ADVERSE CARDIAC EVENTS AMONG OLDER ONTARIO PATIENTS ON VENLAFAXINE: A POPULATION-BASED STUDY

By

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A thesis submitted in conformity with the requirements for the degree of Masters of Science, the Institute for Health Policy, Management and Evaluation, University of Toronto

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1 ABSTRACT

Adverse Cardiac Events Among Older Patients on Venlafaxine: A Population-Based Study
Masters of Science 2015
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Background: It is unknown whether the common antidepressant, venlafaxine, is associated with increased cardiovascular risk.

Objective: To examine the cardiac safety of venlafaxine in older individuals.

Methods: A population-based retrospective cohort study (Ontario, Canada) compared patients aged ≥66 years who commenced treatment with venlafaxine, sertraline or citalopram between 2000 and 2009. The primary outcome was a composite of death or hospitalization for myocardial infarction or heart failure within the first year of therapy.

Results: Following inverse probability of treatment weighting with the propensity score, we found no difference in the primary outcome with venlafaxine relative to sertraline (hazard ratio (HR) 0.97; 95% confidence interval (CI) 0.93 to 1.02). When compared to citalopram, however, an increased risk was observed (HR 1.39; 95% CI 1.19 to 1.62).

Conclusions: As compared with sertraline, venlafaxine was not associated with an increased risk of adverse cardiac events. The increased risk observed in the venlafaxine–citalopram comparison warrants further study.
2 ACKNOWLEDGEMENTS

I would like to thank and acknowledge the following people:

I would like to thank my supervisor, Dr. David Juurlink, for all his guidance, support and patience. In particular, I would like to thank him for allowing me to explore my own research questions (to find that “fire in the belly”) and to pitch them during “Research Dragon’s Den.” Those countless hours spent appraising my research questions taught me the importance of developing meaningful research projects with rigorous methodology. I also thank him for his thoughtful feedback during the writing process and for challenging me to communicate clearly and concisely.

I would like to thank my committee. I thank Dr. Peter Austin for always being available to discuss any methodological detail, Dr. Muhammad Mamdani for helping me with project design and troubleshooting; and Dr. Sharon Straus for her tremendous support and guidance in all aspects of research life.

Many thanks to Ms. Tara Gomes. I sincerely appreciate her abundance of teaching, patience and kindness during this entire process.

I would like to thank Mr. Ashif Kachra, Ms. Karen Hood and Ms. Karen Arbour for administrative support and Ms. Chelsea Hellings for project coordination.

Thank you to the ICES Systems department, particularly Mr. Jesse Stamplecoski and Mr. Jackson Wong for their patience.

Thank you to Minnie for being the most supportive Sister. You were always available to answer questions about epidemiology, or to provide me with precious desk space in your office or nourishment.
Finally, thank you to my Husband, Michael, for his endless patience, support and encouragement, and to my Daughters, Emily and Matilda, both born during this thesis.
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4 BACKGROUND AND RATIONALE

4.1. Background

4.1.1 Depression: Definition and Epidemiology

Depression, or Major Depressive Disorder, is defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (1) as at least two weeks of depressed mood or markedly diminished pleasure that results in a change from previous functioning. This is also accompanied by at least four of the following: changes in appetite or sleep, decreased energy, interest or concentration, feelings of guilt, or psychomotor agitation or retardation. (1) Depression is common, with a lifetime prevalence of 12-16% in North America. (2) Among patients with cardiovascular disease, the prevalence may be as high as 30%. (3-5) Independently associated with morbidity and mortality, (6,7) impaired quality of life and occupational function, depression is one of the main causes of disability worldwide. (2,8-10) By affecting adherence to medication or a healthy lifestyle, depression also impairs a patient’s ability to manage their other chronic diseases. (11,12) A cross-sectional study of diabetic patients with depressive symptoms from 2 primary care clinics in Washington state, United States, found an association between depressive symptom severity and health care utilization. (11) Health care costs of patients with moderate and severe depression were 51% to 85% higher compared to those with low severity depression. (11) The National Health Service in the United Kingdom found that the direct costs of treating depression (£887 million)
exceeded the combined cost of treating hypertension (£439 million) and diabetes (£300 million). (13) Furthermore, the indirect costs of missing work due to depression are substantial to the patient and general economy. (13) As a result, depression impacts millions of people worldwide on individual and societal levels.

4.1.2 Depression: Management

Depression can be treated with nonpharmacological or pharmacological therapy. (14)

4.1.2.1 Depression: Nonpharmacological Therapy

Nonpharmacological therapy includes neurostimulation and psychotherapy and can be administered alone or in combination with pharmacologic therapy. Neurostimulation involves the delivery of either electric or magnetic interventions to the brain. It includes electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation, vagus nerve stimulation and deep brain stimulation. (15) The Canadian Network for Mood and Anxiety Treatment recommends ECT as first line therapy for patients with depression and concomitant psychosis or acute suicidal ideation; or treatment-resistant depression. (15) ECT is effective with response rates of 50-90% among adults (16,17) and is generally regarded as safe. However, the risk of adverse cardiac or cognitive events is higher among patients with pre-existing cardiovascular disease and advanced age (≥65 years) respectively. (18-20)

Psychotherapy requires the establishment of a patient-therapist relationship and can be administered in individual and group settings, alone and in combination with
medication.(14) Psychotherapy (specifically, interpersonal therapy and cognitive
behavioural therapy) for major depressive disorder, has been shown to have equivalent
efficacy to pharmacotherapy and is not associated with adverse drug effects.(14,21) Its
ability to prevent recurrence alone compared to antidepressant therapy however, is
unclear due to heterogeneous results from randomized clinical trials (RCTs).(22-25)
These RCTs often compared psychotherapy with the selective serotonin reuptake
inhibitors (SSRIs), fluoxetine or paroxetine.(22-25) Psychotherapy was equivalent to
pharmacotherapy in preventing recurrence of depression in RCTs that included younger
adults and had experienced practitioners administering psychotherapy.(22-25) Because
psychotherapy alone has a longer time lag effect,(21) it is not recommended in
depressed patients with severe suicidality or psychotic symptoms.(14) Furthermore,
patients often do not seek psychotherapy due to financial cost and depression-
associated “psychological barriers.”(26)

4.1.2.2 Depression: Pharmacological Therapy

Although nonpharmacological treatments are available, medication remains a
common element of therapy for many patients. With a prescription rate exceeding one
prescription for every 10 persons in the United States per year between 2005 and 2008,
antidepressants are used by tens of millions of people every day.(27,28) A population-
based time series analysis of older Ontario adults found an increased prevalence of
antidepressant use from 5.5% in 1993 to 10.9% in 2002.(29) Antidepressants for older
Ontario individuals accounted for 42% of mental health disease medication costs which
totaled $149.4 million in 2002.(29)
Second Generation Antidepressants

Among the various drug treatment options for depression, second generation antidepressants are the most widely prescribed in North America.(27) These include selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRI), and other drugs such as bupropion, mirtazapine and trazodone. Over the past decades, antidepressant prescriptions for older individuals shifted away from first generation antidepressants, such as tricyclic antidepressants and monoamine oxidase inhibitors, towards second generation antidepressants.(29) Potential benefits of this shift in practice among older adults include a lower risk of anticholinergic-mediated adverse events, such as cognitive impairment and falls.(30) This would be achieved through the avoidance of tricyclic antidepressants which possess anticholinergic activity. In addition, monoamine oxidase inhibitors further heighten the increased risk of drug-drug interactions faced by older adults.(29,30) The risks of this shift include a significant cost increase of at least 61% in drug expenditures.(29)

Efficacy

Antidepressant efficacy is conventionally measured with depression rating scales. Depression rating scales can be used to diagnose depression, quantify severity, or assess changes over time, including the response to treatment.(31) There are many validated scales used in research, but the two most commonly used are the observer-rated Hamilton Depression Rating Scale (HDRS) (31,32) and Montgomery Åsberg Depression Rating Scale (MADRS).(31,33) The original 17-item HDRS is widely used in clinical research and practice.(2,31,34) Scores of 0-7, 8-12, 13-17 and ≥18 indicated
normal, mild depression, less than major depression and major depression, respectively. (32) Limitations of this scale include its bias towards somatic, behavioural and anxiety symptoms, and its lack of generalizability across different populations, particularly the older population. (31) The Montgomery-Åsberg Depression Rating Scale (MADRS) is also observer-rated and consists of 10-items. (33) Scores of 0-6, 7-19, 20-34, and ≥35 indicate no symptoms, and mild, moderate and severe depression respectively. It was derived from a heterogeneous pool of depressed patients who were enrolled in RCTs of amitriptyline, clomipramine, mianserin and maprotiline. (31) Compared to the HDRS, the MADRS may be more sensitive to change and does not measure somatic symptoms. (33) Conventionally, response to therapy is defined as a score reduction of ≥50%, while remission is achieved when scores fall within the pre-defined normal ranges. (2,31)

Comparative effectiveness studies have found no difference in efficacy among medication classes in the treatment of depression although up to 30% of patients do not respond to these medications. (14) Patients enrolled in explanatory randomized controlled trials are often different from real-world patients (35-38) and suffer from more severe depression (HDRS score>20). (37) Therefore, the effectiveness, or benefit observed in the real-world, of antidepressant therapy among the general population is unclear.

*Risks of Second Generation Antidepressants*

Although second generation antidepressants as a class do not possess anticholinergic effects, which are undesirable for the older population, (39) they may
cause other adverse effects. (40-42) With the prevalent use of these medications, (25-26) it is important for health care professionals to understand the adverse effect profile and properly inform patients.

Second-generation antidepressants are associated with adverse gastrointestinal, central nervous system, metabolic and cardiovascular effects, and an increased risk of fragility fractures. (43,44,45,46) Gastrointestinal treatment-emergent adverse effects include nausea, vomiting and diarrhea. A range of central nervous system adverse effects associated with second-generation antidepressants include sedation, headaches, nervousness and agitation. (43) Unlike other SSRIs, paroxetine possesses anticholinergic properties, which may manifest as cognitive impairment among older individuals. (43) Metabolic effects of SSRIs include hyponatremia, and although this generation of antidepressants is generally ‘weight neutral,” paroxetine, an SSRI, is associated with weight gain. (43) An increase in upper gastrointestinal bleeding due to the inhibition of serotonergic-mediated platelet adhesion has been observed among patients on non-steroidal anti-inflammatory drugs and concomitant antidepressants that affect serotonin. (43) Sexual dysfunction is common, affecting up to 50% of patients on second generation antidepressants but may occur more frequently given that it is often underreported. (43) Patients on SSRIs, particularly fluoxetine and paroxetine, are more likely than those on SNRIs to experience sexual dysfunction. (43) The risk of fragility fractures has been found to be increased among patients on second generation antidepressants. (45) Mechanisms for this adverse event include decreased bone density, and impaired sleep quality thereby increasing fall risk. (45) Finally, the safety
profiles of individual second generation antidepressants may differ, particularly with regard to cardiovascular safety. (44)

**Cardiac Safety of Second Generation Antidepressants**

Depression is common among patients with cardiovascular disease. (2-4) Left untreated, it can affect an individual’s ability to manage their chronic cardiovascular disease thereby increasing morbidity and mortality. (6,11,12) With the popularity of pharmacologic therapy, (25,26) it is important to determine whether antidepressants might exacerbate cardiovascular disease.

Our literature review of the risk of cardiovascular events among adults using second generation antidepressants found 5 randomized controlled trials, 6 observational studies, 5 case reports and 1 case series of 248 patients with toxic ingestions of venlafaxine.

