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Colloquium Vitae

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THE CORRELATION BETWEEN THE USE OF ESCITALOPRAM IN ELDERLY AND QT PROLONGATION

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ABSTRACT
To achieve the objective of verifying whether there is a correlation between the use of escitalopram in the elderly and QT prolongation, a search was carried out in Pubmed, Scielo and Lilacs. The selected studies were evaluated using the Newcastle-Ottawa scale to assesses study quality. The studies indicate that the link between escitalopram use and serious arrhythmia is weak despite FDA recommendations. The risk of arrhythmia and mortality associated with escitalopram also decreased over time. Cardiac comorbidities increase the risk of QT prolongation and mortality, and modifiable risk factors like hypokalemia and drug interactions should be addressed in at-risk individuals. Healthcare providers face a difficult decision regarding dosage restrictions and medication switching, taking into account escitalopram's effectiveness and tolerability. More research and awareness are needed to optimize antidepressant therapy for cardiac safety.
Keywords: Escitalopram, QT prolongation, arrhythmia, elderly

A CORRELAÇÃO ENTRE O USO DE ESCITALOPRAM EM IDOSOS E O PROLONGAMENTO DO INTERVALO QT.

RESUMO
Para atingir o objetivo de verificar se existe correlação entre o uso de escitalopram em idosos e o prolongamento do intervalo QT, foi realizada uma busca no Pubmed, Scielo e Lilacs. Os estudos selecionados foram avaliados pela escala de Newcastle-Ottawa para avaliar a qualidade do estudo. Os estudos indicam que a ligação entre o uso de escitalopram e arritmia grave é fraca, apesar das recomendações da FDA. O risco de arritmia e mortalidade associada ao escitalopram também diminuiu com o tempo. As comorbidades cardíacas aumentam o risco de prolongamento do intervalo QT e mortalidade, e fatores de risco modificáveis, como hipocalemia e interações medicamentosas, devem ser evitados indivíduos em risco. Os profissionais de saúde enfrentam uma decisão difícil em relação a restrições de dosagem e troca de medicamentos, levando em consideração a eficácia e a tolerabilidade do escitalopram. Mais pesquisas são necessárias para otimizar a terapia antidepressiva e segurança cardíaca.
Palavras-chave: Escitalopram, Prolongação do intervalo QT, arritmia, idosos.

INTRODUCTION

Escitalopram is the active (S)-enantiomer of the antidepressant citalopram, which is a selective serotonin reuptake inhibitor (SSRI)[1]. It is effective in treating major depressive disorder (MDD) and may have a faster therapeutic effect compared to citalopram. Generally, it is well tolerated, although nausea is a common side effect[2].

The inhibition of potassium currents (IKs, IKr, IK1, and/or Ito) by certain drugs can delay repolarization, prolong the QT interval, and increase the risk of Torsades de Pointes (TdP). The most common cause of acquired Long QT Syndrome (LQTS) and TdP is the interference with IKr by various medications such as antiarrhythmics, antibiotics, antivirals, azole antifungals, antimalarials, anticancer drugs, antiemetics, prokinetics, antipsychotics, and antidepressants[3].

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Certain psychotropic medications, especially in individuals with medical conditions, have been associated with QT interval prolongation[4].

There is a reported case of a female patient who experienced QTc prolongation after taking a low dose (5 mg/day) of escitalopram for two days. The QTc interval returned to normal shortly after discontinuing the medication. Healthcare providers should exercise caution regarding the cardiac effects of SSRIs, even at low doses[5]. Regarding overdose, there have been only three previously documented cases in the literature of escitalopram overdose leading to QTc interval prolongation[6].

A population pharmacokinetic/pharmacodynamic linear study established a model that accurately characterized the QT prolongation induced by escitalopram. The average estimated maximal QT prolongation was 5.4 ms (range: 1.9-7.6 ms). The equilibrium half-life of delayed QT prolongation was 1.9 hours[7]. Another linear mixed-effect model study indicated a weak but positive relationship between escitalopram concentration and dQT, with an estimated concentration coefficient of 0.43-0.54[8].

A study investigated reports of QT interval prolongation associated with SSRIs in two pharmacovigilance databases. Among these reports, 172 (20.1%) were associated with escitalopram, while 299 (35.0%) were associated with citalopram[9]. This association was more pronounced in elderly individuals, females, patients with conduction disorders, hemodialysis patients, and those receiving other non-SSRI medications that prolong the QT interval[10].

