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Opioid use disorder deaths and the effects of medication therapy

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In the midst of an opioid epidemic with a steep increase in overdose deaths (1), the term “Medication-Based Treatment” more than “Medication-Assisted Treatment” is apt to describe the central role of pharmacotherapies for opioid use disorder (OUD). The clarification is not formal as it can contribute to shape public health policies and the response to requests of treatment (2). In clinical practice, patients and health care professionals may experience the complementary and enhancing role of psychosocial and behavioral interventions, and the substantial difference made by medications when they are available (3). Thus, delivering safer and more effective medical therapy for OUD is a continuous strive. In the past, oral naltrexone has shown modest results, including a more elevated death risk compared with buprenorphine and methadone (4,5). The introduction of long acting formulations has contributed to improve naltrexone compliance and outcomes (6), but concerns of excessive death risks linked to the antagonist treatment of OUD have lingered among treating professionals and patients. Clinical trials have offered reassuring results but often do not include a direct comparison of naltrexone with opioid substitution therapies (7).

The paper by Kelty, Joyce, and Hulse (2018) in this issue of *The American Journal of Drug and Alcohol Abuse* (8) is a ‘real world’ evaluation of mortality in patients treated with naltrexone implants, buprenorphine, or methadone. In this retrospective, naturalistic study spanning 9 years and surveying more than 8,000 individuals, similar crude mortality rates were recorded across medications, with the exception of the initial month of treatment when

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patients showed a higher risk of death if they were receiving the opioid agonist methadone compared with naltrexone. These results are consistent with a lower craving and opioid use observed during the first month of long-acting naltrexone treatment compared with buprenorphine (9,10), but do not take into account the potentially difficult phase of naltrexone induction (11). As expected when opioid use rises, the number of deaths was increased following OUD treatment discontinuation, though it did in a comparable fashion across treatment groups. Equally comparable was the increased presence of non-opioid drugs and, in particular, benzodiazepine in post-mortem samples, while alcohol was more frequently found in post-treatment deaths of patients in the methadone group than in the naltrexone group. Although naltrexone is effective in curbing alcohol craving and consumption and a post-naltrexone behavioral effect cannot be ruled out, the result may simply depend on selection bias.

There is a quantity of information equally useful for researchers and treating professionals in the Kelty et al. paper (8). One interesting finding is that death from suicide was the second most common diagnosis after drugs and alcohol in the sample. Suicide is a public health priority and opioid involvement with suicide has more than doubled in 15 years (12), while increased access to opioid prescriptions among chronic pain patients has been linked to increased risk of suicide (13). Further studies should elucidate the complex relationship between opioid overdose and suicide (14). Kelty et al. (8) found that women had a proportionally smaller mortality risk following naltrexone implant than receiving methadone. Women made up about one third of the sample and were comparably distributed across treatment groups, but no inference on the random distribution of vulnerable women can be drawn. This point deserve further evaluation; OUD treatment has been often overlooked in a demographic group that counts the highest increase of opioid overdose deaths in the last 20 years (15).

Multiple factors influence and shape the death risk in OUD, and no experimental design can exert a full control. This study offers a retrospective direct comparison of treatments within the same population, a valid alternative to meta-analytic evaluations of heterogeneous clinical trials. Moreover, the subdivision in treatment phases, though sometimes difficult to define, has permitted a more accurate longitudinal examination of the effects of each intervention. However, the investigation consists of a naturalistic observation of a single Australian state’s health mortality data set using a formulation of naltrexone that provides therapeutic levels of medication for about 6 months. Even though Australia, North America, and Western Europe have shared a similar pattern of opioid users’ mortality risk (16), the recent changes in severity of the US epidemic are a warning that there may be a question of generalizability to other populations. In addition, data should be replicated using other long acting formulations of naltrexone with different duration of effects. There is always the possibility of multiple confounding and selection bias. The analysis controlled for age, gender, and time of first treatment, but did not include important co-factors such as psychiatric diagnoses or a complete range of medical comorbidities. Of course, unaccounted changes in drug availability and local policies during the multi-year observation may also have played a role.

A significant proportion of the study sample (about one third) received two treatments and almost one tenth received all three treatments. In the natural history of substance use disorders, the progress of many patients is characterized by cycles of recovery that are marked by repeated treatment episodes and transitions between treatments before a stable recovery occurs (17). Future analyses of treatment pathways using public health and commercial insurance data sets, and the ecological observation of cohorts of patients may offer useful information and assist in the difficult tasks of matching patients with treatment, identify obstacles and predict outcomes.

Despite the limitations, this study is in line with other investigations demonstrating that during OUD treatment mortality rates are at least halved compare with the out-of-treatment conditions (18). The original finding is that long acting naltrexone treatment offers comparable results to buprenorphine and methadone, different of what previously observed using oral naltrexone treatment. Further progress can be envisioned with the improvement of the induction phase of methadone and naltrexone treatments. Future studies will also evaluate whether long acting formulations of opioid agonist and antagonist medications can provide better compliance and a positive shift in the safe and effective management of OUD.