The cardiac safety of second generation antidepressants has been the focus of two clinical trials. (47,48) A randomized controlled trial of 44 outpatients sought to investigate venlafaxine’s effect on heart rate variability. The authors measured ex vivo drug levels and noradrenaline receptor activity, and symptoms of depression and anxiety and demonstrated that patients on venlafaxine exhibited decreased variation in respiratory sinus arrhythmia during paced breathing compared to those on paroxetine. (47) The SADHEART study was a randomized, double-blind, placebo-controlled trial of sertraline in patients with depression who were recently hospitalized for acute coronary syndrome. (48) The authors did not find a difference in adverse cardiac events among the sertraline-treated group. (48) A small nonrandomized
controlled study comparing paroxetine, sertraline and venlafaxine among patients suffering from post-traumatic stress disorder found a higher rate of side effects such as palpitations and subsequent drop-outs among those on venlafaxine. (49) A telephone survey-based case-control study investigated the risk of myocardial infarction among individuals on high serotonin transporter affinity antidepressants compared to those on antidepressants with low and moderate serotonin transporter affinities or no antidepressants. (50) They found a decreased risk of myocardial infarction among patients on antidepressants with high serotonin transporter affinity. This attenuated risk may be due to SSRI-mediated depletion of serotonin stores which may cause decreased platelet adhesion and aggregation, a component of coronary artery thrombosis, and increased release of endothelial nitric oxide. (39) This latter effect causes vasodilation, which is cardioprotective. (39) It should be noted, however, that this study’s participants were relatively young (mean age 51 years with a standard deviation of 9 years), had no history of cardiovascular disease and were not necessarily new users of their antidepressants. (50) Although an observational study by Johnson et al. found an increase in adverse cardiac effects such as increased heart rate and blood pressure among older community-dwelling patients with depression on venlafaxine, there were no cases of myocardial infarction or heart failure. This study, however, had a small sample size thereby limiting its statistical power to detect differences in such cardiac events. (51) To date, there have been no population-based studies specifically comparing the cardiac toxicity of the commonly prescribed antidepressants,
venlafaxine, sertraline or citalopram, and providing further insight into the safety of these drugs among older patients with cardiovascular disease.(52)

With the higher background prevalence of cardiac disease and depression among older patients, a causal association with a medication would be difficult to delineate. Nevertheless, given the millions of antidepressants dispensed annually, any safety differences would be important to establish.(27,28)

4.1.3 Generalizability of Clinical Trial Results to the Real-World Patient

Generalizability, or external validity, is the extent to which study results can be applied to real-world patients. Clinical trials, particularly randomized controlled trials, are necessary to establish drug efficacy.(38) While pragmatic randomized controlled trials attempt to study a drug’s efficacy in the real-world setting, only 10% of randomized controlled trials are of this nature.(53) The majority are explanatory randomized controlled trials which maximize internal validity through the careful selection of trial participants.(35,38,53) In explanatory trials, individuals are subjected to stringent inclusion and exclusion criteria to minimize confounding variables or adverse events; or to maximize the effect size given a limited sample size.(37) Consequently, these explanatory trial patients differ from real-world patients in the setting where they receive treatment, overall medical profile, and degree of monitoring from health care professionals.(38,54) Real-world patients tend to be managed in nonacademic settings, to have advanced age and multi-morbidity; and are often not monitored as closely.(35)
Patients with more comorbidities and increased age are often excluded from explanatory RCTs but not in real-world practice, and these patients are at increased risk of adverse drug events. Comorbidities may result in altered pharmacodynamics, pharmacokinetics and increase the risk for drug-drug and drug-disease interactions. For example, patients with impaired kidney function have a reduced ability to clear renally-excreted drugs, leading to increased serum drug levels and the risk of adverse drug events. Furthermore, normal aging is accompanied by a decrease in renal function thereby predisposing older patients to adverse drug events. Clinical trials that exclude patients with comorbidities and advanced age cannot provide health care professionals with comprehensive drug safety information.

The issue of generalizability has been investigated in a number of areas of medicine including the treatment of depression. Zimmerman and his coauthors applied commonly used trial eligibility criteria to psychiatric outpatients diagnosed with unipolar depression without psychosis. The majority of antidepressant trials excluded patients with less severe depression on the HDRS (score ≤20; score ≥18 indicates severe/major depression), significant suicidality, recent substance or ethanol abuse, and a comorbid psychiatric illness. Of the 599 real-world patients, only 123 (20.5%) would have been included in an antidepressant explanatory clinical trial.

Finally, the cost associated with randomized controlled trials may hinder the ability to have large sample sizes or longer observation times. These trials may be adequately powered to investigate drug efficacy, yet underpowered to detect
uncommon but clinically significant adverse drug events, particularly those that develop after prolonged exposure. Clinicians should be aware of the limitations of available clinical trials when considering pharmacotherapy in the treatment of depression.

4.1.4 Observational Studies

In observational studies, scientists observe the effect of an exposure on a study population. Population-based observational studies include real-world patients and frequently have the added advantage of a large sample size and the potential for a longer observation window. This provides adequate statistical power to characterize uncommon, but clinically significant events, and to detect adverse events which develop with accumulated exposure. This methodology allows one to investigate the risk of adverse events associated with drugs administered in the real-world setting. By complementing randomized controlled trials, population-based studies are powerful tools in post-marketing surveillance of medications.
4.2 Venlafaxine

Venlafaxine was first introduced in 1994 by Wyeth® Pharmaceuticals, and since then has been used by tens of thousands of Ontario residents every year. It is thought to alleviate depression by inhibiting serotonin and noradrenaline reuptake and is in the same SNRI class as duloxetine.

4.2.1 Clinical Use

Since its introduction, venlafaxine has been widely used in the treatment of psychiatric and pain disorders, and hot flashes. Venlafaxine is effective in the treatment of major depressive disorder and a recent systematic review found it to have similar benefits to SSRIs. The Canadian Network for Mood and Anxiety Treatment (CANMAT) and American Psychiatric Association guidelines both identify venlafaxine as a first-line agent for the treatment of depression. Although the benefit of venlafaxine in the treatment of bipolar disease, attention deficit hyperactive disorder and concomitant depression is less clear, it is still used to treat these disorders.

Venlafaxine’s serotonergic and noradrenergic effects have been hypothesized to provide relief to patients suffering from neuropathic pain, particularly diabetic neuropathy, a population with a high prevalence of depression. Finally, venlafaxine has been used in the symptom management of hot flashes, particularly in women undergoing breast cancer treatment. Patients with psychiatric disease and neuropathy are at increased risk for heart disease; and concomitant psychiatric disease affects chronic disease management, thereby increasing cardiovascular morbidity and mortality. As a result, it would be important to understand venlafaxine’s
cardiovascular safety profile since it is frequently prescribed to patients predisposed to adverse cardiac events.

4.2.2 Pharmacokinetics and Pharmacodynamics

4.2.2.1 Pharmacokinetics

Venlafaxine is available in immediate release (IR) and extended release (ER) formulations and is administered orally at doses of 37.5 to 375 mg per day. Although pharmacokinetic studies describe a slower rate of absorption of the ER formulation compared to the IR formulation, the amount of drug absorbed is equivalent. (40) Venlafaxine IR and ER preparations are well absorbed with peak plasma drug levels achieved within 2 and 6 hours respectively, (40,73) but due to significant first pass metabolism, its bioavailability is moderate at approximately 45%. (74) Venlafaxine is metabolized in the human liver into 3 metabolites-O-desmethylvenlafaxine (ODV), N-desmethylvenlafaxine and N,O-desmethylvenlafaxine. The main metabolite, ODV, is formed by the hepatic enzyme cytochrome p450 (CYP) 2D6 and has similar in vitro serotonergic, noradrenergic and dopaminergic activity as the parent compound. (40) Patients may have one of four phenotypes of CYP 2D6 metabolizing phenotypes: poor (little or no 2D6 activity), intermediate (between poor and extensive), extensive (normal activity) and ultrarapid (more than normal). Therefore patients with poor, intermediate, extensive and ultrarapid CYP2D6 phenotypes have low, low-normal, normal and high ratios of ODV/venlafaxine respectively. (75) It is unclear, however, whether these different ratios of ODV/venlafaxine translate to
significant clinical outcomes. A pooled analysis of four RCTs found that extensive metabolizers had greater improvements in their depressive symptoms while on venlafaxine compared to poor metabolizers.\(^{(75)}\) They did not find any difference in the rate of adverse effects. Whyte \textit{et al}. examined the effect of 2D6 phenotype among 46 older adults with depression while on venlafaxine.\(^{(76)}\) They did not find a difference in depressive symptoms, or adverse effects (total or cardiac), among those with poor or intermediate compared to extensive 2D6 phenotypes. They did, however, find a nonsignificant trend towards adverse events in those with poor 2D6 phenotypes. This study’s main limitation was insufficient statistical power, particularly since it included few patients with poor metabolizer phenotype.\(^{(76)}\) Venlafaxine’s minor metabolites, N-desmethylvenlafaxine via cytochrome p450 3A3/4 metabolism and N,O-desmethylvenlafaxine are inactive.\(^{(39,40)}\) CYP3A4 is a minor pathway for venlafaxine’s metabolism, but it produces an inactive N-desmethylvenlafaxine metabolite.\(^{(40)}\)

Pharmacokinetic studies with ketoconazole, a known CYP 3A4 inhibitor, have found increased serum drug concentrations of venlafaxine among extensive and particularly poor metabolizers (CYP 2D6).\(^{(77)}\)

The principal route of excretion of venlafaxine and its metabolites is through the kidney.\(^{(40)}\) Given the decrease in renal function with normal aging, drug clearance may be reduced in the geriatric population.\(^{(40,78)}\) This may predispose older patients to increased drug levels rendering them vulnerable to adverse drug effects.

\textit{4.2.2.2 Pharmacodynamics}
Venlafaxine, a bicyclic phenylethylamine derivative, is a racemic mixture of (R)- and (S)-enantiomers. (40) Both enantiomers inhibit the synaptosomal uptake of serotonin, but only the (R)-enantiomer inhibits the reuptake of noradrenaline. (39,79) This noradrenergic effect is more pronounced at higher doses, such as those exceeding 200mg/day, (59,64,65) therefore venlafaxine acts like an SSRI at lower doses. (41,60,62) Patients who ingest toxic doses of venlafaxine present with signs and symptoms consistent with excessive serotonin and noradrenergic activity. (80,81) Venlafaxine also weakly inhibits the uptake of dopamine. (79) In vitro studies have demonstrated venlafaxine’s ability to block sodium channels, which may increase the risk of cardiac dysrhythmias associated with QRS prolongation. (82) Venlafaxine does not interact with muscarinic anticholinergic, alpha-1 adrenergic or histaminergic receptors in vitro. (73) This lack of anticholinergic activity (39) may make it a favourable agent for older patients; (40-42) however, these patients may also be vulnerable to its noradrenergic effects, which are more pronounced at higher doses. (40,41,83-85)
4.2.3 Venlafaxine and the Cardiovascular System

In theory, venlafaxine could increase the risk of adverse cardiac events through two mechanisms. First, it may potentiate cardiac dysrhythmias and, second, through its noradrenergic effects, it may cause myocardial ischemia or heart failure.

