Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: June 30, 2024

Citation: Lawhern RA, Nadeau SE, 2024. Treating Chronic Pain and Anxiety – a Modest Proposal, Medical Research Archives, [online] 12(6). https://doi.org/10.18103/mra.v12i6.5359

DOI
https://doi.org/10.18103/mra.v12i6.5359

ISSN: 2375-1924

RESEARCH ARTICLE

Treating Chronic Pain and Anxiety – a Modest Proposal

Richard A. Lawhern PhD* and Stephen E. Nadeau MD

***Corresponding author:** lawhern@hotmail.com

ABSTRACT:

Introduction: the CDC guidelines of 2016 and 2022 strongly proscribed the co-prescription of opioids and benzodiazepines, implicitly suggesting that the combination was associated with high risk. This position now strongly influences health provider organizations, clinicians, pharmacies, health insurance companies, and boards of medicine. We have previously comprehensively reviewed the generally high-quality published studies, all employing a retrospective cohort design. These studies suggest that, to the extent that the combination increases mortality risk, the magnitude of the increase is small and it likely reflects a conflation of mortality risk related to the underlying conditions and the risks associated with simultaneous use of drugs of both classes. We here recapitulate the results of our prior analyses, contrast them with CDC positions, and introduce the results of additional studies, some only recently published and some of which we had previously been unaware.

Methods: Analytic review of the scientific literature.

Results and Discussion: Studies previously analyzed by us focused exclusively on risks associated with co-prescription. The results of further studies, reviewed here, suggest that, while there are small populations in whom co-prescription, or even solely prescription of benzodiazepines, may be risky, risks of morbid outcomes in clinic populations in general are dominated by the impact of psychiatric disease and opioids make a very small and indirect contribution. A recently published study has demonstrated the very high mortality risk associated with tapering and discontinuing benzodiazepines. Our modest proposal bears on the importance of applying a deeper understanding of published papers and the de facto meaning of the cited risk factors for death.

Conclusion: There has been substantial misconstrual of association with causation. Opioids and benzodiazepines have emerged as, at worst, very minor contributors to mortality and may often be better viewed as markers of the disorders that actually cause excess deaths: psychiatric disease and undertreatment of physical pain.

Introduction:

There is presently an ongoing concern in public health policy addressing treatment of pain and addiction over potential interactions between opioid analgesics and benzodiazepines [1]. Extensive social media reports reveal a deep bias now exists among clinicians and policy makers against co-prescription of opioid pain relievers and Benzodiazepine-family anti-anxiety agents. This bias operates to such an degree that thousands of patients are now being offered a choice *between* treatment for pain versus treatment for anxiety or insomnia. The US Centers for Disease Control and Prevention (CDC) has advocated for great caution in co-prescription of these medications in their 2022 revised and expanded practice guidelines for prescription of opioids to adults with severe pain [2]. In aggregate effect, the CDC practice guidelines place clinicians on notice that any untoward outcome among their patients who are co-prescribed opioids and benzodiazepine drugs may be interpreted by health care providers, pharmacists, health insurance companies, and State Medical Boards as a violation of usual and accepted prescribing practice.

This paper first reviews clinical literature pertinent to these public health concerns. The authors find that excellent retrospective cohort studies in the clinical literature have established that effects of co-prescription of opioids and benzodiazepines are complex and not susceptible to simple interpretation. Very likely, definitive answers can be achieved only through prospective studies. These may be infeasible because of the very large participant numbers required to achieve adequate statistical power. In this paper we update our previous comprehensive reviews, compare the scientific data with CDC guidelines, and offer a modest proposal for research to resolve uncertainties in the balance of the risks and benefits of co-prescription of benzodiazepines and opioid analgesics.

Clinical Literature Review

First, we offer pertinent extracts from our earlier work in Reference [1]. Reference numbers in this extract are merged with the reference list of the present paper, below:

=========Begin Extract 1==========

"Simultaneous Use of Opioids and Benzodiazepines

The CDC opioid prescribing guidelines [3] strongly discourage the concurrent use of opioids and benzodiazepines. However, two studies warrant particular attention. Sun et al. [4] conducted a case-cohort analysis of 315,428 patients in the Marketscan database (Truven Health Analytics, Ann Arbor, MI) who filled at least one prescription for an opioid between January 1, 2001 and December 31, 2013. The adjusted odds ratio for an emergency room visit or hospital admission for ostensible opioid overdose among those using both classes of drug was 2.14.

