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THE OTHER SUICIDE PILL?

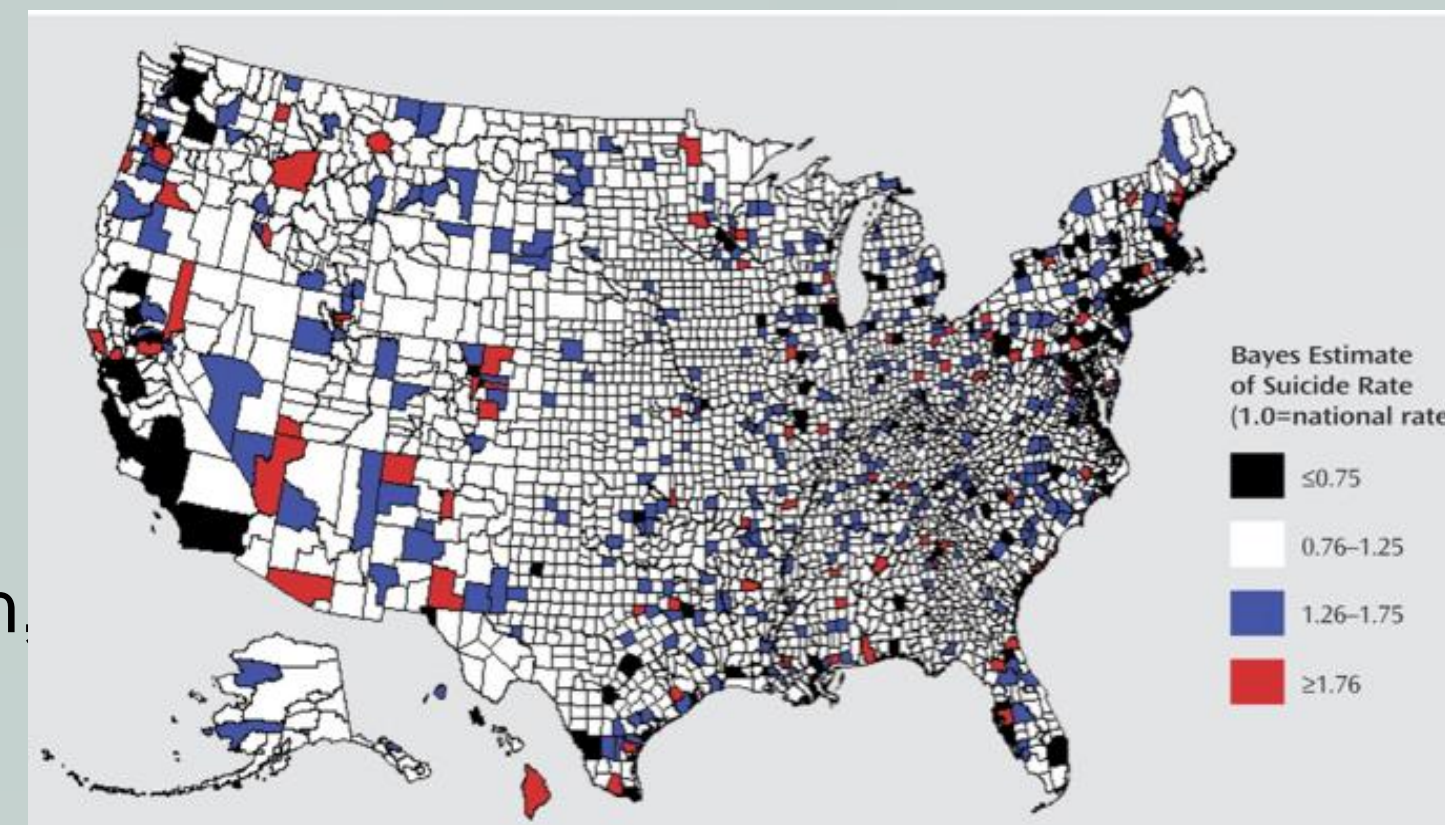
Investigating the potential association between SSRI intake and increased risk of suicide