4.2.3.1 Arrhythmia

Medications that block cardiac ion channels may affect conduction and increase the risk of fatal dysrhythmias. Blockade of sodium and potassium channels may result in QRS and QT interval prolongation respectively, thereby increasing the risk of fatal ventricular dysrhythmias. (86) Although venlafaxine has mild sodium channel blocking properties, (82) QRS widening is rare, even at higher therapeutic doses or following overdose. (87, 88) QT-interval prolongation is also uncommon in the absence of other risk factors such as hypokalemia, hypomagnesemia or other QT prolonging medications (e.g. fluoroquinolones). (80, 87-89)

Previous Observational Studies

To investigate the risk of dysrhythmias in the real-world setting, Martinez et al. conducted a nested case-control study investigating the risk of sudden cardiac death or near death among older patients in those on venlafaxine compared to other antidepressants. (90) This population-based study used the United Kingdom General Practice Research Database, a database of electronic medical records of primary care practices, and did not find an increased risk compared to fluoxetine (odds ratio (OR) 0.66; 95% confidence interval (CI) 0.38 to 1.14), citalopram (OR 0.89; 95% CI 0.50 to
or dosulepin (OR 0.83; 95% CI 0.46 to 1.52).(90) This study matched for age and adjusted for cardiovascular disease and other factors associated with ventricular arrhythmia. This study’s primary outcome, however, focused on venlafaxine’s potential to increase the risk of ventricular arrhythmia through its effect on cardiac sodium channels or the QT interval. Although ventricular arrhythmia may be associated with acute myocardial ischemia, this study’s outcome would not identify cases of myocardial ischemia occurring in the absence of a ventricular arrhythmia, a more common event.(90) A cohort study using Medicare claims from 1999 to 2003 in five different states in the United States compared the risk of sudden cardiac death or ventricular arrhythmia among new users of 21 antidepressants.(91) They found no difference in sudden cardiac death or ventricular arrhythmia among patients on venlafaxine compared to paroxetine, their selected reference drug based on its lack of effect on cardiac conduction.(91) This large observational study accounted for covariates associated with cardiovascular disease. However, the majority of subjects were young adults(<10% age ≥75 years of age).(91) Based on this existing literature, venlafaxine’s independent risk of sudden cardiac death and ventricular arrhythmia does not seem to be a significant concern. Clinicians, however, should still consider arrhythmias in the setting of concomitant drugs or diseases that also cause QT or QRS interval prolongation.

4.2.3.2 Noradrenergic Effects
Venlafaxine’s noradrenergic effects have been demonstrated with *in vitro* studies at the transporter level. (79) Studies conducted among healthy volunteers have illustrated venlafaxine’s ability to potentiate noradrenaline through an attenuated blood pressure response to tyramine and enhanced dorsal vein vasoconstriction in response to noradrenaline. (41,60,62) Patients who overdose on venlafaxine manifest these noradrenergic effects with tachycardia, hypertension and in some cases, heart failure. (80,92)

These noradrenergic effects can also lead to tachycardia and hypertension at therapeutic doses, (51,83,89,93) and some case reports implicate venlafaxine as a possible contributor to acute myocardial infarction and heart failure. (94,95) A small randomized controlled trial (n=52) of long term care patients demonstrated an increase in adverse events necessitating drug cessation of venlafaxine compared to sertraline. (96) Although not sufficiently powered to explore cardiac toxicity, venlafaxine-treated patients exhibited a small increase in heart rate and more cases of heart failure. (96) Among patients enrolled in clinical trials of venlafaxine, 5.5% on doses exceeding 200mg/day experienced clinically significant increases in blood pressure (diastolic blood pressure of ≥15 mm Hg from baseline). (83) Smajkic *et al.* compared patients with post-traumatic stress disorder who received paroxetine, sertraline or venlafaxine and found a higher rate of side effects and subsequent drop-outs among those on venlafaxine. (49) While this study did not specifically assess cardiac outcomes nor include older patients, more venlafaxine patients suffered from palpitations, which may be noradrenergically mediated. (49)
Previous Observational Studies

Since exploratory RCT patients are typically younger, healthier and more closely monitored, real-world patients are likely at higher risk of adverse effects.(35) Results from observational studies have suggested higher risks of adverse events among older depressed patients on venlafaxine. In an observational study of older patients diagnosed with major depressive disorder without psychosis, 28.8% of patients experienced new-onset cardiovascular symptoms, with 24% of normotensive and 54% of hypertensive patients at baseline experiencing clinically significant increases in blood pressure.(51) Coupland et al. conducted an observational study investigating various adverse events associated with numerous classes of antidepressants. Although cardiovascular events were included among the many outcomes, they did not examine this outcome by controlling for specific confounding factors. Finally, rather than studying venlafaxine separately, it was grouped with several other unrelated antidepressants, therefore, venlafaxine’s risk of heart failure and ischemic heart disease is still undefined.(52) A case-control study using telephone surveys investigated the risk of myocardial infarction among users of high serotonin transporter affinity antidepressants compared to nonusers or to users of antidepressants with low and moderate serotonin transporter affinities. They found a decreased risk of myocardial infarction among patients on antidepressants with high serotonin transporter affinity which included sertraline; however, their study participants were younger, had no history of cardiovascular disease and were not necessarily new users of their antidepressants.(50) Furthermore, instead of performing a head-to-head comparison of
sertraline and venlafaxine, this study compared groups of antidepressants with different serotonin transporter affinities. Venlafaxine was assessed along with other non-SSRI antidepressants, along with tricyclic antidepressants, trazodone, bupropion and mirtazapine, which aside from their serotonin transporter affinity properties, are pharmacologically different.

To date, no study has specifically studied the risk of heart failure and ischemic heart disease among real-world patients on venlafaxine. In order to characterize this risk, we conducted a population-based study using the Province of Ontario’s health administrative databases. We hypothesized that by virtue of its noradrenergic effects, venlafaxine may be associated with an increased risk of adverse cardiac events among older patients relative to other antidepressants that do not prevent noradrenaline reuptake (i.e. SSRIs).
4.3 Research Question

Are older patients (aged 66 years or older) started on the serotonin-noradrenaline reuptake inhibitor venlafaxine at different risk of adverse cardiac events, defined as hospitalization for acute myocardial infarction or heart failure, or death, compared to those on the selective serotonin reuptake inhibitors sertraline or citalopram in the first year of use?

4.4 Hypothesis

We hypothesized that older patients who initiated venlafaxine would be at increased risk of adverse cardiac events in the first year of use compared to those who initiated serotonin or citalopram.
5 METHODS

5.1 Study Design and Setting

We conducted a population-based retrospective cohort study of Ontario residents aged 66 years or older who commenced treatment with either venlafaxine, sertraline or citalopram between April 1st 2000 and March 31st 2009. These patients have universal coverage for hospital care, physician services and prescription medications.

5.1.1 Data Sources

At the Institute for Clinical Evaluative Sciences, we linked health administrative databases using an encrypted version of each subject’s unique health insurance number. We used the following databases: Ontario Drug Benefit, Canadian Institute for Health Information’s Discharge Abstract Database and National Ambulatory Care Reporting System, Ontario Health Insurance Plan and the Registered Persons Database. These administrative databases are routinely linked to study drug safety.

5.1.1.1 Ontario Drug Benefit Program

The province of Ontario covers the price of 3,800 prescription medications, and some natural products and supplies for diabetic testing for individuals eligible for the Ontario Drug Benefit (ODB) program. Individuals covered by this program fulfill at least one of the following criteria: all community dwelling individuals at least 65 years of age, individuals residing in a long term care facility or Home for Special Care, individuals receiving Home Care or on social assistance; or individuals with medication costs that far exceed their income (Trillium...
program). The ODB database provides the following information for each covered drug claim since 1997: date the prescription was filled, cost, quantity, the patient’s long term care status, and identifiers for the drug, patient, physician and outpatient pharmacy where the prescription was filled. We used this database’s prescription drug information to define the exposures, and to identify covariates (medications and as surrogate markers of comorbidities).

5.1.1.2 Canadian Institute for Health Information databases

The Canadian Institute for Health Information (CIHI) is an independent nonprofit organization which maintains data from the Canadian health care system by working with provincial ministries of health, Statistics Canada and Health Canada. CIHI used diagnosis codes from the International Classification of Diseases-9 (ICD-9) and ICD-10 prior to 2002, and following 2002 respectively. Procedures are identified with codes from the Canadian Classification of Health Interventions (CCI) and Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP) codes. CIHI maintains its various databases by systematically assessing, documenting and improving data quality. Data abstracted from patient charts or medical records, namely the Discharge Abstract Database, National Ambulatory Care Reporting System and the Canadian Organ Replacement System, undergo re-abstraction studies to ensure data completeness and consistency resulting in increasing accuracy over time.

CIHI Discharge Abstract Database

The CIHI Discharge Abstract Database (CIHI-DAD) contains information about every hospital stay at most acute care hospitals in Canada. It includes data on patient demographics
(date of birth, gender, and postal, county and residence codes), clinical data (ICD-9 and ICD-10 diagnostic codes, CCI and CCP procedure codes, physician identifiers), and administrative data (hospital or institution identifier, admission category, length of stay, disposition). The CIHI-DAD is regularly validated with re-abstraction studies, most recently for ICD-10 codes in 2009-2010, and diagnosis code accuracy for all heart diseases exceeded 80%.(103)

CIHI National Ambulatory Care Reporting System

The CIHI National Ambulatory Care Reporting System (CIHI-NACRS) provides information about patient care administered in Same Day Surgery, outpatient clinics such as renal dialysis or cancer care, and emergency departments. It provides data on patient demographics (date of birth, gender, postal, county and residence codes), clinical data (ICD-9 and ICD-10 diagnostic and CCI and CCP procedural codes, physician identifiers), and administrative data (hospital or institution identifiers, disposition following emergency department visit).

We used both CIHI DAD and NACRS to define our primary outcome, and comorbidities. Although the Ontario Mental Health Reporting System (OMHRS) and Continuing Care Reporting System (CCRS) are part of CIHI, these databases were not used. OMHRS contains clinical and social information about adult patients admitted to mental health beds in the province. Our study period started in 2000, the earliest year when venlafaxine, sertraline and citalopram were available through ODB, whereas OMHRS became available through CIHI only in 2005.(103) CCRS contains clinical information, which includes medical illness, cognition and behaviour, medication use, nutrition and special procedures, about patients residing in long term care or complex continuing care facilities. Although this database was available since 1997, it does not
provide information about all patients included in our study cohort, specifically those not receiving care from such facilities.

5.1.1.3 Ontario Health Insurance Plan Database

The Ontario Health Insurance Plan (OHIP) database contains information regarding claims by health care providers (including physicians and certain laboratories) who provide services to inpatients and outpatients. It provides data on patient demographics (date of birth, gender), clinical data (diagnostic code, health care provider identifiers), administrative data (referring physician, hospital identifier if applicable, service date). Over 95% of outpatient physician fee-for-service billing by primary care physicians are included in OHIP. The remaining 5% of physician claims are provided through alternate funding plans provided through academic centres, family health teams, health service organizations, and some psychiatric hospitals. Unlike CIHI-DAD and CIHI-NACRS, this database is not routinely validated for data accuracy. We used this database in combination with CIHI databases to identify comorbidities.

5.1.1.4 Registered Persons Database

The Registered Persons Database provides demographic information on any individual who possesses an Ontario health card. This demographic information includes date of birth, postal code. Although it provides information regarding death, this database is not updated as regularly as other databases thereby limiting its accuracy especially regarding timing of death. At the time of this study, the Vital Statistics database, which contains the medical cause and date of death, was not available. As a result, we used the Registered Persons Database to identify the outcome, death.
5.2 Cohort Definition

5.2.1 Study and Control Groups

We identified all patients aged 66 years or older who were new users of venlafaxine (study group), sertraline (control) or citalopram (control) during the study period. We defined new users as patients who had not filled a prescription for any antidepressant in the preceding year. Sertraline- and citalopram-treated patients served as control groups because these drugs are similar to venlafaxine in serotonergic activity,(79) efficacy(44) and popularity in Canada(43) but do not potentiate noradrenaline. Patients were followed until they experienced the primary outcome (defined below), switched or discontinued antidepressant therapy, reached the end of the study period (March 31st, 2010) or completed one year of therapy. Based on previous literature, which included case series and observational studies,(51,94-96) this one year observation window was judged to be sufficient time to capture drug-specific adverse cardiac events, particularly because they are most likely to manifest within the first several weeks to months of treatment.(51,94,95,105)

5.2.2. Inclusion Criteria

We included all patients aged ≥66 years of age with a valid Ontario Health Card who started a new prescription for venlafaxine, sertraline or citalopram between April 1st 2000 and March 31st 2009. Patients were only included once in the study accrual period.

