baumann and Larsen,[7] Noble and Benfield,[21] Rochat et al,[22] Rochat et al.[23]

Elimination

Citalopram shows biphasic elimination. The distribution phase lasts about 10 hours. The terminal (or elimination) half-life ($T_{1/2}$) has been determined to be 30 to 35 hours for citalopram, 50 hours for DCT and 100 hours for DDCT.[7] Due to its relatively long half-life, citalopram can be administered once daily.

Up to 23% of the dose of citalopram is excreted unchanged in the urine.[7] Renal clearance is estimated at 2.8 to 3.3 L per hour, whereas systemic clearance ranges from 23 to 28 L per hour.[21]

Factors influencing variability

Age-related pharmacokinetic effects

Studies using single and multiple doses of citalopram in subjects over 60 years of age indicate that the area under the dose concentration curve (AUC) increased between 23% and 30% compared with younger subjects. The $T_{1/2}$ increased by 30% to 50%, and the steady-state plasma level increased 4-fold.[7] The ratio of DCT to citalopram decreased significantly, as compared with that reported in younger patients, suggesting possible age-related changes in the activity of CYP2C19.[27] This drug-to-metabolite ratio was higher in patients in whom the plasma half-life of citalopram was the longest and clearance the shortest.[7] Because of potential pharmacokinetic differences in elderly patients compared with middle-life patients, it is recommended that elderly patients receive lower initial doses, and that the maintenance dosage not exceed 40 mg per day.

Sex-related pharmacokinetic effects

Five studies did not demonstrate sex differences.[26] Similarly, no differences in steady-state plasma levels or other parameters were seen between men and women in clinical studies. Therefore, current recommendations suggest equivalent dosing for male and female patients.

Renal dysfunction and pharmacokinetic effects

In patients with mild to moderate renal impairment (creatinine clearance greater than 20 mL per minute), oral clearance of citalopram was decreased by 17% and $T_{1/2}$ was moderately increased; the peak plasma concentration was unaffected.[28] In these patients, dosage adjustment is not

required. However, since there are no data on the pharmacokinetics of citalopram in patients with chronic or severe renal impairment, caution should be exercised when the drug is used in patients with severe renal dysfunction.

Hepatic dysfunction and pharmacokinetic effects

In patients with impaired hepatic function, oral clearance of citalopram is reduced by 37% and $T_{1/2}$ is doubled; the peak plasma concentration, however, is unaffected.[28] It is recommended that patients with compromised liver function receive lower initial doses and that the maintenance dosage should be carefully monitored.

Drug interactions

Cytochrome activity

In vitro data demonstrate that citalopram is a weak inhibitor of CYP 1A2, 2D6 and 2C19 isoenzymes and that it does not inhibit CYP3A4; this suggests that citalopram would have little inhibitory effect (in vivo) on drugs that are metabolized by these isoenzymes.[29]

CYP3A4 and 2C19 are the primary enzymes involved in the metabolism of citalopram;[24] therefore, potent inhibitors of these isoenzymes (e.g., CYP3A4 inhibitors ketoconazole, itraconazole, macrolide antibiotics and nefazodone; CYP2C19 inhibitor omeprazole) may decrease the clearance of citalopram.[26,30] There are, however, no clinical reports of these interactions to date. Although CYP2D6 is involved in the conversion of DCT to DDCT, inhibition of this isoenzyme is not expected to have clinically significant consequences.[24,31]

Interactions with SSRI antidepressant medications

The SSRIs are dissimilar in their potential for drug interactions when administered with other drugs. Based on in vitro cytochrome P-450 enzyme studies as well as in vivo evidence, both citalopram and sertraline appear to have a lower potential for drug interactions than the other SSRIs when administered in lower therapeutic dosage ranges.[32] In one of the few reports of citalopram in combination with another SSRI, increasing dosages of fluvoxamine over 14 days (50 to 100 mg per day) increased the plasma level of citalopram (40 mg per day) by more than 200% over 21 days; the ratio of S–(+) to R–(–) isomers was also altered, i.e., the pharmacologically more active S–(+) isomer was increased.[33]