Unfortunately, this impressive study suffers a serious methodological weakness: the gold-standard diagnosis was derived from physician judgment, not response to naloxone treatment. Alleged risks of concurrent use of these two drug classes have been sounded for many years despite the absence of adequate data. The very fact that a patient is taking the combination may alter the diagnostic evaluation of and the attribution of cause for altered mental status [5]. Thus, it is possible that in many patients included in the study by Sun et al., the mere discovery that a patient was taking both an opioid and a benzodiazepine increased the likelihood of a diagnosis of opioid overdose. Consistent with this hypothesis, the diagnosis of opioid overdose related to the combination was made twice as often in 2013 as it was in 2001.

In a case-cohort study, Park et al.[6] analyzed opioid-associated mortality rates in 420,386 veterans prescribed opioids, 27% of whom had concurrent or past prescriptions for benzodiazepines [see also Xu et al. [7]]. The past prescription cohort was included in an attempt to control for excess mortality associated with underlying conditions, such as chronic anxiety disorder, post-traumatic stress disorder, and depression, for which benzodiazepines are commonly prescribed and in which drugs are more commonly misused. The adjusted hazard ratio for death in the prior prescription group was 2.33 and in the current prescription group, 3.86. Hazard ratio was elevated for all benzodiazepines except temazepam.

Hazard ratio increased with increasing opioid dosage and increasing benzodiazepine dosage. Because of the challenge of controlling for the differences between the benzodiazepine and non-benzodiazepine cohorts, the authors concluded: "benzodiazepines might be better conceptualized as a marker of risk with unknown direct causal links to death from overdose."

Dasgupta et al. [8], in a population-based cohort study of all North Carolina residents, reported a 10 times elevated risk of death associated with the presence of both opioids and benzodiazepines at time of death. However, 49.6% of decedents had

no active opioid prescription at the time of death, suggesting that in half of the cases, illicit or diverted drugs must have played a role. Therefore, benzodiazepines could have either contributed to risk of death or simply been a marker for polysubstance abuse.

Zedler et al. [9] reported a case-control study (10 controls/case) of 817 VA patients who experienced either opioid overdose or serious opioid-induced respiratory depression. They did identify benzodiazepines as a risk factor (RR 1.49) but also found that antidepressants were actually a greater risk factor (RR 1.98). These findings are consistent with the conclusion of Park et al [6] that benzodiazepines are best viewed as a marker of risk with unknown direct causal links to the outcome measure.

From these studies, we conclude that calculating the additional risk posed by co-administration of benzodiazepines with opioids poses a major scientific challenge and currently available data can best be considered as suggestive of a modest increase in risk (relative risk ~2) -- at least part of which may be attributable to concurrent disease rather than the drug combination.

Finally, the CDC guideline did not consider the prevalence and negative impacts of idiopathic insomnia and anxiety disorders or the paucity of effective and safe alternative treatments for these two disorders."

The Relationship of Depression to Chronic Pain and Its Treatment

Between 30 and 54% of people with chronic pain also have major depressive disorder (MDD) [10]. Patients with moderate to severe pain have a more than 2-fold increase in the risk of developing a mood or anxiety disorder [10]. General practitioners detect on average 50% of cases of depression [11]. Rates of depression reported in large opioid database studies range from 12.9 to 32% [12, 13], suggesting that depression is also commonly missed in patients being treated for chronic pain. Diagnosed depression is often untreated [14].

As Braden et al. [15] put it, "It is possible that opioids prescribed to depressed persons may be treating an undifferentiated state of mental and physical pain." If depression can be viewed as an amplifier of suffering related to pain, then successful treatment of depression might be expected to reduce chronic pain and reduce opioid dosage (a hypothesis testable in a trial employing an EERGW design).