5.2.3 Exclusion Criteria
We did not study patients during their first year of eligibility for prescription drug coverage (age 65) by the ODB. These patients would have incomplete medication records for the preceding one year, which would have prohibited us from measuring variables pertinent to the exposure drugs and outcome. We excluded patients concomitantly taking other antidepressants, as well as those who started any combination of venlafaxine, sertraline or citalopram on the same day. Patients on tamoxifen, an estrogen receptor antagonist used in the treatment of estrogen-receptor positive breast cancer, were excluded because SSRIs and SNRIs may differentially modulate the response to tamoxifen and subsequently mortality.\(^{106}\)

### 5.3 Outcome Definition

We defined the primary outcome *a priori* as a composite of death from any cause or hospital admission for acute myocardial infarction or heart failure. In a secondary analysis, each component was analyzed separately. We identified death using the RPDB, and hospitalization for acute myocardial infarction or congestive heart failure with ICD-9 and ICD-10 codes from the CIHI DAD. We defined acute myocardial infarction using ICD-9 code 410, or ICD-10 codes I21 and I22, and I20 (unstable angina); and congestive heart failure (CHF) using ICD-9 code 428 or ICD-10 code I50. In order to exclude patients with nonischemic chest pain, we limited our definition of myocardial infarction to patients hospitalized for at least three days.\(^{107}\) The date of death or hospital admission was used as the outcome date for all analyses. These outcome definitions for congestive heart failure and myocardial infarction have been previously validated, with positive predictive values of approximately 90%.\(^{108-110}\)

#### 5.3.1 Outcome Validation Studies
Validation studies of these ICD-9 and -10 codes have been performed in Canada, specifically Ontario, Saskatchewan and Alberta. (108-111) Studies linking CIHI-DAD ICD-9 and -10 codes for AMI and CHF with Saskatchewan hospital records and the Ontario-based Fastrak II Acute Coronary Syndrome registry had positive predictive values of 88-95%, however the prevalence of these conditions was high (90-100%). (108,110) Furthermore, in the Ontario-based Fastrak II study, the sensitivity of only the ICD-9 code 410 for myocardial infarction was 89%. (108) In studies that linked these codes with either electronic medical records from primary care physicians, or a chart review of urban and rural hospitals in Ontario, the prevalence of AMI and CHF was lower at 5-10%, yet the positive predictive value remained at 89-94% and sensitivity at 61%. (109,111) Although including outpatient OHIP diagnosis codes for CHF might have increased the sensitivity of our outcome definition to 86% by including mild cases not requiring hospitalization, we decided against this due to their poor positive predictive values ranging from 38 to 46%. (112)

Finally, as a sensitivity analysis to assess the robustness of our findings to potentially unmeasured confounding variables, we conducted a ‘tracer analysis.’ Here we replicated our analyses using gastrointestinal hemorrhage as the outcome of interest, because we expected no differential risk of hemorrhage among the three patient groups. (113,114)

5.4 Covariates

We recorded covariates that would be associated with the prescription of either venlafaxine (study), citalopram (control) or sertraline (control), or with adverse cardiac events (outcome). Broadly, these covariates included demographics, antidepressant dose category, markers of burden of illness, comorbidities related to drug exposure or outcome, and
medications associated with cardiovascular disease, mortality and neuropathic pain. (Tables 1a and b, Appendices 1A and B)

Demographic covariates included age and gender. As markers of burden of illness, we measured a patient’s number of distinct medications (115) and hospitalization status in the past year (116), and the Aggregated Diagnosis Groups within the past 3 years. (117) Aggregated Diagnosis Groups are a validated measure of burden of illness that account for a patient’s diagnoses in the ambulatory and hospitalized setting, chronicity and severity of illness, diagnostic certainty, etiology of the disease and involvement of specialty care. (117) This range of comorbidity markers allowed us to estimate the burden of illness of all patients regardless of their hospitalization status and they have been validated in health services research for mortality and health care utilization. (115,117)

5.4.1 Variables Associated with Drug Exposure or Outcome

5.4.1.1 Variables Associated with Drug Exposure

We measured variables that were associated with exposure to our drugs of interest—venlafaxine, citalopram or sertraline. These included comorbidities such as depression, anxiety, dementia, neuropathic pain and hot flashes associated with tamoxifen therapy among breast cancer patients. We measured depression, anxiety and dementia with ICD-9 and ICD-10 codes from CIHI DAD and NACRS databases. The latter condition is associated with an increased risk of mortality and behavioural psychological symptoms of dementia, which include depression and anxiety. (118,119) As mentioned, we excluded patients on tamoxifen since antidepressants may differentially affect the effectiveness of this medication. (106)
Since venlafaxine’s noradrenergic effects are more prominent at higher doses (≥200 mg per day)(41,60,62,120), we thought that it would be important to explore any association between dose and the primary outcome. In clinical practice, new drugs are introduced to older patients at the lowest possible dose and then slowly titrated upwards while monitoring for adverse effects.(121) Patients on higher antidepressant doses are more likely to suffer from severe depression, and less likely to have genetic polymorphisms that render them intolerant of this medication at even lower doses. We defined low, moderate and high dose categories for venlafaxine, sertraline and citalopram based on clinical and pharmacologic properties. The low dose categories were defined as the usual initiation dose, i.e. the lowest available doses with venlafaxine 37.5 mg/day, sertraline 25 mg/day and citalopram 10 mg/day. High dose categories were defined as venlafaxine >200 mg/day, sertraline >150 mg/day and citalopram >40 mg/day.(84,85,120,122,123) Moderate dose categories were defined as venlafaxine 37.6-200 mg/day, sertraline 26-150 mg/day and citalopram 11-40 mg/day.

As surrogate markers of dementia and neuropathic pain, conditions for which venlafaxine is sometimes used, we recorded the use of other medications often prescribed for these conditions. Venlafaxine has been prescribed for patients with depression and concomitant pain syndromes who may also be taking opioids, a risk factor for mortality.(124,125) As mentioned earlier, venlafaxine has also been used to treat behavioural psychological symptoms of dementia, a known risk factor for mortality.(119,126,127) Since diagnosis codes for “pain syndromes” and “dementia” have not been validated or have variable accuracy,(128-130) we attempted to identify these patients through their use of known pain
medications, opioids and gabapentin; or antipsychotics and cholinesterase inhibitors respectively.

5.4.1.2 Variables Associated with Outcome

Our primary outcome was a composite of ischemic heart disease (acute myocardial infarction and unstable angina), congestive heart failure and all-cause mortality. Therefore, we recorded the proportion of patients with cardiovascular disease and its different variants (included diagnosis codes for congestive heart failure, valvular disease, cardiovascular disease unspecified, angina, myocardial infarction, ischemic heart disease, conduction disorder and cerebrovascular disease) as comorbidities, and renal disease at baseline. (131) (Tables 1a and b) The Aggregated Diagnosis Groups comorbidity tool allowed us to differentiate between stable and unstable cardiovascular disease. (Appendices 1A and B) Medications associated with the treatment or exacerbation of cardiovascular disease were also included. Medications associated with the treatment of cardiovascular disease included antiplatelet agents such as clopidogrel and acetylsalicylic acid, anticoagulants, loop diuretics, statins, negative chronotropes (beta-blockers, non-dihydropyridine calcium channel blockers, digoxin), antiarrhythmics, aldosterone antagonists and renin-angiotensin antihypertensives (angiotensin converting enzyme inhibitors and angiotensin receptor blockers). (132,133) Medications associated with exacerbation of heart disease include nonsteroidal anti-inflammatory drugs, thiazolidinediones and systemic steroids. We were unable to measure other cardiovascular risk factors such as smoking status, waist circumference, family history of cardiovascular disease and the control of blood pressure and cholesterol from our available databases. There is no reason, however, for these risk factors to be differently distributed among the three
antidepressant drug groups at baseline. Finally, antipsychotic and cholinesterase inhibitor use are not only associated with drug exposure as discussed above; but also outcome as they have been linked to increased mortality among older patients. (126,127)

5.5 Statistical Analysis
5.5.1 Baseline Characteristics

We compared the baseline characteristics of patients in the three groups using standardized differences, which are not as sensitive to sample size as conventional P values. (134) A meaningful difference was defined as a standardized difference exceeding 0.10. (134,135)

5.5.2 Propensity Score
5.5.2.1 Introduction to the Propensity Score

Confounding

When estimating the effect a drug treatment or exposure has on a particular outcome, it is important to compare groups of individuals who are otherwise similar. This would allow one to study the association between drug and outcome without interference from a confounder. In our case, a confounder is a variable associated with both exposure drug and the outcome. An example of a confounding variable in this study investigating venlafaxine (study drug) and cardiovascular events (outcome) would be diabetes. Diabetes is associated with neuropathy, for which venlafaxine is prescribed, and cardiovascular disease (outcome). If more patients in the venlafaxine group had diabetes compared to the control groups then the venlafaxine group would be more likely to suffer an adverse cardiac event, a source of bias.
Furthermore, diabetes is not an intermediate pathway between venlafaxine and the development of cardiovascular disease. (56)

In randomized controlled trials, individuals are randomly allocated to either study or control groups. This usually results in an equal distribution of variables, including confounders, thereby allowing one to characterize the association between the study drug and outcome by directly comparing the outcomes between groups. In observational studies, however, investigators do not assign individuals to either study or control groups. Rather, subject characteristics may influence whether they are exposed to the study or control groups. Unless these characteristics, which include confounders, are accounted for, directly comparing outcomes between study groups would be inaccurate. One tool that addresses this issue in observational studies is the propensity score.

The Propensity Score

The propensity score is the probability of receiving a certain study treatment given the individual’s observed characteristics. (136) When deriving the propensity score, one can include variables that are imbalanced between treatment groups and/or that are associated with the treatment and outcome. In general, propensity scores only account for observed covariates, therefore one cannot adjust for unmeasured covariates, a potential source of bias.

Propensity scores can be used for matching, stratification, inverse probability of treatment weighting and covariate adjustment. With matching and stratification, there is an effort to compare subjects or strata from the treatment and comparison groups with similar propensity scores, and therefore similar baseline covariates which may affect treatment assignment or outcome. (136) During covariate adjustment with the propensity score, assuming
there is a linear relationship between propensity scores and the outcome, the outcome is regressed on the propensity score as an indicator for treatment. Unlike the other methods, one cannot easily assess the quality of the propensity score model (balance assessment) in covariate adjustment.\textsuperscript{(137)} Another disadvantage of propensity score covariate adjustment is the slight bias towards the null hypothesis when the outcomes are binary or time-to-event, as in our study. With weighting, each subject is weighted by the inverse probability of the treatment they received (study vs. comparison) and the outcomes from the study and control groups of this derived sample are directly compared.\textsuperscript{(136)} Studies comparing the various methods of propensity score implementation suggest that matching and weighting with the propensity score were more successful than stratification and covariate adjustment at removing systematic differences between study and control groups.\textsuperscript{(136)} In our study, we used the propensity score to weight.

\textbf{5.5.2.2 Implementation of the Propensity Score}

To control for baseline differences between the two treatment groups, we weighted the cohort using inverse probability of treatment weights (IPTW) derived from the propensity score.\textsuperscript{(136)} We used IPTW in order to avoid losing study subjects, which could occur during the matching process, to allow us to perform balance diagnostics after applying the propensity score and to confirm the equalization of differences in baseline covariates between the groups.\textsuperscript{(136,137)} The propensity score was estimated using a logistic regression model that included all potential confounders with the exception of drug dose listed in Tables 1a and b. Separate propensity scores were generated for the venlafaxine/sertraline and venlafaxine/citalopram comparisons. We then performed a balance assessment\textsuperscript{(136,137)} of our
IPTW samples using standardized differences, and visually inspected the weights using boxplots. (138)

5.5.3 Survival Analysis Time-to-Event Analysis

We performed a survival analysis to study the risk of adverse cardiovascular events among patients on venlafaxine compared to those on sertraline or citalopram over time.