Interactions with tricyclic antidepressants

The combination of tricyclic antidepressants such as amitriptyline or maprotiline with citalopram (20 to 60 mg per day) produced no significant increases in the plasma level of either drug.[34] In combination with imipramine, however, 40 mg of citalopram increased the AUC of the imipramine metabolite desipramine by 50%.[35] With clomipramine, one study did not show changes in plasma levels; however, a second study demonstrated that 25 to 150 mg of clomipramine significantly increased the plasma level of both citalopram (prescribed in dosages of 10 to 80 mg per day) and DCT.[21,23,34]

Like the other SSRIs, citalopram may enhance the serotonergic effects of coprescribed drugs, including buspirone, lithium and clomipramine, and these combinations should be used with caution. Serotonin syndrome is characterized by nausea, diarrhea, dizziness, confusion, agitation, sweating, shivering, fever, tremor, incoordination, hyper-reflexia and myoclonus; unless therapy is stopped this may progress to coma and death.

Interactions with monoamine oxidase inhibitors

Citalopram should not be used in combination with either reversible or irreversible monoamine oxidase inhibitors (MAOIs) because of the risk of serotonin syndrome.[6] Myoclonus and death have been reported after overdoses of moclobemide and citalopram in combination.[36–38] Although there is a report on the safe combination of citalopram (20 mg) with the MAO-B inhibitor selegiline (10 mg),[39] caution should be exercised with higher doses of selegiline because of the loss of MAO-B selectivity.

Interactions with antipsychotic medications

There have been no reports of significant changes in the plasma levels of several antipsychotic agents (haloperidol, chlorpromazine, methotrimeprazine, perphenazine, pericyazine, thioridazine and zuclopenthixol) when these drugs are combined with citalopram (40 mg per day) for periods of at least 3 months; the plasma level of citalopram and DCT also remained stable.[23,40] In one study, however, methotrimeprazine was shown to increase the steady-state concentration of citalopram by up to 36% and the steady-state concentration of DCT by 10% to 20%.[35] SSRIs, including citalopram, may aggravate antipsychotic-induced extrapyramidal effects (e.g., parkinsonism).[6]

Interactions with other medications

Serum citalopram levels increased when carbamazepine, which had been coprescribed with citalopram, was discontinued in 2 patients; this suggests possible enzyme induction of citalopram metabolism with carbamazepine.[41] In addition, metoprolol plasma levels were reported to double with the co-administration of citalopram.[42]

Citalopram does not appear to interact with digoxin, mood stabilizers, alcohol and most benzodiazepines.[21,31] A slight increase in the plasma levels of citalopram and DCT has been reported with alprazolam.[23] Although a pharmacokinetic interaction has not been seen with warfarin and citalopram, the prothrombin time was reported to increase by 5%;[43] the significance of this is yet to be determined.

Oral clearance of citalopram was shown to decrease by 29% when cimetidine (400 mg twice daily) was added to a stable regimen of citalopram 40 mg per day. The 24-hour AUC of DCT was increased by 43% and the renal clearance of DCT and DDCT was reduced by 26% and 36%, respectively.[21]

Summaries of pharmacokinetic and pharmacodynamic interactions with citalopram and the clinical significance are listed in Tables 2 and 3.

Adverse reactions

Information on citalopram's side-effect profile is available from controlled and uncontrolled studies as well as postmarketing surveillance reports. Several meta-analyses have also been conducted.[46]

In pooled comparative studies, citalopram's tolerability profile was similar to that of other SSRIs and superior to that of tricyclic antidepressants.[47] A meta-analysis demonstrated that the most common side effects reported with citalopram, at therapeutic doses, are nausea and vomiting (20%), increased sweating (18%), headache (18%), dry mouth (17%), tremor (16%), sedation(15%) and insomnia (15%).[46] Citalopram appears to cause stim-