Among patients with chronic pain, inadequately treated depression is associated with a number of adverse outcomes. Patients with depression are three times as likely to be prescribed opioids as those without [15]. Among 10,311,961 patients who received short term opioid treatment of pain, depression was associated with a doubling of the hazard ratio for long-term opioid use [16]. Patients with depression who are prescribed opioids for non-cancer pain are likely to receive higher doses [15, 17]. MDD is associated with a higher prevalence of alcohol use disorders [18] and of opioid misuse and OUD [19, 20]. Patients with comorbid non-cancer pain and depression have higher pain interference with activities of daily living and higher mental distress [15]. These studies, in aggregate, suggest that aggressive treatment of depression, in addition to its salutary effects on pain management, might mitigate many of the most troublesome issues associated with treatment of chronic pain in patients with comorbid depression."

========== End Extract 1 ==========

Several additional observations serve to focus those of our earlier paper:

1. Risks of respiratory suppression associated with co-prescription of opioids and benzodiazepine drugs are almost certainly increased for higher doses of both [6]. However, one outcome of the 2016 and 2022 CDC opioid prescribing guidelines has been to drive dose levels generally downward while increasing the suffering of patients force-tapered by their physicians. Thus, the risk levels cited above are not likely pertinent to current populations treated with opioids.

2. Past published retrospective studies of electronic healthcare records do not access data on the severity of pain, anxiety or insomnia at the time dual treatment was initiated. Such access would require major revisions to study protocols. Even if such data were available, prescription of benzodiazepine drugs might simply be a marker for the severity of multiple underlying medical entities, each with its own mortality risk – rather than a "cause" of elevated mortality risk from co-prescription per se.

3. The design of future studies of mortality risk from co-prescription must address the very wide variability in individual patient responses to both opioid analgesics and benzodiazepine drugs, due to genetic polymorphism in expression of CYP-450 enzymes governing metabolism in the human liver [25]. None of the existing trials literature on safety of opioid medications addresses this issue.

What Do the 2022 CDC Guidelines Say About Opioids Co-prescribed with Benzodiazepines?

Of particular import from the 2022 CDC practice guidelines for prescription of opioids is Recommendation 11, quoted below in entirety [2]:

Recommendation 11

Clinicians should use particular caution when prescribing opioid pain medication and benzodiazepines concurrently and consider whether benefits outweigh risks of concurrent prescribing of opioids and other central nervous system depressants (recommendation category: B; evidence type: 3).

Implementation Considerations

- Although in some circumstances it might be appropriate to prescribe opioids to a patient who is also prescribed benzodiazepines (e.g., severe acute pain in a patient taking long-term, stable low-dose benzodiazepine therapy), clinicians should use particular caution when prescribing opioid pain medication and benzodiazepines concurrently. In addition, clinicians should consider whether benefits outweigh risks for concurrent use of opioids with other central nervous system depressants (e.g., muscle relaxants, nonbenzodiazepine sedative hypnotics, and potentially sedating anticonvulsant medications such as gabapentin and pregabalin).

- Buprenorphine or methadone for opioid use disorder should not be withheld from patients taking benzodiazepines or other medications that depress the central nervous system.

- Clinicians should check the PDMP for concurrent controlled medications prescribed by other clinicians (see Recommendation 9) and should consider involving pharmacists as part of the management team when opioids are co-prescribed with other central nervous system depressants.

- In patients receiving opioids and benzodiazepines long term, clinicians should carefully weigh the benefits and risks of continuing therapy with opioids and benzodiazepines and discuss with patients and other members of the patient's care team.

- Risks of concurrent opioid and benzodiazepine use are likely to be greater with unpredictable use of either medication, with use of higher-dosage opioids and higher-dosage benzodiazepines in combination, or with use with other substances including alcohol (compared with long-term, stable use of lower-dosage opioids and lower-dosage benzodiazepines without other substances).

- In specific situations, benzodiazepines can be beneficial, and stopping benzodiazepines can be destabilizing.

- Clinicians should taper benzodiazepines gradually before discontinuation because abrupt withdrawal can be associated with rebound anxiety, hallucinations, seizures, delirium tremens, and, rarely, death. The rate of tapering should be individualized.

- If benzodiazepines prescribed for anxiety are tapered or discontinued, or if patients receiving opioids require treatment for anxiety, evidence-based psychotherapies (e.g., cognitive behavioral therapy), specific antidepressants or other nonbenzodiazepine medications approved for anxiety, or both, should be offered.

- Clinicians should communicate with other clinicians managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care."

