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# *Citalopram – induced gastrointestinal disturbances – case report and literature review*

# Citalopram – zaburzenia żołądkowo-jelitowe – opis przypadku i przegląd piśmiennictwa

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## Summary

***Background.*** Depression is one of the most common diseases in the elderly people group. It is associated with the presence of various factors influencing the appearance of this disorder, e.g. somatic diseases, the passage of time and the feeling of loneliness. The depressive disorders have a strong two-way relationship with cardiovascular disease. Depression is not a part of the normal ageing process and requires proper therapy. Citalopram is SSRI approved for the treatment of depressive disorders in adults. Although the safety and efficacy of citalopram are high, there are some restrictions on the use of this drug and the risk of adverse effects, such as drowsiness, insomnia, fatigue, headache, gastrointestinal reactions, and also serious ones, i.a. myocardial infarction, prolonged QT interval, cerebrovascular accident, and suicidal ideation. ***Material and methods.*** We describe a case report of a 62-year-old man who experienced an adverse reaction of abdominal pain and nausea during the therapy with citalopram. ***Results.*** After discontinuation of citalopram and introduction of sertraline instead, the symptoms resolved. ***Conclusions.*** The described case confirms the risk of an adverse reaction in the form of gastrointestinal symptoms such as abdominal pain and nausea due to the therapy with citalopram. *Geriatria 2021; 15: 197-202. doi: 10.53139/G.20211524*

*Keywords: Citalopram, depression in the elderly, adverse drug reactions*

## Streszczenie

***Wstęp.*** W grupie osób w podeszłym wieku obserwuje się znaczny odsetek występowania depresji jako jednego z głównych problemów zdrowotnych w tej populacji. Związane jest to z obecnością różnych czynników wpływających na pojawianie się tych zaburzeń np. choroby somatyczne, poczucie upływu czasu i osamotnienie. Zaburzenia depresyjne mają silny, dwukierunkowy związek z chorobami układu krążenia. Depresja nie jest częścią normalnego procesu starzenia i wymaga odpowiedniej terapii. Citalopram, selektywny inhibitor wychwytu zwrotnego serotoniny (SSRI) to lek dopuszczony do leczenia zaburzeń depresyjnych u osób dorosłych. Chociaż bezpieczeństwo i skuteczność citalopramu jest wysokie, istnieją pewne ograniczenia w stosowaniu tego leku, jak również ryzyko wystąpienia działań niepożądanych, takich jak senność, bezsenność, zmęczenie, ból głowy, reakcje żołądkowo-jelitowe, a także poważnych działań, m.in. zawał mięśnia sercowego, wydłużony odstęp QT, udar naczyniowy mózgu i myśli samobójcze. ***Materiał i metody.*** Przedstawiamy przypadek 62-letniego mężczyzny, u którego wystąpiło działanie niepożądane w postaci bólu brzucha i nudności w trakcie stosowania citalopramu. ***Wyniki.*** Objawy ustąpiły po zaprzestaniu leczenia citalopramem i zastąpieniu go sertraliną. ***Wnioski.*** Opisany przypadek potwierdza ryzyko wystąpienia działania niepożądanego w postaci objawów żołądkowo-jelitowych, takich jak ból brzucha i nudności, jako następstw terapii citalopramem. *Geriatria 2021; 15: 197-202. doi: 10.53139/G.20211524*

*Słowa kluczowe: Citalopram, depresja wieku podeszłego, działania niepożądane leku*

