The non-antidepressant effects of citalopram: a clinician’s perspective

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Submitted: 2013-07-23 Accepted: 2014-01-14 Published online: 2014-02-27

Key words: citalopram; platelet aggregation; serotonin syndrome; hyponatremia; osteoporosis

Abstract
The authors present an overview of the most often discussed questions concerning citalopram, i.e. its proven effect on the QT interval and related dose reductions. They discuss citalopram’s antiplatelet effect including the most recent data and draw attention to serotonin syndrome as its incidence is still underestimated. They go on to discuss hyponatremia pointing out that this condition may develop even in those taking low doses of citalopram. Finally, the authors provide a brief overview of the latest findings on osteoporosis and the serotonergic mechanism inducing it in individuals treated with a selective serotonin reuptake inhibitor.

INTRODUCTION
Citalopram hydrobromide is one of the most frequently used antidepressants belonging to the class of selective serotonin reuptake inhibitors (SSRIs). Its action is highly selective, with minimal effects on noradrenaline and dopamine reuptake. The relatively low incidence of adverse effects, its good tolerability, efficacy, and favorable dosing schedule, have all contributed to the fact that citalopram has become the preferred drug in the treatment of depression. The clinical presentations of a depressive disorder are varied, with insomnia, anxiety, somatization, and hypochondriasis as markers of depression more often encountered in the elderly while younger patients experience a feeling of guilt and genital symptoms (Shahpesandy 2005). Still, about 15% of patients stop taking a drug of the SSRI class soon after therapy initiation (Khawam et al. 2006). The most significant effects of citalopram, which are currently under general scrutiny, include its effect on QT interval prolongation, antiplatelet action, serotonin syndrome, hyponatremia, and osteoporosis.

PHARMACOLOGICAL CHARACTERISTICS OF CITALOPRAM
Following its oral administration, citalopram is quickly absorbed with its plasma concentration peaking within 1–4 hours. Its half-life is about 35 hours. Citalopram is highly lipophilic with a single chiral center. Its accumulation in red blood cells was shown to be significantly higher compared with its plasma concentrations (Fisar et al. 2006). Citalopram is a racemic mixture (50/50) of two isomers: S- and R-citalopram. The effect of selective serotonin reuptake inhibition is due primarily...
to S-citalopram. The bioavailability of citalopram following its oral administration is about 80%. The primary isozymes involved in citalopram demethylation in the liver are CYP3A4 and CYP2C19. Citalopram’s main metabolites are demethylcitalopram (DCT) and didemethylcitalopram (DDCT). Between 12% and 23% of the citalopram administered is excreted unaltered in urine, with about 10% excreted in feces.

I. QT interval prolongation

In a study carried out with 10 dogs given oral citalopram (8 mg/kg/day), there were 5 sudden deaths between weeks 17 and 31 of the study. On the contrary, no sudden deaths were observed in rats (with a dose of 120 mg/kg/day). Follow-up experiments with dogs demonstrated that the QT interval prolongation is due to didemethylcitalopram (DDCT), a citalopram metabolite.

In the postmarketing period, a large number of papers were published, ranging from case reports to large studies documenting the effect of citalopram on the QT interval (Sala et al. 2005; Jolly et al. 2009; Tarabar et al. 2008). After analyzing results of clinical trials as well as its own study showing the QT interval prolongation is associated with citalopram doses, the U.S. Food and Drug Administration (FDA) reduced citalopram dosage in August 2011 (specification in March 2012) (FDA 2011; 2012) (Table 1). The total daily dose for the general population should not now exceed 40 mg; in patients over 60 years of age, the limit is 20 mg. The 20 mg maximum daily dose of citalopram also applies to patients with hepatic impairment, poor CYP2C19 metabolisers, and to patients using drugs inhibiting CYP2C19 such as cimetidine or omeprazole. Similarly, recommendations issued by the European Medicines Agency (EMA) (EMA 2011) suggested the maximum daily dose of escitalopram be 20 mg and only 10 mg/day in elderly patients (EMA 2011). Regarding the efficacy, clinical studies have not documented any differences between treatment with doses of 40 or 60 mg of citalopram per day.

Although some of the experts were somewhat cautious about the above stated recommendations (Sheeler et al. 2012; Vieweg et al. 2012; Cooke & Waring 2013), a most recent clinical study confirmed that citalopram does prolong the QT interval (Castro et al. 2013).