Table 2: Pharmacokinetic interactions with citalopram

Drug class	Example	Effect	Clinical significance
Antidepressant			
Tricyclic	Clomipramine[23]	Increase in plasma level of citalopram	Monitor for serotonergic effects
	Imipramine[35]	Increase in area under the curve (AUC) of the metabolite desipramine by 50%; increased $T_{1/2}$ and decreased level of the hydroxymetabolite	Monitor for increased pharmacological effects of the tricyclic antidepressant
Selective serotonin reuptake inhibitor (SSRI)	Fluvoxamine[33]	Increase in plasma level of citalopram by 207%; change in ratio of S–(+) and R–(–) isomers	Monitor for serotonergic effects; caution when switching from fluvoxamine to citalopram
Anticonvulsant	Carbamazepine[41]	Possible decrease in the plasma level of citalopram	Low clinical significance
Antipsychotic	Clozapine[44]	Case report of increased plasma level of clozapine and desmethylclozapine	Monitor clozapine plasma level with combination in at-risk patients
	Methotrimeprazine[35]	Increased steady-state plasma level of citalopram by up to 36% and DCT by 10% to 20%	Low clinical significance
Benzodiazepine	Alprazolam[23]	Slight increase in plasma level of citalopram and DCT	Low clinical significance
β-blocker	Metoprolol[42]	Increased plasma level of metoprolol by 100%	Monitor for increased effects of metoprolol hypotension, bradycardia
H_2 antagonist	Cimetidine[21]	Oral clearance of citalopram decreased by 29%. Increased 24 h AUC for DCT by 43%; renal clearance of both DCT and DDCT was reduced by 26% and 36%, respectively	Low clinical significance

Table 3: Pharmacodynamic interactions with citalopram

Drug class	Example	Effects	Clinical significance
Antidepressant			
Reversible or irreversible monoamine oxidase inhibitor	Tranylcypromine, moclobemide[37]	Serotonin syndrome; fatalities reported in overdose	Avoid combination
Antipsychotic	Haloperidol[6]	Citalopram may aggravate antipsychotic-induced extrapyramidal effects	Low clinical significance
Anxiolytic	Buspirone[45]	Case report of serotonin syndrome and hyponatremia with combination	Monitor for serotonergic effects
Central nervous system (CNS) depressant	Hypnotics, benzodiazepines[26]	Possible potentiation of CNS effects	Low clinical significance
Lithium	Lithium[26]	Possible enhanced serotonergic effects	Low clinical significance; monitor

ulation only rarely and is relatively well tolerated in elderly patients with depression.[48] The range of reported side effects across several studies is reported in Table 4. Side effects are usually mild to moderate and occur during the first few weeks of treatment. Most side effects decrease over time, except for dyspepsia and sweating.[46]

Various forms of sexual dysfunction have been reported in up to 75% of patients treated with SSRIs.[49] The rate of spontaneously reported sexual dysfunction with citalopram is less than 10%, although this may turn out to be higher when direct questioning is employed.[21] Three cases of transient clitoral priapism have also been reported.[50]

Hepatic, renal or hematological adverse events occur rarely.[26] There is a low potential for seizures or extrapyramidal effects with therapeutic dosages of citalopram.[47]

Citalopram has not been associated with serious cardiovascular toxicity, even in elderly patients or in patients with pre-existing cardiovascular disease. Electrocardiograms (ECGs) recorded during clinical trials of both young and elderly subjects revealed no changes in cardiac conduction.[6] No QTc changes have been reported, to date, in patients with pre-existing conduction disturbances or ischemia.[46] Similarly, citalopram did not affect cardiac conduction in patients taking other medications that could prolong the QTc interval.[46] The only common change in the ECG of patients taking citalopram is a slight decrease in heart rate, which also occurs with other SSRIs.[46]

Phasic craving for carbohydrates and accompanying weight gain was reported in 8 out of 18 patients during short-term treatment with citalopram 20 to 40 mg per day.[51] This was an unexpected side effect, as enhanced 5-HT transmission is usually associated with decreased carbohydrate intake and anorexia.[51]

A favourable side-effect profile in the elderly has been supported by data from a number of meta-analyses. In this population, the most common side effects reported include asthenia, insomnia, somnolence, tremor, dry mouth, headache and nausea.[46] Women reported more adverse effects than men, but only "headache" reached a statistically significant difference between sexes.[46]

