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High-Dose Citalopram and Escitalopram and the Risk of Out-of-Hospital Death

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ABSTRACT

Objective: Studies demonstrating that higher doses of citalopram (> 40 mg) and escitalopram (> 20 mg) prolong the corrected QT interval prompted regulatory agency warnings, which are controversial, given the absence of confirmatory clinical outcome studies. We compared the risk of potential arrhythmia-related deaths for high doses of these selective serotonin reuptake inhibitors (SSRIs) to that for equivalent doses of fluoxetine, paroxetine, and sertraline.

Methods: The Tennessee Medicaid retrospective cohort study included 54,220 persons 30–74 years of age without cancer or other life-threatening illness who were prescribed high-dose SSRIs from 1998 through 2011. The mean age was 47 years, and 76% were female. Demographic characteristics and comorbidity for individual SSRIs were comparable. Because arrhythmia-related deaths are typically sudden and occur outside the hospital, we analyzed out-of-hospital sudden unexpected death as well as sudden cardiac deaths, a more specific indicator of proarrhythmic effects.

Results: The adjusted risk of sudden unexpected death for citalopram did not differ significantly from that for the other SSRIs. The respective hazard ratios (HRs) for citalopram versus escitalopram, fluoxetine, paroxetine, and sertraline were 0.84 (95% CI, 0.40–1.75), 1.24 (95% CI, 0.75–2.05), 0.75 (95% CI, 0.45–1.24), and 1.53 (95% CI, 0.91–2.55). There were no significant differences for sudden cardiac death or all study deaths, nor were there significant differences among high-risk patients (≥ 60 years of age, upper quartile baseline cardiovascular risk). Escitalopram users had no significantly increased risk for any study end point.

Conclusions: We found no evidence that risk of sudden unexpected death, sudden cardiac death, or total mortality for high-dose citalopram and escitalopram differed significantly from that for comparable doses of fluoxetine, paroxetine, and sertraline.

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Questions persist regarding the relative cardiac safety of certain selective serotonin reuptake inhibitor (SSRI) antidepressants, the mainstay of antidepressant therapy for more than 25 years.[1] A thorough QT-interval study[2] of citalopram demonstrated a dose-related increase in the corrected QT (QTc) interval, with an increase of 18.5 milliseconds for a 60-mg daily dose. Furthermore, prior to the US Food and Drug Administration (FDA) warning (http://www.fda.gov/Drugs/DrugSafety/ucm269086.htm), multiple cases of QTc prolongation and torsade de pointes were reported for this SSRI, both in overdose and in the usual clinical doses.[3] These data, coupled with lack of evidence from fixed-dose studies of greater efficacy for the 60-mg dose, led the FDA to warn against citalopram use in doses > 40 mg.

The FDA warning has been controversial,[4] in part because of negative findings from controlled studies of clinical outcomes.[5] A US Department of Veterans Affairs (VA) retrospective cohort study[6] found no evidence that the risk of either diagnosed ventricular arrhythmias or cardiac mortality for higher doses of citalopram differed from that for either lower doses of citalopram or equivalent doses of sertraline. A multistate Medicaid retrospective cohort study[7] found no significant difference in diagnosed ventricular arrhythmia or sudden cardiac death between citalopram doses of ≤ 20 mg and > 40 mg (hazard ratio [HR] of 1.31 [95% CI, 0.88–1.95]).

The FDA asserted that these epidemiologic studies could not be relied upon to detect the adverse cardiac effects of high-dose citalopram.[8,9] One concern was the study end points. Because torsade de pointes and other related arrhythmias often are rapidly fatal, patients may not survive long enough to receive a diagnosis. Overall cardiac mortality includes numerous deaths unlikely to be related to proarrhythmic medication effects, which would bias toward the null. The FDA also questioned comparison of low- versus high-dose citalopram, as patients with greater cardiovascular morbidity could be "channeled" to receive lower doses. Such confounding, if incompletely controlled for, would mask an adverse effect of higher doses. Furthermore, the comparison between low and high doses is less clinically relevant, as patients typically start with lower doses that are titrated upward when response is inadequate.[10]

A thorough QT-interval study[2] of escitalopram, the (*S*)-enantiomer of citalopram, also found a dose-related increase in QTc. The prolongation of 10.7 milliseconds for the 30-mg daily dose was comparable to that for moxifloxacin, known to have proarrhythmic effects.[11] Although the relation between moderate QTc increases and risk of arrhythmias is complex, these data suggest that high-dose escitalopram also might have adverse cardiac effects, particularly given case reports[3] of serious ventricular arrhythmias. Indeed, the European Medicines and Healthcare products

Regulatory Agency issued an advisory for escitalopram recommending a maximum daily dose of 20 mg.[12]

We thus conducted a cohort study to assess the cardiovascular safety of high doses of citalopram and escitalopram relative to other SSRIs. Our study differed in two ways from previous investigations. First, to better identify deaths related to medication effects, we focused on those outside the hospital in a cohort of patients for whom such deaths should otherwise be infrequent. Deaths were classified to identify those most likely to be related to proarrhythmic medication effects. Second, we directly compared high doses of citalopram and escitalopram with comparable doses of other SSRIs.

Clinical Points

- US Food and Drug Administration–mandated studies of 60-mg citalopram and 30-mg escitalopram reported QT prolongation suggestive of increased risk for serious arrhythmias.
- A comparison of high-dose citalopram and escitalopram to comparable doses of other selective serotonin reuptake inhibitors found no increased risk for sudden unexpected death, sudden cardiac death, or total out-of-hospital deaths.
- In the study population, there was no evidence these drugs increased risk of arrhythmia-related deaths.

METHODS

Cohort and Follow-Up

We conducted a retrospective cohort study of Tennessee Medicaid enrollees (see eAppendix at PSYCHIATRIST.COM) with prescriptions for high doses of SSRIs filled from 1998 through 2011. The cohort included patients for whom deaths outside the hospital, absent proarrhythmic medication effects, should be relatively infrequent. To reduce the occurrence of deaths related to terminal illness, we excluded patients 75 years of age or older, those with cancer and other life-threatening diseases, or those residing in a nursing home (Supplementary eTable 1). The cohort also excluded persons less than 30 years of age because cardiac deaths in children and young adults are very rare.[13] Patients in the hospital could not enter the cohort until 30 days after discharge because deaths during this period may be related to the reasons for the hospitalization. For patients who met these eligibility criteria, there were no further restrictions on psychiatric diagnoses.