Current patients are polymorbid and use a variety of other drugs, many of which may affect the QT interval. Although the risk of taking only citalopram may be – in this respect – rather low, a combination of citalopram and another drug may be clinically significant. It is therefore critical to assess the risk for every single patient, indeed a most difficult, if not impossible, task. The solution for the future will be building relevant databases and introducing electronic prescriptions that will automatically consider not only the QT interval but, also, adverse effects, drug-drug interactions, and many other parameters. However, this is an issue beyond the scope of this article involving as it does the area of personalized medicine.

II. Antiplatelet effect

Platelet granules store large amounts of serotonin. Upon their activation, serotonin is released to exert its two main effects, i.e., vasoconstriction and platelet activation. The serotonergic mechanism has long been considered insignificant for hemostasis. Galan et al. (2009), basing their opinion on experimental research, suggest that the role of serotonin in thrombogenesis is much greater than believed until recently.

Once SSRI drugs started to be used for treatment, clinicians sought to determine whether the treatment reduces the incidence of cardiovascular events. In the SANDHART (Sertraline Antidepressant Heart Attack Randomized Trial) study, a group of patients treated with an SSRI had a lower incidence of severe cardiovascular events than the placebo group; however, the sample was too small to consider these findings conclusive (Glassman et al. 2002). In another study, ENRICHD (Enhancing Recovery in Coronary Heart Disease), treatment with an SSRI reduced the risk of myocardial infarction (Berkman et al. 2003). A research project carried out by Finnish experts investigated the impact of SSRI treatment on mortality of patients with depression and showed that SSRI treatment reduced cardiac and cerebrovascular mortality (Tiihonen et al. 2006). The risk of hemorrhagic cerebrovascular events, while 40–50% higher in patients using SSRIs, is actually very low; the estimated incidence is 1 event per 10,000 patients (Hackam & Mrokbbrada 2012). In the case of ischemic vascular events, most studies reported neutral effects of SSRIs, whereas some authors documented a higher risk of ischemic vascular event in patients treated with an SSRI (Chen et al. 2008; Trifiró et al. 2010). Also, the incidence of gastrointestinal bleeding was higher in SSRI-treated patients (Andrade et al. 2010).

Intensive research using modern laboratory methods went hand in hand with clinical trials. Depression patients had higher thrombocyte aggregation rates, which was significantly reduced after 3-month treatment with antidepressants (escitalopram/nortriptyline) (Flöck et al. 2010). Tseng et al. (2010) made the largest progress in their research of the antiplatelet effects of citalopram. They found that citalopram inhibits ADP-

### Tab. 1. Increase in the corrected QT interval for citalopram. FDA analysis (2011).

<table>
<thead>
<tr>
<th>Citalopram Dose (mg/day)</th>
<th>Increase in QT Interval (ms)</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg/day</td>
<td>8.5</td>
<td>(6.2, 10.8)</td>
</tr>
<tr>
<td>60 mg/day</td>
<td>18.5</td>
<td>(16.0, 21.0)</td>
</tr>
<tr>
<td>40 mg/day*</td>
<td>12.6</td>
<td>(10.9, 14.3)</td>
</tr>
</tbody>
</table>

*Estimate based on the relationship between blood citalopram concentration and QT interval.
induced aggregation by its effect on the P2Y12 receptor (Tseng et al. 2013). In the meantime, a new derivative of citalopram, N-methyl citalopram, was synthesized: this derivative does not cross the blood-brain barrier and its inhibition effects on selective serotonin reuptake are confined to the periphery not affecting the central nervous system (Bismuth-Evenzal et al. 2010). It has the potential to become an antiplatelet agent of a new type.

### III. Serotonin syndrome

Serotonin syndrome (some authors prefer the term “serotonin toxicity”) is a potentially life-threatening condition associated with increased serotonergic activity in the central nervous system. Successful treatment is largely dependent on correct and early recognition of the syndrome. The exact incidence of the syndrome is unknown; in reality, its incidence is much higher than actually diagnosed (Lawrence 2013). Its symptoms may be misinterpreted; mild symptoms (drug interaction when using another drug for a short time) may disappear, or the physician may not even consider this diagnosis: in one study, a surprisingly high number – 85% of physicians – did not even know serotonin syndrome was a clinical diagnosis (Mackey et al. 1999).

