

**Commentary**

Scylla and Charybdis: COVID-19 and the Opioid Crisis

Robert G Smith*

Shoe String Podiatry Ormond Beach, Florida, USA

The Centers for Disease Control and Prevention currently recommends social isolation as a key measure for individuals to avoid getting infected with Covid-19 and to curb its spread to others [1]. An undisturbed fact is that Covid-19 pandemic will worsen the opioid overdose crisis if mitigating measures are not employed immediately. Currently, missing from the national discussion, as viewed by public awareness announcements, is the acknowledgment that one vulnerable group are the individuals at greatest risk of Covid-19 infections and possible mortality, i.e., patients with opioid use disorders who are receiving methadone maintenance therapy. The central purpose of this brief report is to present descriptive data between the 1918-1919 “Spanish flu” pandemic and the current Covid-19 pandemic that may allow for the inference that opioid use disorder patients are an at-risk population and that a national awareness platform should be launched to protect this population. First, epidemiology data identify those individuals who could be labeled as opiate addicts or those with opioid use disorder will be offered. Secondly, animal and human studies defining both the pathophysiological and immunological response to Covid-19 as well as the immunological response of opioid administration are offered, which may compound the morbidity and mortality of both pandemics to opioid use disorder patients. Finally, anecdotal data centering on the feasibility of social isolation for opioid use disorder treatment programs and news accounts on the increasing opioid overdose are offered with possible recommendations in an attempt to minimize morbidity and mortality of this at-risk population.

To see the current overlapping shadow of the Covid-19 pandemic on the Opioid Crisis in a better light, an examination of the historic extent of opiate addiction during the 1918–1919 “Spanish flu” pandemic, which was among the deadliest public-health crises in human history, needs to be conducted. An estimated 675,000 people in the

*Corresponding author: Robert G Smith, Shoe String Podiatry Ormond Beach, Florida, USA, Tel: +1 3866739933; E-mail: asamaan@cfl.rr.com

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United States and an estimated 50–100 million people worldwide died as a result of this pandemic [2,3]. Its explosive and still-unexplained pattern of rapid recurrent waves and predilection to kill the young and healthy cast an element of urgency over current pandemic planning [2-7].

According to Morens and Fauci, an explanation for the extraordinary excess influenza mortality in persons aged 20-40 in 1918 is perhaps the most important unsolved mystery of the pandemic [2]. Additionally, Morens and Fauci acknowledged that host and environmental variables have not been systematically investigated as possible causes of increased mortality in the young and healthy [2]. Moreover, they proposed that it was possible that vigorous immune responses directed against the virus in healthy young persons could have caused severe diseases in 1918 [2]. Finally, they stated that it was conceivable that aberrant inflammatory responses played a role in this situation. They defined the frequently proposed notion that a so-called cytokine storm, as a deleterious over-exuberant release of proinflammatory cytokines such as interleukin-6 and -8 and tissue necrosis factor- α , could have contributed to the high mortality and excessive number of deaths among the young and otherwise healthy during the 1918 pandemic [8,9].

To establish and compare these two subsets of individuals described as either opiate addicts or having opioid use disorder, a retelling of both historical and current data collected on the addiction epidemiology state and federal addict registry records need to be examined [10-13]. It is essential to examine historic numbers of opiate addicts attending “Sanitariums” or treatment clinics. It must be noted that heroin is one of the medications dispensed at these opiate addiction treatment clinics [10,11,13]. Courtwright reported that historical documents indicate that as late as 1910, the rate of opiate addiction had continued to increase and that by 1919, there were 1,000,000 or more drug addicts in the United States [10]. An outstanding feature of the nineteenth-century opium and morphine addiction was the fact that the majority of addicts were women [10]. This disproportionate number of female opium and morphine addicts persisted in many United States cities into the twentieth century [10]. It has been established by Kandall [11], that in the last six months of the year 1919, the New York opiate treatment clinic treated 1532 women, which was a mere one-quarter of the registered addicts. They also reported in many other clinics throughout the country, women constituted 25% to 35% of the patients [11]. Further, data from military medical examinations of World War I recruits provided a wealth of information on a variety of conditions including drug addiction [10]. Courtwright used the U.S. Senate’s Digest of the Proceedings of the Council of National Defense to determine the overall figure of 3,764,1010 men examined by local draft boards and compared it to the number of recruits-3,284 in total—that were rejected for heroin addiction and representing a rate of 0.87 per thousand [10,12].

