

COMPARING THE RISK OF SUICIDALITY IN ADULT VERSUS YOUTH PATIENTS TREATED WITH SELECTIVE SEROTONIN REUPTAKE INHIBITORS—A REAL-WORLD EVIDENCE-BASED APPROACH



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BACKGROUND

Selective serotonin reuptake inhibitors (SSRIs) have been deemed the safest pharmacological treatment for major depressive disorder and related disorders. However, in 2004, the FDA issued a black-box warning of a potentially increased risk of suicidality for individuals aged 24 and under (youth). The original meta-analysis which supported this warning has come under fire for potential flaws and biases.

Suicidality is defined as suicidal behavior and/or ideation¹. The posit of increased risk of suicidality when treating youth as opposed to adults with SSRIs has gained continued support from additional meta-analyses² as well as opposition from pharmacoepidemiologic studies³.

OBJECTIVES

This study intended to take a real-world data-based approach to assessing the risk of suicidality in patients treated with SSRIs based on being aged over 24 (adults) or 24 and under at treatment start:

- Can real-world data derived from a federated electronic medical record (EMR)-based network be validly applied in the psychiatric field of study?
- Do real-world data demonstrate an increased risk of suicidality in youths as compared to adults starting treatment with SSRIs, as demonstrated in previous meta-analyses?

METHODS

Data Source: TriNetX, a global federated health research network providing access to aggregate counts on EMRs from approximately 60 million patients across 48 large healthcare organizations, was used for this study (numbers as of October 2018). Of patients with medication data, the network contained 5,328,330 patients aged <25 years and 11,493,754 patients aged ≥30 years.

Patient Cohorts: Patients were required to have started an SSRI (sertraline, fluoxetine, citalopram, escitalopram, or paroxetine) for the first time between April 2013 and April 2018. Patients may not have taken fluvoxamine, vilazodone, or vortioxetine prior to first treatment with an SSRI (Fig. 1a). Cohorts were also divided by age, with youth patients currently aged 24 or younger and adult patients currently aged 30 or older.

Confounding Factors: Common differences in comorbid diagnoses between suicidality-experiencing and non-suicidality-experiencing youth cohorts taking sertraline were explored and compared to differences between all youth and adult patients taking sertraline to determine three factors that may have had the greatest potential to confound results (Table 2).

A conservative approach was taken, selecting only factors that might have skewed results towards youth. Strata for each combination of those factors were created within the platform.

Outcome Definitions: Suicidality was defined as experiencing at least one instance of suicidal ideation (ICD-10 code R45.851) or suicidal attempt (ICD-10 code T14.91) within 1 year of first SSRI treatment. Additionally, patients may not have experienced a suicidality event prior to first SSRI treatment (Fig. 1b).

Confounding Correction: The Cochran-Mantel-Haenszel (CMH) method was used to produce an adjusted risk ratio for suicidality in youth vs. adults, corrected for the effects of three potential confounders based on the cohort strata produced within the platform (Table 3).

