

Review Article

Diabetes Mellitus at the Intersection of the COVID-19 Pandemic and the Opioid Crisis

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Introduction

Boslet et al. used a secondary data analysis of the universe of drug overdoses in 1999-2016 obtained from the National Center for Health Statistics Detailed Multiple Cause of Death records to demonstrate that the number of deaths attributed to opioid-related overdoses could be 28 percent higher than first reported due to incomplete death records [1]. This discrepancy was more pronounced in several states, to include Alabama, Mississippi, Pennsylvania, Louisiana, and Indiana, where the estimated number of deaths more than doubles obscuring the scope of the opioid crisis and potentially affecting programs and funding intended to confront the epidemic [1]. Logistic regression and random forest models were performed to determine contributing causes substantially that improved predictive accuracy, while including county characteristics. Using a superior prediction model, they found that 71.8% of unclassified drug overdoses in 1999-2016 involved opioids, and thus translating into 99160 additional opioid-related deaths, or approximately 28% more than previously reported [1]. It is hoped a physician relies on census data as essential tools for understanding the importance of place-level characteristics on opioid mortality. Opioid mortality rates overall are higher in counties characterized by more economic disadvantage, more blue-collar and service employment, and higher opioid-prescribing rates [2]. Medical literature have reported that high rates of prescription opioid overdoses and overdoses involving both prescription and synthetic opioids cluster in more economically disadvantaged counties with larger concentrations of service industry workers [2]. Further, Monnat et al. suggest national policies to combat the opioid and larger drug crises, emphasis should be on developing locally and regionally tailored interventions, with attention to place-based structural economic and social characteristics [2].

An appreciation 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 [3]. 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 is that only the federal government can address this financial impending crisis [3]. Secondly these authors 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 [3]. 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 [3]. 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 [3]. 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 [4]. Acknowledging that fading economic opportunity has been hypothesized to be an important factor associated with the United States opioid overdose crisis. Automotive assembly plant closures are culturally significant events that substantially erode local economic opportunities [5]. Moreover, Venkataramani et al. explores and investigates a community's economy has on opioid overdose mortality. Their primary outcome was the county-level age-adjusted opioid overdose mortality rate [5]. Their secondary outcomes included the overall drug overdose mortality rate and prescription vs. illicit drug overdose mortality rates [5]. They discovered that from 1999 to 2016, automotive assembly plant closures were associated with increases in opioid overdose mortality [5]. These findings highlight the potential importance of eroding economic opportunity as a factor in the United States opioid overdose crisis [5]. Finally, Langbeer et al. concluded univariate, opioid-related mortality was positively correlated with tobacco use, being non-Hispanic Caucasian individual, living in a rural area, obesity, being 65-years of age or older, and a higher rate of unemployment [6].

Gautam et al. reported that diabetes mellitus has well known costly complications but wanted to show through a retrospective model that costs of care for chronic pain treated with opioid analgesic medications would also be substantial [7]. They found that higher costs of care for opioid-treated patients appeared for all types of services and likely reflects multiple factors including morbidity from the underlying cause of pain, care and complications related to opioid use, and poorer control of diabetes as found in other investigations [7]. Schiemsy et al. reported a case of hypoglycemia caused by inappropriate stimulation of insulin secretion in a patient intoxicated with tramadol [8]. They further explain the sudden hypokalemia was caused by a massive intracellular shift of potassium in response to

the hyperinsulinemia, triggered by the intravenous administration of glucose [8]. Makunts et al. analyzed over twelve million reports from United States Food and Drug Administration Adverse Event Reporting System to provide evidence of increased propensity for hypoglycemia in patients taking tramadol when compared to patients taking other opioids, serotonin-norepinephrine reuptake inhibitors, and drugs affecting (NMDAR) activity [9]. They identified that both tramadol and methadone behave similarly to tramadol and has an association with hypoglycemia [9]. These findings accentuates the need for monitoring of a patient's blood glucose given the overlap of the opioid crisis and COVID-19 pandemic.

As people across the United States and the rest of the world contends with coronavirus disease 2019 (COVID-19), the medical community to include podiatric physicians should realize the possibility that COVID-19 infection could hit some populations with Substance Use Disorders (SUDs) particularly hard [10]. The coronavirus that causes COVID-19 attacks the lungs and could be an especially serious threat to those patients who smoke tobacco, marijuana or who vape. People with Opioid Use Disorder (OUD) and methamphetamine use disorder may also be vulnerable due to those drugs' effects on respiratory and pulmonary health [10]. Additionally, patients with a substance use disorder are more likely to experience homelessness or incarceration than those in the general population, and these circumstances pose unique challenges regarding transmission of the virus that causes COVID-19. All these possibilities should be a focus of active surveillance as we work to understand this emerging health threat [10].

