Received: 16 August 2021 | Accepted: 20 September 2021

DOI: 10.1111/add.15706

LETTER TO THE EDITOR

ADDICTION SSA

Increasing opium use in Iran in response to unsubstantiated rumors that it protects against COVID-19

We write to address misconceptions identified by some commentators on the alleged protective effects of opium consumption and the SARS-CoV-2 virus [1]. This mistaken news caused a flood of opium use in the Iranian society, as field reports from the main squares for the sale of opium, including Shush Square in Tehran, indicated a five to six times increase in the number of customers [2]. Also, some preliminary scientific findings on the protective effects of opium use against SARS-CoV-2 infection led to pseudoscientific speculations on the veracity of this popular belief [3]. For instance, it has been proposed that short-term opium use competes with binding of SARS-CoV-2 to the angiotensin converting enzyme 2 (ACE-2) receptors and suppresses serum levels of interleukins involved in COVID-19-associated hyperinflammatory syndrome [4], but most evidence did not support the claims that opium consumption reduced the risk of contracting COVID-19 or of the severity of infection acquired. Indeed, most studies have reported opium use as a triggering or aggravating factor of COVID-19 [5,6]. So, what is the reason for an increased mortality rate from COVID-19 among individuals who use opium? According to a critical review of recent literature on short-term effects of opium consumption, there are five main relevant reasons: (i) down-regulation of anti-viral cytokine expression such as interferon (IFN)-α and IFN-γ; (ii) development of pulmonary edema following endothelial dysfunction; (iii) increase thrombotic factors such as plasma fibrinogen and plasminogen activator inhibitor 1; (iv) increase ACE-2 via stimulating silent information regulator 1 expression; (v) increased risk of pneumonia due to their effect on the medullary respiratory centers and decreased ventilation; and (vi) QT interval prolongation [7–9].

The morphine-induced immune modulation can also be affected by the chronicity of using this class of agents. In this regard, a systematic review of *in-vitro* studies has revealed that morphine at high doses and over several months could increase the risk of bacterial infections by inhibiting the cellular immune system [10]. Another related study suggested that long-term opium use may be associated with suppression of B and T lymphocyte proliferation, induction of necrosis and apoptosis in immune cells and thymic and splenic atrophy [11]. Recent evidence has also shown that opium, as an immunosuppressive agent, can reduce leukocyte activity by inhibiting the migration of bone marrow-derived cells in the long term [12]. Regardless of the action mechanism of morphine, the scientific consensus has been on its detrimental effects on the immune system and the reasons for the increased risk of mortality among opium-addicted patients with COVID-19 [7]. Because individuals may be rapidly affected by each other's emotional reactions, policymakers and professionals in Iran and world-wide should be aware of the rumors and the potential risk of 'emotional contagion' among the general population. Indeed, raising public awareness about the adverse effects of opium on the clinical course of COVID-19 can be effective in reducing its mortality rate.

DECLARATION OF INTERESTS

None.

ACKNOWLEDGEMENTS

The author received no specific funding for this work.

KEYWORDS

COVID-19, cytokine, leukocyte activity, opium, rumors, SARS-CoV-2

Mohsen Khosravi

Department of Psychiatry and Clinical Psychology, Zahedan University of Medical Sciences, Zahedan, Iran

Email: dr_khosravi2016@yahoo.com

ORCID

Mohsen Khosravi https://orcid.org/0000-0003-2970-6309

REFERENCES

1. Saeedi M, Omrani-Nava V, Maleki I, Hedayatizadeh-Omran A, Ahmadi A, Moosazadeh M, et al. Opium addiction and COVID-19: Truth or false beliefs. Iran J Psychiatry Behav Sci. 2020;14:e103509.
2. Pirnia B, Dezhakam H, Pirnia K, Malekanmehr P, Soleimani AA, Zahiroddin A, et al. COVID-19 pandemic and addiction: Current problems in Iran. Asian J Psychiatr. 2020;54:102313.
3. Hudzik B, Nowak J, Zubelewicz-Szkodzinska B. Consideration of immunomodulatory actions of morphine in COVID-19-short report. Eur Rev Med Pharmacol Sci. 2020;24:13062–4.
4. Roshanravan N, Ghaffari S, Hedayati M. Angiotensin converting enzyme-2 as therapeutic target in COVID-19. Diabetes Metab Syndr. 2020;14:637–9.
5. Wang QQ, Kaelber DC, Xu R, Volkow ND. COVID-19 risk and outcomes in patients with substance use disorders: Analyses from electronic health records in the United States. Mol Psychiatry. 2021;26:30–9.
6. Riahi T, Sadeghzadeh-Bazargan A, Shokri S, Ahmadvand D, Hassanlouei B, Baghestani A, et al. The effect of opium on severity

