Chapter 70
The Risk of Suicide with Selective Serotonin Reuptake Inhibitors in the Elderly

Adan Aslam Khan, Andrew Wong, Vahid Pasovic, and Esther Akinyemi

Authors of the original article David N. Jurrlink, MD, PhD, Muhammed M. Mamdani, Pharm.D, MA, MPH, Alexander Kopp, BA, Donald A. Redelmeier MD, MSc

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Objectives To assess the relationship between initiating treatment with SSRI antidepressants and completed suicide in older adults [1]

Methods This was a population-based study conducted in Ontario, Canada, where all residents ≥65 years have universal access to health insurance for services including prescription drug coverage, physicians' services, and hospital care. Over a 9-year study period (Jan 1, 1992–Dec 31, 2000), cases of suicide were identified

A. A. Khan · A. Wong · V. Pasovic · E. Akinyemi (✉)
Henry Ford Health System, Detroit, MI, USA
e-mail: vpasovi1@hfhs.org; EAkinye2@hfhs.org

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among Ontario residents aged ≥66 years using records from the Office of the Chief Coroner for Ontario. Individuals aged ≥65 years were excluded, and the first year of eligibility (at age 65) for prescription medication benefits was not examined to avoid incomplete medication records. The date of suicide was the index date for all analyses. The final matched analyses included 1138 suicide cases and 4552 comparison subjects.

A comparison patient group was identified from the general population using the propensity score method. A propensity score was calculated for each individual predicting the suicide outcome by balancing multiple characteristics between the suicide cases and comparison subjects. In this score, multiple elements (such as demographic characteristics, medical and psychiatric disorders, admission to a psychiatric facility during the previous year, care by a psychiatrist in the previous year, days in hospital during previous year, and suicide attempt in the previous year) were identified to minimize the difference between the two groups. Propensity scores were also calculated for all possible comparison patients (for each case at every index site) to account for changes in patterns of antidepressant use over the study period. Once these scores were calculated, all eligible comparison patients (if they were within 0.2 standard deviations of the propensity score) were identified. From this group, four comparison subjects (per suicide case) were randomly selected. Subjects ($n = 191$) with propensity scores that were too high to match four comparison subjects were excluded from the matched analyses but retained for descriptive purposes.

The Ontario Drug Benefit program collects comprehensive prescription records (<1% missing data) dispensed to elderly residents in Ontario. Prescription records of suicide cases and comparison groups were examined through this program. Selective serotonin reuptake inhibitor (SSRI) antidepressants included fluoxetine, fluvoxamine, paroxetine, sertraline, and citalopram. Other antidepressants included secondary amine cyclic antidepressants (desipramine, nortriptyline, protriptyline, maprotiline, and amoxapine), tertiary amine cyclic antidepressants (amitriptyline, imipramine, doxepin, trimipramine, and clomipramine), and miscellaneous antidepressants (venlafaxine, trazodone, bupropion, and nefazodone). Monoamine oxidase inhibitors (MAO-I) were not examined due to their infrequent use, and mirtazapine was not studied as it was not insured during most of the study period.

In the primary analyses, "new antidepressant use" was defined as no use of an antidepressant in the same class for the previous 6 months. For the primary analysis, a conditional logistic regression was used to estimate the odds ratio (OR) and 95% confidence interval (CI) for suicide associated with the new use of an antidepressant at monthly intervals from the start of the treatment. Multivariate analysis was used to adjust for rural place of residence (using home postal code), estimated residential income quintile, previous suicide attempt, the number of prescription medications dispensed in the previous year, evidence of alcohol abuse (using prescription records, physician diagnosis codes, or hospital discharged records from the previous year), malignancy, anxiety or sleep disorder, bipolar disorder, depression or other mood disorder, agitation or psychosis, poisoning or other injury, provision of

care by a psychiatrist, or admission to a psychiatric facility. For statistical significance, all test used a two-tailed P-value of 0.05.

Results A total of 1354 cases of suicide (≥66 years) were identified among Ontario residents during the study period. Of the total group, 25 (2%) were excluded because of having an invalid health card number, erroneous identifying data, or principal residence outside of Ontario. A total of 191 (14%) were excluded as their scores were too high to be matched to the comparison subjects. A total of 1138 suicide cases were analyzed using 4552 comparison subjects with comparable demographic characteristics and patterns of illness. Many individuals who died by suicide were men living in an urban setting (80%), and a small percentage of the total group of suicide cases had seen a psychiatrist in the preceding year (13%). The most common methods of suicide were death from a firearm ($n = 370$), hanging ($n = 318$), and self-poisoning ($n = 285$). Of the total 1329 suicide cases (including the 191 individuals whose scores were too high to be matched to a comparison group), 68% ($n = 907$) did not receive antidepressant therapy 6 months before death.