## Introduction

The elderly population often struggles with various health issues. A severe problem that affects the elderly's quality of life to a large extent is depression – one of the most significant causes of emotional suffering and deterioration of physical health. The prevalence of depression among adults aged 65 and older ranges between 5 to 10% [1,2]. Considering that the number of older people is increasing worldwide, the significance of late-life depression is growing even stronger [3]. The elderly often suffer from depression not only of somatogenic or endogenous etiology, but also of psychogenic origin, and thus, it is often not easy to assess which factor plays a decisive role. Many aspects are contributing to the development of depressive disorders in people over 65 years of age, mainly concerning somatic diseases (diabetes, hypertension, pain syndromes, disability), brain ageing, psychosocial aspects (a sense of loss, lack of social support, loneliness, grief), medications (e.g. some antihypertensive drugs, anti-diabetic drugs, steroids), chronic alcohol abuse and socioeconomic status [2-4]. Generally, in terms of demographics, females are more likely to develop depressive disorders [5]. The endogenous depression may result from dysfunctions of the central nervous system at the cellular or protein level, classified as biological causes. Genetic loads, somatic diseases and organic changes in the brain that lead to the loss of the number of neurons and neurotransmitters are some of the causes leading to disorders of the nervous system. The psychological background of the depression in elders includes lowered self-esteem, negative thoughts, loss of relatives, empty nest syndrome, material losses, or burdens resulting from conflicts in the family. However, these types of situations can be aggravated by some type of individuals' personality development (possibly forming throughout childhood and adolescence, accompanied by parallel unfavourable experiences), resulting in increased emotional sensitivity, reduced condition in social functioning and an excessive tendency to feel internal stress. These factors consequently perpetuate the attitude of social withdrawal, inactivity and other depressive symptoms. Another factor known to increase the risk of depression in the elderly are somatic diseases, and more specifically, the complex relationship between depression and somatic disease, which mutually modify their course – it is often tough to distinguish the symptoms of physical illness and depression; moreover, untreated depression worsens the course and prognosis of somatic disease. The prevalence rate of depression in patients with chronic diseases reaches up to 50%. It especially applies to chronic diseases accompanied by constant pain. What is important is the coexistence of depression and chronic pain syndromes, during which the risk of committing suicide increases sixfold. The incidence of depressive symptoms in other somatic diseases is also high, e.g. 30-42% in cancers, 8.5-27.3% in diabetes, 15-20% in coronary artery disease, 9-25% in arterial hypertension, arthritis (34%) and 15-38% in case of vitamin deficiency (especially B12 and folic acid). Depression is most often diagnosed in patients who have had a stroke (25-48%); diagnosed with coronary artery disease (8-44%); cancer (1-40%), Parkinson's disease (4-90%), Alzheimer's disease (20-40%) and Huntington disease (33 do 69%). The relationship between somatic diseases and the occurrence of depressive disorders is mainly found in relation to cardiovascular disease (CVD) – the prevalence of diagnosed depression is 15-60%, and according to the data from the World Health Organization, cardiovascular disease and depressive disorders currently stands for the most common causes of disability in high-income countries [4,6,7].

In older people, mood disorders, especially depressive states, are conditioned by many reasons, which forces them to undertake multidirectional therapeutic procedures- non-pharmacological (e.g. psychotherapy) and pharmacotherapy [8]. Citalopram (CIT; 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-5-carbonitrile) is an FDA-approved selective serotonin reuptake inhibitor (SSRI), evaluated in many neuropsychiatric disorders and has been found beneficial in older adults. It is a frequently used antidepressant, considered the most selective serotonin reuptake inhibitor, exerting minimum effect upon norepinephrine and dopamine reuptake and no significant activity upon other neuroreceptors [9]. An orally bioavailable hydrobromide salt of the racemic derivative citalopram, citalopram hydrobromide (citalopram HBr), is primarily used to treat depression in adults. However, it is also used off-label for the treatment of alcohol use disorder, obsessive-compulsive disorder, panic disorder, coronary arteriosclerosis, postmenopausal flushing, and premenstrual dysphoric disorder [10]. Citalopram's structure is characterised by a chiral centre, to which the fluorophenyl and the dimethyl-3-aminopropyl groups are bonded, which leads to the existence of two enantiomers, S(+)-CIT and R(-)-CIT (it is the only SSRI with both racemic and pure enantiomer formulation available on the market). CIT owes its pharmacological

