



# Response to Comment on “Gabapentinoid Benefit and Risk Stratification: Mechanisms Over Myth”

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## GABAPENTINOIDS: PANACEA OR PANDORA’S BOX?

### DIGITAL FEATURES

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We would like to thank Peckham et al. [1] for their critique of our review [2] outlining the benefits and risks of gabapentinoids (GPNs) in the context of general medical, specialty pain management, and addiction medicine practice. Our targeted narrative review of this subject is intended to present a balanced perspective of salient issues to, and ameliorate current confusion regarding the class of drugs among clinicians, pharmacists, and public health workers alike. It seems as though our respondents have grasped our main point, as evidenced by their statement that “When used appropriately under the guidance of healthcare professionals, these represent relatively safe medication options for most patients.” Here we would like to make it clear to them and our readership that we also urge caution—with rational and evidence-based benefit:risk stratification—in the prescription of these drugs. In particular, among opioid-dependent persons the risks of both (1) misuse, abuse, and addiction, and (2) physical harm, such as synergistic respiratory depression with other CO<sub>2</sub> response-curve shifting agents (e.g., opioids), appear to be elevated.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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## Association Does Not Equal Causality (or, Innocent Until Proven Guilty)

The issue at hand is whether we rush to summary judgment or proceed with good science toward the elucidation of true risk (or lack thereof)—at both public and individual levels. Due process thankfully has evolved in our civilization, not only in the courtroom but also in the realm of the biological and physical sciences. Attributing agency for dependent outcome  $y$  upon independent factor  $x$  requires far more than possible cause; the standard must be one of “beyond reasonable doubt.”

Toward that end, epidemiology does indeed provide substantial mechanisms for determining causality; the discipline is however far more than the trumpeting of descriptive statistics, which Mark Twain so eloquently disparages for us. It rests upon systematically applied criteria overturning the null hypothesis of no association; as such, the burden of proof falls upon the plaintiff.

Sir Bradford Hill’s criteria of causality [3] remain as pertinent today as they did in the previous century and even before. We recognize that many of the criteria await application to the question of whether GPNs are responsible for the alleged adverse outcomes. Nonetheless, let us begin with the consideration of biological plausibility (and coherence).

To be sure, GPNs confer a risk of physical dependence. They certainly display phenomena of tolerance and withdrawal, which both drive physical dependence. However, these phenomena are not dissimilar to other drugs affecting and effecting neural plasticity (such as antidepressants or antipsychotics) or other somatic functions (e.g., proton pump inhibitors and beta-blockers.)

What about psychological/behavioral dependence? GPNs may indeed confer a state of hedonic reward. By the current neurobiologic paradigm, the development of addiction should of course be accompanied by striatal/ventral tegmental area dopaminergic, and although such GPN-mediated mesolimbic phenomena have been refuted by several previous preclinical and clinical studies, one recent study has demonstrated it in a murine model (employing

supratherapeutic doses) [4]. While controversial, we allow that GPNs may confer a dose-dependent increase in limbic-region extracellular GABA-ergic activity [5–7], which in vulnerable individuals could indeed lead to “liking”, misuse, and abuse and, in some cases, even to “wanting” (to use Berridge and Robinson’s well-accepted framework for addiction) and dependence [8]. And in keeping with the theme of appreciating the increased risk of abuse (with potential addiction) in opioid- or other poly-substance-addicted individuals, GABA-ergism may “fast-track” (i.e., via “primed circuitry”) even weak GABA-mimetic agents such as GPNs to a place of “want” [9]; currently argued to be the decisive (psychological) factor in the development of addiction.

The weight of evidence however favors a more prominent “desensitization” action mediated via inhibition of  $\alpha 2\delta$ -subunits of presynaptic voltage-dependent calcium channels (e.g., leading to decreased activity-dependent excitatory neurotransmission), which in essence inhibits the development of addiction’s behavioral sensitization [10, 11]. That is to say, from the laboratory perspective, the GPNs appear to be anti-addictive. Along those lines, even pregabalin (well-accepted as possessing a greater potential for abuse and dependence liability) has been recently shown in a rodent model to confer significant reduction in brain dopamine, glutamate, and norepinephrine [12].

And risks of physical harm? A recent spate of perioperative studies have suggested increased respiratory depression among patients pre-treated with GPNs. In all fairness, however, the postoperative period is a complex one, with residual central nervous system-depressing and  $\text{CO}_2$  response-blunting activity of halogenated ethers, a potential sympatholytic (and therefore respiratory-drive lowering) effect of local/regional anesthetics, and cumulative exhaustion from physical and psychological stress. GPNs have not yet been shown to shift the  $\text{CO}_2$  response curve to the right in any consistent fashion [13, 14], and there are too many confounders in the post-anesthesia care unit. One recent prospective study has also suggested that GPN use increases the apnea-hypopnea index (AHI) in older male volunteers [15], although

the trial only enlisted eight individuals, of whom five also displayed increased AHI with placebo. From the standpoint of plausibility and coherence therefore, there are hardly sufficient data, let alone coherent data, to render a verdict.