According to Volkow those persons who are isolated and stressed as much of the population is during the COVID-19 pandemic frequently turn to substances to alleviate their negative feelings [11]. Those in substance recovery will face stresses and heightened urges to use substances and will be at greatly increased risk for relapse [11]. Further, vulnerable populations those who smoke or vape, use opioids, or have a Substance Use Disorder (SUD) may have direct challenges to respiratory health, those with SUD may be especially susceptible to infection by the virus that causes COVID-19 and associated complications [11]. Impediments to delivering care to this population, persons with SUD who develop COVID-19 may find it harder to get healthcare [11]. Those in recovery will also be uniquely challenged by social distancing measures [11]. Lastly, a risk for severe COVID-19 and death escalates with older age but is also concentrated among those who are immunocompromised or have underlying health conditions, including diabetes, cancer, and heart and respiratory diseases [11].

Mukherjee and El-Bassel report that people with opioid and other substance use disorders are disproportionately incarcerated, and recently released prisoners are ten times more likely to become homeless [12]. During the COVID-19 pandemic coupled without adequate planning, de-carceration efforts in may move people with Opioid Use Disorder from one at risk environment to another at risk environment [12]. Upon release, the risks associated with COVID-19, as well as HIV, viral hepatitis, Tuberculosis, overdose and homelessness that often accompany incarceration must be considered [12].

It is an accepted fact that not only does COVID-19 make addiction services harder to access but people who use drugs may be at higher risk of infection given the dangerous overlap between addiction, incarceration, and the rapid spread of infections within confined spaces. Community campaigns to get nonviolent drug offenders released during this pandemic may not be sufficient to avoid incarcerated persons from becoming infected with COVID-19. A prisoner re-entry into regular society is difficult and dangerous from a health perspective, even during normal times. As the economy collapses, shelters and food banks have been overwhelmed, with already limited resources stretched thin on all levels in many communities.

Opioids and Increase of Infections

Schwetz et al. rely on clinical evidence to assert in their commentary that the rise in Opioid Use Disorder (OUD), bolstered by injection opioid use, conveys numerous downstream consequences and is fueling a surge in infectious diseases, such as Human Immunodeficiency Virus (HIV) infection with or without AIDS, the viral hepatitis, infective endocarditis, pneumonia, and skin and soft-tissue infections [13,14]. Further, Schwetz et al. note the increasing infection rates and demographic trends of bacterial and fungal infections appear to mirror trends observed with the opioid epidemic [13,15]. They cite the example of the rate of methicillin-resistant *Staphylococcus aureus* infections among people who inject drugs more than doubled between the years of 2011 and 2016 [16]. Additionally, they assert the growing evidence has shown that certain opioids to include both morphine and fentanyl that have putative effects on both the innate and adaptive immune systems, dependent on drug dosage and duration of delivery [13]. Finally, these authors concluded using published data that the growing trend of infectious diseases emerging across the United States in areas with high rates of opioid use has created a significant combined impact on morbidity and mortality [13].

Wiese et al. conducted a retrospective cohort study to investigate long-acting opioid use and the risk of serious infections [17]. They used multivariable Poisson regression models to calculate adjusted incidence rate ratios and 95% confidence intervals to compare the infection risk among patients using long-acting opioids with known immunosuppressive properties (morphine, fentanyl, methadone) to the infection risk among patients using long-acting opioids without known immunosuppressive properties (oxycodone, oxymorphone, tramadol) accounting for demographics, opioid dose, comorbidities and pain conditions, medication use, frailty indicators, and healthcare encounter history using exposure propensity scores [17]. Moreover, they compared users of individual long-acting opioids to long-acting morphine users that considered the prototypical immunosuppressive opioid [17]. They determined the risk of serious infections among long-acting opioid users varies by opioid type [17]. They suggest that providers should carefully consider the risk of serious infections when making pain management decisions [17]. Karagiannis et al. acknowledge that chronic opioid usage not only causes addiction behavior through the central nervous system, but also modulates the peripheral immune system [18]. Further they ask the question