Green reported in 2009 that the Data from the Addiction Severity Index Multimedia Version Connect database showed that women

were 1.6 times more likely than men to report prescription opioid use [14]. Back et al., compared the opioid dependence profiles of men and women from national multisite effectiveness trials [15]. This investigation found that a significantly intense craving for opioids at treatment entry and significantly higher rates of comorbid psychiatric conditions and psychological symptoms among women were the motives behind misuse of prescription opioids among women [15]. These findings echo past data of similar profile traits of women addicted to heroin and opium in the 19th century as reported by both Courtwright and Kendall [10,11,13]. Opioid misuse and addiction are a public health crisis resulting in debilitation, deaths and significant social and economic impact both currently and historically. The COVID-19 pandemic is having a profound effect on the health services globally particularly for people with opioid use disorder to access treatment services has become more difficult with a social distance mandate. Most of the countries in the world are adapting lockdown measure to reduce the spread of the infection, the health services are struggling to deal with the daily rise of infected cases hence little attention is provided to the substance user during this pandemic so proper measures and support services should be established to help this vulnerable community. It is highly important to address mental health emergencies like severe and complicated withdrawal symptoms of substanceuse. Many risks of the current pandemic to persons with Substance Use Disorder (SUD) are indirect. They arise from such factors as housing instability and incarceration, as well as reduced access to health care and recovery support services. A high percentage of individuals with SUD experience homelessness and vice versa.

In response to challenges in balancing opioid use disorder and the Covid-19 pandemic providers have requested advice from both the Substance Abuse and Mental Health Services Administration has advised opioid treatment programs to provide take-home medication more flexibly during the pandemic and the Drug Enforcement Administration has issued guidance to facilitate controlled substance prescribing.

Conti et al. [16], reported that Coronavirus-19 infected the upper and lower respiratory tract and caused both mild or highly acute respiratory syndrome with consequent release of pro-inflammatory cytokines including interleukin (IL)-1 β and IL-6. Fung et al., summarized the current understanding about the induction of a pro-inflammatory cytokine storm by other highly pathogenic human corona viruses and their adaptation to human [17]. It has been previously stated that an exuberant release of pro-inflammatory cytokines could have contributed to the high mortality during the 1918 Spanish Flu pandemic [8,9]. Acknowledging these findings now allows for a discussion of the human host inflammatory indices function and becomes a response to both pandemics if compromised by the use of opioids.

Amraei et al., using Wistar rats, conducted an investigation of methadone-based treatment effects on the hepatic tissue as well as its effect on hepatic enzyme levels and inflammatory markers [18]. They discovered that the inflammatory indicators (interleukin-6, tumor necrosis factor-alpha and C-reactive protein) rose significantly in groups that had received various dosages of methadone in contrast to the control group [18]. Finally, they found that the histopathological images of the liver cross-sections revealed dosage-dependent tissue changes in groups that had received various dosages of methadone [18]. Moreover, Boland and Pockley described how opioids have many non-analgesic effects including direct and indirect effects on

cancer cells and anti-tumor immunity [19]. Direct effects on immune cells are manifested in the form of opioid and non-opioid toll-like receptors. These investigations suggest that opioids can also decrease/alter immune cell infiltration into the tumor micro-environment [19].

Methadone is used as a long-acting synthetic opioid agonist that can be dosed once daily and prevents the need for multiple daily heroin doses. It stabilizes the drug-abusing lifestyle, reducing criminal behaviors and needle sharing and promiscuous behaviors that lead to the transmission of HIV and other diseases. Many opioid use disorder patients take either methadone or buprenorphine to treat their opioid use disorder. Being between Scylla and Charybdis is an idiom deriving from Greek mythology, which means having to choose between two evils.

Dunlop et al., report the impact of COVID-19 across health services to include drug addiction treatment services for people who use opioids, is emerging but likely to have a high impact [20]. These treatment services for people who use drugs provide essential treatment services including opiate agonist treatment and needle syringe programs alongside other important treatment programs across all substance types including withdrawal and counseling services [20]. COVID-19 will impact on staff availability for work due to illness. Patients may require home isolation and quarantine periods. Ensuring ongoing supply of opioid treatment during these periods will require significant changes to how treatment is provided [20]. They suggest the use of monthly depot buprenorphine as well as moving away from a framework of supervised medication dosing will be required for patients on sublingual buprenorphine and methadone [20]. Also a need to ensure ready access to take-home naloxone for patients is crucial to reduce overdose risks [20]. Another method is delivery of methadone and buprenorphine to the homes of people with confirmed COVID-19 infections is likely to need to occur to support home isolation [20]. People who use drugs are likely to be more vulnerable during the COVID-19 epidemic, due to poorer health literacy and stigma and discrimination towards this group. People who use drugs may prioritize drug use above other health concerns. Adequate supply of clean injecting equipment is important to prevent outbreaks of blood-borne viruses. Opioid users may misinterpret SARS-CoV2 symptoms as opioid withdrawal and manage this by using opioids. Ensuring people who use drugs have access to drug treatment as well as access to screening and testing for SARS-CoV2 where this is indicated is important.