activity mainly to the S-CIT enantiomer (escitalopram), approximately 30 times more potent than R-CIT [9]. Citalopram HBr antidepressant activity relies on potentiating serotonergic activity in the central nervous system (CNS) – it is an SSRI with minimal effects on norepinephrine (NE) and dopamine (DA) neuronal reuptake. Moreover, its affinity for muscarinic acetylcholine receptors is low, antagonist actions at histamine are mild, and there is no significant effect on alpha- or beta-adrenergic receptors or dopamine-1, dopamine-2, gamma-aminobutyric acid, opioid, or benzodiazepine receptors [10]. CIT is almost completely absorbed after oral administration, its bioavailability is about 80% (tablets and oral solution are bioequivalent), and it is not affected by food intake. CIT is metabolised by CYP450 3A4 and 2C19 and is a weak inhibitor of CYP450 2D6. The metabolism of this drug involves reactions of hepatic N-demethylation to produce active demethylcitalopram (DCIT), didemethylcitalopram (DDCIT), N-oxidation to form N-oxide-citalopram (CIT NO) and oxidative deamination to form inactive propionic acid (CIT-PROP)- all the active metabolites are also SSRIs. Although their potency is not as high as of the parent drug, they contribute to the total antidepressant effect of CIT, and their selectivity ratios are higher than those of many other SSRIs. CIT has dose-proportional linear pharmacokinetics, ranging between 10-60 mg/day. The elimination half-life is approximately 24 to 48 hours (average: 35 hours); however, it may take longer in people with hepatic impairment, mild-to-moderate renal impairment, in elderly patients (60 years or older), and poor CYP2C19 metabolisers. The steady-state plasma concentrations are obtained within 1-4 weeks. However, it may take 8 to 12 weeks to obtain the complete response after initiation of treatment. This drug is excreted mainly hepatically (85%), 12-23% of unchanged CIT is excreted in urine [9,10]. Like all medications, citalopram may exert adverse effects. In this article, we describe a case report of a patient who developed a gastrointestinal reaction during the therapy with citalopram.

## Case report

A 62-year-old male patient reported to a general practitioner due to abdominal pain and nausea. There was a history of outpatient acute coronary syndrome treated with atorvastatin 20 mg/day, ramipril 2.5 mg/day, nebivolol 5 mg/ day, ASA 75 mg/day, clopidogrel 75 mg/day and spironol 25 mg/day. The applied therapy was well tolerated by the patient. The patient complained of a complete lack of energy after hospitalisation. He stopped leaving the house because he admitted that he did not have enough strength, spent most of the time in bed, and complained about a decrease in the sense of pleasure. As a result, the family doctor added citalopram to the therapy. During the first week of treatment, the patient was taking 10 mg/ day, followed by 20 mg/day. After increasing the dose, the patient developed gastrointestinal complaints, which he treated ineffectively with an easily digestible diet. The patient was not taking any other medications or dietary supplements. The doctor advised him to stop citalopram and take sertraline 50 mg/day instead. Modification of the antidepressant therapy resulted in relief of the symptoms.

## Discussion

Depression, an insidious and dangerous disease, is an often underestimated problem but may bring a lot of pain and suffering to a person's life. It is especially serious in elders, as they often struggle with many other age-related health problems, including somatic diseases and psychological issues, such as loneliness, longing, and a feeling of loss and passing. Considering a physiological aspects, there is a strong relationship between depression and cardiovascular disease in the elderly. Unfortunately, the link between CVDs and geriatric depression is still not entirely recognised; however, it is known that chronic diseases such as CVDs can affect the elderly's cognitive functions and self-assessment of health, and thus, lead to somatic dysfunction, which may be responsible for triggering and exacerbating the occurrence and development of depression in older individuals [6]. Patients with CVDs may suffer from depressive disorders more than the rest of the population. Moreover, individuals with depressive disorders have a greater risk to develop acute myocardial infarction, heart failure or stroke [11]. Depressive disorders have been found to be associated with a significant increase (60% to 80%) in the risk of coronary heart disease. Depression is a problem in almost 20% of patients with acute myocardial infarction and 40-63.4% hypertensive patients (63.4% in women and 36.6% in men). Depression symptoms are remarkably associated with an increased incidence of hypertension- depression is both a contributor to hypertension and may affect the outcomes and prognosis of this disease and the efficacy of drugs. Depression increases the risk of coronary artery disease by 1.5-2.0 times in healthy populations, whereas in patients with coronary artery disease, the risk of myocardial infarction is incre-