The study SSRIs were citalopram, escitalopram, fluoxetine, paroxetine, and sertraline. We did not consider fluvoxamine, given its limited use in the study population. High-dose SSRI use was defined as > 40 mg/d for citalopram, fluoxetine, and paroxetine; > 20 mg for escitalopram; and > 150 mg for sertraline. These cut points were based on both clinical guidelines[10] and the cohort dose distribution.

Patients entered the cohort on the date they filled the first SSRI prescription on which they met the study inclusion/exclusion criteria (Supplementary eTables 1 and 2). Patients remained in the cohort until the end of the study, death, failure to meet inclusion/exclusion criteria, or the cessation of study SSRI use. Those who left the cohort could reenter if they subsequently became eligible.

Given that the ventricular arrhythmias of concern are acute drug effects,[14,15] cohort follow-up consisted of current use of study SSRIs (Supplementary eFigure 1). We excluded person-time during and in the 30 days following hospitalization, which led to exclusion of deaths for patients admitted to the hospital. We believed this would reduce potential confounding and improve capacity to detect adverse SSRI effects, given that many inpatient deaths are unlikely to be related to the cardiac effects of SSRIs. Bias could have been introduced if the study groups differed with regard to the proportions of patients with an SSRI-related arrhythmia who survived until hospital admission but ultimately died in the hospital. However, this scenario seems unlikely, given that medication-related ventricular arrhythmias are rapidly lethal, most frequently leading to death before the patient can seek medical care.[16–18]

End Points

The primary end point was sudden unexpected deaths, the composite of sudden cardiac deaths, other cardiovascular deaths, and unintentional medication overdose deaths. These deaths were considered most likely to be related to serious ventricular arrhythmias.

Sudden cardiac deaths were defined as an ultimately fatal, sudden, pulseless condition consistent with a ventricular tachyarrhythmia occurring in the absence of a known noncardiac condition as the proximate cause of the death.[19] Because sudden cardiac deaths frequently are due to serious ventricular arrhythmias, they have been considered an indicator of proarrhythmic medication effects.[15,20–22] We identified these deaths from a previously validated computerized definition that utilized multiple sources of data, including computerized death certificates, hospital discharge files, and Medicaid files with terminal outpatient medical care encounters (eAppendix 1).[15] In the validation studies,[15,21] this definition had positive predictive values of 87%–90%.

Some sudden cardiac deaths could be misclassified as due to other cardiovascular causes. Thus, the primary end point included other cardiovascular deaths: cardiovascular deaths that did not meet the definition for sudden cardiac death (Supplementary eTable 3).

Although SSRI overdose is infrequently fatal,[23] proarrhythmic effects could increase the risk of death from other medications commonly taken by antidepressant users, including opioids and cyclic antidepressants. Because such deaths can be difficult to distinguish postmortem from those due to arrhythmias,[24,25] the sudden unexpected death category also included unintentional medication overdose deaths (Supplementary eTable 4).

Other deaths included all other deaths during follow-up. All study deaths were the total of sudden unexpected deaths and other deaths.

Table 1. Cohort Characteristics at the Time of Filling of Study SSRI Prescriptions[a]

Variable	Citalopram	Escitalopram	Fluoxetine	Paroxetine	Sertraline
Persons in cohort, n	9,860	4,185	13,692	11,080	15,403
No. of SSRI prescriptions	88,243	27,850	160,144	99,630	181,652
Age, mean, y	46.6	46.2	47.2	47.0	46.9
Age ≥ 65 y, %	2.4	2.5	2.6	3.3	3.2
Women, %	76.5	75.1	78.9	74.7	75.1
Other antidepressants, %					
TCA: any past year	16.1	14.8	20.6	20.5	17.3
Trazodone: any past year	26.2	23.2	26.1	26.2	26.0
Other antidepressant: any past year	30.9	40.3	24.6	25.0	28.6
Psychiatric diagnosis and health care, %					
Schizophrenia/psychosis	11.4	10.6	9.8	10.3	10.1
Bipolar disorder	18.4	21.3	15.7	14.0	15.5
Major depression	46.0	50.0	46.2	43.3	44.1
Other mood disorder	37.1	40.0	36.8	36.5	36.5
Panic disorder	11.5	11.4	9.7	17.0	11.0
Psychiatric hospitalization past year	5.3	7.5	3.9	4.0	4.7
Psychiatric and analgesic medications, %					
Antipsychotic: any past year	44.2	54.1	37.9	41.1	42.6
Benzodiazepine: any past year	54.3	67.9	57.8	62.4	57.1
Mood stabilizer: any past year	25.6	31.9	22.2	20.8	23.2
Opioid: any past year	72.5	76.4	70.8	67.9	70.6
Musculoskeletal relaxant: any past year	40.1	45.2	39.6	37.2	39.3
Cardiovascular diagnosis and health care, %					
Coronary heart disease	9.7	10.7	9.4	9.5	9.9
Arrhythmia	4.6	4.7	3.8	4.2	4.3
Congestive heart failure	3.8	4.3	4.0	3.9	3.8
Cerebrovascular disease	4.1	4.8	4.1	4.2	4.4
Diabetes	21.7	21.7	20.8	22.3	21.1
Cardiovascular hospitalization past year	1.6	2.0	1.7	1.9	1.8
Other hospitalization past year	9.5	10.8	9.9	9.8	9.6
Cardiovascular medications, %					
ACE inhibitor/angiotensin receptor blocker	31.9	32.1	30.4	30.8	31.4
β-Blocker	22.1	22.7	20.8	21.8	21.2
Calcium channel blocker	16.7	16.9	18.0	18.2	17.5
Digoxin	1.3	1.3	1.4	1.4	1.4
Loop diuretic	16.1	18.6	18.8	16.7	16.0
Insulin or other injectable hypoglycemic	6.8	6.6	7.5	7.6	7.2
Statin	30.3	31.9	29.5	28.5	32.5
Summary measures of disease risk					
Disease risk score quantile, mean[b]					
Sudden unexpected death	9.6	9.8	9.5	9.4	9.4
Other death	9.8	9.5	9.5	9.4	9.4
All study deaths	9.8	9.8	9.5	9.4	9.4

[a]All values are proportions unless otherwise noted. Unless otherwise stated, medication and diagnosis variables reflect the year preceding the prescription fill date.
[b]Ranges from 0 to 19, where 0 is the lowest and 19 the highest risk quantile. Because the values represent 20 quantiles, by definition the mean for the entire population is 9.5.
Abbreviations: ACE = angiotensin-converting enzyme, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Statistical Analysis

For each of the study end points, we compared the risk among current users of citalopram to that for each of escitalopram, fluoxetine, paroxetine, and sertraline. The comparisons were to individual SSRIs because it is possible that each has different cardiac effects.[1] We performed a similar comparison for escitalopram.