how do opioids impact the immune system and recognize it is still barely characterized systematically [18]. In order to understand the immune modulatory effect of opioids in an unbiased way, here they perform single-cell RNA sequencing (scRNA-seq) of peripheral blood mononuclear cells from opioid-dependent individuals and controls to show that chronic opioid usage evokes widespread suppression of antiviral gene program in naive monocytes, as well as in multiple immune cell types upon stimulation with the pathogen component lipopolysaccharide [18]. Furthermore, scRNA-seq reveals the same phenomenon after a short in vitro morphine treatment was discovered [18]. Their findings indicate that both acute and chronic opioid exposure may be harmful to our immune system by suppressing the antiviral gene program [18]. Lastly, their results suggest that further characterization of the immune modulatory effects of opioid is critical to ensure the safety of clinical opioids [18]. These results are of utmost importance in understanding the use of opioids in patients with diabetes mellitus during the current COVID-19 pandemic.

Diabetes Mellitus and COVID-19 Pandemic

In the United States, 34.2 million or 10.5% of the total population have diabetes mellitus [19]. Among those aged 65 years or older, a population at higher risk for death from COVID-19, 26.8% has diabetes mellitus [19]. Muniyappa and Gubbi summarize that individuals with diabetes mellitus, hypertension, and severe obesity (BMI 40 kg/m²) are more likely to be infected and are at a higher risk for complications and death from COVID-19 [20]. Given, consideration to the high prevalence of cardiovascular disease (CVD), obesity, and hypertension in patients with diabetes mellitus, according to Muniyappa and Gubbi it is unknown whether diabetes mellitus independently contributes to the increased risk of being infective with COVID-19 [20]. However, plasma glucose levels and diabetes mellitus are independent predictors for mortality and morbidity in patients with SARS [21]. Potential mechanisms that may increase the susceptibility for COVID-19 in patients with diabetes mellitus include: 1) higher affinity cellular binding and efficient virus entry, 2)

decreased viral clearance, 3) diminished T cell function, 4) increased susceptibility to hyperinflammation and cytokine storm syndrome, and 5) presence of cardiovascular disease [20]. Additionally, diabetes mellitus inhibits neutrophil chemotaxis, phagocytosis, and intracellular killing of microbes. Impairments in adaptive immunity characterized by an initial delay in the activation of Th1 cell-mediated immunity and a late hyperinflammatory response is often observed in patients with diabetes [22].

Another point explained by Hussain et al. is that the clinical spectrum of COVID-19 is heterogeneous, ranging from mild flu-like symptoms to acute respiratory distress syndrome, multiple organ failure and death [23]. Older age, diabetes and other comorbidities are reported as significant predictors of morbidity and mortality [23]. Chronic inflammation, increased coagulation activity, immune response impairment, and potential direct pancreatic damage by SARS-CoV-2 might be among the underlying mechanisms of the association between diabetes and COVID-19 [23].

Finally, Bode et al. proposed the concept that diabetes and/or uncontrolled hyperglycemia occur frequently among hospitalized patients with COVID-19 and are associated with worse outcomes [24]. To investigate this concept they performed a retrospective observational study of laboratory-confirmed COVID-19 adults evaluated glycemic and clinical outcomes in patients with and without diabetes and/or acutely uncontrolled hyperglycemia who were hospitalized [24]. Among hospitalized patients with COVID-19, diabetes and/or uncontrolled hyperglycemia occurred frequently [24]. These COVID-19 patients with diabetes and/or uncontrolled hyperglycemia had a longer length of stay and markedly higher mortality than patients without diabetes or uncontrolled hyperglycemia [24]. These investigators observed that patients with uncontrolled hyperglycemia had a particularly high mortality rate [24]. The physician can appreciate the potential effects of drug treatment options being used in the management of COVID-19 on glucose and lipid profiles summarized in Table 1 [25].

Table 1: Summary of the potential effects of Medications options being used in the management of COVID-19 on glucose and lipid profiles.

