



Association between selective serotonin reuptake inhibitors and violent crime - could underlying psychopathology be the cause?

Aiste Lengvenyte^a, Eduard Vieta^{b,*}

^a*Faculty of Medicine, Institute of Clinical Medicine, Psychiatric Clinic, Vilnius University, Vilnius, Lithuania*

^b*Hospital Clinic, Institute of Neuroscience, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain*

Available online xxx

Fuelling the discussion regarding the safety of selective serotonin reuptake inhibitors (SSRIs), the present large Swedish nationwide cohort registry study (Lagerberg et al., 2020) tries to answer whether treatment with SSRIs is associated with increased risk of committing a violent crime. This is a substantial extension of a previous population-based study (Molero et al., 2015), which reported a positive association between SSRI use and violent crime only in individuals younger than 25. As the previous study was possibly underpowered to detect differences in other age groups, the present study has twice as long follow-up period, and almost three times higher number of events, with more than 32 thousand violent crimes committed by 20 thousand individuals.

By using within-individual analyses, which automatically adjusts for time-static confounding within individuals, the authors report increased risk of violent crime during SSRI treatment and up to three months after treatment discontinuation, as compared to the period before the treatment in the same individual. Complementing the results from the previously mentioned study, the authors report statistically

or almost significant associations in all age groups. However, after the stratification by age group and duration of the SSRI therapy, the risk of violent crime during SSRI therapy was statistically significantly increased only in individuals aged up to 34 years, possibly showing that such associations would need even larger sample sizes. Notably, only 2.6% of SSRI users that committed violent crimes made it to the final analysis. This way, the final sample consisted of a possibly very specific population of offenders, raising the question of generalizability to all SSRI users. Indeed, the final analysis was based on predominantly young and male individuals, whereas SSRIs were mostly dispensed to females and older adults.

In line, when stratified by history of previous convictions, the risk for a violent crime during SSRI treatment was only increased in past offenders. Could it be that people that have been convicted for crimes are more likely to be in touch with the healthcare system and get treatment for their underlying conditions (e.g. perpetrators treated in prisons)? Male inmates are at increased risk of affective, psychotic, substance-use and personality disorders (Verdolini et al., 2017a). Furthermore, individuals with increased propensity to commit violent crimes might differ in their response to SSRIs from the general population. Firstly, such individuals generally live in unfavourable en-

* Corresponding author.

E-mail address: vieta@clinic.cat (E. Vieta).

<https://doi.org/10.1016/j.euroneuro.2020.04.005>

0924-977X/© 2020 Elsevier B.V. and ECNP. All rights reserved.

vironments, and SSRI-induced brain plasticity, allowing environmental stimuli to reorganise abnormally wired networks (Castrén and Antila, 2017), could lead to detrimental consequences. Secondly, individuals with psychopathic traits, that are strongly associated with criminal behaviour, have been reported to have a distinctive neural organisation, with the amygdala having a smaller role (Tillem et al., 2019). Meanwhile, sertraline treatment has been associated with increased scores of "fearless dominance" on the scale measuring psychopathic personality, reflecting heightened social confidence and diminished interpersonal and physical fear (Dunlop et al., 2011). A troubling possibility could be that certain SSRIs might amplify traits that could facilitate planning and accomplishing criminal acts in predisposed individuals. An alternative hypothesis would be that SSRIs might have been prescribed to patients with a bipolar spectrum disorder. Indeed, aggressiveness as a symptom may be overrepresented in patients with depression and underlying mixed features (Verdolini et al., 2017b). Moreover, SSRIs are not advised in patients with mixed states (Pacchiarotti et al., 2013).