The relative risk of death, adjusted for patient characteristics, was estimated with the hazard ratio (HR) from a proportional hazards regression model, with SSRI use as a time-dependent covariate. Hazard ratios were adjusted for potential differences between users of different SSRIs, as described by 111 covariates (Supplementary eTable 5). These included calendar time; demographic factors; antidepressants not included in the study; diagnoses and medications related to psychiatric, neurologic, musculoskeletal, cardiovascular, and respiratory conditions; indicators of frailty; other proarrhythmic medications; other comorbidity; and recent medical care utilization. Because patient comorbidity could vary during follow-up, all covariates were time dependent.

We controlled for the large number of study covariates by stratifying the regression analysis by 20 quantiles of a time-dependent disease risk score (eAppendix 1).[26–28] The disease risk score, the risk of death as a function of the study covariates, facilitates analyses for multiple exposure categories, given that propensity scores are less suited to nonbinary comparisons.[26–28] Because the disease risk score models the probability of the outcome, a separate score was calculated for each study end point.

All analyses were done with SAS version 9.4 (SAS Institute, Inc). All *P* values are 2-sided.

Figure 1. Number and Incidence of Study Deaths per 10,000 Person-Years of Study Follow-Up

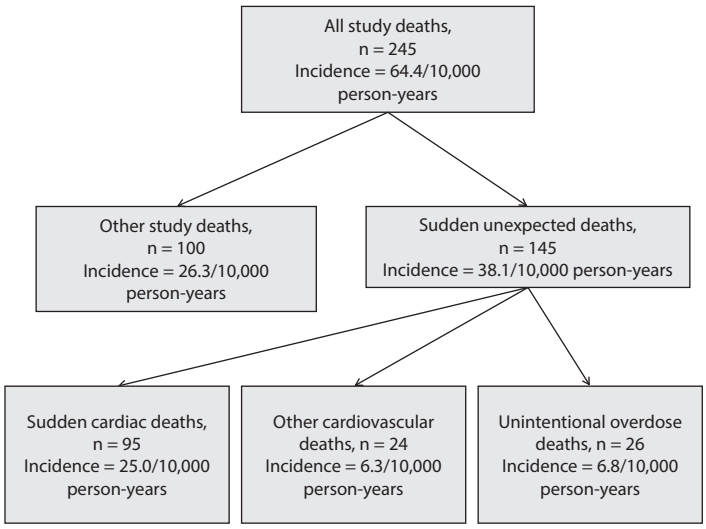

Table 2. Unadjusted Incidence of Study End Points According to Current Use of Individual Selective Serotonin Reuptake Inhibitors

	Citalopram (6,011 person-years)		Escitalopram (1,700 person-years)		Fluoxetine (11,117 person-years)		Paroxetine (6,714 person-years)		Sertraline (12,518 person-years)	
Variable	Deaths, n	Rate[a]	Deaths, n	Rate[a]	Deaths, n	Rate[a]	Deaths, n	Rate[a]	Deaths, n	Rate[a]
Sudden unexpected death	26	43.3	10	58.8	38	34.2	37	55.1	34	27.2
Sudden cardiac death	15	25.0	7	41.2	23	20.7	27	40.2	23	18.4
Other deaths	13	21.6	2	11.8	36	32.4	20	29.8	29	23.2
All deaths	39	64.9	12	70.6	74	66.6	57	84.9	63	50.3

[a]Rates are per 10,000 person-years of follow-up.

RESULTS

The cohort included 54,220 persons with 557,519 qualifying prescriptions for high doses of the study SSRIs (Table 1). The mean age was 47 years, 76% were female, and 10% were 60 years of age or older. There were 45% with a diagnosis of major depression, 16% with bipolar disorders, and 10% with schizophrenia or a related psychosis. Coprescribing of other psychiatric medications was common; in the past year, 42% had filled a prescription for an antipsychotic, 58% for a benzodiazepine, and 23% for a mood stabilizer. Cohort members frequently used analgesics; in the past year, 71% had filled an opioid prescription and 39% a skeletal muscle relaxant prescription. The covariates distributions for the individual SSRIs were comparable. The summary measures of the risk for study end points, the disease risk scores, for the specific SSRIs were comparable.

There were 245 deaths during 38,061 person-years of study follow-up, or 64.4 deaths per 10,000 person-years (Figure 1). These consisted of 145 sudden unexpected deaths (38.1 per 10,000) and 100 (26.3 per 10,000) other deaths. The sudden unexpected deaths included 95 (25.0 per 10,000) sudden cardiac deaths, 24 (6.3 per 10,000) other cardiovascular deaths, and 26 (6.8 per 10,000) unintentional overdose deaths.

There was some variation in the unadjusted incidence of study end points among the individual SSRIs (Table 2). The incidence of sudden unexpected death ranged from 27.2 per 10,000 person-years for sertraline to 58.8 per 10,000 person-years for escitalopram. The incidence of all deaths ranged from 50.3 per 10,000 person-years for sertraline to 84.9 per 10,000 person-years for paroxetine.

However, when the adjusted risk of sudden unexpected death for citalopram was compared to that for the other SSRIs (Table 3), none of the resulting HRs were statistically significant. The HRs for citalopram versus escitalopram, fluoxetine, paroxetine, and sertraline were 0.84 (95% CI, 0.40–1.75), 1.24 (95% CI, 0.75–2.05), 0.75 (95% CI, 0.45–1.24), and 1.53 (95% CI, 0.91–2.55), respectively. There also were no significant differences for sudden cardiac death, other deaths, and all study deaths. Similarly, there were no statistically significant differences for any of the study end points when escitalopram was compared to fluoxetine, paroxetine, and sertraline (Table 3). We also compared both citalopram and escitalopram versus a pooled comparison group consisting of all of the other 3 SSRIs. The respective HRs for sudden unexpected death were 1.16 (0.75–1.78) and 1.37 (0.71–2.64), those for sudden cardiac death were 0.96 (0.55–1.68) and 1.31 (0.60–2.87), and those for all study deaths were 0.93 (0.66–1.31) and 0.91 (0.50–1.63).

