SAMHSA
Substance Abuse and Mental Health Services Administration

Substance Abuse and Mental Health Services Administration

Listening Session:

Use of High Dose Buprenorphine for the Treatment of Opioid Use Disorder

December 11, 2023

1:00 – 5:00 p.m. EST

MEETING SUMMARY

NOTE: The listening session report represents the opinions and recommendations of the participants and does not reflect an official position, policy, or set of recommendations from any federal or state agency.

OVERVIEW

On December 11, 2023, the Substance Abuse and Mental Health Services Administration (SAMHSA), in partnership with the U.S. Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA), hosted a listening session to discuss the medical need, emerging data, and barriers to accessing higher doses of buprenorphine in the context of high potency synthetic opioid (HPSO) exposure. The meeting focused on gathering quantitative and qualitative data on the need for, effectiveness of, and safety of "high dose" buprenorphine (defined as ≥ 24 mg of buprenorphine per day) in the treatment of opioid use disorders (OUD), to inform federal guidelines and policies. This document summarizes the recommendations and opinions of the participants and does not reflect an official position, policy, or set of recommendations from any federal or state agency.

More than 300 individuals registered for the virtual listening session, with over 200 attending the Zoom meeting. Participants represented a wide range of disciplines related to OUD services, including providers, academics, researchers, and those with lived experience. The meeting was structured around four panels:

- Setting the Context: The Current Landscape, Guidance, and Use of High Dose Buprenorphine
- New and Original Data on the Use of High Dose Buprenorphine
- Qualitative Data and Implementation Insights
- Identifying Barriers to Accessing High Dose Buprenorphine and Potential Solutions

Key Takeaways from Meeting Participants

I. Growing Body of Evidence: Participants agreed on the role of high-dose buprenorphine (24 mg+) in treating OUD, in the era of HPSO use, with minimal safety concerns. The challenge lies in using this evidence effectively to inform policies and programs.

II. Clinical Considerations and Studies: Studies indicate improved retention in treatment without adverse events associated with higher doses of buprenorphine. Doses ranging from 24-32 mg/day of sublingual buprenorphine or extended-release buprenorphine (300 mg/SC) are found to be effective at suppressing withdrawal symptoms and promoting retention in care, especially for individuals exposed to high potency synthetic opioids.

III. Pharmacological Rationale: Higher buprenorphine concentrations ensure sufficient minimum concentrations at the drug's trough level, which helps to suppress more of the symptoms of OUD, not just withdrawal, among those who use HPSOs.

IV. Empirical Data: Observational studies indicate better treatment retention and reduced illicit opioid use among individuals prescribed higher doses of buprenorphine over extended periods.

V. The Experience of Those With Lived/Living Experience: Tailoring treatment to individual need improves outcomes, but those with lived experience revealed real world challenges, such as limited access to different formulations of buprenorphine, difficulty finding practitioners willing to treat OUD, and stigma.

VI. Reduced Mortality: Increased retention and reduced mortality rates are observed among patients on higher doses, indicating the necessity of individualized dosing based on treatment needs.

Potential Action Items Recommended by Meeting Participants

I. Promote Education on High Dose Prescribing: Promote education among healthcare providers regarding the acceptability and benefits of using high dose buprenorphine, along with efforts to bring evidence-based standards of individualized treatment dosing, including high-dose buprenorphine, to scale. Provide a focus on when and under which circumstances to initiate buprenorphine. This follows thorough patient assessment and considerations of substance use history, tolerance, and other factors.

II. Research and Data: Expedite and expand high quality research and public dissemination of data on high-dose buprenorphine to inform federal action and public perception.

III. Enhance Access, Particularly in Rural Areas: Ensure ready access to medication across clinical environments, especially in rural settings, to prevent delays that can contribute to return to opioid use. This includes speaking with insurance agencies, dispensing pharmacies, pharmacists and pharmacy wholesalers, distributors, Drug Enforcement Administration (DEA) field agents, and other stakeholders. This will also involve reviewing current prior-authorization requirements, as well as disparity in access to buprenorphine across geographic settings.

IV. Pharmacy Dispensing and Distributor Challenges: Address the challenges faced by pharmacies and distributors, such as concern around DEA oversight and "suspicious order" systems, to facilitate dispensing of buprenorphine. In cases where pharmacies have proven success, seek to understand facilitators. Find key stakeholders who can identify current barriers and impact positive solutions. It is also imperative to ensure access to different formulations and brands of buprenorphine to facilitate dispensing and to promote consumer choice. This also requires work to understand why pharmacies stock limited quantities/formulations/brands.