Table 4: Reported adverse effects of citalopram

Effect	Frequency, % of patients
Autonomic	
Dry mouth	10–28
Increased sweating	7–20
Blurred vision	2–12
CNS	
Somnolence, sedation	11–18
Insomnia	11–19
Anxiety, agitation	3–9
Gastrointestinal	
Nausea	7–21
Vomiting	4
Diarrhea	8
Constipation	7–13
Anorexia	4–5
Cardiovascular	
Palpitations	4–10
Dizziness	5–13
Tachycardia	4–6
Musculoskeletal	
Fatigue	5
Asthenia	12–20
Yawning	2
Tremor	7–16
Restlessness	10
Urogenital	
Dysmenorrhea	3
Decreased libido	2
Ejaculation disorder	3–6
Impotence	3
Other	
Headache	6–20
Arthralgia, myalgia	2
Fever	2
Rhinitis, sinusitis	3–5

Precautions and contraindications

Although studies of citalopram in normal volunteers, using dosages of 40 mg per day, did not produce impairment of intellectual function or psychomotor performance, the same cautions that apply to the use of psychoactive drugs while driving or operating hazardous machinery apply to citalopram.

Use of antidepressants in patients with bipolar disorder has been associated with an increased risk of mania or hypomania. Placebo-controlled studies in predominantly unipolar populations suggest that the risk of inducing mania with citalopram is low (occurring in 0.2% of 1063 patients);[26] the risk of inducing mania in bipolar patients is likely similar to the reported risk with other SSRIs.

Increased risk of suicide attempts is inherent in depression and may persist until there is significant remission of mood symptoms. Patients at high risk for suicide should be supervised when antidepressant therapy is initiated, and prescriptions for citalopram should be written for small drug quantities to minimize the risk of intentional overdose.

Hyponatremia and the syndrome of inappropriate antidiuretic hormone secretion have been reported as rare adverse events in citalopram use.[26] Clinical symptoms include increased water intake, weight gain, weakness, lethargy and confusion.

In clinical trials, seizures were reported in 0.25% of patients receiving therapeutic doses of citalopram,[26] which is comparable to reported rates with most other antidepressants.

Overdose

When taken in overdose, citalopram appears to have a relatively wide safety margin.[52] In an evaluation of 44 cases of overdose involving citalopram alone, Personne et al[53] reported that ingestion of 600 mg or less resulted in mild symptoms only. The most common symptoms following mild overdose include tiredness, confusion, dizziness, stomach pain, sweating, nausea, sinus tachycardia and tremor.[7]

Convulsions were seen in 6 of 34 patients (18%) who took between 600 and 1900 mg of citalopram, and some ECG abnormalities were also evident. Ingestion of more than 1900 mg resulted in ECG changes as well as seizures in 47% of patients.[53] Additional rare adverse effects following massive ingested doses, have included amnesia, hyperventilation, cyanosis, coma, rhabdomyolysis and ECG changes (including QTc prolongation).[26,46]

In a review of 6 deaths following citalopram overdose, additional drugs were detected in 5 of the cases.[26] Moclobemide was ingested with citalopram in 3 reported deaths, and the plasma levels of both drugs were high.[37]

Following overdose, gastric evacuation by lavage and the use of activated charcoal should be considered. Symptomatic and supportive treatment is recommended. Due to the large volume of distribution of citalopram, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.[26]

Drug discontinuation effects

Short-term clinical trials have not demonstrated evidence of the discontinuation (withdrawal) symptoms that may occur with other SSRIs,[47] although, in contrast to other specific trials designed to examine drug discontinuation effects across SSRIs,[54] there have been no specific evaluations of symptoms following citalopram discontinuation. There is anecdotal evidence that citalopram may be associated with symptoms similar to those associated with discontinuation of other SSRIs, including nausea, vomiting, insomnia, somnolence, dizziness, agitation, asthenia, headache and impaired concentration.[26,55] As with other SSRIs, gradual tapering should minimize discontinuation symptoms.

Switching antidepressants

From tricyclic antidepressants to citalopram

At standard therapeutic dosages, the potential for a drug interaction between citalopram and most tricyclic antidepressants is low, although elevated plasma levels of desipramine and imipramine have been reported in combination with citalopram. Conversely, citalopram levels were elevated in combination with clomipramine.[25,35]

When switching to citalopram, we suggest a cautious approach that would involve tapering the tricyclic antidepressant by 25 to 50 mg every 2 to 3 days and, midway through this period, initiating citalopram therapy at 10 mg daily, increasing to 20 mg daily after 5 to 7 days.