Table 3. Study End Point Hazard Ratios (95% CI) for Citalopram and Escitalopram Compared to Other Study Selective Serotonin Reuptake Inhibitors

Variable	Escitalopram	Fluoxetine	Paroxetine	Sertraline
Citalopram vs comparator				
Sudden unexpected death	0.84 (0.40–1.75)	1.24 (0.75–2.05)	0.75 (0.45–1.24)	1.53 (0.91–2.55)
Sudden cardiac death	0.73 (0.30–1.80)	1.12 (0.58–2.16)	0.56 (0.30–1.05)	1.28 (0.67–2.47)
Other deaths	1.80 (0.41–7.98)	0.59 (0.31–1.11)	0.64 (0.32–1.29)	0.81 (0.42–1.57)
All deaths	1.02 (0.53–1.96)	0.89 (0.60–1.31)	0.70 (0.47–1.06)	1.18 (0.79–1.77)
Escitalopram vs comparator				
Sudden unexpected death		1.47 (0.73–2.98)	0.89 (0.44–1.80)	1.82 (0.89–3.70)
Sudden cardiac death		1.54 (0.65–3.63)	0.76 (0.33–1.77)	1.76 (0.75–4.14)
Other deaths		0.33 (0.08–1.36)	0.36 (0.08–1.52)	0.45 (0.11–1.90)
All deaths		0.87 (0.47–1.61)	0.69 (0.37–1.29)	1.16 (0.62–2.15)

We conducted sensitivity analyses for patients thought to be at greatest risk for the adverse effects of QT prolongation.[29] For patients 60 years of age or older, the HRs for sudden unexpected death for citalopram versus fluoxetine, paroxetine, and sertraline were 1.28 (95% CI, 0.36–4.59), 0.72 (95% CI, 0.21–2.46), and 1.71 (95% CI, 0.46–6.44), respectively (escitalopram numbers inadequate). For patients in the upper quartile for risk of sudden cardiac death, the HRs for citalopram versus escitalopram, fluoxetine, paroxetine, and sertraline were 0.87 (95% CI, 0.34–2.25), 1.04 (95% CI, 0.55–1.99), 0.64 (95% CI, 0.34–1.23), and 1.17 (95% CI, 0.61–2.22), respectively.

DISCUSSION

In this cohort study of high-dose users of SSRIs, we found no evidence that the risk of sudden unexpected death for citalopram differed from that for comparable users of other SSRIs. Although the incidence of death varied among the users of the different medications, there was no consistent pattern indicating greater risk for citalopram and, when citalopram was compared with each of the other SSRIs, none of the differences were statistically significant. Furthermore, there was no evidence of increased risk for citalopram in groups thought to be at particular risk for proarrhythmic medication effects: persons who were aged 60 years or older or who were in the upper quartile with regard to baseline cardiovascular risk factors. A similar finding was present for high doses of escitalopram.

One study limitation is that the end point for sudden unexpected death potentially lacks specificity for arrhythmia-related deaths, a criticism of the mortality end point in the VA cohort study.[8] We chose the broader end point because of concerns that in a population with frequent use of medications with high overdose risk, arrhythmia-related deaths might be misclassified. To limit the bias inherent in increasing sensitivity at the potential expense of specificity, we restricted the cohort to nonhospitalized patients for whom deaths unrelated to adverse medication effects should be relatively infrequent. We also did not consider in-hospital cardiovascular deaths (eg, heart failure, stroke), which are unlikely to be related to proarrhythmic effects of outpatient medications. Furthermore, we also performed all study analyses for sudden cardiac death, a more specific indicator of proarrhythmic medication effects.[15,20–22] Findings were essentially unchanged.

Confounding could affect study findings if higher-risk patients were selectively prescribed SSRIs other than citalopram. The FDA warning published in late 2011, the last year of our study, is unlikely to have affected our findings. However, prior case reports[3] of QTc prolongation could have led to avoidance of high-dose citalopram in patients with elevated cardiac risk. The minor differences between SSRI users in demographic characteristics and comorbidity did not support such channeling, as indicated by the comparable summary disease risk scores for the study SSRIs. Furthermore, these factors were accounted for in the statistical analysis. Nevertheless, because we relied upon medical care encounters to define comorbidity, we thus could not control for several potential confounders such as smoking, family history of cardiac disease, or measures of depression severity and other psychiatric comorbidity.

Study power was limited for some of the individual drug comparisons. When citalopram was compared to sertraline, the upper bound of the 95% CI for the sudden unexpected death HR was 2.55, indicating that clinically important risks might not have been detected. However, for paroxetine, a drug thought to have good cardiac safety,[1] the upper bound was 1.24. Thus, it seems unlikely that a large, consistent difference between citalopram and other SSRIs would have been missed.

Our study findings must be interpreted in the context of limited information on the cardiac safety of high doses of fluoxetine, paroxetine, and sertraline, given the absence of thorough QT studies for these drugs. There are reported cases[3,30] of increased QT and/or ventricular arrhythmias for all of the study SSRIs, although these are infrequent.[3] The SADHEART study,[31] a placebo-controlled randomized controlled trial in patients with recent myocardial infarction or unstable angina and major depression, found that sertraline patients had no significant changes in QTc or other measures of cardiac function, although data were not reported for high doses. Further study of the cardiac effects of high doses of the other SSRIs would be useful.

CONCLUSION

In this cohort study of high-dose SSRI users, we found no evidence that the risk of sudden unexpected death, sudden cardiac death, or total out-of-hospital mortality for citalopram and escitalopram differed significantly from that for fluoxetine, paroxetine, or sertraline.

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Drug names: citalopram (Celexa and others), digoxin (Lanoxin and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), moxifloxacin (Avelox and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), trazodone (Desyrel and others).

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Supplementary material: Available at PSYCHIATRIST.COM.