Moving on to other criteria, while far from complete, our collective knowledge of the subject at hand to date does not support temporal sequence, consistency, or strength of association/biological gradient, nor has there been ample experimentation. To evaluate the real abuse liability and addictive power of GPNs, prospective clinical studies employing operationalized addiction criteria, collecting precise addiction and other medical history, and utilizing biomarkers (e.g., urine screens) are required.

### Who Wants Inflation?

Causality aside, let's back up and talk strictly about descriptive statistics and scale for a moment. We have no issue with our respondents' claim that "there is significant evidence that these medications are being misused outside of medical recommendations." (In fact we communicated this within the article.) But this is also true of glue among bored/troubled youth, or of mouthwash among severe alcoholics. Epidemiology begins with the identification of a disease cluster, to be sure, but the denominator is of equal if not greater importance: Elmer's® and Listerine® products don't pose major public health problems; and neither Neurontin® (Pfizer Inc., New York, NY, USA) nor Lyrica® (Pfizer Inc.) have convincingly been shown to either in the general population.

Over a denominator of hundreds of millions (perhaps even billions) of prescriptions, psychological dependence on and social impoverishment due to GPNs are not prevalent findings. We (and countless other clinicians involved in the real-world medical management of individuals suffering with chronic pain, psychiatric comorbidities, and 'dual-diagnosis' states comprising substance use disorders and other psychiatric problems, none of which preclude coexisting chronic pain) have not encountered

the thousands or even millions of cases of actual addiction to GPNs that are to be expected if this class of drugs indeed possesses significant dependence liability. One of us performed a systematic review [16] on this topic and did not find data remotely supportive of even a fraction of the cases of addiction to be expected from the sheer number of these medications being used by a substantial proportion of the world's population, with an overrepresentation of addictive diatheses, to boot.

Questionable abuse and misuse prevalence estimates have pervaded the literature on the topic, derived from sources such as extrapolation from a (frequently cited) single small internet survey performed by a global market research company [17] and from prescription databases [18]. Pharmacovigilance is outside the scope of our practice, and we do not pretend to possess expert knowledge of the methods involved in arriving at conclusions regarding the population-level dangers of medications. However, as mentioned in the original article, we would like to point out once again that the use of techniques such as Lorenz curves to identify abuse-labile substances should also cast suspicion upon other commonly prescribed medications such as antibiotics [19] and nonsteroidal anti-inflammatory drugs (NSAIDs) [20]. A quarter century ago, using similar modeling methods, triptans were similarly implicated as substances of abuse [21–23]. Inequity of use may indeed represent misuse (or disease clustering) among a small fraction of the population, but it may also represent pharmacokinetic ( $\pm$  pharmacogenomics) heterogeneity, socioeconomic disparities, among others and, in the case of gabapentin proper, the underlying asymptotic active transport curve.

As far as hard outcomes are concerned, the most recent systematic review [24] of clinical and forensic toxicology studies reporting adverse safety outcomes such as impaired driving, overdoses or deaths showed all events on the order of  $10^3$  (among the studies cited) in association with GPN use. When considering mortality statistics, as pointed out in our article, during a 15-year period (2000–2014) of data collection by the American Association of Poison Control Centers [25], deaths attributed to

antidepressants ( $n > 300$ ) were two orders of magnitude greater than deaths from GPNs ( $n = 8$ ). A more recent investigation of gabapentin toxicity numbers reported to the U.S. National Poison Data System between 2013 and 2017 identified 17 deaths where gabapentin was involved [26]. While every individual death is a tragedy that may or may not be attributable to GPNs, the question of safety from a public health standpoint again really boils down to a question of scale—the denominator numbers in the hundreds of millions (if not billions) of prescriptions. Furthermore, it should be pointed out again that GPN use/presence in these cross-sectional descriptive analyses represents just that: use/presence. Tobacco (and its metabolites) were undoubtedly also present in a substantial fraction of these samples but almost certainly did not comprise the acute/proximate cause of death.

## CONCLUSION

“Knee-jerk” prescription of GPNs in response to a well-intentioned and warranted push toward multimodal and opioid-sparing analgesic regimens has undoubtedly opened the door for misuse, abuse, and even dependence/addiction among many high-risk individuals. The agents are not as benign as perhaps commonly held among clinicians (nor to be fair are NSAIDs or acetaminophen, which pose a significantly greater public health risk in terms of physical morbidity and mortality), and most certainly they are not a panacea. We repeat: evidence-based prescription and cautious monitoring are certainly urged.

Neither however are they the Pandora’s box alleged by some. In clinical practice, we counsel patients regarding the individual benefit:risk ratio of medical and surgical interventions. We urge similar rational and evidence-based decision-making at the public health level: the indictment and sentencing of safe pharmacotherapeutic agents with proven benefit [27, 28] on the basis of suspicion alone risks causing great harm to hundreds of millions of individuals who are currently benefiting, or who may in the future benefit from appropriate

therapy—including indications perhaps heretofore not yet appreciated.

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