Using the weighted sample, we performed time-to-event analyses with sertraline and citalopram as reference groups. We estimated hazard ratios with 95% confidence intervals in the weighted sample using Cox proportional hazards regression and obtained a robust variance estimate. From the fitted model, we derived survival curves for each treatment group. Because of the observational nature of our study and subsequent lack of randomization, we did not construct unadjusted Kaplan-Meier survival curves (1-probability of outcome). This analysis does not allow one to account for confounding variables and other sources of bias. For example, patients with cardiovascular disease are at increased risk for future cardiovascular events compared to those without a history of cardiovascular disease. If patients with cardiovascular disease had physicians who were concerned about venlafaxine’s noradrenergic effects and therefore more likely to be prescribed sertraline or citalopram, then the unadjusted Kaplan-Meier curve for these drugs may be lower than that of venlafaxine. Instead, we used the method described by Cole et al. where we derived adjusted survival curves using inverse probability weights. (139)

Supplementary analyses included stratification for pre-existing cardiovascular disease and replication of all analyses with trimmed and stabilized weights. (138)
5.5.4 Regression-based analysis

We explored the relationship between drug dose and the primary outcome with regression-based analyses. As previously described, we defined 3 drug dose categories: low, moderate and high. Individuals would be classified into one of each drug dose category based on the highest prescription dose filled during the observation window. Because it is customary for patients to start with the lowest dose of medication and then increase according to response and tolerance to treatment, patients tended to receive moderate or high doses later on during the observation window. Therefore, by the time patients were administered these higher doses, their propensity scores, which were derived from covariates at baseline and in the preceding 3 years, may no longer be accurate. Because conventional IPTW using the propensity score is designed for use with exposures that are fixed at baseline or in the preceding 3 years, the exploratory secondary analyses that incorporated time-dependent covariates like dose were conducted in the original, unweighted sample. A Cox proportional hazards model was fit to estimate the effect of dose on the hazard of the composite outcome. In this set of analyses, dose was treated as a time-varying covariate, and we adjusted for type of antidepressant (venlafaxine vs. sertraline or citalopram) and all measured confounding variables that achieved clinical and statistical significance (defined as a standardized difference >0.1)(Tables 1A and B, Appendices 1A and B).

All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, North Carolina).

5.6 Ethics
This study was approved by the Research Ethics Boards of Sunnybrook Health Sciences Centre and the University of Toronto.
6 RESULTS

6.1 Description of study and control cohorts

During the 10-year study period, we identified 48,876 patients with depression who commenced treatment with venlafaxine, 41,238 who commenced sertraline and 3,909 patients who commenced citalopram. These patients were followed for a median of 105 (Interquartile Range (IQR) 45 to 365), 90 (IQR 45 to 317) days and 287 (IQR 102 to 365) days respectively. During the observation window, 65% of venlafaxine, 62% of sertraline and 76% of citalopram patients switched doses. Only 2.9%, 2.3% and 12% of patients were in the high dose category for venlafaxine, sertraline and citalopram respectively.(Tables 1a and 1b) During the one year of follow-up, 8.5% of patients experienced the primary composite outcome, 1.4% switched antidepressants, 63.7% discontinued their antidepressant and 26.3% completed the full year of follow up without experiencing the primary outcome.

6.1.1 Venlafaxine-Sertraline Comparison

Subjects treated with venlafaxine and sertraline exhibited similar baseline demographics (IPTW range 1.2 to 7.4, IQR 1.9 to 2.4)(Figure 1) and comorbidities, although minor differences were found with regard to age and history of cardiovascular and psychiatric disease (Table 1a, Appendix 1A). We successfully adjusted for these differences by weighting with the propensity score (Table 1a, Appendix 1A). In the weighted samples, all variables had standardized differences less than or equal to 0.007, indicating that all meaningful differences in means and prevalence estimates of measured baseline covariates had been eliminated. Approximately half of the study population on these two antidepressants had preexisting cardiovascular disease at the outset of antidepressant therapy.
6.1.2 Venlafaxine-Citalopram Comparison

Patients on citalopram exhibited different characteristics from those on venlafaxine and sertraline. This cohort of patients was much smaller, generally older (citalopram median age 81 years (IQR 74 to 87), venlafaxine median age 75 years (IQR 70 to 81)), received more medications (citalopram median 11 (IQR 8-16) compared to venlafaxine 9 (IQR 5-13), less likely to have anxiety and more likely to have a previous history of heart failure, stroke, renal disease, dyslipidemia and dementia (Table 1b). Patients on citalopram had a longer duration of therapy (median 287 days, IQR 102-365). They were also more likely to be on concomitant loop diuretics, renin angiotensin agents, statins, warfarin, thiazolidinediones, and antipsychotics, but less likely to be taking nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids. From the Aggregate Diagnosis Groups tool, the citalopram group was less likely than the venlafaxine and sertraline groups to have a previous minor primary infection, allergies, asthma, stable chronic medical disease, stable ophthalmologic disease, dermatologic conditions, and stable psychosocial disease; and more likely to have progressive, recurrent diseases, unstable chronic medical disease, major injury, and unstable psychosocial disease (Table 1b). Similar to the venlafaxine-sertraline comparison, we generated propensity scores with all the variables in Table 1b and Appendix 1b. These scores were then used to IPTW the samples and balance diagnostics were performed (Table 1b). The citalopram group had several differences compared to venlafaxine, which were balanced with IPTW (Table 1b) albeit with a greater range of weights compared to the venlafaxine-sertraline comparison (IPTW range 1.1 to 372.8 (IQR 3.9 to 17.2))(Figure 1). In light of these inherent differences, we compared venlafaxine to sertraline and citalopram separately rather than pooling the sertraline and citalopram groups as one
comparison group. These numerous differences also hindered us from performing the time-varying dose analysis of venlafaxine compared to citalopram. With 23 covariates which would be adjusted for in the analysis (18 observed covariates which differed between the drug groups and an additional 5 clinically significant covariates)\(k\), 7.5% weighted proportion of citalopram patients experiencing the outcome \(p\), and the 10 event per variable rule for proportional hazards regression (Sample size \(N = 10 \, k/p\),\(140\) we were underpowered for this analysis. Furthermore, we were concerned that there were additional unmeasured confounders at baseline or which may have arisen over time.

6.2 Primary Analysis

6.2.1 Venlafaxine-Sertraline Comparison

In the primary analysis, 3966 (8.1%) of venlafaxine- and 3707 (9.0%) of sertraline–treated patients experienced the composite outcome of death or hospital admission for acute myocardial infarction or heart failure (Table 2a). After weighting with the propensity score, we found no significant difference in the risk of the primary outcome in patients started on venlafaxine compared to sertraline (weighted hazard ratio 0.97; 95% confidence interval 0.93 to 1.02; Table 2a; Survival curves Figure 2a). We also found no significant difference in the secondary outcomes of death or acute myocardial infarction (Table 2a). However, we unexpectedly found that venlafaxine use was associated with a lower incidence of heart failure (weighted hazard ratio 0.87; 95% CI 0.80 to 0.95). The propensity score-generated weights for venlafaxine and sertraline groups were similar, and supplementary analyses using the stabilized and trimmed inverse probability of treatment weights yielded similar results. As expected, we
found no significant difference in the risk of gastrointestinal hemorrhage (weighted hazard ratio 0.99; 95% CI 0.84 to 1.16).

### 6.2.2 Venlafaxine-Citalopram Comparison

In the venlafaxine-citalopram comparison, 3,966 (8.1%) of venlafaxine patients and 456 (11.7%) of citalopram patients experienced the primary outcome (Table 2b). After weighting with the propensity score, there was an increased risk of the primary outcome in venlafaxine patients with a weighted hazard ratio 1.39 (95% CI 1.19 to 1.62) (Table 2b; Survival curves Figure 2b). We found an increased risk of death and acute myocardial infarction among users on venlafaxine compared to citalopram (weighted hazard ratio 1.49 (95% CI 1.26 to 1.76) and 1.59 (95% CI 1.5 to 2.41) respectively) however, there was no significant difference in the incidence in heart failure (weighted hazard ratio 1.22 (95% CI 0.87 to 1.72). Finally, we did not find a difference in venlafaxine- and citalopram-users in the tracer outcome, gastrointestinal bleed (weighted hazard ratio 1.27 (95% CI 0.82 to 1.96). Although there was a wide range of weights in this comparison, (Figure 1) which could affect results by providing estimates with high variance, (138) we acquired similar results when the analysis was repeated with trimmed and stabilized weights. (138)

### 6.3 Secondary Analysis

#### 6.3.1 Stratified Analysis

We performed a stratified analyses examining the risk of the primary outcome among patients with or without pre-existing cardiovascular disease. The trends from the primary analysis persisted in our secondary analysis in which we stratified for baseline cardiac disease (Figures 3A and 3B, 4A and 4B).
6.3.2 Time-Varying Analysis of Dose: Venlafaxine-Sertraline Comparison

During the exploratory time-varying analysis of dose for the primary outcome, we could not use the propensity scores for IPTW that were derived from baseline patient characteristics. Instead, we adjusted for the variables that were statistically different between the venlafaxine and sertraline cohorts (standardized difference >0.10)(Table 1a, Appendix 1A) or clinically significant.(Table 3) These included age, sex, hospitalization status in the preceding 12 months, stroke, congestive heart failure or cardiovascular disease, use of statin and antiplatelet medications; and the Aggregated Diagnosis Group, “progressive symptoms” and “stable/persistent psychosocial disease.”

Similar to the primary analysis, we found no difference in the primary outcome between venlafaxine and sertraline. There was an increased risk for adverse cardiac events among patients on high dose antidepressants compared to low dose antidepressants (Table 3). This was not unexpected, since high dose antidepressants are often used in patients with more severe depression, a known risk factor for adverse cardiac events.(7,70,141)

6.3.3 Time-Varying Analysis of Dose: Venlafaxine-Citalopram Comparison

Unlike the venlafaxine-sertraline scenario, patients in the venlafaxine and citalopram cohorts were dissimilar (Table 1b). We identified 18 baseline covariates in which the groups differed, and there remained the possibility of additional unmeasured confounders. There could be differences over time, in addition to dose, that we would be unable to measure in this study. Of note, citalopram patients continued their antidepressant for twice as long as venlafaxine and sertraline patients (citalopram median 287 (IQR 102 to 365) days; venlafaxine median of 105 days (IQR) 45 to 365; sertraline median 90 (IQR 45 to 317) days) and they were
more likely to be in the high dose category (citalopram 12% compared to venlafaxine 3%). Therefore it is likely that additional differences between the study groups developed over time. Furthermore, the propensity score was derived from baseline characteristics, therefore we were unable to use it as covariate adjustment during the time-varying analysis. (Table 1b, Appendix 1B). Due to these differences, and the inability to use the propensity score, the time varying analysis of dose was not performed for the venlafaxine-citalopram drug comparison.

7 DISCUSSION

7.1 Major Findings

Using the health records of more than 94,000 older patients, we found no increased risk of adverse cardiac events among patients treated with low to moderate-doses of venlafaxine as compared with sertraline. However, when compared to citalopram, we found an increased risk of adverse cardiac events, specifically acute myocardial infarction and death among venlafaxine patients. These findings held regardless of baseline cardiovascular disease. This finding is important in light of limited evidence that venlafaxine’s noradrenergic effects might confer increased cardiovascular risk.

The lower risk of heart failure among venlafaxine patients compared to sertraline patients was an unexpected finding. One hypothesis is that venlafaxine triggered cardiovascular symptoms of palpitations, similar to the observational study by Johnson and colleagues,(51) leading patients to seek medical attention. Patients treated in the community for cardiovascular symptoms, such as hypertension or tachycardia, or mild cases of heart failure or myocardial ischemia might avoid a hospital admission. Since our primary outcome only
looked at serious cardiac events resulting in death or hospitalization, these events may have been missed and therefore resulted in a lower incidence of heart failure. Another hypothesis is that venlafaxine might be more effective than sertraline or citalopram at treating depression,(44) allowing patients to better manage their chronic medical conditions, particularly cardiovascular disease. We observed no difference in the tracer outcome (gastrointestinal bleeding) between groups, however this disease is less dependent on adherence to medical therapy. Finally, there exists the possibility that residual confounding could have influenced our findings. Future observational studies that include electronic medical record databases in primary care practices or pragmatic randomized controlled trials could be helpful to explore the basis of this association.