When switching from desipramine, imipramine or clomipramine, citalopram should be initiated at 10 mg daily when the dosage of tricyclic drug has been reduced to 50 mg per day.

From SSRI antidepressants to citalopram

When switching from sertraline or paroxetine to citalopram, a simple crossover approach to citalopram at a dose of 20 mg can be adopted. In the case of fluoxetine, since residual norfluoxetine continues to inhibit CYP3A4, a starting dose of citalopram 10 mg is recommended. Since fluvoxamine has been shown to double the plasma level of citalopram owing to its inhibitory effect on CYP2C19 and 3A4, it is advisable to taper fluvoxamine to 50 mg per day for at least 5 days before starting citalopram at a dosage of 10 mg per day.

From reversible and irreversible MAOI antidepressants to citalopram

Moclobemide should be discontinued for a minimum of 48 hours before starting citalopram 10 mg daily. A minimum of 14 days must elapse from the discontinuation of an irreversible MAOI (e.g., phenelzine, tranylcypromine, isocarboxazid) before starting citalopram.

Safety in special populations

Pregnant and lactating women

In preclinical studies, citalopram was shown to have adverse effects on embryo/fetal and postnatal development when given in doses that were toxic to the animal

mother and greater than the human therapeutic dose.[26] There are no available controlled studies in pregnant women; therefore, citalopram should be used in this population only when the potential benefits justify the risk.

Citalopram is excreted in human breast milk. It was estimated in one study that the infant would receive 1.8% of the weight-adjusted maternal dose of citalopram.[56] There are 2 reports of infants experiencing excessive sedation, decreased feeding and weight loss when exposed to citalopram through breastfeeding.[26]

Children and adolescents

There have been no double-blind studies and few open trials of citalopram in children or adolescents. In one open-label assessment of the safety and efficacy of citalopram in children with obsessive–compulsive disorder, 75% of patients' symptoms improved at dosages up to 40 mg per day, and side effects were considered to be minor and transient.[57]

Elderly patients

A number of double-blind studies have been performed in patients older than 60 years of age. No overall differences in efficacy or safety were documented in these clinical trials.[46,48] Because of changes observed in the pharmacokinetic parameters of citalopram in elderly subjects (i.e., AUC, $T_{1/2}$), use of lower doses is recommended in this population.[7]

Human clinical trials

Comparisons with other antidepressants

Citalopram has demonstrated efficacy in the treatment of major depression (Table 5). In comparison with tricyclic antidepressants, citalopram is equally effective, with fewer reported adverse events. When administered in dosages of 10 to 60 mg daily, citalopram was as effective and better tolerated than 50 to 150 mg daily of imipramine and 75 to 225 mg daily of amitriptyline.[58,59] In a double-blind multicentre clinical study, citalopram (40 mg daily) was found to be as effective as clomipramine (150 mg per day) in the treatment of nonendogenous depression; however, clomipramine was found to be superior to citalopram in the treatment of endogenous depression.[60]

Citalopram has also been compared with other SSRI antidepressant medications. At a dosage of 20 to 40 mg daily, citalopram was comparable in efficacy to 100 to 200 mg daily of fluvoxamine in the treatment of unipolar major depression,[61] and 20 mg of citalopram was as effective as treatment with 20 mg of fluoxetine.[62] An additional study used a flexible regime of up to 60 mg daily, and noted that citalopram was as effective and well tolerated as sertraline.[63]

Placebo-controlled studies in acute and maintenance treatment of major depression

Placebo-controlled trials have demonstrated that citalopram is effective not only in the acute treatment of depression but also during continuation therapy to prevent relapse (Table 6). In a meta-analysis of 9 placebo-controlled studies, citalopram was superior to placebo at both 20 and 40 mg daily dosages.[64] Furthermore, in 2 placebo-controlled studies conducted by Montgomery et al,[65,66] citalopram was effective in preventing relapse of depressive symptoms at 20, 40 and 60 mg daily, for periods of up to 6 months.

