

Editorial

In this issue of *IJRSM*, Brookwell, Hogan, Healy and Mangin ('authors') describe an observational study highlighted a possible association between SSRI drugs and alcohol dependence [1]. This new study is a follow-up to an anecdotal case report previously published in this *Journal* in 2013. The prior article described an English woman whose alcohol use reportedly worsened while taking two different SSRIs (citalopram, paroxetine) and improved when she discontinued those drugs in favor of mirtazapine [2]. That case report suggested the possibility that the SSRI class of antidepressants may be responsible for the change in her behavior. However, unlike the SSRI class, mirtazapine has pharmacological basis of action that is putatively different from SSRIs. Mirtazapine is a tetracyclic antidepressant that is a potent antagonist of serotonin 5-HT₂ and 5-HT₃ receptors which also appears to stimulate central noradrenergic and serotonergic (5-HT_{1A}) activity [3, 4]. The authors infer that there is the possibility that their findings signal a safety risk for individuals whose alcohol use disorder (AUD) may be initiated or aggravated by the ingestion of SSRI antidepressants.

The observation of a signal and its rigorous evaluation have long been a cornerstone of adverse event reporting. The comprehensive collection of publicly submitted reports and review of safety data from clinical trials forms the basis for the US Food and Drug Administration's safety surveillance. Similar systems form the framework for reporting incidents in Europe. For example, since 1997, the Medical Devices Directive became mandatory for European manufacturers to report adverse events. Similarly, the European Medicines Agency (EMA) launched, in 2012, a website to provide public access to reports of suspected side effects and adverse drug reactions, a move that increased transparency of their adverse event data collection. Whether the information for the data safety sets comes from individual consumers, healthcare personnel or researchers collecting the information during a clinical study or in post-study analysis, the voluntary or mandated reporting of adverse events is central to illuminating signals of common and less common adverse events whose notice merits further study.

Returning to the article that appears in this issue of the *Journal*, we must be duly diligent, I believe, when we review how the data was obtained, in what manner it was collated and the methodological approach used to understand and extrapolate from that data. How credible are the reports? Is there bias in obtaining, selecting or processing the data? What is the verification process? Are there alternate explanations to consider when reviewing the analysis? What would be a reasonable comparative group for analysis? Can the data analysis be subjected to any statistical measurements that would help define probabilities associated with assumptions or the authors' hypotheses? Have the authors elaborated the limitations of their data set, above and beyond simply describing the nature of the data collection? In the context of two immense global issues (alcohol abuse and depression) whose manifestations are varied, often unpredictable and whose population numbers are huge, how significant or reliable is a signal based upon relatively few case reports?

There are special questions that need to be asked in this case: How reliable are the reports from individuals who self-report to a website of a distinguished physician whose interests may be primarily devoted to pharmaceutical side-effects? Although the authors use the Bradford Hill criteria to examine causality, they do not mention the limitation imposed by using a data set from individuals who self-select to report and then whose data is further subjected to possible arbitrariness and bias in selection and review by the authors. How reproducible are extrapolations from challenge-dechallenge assertions when the challenge-dechallenge has not been monitored in a controlled setting? Is the data generalizable?

It is not only the accumulation of anecdotal reports in a somewhat random manner that may be a concern here. Are the various ways in which alcohol use and dependence consistently present with protean manifestations and varied timelines duly considered before extrapolations of cause and effect are made? Should we not anticipate that individuals who have, or who suddenly develop, an alcohol problem will suffer from the negative consequences of alcohol (egs, relationship problems, financial difficulties, occupational problems, medical problems, legal issues) without attribution to an external inciting cause, as in SSRIs? In other words, as in Table IV, are not the consequences of alcoholism and the consequences of SSRI-induced alcoholism, (if that relationship can be established) exactly the same? That is a rhetorical question, because Table IV could be titled, "Consequences of alcoholism" which would similarly reflect the problems associated with alcoholic drinking.

It is widely known in the addiction community that alcohol use disorders and alcoholism manifest variably even within the lifespan of one person. Some persons can drink successfully for years, while others may be obtunded after the first drink. In some, the disease has an intractable downhill course, while in others it is vexing and unpredictable. This variability in the course of alcohol drinking might explain the data, although it would certainly not preclude an association between SSRIs and alcoholic drinking.

Finally, I would urge caution in the interpretation of any research report, but especially a small sample of random self reports. The delight of this report is that the authors may be illuminating yet another signal/agent that increases the likelihood of alcohol use or misuse. On the other hand, as scientists we know that the reliable and reproducible clinical investigations necessary to establish cause and effect are a long way from the signal that may or may not ultimately be confirmed by further study.

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