------- End Quotation from Reference 3 ---------

These recommendations are substantially at odds with well-established science. They reflect major oversimplification of the problem. The recommendation also presumes that clinicians are adequately trained to accurately weigh benefits against risk, which they are not [27]. In fact, it is only since publication of papers we review below that it has become possible for experts in pain management *who are thoroughly versed in this literature* to make this assessment.

Furthermore, while Prescription Drug Monitoring Plans (PDMPs) serve an indispensable role in preventing the redevelopment of the pill mills that contributed to the modern opioid crisis, their reports inevitably include what is called an "opioid overdose risk score" -- an entirely misleading measure concocted using a secret proprietary

algorithm carefully guarded by the vendor that supports PDMP websites, Bamboo Health [28]. In fact, calculation of a reasonably accurate overdose risk score would require free access to HIPAA protected patient information, which Bamboo does not have.

The STORM Model of Oliva, Bowe and Tavakoli et al

A key paper by Oliva, Bowe, and Tavakoli et al [2] offers a unifying framework for understanding and resolving the "major scientific challenges" that remain in determining a balanced standard of care for medical practice in the integrated treatment of severe pain and clinical anxiety. The following extract from more recent published work by the authors [22] expands on the implications of this key paper:

======== Begin Extract 2 =======

> **"Clinical pain populations and the manufactured crisis**
> *Overdoses, suicide attempts, and deaths associated with prescription opioid use*
>
> "Important studies by Oliva et al [2] and Bohnert et al [21] … tell us that long before the CDC weighed in and during a time when there was likely more liberal use of pharmaceutical grade opioids, the major cause of overdoses and suicide attempts (and presumably deaths) was not opioids *per se* but rather mental illness, desperation, and despair. Restriction of opioid use and dosage would not be expected to ameliorate these problems and might worsen them. However, recognition of these issues provides us a clear pathway to what can be done to reduce mortality associated with opioid prescription. A good example is the Stratification Tool for Opioid Risk Mitigation (STORM) program developed by the Veterans Administration on the basis of the results of Oliva et al[2]. The STORM program has been shown, in a cluster RCT, to reduce all-cause mortality within four months of participant inclusion (RR 0.78) [28].
>
> "…Oliva, Bowe, Tavikoli et al [2] developed the Stratification Tool for Opioid Risk Mitigation -- a highly accurate predictive model to identify Veterans Administration patients prescribed opioid analgesics, who might be at elevated risk of drug overdose, suicide-related events (ideation or attempt) or death. The model was applied to a population of 1,135,601 patients followed from Fiscal Year 2010 to 2011, employing Veterans Administration electronic health record data. Several types of short-acting and long-acting opioid analgesics were included.
>
> "In this population, 2.1% (23,790) of patient records followed from 2010 had codes for a drug overdose, suicide-related event, or death during Fiscal Year 2011. Among the 1,000 patients deemed to be at highest risk in the predictive model, only one of 11 risk factors (number of classes of sedating medications other than opioids) was related to medical treatment choices per se. The remaining 10 major risk factors related to prior attempted suicides, inpatient mental health treatment, previous drug or alcohol abuse, or diagnoses of major depressive disorder. Medical co-morbidities were also tracked in the analysis -- but risk factors associated with these co-morbidities were substantially lower than the top eleven. Risk factors for the cataloged negative outcomes varied over a relatively small range (1.1 to 1.5) between types and strengths of opioids used."

========== End Extract 2==========

A Modest Proposal

The authors observe that careful oversight of benzodiazepine-family prescriptions is certainly warranted. This is true whether these medications are prescribed alone to patients with clinical depression and/or anxiety, or co-prescribed to reduce anxiety and improve sleep in patients treated for severe pain.

Opioids are known to have addictive potential, although this is very rarely realized in clinical populations [22]. Forty years ago, evidence of a withdrawal syndrome in patients prescribed benzodiazepines — a well-established and universally accepted pharmacodynamic phenomenon — was misconstrued as evidence of incipient addiction. This misconception is still highly prevalent today and it has led to the widespread prescription of alternative medications that have well established harms.

Both opioids and benzodiazepines may cause significant sedation or contribute to respiratory depression. Alteration of cognitive or neurologic function by opioids should always be a strong signal to either reduce dosage or switch to a different opioid that may, properly titrated, enable

adequate control of pain without cognitive or neurological consequence.