7.1.1 Consistency with Existing Literature

Our findings complement those of other recent population-based studies that found no increased risk of death or cardiac arrhythmia among patients on venlafaxine;(90,91,142) although these studies did not examine the risk of myocardial infarction or heart failure, which might be particularly important given the drug’s noradrenergic effects.

7.1.1 Existing Literature

Clinical Trials

As mentioned above, a number of clinical trials of second generation antidepressants found no increased risk in adverse cardiac events among patients on sertraline or venlafaxine.(47,48) With small numbers of older patients, however, the results from these clinical trials could not be generalized to this vulnerable population.(47,48) A recent meta-analysis and meta-regression of randomized trials of the effect of antidepressants and late-life
depression found that few clinical trials included older individuals, however none included safety as an outcome.(36) To date, the existing clinical trials do not adequately address cardiac safety of venlafaxine among older patients with comorbidities.

Observational Studies

Several observational studies have tried to characterize the cardiac risk of antidepressants in real-world patients. The case-control study by Sauer et al. using telephone surveys found a decreased risk of myocardial infarction among patients on antidepressants with high serotonin transporter affinity, which included sertraline, compared to those with low serotonin transporter affinity; however, their study participants were younger, had no history of cardiovascular disease and were not necessarily new users of their antidepressants.(50) Furthermore, as previously mentioned, instead of performing a head-to-head comparison of sertraline and venlafaxine, this study compared groups of antidepressants with different serotonin transporter affinities.(50) Venlafaxine was grouped among other non-SSRI antidepressants, along with tricyclic antidepressants, trazodone, bupropion and mirtazapine, which aside from their serotonin transporter affinity properties are pharmacologically different. Although, the observational study by Johnson et al. found an increase in adverse cardiac effects such as increased heart rate and blood pressure among depressed older community-dwelling patients on venlafaxine, there were no cases of myocardial infarction or heart failure. This study’s small sample size, however, limited its statistical power to detect such cardiac events.(51)

Our study is the first population-based study to specifically compare the cardiac safety of the commonly prescribed antidepressants, venlafaxine, sertraline, and citalopram and it
provides further insight into the safety of these drugs among older patients with cardiovascular disease. (52) Overall, our results provide a measure of reassurance to physicians treating depression among older patients, particularly those with cardiovascular disease.

7.1.2 Limitations

Some limitations of our study merit discussion. The results derive from older patients, and the generalizability to younger patients is unknown. However, our study addresses venlafaxine’s risk in an understudied population in a real-world setting; this is relevant since most real-world patients treated for depression are excluded from randomized controlled trials. (35) Although we utilized a propensity score incorporating variables that might relate to both exposures and outcomes, we had no information on important factors such as body weight, waist circumference, smoking status, cholesterol and blood pressure control, and CYP2D6 phenotype. However, there is no apparent reason why these factors might differ between venlafaxine, sertraline and citalopram groups. Nevertheless, the venlafaxine and sertraline cohorts were generally similar even before weighting and we found no significant difference in our tracer outcome. Patients on citalopram, however, were different from the other antidepressant groups. In general, this smaller cohort consisted of older and frailer patients with a heavier burden of disease, including cardiovascular disease. Therefore, despite weighting with the propensity score and achieving similar results with trimmed and stabilized weights and the tracer outcome, unmeasured confounders may have influenced the study. We suggest a cautious interpretation of this study’s venlafaxine-citalopram comparison and feel that further research with randomized controlled trial or propensity score matched cohort study designs to explore this association is indicated.
The administrative nature of our data only allowed us to estimate dose, thereby limiting our ability to study the risk of adverse cardiac events at higher venlafaxine doses where noradrenergic effects are more pronounced. Although we used prescription day supply data from the ODB database to characterize patient adherence to drug therapy, it is possible that patients filled their prescription but did not take the medication. If venlafaxine patients were less adherent, this would have biased the study results towards the null hypothesis. However, there should be no reason for differences in adherence between venlafaxine and sertraline and patients on those medications had similar durations of therapy. Conversely, citalopram patients had longer courses of therapy and could have had greater adherence. These patients were more likely to be older and have greater burdens of illness and dementia, which could have resulted in placement at long term care facilities where medications are administered by a second party. This, however, should not have affected the observed increased risk of adverse cardiac events among patients on venlafaxine compared to citalopram. In addition, we could not use the propensity score for this regression analysis with the time-dependent covariate, dose, because this score was derived from baseline characteristics which may have changed over time. We did, however, adjust for characteristics which were either clinically and/or statistically significant in our venlafaxine-sertraline time-varying dose comparison. A potential source of bias associated with this analysis is the nonrandom changes in drug dose. Increases in drug dose may not have been random but rather preceded by an exacerbation of depression or an indication of more severe disease.(143) By hindering one’s ability to manage his or her chronic diseases, depression is associated with mortality and morbidity.(11,12) Although we adjusted for covariates that were clinically and/or statistically significant, which may reduce this
bias, the nonrandom changes in drug dose should still be acknowledged. As mentioned previously, due to the multiple differences between patients using citalopram compared to venlafaxine or sertraline, we were unable to conduct a similar time-varying dose analysis between venlafaxine and citalopram. Therefore, whether high-dose venlafaxine is associated with increased cardiac risk remains unknown.

Because some clinicians concerned about the hemodynamic effects of venlafaxine might have avoided this drug in those with cardiovascular or hypertensive disease, there is a risk of channeling bias. Although this difference in baseline cardiovascular disease between groups was successfully balanced with IPTW, this potential bias deserves mention.

Our validated primary outcome allowed us to identify adverse cardiac events severe enough to result in death or hospitalization. It did not, however, allow us to capture less severe cardiac events and effects such as mild heart failure, exacerbated hypertension or tachycardia that might have been induced by venlafaxine. If these mild conditions prompted timely outpatient interventions, hospitalization could be prevented, therefore resulting in the decreased risk of hospitalization for heart failure. As previously mentioned, although outpatient OHIP diagnosis codes for hypertension, tachycardia, and heart failure exist, we did not include them in our outcomes because they are not well validated in isolation.

7.1.3 Implications for Clinical Practice

In summary, our population-based study of older Ontario adults found no significant difference in the cardiovascular safety profiles of venlafaxine compared to sertraline. Our results offer a measure of reassurance about the drug’s cardiac safety, however physicians
should still exercise caution in patients on higher doses or those who manifest overt noradrenergic effects.

7.2 Contributions

Our study is interesting from methodological and clinical points of view.

Our study used the propensity score as IPTWs to weight our sample and therefore was able to include all older individuals in Ontario who fulfilled our inclusion and exclusion criteria. We recognized that using the propensity score in this fashion, however, limited our ability to study the time-dependent covariate of dose. We found that IPTW was more successful when comparing similar cohorts as in the venlafaxine/sertraline comparison.

Older Ontario patients on citalopram were more likely to be older, have cardiovascular disease and to have a larger burden of illness compared to those on venlafaxine or sertraline. Not only did we find that the majority of patients were on low to moderate doses of antidepressants, but there was no significant difference in adverse cardiac events among those patients on low to moderate doses of venlafaxine compared to sertraline.

7.3 Future Directions

A methodological study to investigate the risk of cardiac events among older patients on venlafaxine compared to sertraline or citalopram may include a cohort study using propensity score matching instead of IPTW. While this may result in the loss of venlafaxine patients who were not successfully matched to citalopram patients, it would allow us to better characterize the risk of venlafaxine compared to citalopram.
In light of the FDA’s recent alert regarding high-dose citalopram and the risk of cardiac dysrhythmias, a population-based case-control study to compare citalopram to sertraline and venlafaxine could be important to physicians, patients and health policy makers.
8 REFERENCES


(37) Zimmerman M, Chelminski I, Posternak MA. Generalizability of antidepressant efficacy trials: differences between depressed psychiatric outpatients who would or would not qualify for an efficacy trial. Am J Psychiatry 2005 Jul;162(7):1370-1372.

(38) Maclure M. Explaining pragmatic trials to pragmatic policy-makers. CMAJ 2009 May 12;180(10):1001-1003.


(67) Gelenberg AJ. Practice Guideline for the Treatment of Patients with Major Depressive Disorder: Approved in May 2010 and Published in October 2010. : American Psychiatric Association; 2010.


9 TABLES AND FIGURES

9.1 TABLES

9.1.1 Table 1a: Baseline Characteristics of Older Patients on Venlafaxine Compared to Sertraline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sertraline</th>
<th>Venlafaxine</th>
<th>Standardized Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=41,238</td>
<td>N=48,876</td>
<td>Crude</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weighted</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at start of cohort drug (Median (IQR))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>66 to 75 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18,090 (43.9%)</td>
<td>25,197 (51.6%)</td>
<td>0.15 &lt;0.001</td>
</tr>
<tr>
<td>76 to 85 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17,095 (41.5%)</td>
<td>17,828 (36.5%)</td>
<td>0.1 &lt;0.001</td>
</tr>
<tr>
<td>86 years and over&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6,053 (14.7%)</td>
<td>5,851 (12.0%)</td>
<td>0.08 &lt;0.001</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14,538 (35.3%)</td>
<td>17,373 (35.5%)</td>
<td>0.01 0.007</td>
</tr>
<tr>
<td><strong>Number of medications (past 12 months)</strong> (Median (IQR))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization (past 12 months)</td>
<td>12,406 (30.1%)</td>
<td>12,769 (26.1%)</td>
<td>0.09 &lt;0.001</td>
</tr>
<tr>
<td><strong>Drug Dose&lt;sup&gt;a,b&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>(38.0%)</td>
<td>(35.0%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>(60.0%)</td>
<td>(62.2%)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>(2.3%)</td>
<td>(2.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Comorbidities (past 36 months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>6,815 (16.5%)</td>
<td>6,538 (13.4%)</td>
<td>0.09 0.001</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>22,725 (55.1%)</td>
<td>23,938 (49.0%)</td>
<td>0.12 &lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>7,838 (19.0%)</td>
<td>7,844 (16.0%)</td>
<td>0.08 &lt;0.001</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>1,367 (3.3%)</td>
<td>1,203 (2.5%)</td>
<td>0.05 &lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>15,174 (36.8%)</td>
<td>16,416 (33.6%)</td>
<td>0.07 &lt;0.001</td>
</tr>
<tr>
<td>Conduction disorder</td>
<td>4,931 (12.0%)</td>
<td>4,782 (9.8%)</td>
<td>0.07 &lt;0.001</td>
</tr>
<tr>
<td>Renal disease</td>
<td>5,228 (12.7%)</td>
<td>5,750 (11.8%)</td>
<td>0.03 &lt;0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>6,055 (14.7%)</td>
<td>8,017 (16.4%)</td>
<td>0.05 &lt;0.001</td>
</tr>
<tr>
<td>Anxiety</td>
<td>30,214 (73.3%)</td>
<td>37,027 (75.8%)</td>
<td>0.06 &lt;0.001</td>
</tr>
<tr>
<td>Dementia</td>
<td>7,115 (17.3%)</td>
<td>8,730 (17.9%)</td>
<td>0.02 &lt;0.001</td>
</tr>
<tr>
<td><strong>Medications to treat cardiac disease (past 12 months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>7,797 (18.9%)</td>
<td>8,075 (16.5%)</td>
<td>0.06 0.001</td>
</tr>
<tr>
<td>ACE inhibitors/ARBs</td>
<td>18,299 (44.4%)</td>
<td>22,376 (45.8%)</td>
<td>0.03 &lt;0.001</td>
</tr>
<tr>
<td>Negative chronotropic drugs</td>
<td>16,499 (40.0%)</td>
<td>18,151 (37.1%)</td>
<td>0.06 &lt;0.001</td>
</tr>
<tr>
<td>Statins</td>
<td>12,411 (30.1%)</td>
<td>17,422 (35.6%)</td>
<td>0.12 0.001</td>
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<td>Anti-arrhythmic drugs</td>
<td>1,133 (2.7%)</td>
<td>1,109 (2.3%)</td>
<td>0.03 &lt;0.001</td>
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<tr>
<td>Anti-platelet drugs</td>
<td>8,913 (21.6%)</td>
<td>8,232 (16.8%)</td>
<td>0.12 &lt;0.001</td>
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<td>Warfarin</td>
<td>4,489 (10.9%)</td>
<td>5,050 (10.3%)</td>
<td>0.02 &lt;0.001</td>
</tr>
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<td>Aldosterone antagonists</td>
<td>1,749 (4.2%)</td>
<td>1,677 (3.4%)</td>
<td>0.04 &lt;0.001</td>
</tr>
<tr>
<td><strong>Medications that might trigger cardiac disease (past 12 months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>Proportion (Number, Percent)</td>
<td>Proportion (Number, Percent)</td>
<td>p-value</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>------------------------------</td>
<td>------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>232 (0.6%)</td>
<td>484 (1.0%)</td>
<td>0.05</td>
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<td>Systemic steroids</td>
<td>3,648 (8.8%)</td>
<td>4,317 (8.8%)</td>
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<td>Non-steroidal anti-inflammatory drug</td>
<td>12,555 (30.4%)</td>
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<tr>
<td>Medications associated with neuropathic pain (past 12 months)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td>11,917 (28.9%)</td>
<td>13,792 (28.2%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>200 (0.5%)</td>
<td>388 (0.8%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Medications associated with mortality (past 12 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholinesterase inhibitors</td>
<td>2,105 (5.1%)</td>
<td>3,233 (6.6%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Antipsychotic drugs</td>
<td>3,499 (8.5%)</td>
<td>5,097 (10.4%)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Interquartile Range (IQR)