Severe and treatment-resistant depression

Although there is evidence that 20 mg per day of citalopram is the minimum effective dosage for the treatment of major depression, in at least one study there was evidence of a dose–response relation according to severity of depression. Montgomery et al,[23] using a placebo-controlled design, found that patients who were severely depressed responded to a dosage of 40 mg of citalopram daily, but not to a lower dosage of 20 mg daily. Citalopram may also be effective at higher doses or with augmentation strategies in the treatment of refractory depression. A double-blind, placebo-controlled trial conducted by Baumann et al[67] found that the combination of lithium and 20 to 60 mg daily of citalopram was superior to placebo and to citalopram alone in relieving unipolar resistant depression (Table 7).

Other depressive disorders

There is tentative evidence to support the use of citalopram in combination with light therapy in the treatment of seasonal affective disorder.[68] Citalopram has also proven to be effective in the treatment of depression related to physical illnesses, including poststroke depression[69] and depression in dementia (Table 8).[70]

Anxiety disorders

Several anxiety disorders have also been treated successfully with citalopram. Citalopram, at dosages of either 20 to 30 mg daily or 40 to 60 mg daily, was significantly more effective than placebo in the treatment of panic disorder, with the lower dosage range (20 to 30 mg daily) of citalopram being more effective than the higher range (40 to 60 mg daily).[71] This is in contrast to findings in studies of major depression, in which high-

Table 5: Randomized, placebo-controlled trials of citalopram versus active comparison medication in therapy for major depressive disorder*

Study	Description	Duration	Patients	Outcome
Amitriptyline v. citalopram[59]	Multicentre, double-blind Treatment groups: 30–60 mg citalopram 75–225 mg amitriptyline	3 wk	43	A statistically significant reduction of MADRS† scores was recorded in both groups. Side effects were recorded more frequently in the amitriptyline group compared with the citalopram group
Imipramine v. citalopram[58]	Multicentre, double-blind Treatment groups: 10–30 mg citalopram 20–60 mg citalopram 50–150 mg imipramine	6 wk acute 16 wk continuation	472	400 completed 6-wk period; 297 completed 22-wk period. Ham-D‡, CGI§ and VAS¶ scores indicated no significant difference between imipramine and citalopram. UKU global scores of adverse events indicated that citalopram was better tolerated
Clomipramine v. citalopram[60]	Multicentre, double-blind Treatment groups: 40 mg citalopram 150 mg clomipramine	6 wk	150	102 completed study. Higher percentage of endogenously depressed patients on clomipramine were complete responders according to Ham-D; nonendogenously depressed subjects showed that clomipramine and citalopram were equivalent in efficacy
Fluvoxamine v. citalopram[61]	Multicentre, double-blind Treatment groups: Start at 100 mg, progress to 200 mg fluvoxamine Start at 20 mg, progress to 40 mg citalopram	6 wk	217	167 completed study. Ham-D and CGI scores showed equal efficacy between 2 groups. UKU** global scores showed fluvoxamine contributed to a higher frequency of adverse events
Fluoxetine v. citalopram[62]	Multicentre, double-blind Treatment groups: 20 mg fluoxetine 20 mg citalopram	8 wk	357	312 completed study. Ham-D, MADRS and CGI scores showed equal efficacy between 2 treatment groups
Sertraline v. citalopram[63]	Multicentre, double-blind Treatment groups: 50–150 mg sertraline 20–60 mg citalopram	24 wk	400	308 completed study. MADRS, CGI and UKU scores showed equal efficacy and safety among treatments

* Adapted from Noble and Benfield,[21] Citalopram Product Monograph,[26] Baettig et al[24]
†Montgomery Åsberg Depression Rating Scale
‡Hamilton Depression Rating Scale
§Clinical Global Impression
¶Visual analogue scale
**UKU Side Effects Rating Scale

Table 6: Randomized, placebo-controlled trials of citalopram in acute, continuation and maintenance therapy for major depressive disorder