The presence of neuromuscular disease or severe chronic obstructive pulmonary disease is generally a serious contraindication to use of benzodiazepines because of the depressant effect they might have on respiration, even when used in modest dosage. There are a number of causes of insomnia, only some of which are optimally treated with a benzodiazepine. In most cases, anxiety can be adequately controlled through use of an antidepressant such as a serotonin selective re-uptake inhibitor (SSRI), which will have no effect on respiration. For either class of medication, but particularly opioids, very slow titration is warranted — considerably slower than is often recommended and vastly slower than in the over 100 randomized controlled trials that have attempted to test opioid efficacy. This is to assure safety, precision in titration, minimization of side effects, and time to treat important and almost ubiquitous co-morbidities such as depression, which may amplify suffering due to pain.

As noted above, it is also known that incidence of hospitalizations or overdose mortality is elevated among patients who are co-prescribed benzodiazepines and opioid analgesics. However, we suggest that it is important to understand that elevated mortality is occurring in a very small number of clinical patients -- and quite possibly *not* from any cause-and-effect relationship deriving from co-prescription as such. As demonstrated by Oliva et al, a medical history of "inpatient mental health treatment, previous drug or alcohol abuse, or diagnoses of major depressive disorder" is a far more significant contributor to bad outcomes in clinically managed patients than is exposure to opioid analgesics.

A diagnosis of opioid use disorder (OUD) is also a fairly strong predictor of future adverse outcomes [(1), (29) (30).] To the extent that this is true, then a diagnosis of OUD is probably merely a *marker* of inadequately treated pain and the likelihood is that physical pain constitutes an important addition to the extreme psychic pain these patients are suffering. In this case, the prescription of opioids is a contributor to bad outcomes only to the extent that dosage is inadequate or that no dosage will suffice given the magnitude of psychic pain. This hypothesis receives strong support from the study of Oliva et al. [(22)], which found that opioid dosage accounted for only a tiny portion of the variance in outcome.

As we have discussed [[1]], our current DSM scale for diagnosis of OUD is seriously flawed and could easily reflect the symptoms of a patient in severe, inadequately treated pain, desperately seeking relief — in short, what has been termed "pseudo-addiction" [(29)] .

Thus, it is entirely believable that US CDC and earlier consensus participants have fallen victim to what might best be characterized as a mis-construal of statistical association as evidence of a simple cause-effect phenomenon. Elevated mortality rates among patients co-prescribed opioid analgesics and benzodiazepine drugs may be primarily driven by a combination of under-treatment of pain and persisting effects of the disorders that prompted treatment with benzodiazepines. For patients suffering from both severe pain and chronic anxiety, the benefits of co-prescribing benzodiazepines and opioid analgesics may in fact be significantly greater than risks of overdose or death.

However, establishing the relative contribution of the underlying comorbidities for which benzodiazepines might be prescribed and the direct contribution of the opioid-benzodiazepine combination constitutes a thorny scientific problem. It might best be settled by prospective randomized controlled trials, which would have the particular value of enabling entry of quantitative estimates of severity of pain, anxiety, and insomnia as independent variables in the mixed methods regression analysis — variables that cannot be accurately measured in retrospective cohort studies. However, because the incidence of morbid outcomes observed in among populations prescribed opioids in dosage >100 MMED is so low, it would be a major challenge to mount a prospective study large enough to provide sufficient statistical power (Bohnert et al., 2008, estimated an average annual opioid-associated mortality rate of 0.25%/year).[(31)]

It should also be borne in mind that recently published data [(32)] have shown that in people prescribed both opioids and benzodiazepines, 1-year mortality was increased from 3.9% in people who continued on benzodiazepines to 6.3% in patients in whom benzodiazepines were discontinued. This increment in absolute risk of death of 2.4% dwarfs the estimated *average* annual risk of death associated with opioids prescriptions of >100 MMED, reported by Bohnert et al.

Genetically-based inter-individual variability in minimum effective doses for both classes of therapy [(1, 23, 24)] pose a major additional challenge.

Significant investment may be required in new large-scale trials using fully adaptable protocols [25] or retrospective electronic medical records analyses, to fully address this challenge. After such analyses are published, American Colleges of Medicine, specialty academies, and certification boards can then publish revised and balanced practice guidelines for integrated treatment of pain, clinical depression and anxiety. Revision of practice guidelines for treatment of opioid use disorder may also be warranted. We have published a framework for treatment of chronic nonmalignant pain that might serve as a practical guide in the interim .