ased by 1.5-4.5 times due to depression. Cardiovascular diseases are characterised by a prolonged course and require long-term treatment, often accompanied by various complications, a decline in physical functions, financial problems, and increased dependence on other people, which may affect the psychological state and increase depression symptoms in the elderly. There are four factors suspected of being related to the impact of depression on CVDs in elders: impaired heart rate variability, chronic systemic inflammation, hypothalamic–pituitary–adrenal (HPA) axis dysfunction and endothelial dysfunction [6]. Depression also often occurs together with ischemic heart disease (IHD). In a meta-analytical study by Thombs et al., almost 20% of patients after acute myocardial infarction (AMI) were identified with major depression. Significant depressive symptoms based on a Beck Depression Inventory score > or =10 were present in 31.1% of subjects [12]. The prevalence of anxiety in the first week after percutaneous coronary intervention (PCI) ranges from around 25-37%; nevertheless, even around 67% of patients may suffer from depression after PCI. The first symptoms of depression appear between 48 and 72 hours after MI and usually disappear within 5 or 6 days in most patients. However, according to a study by Damen et al. describing intra-individual changes in depression and anxiety during the one-year follow up of patients after PCI, after 12 months, 81% of patients still had symptoms of depression, and 76% of patients still had symptoms of anxiety [13]. Another study by Damen et al. showed that depression increased the likelihood of death 1.6 – times in the long term horizon of 7 years after PCI [14]. Patients after myocardial infarction suffering from anxiety are at a higher risk of both adverse cardiac events and all-cause mortality. The first month after discharge from hospital for MI is critical as the risk of suicide due to depression is highest during this period, both for patients with a history of psychiatric disorders and those without one, but the suicide risk may remain higher even for few years after the MI [15]. The frequent coexistence of depression and heart disease has many culprits. The most likely ones could be unhealthy lifestyles, non-adherence to the treatment, seeking medical care too late, increased activation of the hypothalamic-pituitary-adrenal axis, increased activation of platelets, abnormal endothelial function, and many others [16].

Citalopram, a reasonably well-tolerated SSRI, is commonly prescribed for older people with neuropsychiatric diseases. The drug can cause adverse reactions in some people (up to 10% of patients), including more common drowsiness, insomnia, dizziness, headache; gastrointestinal reactions such as nausea, vomiting, xerostomia, constipation, diarrhea, but also diaphoresis, and problems with ejaculation. Adverse effects such as impotence, fatigue, somnolence, insomnia, sweating, yawning, and their severity may be directly correlated with the dose of CIT. More serious adverse effects can also appear, including cerebrovascular accidents, suicidal ideation, suicide (mostly in children, adolescents, and young adults <24 years old), induction of mania, serotonin syndrome, hemorrhage, and myocardial infarction torsades de pointes, and prolonged QT interval. Citalopram is, in general, considered a safe and tolerable drug. Klysner et al. aimed to evaluate the prophylactic efficacy and long-term tolerability of citalopram in a group of elderly patients (> or = 65 years) with depression. The study consisted of three periods: Period I (8 weeks of open, acute treatment with citalopram); Period II (16 weeks of open continuation treatment with citalopram to consolidate remission); Period III (double-blind treatment with citalopram or placebo for a potential minimum of 48 weeks). Some of the participants were given placebo and the others were taking citalopram, which dosage started from 10 mg/day for the first 3 days and over time, it was increased to 20, 30 or 40 mg/day (the dosage was maintained through the three periods of the study). The number of subjects entering the Period I was 230, but 109 participants remitted, which resulted in the number of 121 patients in the Period III (60 taking citalopram, 61 taking placebo). The most frequent adverse events (≥5%) reported during Period I were nausea, diarrhoea, headache, increased sweating, tremor, dizziness and fatigue. In the Period II the symptoms were similar, but with a reduced frequency. Weight gain/loss and sexual side-effects were rare. A total of 34 serious adverse events were reported in 28 patients and two deaths (one from oesophageal carcinoma and one for unknown reasons- in a placebo patient), but neither of these deaths nor the other serious adverse events were related to treatment with citalopram. Nineteen of the 60 patients using citalopram had a recurrence of depression, compared to 41 out of 61 on placebo. The researchers concluded that long-term treatment was well tolerated and effective in preventing recurrence of depression in older patients [17]. This drug has also been shown to induce hyponatremia, especially in elderly patients, but this is a rare effect of this medication [10]. The maximum dose of CIT is 40 mg daily. However, a