Study	Description	Duration	Patients	Outcome
Citalopram v. placebo[64]	A meta-analysis of 9 placebo-controlled flexible or fixed-dose (10 to 80 mg daily) trials	4 to 6 wk	949	Ham-D, MADRS and CGI scores showed that citalopram was superior to placebo at both 20 and 40 mg daily
Citalopram in relapse prevention[65]	Double-blind, placebo-controlled Treatment groups: 1. 40 mg citalopram 2. 20 mg citalopram 3. Placebo	6 wk acute 24 wk continuation	207	168 patients completed study. MADRS and CGI scores indicated that both doses of citalopram (20 and 40 mg) effectively prevented relapse compared with placebo. There was no significant difference between citalopram doses in terms of efficacy
Citalopram in relapse prevention[66]	Continuation therapy Treatment groups: 1. Open citalopram, flexible 20, 40 or 60 mg 2. Responders received double-blind: placebo OR same dose of citalopram as open therapy	1. 8 wk acute 2. 24 wk continuation	1. 391 2. 226	Patients treated with citalopram had a significantly lower relapse rate compared with placebo according to the Ham-D and MADRS. There was little difference in tolerability between placebo and citalopram according to UKU scale

er dosages tend to show increased efficacy. In addition, there is open-label evidence suggesting that citalopram is effective in the treatment of generalized social phobia;[72] however, further controlled studies are needed to corroborate this finding. There is also preliminary evidence that 40 to 60 mg daily of citalopram may be effective in the treatment of obsessive–compulsive disorder in adults[73] as well as in children.[57] A summary of studies using citalopram in the treatment of anxiety disorders is presented in Table 9.

Addiction disorders or alcohol abuse

Balldin et al[74] demonstrated that citalopram, at 40 mg daily, reduced alcohol intake in male heavy drinkers who consumed 60 to 100 g of pure alcohol daily. Another study conducted by Naranjo et al[75] examined the effects of 40 mg daily of citalopram on alcohol consumption in both men and women. In this study, citalopram was administered in a double-blind fashion, and it significantly decreased desire and craving for alcohol, in addition to consumption and liking of alcohol (Table 10).

Other medical conditions

Citalopram may also be effective in the treatment of certain medical conditions, including diabetic neuropathy[76] and poststroke crying (Table 11).[77]

Role in current pharmacotherapy

Citalopram is an antidepressant agent with a mechanism of action similar to that of other SSRI antidepressant agents, and it is the most selective inhibitor of 5-HT reuptake currently available. It has minimal potential for drug interactions, although it is contraindicated in combination with MAOI antidepressants. Furthermore, citalopram is well tolerated, and side effects are usually mild to moderate. It is suitable for populations such as the elderly and patients with renal and hepatic dys-

Table 7: Randomized, placebo-controlled trials of citalopram in refractory depression

Study	Description	Duration	Patients	Outcome
Citalopram v. placebo in severe depression[23]	Double-blind, placebo-controlled Treatment groups: 40 mg citalopram 20 mg citalopram Placebo	6 wk	199	134 completed treatment. Ham-D, MADRS and CGI scores showed that there was a significant advantage for 40 mg citalopram compared with 20 mg citalopram and placebo. There was no significant difference in efficacy between 20 mg citalopram and placebo
Citalopram combined with lithium in treatment-resistant depression[67]	After 4 wks of 40-60 mg open label treatment with citalopram, non-responders received, double-blind: lithium (800 mg) OR citalopram + placebo OR citalopram + lithium (800 mg)	2 wk	24	Ham-D and UKU scores indicated that citalopram-lithium combination was significantly more effective and better tolerated than other treatments

Table 8: Randomized, placebo-controlled trials of citalopram in therapy for other depressive disorders

Study	Description	Duration	Patients	Outcome
Citalopram in combination with light therapy in SAD*[68]	Double-blind, placebo-controlled Treatment groups: 40 mg citalopram + light therapy Placebo + light therapy	1 yr	8 (female)	CPRS† and VAS scores indicated that treatment with citalopram was significantly more effective than treatment with placebo in relieving SAD
Citalopram v. placebo in poststroke depression[69]	Double-blind, placebo-controlled Treatment groups: 10–40 mg citalopram Placebo	6 wk	66	57 completed the study. Ham-D, MES‡ and UKU scores showed a greater degree of recovery among citalopram-treated patients and alleviation of depressive symptoms
Citalopram v. placebo in elderly depression with and without dementia[70]	Multicentre, double-blind, placebo-controlled Treatment groups: 10–30 mg citalopram Placebo	6 wk	149	101 completed the study. Ham-D, MADRS and CGI scores showed that citalopram was significantly more effective than treatment with placebo in depression and improved cognitive and emotional functioning associated with elderly dementia. UKU scores showed that citalopram was as tolerable as placebo among patients

*Seasonal affective disorder
†Comprehensive Psychopathological Rating Scale
‡Melancholia Scale

function; however, clinicians may need to make dosage adjustments to meet their special requirements.