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Background

Antidepressants are prescribed as the main treatment of depression for severe depressive episodes and will often be used in conjunction with therapy for mild or moderate depression. While the prescription of antidepressants aims to reduce the severity of affective disorders, their use has been associated with adverse effects, including aggression, agitation, insomnia, and suicide. In 2003, the FDA released a study reporting results of a two-fold increase in suicidal behaviours for children and adolescents, and consequently has issued a warning detailing suicidal ideation as an adverse effect of SSRI use in youth with major affective disorders. The FDA had also emphasized the continuing uncertainty surrounding this association and has called for additional research on the topic.

Figure 1. Annual suicide rates in the United States by country from 1996-1998.



Abstract

Selective Serotonin Reuptake Inhibitors (SSRIs) are the most frequently prescribed antidepressant in the world (Bridge et al., 2007), and though they are meant to reduce depressive symptoms such as suicidal thoughts, some studies have associated their use with an increase in suicidal ideation, particularly in youth (defined as those under 19 years old).

This study investigates the association between SSRI intake and increased risk of suicide as a consequent adverse effect. This was done by conducting a structured literature review. Two independent reviewers analyzed and compared relevant research from peer-reviewed journals obtained from online databases including PubMed, JAMA Network, and the University of Ottawa online databases. A combination of observational studies, RCTs, and meta-analyses were reviewed. These studies analyzed the association between suicide rate and self-reported suicidal ideation in relation with different durations of SSRI intake and severities of disease, and had to include a comparison between randomly selected treatment groups and placebo control groups.

After reviewing 10 peer-reviewed articles, the results appear to be mixed from one study to another. Some studies report slight increases in suicidality, while others report a decrease associated with SSRI intake. Overall, the evidence is inconclusive as to an association with suicidal ideation and SSRI intake. However, as Antonuccio & Healy (2012) observed, a drug that is prescribed with the promise of treating depression should have a distinguished effect in reducing conditions such as suicidal ideation compared to placebo. The lack of conclusive evidence is thus a problem in itself, and further investigation is required as well as consideration regarding SSRI prescription.

Research Question

Does the use of prescription SSRIs to treat Major Depressive Disorder, OCD, or General Anxiety disorder increase risk of suicidal ideation and suicide attempts in children and adolescents (aged under 19)?

Methods

PubMed, JAMA Network and the University of Ottawa online databases were systematically searched using the keywords 'SSRIs', 'Depression', 'Association', 'Suicide Risk' and 'Literature Review'. Meta-analyses, Observational studies and Randomized control trials were reviewed. The inclusion and exclusion criteria represented in the table below were used to determine which articles to include and which to exclude for the study. The articles obtained from the searches were then assessed by appraisal of the abstract for relevance to the research topic after a screening of the titles. Two independent reviewers then analyzed and compared relevant research.

Table 1. Inclusion/Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
Population		
Age	Under 19 years old	19 and above with previous suicide attempts
Sex	Male, Female	None
Intervention		
Drug	Selective Serotonin Reuptake Inhibitors (Fluoxetine, Citalopram, Paroxetine, Sertraline, Fluvoxamine)	All other antidepressants (Serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, tetracyclic antidepressants)
Outcomes	Suicide, Suicidality, Suicide ideations	Other secondary effects (agitation, anxiety)
Information		
Study Design	Randomized control trials, Meta-analyses, Observational studies	Qualitative studies (case studies)
Language	English	Other languages
Date published	2003 – 2015	Before 2003
Publication	Peer-reviewed	Not peer-reviewed
Availability	Available through University of Ottawa databases	Unavailable through University of Ottawa databases
Comparators	Placebo or any other antidepressants	Single arm studies

Results

Based on inclusion and exclusion criteria, 10 articles were included in our study. The association between SSRI intake and increased suicide showed conflicting results. For this reason, the findings of each study were summarized into the following table.

