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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.

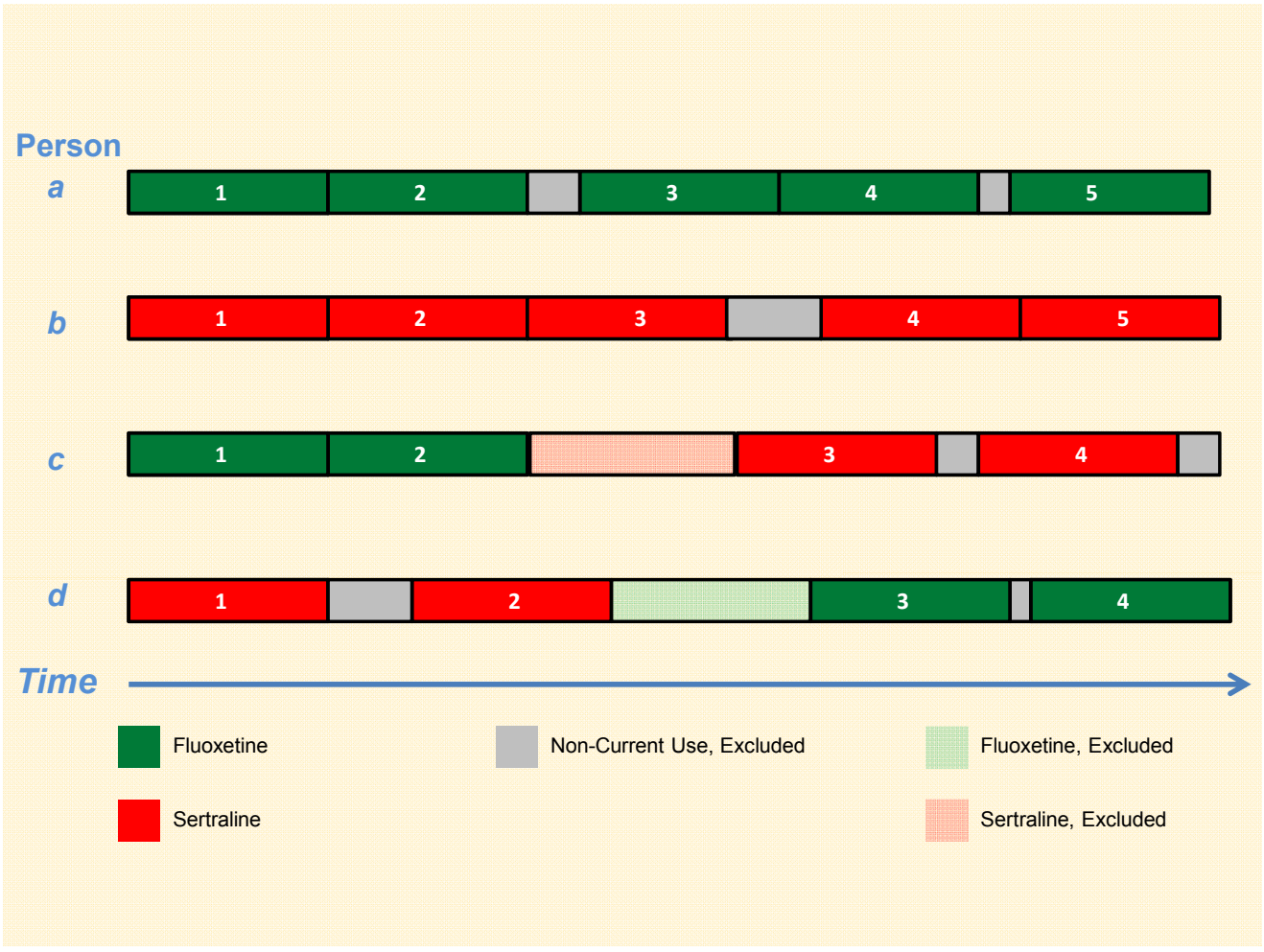
To define study followup, we evaluated all SSRI prescriptions filled during the study period. Those that met the inclusion/exclusion criteria on the day the prescription was filled contributed to current use person-time.

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%

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