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Short communication

Prescription fill patterns for benzodiazepine and opioid drugs during the COVID-19 pandemic in the United States

Constanza de Dios^a, Brisa S. Fernandes^a, Kristine Whalen^b, Shruti Bandewar^b,
Robert Suchting^a, Michael F. Weaver^a, Sudhakar Selvaraj^{a,*}

^a Louis A. Faillace, MD, Department of Psychiatry and Behavioral Sciences, University of Texas Health Science Center at Houston, McGovern Medical School, Houston, TX, USA

^b Bamboo Health, Louisville, KY, USA



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ABSTRACT

Background: COVID-19 and resulting mitigation measures in the United States (US) brought about limited access to medical care that has been linked to increases in mental health problems, excessive substance use, and drug overdoses. The increase in co-prescription of benzodiazepines and opioids may indicate population-level changes in health behaviors that can be exacerbated by limited access, hence necessitating the tracking of these drugs during COVID-19. We evaluated the impact of the declaration of COVID-19 as a US national emergency on prescription patterns in 2020.

Methods: Prescriptions of benzodiazepines and opioids were analyzed using data aggregated on a weekly basis across 38 states over the January 2019–December 2020 period. Data were from Bamboo Health Prescription Drug Monitoring Program and covered all individuals regardless of insurance status. Generalized additive models estimated the effects of the March 13, 2020 declaration on proportion of prescriptions to all controlled substances by comparing volumes before to after the week of March 13 in 2020 (range: January 27–May 24) and comparing this trend to its 2019 counterpart.

Results: When comparing the January 27–March 9 period to the March 16–May 24 period in 2020, there was a statistically significant 2.0% increase in the proportion of benzodiazepine dispensations to all controlled substances, and a significant 1.7% mean decrease in proportion of opioid dispensations to all controlled substances. A significant return approaching pre-declaration levels was observed only for opioids (beginning week of May 18, 2020).

Conclusions: The results suggest significant impacts of the COVID-19 pandemic on dispensations of benzodiazepines and opioids across the US. Continued monitoring of prescription trends and maintenance of adequate and accessible access to mental healthcare are important for understanding public health crises related to substance use.

1. Introduction

The Coronavirus disease 2019 (COVID-19) pandemic has severely affected people's everyday lives worldwide with substantial personal and societal concerns about health and safety. On March 13, 2020, the President of the United States (US) declared the COVID-19 pandemic a national emergency. Consequently, several states across the US instituted mitigation measures of varying degrees, from curfews and bans of large gatherings, to stay-at-home orders for implementing social

distancing (Gostin and Wiley, 2020). Due to COVID-19 related restrictions, many people had limited or delayed access to medical care that has been linked to increases in mental health problems, excessive use of alcohol and controlled or illegal substances, drug overdoses and violence (Holland et al., 2021).

Benzodiazepines are prescribed mainly for anxiety, sleep, and seizures; opioids for pain and post-surgery care, among others. Overdose-related emergency room visits and death linked to overdoses with opioids and benzodiazepines have significantly increased in the last two

* Corresponding author at: Louis A. Faillace, MD, Department of Psychiatry and Behavioral Sciences, University of Texas Health Science Center at Houston, McGovern Medical School, 1941 East Road, Houston, TX 77054, USA.

E-mail address: Sudhakar.selvaraj@uth.tmc.edu (S. Selvaraj).

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decades (Hwang et al., 2016; McClure et al., 2017; Volkow, 2020). Co-prescription of benzodiazepines and opioids has increased significantly in clinical practice, which may indicate population-level changes in behaviors of public health concern such as those that could lead to increased risk of overdose (Liang and Shi, 2019). Thus, tracking aggregate prescriptions of these drugs may provide clues about health behaviors following significant events such as pandemics. We hypothesized that the prescription volume of these substances increased during the early phase of the COVID-19 pandemic in the US.