Citalopram has proven to be effective in treating major depression, other depressive disorders and panic disorder. It may be effective in the treatment of other anxiety disorders, substance use disorders and a few medical conditions. Consequently, citalopram can be implemented as standard antidepressant therapy in the treatment of major depressive disorder and may be indicated in the future for treatment of other psychiatric disorders.

Table 9: Open and controlled trials of citalopram in anxiety disorders

Study	Description	Duration	Patients	Outcome
Citalopram v. placebo in panic disorder[71]	Multicentre, double-blind, flexible-dose within fixed-dose range Treatment groups: Placebo 60 or 90 mg clomipramine 10 or 15 mg citalopram 20 or 30 mg citalopram 40 or 60 mg citalopram	8 wk	475	360 completed the study. CAS†, HAS‡ and MADRS scores showed that 20 or 30 mg daily citalopram contributed to significantly greater improvement than 40 or 60 mg daily citalopram; 20 or 30 mg, or 40 or 60 mg citalopram, and 60 or 90 mg clomipramine were all significantly better than placebo
Citalopram in adult OCD*[73]	Multicentre, open-label pilot project 20–60 mg citalopram	24 wk	29	All patients completed study. Y-BOCS§ scores indicated that 76% of patients showed a significant improvement at both doses
Citalopram in childhood and adolescent OCD[67]	Open-label 10–40 mg citalopram	10 wk	23 (aged 9–18)	All patients completed study. Y-BOCS/CY-BOCS¶ and CGAS** scores showed that 75% showed a significant improvement with minor adverse events reported
Citalopram in generalized social phobia[72]	Open-label, naturalistic study 40 mg citalopram	12 wk	22	The CGI and LSAS†† scores indicated that 86% of patients were responders

*Obsessive–compulsive disorder
†Clinical Anxiety Scale
‡Hamilton Anxiety Rating Scale
§Yale-Brown Obsessive Compulsive Scale
¶Children's Yale-Brown Obsessive Compulsive Scale
**Children's Global Assessment Scale
††Liebowitz Social Anxiety Scale

Table 10: Randomized, placebo-controlled trials of citalopram in the treatment of addiction disorders

Study	Description	Duration	Patients	Outcome
Citalopram v. placebo in heavy male drinkers[74]	Double-blind, placebo-controlled, crossover Treatment groups: 1. 40 mg citalopram 2. Placebo	1. 5 wk 2. 5 wk	35 (male)	30 patients completed study. There was no difference found in heavy drinkers (consuming greater than 107 g pure alcohol daily) compared with placebo; there was a significant improvement in lighter heavy drinkers (consuming 60–100 g pure alcohol daily) compared with placebo
Citalopram v. placebo in heavy drinkers[75]	Double-blind, placebo-controlled, crossover Treatment groups: 1. 40 mg citalopram 2. Placebo	1. 1 wk 2. 1 wk	16	Citalopram significantly decreased interest, desire, craving and liking for alcohol

Table 11: Randomized, placebo-controlled trials of citalopram in the treatment of other medical conditions

Study	Description	Duration	Patients	Outcome
Citalopram v. placebo in diabetic neuropathy[74]	Double-blind, placebo-controlled, crossover Treatment groups: 1. 40 mg citalopram 2. Placebo	1. 3 wk 2. 2 wk	18	15 patients completed the study. There was a significant improvement in diabetic neuropathy as witnessed by observer and self-rating
Citalopram v. placebo in post-stroke pathological crying[75]	Double-blind, placebo-controlled, crossover Treatment groups: 1. 10–20 mg citalopram 2. Placebo	1. 3 wk 2. 6 wk	16	13 patients completed the study. The number of daily crying episodes decreased by at least 50% in all cases during citalopram treatment compared with 2 patients receiving placebo treatment

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