When Two Drugs Are not Better than One: Treating Mood Symptoms in Patients with Chronic Opioid Use

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To the Editors:

Drug overdose fatalities in the United States have reached an all-time high. Deplorably, many other countries are following suit. The Centers for Disease Control and Prevention reports that, in 2017, opioids were involved in 47,600 overdose deaths (CDC, 2018), a number which dwarfs the number of car crash fatalities in the same year. Regrettably, the 'Inexorable March to Death and Addiction' (Theisen & Davies, 2019) is fueled, to a large part, by an invidious trend of medical overprescribing and misprescribing, which disproportionately affects patients with mental health disorders (Seal et al., 2012). Moreover, accruing evidence suggests that opioid use may directly precipitate depressive symptoms. For example, a large retrospective cohort study collating data from three independent healthcare systems including the Veterans Health Administration demonstrated that duration of opioid use is associated with the new onset of depression (Scherrer et al., 2016a). The risk of developing treatment-resistant depression was also found to grow with duration of opioid exposure (Scherrer et al., 2016b).

With increasing frequency, psychiatrists are confronted with patients complaining of mood symptoms in the context of chronic opioid use. Oftentimes, these patients will be referred from primary care with the implicit expectation that antidepressant medication will be prescribed. What is the best course of action in this situation? Judging from a recent article on off-label ketamine infusions in patients with treatment-resistant depression and concurrent chronic opioid use, highly aggressive psychopharmacotherapy (e.g., on average, more than eight failed antidepressant trials; one 24 year-old patient with an incredible 18 failed antidepressant trials)

together with continuation of opioid prescriptions seems, at this time, to be the general rule rather than the rare exception in many places (Marton et al., 2019).

We fully acknowledge that there is no ‘fit-all’ solution to this complex clinical problem. At the same time, we strongly argue that, first, clarity on the reasons for chronic opioid prescriptions should be sought. In the non-cancer, non-palliative setting, a determination has to be made whether opioids are still being prescribed for pain. If possible, ambiguity as regards the indication for opioid prescriptions should be avoided (e.g., dual indication treatment for pain and opioid use disorder). If it is established that opioids are explicitly being prescribed as opioid substitution therapy, the approach to treating mood symptoms should critically be shaped by the fact that the patient suffers from opioid dependence. In this case, social and psychological interventions may prove to be more effective strategies for alleviating stress-related mood symptoms than the co-prescription of an antidepressant. Drug use, including illicit drug use along with the use of benzodiazepines and alcohol, should be queried. Furthermore, an adjustment in opioid dosage or switching to a different opioid should be considered carefully before adjunctive antidepressant treatment is begun. Finally, each individual decision to prescribe an antidepressant to a patient on opioid maintenance therapy should be weighed in light of the fact that, at present, the available literature does not provide a sufficient evidence base to support this practice (Pani et al., 2010).

Mounting evidence also indicates that, in the case of chronic non-malignant, non-HIV pain, opioid treatment contributes little to remedy the problem and, in fact, frequently

exacerbates it (Belkin et al., 2017). Conversely, opioid-induced hyperalgesia may dramatically be improved by detoxification, counseling, and medical management (Belkin et al., 2017). An exciting new study also provides preliminary support regarding the efficacy of cessation of chronic opioid use for improving depression symptoms (Scherrer et al., 2018). Lastly, another important consideration that, in our opinion, deserves more attention relates to potentially perilous drug-drug interactions such as the emergence of serotonin syndrome with the concomitant use of serotonergic antidepressants and opioids, in particular the phenylpiperidine series opioids fentanyl, meperidine, methadone, and tramadol (Gilman, 2005).

In sum, there are many reasons militating against the co-prescription of opioids and antidepressants. Where a clinician wishes to depart from this default position, the decision to do so should be subject to careful deliberation. In general, if a patient presents with significant mood symptoms in the context of chronic opioid use for non-malignant pain, an opiod taper together with non-opioid pain management should be attempted to alleviate affective symptoms.

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Conflict of Interest

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