REFERENCES

1. Beach SR, Kostis WJ, Celano CM, et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. *J Clin Psychiatry*. 2014;75(5):e441–e449. *10.4088/JCP.13r08672*
2. Temple R, Laughren T, Stockbridge N. Removal from labeling of 60-mg citalopram dose. *Pharmacoepidemiol Drug Saf*. 2012;21(7):784–786.
3. Beach SR, Celano CM, Noseworthy PA, et al. QTc prolongation, torsades de pointes, and psychotropic medications. *Psychosomatics*. 2013;54(1):1–13.
4. Vieweg WVR, Hasnain M, Howland RH, et al. Citalopram, QTc interval prolongation, and torsade de pointes: how should we apply the recent FDA ruling? *Am J Med*. 2012;125(9):859–868.
5. Howland RH. A critical evaluation of the cardiac toxicity of citalopram: part 2. *J Psychosoc Nurs Ment Health Serv*. 2011;49(12):13–16.
6. Zivin K, Pfeiffer PN, Bohnert ASB, et al. Evaluation of the FDA warning against prescribing citalopram at doses exceeding 40 mg. *Am J Psychiatry*. 2013;170(6):642–650.
7. Leonard CE, Bilker WB, Newcomb C, et al. Additional data on citalopram and the risk of sudden cardiac death and ventricular arrhythmia. *Pharmacoepidemiol Drug Saf*. 2012;21(3):331–332.
8. Bird ST, Crentsil V, Temple R, et al. Cardiac safety concerns remain for citalopram at dosages above 40 mg/day. *Am J Psychiatry*. 2014;171(1):17–19.
9. Zivin K, Pfeiffer PN, Bohnert AS, et al. Safety of high-dosage citalopram. *Am J Psychiatry*. 2014;171(1):20–22.
10. Lam RW, Kennedy SH, Grigoriadis S, et al; Canadian Network for Mood and Anxiety Treatments (CANMAT). Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults, III: pharmacotherapy. *J Affect Disord*. 2009;117(suppl 1):S26–S43.
11. Falagas ME, Rafailidis PI, Rosmarakis ES. Arrhythmias associated with fluoroquinolone therapy. *Int J Antimicrob Agents*. 2007;29(4):374–379.
12. Citalopram and escitalopram: QT interval prolongation—new maximum daily dose restrictions (including in elderly patients), contraindications, and warnings. *Drug Safety Update*. 2001;5(5):A1.
13. Liberthson RR. Sudden death from cardiac causes in children and young adults. *N Engl J Med*. 1996;334(16):1039–1044.
14. Deshmukh A, Ulveling K, Alla V, et al. Prolonged QTc interval and torsades de pointes induced by citalopram. *Tex Heart Inst J*. 2012;39(1):68–70.
15. Chung CP, Murray KT, Stein CM, et al. A computer case definition for sudden cardiac death. *Pharmacoepidemiol Drug Saf*. 2010;19(6):563–572.
16. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med*. 2001;345(20):1473–1482.
17. Marcus FI, Cobb LA, Edwards JE, et al. Mechanism of death and prevalence of myocardial ischemic symptoms in the terminal event after acute myocardial infarction. *Am J Cardiol*. 1988;61(1):8–15.
18. Hinkle LE Jr, Thaler HT. Clinical classification of cardiac deaths. *Circulation*. 1982;65(3):457–464.
19. Siscovick DS, Raghunathan TE, Psaty BM, et al. Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med*. 1994;330(26):1852–1857.
20. Krantz MJ, Martin J, Stimmel B, et al. QTc interval screening in methadone treatment. *Ann Intern Med*. 2009;150(6):387–395.
21. Kawai VK, Murray KT, Stein CM, et al. Validation of a computer case definition for sudden cardiac death in opioid users. *BMC Res Notes*. 2012;5:473.
22. Ray WA, Meredith S, Thapa PB, et al. Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry*. 2001;58(12):1161–1167.
23. Barbey JT, Roose SP. SSRI safety in overdose. *J Clin Psychiatry*. 1998;59(suppl 15):42–48.
24. Kao D, Bucher Bartelson B, Khatri V, et al. Trends in reporting methadone-associated cardiac arrhythmia, 1997–2011: an analysis of registry data. *Ann Intern Med*. 2013;158(10):735–740.
25. Stringer J, Welsh C, Tommasello A. Methadone-associated Q-T interval prolongation and torsades de pointes. *Am J Health Syst Pharm*. 2009;66(9):825–833.
26. Arbogast PG, Kaltenbach L, Ding H, et al. Adjustment for multiple cardiovascular risk factors using a summary risk score. *Epidemiology*. 2008;19(1):30–37.
27. Arbogast PG, Ray WA. Use of disease risk scores in pharmacoepidemiologic studies. *Stat Methods Med Res*. 2009;18(1):67–80.
28. Arbogast PG, Ray WA. Performance of disease risk scores, propensity scores, and traditional multivariable outcome regression in the presence of multiple confounders. *Am J Epidemiol*. 2011;174(5):613–620.
29. FDA Drug Safety Communication: Revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. US Food and Drug Administration Web site. http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm. Updated 2011.
30. Erfurth A, Loew M, Dobmeier P, et al. ECG changes after paroxetine. 3 case reports [in German]. *Nervenarzt*. 1998;69(7):629–631.
31. Glassman AH, O'Connor CM, Califf RM, et al; Sertraline Antidepressant Heart Attack Randomized Trial (SADHEART) Group. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA*. 2002;288(6):701–709.

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Supplementary Material

Article Title: High-Dose Citalopram and Escitalopram and the Risk of Out-of-Hospital Death

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List of Supplementary Material for the article

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Appendix

This appendix provides additional details for the study of high-dose citalopram and should be read in conjunction with the primary manuscript (MS).

1. Cohort

All study data were obtained from Tennessee Medicaid files, which provided an efficient source of data for identifying the cohort, determining periods of probable exposure to medications, and ascertaining deaths.[1;2] The study Medicaid database included enrollment, pharmacy, hospital, outpatient, and nursing home files and was augmented with linkage to death certificates[1;3] and a statewide hospital discharge database. The data are provided by the State of Tennessee Bureau of TennCare and Department of Health. The State, which has ownership of these data, grants Vanderbilt researchers data access for public-health relevant investigations.

The cohort included all Medicaid enrollees with at least one prescription for a high-dose study SSRI during the period 1/1/1998 through 12/31/2011. The study SSRIs were citalopram, escitalopram, fluoxetine, paroxetine, and sertraline. Fluvoxamine was not included as a study SSRI, given its limited use in the study population. Throughout the MS and Appendix, we use the term "SSRI" to denote "a study SSRI".

To enter the cohort, patients had to meet study inclusion/exclusion criteria (Appendix Table 1) on the day the prescription was filled (t_0). Criterion 1 identifies the age range of study interest (see MS). Criterion 2 is necessary to assure the availability of study data.

Criteria 3-5 are designed to identify a population in which the occurrence of sudden cardiac death should be infrequent. See the MS for the rationale for each criterion.

Criterion 6 is designed to exclude persons with recorded evidence of drug abuse.

Criteria 7 is related to the availability in the Medicaid files of the medical encounters needed to define exposure to SSRIs and comorbidity. In addition to requiring that cohort members have Medicaid enrollment with pharmacy benefits for at least one year (criterion 1), we also require medical care utilization during that year. Given that most study covariates were ascertained from medical care encounters, this assured some degree of medical surveillance.

Criterion 8 does not allow a filled prescription for another SSRI in the past 30 days because of potentially overlapping use.

Criterion 9 excluded prescriptions for fluvoxamine, infrequently used in the study population.

Criterion 10 restricted the cohort to users of high-dose SSRIs, the subject of the FDA and MHRA warnings.

Appendix Table 2 shows the numbers of persons meeting each study criterion.

Appendix Table 1 Cohort inclusion/exclusion criteria; t_0 is the date of the SSRI prescription fill.

