Commented Summary

"Commentary on Opium Use and Mortality in Golestan Cohort Study"

Summary: To investigate the association between opium use and subsequent risk of death. Design Prospective cohort study. The Golestan Cohort Study in north-eastern Iran collected detailed validated data on opium use and other exposures at baseline. Participants were enrolled between January 2004 and June 2008 and were followed to May 2011, with a follow-up success rate of over 99%.

50045 participants aged 40 – 75 at baseline. Main outcomes Mortality, all cause and major subcategories. 17% (n = 8487) of the participants reported opium use, with a mean duration of 12.7 years. During the follow-up period 2145 deaths were reported. The adjusted hazard ratio for all cause mortality associated with ever use of opium was 1.86 (95% confidence interval 1.68 to 2.06). Opium consumption was significantly associated with increased risks of deaths from several causes including circulatory diseases (hazard ratio 1.81) and cancer (1.61). The strongest associations were seen with deaths from asthma, tuberculosis, and chronic obstructive pulmonary disease (11.0, 6.22, and 5.44, respectively). After exclusion of people who self- prescribed opium after the onset of major chronic illnesses, the associations remained strong with a dose-response relation. Opium users have an increased risk of death from multiple causes compared with non-users. Increased risks were also seen in people who used low amounts of opium for a long period and those who had no major illness before use.

Source: Khademi H, Malekzadeh R, Pourshams A, Jafari E, Salahi R, Semnani S, Abaie B, Islami F, Nasseri-Moghaddam S, Etemadi A, Byrnes G, Abnet CC, Dawsey SM, Day NE, Pharoah PD, Boffetta P, Brennan P, Kamangar F. Opium use and mortality in Golestan Cohort Study: prospective cohort study of 50,000 adults in Iran. *BMJ*. 2012; **344:** e2502.

Comments: At a time when there are an estimated 20 million opiate addicts globally and drug abuse is widely recognized as an increasing worldwide problem, it is a truism that the literature relating to the pathophysiological and toxic effects of long term opiate addiction is fragmented and largely hypothesis-driven with the result that many works show only a part of the problem, many papers are short term, and many papers have suboptimal designs and often poor follow-up which introduce uncertainty into their interpretation and the conclusions which flow from them. Into this situation the authoritative, methodologically rigorous, large (50,045 participants and 234,928 participant-years), prospective, five year observational study with 99% follow-up and 17% population prevalence of opium addiction from Golestan province in north-eastern Iran recently published in the BMJ by Khademi and colleagues from Iran, France, the UK and the US with the support of the Cancer Research UK and the National Cancer Institute from NIH shines like a bright beacon.[1] As opium use in Golestan is not accompanied by social stigmatization it cannot be said that the findings are related to the legal or social status of opiate drugs. Elevated adjusted hazard ratios (A.H.R.) of death from cardiovascular causes (1.81), cancer (lung and oesophagus; 1.61 for all cancer), digestive (3.12) and respiratory disease (3.78) were found in virtually all subgroups, and were most pronounced amongst women (2.43, 95%C.I. 2.05 – 2.88 compared to men 1.86, 1.44 – 1.84), urban dwellers, the obese and non-smokers. Indeed the effect of opium (1.86) was a more powerful predictor of death than tobacco use (1.53). Opium use remained a powerful predictor of death after multivariate adjustment for many dietary, wealth, health and biophysical parameters. When healthy patients were compared with opium users the adjusted hazard ratio for all cause mortality was 1.90 (1.55 – 2.33). A dose response relationship was proven in many analyses which is powerful evidence for the causality of the observed relationship. Reverse causality was excluded by omitting patients with a major diagnosis during the first few years of the study. Moreover the risk of death decreased after about 14 years of cessation of use. The findings were not related to the route of administration be it inhaled (1.68) or oral (2.08) or both (2.34). Only four participants injected heroin of whom three died (25.4). 15% of all the observed deaths in the study were attributed to opium use. As noted in the accompanying editorial the clinical observation was made as long ago as 1899 that opium addicted patients look "old".[2] Another important reason why this paper dominates the published landscape in the field is the detailed consideration given to the known underlying cellular and molecular mechanisms to explain these robust and very concerning findings. This is in stark contrast to the frequently benign view which is often propounded for the pathophysiological activities of opiates.[3]