2. Materials and methods

Mean weekly dispensations of benzodiazepines and opioids from weeks 5 through 21 in 2019 (January 28–May 26) and 2020 (January 27–May 24) were analyzed using generalized additive models (GAMs) to estimate the effects of the declaration of COVID-19 as a pandemic (March 13, 2020) on dispensations following this period (week 12, or week with start date March 16). We used data from the Bamboo Health Prescription Drug Monitoring Program (PDMP), which is the vendor for prescription monitoring programs in 43 states and territories in the US, covering all individuals regardless of insurance status. PDMPs are databases of all controlled substance and reportable drugs dispensed in a state, and are intended to give providers and pharmacists up-to-date information on patient behaviors that elevate that patient's risk of opioid-related harms, such as overdose. PDMPs have been established in states using data collected from pharmacies and dispensaries.

We used collaborated data from 38 states and the military health system for benzodiazepine and opioid dispensations. States included in the given consolidated data are Vermont, New Jersey, Colorado, North Dakota, Ohio, Louisiana, Massachusetts, Maine, Missouri, Alaska, Connecticut, Georgia, Guam, Indiana, New Hampshire, Rhode Island, Washington, North Carolina, Hawaii, Nevada, Idaho, Kansas, Michigan, Arkansas, Pennsylvania, Puerto Rico, Minnesota, Arizona, District of Columbia, Oklahoma, Texas, Virginia, Delaware, Mississippi, Iowa, New Mexico, Oregon, South Carolina, and South Dakota. Drugs classified as benzodiazepines contain these active ingredients: Alprazolam, Chlordiazepoxide, Clobazam, Clonazepam, Clorazepate, Diazepam, Estazolam, Flurazepam, Lorazepam, Midazolam, Oxazepam, Quazepam, Temazepam, Triazolam. Drugs classified as opioids contain these active ingredients: Eluxadoline, Hydromorphone, Pentazocine, Dihydrocodeine, Codeine, Oxycodone, Hydrocodone, Methadone (currently only captures usage for pain indications), Meperidine, Remifentanyl, Alfentanil, Butorphanol, Opium, Oxymorphone, Sufentanyl, Tapentadol, Levorphanol, Buprenorphine, Fentanyl, Tramadol, Morphine, and Propoxyphene.

Count data of dispensations and of distinct patients were first taken as a proportion of all major controlled substances for each week in their respective year prior to analysis (controlled substances included: sedatives, stimulants, opioids, benzodiazepines, steroids, gastrointestinal opioids, cannabinoids, anesthetics, muscle relaxants, and a very small subset of drugs related to diabetes such as insulin drugs). Distinct patients' data captures a distinct fill of a given prescription, including refills. We analyzed proportion as the outcome measure as this would already account for general trends of major controlled substances in the analysis, given that all prescriptions of many medications were affected during the pandemic (Vaduganathan et al., 2020).

The primary analysis evaluated the impact of the US emergency declaration on benzodiazepine and opioid prescription proportions to controlled substances. GAMs modeled each measure as a function of the fixed effects Year (2020, 2019), Period (with respect to emergency declaration: whether prescription occurred within weeks 5–11 [before declaration], or week 12–20 [after declaration]) and their interaction, controlling for trend and seasonal components. Trend component Time (weekly start date) was smoothed using a thin plate spline, and seasonal component Week number using a cyclic smooth with a basis dimension of 16, the number of weeks in the test period. An effect of Period unique

to 2020 (increase or decrease from before to after week 12 within weeks 5–20 in 2020, but not 2019) would be indicated by a significant ($p < 0.05$) Year x Period interaction. Significant Year x Period interactions were further identified via post-hoc contrasts (*t*-tests) using a Bonferroni correction, yielding estimated marginal means before and after the declaration (M_{Before} , M_{After}). In a secondary analysis, GAMs testing any return to pre-declaration (prior to week of March 13) levels were fit using similar steps, by comparing weeks 12–20 to weeks 21–37 (March 3–May 17 vs. May 18–September 13 in 2020). Fig. 1 shows data for the entire year, however analyses were focused only on a specific portion of both years (weeks 5–37). Analyses were performed using R package *mgcv* (Wood, 2011) on R Software Version 4.0.2.