Table 2. Results of 10 included articles.

Study	Population	Design	Outcome measure	Results
Bridge et al., 2007	Youth (under 19) with Major Depressive Disorder, OCD and anxiety.	Meta-Analysis of randomized, placebo-controlled RCTs	Relative Risk (0.9 MDD) (0.7 OCD) (0.7 anxiety)	Slight, but insignificant increase in suicidal ideation, particularly for Major Depression. No association drawn from results.
Antonuccio & Healy, 2012	Youth (under 19) with depression.	Meta-Analysis of randomized, placebo-controlled RCTs	Compared absolute risk (2% in placebo, 4% in treatment)	Found a two-fold increase in risk of suicidal ideation in youth with major depression on SSRIs vs placebo.
Jick, Kaye & Jick, 2004	Youth aged 10-19 years old from sample of N: 159,810	Matched Case-control study	Relative Risk: Frequency of first-time exposure to SSRI in suicidal behaviour patients compared with comparable non-suicidal patient	Increased risk (Relative risk 4.07) in first 1-9 days of SSRI use for treatment. RR decreased with time after initial peak. Not sufficient evidence for positive association.
Tiihonen et al., 2006	Patients hospitalized for suicide attempt between 1997-2003 in Finland N: 15,390	Nationwide cohort study of suicidal patients. Mean follow-up: 2.4 years	Proportionally score-adjusted relative risks (RRs) during monotherapy with antidepressant use vs no antidepressant treatment.	Increased risk of attempted suicide (39%, P<.001), but decreased risk of completed suicide (-32%, P=.002) and mortality (-49%, P<.001) in SSRI users vs non-SSRI users.
Healy, 2003	Specific to each study reviewed. Youth aged below 19 presenting affective disorders selected for literature review.	Literature Review of RCTs, Meta-Analyses, Epidemiological studies and Health volunteer studies.	Qualitative analysis of RCTs, Meta-Analyses, Epidemiological studies and Health volunteer studies.	Data reviewed indicates a possible doubling of suicidal ideation and attempts in SSRI users compared to older antidepressant users or placebo groups. Further research recommended.
Lapierre, 2003	Depressive patients under 18, excluding those with suicide attempts.	Literature Review of RCTs and Meta-Analyses	Qualitative retrospective analysis of RCTs and Meta-analyses	Conclusions from single RCTs are limited and highly tentative. There is no evidence to suggest an association between SSRI use and increased suicidal ideation.
Triedei, Tripathi, Nischal, Nischal, 2012	Youth aged below 19 presenting affective disorders selected for literature review.	Literature Review of RCTs, Meta-Analyses and observational studies	Qualitative summary of current evidence to generate evidence-based suggestions, for day-to-day clinical work.	No conclusive relationship between suicidal ideation and behavior after use of SSRIs. At best it suggests some increased risk for children and adolescents.
Botswick, 2006	24,119 adolescents aged 12 to 18 with major depressive disorder using SSRIs	Literature Review of RCTs, Meta-analyses and statistical analysis of observational studies.	Proportionally analysis to study a national database of 24,119 adolescents	SSRIs did not increase the risk of suicide attempts. Those who used SSRIs for 6 months or more had suicide attempt risk two-thirds lower than those not on medication or just starting it.
Hall, 2006	Youth (under 19) prescribed	Literature Review of	Meta-Analyses used Relative Risk	Meta-Analyses found increased suicidal ideation in days 1-9 RR:

Table 3. Strengths and weaknesses of evidence on SSRIs and suicide

	Findings	Strengths	Limitations
Meta-analyses	Evidence of increased suicidal ideation and acts	Aggregated number increases statistical power	Short study periods
Randomised trials	No evidence of increased risk	Random assignment to SSRI or placebo	Uncertainty about suicidal ideation as surrogate for suicide risk
Observational studies	Limited evidence of greater risk for SSRIs than TCAs	Larger than randomised trials. Observe risks under routine practice	Limited ability to detect effects because studies: Too small, Too short, Often exclude at-risk patients
Ecological studies	Suggestive evidence that suicide rates have declined as SSRI prescriptions have increased	Ability to detect small effects, aggregated over large exposed populations	Confounding by indication, Too few suicides, Limited capacity to test alternative explanations —eg, confounding