Further, Green et al., have reported in times of crisis, the current regulations that exist in the substance use treatment world has intensify the barriers that already exist for patients because of regulation and policies in the United States [21]. In the face of the COVID-19 pandemic, providers have been challenged to address the needs of patients with opioid use disorder in the context of longstanding rules and regulations around medications such as methadone and buprenorphine [21]. A mitigating initiative they report are directives by the Substance Abuse and Mental Health Administration (SAMHSA) exempted opioid treatment programs from the requirement to perform an inperson physical examination for consideration of buprenorphine treatment, but not for methadone treatment [21,22]. Levine and Wein describe that under the Control Substance Act, specifically, the Ryan Haight Online Pharmacy Consumer Protection Act of 2008 (the Ryan Haight Act), in order to prescribe a controlled substance, an authorized provider is required to conduct at least one in-person

examination of the patient, unless an exception applies [23]. In a response to the COVID-19 public health emergency, this in-person requirement has become a barrier to treatment, as patients and providers are advised to shelter at home to prevent further spread of the virus [23]. Finally, the report governmental authorities are relaxing restrictions and allowing providers to meet the in-person examination requirement through alternative means, including telemedicine [23].

Up to April 2020, patients in methadone treatment programs are choosing between Scylla and Charybdis during this Covid-19 pandemic. At this point, the telemedicine guideline does not allow a medical practitioner to prescribe narcotic and drugs directly. Hence an e-prescribing, e-consulting that can be adapted for provider smart phones. should be funded by the federal government along with existing online mental health services has the potential to enable cost effective and convenient care for patients in this COVID crisis as well as the future. These patients are not able to stay at home because of the current government regulations that limit how these medications are prescribed and dispensed. It is recommended that states and federal governments allow for pandemic emergency opioid use disorder amendments to the current regulations. Currently, clinical pharmacy services are underused and pharmacists are strategically poised to provide services in opioid maintenance therapy, pain management and opioid dosage reduction with weaning schedules. One recommendation is for pharmacy involvement in methadone maintenance therapy by becoming a medication unit with an already established and certified opioid treatment program to ease the currently over-taxed established program locations. A pharmacy setting could be used as a medication unit in a convenient, comfortable location for dispensing opioid maintenance program and to provide counseling and supportive services. Moreover, the pharmacy-based opioid maintenance program can be married to the Covid-19-based testing and allow for a more effective data collection for possible contact tracing. In cities across the United States, early morning is the peak time at almost any opioid treatment program with long lines that stretch from the front counter to the back door as patients wait to get their daily dose of methadone. Though this is an absolute essential gathering to prevent withdrawal symptoms, it counters the containment of the Covid-19 outbreak. Two negative outcomes are presented to the opioid disorder patient participating in opioid treatment programs. The first is patients will continue to come and get their medication even though they have symptoms of Covid-19 with the possibility of exposing other patients participating in the program and the medical staff caring for them to the virus. For this reason, an establishment between opioid treatment programs with corporate alliances to donate hand sanitizers, gloves and masks is essential to prevent Covid-19 exposure. The second possibility is that individuals will not or cannot participate in the program because of infection, leading to missed doses of medications, which will be followed by opioid withdrawal and an increased risk of relapsing drug use and overdose.

Azpiri recently reported that Vancouver saw a rise in overdose deaths amid the Covid-19 crisis [24]. According to Azpiri, there has been a spike in opioid overdose deaths in Vancouver amid the Covid-19 crisis, as per city officials [24]. More than 4,700 fatal overdoses have been reported in B.C. with more than 1,200 of those deaths happening in Vancouver. On April 9, 2020, Dimascio reported that the Rensselaer County in New York reported eight fatal overdoses in the previous two weeks [25]. Further, the Rensselaer County Public Health Director Mary Fran Wachunas offered the assertion