The investigators found that the risk of suicide in the first month of treatment with an SSRI is fivefold higher than that with other antidepressants ($P = 0.0009$), but no difference is seen with continued therapy. This comparison was noted after adjustments were made through a multivariate analysis.

Tertiary amines may be used for illnesses other than depression (such as neuropathic pain, pruritis, migraine). Findings did not change significantly when tertiary amines were excluded from the group of non-SSRI antidepressants. Venlafaxine is an antidepressant that blocks serotonin and norepinephrine reuptake (SNRI) at higher doses. Consistent results were obtained when venlafaxine was categorized as an SSRI antidepressant. These findings were also consistent when amoxapine and maprotiline (which are structurally different from other secondary amine cyclic antidepressants) were excluded from the analysis and when clomipramine (which selectively interferes with serotonin transport) was excluded from the group of tertiary amine cyclic antidepressants.

During the secondary analysis, the "new antidepressant use" was defined as no use of any other antidepressant in the previous 6 months. The findings of this analysis were consistent with the original results and persisted in the replicated analysis. In most aspects, in the first month of treatment with an SSRI antidepressant (in comparison with non-SSRI antidepressants), there was noted to be a disproportionate increase in suicide among the elderly population. These results were consistent within a series of subgroup analyses stratified by demographic characteristics, mental health history, and patterns of medical illness. The only exception was that this finding was not found among women.

The investigators also reported that relative to non-SSRI antidepressant treatment, suicides of a violent nature were more strongly associated with SSRI antidepressant treatment during early therapy ($P = 0.0016$). Suicides of a violent nature were described as hanging, gunshot, jumping, stabbing, vehicle collision, blunt trauma, explosion, electrocution, and self-immolation. Nonviolent suicides were equally common among patients treated with SSRI and non-SSRI antidepressants.

The absolute risk of suicide during the first month of treatment was calculated to be low in both the group receiving treatment with an SSRI antidepressant (1 in 3353) and non-SSRI antidepressant (1 in 16,037). Additionally, the authors note that the risk of suicide due to an antidepressant is probably lower, as many of the suicides in the first month of treatment likely resulted from depression rather than as an adverse effect of treatment.

Conclusions This study shows a substantial increase in the relative risk of suicide only within the first month of SSRI treatment compared to other antidepressants which did not persist. Proposed mechanisms include improving aspects of depression such as psychomotor retardation "energizing the patient to suicide," the development of akathisia-like symptoms, agitation or dysphoria, and use of SSRI antidepressants in patients at high risk for suicide as they are safer in overdose. However, this was considered less likely as physicians may be unable to identify high-risk patients in the elderly population, comparison patients were matched on important characteristics, and consistent results were found in this study regardless of previous psychiatric treatment. Additionally, the higher risk was not noted beyond the first month of treatment with an SSRI antidepressant. The investigators explain that if depression explained their findings, then the persistent risk should have been identified with SSRI therapy as they rarely abate after the first month of treatment.

This study also showed that the absolute risk of suicide during initial treatment with an SSRI antidepressant was very low. The majority of patients treated with SSRI antidepressants do not attempt suicide, although in rare instances an idiosyncratic response may occur and individuals may experience suicidal ideation during the first weeks of therapy. The etiology of this is unknown and may have a pharmacogenetic contribution. It was also noted that there was an undertreatment of depression in the elderly as a significant proportion of individuals (two-thirds) that died by suicide were not receiving an antidepressant.

Lastly, this study shows increased risk of violent suicides with SSRI antidepressant treatment compared to other antidepressants.

Strengths of the Study

1. This study had a large sample size.
2. The study duration long.
3. There were many covariables were assessed during multivariable analysis to minimize confounding effects.

Limitations of the Study

1. A large proportion of the population were males from urban settings.
2. The availability of mental health resources and access to psychiatrist/psychotropic medications were not addressed.
3. There was no direct measure of antidepressant doses, duration of treatment, or adherence to treatment.
4. The severity of depression in each group of treatment could not be assessed.

5. Other important variables including pain control, social support, and bereavement that may contribute to mood symptoms and increase risk of suicidality were not measured.
6. A portion of the group was excluded as the scores were "too high" to be matched to comparison subjects. This may have resulted in selection bias.
7. It is unclear what constitutes early therapy for violent suicide with SSRI treatment.

Take-home points In elderly patients, there has been a significant undertreatment of depression and increased suicide risk. The risks of undertreatment are often greater than the risks of treatment with an SSRI antidepressant. At the onset of treatment with an SSRI antidepressant, it is important to educate patients and family of the increased risk of suicide in the first month, and keeping the environment safe, as well as monitor individuals closely during this period.

Practical applications of the take-home points Among elderly patients with depression and increased suicide risk, SSRI antidepressant is an option for treatment. Close monitoring of tolerability, mood symptoms, and suicide risk, especially at the onset of treatment, is fundamental in the care of these individuals. Additionally, limiting access to violent means of suicide should also be an integral part of treatment planning.

Reference

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