of COVID-19 infection: An original study from Iran. Med J Islam Repub Iran. 2021;35:870–4.
7. Dolati-Somarin A, Bahareh AN. The reasons for higher mortality rate in opium addicted patients with COVID-19: a narrative review. Iran J Public Health. 2021;50:470–9.
8. Javadi HR, Mirakbari SM, Allami A, Yazdi Z, Katebi K. Opium-associated QT interval prolongation: a cross-sectional comparative study. Indian J Crit Care Med. 2021;25:43–7.
9. Ataei M, Shirazi FM, Lamarine RJ, Nakhaee S, Mehrpour O. A double-edged sword of using opioids and COVID-19: a toxicological view. Subst Abuse Treat Prev Policy. 2020;15:91.
10. Steffens C, Sung M, Bastian LA, Edelman EJ, Brackett A, Gunderson CG. The association between prescribed opioid receipt and community-acquired pneumonia in adults: a systematic review and meta-analysis. J Gen Intern Med. 2020;35:3315–22.
11. Nabati S, Asadikaram G, Arababadi MK, Shahabinejad G, Rezaeian M, Mahmoodi M, et al. The plasma levels of the cytokines in opium-addicts and the effects of opium on the cytokines secretion by their lymphocytes. Immunol Lett. 2013;152:42–6.
12. Mirzaeipour F, Azdaki N, Mohammadi GA, Addasi E. The effects of opium addiction through different administration routes on inflammatory and coagulation factors. J Kerman Univ Med Sci. 2013;20:292–300.

Received: 3 October 2021 | Accepted: 8 October 2021
DOI: 10.1111/add.15719

There is no causality in the 'gateway hypothesis': another test gone amiss

This letter responds to the article by Reed *et al*. [1]. As indicated in its title, the study used 'Mendelian randomization to explore the gateway hypothesis.' There are reasons, however, why it failed to, and could not, reach its stated goal.

First, like in a recent similar paper [2], the 'gateway hypothesis' (GH), as presented in the article in its 'simplest form,' is misstated [3]. In the small print of the *Notes* to the original article introducing the GH [4], there is a caveat, still valid, that the 'stages' pertain only to substance use initiation rather than progression of involvement and severity. The GH is merely an observation of a temporal order that is frequently found in the United States population (but not, for instance, in Japan [5]). Although the *post hoc ergo propter hoc* causality conjecture was implicit virtually from the GH introduction, the GH supporters for a long time avoided direct causal statements ('causal claims in the Gateway Hypothesis…are still beyond reach' [6] (p. 371). Notably, the attempt to support causality experimentally, showing sensitization to cocaine-induced locomotion in mice by pre-treatment with nicotine and lack of sensitization when the experiment was reversed [7], was faulty [8], because nicotine, in contrast to cocaine, has no locomotion effect to start with. Moreover, a murine locomotion response has little to do with a human behavioural pattern that reflects drug availability and the personal cost of use. In turn, that pattern has been shown to have no relation to the use outcome [9]). The 'gateway drug' itself remains as conceptually undefined by Reed *et al*. as it was by the GH author herself who called the notion 'vague' [10] (p. 7).

Second, using genetic polymorphisms as instrumental variables to test the causal interpretation of the GH is faulty, because the main assumption of the analysis, that an instrument is related to the outcome only via influence on the independent variable, does not hold. There is no compelling reason to assume that the SNPs influencing variation in the initiation of nicotine/alcohol use are not pleiotropically related to the initiation of use of other psychoactive substances. Indeed, most drug-related findings are with the loci that are not specific—not only to any particular substance, but to the drugs in general [11–15].

Third, the latter fact is consistent with the alternative to the GH that has been considered its 'fundamental theoretical antithesis' by the GH originators [16], but ignored by Reed *et al*. Namely, as extensively reviewed previously [8,17,18], the various patterns of initiation, polydrug use, as well as the development of addiction, are readily accounted for by the parsimonious construct of common liability to drug use/addiction (CLA). This position is grounded in the long-standing human genetics concept [19] and the abundant data on common mechanisms of drug response and behaviour regulation. From the CLA standpoint, the order of substance use initiation is opportunistic. Its unjustified interpretation in causal terms has led to misdirection of prevention, intervention, and policy efforts.

DECLARATION OF INTERESTS

None.

ACKNOWLEDGMENT

The author is thankful to the editor, Dr. Keith Humphreys, for valuable comments.

AUTHOR CONTRIBUTION

The author, Michael Vanyukov, is the only contributor to this publication.

KEYWORDS

Common liability, drug policy, gateway drug, gateway theory, instrumental variable, stepping-stone