Angiotensin Converting Enzyme (ACE), Angiotension II Receptor Blocker (ARB)

Negative chronotropic drugs include beta blockers and non-dihydropyridine calcium channel blockers.

a Due to rounding, proportions do not add up to 100%

b Maximal dose reached during observation window
### 9.1.2 Table 1b: Baseline Characteristics of Older Patients on Venlafaxine Compared to Citalopram

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Citalopram</th>
<th>Venlafaxine</th>
<th>Standardized Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=3,909</td>
<td>N=48,876</td>
<td>Crude</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weighted</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at start of cohort drug</td>
<td>Media n (IQR)</td>
<td>81 (74-87)</td>
<td>75 (70-81)</td>
</tr>
<tr>
<td>66 to 75 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1,139 (29.1%)</td>
<td>25,197 (51.6%)</td>
<td>0.15</td>
</tr>
<tr>
<td>76 to 85 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1,561 (39.9%)</td>
<td>17,828 (36.5%)</td>
<td>0.1</td>
</tr>
<tr>
<td>86 years and over&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1,209 (30.9%)</td>
<td>5,851 (12.0%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Male</td>
<td>1,220 (31.2%)</td>
<td>17,373 (35.5%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Number of medications (past 12 months)</td>
<td>Media n (IQR)</td>
<td>11 (8-16)</td>
<td>9 (5-13)</td>
</tr>
<tr>
<td>Hospitalization (past 12 months)</td>
<td>1,140 (29.2%)</td>
<td>12,769 (26.1%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Drug Dose&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>(24.0%)</td>
<td>(35.0%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>(64.0%)</td>
<td>(62.2%)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>(12.0%)</td>
<td>(2.9%)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities (past 36 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>720 (18.4%)</td>
<td>6,538 (13.4%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>2,061 (52.7%)</td>
<td>23,938 (49.0%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Stroke</td>
<td>912 (23.3%)</td>
<td>7,844 (16.0%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>90 (2.3%)</td>
<td>1,203 (2.5%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1,297 (33.2%)</td>
<td>16,416 (33.6%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Conduction disorder</td>
<td>472 (12.1%)</td>
<td>4,782 (9.8%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Renal disease</td>
<td>728 (18.6%)</td>
<td>5,750 (11.8%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Depression</td>
<td>687 (17.6%)</td>
<td>8,017 (16.4%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2,765 (70.7%)</td>
<td>37,027 (75.8%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Dementia</td>
<td>1,897 (48.5%)</td>
<td>8,730 (17.9%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Medications to treat cardiac disease (past 12 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>1,051 (26.9%)</td>
<td>8,075 (16.5%)</td>
<td>0.06</td>
</tr>
<tr>
<td>ACE inhibitors/ARBs</td>
<td>2,034 (52.0%)</td>
<td>22,376 (45.8%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Negative chronotropic drugs</td>
<td>1,625 (41.6%)</td>
<td>18,151 (37.1%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>
### Medications that might trigger cardiac disease (past 12 months)

<table>
<thead>
<tr>
<th>Medication</th>
<th>N 1</th>
<th>N 2</th>
<th>p-value</th>
<th>Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>1,756 (44.9%)</td>
<td>17,422 (35.6%)</td>
<td>0.12</td>
<td>0.001</td>
</tr>
<tr>
<td>Anti-arrhythmic drugs</td>
<td>79 (2.0%)</td>
<td>1,109 (2.3%)</td>
<td>0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-platelet drugs</td>
<td>640 (16.4%)</td>
<td>8,232 (16.8%)</td>
<td>0.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Warfarin</td>
<td>592 (15.1%)</td>
<td>4,503 (10.3%)</td>
<td>0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>175 (4.5%)</td>
<td>1,677 (3.4%)</td>
<td>0.04</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Medications that might trigger cardiac disease (past 12 months)

<table>
<thead>
<tr>
<th>Medication</th>
<th>N 1</th>
<th>N 2</th>
<th>p-value</th>
<th>Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinediones</td>
<td>79 (2.0%)</td>
<td>484 (1.0%)</td>
<td>0.05</td>
<td>0.002</td>
</tr>
<tr>
<td>Systemic steroids</td>
<td>319 (8.2%)</td>
<td>4,317 (8.8%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drug</td>
<td>722 (18.5%)</td>
<td>14,886 (30.5%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Medications associated with neuropathic pain (past 12 months)

<table>
<thead>
<tr>
<th>Medication</th>
<th>N 1</th>
<th>N 2</th>
<th>p-value</th>
<th>Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>926 (23.7%)</td>
<td>13,792 (28.2%)</td>
<td>0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>63 (1.6%)</td>
<td>388 (0.8%)</td>
<td>0.04</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Medications associated with mortality (past 12 months)

<table>
<thead>
<tr>
<th>Medication</th>
<th>N 1</th>
<th>N 2</th>
<th>p-value</th>
<th>Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinesterase inhibitors</td>
<td>896 (22.9%)</td>
<td>3,233 (6.6%)</td>
<td>0.06</td>
<td>0.003</td>
</tr>
<tr>
<td>Antipsychotic drugs</td>
<td>927 (23.7%)</td>
<td>5,097 (10.4%)</td>
<td>0.07</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Interquartile Range (IQR)

Angiotensin Converting Enzyme (ACE), Angiotension II Receptor Blocker (ARB)

Negative chronotropic drugs include beta blockers and non-dihydropyridine calcium channel blockers.

*a* Due to rounding, proportions do not add up to 100%

*b* Maximal dose reached during observation window
### 9.1.3 Table 2a: Adverse Cardiac Events in Older Patients on Venlafaxine Compared to Sertraline (N=90,114)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Events in Venlafaxine Patients N (%)</th>
<th>Events in Sertraline Patients N (%)</th>
<th>Weighted Events in Venlafaxine N (%)</th>
<th>Weighted Events in Sertraline N (%)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite</td>
<td>3966 (8.1)</td>
<td>3707 (9.0)</td>
<td>4259 (8.7)</td>
<td>3459 (8.4)</td>
<td>0.97 (0.93 to 1.02)</td>
</tr>
<tr>
<td>Acute Myocardial Infarction</td>
<td>430 (0.9)</td>
<td>404 (1.0)</td>
<td>447 (0.9)</td>
<td>385 (0.9)</td>
<td>0.91 (0.80 to 1.05)</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>986 (2.0)</td>
<td>1109 (2.7)</td>
<td>1094 (2.2)</td>
<td>995 (2.4)</td>
<td>0.87 (0.80 to 0.95)</td>
</tr>
<tr>
<td>Death</td>
<td>3098 (6.3)</td>
<td>2770 (6.7)</td>
<td>3325 (6.8)</td>
<td>2602 (6.3)</td>
<td>1.01 (0.96 to 1.06)</td>
</tr>
<tr>
<td>Gastrointestinal Hemorrhage</td>
<td>333 (0.7)</td>
<td>298 (0.7)</td>
<td>353 (0.7)</td>
<td>282 (0.7)</td>
<td>0.99 (0.84 to 1.16)</td>
</tr>
</tbody>
</table>

Confidence Interval (CI)

### 9.1.4 Table 2b: Adverse Cardiac Events in Older Patients on Venlafaxine Compared to Citalopram (N=52,785)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Events in Venlafaxine Patients N (%)</th>
<th>Events in Citalopram Patients N (%)</th>
<th>Weighted Events in Venlafaxine N (%)</th>
<th>Weighted Events in Citalopram N (%)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite</td>
<td>3966 (8.1)</td>
<td>456 (11.7)</td>
<td>4259 (8.7)</td>
<td>294 (7.5)</td>
<td>1.39 (1.19 to 1.62)</td>
</tr>
<tr>
<td>Acute Myocardial Infarction</td>
<td>430 (0.9)</td>
<td>38 (1.0)</td>
<td>447 (0.9)</td>
<td>27 (&lt;0.1)</td>
<td>1.59 (1.5 to 2.41)</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>986 (2.0)</td>
<td>88 (2.2)</td>
<td>1094 (2.2)</td>
<td>80 (2.0)</td>
<td>1.22 (0.87 to 1.72)</td>
</tr>
<tr>
<td>Death</td>
<td>3098 (6.3)</td>
<td>371 (9.5)</td>
<td>3325 (6.8)</td>
<td>216 (5.5)</td>
<td>1.49 (1.26 to 1.76)</td>
</tr>
<tr>
<td>Gastrointestinal Hemorrhage</td>
<td>333 (0.7)</td>
<td>32 (0.8)</td>
<td>353 (0.7)</td>
<td>27 (&lt;0.1)</td>
<td>1.27 (0.82 to 1.96)</td>
</tr>
</tbody>
</table>

Confidence Interval (CI)
### 9.1.5 Table 3: Exploratory Time-Dependent Dose Analysis of Older Patients on Venlafaxine Compared to Sertraline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude Hazard Ratio (95% Confidence Interval)</th>
<th>Adjusted Hazard Ratio&lt;sup&gt;a&lt;/sup&gt; (95% Confidence Interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.84 (0.80 to 0.87)</td>
<td>1.00 (0.96 to 1.05)</td>
<td>0.89</td>
</tr>
<tr>
<td>Moderate dose&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.90 (0.85 to 0.94)</td>
<td>1.06 (1.01 to 1.12)</td>
<td>0.01</td>
</tr>
<tr>
<td>High dose&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.98 (0.94 to 1.06)</td>
<td>1.41 (1.25 to 1.59)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adjusted for age, female sex, hospitalization in the past year, stroke, heart failure, cardiovascular disease, use of statins and antiplatelets, and the aggregated diagnosis groups, limited minor and stable but persistent psychosocial disease.