Criterion	Description
1. Age	Age 30-74 years at t_0.
2. Enrollment	Enrolled with full pharmacy benefits on t_0 and the preceding 365 days.
3. Cancer or other serious illness	No evidence of illness on t_0 or the preceding 365 days for which an out-of-hospital death might be expected. Exclusion diseases were cancer, HIV, renal/liver/cardio-respiratory failure, organ transplant, degenerative musculoskeletal disorders (e.g., multiple sclerosis), potentially lethal congenital anomalies or childhood conditions, or other evidence of end-stage illness.
4. Institution	Not residing in a nursing home or other residential institution on t_0 or at any time in the preceding 365 days, except for stays of <30 days following hospital discharge.
5. Recent hospitalization	Not in the hospital on t_0 or the preceding 29 days.
6. Drug abuse	No recorded evidence of drug abuse (except for alcohol/tobacco) on t_0 or the preceding 365 days.
7. Medical care	At least one filled prescription as well as two encounters with a diagnosis in the 365 days preceding t_0.
8. Multiple SSRIs	No prescription for a different SSRI (includes fluvoxamine) filled on t_0 or the preceding 30 days
9. Study SSRIs	Prescription not for fluvoxamine, little used in the study population.
10. Dose	Dose well defined and >40 mg citalopram-equivalents (40 mg for fluoxetine, paroxetine; 20 mg for escitalopram, 150 mg for sertraline). These equivalents were chosen based on both clinical guidelines and the distribution of doses in the cohort for all SSRI users. The proportions of prescriptions for high doses were citalopram: 11.1%, escitalopram: 6.0%, fluoxetine: 12.8%, paroxetine: 6.8%, sertraline: 15.6%.

Appendix Table 2. Cohort members qualifying after exclusions.

	N of persons
1. Age	411,788
2. Enrollment	344,926
3. Cancer or other serious illness	314,431
4. Institution	307,210
5. Recent hospitalization	301,073
6. Drug abuse	289,793
7. Medical care	279,026
8. Multiple SSRIs	278,481
9. Study SSRIs	277,614
10. Dose	54,220

2. Followup

The patient entered the cohort on the date of filling of the first prescription for an SSRI during the study period that met the criteria in Appendix Table 1.

Followup consisted of periods of current SSRI use that met the study inclusion/exclusion criteria. These periods were identified from filled prescriptions for SSRIs. The duration of current use for the prescription was identified from the dispensed days of supply, edited to resolve infrequent inconsistencies with quantity dispensed. In Tennessee Medicaid, filled prescriptions during the study period almost always were limited to 30 days of supply.

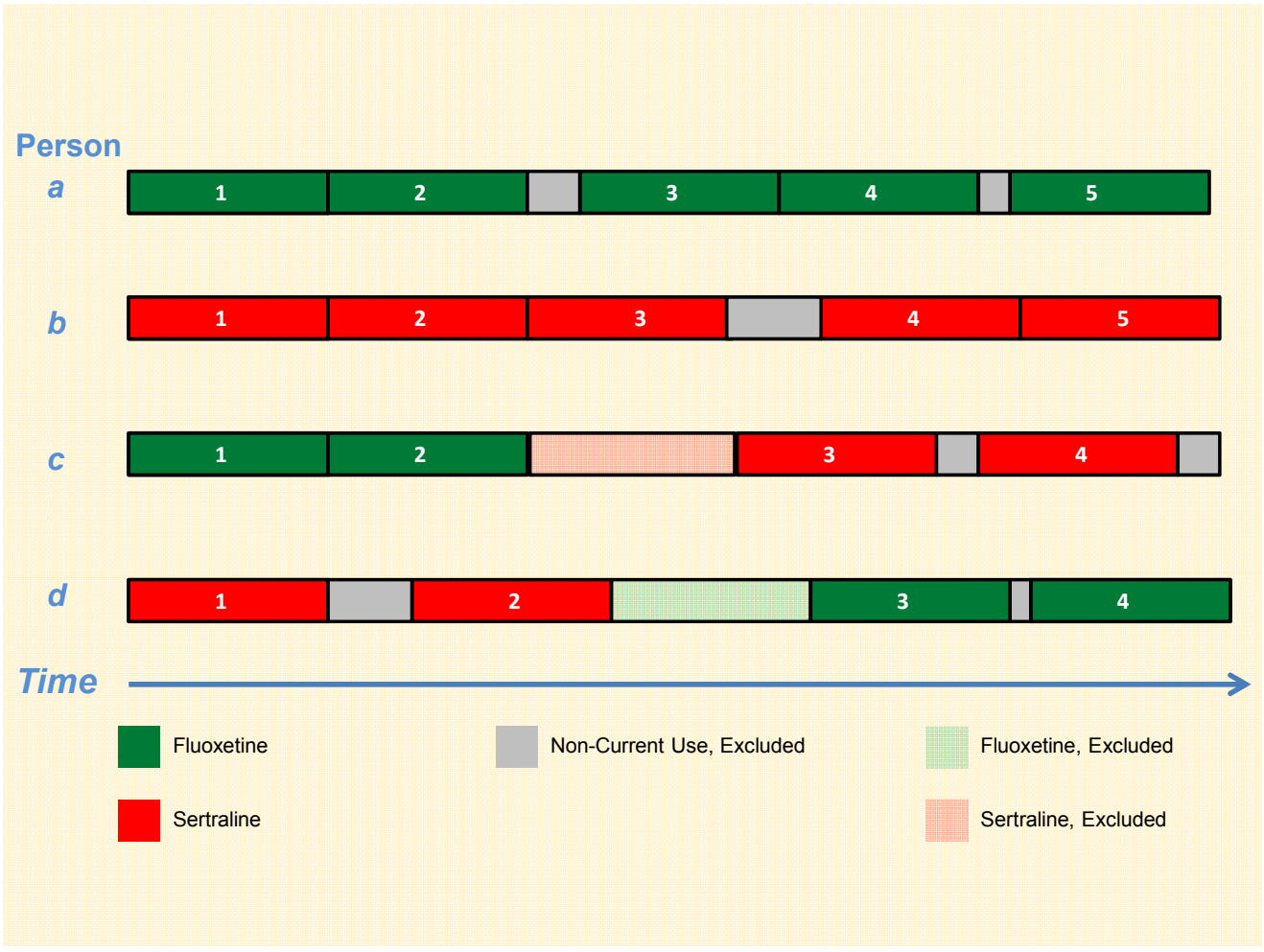
To define study followup, we evaluated all SSRI prescriptions filled during the study period. Those that met the inclusion/exclusion criteria on the day the prescription was filled contributed to current use person-time.