Between-individual analyses with controlling for various factors demonstrated increased risk in younger, but not older age groups, whereas uncontrolled between-individual analyses found reduced violent crime rates in all SSRI users, except the youngest. These differences reflect the importance of these factors for the outcome. However, while authors controlled for sociodemographic factors and lifetime diagnoses, they ignored the information regarding the current psychiatric conditions for which the medications were prescribed, possibly resulting in residual confounding from underlying conditions. Symptoms fluctuate, and diagnoses change. Therefore, it is possible that deteriorating mental states, but not the treatment for them, could prompt certain individuals to commit violent crimes. Diagnosis-related concerns are particularly relevant while discussing the effects of SSRIs. Previously reported association between SSRI use and increased risk of suicide in young age has resulted in warnings on the package and wide media coverage. After years of discussion whether the evidence base for the warning was sufficient and if it was harmful or beneficial, an umbrella review of forty-five meta-analyses rejected the association between antidepressant use and risk of suicide attempt or completion among children and adolescents after adjustment for confounding by indication (Dragioti et al., 2019).

Furthermore, it is important to note that the dispensation of SSRI was used as a proxy for use. While the study used a rigorous technique to get information about all drug dispensations, the exact rates of full compliance are unclear. Indeed, only a 70% agreement between post-mortem toxicology findings and prescription-based estimates of antidepressant use has been reported by another Swedish registry study (Forsman et al., 2018). It is possible that the individuals that dispensed prescriptions but later went on to use the drugs sporadically or not to use them at all were the ones that committed violent crimes. Dispensations do, however, indicate the need for treatment.

Authors explored the role of SSRI as a group while controlling for the use of other psychotropic drugs in their analyses. Several points should be raised regarding this analysis. Firstly, while SSRIs are often regarded as one group,

they have varying effects on different neurotransmitters and could differ significantly in their effects on violence. For example, an adverse drug reports study has found the strongest association between violence and varenicline, which increases the availability of dopamine, among all drugs, followed by SSRIs (Moore et al., 2010), suggesting that drugs with different dopaminergic profiles could have different effects. It should also be underlined that benzodiazepine use was also independently associated with violent crime - an important point for clinicians, as prescription of benzodiazepines instead SSRIs would certainly do more harm than good.

In conclusion, this observational study presents a strong basis for further investigations on SSRI use and criminality. However, it should be emphasised that causality cannot be inferred from such studies, that the indication confounder is extremely likely in an observational study, and that the vast majority (97%) of patients prescribed SSRI will not commit violent crimes either before, during or after the therapy. Instead, only past offenders were more likely to commit a violent crime during SSRI treatment in the present study, which could be the primary focus in future research on the topic.

References

- Castrén, E., Antila, H., 2017. Neuronal plasticity and neurotrophic factors in drug responses. *Mol. Psychiatry* doi:[10.1038/mp.2017.61](https://doi.org/10.1038/mp.2017.61).
- Dragioti, E., Solmi, M., Favaro, A., Fusar-Poli, P., Dazzan, P., Thompson, T., Stubbs, B., Firth, J., Fornaro, M., Tsartalis, D., Carvalho, A.F., Vieta, E., McGuire, P., Young, A.H., Shin, J.I., Correll, C.U., Evangelou, E., 2019. Association of antidepressant use with adverse health outcomes: a systematic umbrella review. *JAMA Psychiatry* doi:[10.1001/jamapsychiatry.2019.2859](https://doi.org/10.1001/jamapsychiatry.2019.2859).
- Dunlop, B.W., Defife, J.A., Marx, L., Garlow, S.J., Nemeroff, C.B., Lilienfeld, S.O., 2011. The effects of sertraline on psychopathic traits. *Int. Clin. Psychopharmacol.* 26, 329-337. doi:[10.1097/YIC.0b013e32834b80df](https://doi.org/10.1097/YIC.0b013e32834b80df).
- Forsman, J., Taipale, H., Masterman, T., Tiihonen, J., Tanskanen, A., 2018. Comparison of dispensed medications and forensic-toxicological findings to assess pharmacotherapy in the Swedish population 2006 to 2013. *Pharmacoepidemiol. Drug Saf.* 27, 1112-1122. doi:[10.1002/pds.4426](https://doi.org/10.1002/pds.4426).
- Lagerberg, T., Fazel, S., Molero, Y., Franko, M.A., Chen, Q., Hellner, C., Lichtenstein, P., Chang, Z., 2020. Associations between selective serotonin reuptake inhibitors and violent crime in adolescents, young, and older adults - a Swedish register-based study. *Eur. Neuropsychopharmacol.* doi:[10.1016/j.euroneuro.2020.03.024](https://doi.org/10.1016/j.euroneuro.2020.03.024).
- Molero, Y., Lichtenstein, P., Zetterqvist, J., Gumpert, C.H., Fazel, S., 2015. Selective serotonin reuptake inhibitors and violent crime: a cohort study. *PLoS Med.* 12. doi:[10.1371/journal.pmed.1001875](https://doi.org/10.1371/journal.pmed.1001875).
- Moore, T.J., Glenmullen, J., Furberg, C.D., 2010. Prescription drugs associated with reports of violence towards others. *PLoS One* 5. doi:[10.1371/journal.pone.0015337](https://doi.org/10.1371/journal.pone.0015337).
- Pacchiarotti, I., Bond, D.J., Baldessarini, R.J., Nolen, W.A., Grunze, H., Licht, R.W., Post, R.M., Berk, M., Goodwin, G.M., Sachs, G.S., Tondo, L., Findling, R.L., Youngstrom, E.A., Tohen, M., Undurraga, J., González-Pinto, A., Goldberg, J.F., Yildiz, A., Altshuler, L.L., Calabrese, J.R., Mitchell, P.B., Thase, M.E., Koukopoulos, A., Colom, F., Frye, M.A., Malhi, G.S., Fountoulakis, K.N., Vázquez, G., Perlis, R.H., Ketter, T.A., Cassidy, F., Akiskal, H., Azorin, J.M., Valentí, M., Mazzei, D.H.,