that the numbers are very concerning and adds that the county has had 16 overdose deaths so far in 2020 when compared to the total of ten last year [25]. Finally, on April 15, 2020, Mallin reported how health officials have raised concerns about the safety of those suffering from substance use disorders amid the COVID-19 pandemic [26]. As Mallin further points out, the fire and rescue departments in Jacksonville, Florida, reported a 20 percent increase in opioid overdose emergency calls in March 2020; [26], in Columbus, Ohio, the county coroner's office acknowledged a surge in overdose deaths, including 12 in a 24-hour period in the first week of April 2020 [26]. In New York State, at least four counties have acknowledged an increase in reported overdoses, including Erie County where officials saw at least 110 drug overdoses, including 36 deaths reported since the beginning of March 2020 [26]. Updated fatal opioid overdose data in more United States cities amid the COVID-19 crisis is necessary to fully see how these two crises intersect and overlap when related to fatalities so that realistic preventative measures can be implemented to protect populations vulnerable to the opioid disorder.

As of April 2020, the United States now has 22 million unemployed, wiping out a decade of job gains. Woolhandler and Himmelstein assert with jobs and health insurance coverage disappearing as the COVID-19 pandemic rages, states that have declined to expand Medicaid should urgently reconsider [27]. Moreover, state tax revenues are plunging due to shelter in place orders and initiatives in place to have only essential workers to attend their place of business. The foreboding realization that only the federal government can address this financial impending crisis [27]. Secondly they state health care coverage losses are likely to be steepest in states that have turned down the Patient Protection and Affordable Care Act's Medicaid expansion [27]. Additionally, in expansion states, the share of persons who have lost or left a job who lacked coverage was 22.1% versus 8.3% for employed persons-a difference of 13.8 percentage points [27]. These authors acknowledge that although the COVID-19 crisis demands urgent action, it also exposes the carelessness of tying health insurance to employment and the need for more thoroughgoing reform [27]. It is hoped that the issue of families who face the dual disaster of job loss and health insurance loss and who may suffer from opioid use disorder will be among the foremost issues on the legislative branch of the United States' agenda. Haffajee et al., report opioid overdose deaths in the United States continue to increase, reflecting a growing need to treat those with opioid use disorder [28].

Building on both Woolhandler and Himmelstein assertion and using Haffajee et al., analysis of the characteristics of counties that exhibited both historically high rates of opioid overdose mortality and low medication for opioid use disorder provider availability as of late 2017 [28], can be used to formulate the proclamation can be made that indeed federal financial grant funding to assist opioid use disorder patients in the mist of the Covid-19 is warranted and essential. COVID-19 funding and funding opportunities exists from National Institutes of Health (NIH). Information is provided by the NIH as a service to our applicant and recipient communities in the hopes it will address high-level questions that may arise in this regard. Training grant applications submitted to the Parent Funding Opportunity Announcements PA-20-142 and PA-20-162 with a due date of May 25 will be accepted through June 30, 2020. Also, NIH posted they understand that the emergency declaration related to novel coronavirus (COVID-19) will adversely affect many NIH applicants' ability to submit applications in a timely manner. The Emergency Competitive

Revision Funding Opportunity Announcements (FOA) can only be used for funding available for applications based on a presidentially declared disaster under the Stafford Act, a public health emergency declared by the Secretary, HHS, or other local, regional or national disaster. This means that for COVID-19 funding, it can only be used by those NIH Institutes and Centers. Currently, it can only be concluded that NIH funding opportunities directed to mitigate the impact of Covid-19 pandemic on opioid use disorder patients who are receiving avoidance medications is not currently available. It is hope that the NIH officials will declare that opioid use disorder patients are an at risk population that are worthy of financial assistance and will address this overlooked public health crisis that was unforeseen.

Conclusion

Social isolation is a key measure for individuals to prevent avoid infected with Covid-19. Currently missing from the national discussion is the acknowledgment that one vulnerable group of individuals at-risk of Covid-19 infections and possible mortality are patients with opioid use disorders who are receiving methadone maintenance therapy. The central purpose of this brief report is to present descriptive data found between the 1918–1919 “Spanish flu” pandemic and the current Covid-19 pandemic that may allow for the inference that opioid use disorder patients are an at-risk population and the need for a national awareness platform that should be launched to protect this population. Epidemiology data identifying those individuals who could be labeled as opiate addicts or individuals with opioid use disorder will be presented. Secondly, animal and human studies defining both the pathophysiological and immunological response to Covid-19 as well as the immunological response of the opioid administration was presented. Finally, anecdotal data centering on the feasibility of social isolation for opioid use disorder treatment programs and opioid overdose was presented. It is hope that under no circumstances can we forget or marginalize persons with opioid use disorder during this new public health crisis.

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