3. Results

Maximum counts of benzodiazepine prescriptions by dispensation were 1,374,824 in 2019, and 1,432,383 in 2020 (distinct patients: 1,314,125 in 2019; 1,372,426 in 2020). Maximum counts of opioid prescriptions by dispensation were 2,613,756 in 2019, and 2,487,034 in 2020 (distinct patients: 2,376,385 in 2019; 2,260,346 in 2020) (Fig. 1B). Table 1 shows GAM estimates and estimated marginal means for significant Year (2019, 2020) x Period (before or after week 12) interactions within weeks 5–20 of years 2019 and 2020. The share of benzodiazepine fills to controlled substances in this time window significantly increased after week 12 only in 2020 (Fig. 1A); the same was true for the proportion of distinct patients. Post-hoc contrasts indicated a 2.0%-increase in share of benzodiazepine dispensations in 2020 from weeks 5–11 to weeks 12–20. The decrease towards pre-declaration levels at week 21 was not significant (0.1%-decrease from the week 12–20 period [$M = 25.3\%$] to week 21–37 period [$M = 25.2\%$] in 2020, $t = 0.56$, $p = 0.58$).

Opposite patterns were observed for opioids. The share of opioid fills to controlled substances significantly decreased after week 12 in 2020, both in dispensations and distinct patients (Fig. 1A). Post-hoc tests indicated a 1.7% decrease in share of opioid dispensations in 2020 from weeks 5–11 to weeks 12–20. An increase approaching pre-declaration levels was observed at week 21 (0.84% increase from week 12–20 period [$M = 38.3\%$] to week 21–week 37 period [$M = 39.1\%$] in 2020, $t = 2.73$, $p = 0.01$). Addressing concerns regarding off-label buprenorphine usage, a follow-up analysis was conducted, separating buprenorphines from opioids and testing their decrease in dispensations following week 12. Models revealed no significant change in share of buprenorphine dispensations to all controlled substances during this period (Year x Period interaction $b = 0.001$, $p = 0.14$; 0.00002% increase from weeks 5–11 to weeks 12–20, $t = 0.02$, $p = 0.98$). Meanwhile, the decrease in proportion of opioids excluding buprenorphines remained significant after week 12 in 2020 (Year x Period interaction $b = -0.013$, $p = 0.01$; 0.01% decrease between weeks 5–11 and weeks 12–20, $t = 4.45$, $p < 0.001$).

No other changes were observed in the later part of 2020 for both substances (Fig. 1).

4. Discussion

Evidence from population surveys shows elevated mental health concerns during the COVID-19 pandemic (Czeisler et al., 2020). The current study adds to the growing body of literature on prescription patterns of controlled medications during the COVID-19 pandemic in the US in 2020. We found an increase in benzodiazepine dispensations following the US emergency declaration, as hypothesized. This finding is consistent with results of Jones et al. (2021) who reported an increase in monthly number of patients dispensed antidepressants and benzodiazepines in March 2020, which came back to forecasted prescription patterns in April–May 2020. The increase in benzodiazepines during the weeks immediately following March 13 may be considered a proxy for increased anxiety (McGinty et al., 2020), sleep disorders, excessive