drug safety warning for citalopram, issued by the FDA in 2011, included a recommendation for a maximum daily dose of 20 mg in patients over 60 years. It emerged after the information about a dose-dependent increase in the QTc interval in older patients, but also in those with hepatic impairment, poor CYP2C19 metabolisers, and patients taking CYP2C19 inhibitors [18-19]. Considering the issue of adverse reactions of citalopram and escitalopram in the gastrointestinal tract, such as nausea, vomiting, and abdominal pain, are dose--dependent and higher for patients taking >40 mg/day of citalopram and >10 mg/day of escitalopram. The reasons should be sought in the complex, bidirectional relationship between the central nervous system (CNS) and enteric nervous system (ENS). Neurotransmitters and psychotropic drugs may act both on the brain and gut. Both CNS and ENS are regulated by the body serotonin (5-HT), which has a role in their development and the long-term functionality of sensory and motor functions. Serotonergic neurons have an essential role in physiological gastrointestinal motility. Nausea and vomiting are adverse reactions associated with many antidepressants. These symptoms may occur due to the increased availability of 5-HT in the gastrointestinal tract and central nervous system. The occurrence of abdominal pain may be related to motility disturbances, visceral and/or central hypersensitivity, altered mucosal immune function and dysregulation of the brain-gut axis. Oliva et al. summarised that out of 15 most used antidepressants (i.e., agomelatine, bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine, and vortioxetine), fourteen drugs were reported to cause higher rates short-term nausea and vomiting than placebo. When it comes to short-term abdominal pain, significantly higher rates compared to placebo were exerted by two out of 15 drugs, i.e. escitalopram and citalopram. In the study by Janssen et al., citalopram was shown to shorten the migrating motor complex (MMC) cycle length. MMC is a cyclic motility pattern of the smooth muscle layers that occurs during fasting in the stomach, small intestine or colon, programmed by the enteric nervous system and consisting of four phases. Intravenous administration of citalopram significantly shortened the MMC cycle length at the expense of phase I and phase II and increased the motility index during phase II in the antrum and the small intestine [20]. Interestingly, citalopram has been shown to have therapeutic effects in patients suffering from functional bowel disease. It can be explained by the fact that citalopram increases colonic contractility, reduces colonic tone during fasting conditions and narrows the colonic tone increase after meals [21]. Moreover, citalopram has been shown to reduce esophageal hypersensitivity, induce gastric relaxation, and alter gastric emptying, but also may have an impact in the pathogenesis of globus [22]. Although the adverse effects may discourage patients from continuing the therapy with citalopram, abrupt discontinuation of this drug may lead to the discontinuation syndrome. A sudden drug withdrawal may result in nausea, vomiting, diarrhea, headaches, light-headedness, dizziness, diminished appetite, sweating, chills, tremors, fatigue, somnolence, and sleep disturbances (most common); moreover, some patients may experience electric shock--like sensations, cardiac arrhythmias, myalgia, arthralgia, and balance difficulties. Considering the duration of the therapy and the half-life of this drug (as well as many other antidepressants), gradual withdrawal of the drug is recommended [10].

## Conclusion

Depression is a serious disease, reducing the patient's quality of life as it may lead to various functional somatic disorders and seriously affects the attitude of treatment in patients with diseases. Depression in older adults is undoubtedly a serious problem as it is more persistent than depression in younger individuals, often running a chronic, remitting course. Moreover, most elderly patients with depression are clinically undiagnosed and lack sufficient support from their relatives and the community. Depression in older people is often accompanied by cardiovascular disease (a two-way relationship), and these two, according to the data from the World Health Organization, are currently the most common causes of disability in high-income countries. Clinical depression is not a part of the normal ageing process and should not be disregarded as it contributes to a wide range of health problems (such as ischemic heart disease) and requires appropriate treatment. A selective serotonin reuptake inhibitor, citalopram, is FDA-approved for the treatment of depression in adults. The most adverse reactions to this antidepressant are drowsiness, insomnia, dizziness, headache, gastrointestinal reactions such as nausea, vomiting, xerostomia, constipation, diarrhea. Although the treatment with citalopram has some limitations (i.e. in patients over the age of 60 years and poor metabolisers of CYP2C19, the recommended maximum

daily dose is 20 mg), it is considered safe, well-tolerated and is efficacious for the treatment of depressive disorders in older patients. Early identification and rational intervention of depression would undoubtedly help to improve the quality of life, increase life expectancy, and lower medical costs in elders.

Conflict of interest
None

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