Table: Strengths and weaknesses of evidence on SSRIs and suicide

Discussion

- 6/10 studies found that SSRI use led to increased suicidal ideation/behaviour in youth.
- 2/10 studies found SSRI use decreased suicidal risk and ideation.
- 8/10 studies suggested further investigation due to inconclusive evidence or negligible differences between treatment and placebo group.

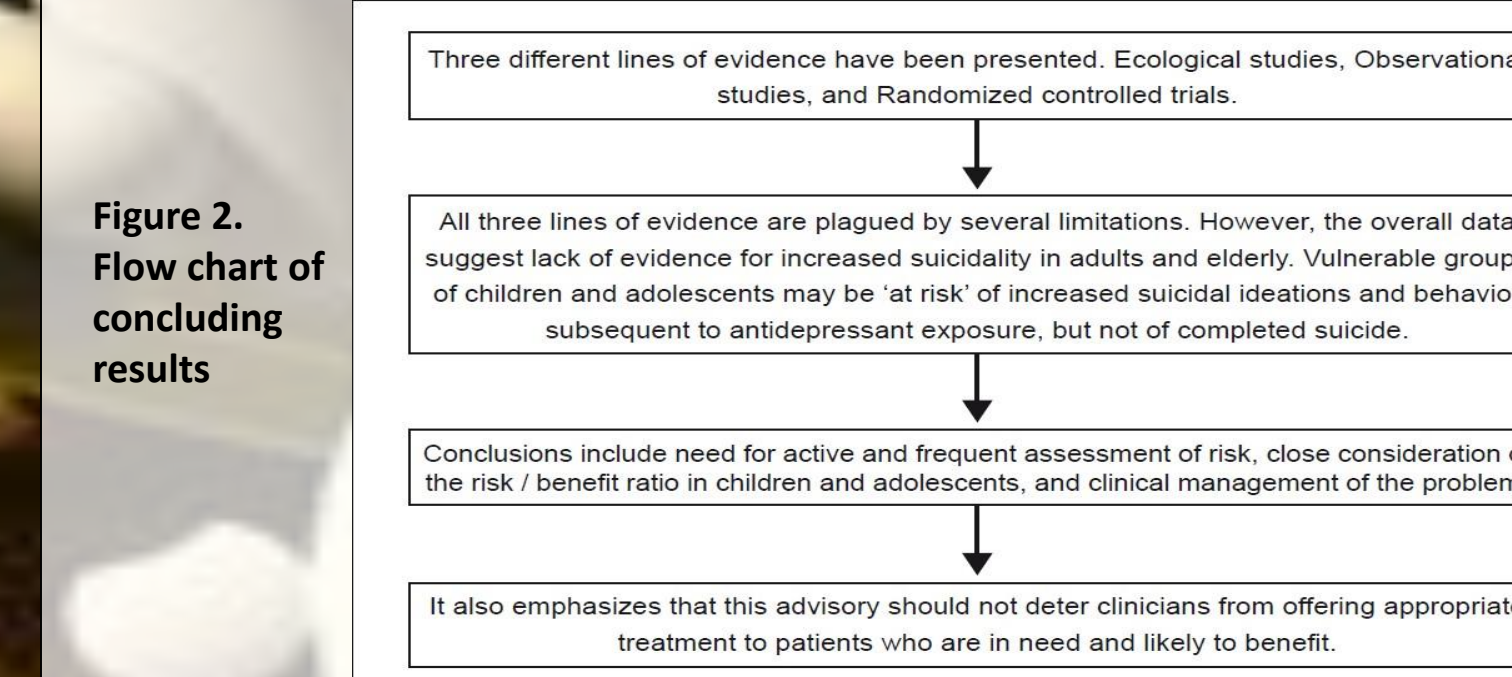


Figure 2. Flow chart of concluding results

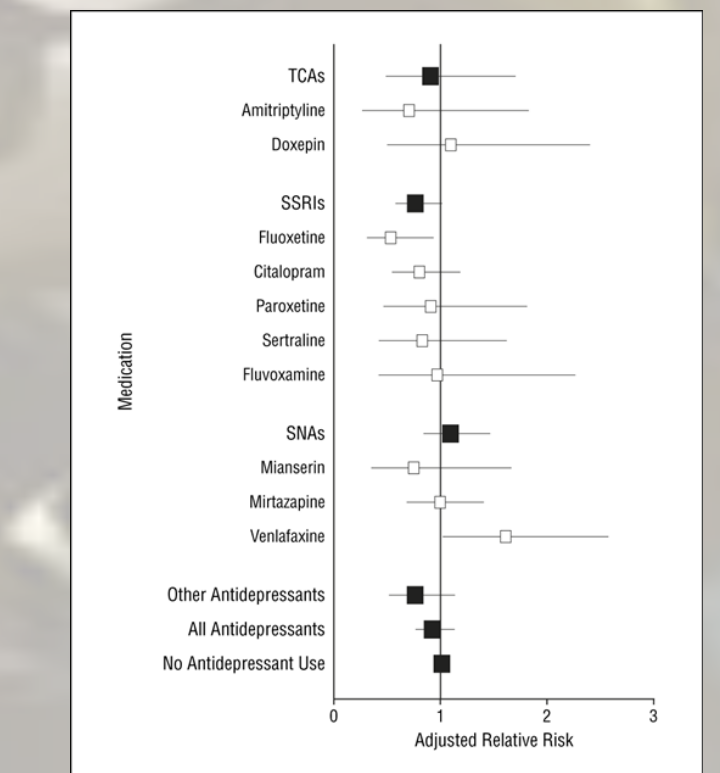


Figure 3. Relative risk and 95% confidence interval of suicides obtained by using medication as a time-dependent variable.

While the majority of studies (6/10) selected did show a statistical increase in suicidal behaviour during SSRI use, only one determined this increase to be significant enough for a positive association to be drawn between both factors. 10 years of mixed results without a trend developing is disconcerting and suggests there may be confounding variables that are not accounted for. Botswick (2006) suggests that psychiatric comorbidity and certain demographic factors, rather than medication, may be the actual cause for an increase in the risk of suicide attempts in certain cases. Regardless, a noticeable trend that has arisen from these studies is that few of them have been able to show a marked difference between treatment and placebo groups with regard to consequent suicidal attempts or behaviours. Thus, while no research study has been able to demonstrate that SSRIs increase risk of suicide in youth, they have not been shown to decrease it either, which is one of their purposes. Future considerations must therefore be taken by practitioners when prescribing SSRIs to children since the literature provides mixed results regarding their efficacy and adverse effects.

Limitations

- Subjects with previous suicide attempts excluded from these studies due to ethical concerns. Thus, the strength of association between SSRI use and suicidal ideation is not fully represented or generalizable to real world circumstances.
- 'Suicidal Ideation' is a subjectively defined concept that cannot be quantitatively measured.
- Not all included studies adjusted for confounders, particularly long-term studies such as cohort and case-control studies.
- Studies measured different age ranges, all categorized as 'youth' under each study's subjective definition (all fell under 19 years of age).

Conclusion

From the literature reviewed, mixed results regarding SSRI influence on suicidal ideation and attempts means there is no conclusive evidence to ascertain an association between the two. Further investigation must therefore be conducted regarding the association between SSRI intake and suicidal ideation in youth with major affective disorders, with a particular emphasis on identifying possible confounding variables.

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