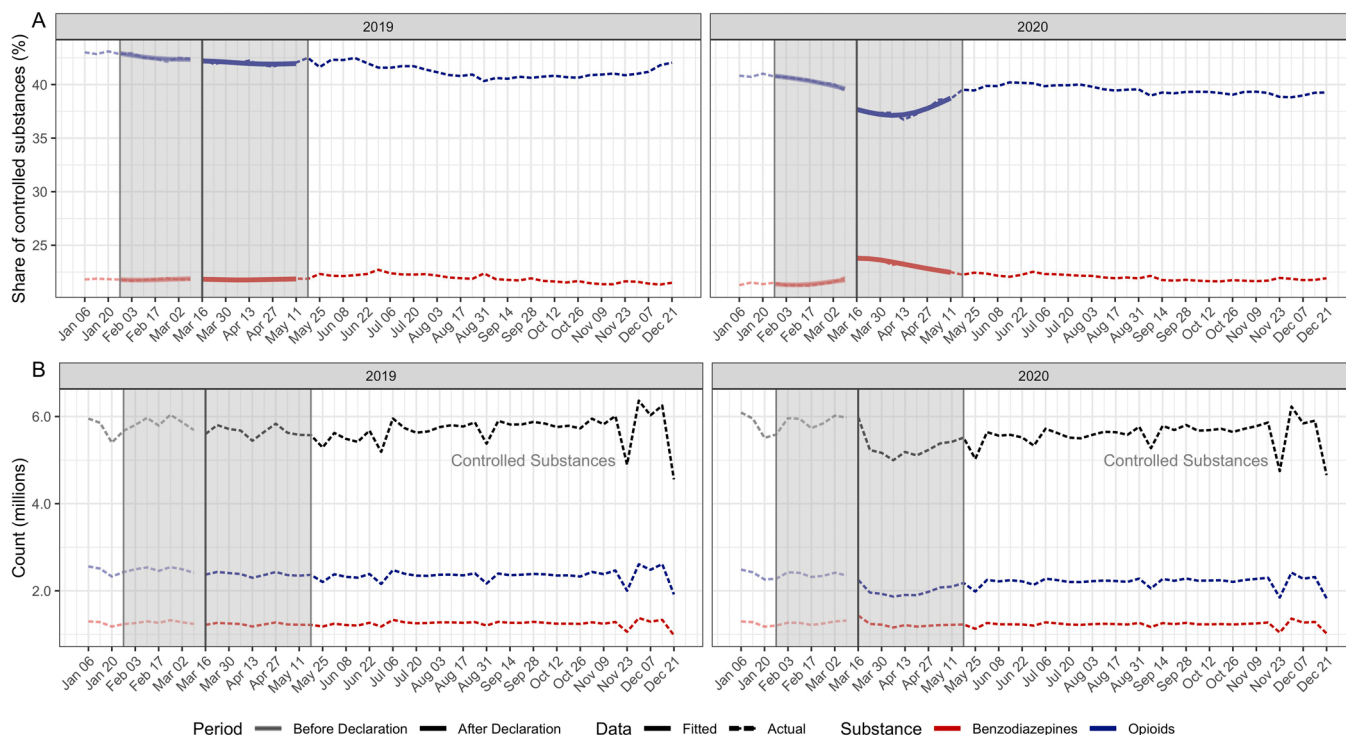


Fig. 1. Benzodiazepine and Opioid Prescription Patterns by Dispensation During the COVID-19 Pandemic in the US. Caption: Dispensation of benzodiazepines (red) and opioids (blue) before (light lines) and since (dark lines) the week of declaration of COVID as a pandemic in the USA (March 16, 2020, solid vertical line). Each date on the x-axis refers to the first day of the week in 2020. Actual data (dotted line) for the entire duration of 2019 and 2020 are shown. (A) Proportion of dispensations to all controlled substances. A subset of the benzodiazepine and opioid data fitted with GAM curves per the primary analysis (see Materials and Methods) are shown via solid lines in the shaded region. (B) Number of dispensations overall for all controlled substances (black), for benzodiazepines (red), and for opioids (blue) (illustration only).

Table 1
GAM estimates and Post-hoc Comparisons for Benzodiazepine and Opioid Prescriptions.