Serotonin (5-hydroxytryptamine or 5-HT) is a neurotransmitter playing an important role in many conditions such as aggression, pain, sleep, anxiety, depression, appetite, migraine or vomiting. Serotonin is synthesized in neurons of the brainstem and gastrointestinal tract. Cognitive functions are affected by the serotonin synthesized in the brain; it is estimated this serotonin represents 1–2% of its total amount in the body. About 95% of the total amount of serotonin is produced in chromatophore cells of the gastrointestinal tract, especially in the duodenum from where it is released into circulation to be reuptaken by thrombocytes through specific transporters. A small amount remains unbound in blood where it exerts the effects of hormones modulating, e.g., bone metabolism. Serotonin is metabolized mainly by monoamine oxidase (MAO) and excreted in urine as 5-hydroxyindoleacetic acid. At the same time, MAO activity is directly inhibited by citalopram (Fisar et al. 2010).

An important role in the pathogenesis of the syndrome is believed to be played by stimulation of post-synaptic 5-HT1A and 5-HT2A receptors. Serotonin syndrome may develop even when using a drug within the therapeutic range, but is more likely to develop following serotonin overdose or when combining serotonin with drugs boosting serotonergic neurotransmission including interactions (Table 2), (Isbister et al. 2007). The most frequent overdose related to SSRI use with serotonin toxic symptoms seen in 14% of patients taking excessive doses (Isbister et al. 2004).

The clinical features of serotonin toxicity are characterized by three types of symptoms: (a) neuromuscular excitation, (b) the autonomous nervous system, and (c) changes in mental status (Table 3), (Isbister et al. 2007).

### Table 2. Drugs most frequently associated with serotonin toxicity.

<table>
<thead>
<tr>
<th>Serotonin reuptake inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Selective serotonin reuptake inhibitors (SSRI): fluoxetine, fluvoxamine, citalopram, escitalopram, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, paroxetine, sertraline,</td>
</tr>
<tr>
<td>• Other antidepressants: venlafaxine, clomipramine, imipramine,</td>
</tr>
<tr>
<td>• Opioid analgesics: pethidine, tramadol, fentanyl, dextromethorphan</td>
</tr>
<tr>
<td>• St. John’s wort</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Monoamine oxidase inhibitors</th>
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</thead>
<tbody>
<tr>
<td>• Irreversible monoamine oxidase A inhibitors: phenelzine, tranylcypromine</td>
</tr>
<tr>
<td>• Reversible monoamine oxidase A inhibitors: moclobemide</td>
</tr>
<tr>
<td>• Other: linezolid</td>
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</tbody>
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<tr>
<th>Serotonin-releasing agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fenfluramine</td>
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<tr>
<td>• Amphetamines</td>
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<tr>
<td>• Methyleneoxyamphetamine (MDMA; ecstasy)</td>
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</table>

<table>
<thead>
<tr>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lithium</td>
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<tr>
<td>• Tryptophan</td>
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</tbody>
</table>

### Table 3. Clinical features of serotonin toxicity.

<table>
<thead>
<tr>
<th>Neuromuscular effect changes</th>
<th>Autonomic effect</th>
<th>Mental status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperreflexia</td>
<td>Hyperthermia: mild, below 38.5°C</td>
<td>Agitation</td>
</tr>
<tr>
<td>Shivering</td>
<td>Flushing</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Hypomania</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>Mydriasis</td>
<td></td>
</tr>
<tr>
<td>Hypertonia/rigidity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
have several diagnostic criteria: the most often used ones include the Hunter criteria (Table 4) with a 84% sensitivity and 97% specificity (Dunkley et al. 2003). To establish the diagnosis, the patient should be receiving a serotonergic drug and meet at least one of the above criteria. Once the diagnosis has been established, the administration of any serotonergic drugs should be discontinued. Symptoms usually disappear within 24 hours of the end of treatment although, in the case of drugs with long half-time, the symptoms may persist longer; with irreversible MAO inhibitors, the symptoms may persist for several days (Boyer 2013). Supportive therapy (oxygen, i.v. fluids, monitoring) is aimed at normalizing the vital signs. Agitation is treated with benzodiazepines. Patients showing severe intoxication with hyperthermia, metabolic acidosis, convulsions, rhabdomyolysis, and other complications require aggressive procedures including mechanical ventilation, elimination of muscle activity, administration of an antidote for serotonin (cyproheptadine). Once the condition – even in cases of mild intoxication – is under control, it is critical to reassess the therapeutic strategy and decide whether a serotonergic drug therapy should be continued or whether another suitable option is available.