Although citalopram shows a greater magnitude of QTc prolongation compared to escitalopram, the correlation between dose and QTc prolongation is similar for both drugs. While warnings have been issued by the U.S. Food and Drug Administration and Health Canada only for citalopram, the Medicines and Healthcare Products Regulatory Agency in the United Kingdom has issued safety warnings for both citalopram and escitalopram[11].

Despite this, there is still a high occurrence of hospital prescriptions including citalopram or escitalopram with other QT-prolonging drugs, emphasizing the importance of involving clinical pharmacists in preventing potential adverse drug reactions related to such contraindications[12]. So, to achieve the objective of verifying whether there is a correlation between the use of escitalopram in the elderly and QT prolongation, this integrative review was carried out.

METHODOLOGY

The research is a integrative review carried out in May 2023. The following databases were used: Pubmed, Scielo and Lilacs. The keywords searched were: ("escitalopram") AND (" QT prolongation" OR "arrhythmia") AND ("older adults" OR "elderly") in Portuguese, English and Spanish.

The selected surveys were consistent with the PICO question proposed for the study:

- Population: Older adults, age > 65 years
- Intervention: Use of escitalopram.
- Comparison: Do not use of escitalopram
- Outcomes: Development of arrhythmias, sudden death or changes in the Qt interval.

Only cohort studies were included and there was no limitation regarding the date of publication of the articles.

From the search for keywords, 5 results were found in Pubmed and after analyzing the title and abstracts, 2 articles were excluded because they were not cohort studies and were not consistent with the PICO question. As for Scielo the searches found no results and only one study from Lilacs was included.

The Newcastle-Ottawa scale was used to examine every study that was included. Eight items are included in NOS, which are divided into three categories: outcome, comparability, and selection. A number of response alternatives are offered for each issue. A star system is employed to provide a semi-quantitative evaluation of study quality, with the exception of the comparability item, which permits the assignment of two stars, the highest quality studies receiving a maximum of one star for each item. The NOS has a star rating from 0 to 9[13].

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RESULTS

Table 1. Basic informations about included studies

Authorship and year	Country	Periodic	Data source
Fung et al. (2021)	United States	Drugs Real World Outcomes	Medicare
Aakjaer et al. (2022)	Denmark	Clinical and Translational Science	Danish healthcare register data
Qirjazi et al.(2016)	Canada	PLoS One	Ontario Drug Benefit database
Crépeau-Gendrona et al. (2019)	Canada	Journal of Affective Disorders	

Table 2. Summaery of included studies

Title	Methodology	Results
Using Medicare Data to Assess the Proarrhythmic Risk of Non-CardiacTreatment Drugs that Prolong the QT Interval in Older Adults: An Observational Cohort Study	The study involved 1.2 million Medicare beneficiaries who were using 17 arrhythmic drugs. Among the beneficiaries, a total of 65,142 individuals were using escitalopram. Cox regressions were conducted to analyze the effects of use of these drugs. The primary outcome measured was a combination of ventricular arrhythmias and/or sudden death, identified using ICD diagnostic codes	Users of escitalopram had a 31% higher risk compared to former users (HR 1.31; 95% CI 1.28–1.35), a 21% higher risk compared to current users of SNRIs (HR 1.21; 95% CI 1.18–1.23), and an 18% higher risk compared to individuals who had never used these drugs (HR 1.18; 95% CI 1.16–1.20). However, the increased risk associated with escitalopram decreased from 34% to 4% when compared to individuals who had never used the drug, after more than 12 months of cumulative use. Additionally, a direct comparison between current users of citalopram and escitalopram showed that citalopram was safer, with a 13% lower risk (HR 0.87; 95% CI 0.86–0.89).
Serious arrhythmia in initiators of citalopram, escitalopram, and other selective serotonin reuptake inhibitors: A population-based cohort study in older adults	The study used the Danish healthcare register data from 2002 to 2016. The outcome measured was the occurrence of serious arrhythmia. Risk ratios (RRs) and 95% confidence intervals (CIs) were estimated using log-binomial regression analyses. The study included 146,014 individuals for citalopram, 37,069 individuals for escitalopram, and 44,754 individuals for other SSRIs.	No significantly increased risks of serious arrhythmia were observed during the study period for either citalopram (RR 0.87 [0.62–1.22]) or escitalopram (RR 0.86 [0.53–1.40]) when compared to other SSRIs. The study also showed that reported cases of arrhythmias decreased after FDA warning.
Risk of ventricular arrhythmia with citalopram and	This population-based retrospective cohort study conducted in Ontario, Canada, from 2002 to 2012 included older adults who were newly	Escitalopram was not found to be associated with a higher risk of ventricular arrhythmia compared to the referent antidepressants. The incidence of