Medications	Mechanism of action on COVID-19	Effect on glucose profile	Effect on lipid profile	
Corticosteroids	Anti-inflammatory, blocks cytokine storm	Hyperglycemia	Dyslipidemia	↑
Lopinavir/Ritonavir	Protease inhibitors, blocks viral cellular entry	Hyperglycemia Lipodystrophy	Dyslipidemia	↑
Darunavir/Cobicistat	Protease inhibitors, blocks viral cellular entry	Hyperglycemia Lipodystrophy	Dyslipidemia	↑
Remdesivir	Adenosine analogue, inhibits viral replication	Increased blood glucose	Increased blood lipids	
Interferons (b1)	Cytokine, stimulate innate antiviral immunity	Can lead to autoimmune b-cell damage thereby, precipitating or worsening diabetes mellitus	Dyslipidemia	↑
Chloroquine/Hydroxychloroquine	Increases host cell endosomal pH, prevents viral entry and immunomodulator	Improves glucose profile and HbA1c in people with Type 2 Diabetes Mellitus	Improves lipid profile in people with Type 2 Diabetes Mellitus	
Azithromycin	Macrolide antibiotic	Risk of dysglycemia in people with diabetes mellitus	No robust data Being an enzyme inhibitor, may prolong half-life of statins	
Camostat mesilate	Protease inhibitors, blocks viral maturation and entry into cells	Found to lower blood glucose levels in insulin-treated patients with diabetes mellitus	Not known	
Tocilizumab	Monoclonal antibody against IL-6, blocks cytokine storm	Improves glucose profile and reduces HbA1c in people with rheumatoid arthritis and diabetes mellitus	Alters lipid profile in people with rheumatoid arthritis	
Convalescent plasma	Provides anti-SARS-CoV-2 antibodies	Not known	Not known	

Table 2: Comparison List of the Typical Symptoms of Covid-19 Infection and Opioid Withdrawal Symptoms.

Covid-19 Infection Symptoms [25]		Opioid Withdrawal Symptoms [26] Symptoms appear 72 hours after last dose
Fever	87.90%	Fever
Dry Cough	67.70%	Chills
Fatigue	38.10%	Body Aches
Sputum Production		Diarrhea
Shortness of Breath		Insomnia
Myalgia-Arthralgia	14.80%	Muscle Pain
Sore Throat	13.90%	Nausea
Headache	13.60%	Dilated Pupils
Chills	11.40%	
Nausea-Vomiting	5%	
Nasal Congestion	4.80%	
Diarrhea	3.70%	

Source: National Institute of Drug Abuse.

Source: Report of the WHO China.

Joint Mission on Coronavirus Disease 2019.

Strategies for Managing Chronic Pain

The COVID-19 public health crisis has strained health care systems, creating an enigma for patients, pain medicine practitioners, hospital leaders, and regulatory officials [26]. Pain management providers rely on infection control precautions form a backbone of interventional-based and some alternative medicine to include: acupuncture, hands-on therapies such as massage and manual therapy practices [26]. These precautions are even more important during a pandemic where the potential exists for viral shedding from asymptomatic patients and disease transmission [26]. The clinicians need to acknowledge that many patients who would be seen in for chronic pain issues during the COVID-19 pandemic are in higher risk groups and full consideration should be given to minimizing patients congregating in a waiting room. Specialists should familiarize themselves to the new Health Human Services and Centers for Medicare and Medicaid Services relaxations on telemedicine provide a method for new patient and established patient visits [26]. In patients on opioids who may have run out of medications because of logistical obstacles or overuse, assessment of withdrawal signs can be challenging during remote visits. These symptoms such as diarrhea, rhinorrhea, abdominal pain and chills can be garnered from patient interviews, but may be difficult to corroborate [26]. On the other hand, some physical signs indicative of opioid withdrawal, particularly if prominent, can be observed remotely such as agitation, diaphoresis, piloerection, and possibly even pupillary size [26]. Monitoring patients for an elevated heart or pulse rate, which is a classic sign of opioid withdrawal, can sometimes be done by reliable patients or their caregivers [26]. The salient point that typical symptoms of COVID-19 overlap the typical symptoms of opioid withdrawal has to be realized by the podiatric physician so that a correct diagnosis can be determined and a negative outcome can be avoided. A list of the typical symptoms of COVID-19 infection along with the presenting typical symptoms of opioid withdrawal are presented in Table 2 so a comparison can be appreciated [27,28].

Conclusion

First, the negative economic impact of the COVID-19 pandemic and how it exacerbates the opioid crisis in America was presented.

Then certain factors of patients with substance abuse disorders and how they are disadvantaged by excessive and prolonged isolation and social distancing is presented. The effects of opioid use and addiction as well as the pathology Diabetes Mellitus on pulmonary and immune function that effect a patient's response COVID-19 was presented. Lastly, strategies for managing chronic pain and access to medical care were presented. It is hoped the physician can appreciate the over shadowed area at the intersection of the COVID-19 Pandemic and the Opioid Crisis.

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