Conclusion

With regard to co-prescription of opioid pain relievers and benzodiazepine drugs, there has been substantial misconstrual of association with causation in elevated rates of overdose mortality among clinically managed patients. Opioids and benzodiazepines have emerged as, at worst, very minor contributors to mortality and may often be better viewed as markers of the disorders that actually cause excess deaths: psychiatric disease and undertreatment of physical pain.

About the Authors:

Dr. Lawhern is a technically trained non-physician patient advocate with 27 years' research experience in the medical literature of US public health policy for chronic pain. He has made tens of thousands of person-to-person contacts while moderating on-line patient support groups. His contact address is lawhern@hotmail.com

Dr Nadeau has been member of the faculty of the University of Florida College of Medicine since 1987. He has provided clinical care, taught residents and medical students, and pursued research, primarily in behavioral neurology, neuroplasticity, and neuro-rehabilitation. He is a former Associate Chief of Staff for Research at the Malcom Randall Veterans Administration Medical Center. Positions expressed in this paper may not reflect those of the Veterans Administration or the Florida College of Medicine.

References

1. Nadeau SE, Wu JK, and Lawhern RA. Opioids and chronic pain: an analytical review of the clinical evidence. *Front. Pain Res. Pharmacological Treatment of Pain.* 2021;2:721357 https://doi.org/10.3389/fpain.2021.721357 accessed May 24, 2024

2. Oliva EM, Bowe T, and Tavakoli S, et al, Development and applications of the Veteran Health Administration's stratification tool for opioid risk mitigation (STORM) to improve opioid safety and prevent overdose and suicide. *Psychol Serv*. 2017;14(1):34-49. Doi:10.1037/ser0000099

3. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R, CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022" *MMWR Morb Mortal Wkly Rep*. 2022;71(3):1-95. Doi:10.15585/mmwr.rr7103a1

4. Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. *BMJ*. 2017;356:J760. Doi:10.1136/bmj.j760

5. Peppin JF. The marginalization of patients on chronic opioid therapy. *Pain Physician*. 2009;12:493–8. Doi:10.36076/ppj.2009/12/493

6. Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert ASB. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. *BMJ*. 2015;350:h2698. Doi: 10.1136/bmj.h2698

7. Xu KY, Hartz SM, Borodovsky JT, Bierut LJ, Grucza RA. Association between benzodiazepine use with or without opioid use and all-cause mortality in the United States, 1999-2015. *JAMA Netw Open*. 2020;3:e2028577. Doi: 10.1001/jamanetworkopen.2020.28557

8. Dasgupta N, Funk MJ, Proescholdbell S, Hirsch A, Ribisi KM, Marshall S. Cohort study of the impact of high-dose opioid analgesics on overdose mortality. *Pain Med*. 2016;17:85–98. Doi: 10.1111/pme.12907

9. Zedler B, Xie L, Wang L, Joyce A, Vick C, Brigham J, et al. Development of a risk index of serious prescription opioid-induced respiratory depression or overdose in Veterans' Health administration patients. *Pain Med*. 2015;16:1566–79. Doi: 10.1111/pme.12777

10. Banks S, Kerns R. Explaining high rates of depression in chronic pain: a diathesis-stress framework. *Psychol Bul*. 1996;119:95–110. Doi:10.1037/0033-2909.119.1.95

11. Mitchell AJ, Vaze A, Rao S. Clinical diagnosis of depression in primary care: a meta-analysis. *Lancet*. 2009;374:609–19. Doi:10.1016/S0140-6736(09)60879-5

12. Braden JB, Russo J, Fan MY, Edlund MJ, Martin BC, DeVries A, et al. Emergency department visits among recipients of chronic opioid therapy. *Arch Intern Med*. 2010;170:1425–32. Doi:10.1001/archinternmed.2010.273

13. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, et al. Opioid prescriptions for chronic pain and overdose. *Ann Intern Med*. 2010;152:85–92. Doi:10.7326/0003-4819-152-2-201001190-00006

14. Craven MA, Bland R. Depression in primary care: current and future challenges. *Can J Psychiatry*. 2013;58:442–8. Doi:10.1177/070674371305800802

