Prescribing citalopram safely: an update

Evidence of adverse cardiac effects associated with citalopram has prompted a reduction in the recommended maximum daily dose to 40 mg per day in adults. It is also recommended that doses above 20 mg are avoided in people aged over 65 years or in people with hepatic impairment. These changes are due to two recent clinical studies which found that citalopram is associated with a dose dependent change in the electrical activity of the heart, potentially leading to QT interval prolongation.*

*Citalopram is not approved for use in people aged under 18 years

Why the change?

The maximum daily dose of citalopram has been reduced because evidence shows that higher doses increase the risk of QT prolongation and incidence of Torsades de Pointes (a type of ventricular tachycardia).[1–3] It is also considered that there is no treatment benefit at doses higher than 40 mg per day.[1] After reviewing the recent study and several clinical and non-clinical trials, the United States Food and Drug Administration issued a recommendation in August 2011, that the recommended maximum dose of citalopram be lowered to 40 mg.[1] In response Medsafe, in New Zealand, has asked manufacturers to amend medicine datasheets to reflect this change in dose for all preparations containing citalopram.

For full details of the FDA release see: "FDA drug safety communication: Abnormal heart rhythms associated with high doses of Celexa (citalopram)", Sept, 2011. Available from: www.fda.gov/Drugs/DrugSafety/ucm269086.htm

Indications for treatment with citalopram and recommended dosing

The recommended doses for citalopram used for the treatment of adult depression are shown in Table 1:[4]

Doses can be increased in 10 mg increments if the patient's response is limited or the severity of depression warrants it. It takes several weeks for clinically effective results to be achieved with all SSRIs so assessment of efficacy and increase in dose should only be made after two to three weeks of treatment.

For people already taking citalopram

For patients already being treated with citalopram at less than the new recommended doses there is no need for change. However, patients should be instructed to report any adverse effects and to seek immediate medical attention if they develop symptoms suggestive of arrhythmia, e.g. shortness of breath, dizziness, palpitations or feeling faint. ECG monitoring may be appropriate for patients with other risk factors for QT prolongation (over page).

Patients taking doses greater than those recommended should ideally have their dose reduced or be trialled on another medicine. In cases where the dose cannot be reduced, vigilant monitoring for adverse effects and regular ECG monitoring is required.

Patients should be counselled through any changes and the reasons for the change should be discussed. It may be helpful to explain that the new research indicates that there is no clinical advantage in taking more than 40 mg of citalopram per day and that all SSRIs have similar clinical efficacy.[1]

Escitalopram not associated with an increased risk of QT prolongation

Escitalopram is the S-enantiomer of citalopram. This means that it is the chemical mirror-image of citalopram. It is clinically very similar to citalopram except it is more potent and thus dosed at lower levels.[6–8] Escitalopram is fully funded on the New Zealand Pharmaceutical Schedule.

While the adverse effects associated with escitalopram are very similar to those with citalopram, there is no evidence to suggest that escitalopram causes QT-prolongation at high doses.[8] Medsafe considers that at standard doses, escitalopram is associated with a lower risk of QT prolongation than citalopram.

The recommended maximum daily dose of escitalopram is 20 mg for people aged 18 – 64 years (with no risk factors) and 10 mg for people aged over 65 years and those with hepatic impairment.

Table 1. Recommended doses of citalopram for the treatment of adult depressive order

Patient group	Starting dose	Maximum dose	Notes
Adults 18 – 65 years	20 mg	40 mg	People without risk factors
Adults > 65 years	10 mg	20 mg	Reduced metabolism in this age group leads to a longer half-life of citalopram
Adults with impaired hepatic function	10 mg	20 mg	Citalopram is metabolised primarily by the liver, therefore hepatic impairment can lead to increased blood levels

Patients being treated with a SSRI may experience withdrawal symptoms if the medicine is stopped abruptly or lowered significantly or rapidly. Withdrawal symptoms for citalopram include dizziness, headache, anxiety and nausea and can last between one to two weeks. Tapering the dose over one to two weeks will help to avoid these symptoms. When switching to another antidepressant a "wash-out" period may be necessary: taper citalopram over approximately one week before commencing the new medicine and in some cases, such as with venlafaxine, having an antidepressant-free period of one to two days is recommended.[5] People with severe depression may require more intensive monitoring during the change-over period, and in extreme cases this may involve hospitalisation.

 For further information on changing antidepressants see: "Pharmacological management of depression in adults", in Adult depression, BPJ Special Edition (Jul, 2009).

Other adverse effects associated with citalopram

Citalopram is associated with a number of adverse affects and contraindications in addition to QT interval prolongation.

The most significant adverse reaction is an increase in, or the emergence of, suicidal ideation and behaviour. This adverse effect is common to all SSRIs. SSRIs are also often associated with mood changes and initial worsening of depressive symptoms. It is therefore essential to discuss the possibility of these adverse effects with all patients before initiating a SSRI. Family and caregivers should be included in the discussion and made aware of the increased risks. Patients not considered to be at risk of suicide should be reviewed one to two weeks after beginning treatment. Those at risk should be assessed more frequently.

Adverse effects and interactions

Citalopram is contraindicated in people with the following risk factors:[1, 4, 6]

- Congenital long QT syndrome
- Concurrent use of a monoamine oxidase inhibitor (MAOI) – may cause serotonin syndrome
- Concurrent use of pimozide – an antipsychotic medicine which is also associated with QT-prolongation (Medicine available under section 29 only)

People who are poor CYP2C19 metabolisers, or those taking a CYP2C19 inhibitor such as cimetidine, should be limited to a maximum dose of 20 mg citalopram per day. This is because of an increased risk of QT-prolongation due to the resulting increased plasma concentrations.

Citalopram (as with any other medicine with the potential to cause QT prolongation) may not be appropriate for people with the following factors:

- People with risk factors for QT-prolongation, such as structural heart disease, bradycardia, hypokalaemia , hypomagnesaemia or hypocalcaemia
- People taking other medicines that can affect the QT interval, e.g. lithium, sotalol (for a full list of medicines see: www.azcert.org/index.cfm N.B. this is a US based reference so may not include all medicines available in New Zealand)
- People with severely reduced renal function (creatinine clearance <20 mL/minute)

Managing the risk of QT prolongation with citalopram

- Patients should be screened for other risk factors for QT prolongation prior to initiating treatment with citalopram
- Citalopram should be used with caution, and ECG monitoring should be performed in patients with other risk factors for QT prolongation - a lower risk SSRI such as escitalopram might be more appropriate
- Hypokalemia and hypomagnesaemia should be corrected before administering citalopram and electrolytes should be monitored periodically in patients at risk for electrolyte disturbance, e.g. due to use of diuretics, severe vomiting or diarrhoea
- Patients should be advised to seek medical attention immediately if they experience signs or symptoms of an

abnormal heart rate or rhythm (e.g. syncope, palpitations, new onset seizures) while taking citalopram. An ECG should be performed in all patients with these symptoms.

- Discussion with a cardiologist is recommended if significant QT prolongation (QTc > 500 ms or an increase of > 60 ms) occurs. Consideration should be given to changing to an alternative antidepressant.

For further information on medicine-induced QT prolongation and Torsades de Pointes see: **www.medsafe.govt.nz/profs/PUArticles/DrugInducedQTProlongation.htm**

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