### IV. Hyponatremia

In clinical practice, hyponatremia (defined as serum sodium levels below 134 mmol/L) is an oft-diagnosed electrolyte disorder (Liamis et al. 2008) caused, in most cases, by drugs, particularly thiazide diuretics. Antidepressants are just another well-known cause, of which SSRIs cause hyponatremia twice as often as other antidepressants. The incidence of SSRI-induced hyponatremia is widely reported to be between 0.5% and 32%. The mechanism responsible for hyponatremia is induction of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Hyponatremia develops within the first weeks of treatment and disappears within two weeks post-treatment. Clinical symptoms include non-specific ones such as headache, poor concentration, memory problems, confusion, weakness and dizziness, which may result in falls. More severe forms of hyponatremia manifest themselves with hallucinations, synapses, convulsions, coma, respiratory arrest or death. High-risk factors for hyponatremia in SSRI-treated patients are considered to be advanced age, female sex, concomitant use of diuretics, low body weight, and lower baseline levels of serum sodium (Jacob & Spinler 2006). In 2008, the FDA issued a black box warning related to this adverse effect of citalopram (FDA 2008). Hyponatremia has been observed not only after treatment with citalopram but, also, with escitalopram (Covyeou & Jackson 2007; Tsai et al. 2012). The condition may develop even with low doses of citalopram (RoopaSethi et al. 2011), which is why it is crucial to obtain a full list of all the drugs used. Citalopram and escitalopram have been shown to have more drug interactions than any other SSRIs, with hyponatremia being among the most frequent side effects (Montastruc et al. 2012). In patients with hyponatremia confirmed by laboratory tests and mild symptoms, it is sufficient to discontinue the suspected drug; when severe symptoms are present aggressive therapy should be initiated.

### V. Osteoporosis

The effect of serotonin on bone metabolism was first reported by Bliziotes et al. (2001). Bliziotes’s research group demonstrated that the serotonergic system plays an important role in bone metabolism. These findings were later confirmed by Westbroek et al. (2001). In an experiment with knockout mice without serotonin transport, the above authors showed that not only was the density of the murine bone reduced but, also, the architecture and mechanical properties were impaired. A research project reported by Yadav et al. (2008) was just another major step forward in this field, since it demonstrated that even when the majority of the serotonin synthesized in the gastrointestinal tract reaches the circulation to be subsequently reuptaken by thrombocytes, a small amount of serotonin remains unbound in the serum and gets into the bones where it blocks the cell activity of osteoblasts. An important role in this entero–bone endocrine axis is played by LDL-receptor related protein 5 (LRP5). Many other clinical studies have been carried out and – based on the results obtained to date – SSRIs could be listed among drugs contributing to osteoporosis induction. However, assessment of the results of those studies often proved difficult because of the fact that depression itself is a risk factor for osteoporosis while other factors such as malnutrition, low physical activity, comorbidity, smoking, other administered drugs, etc. further complicate the ultimate assessment in patients with depression. Chau et al. (2012) have recently published an elegant review on these problems. A landmark work in this field is a study by Rizzoli et al. (2012) who demonstrated a direct relationship between antidepressant use and increased risk of fractures. The risk associated with SSRI use is highest in the first 8 months of treatment. Despite the indisputable progress in this area in recent years, many questions remain unanswered, e.g., whether SSRIs also increase (besides serotonin in the brain) serotonin production in the gastrointestinal tract or whether sero-

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**Tab. 4. Hunter serotonin toxicity criteria**

<table>
<thead>
<tr>
<th>To fulfill the Hunter criteria, a patient had to take a serotonergic agent and meet one of the following conditions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Spontaneous clonus</td>
</tr>
<tr>
<td>• Inducible clonus plus agitation or diaphoresis</td>
</tr>
<tr>
<td>• Ocular clonus plus agitation or diaphoresis</td>
</tr>
<tr>
<td>• Tremor plus hyperreflexia</td>
</tr>
<tr>
<td>• Hypertonia plus temperature above 38°C plus ocular clonus or inducible clonus</td>
</tr>
</tbody>
</table>
Serotonin does achieve higher concentrations in blood and bone marrow where it might block bone formation, etc. In practice, before administering an SSRI, the first step is a thorough assessment of the patient taking into account any risk factors of osteoporosis, this is followed by a bone density test with patient follow-up during treatment; if needed, pharmacological treatment of osteoporosis is initiated.

**CONCLUSION**

Citalopram is a time-proven drug, which has been widely used for many years in clinical practice on a daily basis. A dose reduction based on QT interval prolongation will increase its safety. Concerning the antiplatelet effects of citalopram, its mechanism is well understood. N-methylcitalopram, a citalopram derivative, holds promise as an antiplatelet agent of a new type. Information about serotonin syndrome will increase the awareness of a condition that is still being misdiagnosed. The non-antidepressant effects of citalopram

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