GAM Estimates ^a					Post-hoc comparisons ^b					
Unit	Adj. R ²	b	SE	p	Year	M _{Before} [95% CI ^d]	M _{After} [95% CI]	Diff. ^e	t ^f	p
Benzodiazepines by dispensation %	0.97	2.03	0.25	< 0.001	2019	22.7 [17.6, 27.7]	22.6 [17.6, 27.6]	0.1	0.3	0.75
					2020	22.0 [17.0, 27.0]	24.0 [18.9, 29.0]	-2.0	-10.0	< 0.001
Benzodiazepines by distinct patient %	0.97	2.50	0.31	< 0.001	2019	26.0 [20.6, 31.4]	25.8 [20.5, 31.2]	0.2	0.9	0.36
					2020	24.2 [18.9, 29.6]	26.5 [21.1, 31.9]	-2.3	-9.5	< 0.001
Opioids by dispensation %	0.99	-1.53	0.45	0.003	2019	42.8 [32.1, 53.5]	42.7 [32.0, 53.4]	0.1	0.4	0.70
					2020	41.6 [31.0, 52.3]	40.0 [29.3, 50.6]	1.7	5.2	< 0.001
Opioids by distinct patient %	0.99	-1.62	0.49	0.003	2019	45.5 [34.4, 56.7]	45.3 [34.2, 56.4]	0.3	0.8	0.43
					2020	44.9 [33.8, 56.0]	43.0 [31.9, 54.1]	1.9	7.1	< 0.001

^a GAM (generalized additive model) estimates for Year x Period interaction. Year (2019, 2020); Period (before or following week of March 16).

^b Post-hoc comparisons are estimated marginal means (M) for significant (p < 0.05) Year x Period interactions.

^c Adjusted R-squared (model fit).

^d 95% confidence interval

^e Difference derived by subtracting M_{After} (estimated marginal mean following week with start date March 16) from M_{Before} (estimated marginal mean before week with start date March 16).

^f Bonferroni-corrected t-test comparing M_{Before} and M_{After}

concerns about healthcare disruption, and long-term prescription use (Agarwal and Landon, 2019). The National Survey on Drug Use and Health data from 2015 and 2016 suggest the usage of benzodiazepines has increased, with nearly 30.6 million adults (12.6%) reporting benzodiazepine use in the past year (Maust et al., 2019). Misuse without a prescription or increased prescription usage for anxiety and sleep were

the commonly reported reasons (Maust et al., 2019). In this context, anticipated social isolation elicited by stay-home orders (Brooks et al., 2020) and health concerns related to COVID-19 likely worsened mental health, anxiety and sleep, and are thus likely associated with increased benzodiazepine prescriptions. While Jones et al. found a significant return of benzodiazepine patient volume back to baseline in April 2020,

the return of benzodiazepine prescriptions in our study toward pre-COVID levels the week of May 18, 2020 was not statistically significant, a difference that is potentially due to different geographical coverage and type of prescription data used between Jones et al. and our study. We attribute the nonsignificant return to baseline to the decrease being gradual rather than steep (Fig. 1B). Although our findings suggest benzodiazepine prescriptions post-declaration slowly approached pre-COVID levels, surveillance of population mental health and medication access is still critically needed as the ongoing COVID crisis can overwhelm the healthcare system.

Contrary to our hypothesis, we found a decrease in opioid prescriptions following the emergency declaration. The decrease may be explained by disruptions to outpatient and hospital clinical services and elective surgeries mandated during the early phase of the pandemic. Our results are consistent with a report indicating that existing patients maintained access to opioid medications, but the weekly number of opioid-naïve patients receiving opioid prescriptions decreased over March 18-May 19, 2020 (Currie et al., 2021). A similar study reported plateauing of buprenorphine prescriptions (Nguyen et al., 2021). Although these studies show a lack of increase in opioid prescriptions during the early phase of the pandemic, a recent study showed an increase in US emergency department visits for opioid overdoses during the March-October 2020 period (Holland et al., 2021). The Centers for Disease Control and Prevention data show an alarming increase in opioid-related overdoses, killing nearly 50,000 people in 2019 (Mattson et al., 2021). The increase in opioid overdoses during the pandemic is likely due to illicit opioids, including potent synthetic opioids such as fentanyl, rather than prescribed opioids. Thus, the opioid prescription decrease in our study may not be strongly related to recent opioid overdoses. However, enhanced monitoring of prescription trends is still essential to understanding the public health crisis of substance use-related problems, especially with the increase in alcohol and substance use during the pandemic suggesting increased stress and coping behaviors (Pollard et al., 2020).