This landmark study needs to be seen in its context within the literature. The closest study to this is that of a Sydney group who reviewed a 21 year history with a state wide methadone treated cohort, and in the process amassed some 42,676 patients with some 425,998 person-years of follow-up.[4] Interestingly the age- and sex- standardized mortality rate (SMR) was also higher in that series amongst females being 8.7 (8.1 – 9.2) than males 5.9 (5.7 – 6.1) throughout the time series observed (1983 – 2006). As often happens when series of drug dependent patients were reviewed in western nations, the drug overdose and accidental SMR's were elevated 30 – 65 times (Appendix 6). What is fascinating is that the SMR's of death from cardiovascular disease, cancer, digestive disorders and chronic respiratory disease, suicide and alcohol related disease were significantly elevated 2.2 (1.9 – 2.5), 1.6 (1.4 – 1.9), 7.7, 3.9, 6.0 and 5.4 respectively. These rates are very similar indeed to the above noted A.H.R.'s in the present Iranian study. It is important to consider that suicide may be seen as a fatal clinical end point of depression. Depression and many psychiatric illnesses have been linked with hypothalamic and hippocampal inflammatory processes. A 33 year follow-up of Californian opiate dependent patients found a highly significant ($P < 0.005$) overwhelming excess of deaths from cardiovascular (coronary and cerebrovascular) disease, cancer, trauma, suicide, liver disease and injury amongst 581 patients, which was little disturbed by sub-analysis by racial stratification.[5] On the basis of poorer physical (hypertension, arthritis and diabetes) and mental (depression and anxiety) health and multi-system disease in methadone patients over the age of 50 years, workers in Pittsburgh called for methadone patients over the age of 50 years to have geriatricians appointed to their care beyond the age of 50 years.[6] This is all reminiscent of the clinical observation that such patients appear unduly "old" alluded to in the BMJ editorial, and ascribed to physicians working in China in 1899.[2] An Australian analysis of 1,193 coronial cases comparing methadone to heroin patients found that methadone exposure

was more deleterious than heroin exposure for any heart disease (adjusted O.R. (A.O.R) = 3.13, 2.00 – 4.90 adjusted for age, sex, BMI and treatment status), severe coronary artery disease (A.O.R. = 1.11, 0.69 – 2.17), lung disease (A.O.R. = 2.03. 1.36-3.03), kidney disease (A.O.R. = 2.76, 1.58 – 4.81) and multisystem disease (A.O.R. = 3.29, 2.11 – 5.11).[3] Previous studies from Iran report elevated rates of oesophageal, laryngeal, and bladder cancer and particularly cardiovascular disease. Virtually all studies of intravenous opiate use document greatly elevated mortality, usually 10 – 20 times that of matched control populations. Similar observations have been made in recent well known studies for chronic pain patients with non-malignant conditions, giving rise to great public health concerns. Hence there are several studies which support the message of the present study that opiate use per se is inimical to sustained good health irrespective of the route. The accompanying editorial by Dhalla is quite correct to note that overdose is NOT the main driver of this elevated mortality amongst non-parenteral drug using populations, notwithstanding the popular professional perception to the contrary.[2]