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escitalopram: a population-based study	prescribed either citalopram or escitalopram, compared to those prescribed referent antidepressants sertraline or paroxetine. The study included a total of 137,701 individuals prescribed citalopram, 38,436 individuals prescribed escitalopram, and 96,620 individuals prescribed referent antidepressants.	ventricular arrhythmia within 90 days of a new prescription was 0.03% for escitalopram and 0.04% for referent antidepressants, with a risk ratio (RR) of 0.84 and a 95% confidence interval (CI) of 0.42 to 1.68. However, escitalopram was associated with a higher risk of mortality within 90 days, with an incidence of 2.86% compared to 2.63% for referent antidepressants, resulting in a RR of 1.09 and a 95% CI of 1.01 to 1.18. Among those with congestive heart failure who were prescribed escitalopram, the RR of ventricular arrhythmia was 2.53 (95% CI 0.96 to 6.67), while for those without congestive heart failure, the RR was 0.47 (95% CI 0.18 to 1.21).
Association between citalopram, escitalopram and QTc prolongation in a real-world geriatric setting.	The research examined the electronic health records of a geriatric healthcare center associated with a university. The study spanned seven years and focused on patients who were prescribed citalopram or escitalopram. The analysis specifically looked at patients who received an electrocardiogram (ECG) within 24 hours to 90 days after starting these medications or those who were already taking the medication and experienced a change in dosage (citalopram=97, escitalopram=40) The researchers used linear regression analyses to investigate the connection between the dosage of antidepressants and the QTc interval..	The researchers conducted both univariable and multivariable regression analyses and no association was documented. They combined the analysis of citalopram and escitalopram as a single predicto and excluded subjects who had an electrocardiogram (ECG) within 7 days of starting and it did not impact the results. Among the factors taken into account, age showed a significant association with QTc in the escitalopram group during univariable analyses and multivariable regression analyses. The study did not document any cases of Torsades de Pointes (TdP).

Table 3. Information about included studies:

Authorship and year	Follow-up time	Age mean	Women percentage
Fung et al. (2021)	12 months	65.0	58.5%
Aakjaer et al. (2022)	Maximum of 6 months in (prescription with a 1-year washout period before the index date)	Not disponible but 42% were 65–74 years	63.66%
Qirjazi et al.(2016)	6 years	76	63.0%
Crépeau-Gendrona et al. (2019)	24 hours to 90 days	81.2	62.5%

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Newcastle-Ottawa for study 1:

Selection criteria	
Cohort Representativity	☆ – Medicare include people who have contributed to the system for at least 10 years, are over 65 and live permanently in the United States.
Selection criteria	☆ Controls and exposed are in same source
Determination of the exposition	☆ The source is considered safe
Outcome not present at baseline	☆
Comparability criteria	
Chort comparability based on study design and analysis	☆☆ Study controlled by more than one factor
Outcome criteria	
Determination of the outcome	☆ Evaluation by record
Follow-up was sufficient for the occurrence of outcomes	☆
Adequacy of follow-up	☆ Complete follow-up
Total: 9 stars	

Newcastle-Ottawa for study 2:

Selection criteria	
Cohort Representativity	☆ – Data is collected in national health danish registers
Selection criteria	☆ Controls and exposed are in same source
Determination of the exposition	☆ The source is considered safe
Outcome not present at baseline	☆
Comparability criteria	
Chort comparability based on study design and analysis	☆ Study controlled by one factor
Outcome criteria	
Determination of the outcome	☆ Evaluation by record
Follow-up was sufficient for the occurrence of outcomes	☆
Adequacy of follow-up	☆ Complete follow-up
Total: 8 stars	

Newcastle-Ottawa for study 3:

Selection criteria	
Cohort Representativity	☆ – Ontario Drug Benefit database contains highly accurate records for outpatient prescriptions dispensed to patients aged 65 years or older (error rate less than 1%)
Selection criteria	☆ Controls and exposed are in same source
Determination of the exposition	☆ The source is considered safe
Outcome not present at baseline	☆
Comparability criteria	
Chort comparability based on study design and analysis	☆☆ Study controlled by more than one factor
Outcome criteria	
Determination of the outcome	☆ Evaluation by record
Follow-up was sufficient for the occurrence of outcomes	☆

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Adequacy of follow-up	☆ Complete follow-up
Total: 9 stars	

Newcastle-Ottawa for study 4:

Selection criteria	
Cohort Representativity	The small sample sizes makes this cohort representative only to its geriatric center
Selection criteria	☆ Controls and exposed are in same source
Determination of the exposition	☆ The exposition is registred
Outcome not present at baseline	The study include patients who had prescribed dosage change.
Comparability criteria	
Cohort comparability based on study design and analysis	☆ Study controlled by one factor
Outcome criteria	
Determination of the outcome	☆ Evaluation by record
Follow-up was sufficient for the occurrence of outcomes	☆ No outcome happend. The follow-up time was 24 hours to 90 days, a reduced number compared to other studies.
Adequacy of follow-up	☆ Complete follow-up
Total: 6 stars	

DISCUSSION

The FDA issued a warning in August 2011 and March 2012, advising that individuals over the age of 60 should not exceed a maximum dosage of 20 mg of citalopram. This warning was prompted by concerns of corrected-QT (QTc) prolongation on electrocardiogram (ECG), which is a risk factor for the potentially fatal arrhythmia torsades de pointes[14]. In addition, cause escitalopram is a (S)-enantiomer of the citalopram, concern arose that it might also cause QT prolongation.

Although, these recommendations were based on data from Forest Laboratories, involving healthy volunteers aged 19-45. The study demonstrated QTc changes but no adverse cardiac outcomes[15].

Due to their effectiveness and tolerability, citalopram and escitalopram are frequently prescribed to adult and elderly patients. This poses a difficult decision for healthcare providers: whether to adhere to the dosage restrictions advised by health regulations or to switch medications, which could potentially disrupt patients who have been effectively treated with therapeutic doses of these antidepressants[2].

A study conducted in Denmark found no connection between the use of escitalopram and serious arrhythmia. Additionally, the study observed a decrease in the overall usage of citalopram and escitalopram, which could be attributed to the warnings issued in 2011. The study revealed higher estimates of serious arrhythmia prior to the warning, followed by lower estimates after the warnings. This outcome may be attributed to prescribers being more cautious regarding cardiovascular risk among patients after the warning[16].

These findings align with the limited number of reported adverse reactions found in Vigimed. From 2018 to 2021, only two cases of arrhythmia associated with escitalopram use were reported on the website[17]. However, there is a suspicion of underreporting due to the significantly lower notification rate per million inhabitants per year in Brazil compared to middle and high-income countries. One possible explanation for this phenomenon is the lack of awareness about this tool[18].

Another study conducted in Canada discovered that initiating citalopram was linked to a slight 90-day risk of ventricular arrhythmia (0.03%) as well as a small risk of death. The potential increase in arrhythmia risk may have contributed to the observed slightly elevated 90-day mortality risk[19].

A similar pattern of an increased risk of arrhythmic events during the initial months followed by a decrease over time was also observed in another study. This risk decreased from 34% to 4% after more than 12 months of cumulative use. This study is the only one that compared individuals who had never used the drug, revealing an 18% increased risk[20].

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Furthermore, the higher association between 90-day all-cause mortality and increased ventricular arrhythmia risk in the subgroup with congestive heart failure in canadian study demonstrates that existing cardiac comorbidities amplify QT prolongation[21].

Risk factors for drug-induced TdP (Torsades de Pointes) and QT prolongation include hypokalemia, female sex, drug-drug interactions, advancing age, genetic predisposition, hypomagnesemia, heart failure, and bradycardia[22]. A small study indicated that age exhibited a significant association with QTc (corrected QT interval) in the escitalopram group during both univariable and multivariable regression analyses, despite no overall association being documented. Moreover, cardiac comorbidities tend to increase with age[14,23].

Many risk factors, such as hypokalemia and drug interactions, are potentially modifiable and should be addressed in individuals at risk of QT interval prolongation. It is advisable to avoid combining these risk factors with escitalopram or citalopram[22].

CONCLUSION

The studies found a low connection between the use of escitalopram and serious arrhythmia, suggesting a potential overestimation of risk. The overall usage of citalopram and escitalopram decreased after the warnings, possibly due to increased caution among prescribers. Also, the slight risk of arrhythmia and mortality associated with edcitalopram initiation decreased over time. Cardiac comorbidities were found to amplify the risk of QT prolongation and mortality. Various modifiable risk factors, such as hypokalemia and drug interactions, should be addressed in individuals at risk of QT interval prolongation. Considering these findings, healthcare providers face a challenging decision of whether to adhere to dosage restrictions or switch medications according to FDA, considering the effectiveness and tolerability of escitalopram in treating patients. Further research and awareness are needed to better understand the true risks and optimize the management of antidepressant therapy in relation to cardiac safety.

CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest that could interfere with the impartiality of this scientific work.

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