Persons prescribed multiple SSRIs contributed person-time to the corresponding categories, although overlapping use was not permitted. Thus, if a person changed to a different SSRI during followup, we excluded the 30 days following the end of the last prescription for the prior SSRI from followup. This "wash out" period reduced the potential for exposure misclassification, given the potential overlap in SSRI use. Subsequent current use person-time accrued to the second SSRI.

Study followup ended with the last day of the study period, the last day of supply of the last qualifying prescription, irreversible failure to meet the inclusion/exclusion criteria (e.g., age 75+), or death.

Appendix Figure 1 depicts cohort followup for 4 hypothetical persons. These persons fill prescriptions for two SSRIs, fluoxetine and sertraline (chosen as illustrative examples). Person a has 5 qualifying prescriptions for fluoxetine, with a short interval between the end of the days of supply for prescription 2 and the filling of prescription 3, as indicated in gray. This period is excluded from study followup to reduce misclassification; it is unclear whether it represents current use or non-use. All current use person-time defined by the 5 prescriptions goes into the fluoxetine category. Person b has a similar pattern of use of sertraline. Person c has 2 qualifying prescriptions for fluoxetine, which contribute to fluoxetine SR person-time. After the second prescription, person 2 switches to sertraline. The first prescription for sertraline, indicated by a lighter color, is the "wash out" period and is not included in followup. However, the next 2 qualifying prescriptions (3 and 4) contribute person-time to the sertraline current use category. Person d shows a similar switch from sertraline to fluoxetine.

A single person could have person-time for multiple SSRIs in the analysis (Appendix Figure 1). Because these time periods were non-overlapping and the endpoint (death) occurred only once, statistical independence assumptions were not violated.[4]



Appendix Figure 1. Study followup for four hypothetical cohort members (persons a, b, c, d). Numbers in bars represent qualifying SSRI prescriptions.

3. Endpoint Classification

Deaths during followup were identified from the linked death certificate-Medicaid enrollment file. These were further classified to identify those deaths most likely to be related to drug-induced adverse cardiac effects.

Sudden cardiac deaths. The study clinical definition for sudden cardiac death was a death within one hour of symptom onset or in a patient who was alive and in the usual state of health within 24 hours of death and had no plausible non-cardiac cause of death.[5-7] This definition excludes deaths with an underlying noncardiac cause (e.g., pneumonia) or a different cardiac etiology (e.g., heart failure or bradyarrhythmia).

We identified sudden cardiac deaths from a computer definition based on both death certificate diagnosis and terminal medical care encounters. This definition had an estimated positive predicted value of 87%-90%.[5;6] However, the estimated sensitivity of this definition was less than 75% because it was restricted to underlying cause of death codes with a good positive predictive value.[5]

Other cardiovascular deaths. Deaths from cardiovascular causes were defined as any death with the underlying/primary cause of death coded as due to cardiovascular disease (ICD9 and ICD10 codes are shown in Appendix Table 3) that did not qualify as a sudden cardiac death. A previous validation study suggests these codes identify an additional 25% of sudden cardiac deaths, but with lower positive predictive value.[5]

Unintentional medication overdose deaths. We based this definition on the underlying cause of death code[a] because previous experience indicates this diagnosis reliably identifies overdose deaths. A comparison of death certificate diagnoses of overdose deaths with medical examiner data reported a sensitivity of 95% and a positive predictive value of 94%.[8] Thus, overdose deaths had a death certificate underlying cause of death code indicating unintentional or intent undetermined poisoning (Appendix Table 4).

[a] The multiple cause of death data were not available for the entire study period.

Appendix Table 3. Deaths from Cardiovascular Causes, ICD-9 and ICD-10[a].

ICD-9	ICD-10
250 Diabetes	E10, E11, E13, E14 Diabetes[a]
390-392 Acute rheumatic fever	I00-I02 Acute rheumatic fever
393-398 Chronic rheumatic heart disease	I05-I09 Chronic rheumatic heart disease
401-405 Hypertensive disease	I10-I15 Hypertensive diseases
410-414 Ischemic heart disease	I20-I25 Ischemic heart disease
415-417 Diseases of pulmonary circulation	I26-I28 Diseases of pulmonary circulation
420-429 Other forms of heart disease	I30-I52 Other forms of heart disease
430-438 Cerebrovascular disease	I60-I69 Cerebrovascular disease
440-448 Diseases of arteries, arterioles, and capillaries	I70-I79 Diseases of arteries, arterioles, and capillaries
451-459 Diseases of veins, lymphatic and other diseases of the circulatory system	I80-I89 Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified
	I95-I99 Other and unspecified disorders of the circulatory system
798.1 Instantaneous death	R96.0 Instantaneous death
798.2 Death in <24 hours	R96.1 Death in <24 hours
798.9 Unattended death	R98 Unattended death

[a]Excludes pregnancy-related diabetes. Does not include the unknown cause of death (ICD10 = R99) because review of profiles suggested many of these were more likely related to suicide/overdose than to cardiovascular death.

Appendix Table 4. Cause of death codes consistent with unintentional medication overdose death.

ICD-9	ICD-10	
E850-E858	X40-X44	Unintentional poisoning
E930-E947	Y40-Y57	Adverse effects of medications
E980.1-E980.4	Y10-Y14	Undetermined intent poisoning

4. Statistical Analysis

Study Covariates

The 111 study covariates are listed in Appendix Table 5. Each covariate is represented as a binary indicator variable; the table shows the proportion with the characteristic. All covariates were time-dependent, updated on the date of each prescription fill.

Disease Risk Score

We calculated a time-dependent disease risk score for each of the 6 study endpoints. The disease risk score, often described as the prognostic analogue of the propensity score,[9] is the risk of the study endpoint as a function of the covariates, given the reference category for the exposure. Disease risk scores are more suitable than propensity scores for non-binary comparisons.[10-12]

In the present study, the incidence of a study endpoint during the period of current use for a given prescription can be described as

$$I = L*\exp(z'b)$$

where

I is the incidence of death, expressed as deaths per person-year

L is the length of the period of current use, expressed in years

z is the vector of covariates at the time of the prescription fill

b are the logs of the incidence rate ratio for each covariate.

We used Poisson regression to estimate exp(z'b), which in turn estimates the annual risk of death (when endpoints are infrequent), given the covariate values at the time of the prescription fill. The regression was performed for the entire cohort and then z'b was calculated, with the coefficient for antidepressant use (citalopram vs. other study SSRI) and set to the value for SSRIs other than citalopram. Although it is possible to estimate the score in the subgroup not using citalopram, experience suggests that in the absence of effect modification, the estimate is better if the entire cohort is used.[12]

Each disease risk score was expressed as 20 quantiles, ranging from 0 (lowest risk) to 19 (highest risk).