Telemedicine during the pandemic provided mental health access to people who may have been trying to avoid emergency visits (Patel et al., 2021), as federal authorizations allowed prescription of controlled substances during this period (Drug Enforcement Administration, 2020). The observed increase in benzodiazepine prescriptions in our study may be partly explained by the pivot toward telemedicine, which has been shown to be related to less attrition and improved depression symptoms in patients receiving teletherapy (Mohr et al., 2008). Given the low rate of buprenorphine initiation during the pandemic (Currie et al., 2021) and the prevalence of chronic pain in US adults (20.4% as of 2016, Dahlhamer et al., 2018), our finding of decreased opioid prescriptions following the emergency declaration suggests the need for further structural support in increasing telemedicine access among patients needing opioid prescriptions. Research on increasing and maintaining access to telemedicine across all patient needs including antidepressants, analgesics, and substance use disorder treatment remains crucial (Di Carlo et al., 2021).

The study has limitations. First, the 38 states in the aggregated data do not include the largest or earliest-impacted states by the pandemic in March 2020 (i.e., California, New York) which do not utilize Bamboo Health's PDMP database product; therefore, the current study may underestimate the true effect of the emergency declaration on shifts in controlled substance prescriptions. Second, although prescription databases can be helpful to prescribers to detect medication misuse that may indicate a substance use disorder (Weaver, 2009), they do not provide details on prescription disease indications. Therefore, it is not clear if the increases in benzodiazepines are specifically related to mental or physical (e.g., epilepsy, restless legs syndrome, alcohol withdrawal syndrome) health conditions. The lack of indications and diagnosis code also meant the inability to disentangle the opioid class further by usage, primarily due to off-label usage for the opposite indication (e.g. buprenorphine indicated for medication-assisted treatment for pain).

Off-market opioids (e.g, Propoxyphene), although in very low levels to influence the results, were included in the opioid category based on submission by state PDMPs in the time period of interest. Next, prescription does not necessarily mean increased utilization. However, surveys and reports suggest a significant increase in stress-related problems, anxiety, insomnia, and intimate partner violence during the pandemic that collectively suggest an increase in mental health problems (Czeisler et al., 2020; Holland et al., 2021; McGinty et al., 2020).

These data emphasize the need for planning in health systems to develop long-term strategies that involve multidisciplinary teams to improve the wellbeing of individuals with COVID-19 and others who are impacted by the disease (Al-Aly et al., 2021). Further, maintaining adequate access to specialist psychiatric care and substance misuse programs is critical to providing safer treatment approaches and minimizing the risk of mental health deterioration, especially to people with prior psychiatric disorders who are already at higher risk of COVID-related mortality (Wang et al., 2021). Strengthening public health strategies related to substance use and that prioritize widespread access to mental healthcare, including telehealth, is urgently needed.

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CRediT authorship contribution statement

Constanza de Dios, Sudhakar Selvaraj: Conceived of the study. **Constanza de Dios, Robert Suchting, Kristine Whalen, Shruti Bandewar:** Performed the data analyses. **Constanza de Dios, Brisa S. Fernandes, Sudhakar Selvaraj:** Drafted the manuscript. **Robert Suchting, Michael Weaver, Sudhakar Selvaraj:** Provided critical revisions to the manuscript.

Conflict of Interest Disclosures

Constanza de Dios, Brisa S. Fernandes, Robert Suchting, and Michael F. Weaver declare no conflicts of interest. Kristine Whalen and Shruti Bandewar are employees of Bamboo Health. SS has received grants/research support from NIH and SAMHSA, Compass Pathways, LivaNova, received speaking honoraria from Global Medical Education, honoraria from British Medical Journal Publishing Group, and owns shares at Flow Med Tech (received research support from outside the submitted work). All other authors have no conflicting interests to disclose.

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