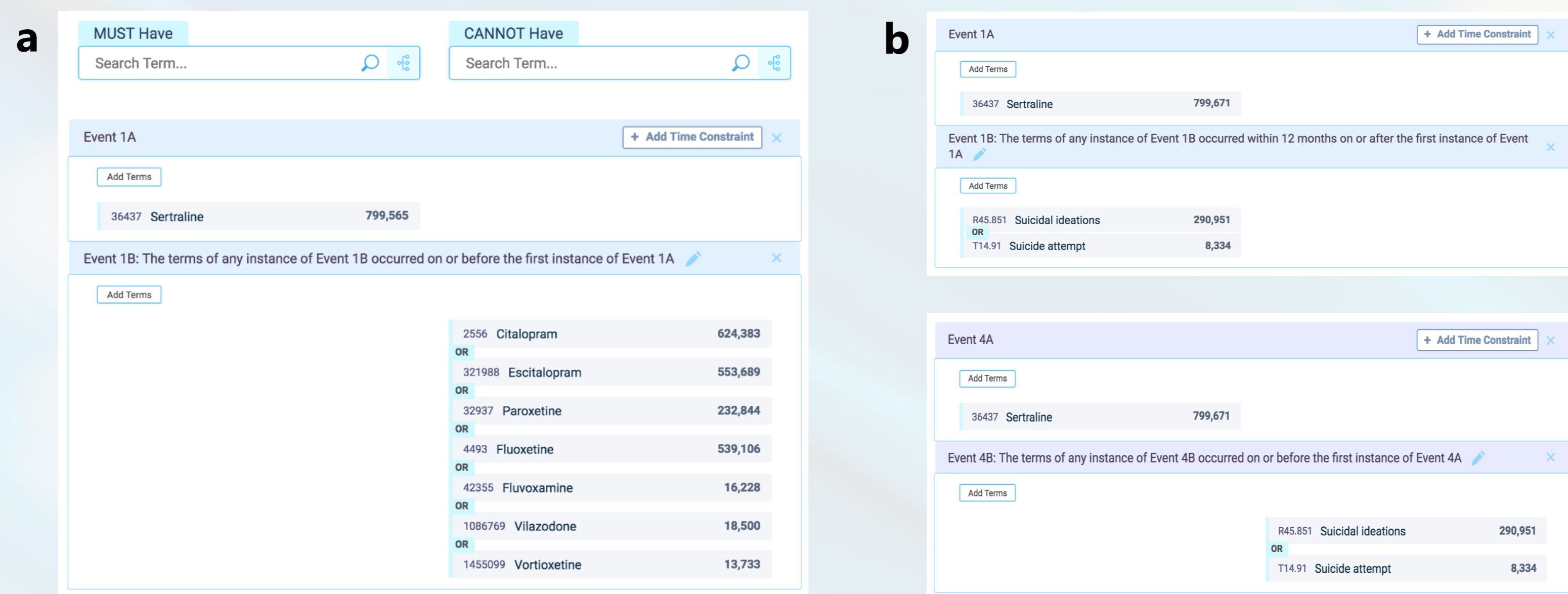


Figure 1: Definition of first SSRI (example for sertraline) (1a) and definition of suicidality (1b)

Table 1: Comparison of age specific risks for drug effect on suicidality

Age Range	Ratio (95% CI)	P Value	Risk Difference/1,000 (95% CI)	P Value
Ideation or Worse				
<25 v ≥25	2.05 (1.26 to 3.34)	0.004	6.19 (1.76 to 10.6)	0.006
25-64 v ≥65	2.14 (1.08 to 4.24)	0.03	3.81 (0.34 to 7.28)	0.03
Ideation Alone				
<25 v ≥25	1.84 (0.92 to 3.67)	0.08	2.75 (-0.61 to 6.12)	0.11
25-64 v ≥65	1.45 (0.65 to 3.27)	0.37	1.55 (-1.30 to 4.40)	0.29
Preparation or Worse				
<25 v ≥25	2.57 (1.07 to 6.15)	0.04	3.43 (0.51 to 6.36)	0.02
25-64 v ≥65	13.8 (1.61 to 118)	0.02	2.42 (0.47 to 4.37)	0.02

Metanalysis of 372 double blind randomized placebo-controlled studies demonstrating an increased risk of suicidal ideation or worse in patients ≤ 24 years of age (at least 15 years) taking SSRIs. Source: literature²

Table 2: Exploration of potential confounding

ICD10 Parent Group	Potential Factors with Largest Difference	≤24 Yrs. Suic.	≥24 Yrs. Non-Suic.	Percent Diff.	≤24 Yrs. Suic. All	≥30 Yrs.	Percent Diff.	Weighted Diff.
Mood	Major Depressive Disorder, Single Episode	80%	33%	47%	39%	43%	-4%	-1.88%
	Major Depressive Disorder, Recurrent	43%	9%	34%	13%	9%	4%	1.36%
	Unspecified Mood (Affective) Disorder	26%	7%	19%	9%	4%	5%	0.95%
	Persistent Mood (Affective) Disorders	15%	6%	9%	7%	7%	0%	
Anxiety	Bipolar Disorder	14%	3%	11%	4%	4%	0%	
	Other Anxiety Disorders	77%	50%	27%	53%	40%	13%	3.51%
	Reaction to Severe Stress and Adjustment Disorders	31%	12%	19%	14%	11%	3%	0.57%
Personal Risk	Other Nonpsychotic Mental Disorders	17%	3%	14%	5%	1%	4%	0.56%
	Social Phobias	9%	3%	6%	4%	0%	4%	0.24%
	Personal History of Self-Harm	20%	1%	19%	4%	1%	3%	0.37%
Sleep	Patient's Noncompliance with Medical Treatment and Regimen	9%	2%	7%	3%	4%	-1%	-0.07%
	Personal History of Psychological Trauma, Not Elsewhere Classified	9%	1%	8%	2%	1%	1%	0.08%
	Insomnia	18%	6%	12%	8%	13%	-5%	-0.60%
Socioeconomic Risk	Personal History of Abuse in Childhood	10%	1%	9%	2%	0%	2%	0.18%
	Parent-Child Conflict	7%	1%	6%	2%	0%	2%	0.12%
	Other Specified Problems Related to Primary Support Group	6%	1%	5%	2%	0%	2%	0.10%
Other Circumstances	Problems Related to Education and Literacy	12%	2%	10%	3%	0%	3%	0.30%
	Problems Related to Other Psychosocial Circumstances	7%	2%	5%	2%	2%	0%	
	Problems Related to Social Environment	6%	1%	5%	2%	0%	2%	0.10%
Substances	Problems Related to Lifestyle	13%	4%	9%	5%	7%	-2%	-0.18%
	Cannabis Related Disorders	16%	3%	13%	5%	3%	2%	0.26%
	Nicotine Dependence	12%	4%	8%	5%	18%	-13%	-1.04%
Personality	Alcohol Related Disorders	9%	2%	7%	2%	7%	-5%	-0.35%
	Other Psychoactive Substance Related Disorders	6%	1%	5%	2%	3%	-1%	-0.05%
	Specific Personality Disorders	13%	2%	11%	3%	1%	2%	0.22%
Poisoning	Impulse Disorders	7%	2%	5%	2%	1%	1%	0.05%
	Poisoning by Adverse Effect of and Underdosing of Diuretics and Other	12%	3%	9%	4%	4%	0%	
	Poisoning by Adverse Effect of and Underdosing of Psychotropic Drugs	8%	1%	7%	2%	1%	1%	0.07%

