No space for all-or-nothing in epidemiology: The art of parsimony and interpretation — Authors' reply

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We appreciate the comments from McAnally regarding our recent article.[1] Debate is welcome to good scientific practice, and discussions about methodology are essentially important in the field of epidemiology.

McAnally claims the methods used to assign the T42.6 and T42.7 ICD-10 codes are unclear. Although we recognize — and report as a limitation — that there are no specific ICD-10 codes for gabapentinoids and z-drugs, the labels "Poisoning by, adverse effect of and underdosing of other antiepileptic and sedative-hypnotic drugs" (T42.6) and "Poisoning by, adverse effect of and underdosing of unspecified antiepileptic and sedative-hypnotic drugs" (T42.7) are as clear as non-specified codes can be with regards to the drug categories they should encompass. It is well known that data from death certificates are unavoidably subject to a certain extent of misclassification, especially when a postmortem examination is not performed.[2] However, ICD-10 repositories intended to guide clinicians do include poisoning by z-drugs and gabapentinoids[3] as synonyms to the referred codes.

McAnally also states "It is highly misleading to incriminate any specific drug class based on deliberately non-specific codes, which the authors also recognize may include fentanyl/analogues". We did not make this strong affirmation at any point in the article. We do, however, mention the difficulty to code fentanyl analogues, as they also do not have a name-specific ICD-10 code, as a limitation to measuring the proportion of casualties with T42.6/T42.7 ICD codes with a concurrent opioid poisoning code. In fact, a large number of studies recently published on fentanyl poisoning consistently include the drug and its analogues in the ICD-10 code T40.4 ("Poisoning by, adverse effect of and underdosing of other synthetic narcotics").[4-7] Those studies include reports from the Center for Disease Control and Prevention (CDC). It is important not only to clarify that the T42.6/T42.7 codes do not include fentanyl and analogues but also to illustrate another situation where a drug is associated with an ICD-10 code that does not contain its name.

We agree with the claim that our findings do not imply causality, which is not stated at any point in our article. We were careful enough to use the expression "deaths with a T42.6/T42.7 ICD code" throughout the manuscript, and our objective was to describe trends in those deaths and their co-occurrence with other intoxication ICD-10 codes. The finding of increasing trends suggests these drugs are being more frequently involved in overdose deaths and, moreover, in overdose deaths involving benzodiazepines and opioids. This possibly indicates that z-drugs and gabapentinoid are not preventing overdose deaths from opioids and benzodiazepines and possibly adding harm to individuals who use them simultaneously with those drugs. Findings from two recent meta-analyses[8,9] challenge McAnally's affirmation of "no robust evidence of any serious harms from any line of rigorous investigation" and largely recommend weighing risks and benefits before prescribing them — especially for individuals at risk for medication abuse. In fact, Evoy and colleagues have found that having an opioid use disorder is the greatest risk factor for gabapentinoid abuse.[9] We are by no means advocating against the prescription of gabapentinoids when the indication is right and when the patient is carefully monitored by zealous clinicians. Rather, we simply point out that such medications are not free of risks and should be prescribed with appropriate clinical reasoning and careful monitoring — and even more so in populations at higher risk of potentially developing abuse. This is no different from the conclusion of McAnally's paper about the risk stratification of gabapentinoids, which acknowledges its abuse potential by individuals with an opioid use disorder.[10]

Finally, we quote Slattery, who says "The science of epidemiology entails applying classic epidemiological methods to understanding the distribution of diseases in

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populations. The art of epidemiology is interpreting the findings".[11] Proper interpretation of epidemiological findings is as important as the findings themselves. Rather than pointing out drugs as "guilty or innocent", our manuscript intends to bring new data to a scientifically rigorous debate on the risks and benefits of gabapentinoids and z-drugs, with the ultimate goal to refine and advance knowledge to better inform clinical practice.

Contributors

VST: study conception, writing
MCMB: editing
RP: editing
LES: editing
JMCM: editing
TMF: editing
SSM: study conception writing

Declaration of interests

The authors declared no conflicts of interest.

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References

1 McAnally, et al. Guiltyuntil proven innocent? *Lancet Reg Health Ame*. 2022;10: 100280.
2 Smith Sehdev AE, Hutchins GM. Problems with proper completion and accuracy of the cause-of-death statement. *Arch Intern Med*. 2001;161(2):277–284. https://doi.org/10.1001/archinte.161.2.277. Epub 2001/02/15 PubMed PMID:11176744.
3 https://icdlist.com/icd-10/T42.6X1A.
4 Ahmad FB RL, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. 2021., Designed by LM Rossen AL, FB Ahmad, JM Keralis, and Y Chong: National Center for Health Statistics.
5 Althoff KN, Leifheit KM, Park JN, Chandran A, Sherman SG. Opioid-related overdose mortality in the era of fentanyl: Monitoring a shifting epidemic by person, place, and time. *Drug Alcohol Depend*. 2020;216: 108321. https://doi.org/10.1016/j.drugalcdep.2020.108321. Epub 2020/10/03 PubMed PMID:33007700; PMCID: PMC7606594.
6 Tadrous M, Greaves S, Martins D, et al. Evaluation of the fentanyl patch-for-patch program in Ontario, Canada. *Int J Drug Policy*. 2019;66:82–86. https://doi.org/10.1016/j.drugpo.2019.01.025. Epub 2019/02/12 PubMed PMID:30743092.
7 Slavova S, Costich JF, Bunn TL, et al. Heroin and fentanyl overdoses in Kentucky: Epidemiology and surveillance. *Int J Drug Policy*. 2017;46:120–129. https://doi.org/10.1016/j.drugpo.2017.05.051. Epub 2017/07/25 PubMed PMID:28735777.
8 Smith RV, Havens JR, Walsh SL. Gabapentin misuse, abuse and diversion: a systematic review. *Addiction*. 2016;111(7):1160–1174. https://doi.org/10.1111/add.13324. Epub 2016/06/07 PubMed PMID:27265421; PMCID: PMC5573873.
9 Evoy KE, Sadrameli S, Contreras J, Covvey JR, Peckham AM, Morrison MD. Abuse and Misuse of Pregabalin and Gabapentin: A Systematic Review Update. *Drugs*. 2021;81(1):125–156. https://doi.org/10.1007/s40265-020-01432-7. Epub 2020/11/21 PubMed PMID:33215352.
10 McAnally H, Bonnet U, Kaye AD. Gabapentinoid Benefit and Risk Stratification: Mechanisms Over Myth. *Pain Ther*. 2020;9(2):441–452. https://doi.org/10.1007/s40122-020-00189-x. Epub 2020/08/02 PubMed PMID:32737803; PMCID: PMC7648827.
11 Slattery ML. The science and art of molecular epidemiology. *J Epidemiol Community Health*. 2002;56(10). https://doi.org/10.1136/jech.56.10.728. 728-9. Epub 2002/09/20 PubMed PMID:12239192; PMCID: PMC1732025.