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References

1. Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G. Drug and opioid-involved overdose deaths — United States, 2013–2017. MMWR Morb Mortal Wkly Rep 2019;67:1419–27. doi:10.15585/mmwr.mm675152e1.
2. Robinson SM, Adinoff B. The mixed message behind “Medication-Assisted Treatment” for substance use disorder. Am J Drug Alcohol Abuse 2018;44 (2):147–50. doi: 10.1080/00952990.2017.1362419. [PubMed: 28920715]
3. Sofuoglu M, DeVito EE, Carroll KM. Pharmacological and behavioral treatment of opioid use disorder. Psyc Res Clin Pract 2018 12 5 10.1176/appi.prcp.20180006
4. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database Syst Rev 2011;4:CD001333.
5. Degenhardt L, Larney S, Kimber J, Farrell M, Hall W. Excess mortality among opioid-using patients treated with oral naltrexone in Australia. Drug Alcohol Rev 2015 1; 34(1): 90–96. doi:10.1111/dar.12205. [PubMed: 25302627]
6. Krupitsky E, Zvartau E, Blokhina E, Verbitskaya E, Wahlgren V, Tsoy-Podosenin M, Bushara N, Burakov A, Masalov D, Romanova T, et al. Randomized trial of long-acting sustained-release naltrexone implant vs. oral naltrexone or placebo for preventing relapse to opioid dependence. Arch Gen Psychiatry 2012 9; 69(9): 973–81. doi:10.1001/archgenpsychiatry.2012.1a. [PubMed: 22945623]

7. Jarvis BP, Holtyn AF, Subramaniam S, Tompkins DA, Oga EA, Bigelow GE, Silverman K. Extended-release injectable naltrexone for opioid use disorder: a systematic review. Addiction 2018 7; 113(7): 1188–209. doi:10.1111/add.14180. [PubMed: 29396985]
8. Kelty E, Joyce D, Hulse G. A retrospective cohort study of mortality rates in patients with an opioid use disorder treated with implant naltrexone, oral methadone or sublingual buprenorphine. Am J Drug Alcohol Abuse 2019.
9. Lee JD, Nunes EV Jr, Novo P, Bachrach K, Bailey GL, Bhatt S, Farkas S, Fishman M, Gauthier P, Hodgkins CC, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. Lancet 2018 1 27;391 (10118):309–18. doi:10.1016/S0140-6736(17)32812-X. [PubMed: 29150198]
10. Tanum L, Solli KK, Latif ZE, Benth JŠ, Opheim A, Sharma-Haase K, Krajci P, Kunøe N. Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: a randomized clinical noninferiority trial. JAMA Psychiatry 2017 12 1;74(12):1197–205. doi:10.1001/jamapsychiatry.2017.3206. [PubMed: 29049469]
11. Bisaga A, Mannelli P, Sullivan MA, Vosburg SK, Compton P, Woody GE, Kosten TR. Antagonists in the medical management of opioid use disorders: historical and existing treatment strategies. Am J Addict 2018 4; 27(3): 177–87. doi:10.1111/ajad.12711. [PubMed: 29596725]
12. Braden JB, Edlund MJ, Sullivan MD. Suicide deaths with opioid poisoning in the United States: 1999–2014. Am J Public Health 2017 3; 107(3): 421–26. doi:10.2105/AJPH.2016.303591. [PubMed: 28103068]
13. Ilgen MA, Bohnert AS, Ganoczy D, Bair MJ, McCarthy JF, Blow FC. Opioid dose and risk of suicide. Pain 2016 5; 157(5): 1079–84. doi:10.1097/j.pain.0000000000000484. [PubMed: 26761386]
14. Bohnert ASB, Ilgen MA. Understanding links among opioid use, overdose, and suicide. N Engl J Med 2019 1 3;380(1):71–79. doi:10.1056/NEJMra1802148. [PubMed: 30601750]
15. VanHouten JP, Rudd RA, Ballesteros MF, Mack KA. Drug overdose deaths among women aged 30–64 years — united States, 1999–2017. MMWR Morb Mortal Wkly Rep 2019;68:1–5. doi: 10.15585/mmwr.mm6801a1. [PubMed: 30629574]
16. Degenhardt L, Bucello C, Mathers B, Briegleb C, Ali H, Hickman M Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. Addiction 2010;106:32–51. [PubMed: 21054613]
17. Wu LT, Woody GE, Yang C, Mannelli P, Blazer DG. Differences in onset and abuse/dependence episodes between prescription opioids and heroin: results from the national epidemiologic survey on alcohol and related conditions. Subst Abuse Rehabil 2011;2011 (2):77–88. doi:10.2147/SAR.S18969. [PubMed: 21686045]
18. Sordo L, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, Ferri M, Pastor-Barriuso R. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. bmj 2017 4 26;357:j1550. doi:10.1136/bmj.j2024. [PubMed: 28446428]