Appendix Table 5. Study covariates.

Covariate	%	Covariate	%	Covariate	%
Year: 1998-2001	24.4%	Benzodiazepine current: 20+mg	11.7%	Oral hypoglycemic	17.3%
Year: 2002-2004	37.7%	Mood stabilizer: Any past year	23.3%	Statin	30.6%
Year: 2005-2007	21.1%	Hypnotic-GABA: Any past year	17.2%	Fibrate	7.1%
Female,%	76.4%	Back pain	45.9%	Nitrate or other anti-anginal	7.9%
White race,%	81.7%	Fibromyalgia	11.8%	Other antihypertensive	6.0%
Age: 35-39 years	14.2%	Other pain	72.3%	Platelet inhibitor	4.2%
Age: 40-44 years	17.8%	Opioid: Any past year	70.8%	New cardiovascular drug, past 180 days	12.4%
Age: 45-49 years	18.4%	Opioid, current: <90mg (morphine)	23.7%	New cardiovascular drug, past 30 days	4.3%
Age: 50-54 years	16.8%	Opioid, current: 90+mg (morphine)	5.1%	Home health care: any past year	1.6%
Age: 55-59 years	12.7%	Systemic corticosteroid, any past year	2.2%	Beta agonist	30.9%
Age: 60 plus years	10.0%	Musculoskeletal relaxant: Any past year	39.4%	Other bronchodilator	15.4%
Standard Metropolitan Statistical Area	56.5%	Gabapentin/pregabalin: Any past year	16.4%	COPD	14.9%
Medicaid enrollment uninsured,%	18.4%	Gabapentin or pregabalin: Current	9.1%	Pneumonia	4.5%
Medicaid enrollment disabled, %	65.9%	Anticonvulsant: Any past year	9.7%	Home oxygen	5.4%
Different SSRI in past year	11.5%	NSAID: Any past year	57.8%	Pro-arrhythmic drug: current use	1.5%
TCA: Any past year	18.5%	Coronary heart disease	9.7%	Cardiovascular hospitalization past year	1.8%
TCA: Current, <100mg amitriptyline	5.0%	Arrhythmia	4.2%	Psychiatric hospitalization past year	4.6%
TCA: Current, 100+mg amitriptyline	4.3%	Congestive heart failure	3.9%	Other hospitalization past year	9.8%
Trazodone: Any past year	26.0%	Cerebrovascular disease	4.3%	Psychiatric ED visit past year	7.1%
Other antidepressant: Any past year	27.8%	Peripheral vascular disease	2.3%	Cardiovascular ED visit past year	5.7%
Schizophrenia/psychosis	10.3%	Hypertension	39.1%	Other ED visit past year	54.0%
Bipolar disorder	16.0%	Hyperlipidemia	24.0%	Any ED visit in [t0-30,t0-1]	9.1%
Major depression	45.2%	Chronic renal failure/renal insufficiency	1.8%	Psy Outpat, 1-9 past year	49.5%
Other mood disorder	36.8%	Diabetes, diagnosed	21.4%	Psy Outpat, 10-19 past year	19.1%
Panic disorder	11.8%	Smoking, recorded diagnosis	14.9%	Psy Outpat, 20+ past year	15.1%
Alcohol abuse	4.0%	Other cardiovascular	8.6%	CV Outpat, 1-2 past year	24.7%
Psychiatric care	73.4%	New cardiovascular diagnosis	5.8%	CV Outpat, 3-5 past year	13.3%
Self harm	3.8%	ACE inhibitor/ARB	31.1%	CV Outpat, 6-9 past year	12.6%
Other psychiatric diagnoses	45.5%	Anticoagulant	3.4%	CV Outpat, 10+ past year	4.4%
Antipsychotic: Any past year	41.8%	Antiarrhythmic	2.2%	Oth Outpat, 1-4 past year	22.5%
Antipsychotic, current: <100mg	3.7%	Aspirin	8.7%	Oth Outpat, 6-24 past year	61.8%
Antipsychotic, current: <200mg	5.8%	Beta blocker	21.4%	Oth Outpat, 25+ past year	10.2%
Antipsychotic, current: <300mg	6.0%	Calcium channel blocker	17.6%	Injury ED visit, 1 past year	16.6%
Antipsychotic, current: 300+mg	16.9%	Digoxin	1.4%	Injury ED visit, 2+ past year	8.1%
Benzodiazepine: Any past year	58.3%	Loop diuretic	17.1%	Injury Outpatient visit, 1 past year	12.4%
Benzodiazepine current: <10mg	15.1%	Other diuretic	22.5%	Injury Outpatient visit, 2+ past year	10.9%
Benzodiazepine current: 10-19mg	15.6%	Insulin or other injectable hypoglycemic	7.3%	Any poisoning-related inpatient/ED past year	3.2%

Reference List

(1) Ray WA, Griffin MR. Use of Medicaid data for pharmacoepidemiology. *Am J Epidemiol* 1989;129:837-849.

(2) Ray WA. Population-based studies of adverse drug effects. *N Engl J Med* 2003;349:1592-1594.

(3) Piper JM, Ray WA, Griffin MR, Fought R, Daugherty JR, Mitchel E, Jr. Methodological issues in evaluating expanded Medicaid coverage for pregnant women. *Am J Epidemiol* 1990;132:561-571.

(4) Arnold SF. Mathematical statistics. *Prentice-Hall* 1990;157.

(5) Chung CP, Murray KT, Stein CM, Hall K, Ray WA. A computer case definition for sudden cardiac death. *Pharmacoepidemiol Drug Saf* 2010;19:563-572.

(6) Kawai VK, Murray KT, Stein CM et al. Validation of a computer case definition for sudden cardiac death in opioid users. *BMC Research Notes* 2012;5:473.

(7) Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry* 2001;58:1161-1167.

(8) Landen MG, Castle S, Nolte KB et al. Methodological issues in the surveillance of poisoning, illicit drug overdose, and heroin overdose deaths in New Mexico. *Am J Epidemiol* 2003;157:273-278.

(9) Hansen BB. The prognostic analogue of the propensity score. *Biometrika* 2008;95:481-488.

(10) Arbogast PG, Kaltenbach L, Ding H, Ray WA. Adjustment of multiple cardiovascular risk factors with a summary risk score. *Epidemiol* 2008;19:30-37.

(11) Arbogast PG, Ray WA. Use of disease risk scores in pharmacoepidemiologic studies. *Statistical Meth Med Res* 2009;18:67-80.

(12) Arbogast PG, Ray WA. Performance of disease risk scores, propensity scores, and traditional multivariable outcome regression in the presence of multiple confounders. *Am J Epi* 2011;174:613-620.