<sup>b</sup>Sertraline is reference

<sup>c</sup>Low dose is reference
9.2 FIGURES

9.2.1 Figure 1: Boxplot Distribution of Inverse Probability of Treatment Weights for Venlafaxine to Sertraline and Venlafaxine to Citalopram Comparisons
9.2.2 Figure 2a: Crude and Weighted Survival Curves for Adverse Cardiac Events among Individuals on Venlafaxine Compared to Sertraline

**Crude Survival Curve for Primary Outcome from Start of Therapy with Venlafaxine or Sertraline**

**Weighted Survival Curve of Primary Outcome from Start of Therapy with Sertraline or Venlafaxine**
9.2.3 Figure 2b: Crude and Weighted Survival Curves for Adverse Cardiac Events among Individuals on Venlafaxine Compared to Citalopram

Crude Survival Curve for Primary Outcome from Start of Therapy with Venlafaxine or Citalopram

Weighted Survival Curve for Primary Outcome from Start of Therapy with Venlafaxine or Citalopram
9.2.4 Figure 3a: Adverse Cardiac Events in Older Patients without Cardiovascular Disease on Venlafaxine Compared to Sertraline (N=43,451)

Weighted Hazard Ratio

Composite: 0.94 (0.86 to 1.03)
Acute Myocardial Infarction: 1.01 (0.76 to 1.34)
Congestive Heart Failure: 0.88 (0.71 to 1.10)
Death: 0.93 (0.85 to 1.02)
Gastrointestinal Hemorrhage: 0.80 (0.60 to 1.07)

9.2.5 Figure 3b: Adverse Cardiac Events in Older Patients with Cardiovascular Disease on Venlafaxine Compared to Sertraline (N=46,663)

Weighted Hazard Ratio (95% CI)

Composite: 0.99 (0.94 to 1.04)
Acute Myocardial Infarction: 0.89 (0.76 to 1.05)
Congestive Heart Failure: 0.87 (0.80 to 0.96)
Death: 1.05 (0.98 to 1.11)
Gastrointestinal: 1.10 (0.90 to 1.33)
9.2.6 Figure 4a: Adverse Cardiac Events in Older Patients without Cardiovascular Disease on Venlafaxine Compared to Citalopram (N=26,786)

Weighted Hazard Ratio (95% CI)

- Composite: 1.39 (1.09 to 1.77)
- Acute Myocardial Infarction: 2.75 (1.06 to 7.12)
- Congestive Heart Failure: 1.54 (0.67 to 3.53)
- Death: 1.33 (1.03 to 1.72)
- Gastrointestinal Hemorrhage: 0.96 (0.49 to 1.86)

9.2.7 Figure 4b: Adverse Cardiac Events of Older Patients with Cardiovascular Disease on Venlafaxine Compared to Citalopram (N=25,999)

Weighted Hazard Ratio (95% CI)

- Composite: 1.34 (1.08 to 1.65)
- Acute Myocardial Infarction: 1.24 (0.77 to 2.02)
- Congestive Heart Failure: 1.07 (0.71 to 1.61)
- Death: 1.56 (1.24 to 1.96)
- Gastrointestinal Hemorrhage: 1.53 (0.84 to 2.78)
10 APPENDICES

10.1.1 APPENDIX 1a: Aggregated Diagnosis Groups of Older Individuals on Venlafaxine Compared to Sertraline
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sertraline</th>
<th>Venlafaxine</th>
<th>Standardized Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=41,238</td>
<td>N=48,876</td>
<td>Crude</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weighted</td>
</tr>
<tr>
<td>Aggregated Diagnosis Groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time Limited</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>18,315 (44.4%)</td>
<td>22,435 (45.9%)</td>
<td>0.03 0.001</td>
</tr>
<tr>
<td>Minor-Primary Infections</td>
<td>28,361 (68.8%)</td>
<td>33,464 (68.5%)</td>
<td>0.01 &lt;0.001</td>
</tr>
<tr>
<td>Major</td>
<td>10,191 (24.7%)</td>
<td>11,094 (22.7%)</td>
<td>0.05 &lt;0.001</td>
</tr>
<tr>
<td>Major-Primary Infections</td>
<td>7,710 (18.7%)</td>
<td>8,677 (17.8%)</td>
<td>0.02 0.001</td>
</tr>
<tr>
<td>Allergies</td>
<td>4,017 (9.7%)</td>
<td>4,713 (9.6%)</td>
<td>0 0.001</td>
</tr>
<tr>
<td>Asthma</td>
<td>4,826 (11.7%)</td>
<td>5,393 (11.0%)</td>
<td>0.02 &lt;0.001</td>
</tr>
<tr>
<td>Likely to Recur</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discrete</td>
<td>25,095 (60.9%)</td>
<td>29,848 (61.1%)</td>
<td>0 &lt;0.001</td>
</tr>
<tr>
<td>Discrete-Infections</td>
<td>15,601 (37.8%)</td>
<td>18,381 (37.6%)</td>
<td>0 &lt;0.001</td>
</tr>
<tr>
<td>Progressive</td>
<td>9,931 (24.1%)</td>
<td>10,003 (20.5%)</td>
<td>0.09 &lt;0.001</td>
</tr>
<tr>
<td>Chronic Medical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>36,730 (89.1%)</td>
<td>43,573 (89.2%)</td>
<td>0 0.001</td>
</tr>
<tr>
<td>Unstable</td>
<td>28,371 (68.8%)</td>
<td>32,026 (65.5%)</td>
<td>0.07 &lt;0.001</td>
</tr>
<tr>
<td>Chronic Specialty</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable-Orthopedic</td>
<td>2,053 (5.0%)</td>
<td>2,272 (4.6%)</td>
<td>0.02 &lt;0.001</td>
</tr>
<tr>
<td>Stable-Ear,Nose,Throat</td>
<td>4,052 (9.8%)</td>
<td>4,558 (9.3%)</td>
<td>0.02 0.001</td>
</tr>
<tr>
<td>Stable-Eye</td>
<td>15,148 (36.7%)</td>
<td>16,721 (34.2%)</td>
<td>0.05 &lt;0.001</td>
</tr>
<tr>
<td>Unstable-Orthopedic</td>
<td>2,921 (7.1%)</td>
<td>3,644 (7.5%)</td>
<td>0.01 &lt;0.001</td>
</tr>
<tr>
<td>Unstable-Ear,Nose,Throat</td>
<td>1,112 (2.7%)</td>
<td>1,165 (2.4%)</td>
<td>0.02 &lt;0.001</td>
</tr>
<tr>
<td>Unstable-Eye</td>
<td>8,005 (19.4%)</td>
<td>9,171 (18.8%)</td>
<td>0.02 &lt;0.001</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>9,659 (23.4%)</td>
<td>11,902 (24.4%)</td>
<td>0.02 &lt;0.001</td>
</tr>
<tr>
<td>Injuries or Adverse Effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>14,103 (34.2%)</td>
<td>16,694 (34.2%)</td>
<td>0 &lt;0.001</td>
</tr>
<tr>
<td>Major</td>
<td>14,939 (36.2%)</td>
<td>17,518 (35.8%)</td>
<td>0.01 &lt;0.001</td>
</tr>
<tr>
<td>Psychosocial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time Limited, Minor</td>
<td>4,354 (10.6%)</td>
<td>4,890 (10.0%)</td>
<td>0.02 &lt;0.001</td>
</tr>
<tr>
<td>Stable, Recurrent or Persistent</td>
<td>25,155 (61.0%)</td>
<td>32,589 (66.7%)</td>
<td>0.12 0.001</td>
</tr>
<tr>
<td>Unstable, Recurrent or Persistent</td>
<td>9,327 (22.6%)</td>
<td>11,486 (23.5%)</td>
<td>0.02 0.001</td>
</tr>
<tr>
<td>Signs or Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>27,612 (67.0%)</td>
<td>32,471 (66.4%)</td>
<td>0.01 &lt;0.001</td>
</tr>
<tr>
<td>Uncertain</td>
<td>34,365 (83.3%)</td>
<td>40,700 (83.3%)</td>
<td>0 &lt;0.001</td>
</tr>
<tr>
<td>Major</td>
<td>24,808 (60.2%)</td>
<td>28,952 (59.2%)</td>
<td>0.02 0.001</td>
</tr>
<tr>
<td>Discretionary</td>
<td>14,760 (35.8%)</td>
<td>17,376 (35.6%)</td>
<td>0.01 0.001</td>
</tr>
<tr>
<td>See and Reassure</td>
<td>1,300 (3.2%)</td>
<td>1,343 (2.7%)</td>
<td>0.02 &lt;0.001</td>
</tr>
<tr>
<td>Prevention or Administrative</td>
<td>20,534 (49.8%)</td>
<td>24,515 (50.2%)</td>
<td>0.01 0.001</td>
</tr>
<tr>
<td>Category</td>
<td>Count 1</td>
<td>Count 2</td>
<td>p-value</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Malignancy</td>
<td>10,128</td>
<td>12,527</td>
<td>0.02</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>213</td>
<td>210</td>
<td>0.01</td>
</tr>
<tr>
<td>Dental</td>
<td>891</td>
<td>1,049</td>
<td>0</td>
</tr>
</tbody>
</table>
10.1.2 APPENDIX 1b: Aggregated Diagnosis Groups of Older Individuals on Venlafaxine Compared to Citalopram
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Citalopram</th>
<th>Venlafaxine</th>
<th>Standardized Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=3,909</td>
<td>N=48,876</td>
<td>Crude</td>
</tr>
<tr>
<td><strong>Aggregated Diagnosis Groups</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time Limited</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>1,749 (44.7%)</td>
<td>22,435 (45.9%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Minor-Primary Infections</td>
<td>2,499 (63.9%)</td>
<td>33,464 (68.5%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Major</td>
<td>956 (24.5%)</td>
<td>11,094 (22.7%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Major-Primary Infections</td>
<td>829 (21.2%)</td>
<td>8,677 (17.8%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Allergies</td>
<td>231 (5.9%)</td>
<td>4,713 (9.6%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Asthma</td>
<td>292 (7.5%)</td>
<td>5,393 (11.0%)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Likely to Recur</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discrete</td>
<td>2,224 (56.9%)</td>
<td>29,848 (61.1%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Discrete-Infections</td>
<td>1,574 (40.3%)</td>
<td>18,381 (37.6%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Progressive</td>
<td>1,139 (29.1%)</td>
<td>10,003 (20.5%)</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Chronic Medical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>3,352 (85.8%)</td>
<td>43,573 (89.2%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Unstable</td>
<td>2,754 (70.5%)</td>
<td>32,026 (65.5%)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Chronic Specialty</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable-Orthopedic</td>
<td>175 (4.5%)</td>
<td>2,272 (4.6%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Stable-Ear,Nose,Throat</td>
<td>294 (7.5%)</td>
<td>4,558 (9.3%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Stable-Eye</td>
<td>1,081 (27.7%)</td>
<td>16,721 (34.2%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Unstable-Orthopedic</td>
<td>198 (5.1%)</td>
<td>3,644 (7.5%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Unstable-Ear,Nose,Throat</td>
<td>68 (1.7%)</td>
<td>1,165 (2.4%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Unstable-Eye</td>
<td>722 (18.5%)</td>
<td>9,171 (18.8%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>764 (19.5%)</td>
<td>11,902 (24.4%)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Injuries or Adverse Effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>1,452 (37.1%)</td>
<td>16,694 (34.2%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Major</td>
<td>1,656 (42.4%)</td>
<td>17,518 (35.8%)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Psychosocial</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time Limited, Minor</td>
<td>392 (10.0%)</td>
<td>4,890 (10.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stable, Recurrent or Persistent</td>
<td>2,389 (61.1%)</td>
<td>32,589 (66.7%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Unstable, Recurrent or Persistent</td>
<td>2,001 (51.2%)</td>
<td>11,486 (23.5%)</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>Signs or Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>2,511 (64.2%)</td>
<td>32,471 (66.4%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Uncertain</td>
<td>3,258 (83.3%)</td>
<td>40,700 (83.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major</td>
<td>2,356 (60.3%)</td>
<td>28,952 (59.2%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Discretionary</td>
<td>1,117 (28.6%)</td>
<td>17,376 (35.6%)</td>
<td>0.15</td>
</tr>
<tr>
<td>See and Reassure</td>
<td>92 (2.4%)</td>
<td>1,343 (2.7%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Prevention or Administrative</td>
<td>2,108 (53.9%)</td>
<td>24,515 (50.2%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Malignancy</td>
<td>913 (23.4%)</td>
<td>12,527 (25.6%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>21 (0.5%)</td>
<td>210 (0.4%)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>----------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>Dental</td>
<td>99 (2.5%)</td>
<td>1,049 (2.1%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>