Table 3: CMH strata

Strata	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	17
MDD, Recurrent	Yes							No								
Other Anxiety Disorders	Yes				No			Yes				No				
History of Self-Harm	Yes		No		Yes		No		Yes		No		Yes		No	
Age Group	≤24 Yrs.	≥30 Yrs.	≤24 Yrs.	≥30 Yrs.	≤24 Yrs.	≥30 Yrs.	≤24 Yrs.	≥30 Yrs.	≤24 Yrs.	≥30 Yrs.	≤24 Yrs.	≥30 Yrs.	≤24 Yrs.	≥30 Yrs.	≤24 Yrs.	≥30 Yrs.
Total Patients	3,651	2,498	15,173	44,736	801	538	5,728	24,884	2,523	1,815	71,098	286,189	979	822	78,074	506,997
Outcome Suicidality	623	357	1,313	1,579	45	41	312	404	298	178	1,595	1,921	66	41	824	977

Table 4: CMH adjusted risk ratio & confidence interval

	CMH Adj. RR	CMH Adj. RR CI (95%)	P-Value	
All	2.70405163	2.6067497	2.8049855	0.0000

Table 5: Total patient numbers across group and outcome

All	≤24 Yrs.	≥30 Yrs.	Total
Yes Suicide	5,077	5,499	10,576
No Suicide	172,978	863,246	1,036,224
Total	178,055	868,745	1,046,800

RESULTS

- Exploration for potentially confounding diagnoses found the following three to be of greatest interest: Major depressive disorder, recurrent; Other anxiety disorders; History of self-harm.
- After CMH adjusting for these factors, there was a significant 2.7 risk ratio for suicidality in youth to adults ($p < 0.0001$) (Table 4).
- These findings support the conclusions of randomized clinical trial meta-analyses and contrast those of epidemiological studies.
- There were limits in determining the cause for treatment with an SSRI in a hospital setting, and, with some patients, there may have been a more severe reason for treatment, which may, in turn, confound the risk of suicidality.
- However, we would expect the proportion of severe cases treated with SSRIs to be no different between both groups.

Patients: 1,046,800 total patients were included in this study. The majority of patients (868,745) were greater than 30 years of age and were therefore included in the adult group. 178,055 patients were 24 years of age or younger, as part of the youth group.

10,576 patients experienced an outcome indicative of suicidality within one year of their first use of an SSRI. These were divided nearly equally between the youth and adult groups, with 5,077 patients experiencing an outcome in the youth group and 5,499 in the adult group. See Table 5 for details.

CONCLUSION

- Real-world data demonstrates youth patients treated with SSRIs were, on average, 2.7 times as likely to experience suicidality within one year of starting SSRI treatment compared to adult patients.
- This study is the first use of a large EMR dataset to explore the risk of psychiatric outcomes across a population treated with SSRIs.
- These findings provide real-world evidence in support of findings generated by arguably more 'artificial' randomized clinical trial-based studies.
- Further research may wish to explore the biological mechanisms through which SSRIs might affect serotonin system in youth brains differently than those of adult brains, inducing an increased risk of suicidality.

(1) Hammed, T. A., Laughren, T., & Racoosin, J. (2006). Suicidality in Pediatric Patients Treated With Antidepressant Drugs. Archives of General Psychiatry, 63(3), 332-339. <https://doi.org/10.1001/archpsyc.63.3.332>

(2) Stone, M., Laughren, T., Jones, M. L., Levenson, M., Holland, P. C., Hughes, A., ... Rochester, G. (2009). Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. BMJ, 339, b2880. <https://doi.org/10.1136/bmj.b2880>

(3) Bridge, J. A., Yeungar, S., Salary, C. B., Barbe, R. P., Birmaher, B., Pincus, H. A., ... Brent, D. A. (2007). Clinical Response and Risk for Reported Suicidal Ideation and Suicide Attempts in Pediatric Antidepressant Treatment: A Meta-analysis of Randomized Controlled Trials. JAMA, 297(15), 1683-1696. <https://doi.org/10.1001/jama.297.15.1683>