It is therefore an increasingly important public health question to understand why this might be. One important clue would appear to be in the plethora of organ system dysfunction which is reported by this literature. In addition to those noted above might be added hair greying, advanced dental disease psychiatric disorders and a relative reduction in circulating stem cell numbers.[7,8] This suggests that some general cellular mechanisms may be operating throughout the body. A negative effect on the cell cycle has long been documented by the Pittsburgh group acting via P16 at the G1/S transition, which can be expected to have a generalized effect on cell and tissue regeneration organism-wide.[9] The morphinan nucleus of the opiates has now been shown to bind to the endotoxin groove of myeloid differentiation factor 2 (MD2) which is the binding partner of TLR4, the endotoxin receptor, which is found widely distributed on most body cells.[10] Signalling through MD2/TLR4/My88/TRIF/TRAM (toll/interleukin-1 receptor (TIR) domain adaptor inducing interferon-β (TRIF) related adaptor molecule (TRAM)) receptor precipitates numerous and profoundly powerful immunological cascades including interleukin (IL-) -1 and -18 biosynthesis and later processing, cytokine production particularly TNFα (tumour necrosis factor-α) and IL-6, MCP-1/CCL2 (macrophage chemotactic factor-1/ cytokine / chemokine ligand-2) , interferon production, mitogen activated kinase (MAPK), phosphoinositol-3 kinase (PI3K) and transforming growth factor-β (TGFβ), Jun and Fos in the Activating protein-1 (AP-1) pathway, acute phase responses in liver, and adaptive immune processes. Innate immune signalling is also associated with endothelial activation and induction of the hypoxia inducing factor-α (HIFα) response. Many of these pathways long been known to be strongly implicated as major players in atherogenesis and carcinogenesis. Opiate dependence has also been shown to be accompanied by a lymphocytosis and a monocytosis and a polyclonal gammopathy.[11] Particularly interesting is the signalling from TLR4 both directly and indirectly to the sphingosine-1-phosphate receptors-5 which appear to control endothelial cell-cell interactions and thus the integrity of the endothelial barrier, and the blood brain barrier in the brain in particular.[12] This interaction appears to act as a gateway for cerebral inflammation in many disorders, and has been particularly implicated as a key player and major therapeutic target in multiple sclerosis.

Cross-interference between toll-like receptor signalling and retinoic acid inducible protein-1 (RIG) –like receptors (RLR)'s and various other mechanisms account for the immunosuppressive effects seen in the context of immune stimulation.[13] This is a situation not unlike the stigmata of immunosuppression seen in endogenous autoimmune and autoinflammatory disorders such as rheumatoid arthritis and systemic lupus ethythematosus. Moreover stem cells are particularly sensitive to immune stimulation and carry powerful down-regulatory cytokine receptors on their surface, and have intact JAK-STAT (Janus activated kinase – signal transducer and activator of transcription) signalling cascades in the cytoplasm. Hence much of the previously described actions of opiates may actually be mediated by the endotoxin signalling system. Indeed not only will stem and other cells be subject to a direct impact on their cycling by P16, but they will also be subject to the interactive effects of immune attack. Moreover the implication of increased atherosclerosis in opiate dependence, in the context of increased monocytes, lymphocytes, cytokine, MCP-1, IL-1β, IL-6, CCL2-CCR2, endothelial activation, diffuse polyclonal gammopathy and greatly elevated C-reactive protein ((10)) is of particular relevance. Atherosclerosis is now seen as a chronic inflammatory disorder of the vascular wall. In that most deaths in aged patients are related to cardiovascular causes, aging has been thought to be in large part a vascular phenomenon. Hence the demonstration of increased cardiovascular disease in these patients is consistent with an acceleration of the ageing process in these patients. Similarly cancer is also a disease of aging. The present study shows an elevation in oesophageal and lung cancer in opiate dependence and upper airways and bladder cancer have also been reported in Iran. So too is stem cell deficiency believed to be associated with age related dysfunction.[8] Hair greying is a *sine qua non* of acceleration of the human aging process, as is chronic periodontitis or growing "long in the tooth".[7] The inflammatory component of many brain and psychiatric disorders, including depression, is increasingly recognized. Hence the present large prospective study by Khademi and colleagues powerfully and definitively and causally demonstrates the exacerbation of aged related disease by opiate dependence in most major organ systems, in a manner unrelated of the route of administration, significantly worse in females, in non-smokers and in intravenous users, and dose-dependently related to cumulative lifetime opiate exposure. The population prevalence of opium use was 17% in the study, and the deaths attributable to opium were estimated to be 15%. The effect took 10 – 14 years to subside after opium cessation. As flagged by the authors, the outstanding issues relate to the likely mechanisms responsible for this effect; its existence has now been placed effectively beyond reasonable dispute. Many molecular pathways suggest themselves for further study. At this point in time, opiate dependence appears to be a very powerful example of the interplay of stem cell failure and immune stimulation believed to underlie many chronic degenerative disorders including atherosclerosis, cancer and the aging process itself. As such the mechanisms responsible merits further study in their own right. Our Iranian colleagues, their international collaborators and the NCI have ignited a brightly shining beacon to illumine the way forward.

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