15. Braden JB, Sullivan MD, Ray GT, Saunders K, Merrill J, Silverberg MJ, et al. Trends in long-term opioid therapy for noncancer pain among people with a history of depression. *Gen Hosp Psychiatry*. 2009;31:564–70. Doi:10.1016/j.genhosppsych.2009.07.003

16. Quinn PD, Hur K, Chang Z, Krebs EE, Bair MJ, Scott EL, et al. Incident and long-term opioid therapy among patients with psychiatric conditions and medications: a national study of commercial health care claims. *Pain*. 2017;158:140–8. Doi:10.1097/j.pain.0000000000000730

17. Elrashidi MY, Philpot LM, Ramar P, Leasure WB, Ebbert JO. Depression and anxiety among patients on chronic opioid therapy. *Health Serv Res Manag Epidemiol*. 2018;5:1–7. Doi:10.1177/2333392818771243

18. Grant BF, Stinson FS, Dawson DA, Chou P, Dufour MC, Compton W, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders. *Arch Gen Psychiatry*. 2004;61:8070816. Doi:10.1001/archpsyc.61.8.807

19. Han B, Compton WM, Bianco C, Crane E, Lee JD, Jones CM. Prescription opioid use, misuse, and use disorders in U.S. adults: 2015 national survey on drug use and health. *Ann Intern Med.* 2017;167:293–301. Doi:10.7326/M17-0865

20. Grattan A, Sullivan MD, Saunders KW, Campbell CJ, Von Korff MR. Depression and prescription opioid misuse among chronic opioid therapy recipients with no history of substance abuse. *Ann Fam Med.* 2012;10:304–11. Doi:10.1370/afm.1371

21. Bohnert ASB, Logan JE, Ganoczy D, Dowell D. A detailed exploration into the association of prescribed opioid dosage and overdose deathes among patients with chronic pain. *Med Care.* 2016;54:435-41. Doi:10.1097/MLR.0000000000000505

22. Nadeau SE, Lawhern RA. The two opioid crises – problems, causes, and potential solutions: an analytic review", *Med Res Arch,* 2023;11(12). Doi:10.18103/mra.v 11i12.4846

23. Lötsch J, Skarke, C, Liefhold J, Geisslinger G. Genetic Predictors of the Clinical Response to Opioid Analgesics. Clinical utility and future perspectives. *Clin Pharmacokinet.* 2004;43(4):983-1013. Doi: 10.2165/00003088-200443140-00003

24. Agrawal D, Udoji MA, and Trescot A. Genetic Testing for Opioid Pain Management: A Primer. *Pain Ther. 2017;6:93-105.* Doi:10.1007/s40122-017-0069-2.

25. Nadeau, SE, Del Rocco N, and Wu S, "Opioid trials: time for a new approach? Enriched enrollment, randomized gradual withdrawal designs." *Pain Manag.* 2022;12(3):243-247. Doi:10.2217/pmt-2021-0112

26. Nadeau SE, Lawhern RA. Management of chronic non-cancer pain: a framework. *Pain Manag.* 2022;12(6):751-777. Doi:10.2217/pmt-2022-0017

27. Lawhern, RA Doctors diagnosing addiction – are the blind leading the blind? *Med Res Arch.* 2023,11(11):4726. Doi:10.18103/mra-v11i11.4726

28. Nadeau SE, Lawhern RA. The two opioid crises. Problems, causes, and potential solutions: an analytic review. *Med Res Arch.* 2023;11(12). Doi:10.18103/mra.v 11i12.4846

29. Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomof RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review." *Pain Med.* 2008;9:445-59. Doi: 10.1111/j.1526-4637.2007.00370.

30. Weissman DE, Haddox JD. Opioid pseudoaddiction—an iatrogenic syndrome. *Pain.* 1989;36:363-6.

31. Bohnert ASB, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA.* 2011;305:1315-21. Doi:10.1001/jama.2011.370

32. Maust DT, Petzold K, Strominger J, Kim M, Bohnert ASB. Benzodiazepine discontinuation and mortality among patients receiving long-term benzodiazepine therapy. *JAMA Netw Open.* 2023;6(12):e2348557. Doi: jamanetworkopen.2023.48557