- Lafer, B., Kato, T., Mazzarini, L., Martinez-Aran, A., Parker, G., Souery, D., Ozerdem, A., McElroy, S.L., Girardi, P., Bauer, M., Yatham, L.N., Zarate, C.A., Nierenberg, A.A., Birmaher, B., Kanba, S., El-Mallakh, R.S., Serretti, A., Rihmer, Z., Young, A.H., Kotzalidis, G.D., MacQueen, G.M., Bowden, C.L., Ghaemi, S.N., Lopez-Jaramillo, C., Rybakowski, J., Ha, K., Perugi, G., Kasper, S., Amsterdam, J.D., Hirschfeld, R.M., Kapczinski, F., Vieta, E., 2013 Nov. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am J Psychiatry* 170 (11), 1249-1262. doi:[10.1176/appi.ajp.2013.13020185](https://doi.org/10.1176/appi.ajp.2013.13020185), PubMed PMID: 24030475; PubMed Central PMCID: PMC4091043.
- Tillem, S., Harenski, K., Harenski, C., Decety, J., Kosson, D., Kiehl, K.A., Baskin-Sommers, A., 2019. Psychopathy is associated with shifts in the organisation of neural networks in a large incarcerated male sample. *NeuroImage Clin.* 24. doi:[10.1016/j.nicl.2019.102083](https://doi.org/10.1016/j.nicl.2019.102083).
- Verdolini, N., Murru, A., Attademo, L., Garinella, R., Pacchiarotti, I., Bonnin, C.D.M., Samalin, L., Pauselli, L., Piselli, M., Tamantini, A., Quartesan, R., Carvalho, A.F., Vieta, E., Tortorella, A., 2017 Jul. The aggressor at the mirror: psychiatric correlates of deliberate self-harm in male prison inmates. *Eur. Psychiatry* 44, 153-160. doi:[10.1016/j.eurpsy.2017.04.002](https://doi.org/10.1016/j.eurpsy.2017.04.002), Epub 2017 Apr 14. PubMed PMID: 28641217.
- Verdolini, N., Perugi, G., Samalin, L., Murru, A., Angst, J., Azorin, J.M., Bowden, C.L., Mosolov, S., Young, A.H., Barbuti, M., Guiso, G., Popovic, D., Vieta, E., Pacchiarotti, I., 2017 Oct. BRIDGE-II-mix study group. Aggressiveness in depression: a neglected symptom possibly associated with bipolarity and mixed features. *Acta Psychiatr. Scand.* 136 (4), 362-372. doi:[10.1111/acps.12777](https://doi.org/10.1111/acps.12777), Epub 2017 Jul 25. PubMed PMID: 28741646.