V. Insurance and Payor Policy Reforms: Work on payor policy to accommodate high dose buprenorphine, ensuring that patient costs are reasonable and that payors understand the need for higher doses in certain cases. Address issues like prior authorization, dose/quantity limits, and the rigid approach of payors to current coverage of buprenorphine. Include the Centers for Medicare & Medicaid Services (CMS) and other stakeholders to better understand barriers and facilitators.

WELCOME

Dr. Yngvild K. Olsen, Director, Center for Substance Abuse Treatment, SAMHSA

Dr. Olsen briefly welcomed the participants, outlined the structure of the meeting, and presented a brief overview of the objectives. Dr. Olsen provided an overview of the current overdose crisis faced by the U.S. and highlighted that close to 70% of the 109,000 deaths reported in the 12-month period ending in December 2022 involved HPSO or illicitly manufactured fentanyl. Although there are effective treatments, particularly medications for OUD, including buprenorphine and methadone, there remain many access issues. The Centers for Disease Control and Prevention (CDC), FDA, NIDA, CMS, and other federal agencies are working to support the expansion of access through guidance, technical assistance, training, and research. Medical practice has evolved to respond to the new challenge fentanyl brings, and federal agencies need to better understand that evolution, as well as emerging data, to better support these efforts.

Dr. Olsen also highlighted an Office of Inspector General report that revealed in 2021, buprenorphine 24 mg/day was often prescribed to Medicare beneficiaries.[1] The report also suggested that the risk of misuse and diversion was low among Medicare Part D patients.

The focus of the meeting was to gather quantitative and qualitative data on the effectiveness and safety of high dose buprenorphine (≥24 mg/day). Key framing questions for the meeting included:

1) What current quantitative data exist on the use of high-dose buprenorphine, especially regarding effectiveness and safety in the context of fentanyl?
2) What qualitative data insights can be gathered from the real-world experiences with higher-dose buprenorphine?
3) What are the primary barriers to accessing higher-dose buprenorphine and how these might be overcome?
4) What knowledge gaps persist regarding high dose buprenorphine and what areas require further research?

PANEL – Setting the Context: The Current Landscape, Guidance, and Use of High Dose Buprenorphine

Moderator: *Marta Sokolowska, Ph.D., Deputy Center Director, Substance Use and Behavioral Health, Center for Drug Evaluation and Research (CDER), FDA*

Panelists: *Kelly Ramsey, MD, DFASAM, board-certified internal medicine and addiction medicine physician; Mark Greenwald, MD, Associate Chair, Psychiatry, Wayne State University Medical School; Adam Gordon, MD, Professor of Medicine and Psychiatry, University of Utah School of Medicine and the Section Chief of Addiction Medicine, Veterans Administration Salt Lake City Health Care System; Paxton Bach, Clinical Assistant Professor, Department of Medicine, University of British Columbia, Canada*

[1] Office of Inspector General, U.S. Department of Health and Human Services (2023). Data Brief: The Risk of Misuse and Diversion of Buprenorphine for Opioid Use Disorder Appears to Be Low in Medicare Part D. OEI-02-22-00160. Washington, D.C.

Dr. Ramsey's presentation focused on the *American Society of Addiction Medicine (ASAM) Clinical Considerations: Buprenorphine Treatment of Opioid Use Disorder for Individuals Using High-Potency Synthetic Opioids*.[2] This paper is based on expert consensus and includes some evidence but recognizes that there may not yet be a substantial body of evidence to address the need for high-dose buprenorphine. In short, a clinical consideration is less rigorous than a clinical practice guideline or a clinical consensus document. The *ASAM National Practice Guideline* elucidates that a dose of 24 mg/day is based on limited evidence for the relative efficacy of higher doses, but there now exists high-quality studies that show improved retention in treatment without adverse events associated with higher doses.

The ASAM clinical considerations document arose from a request that the ASAM Board of Directors support a petition to the FDA to consider changing buprenorphine FDA labeling to support >16 mg/day as an effective treatment dose, particularly in the age of fentanyl exposure or use.[3] Dr. Ramsey presented an overview of one of the six key questions in the report, which focuses on what buprenorphine dosing and/or dosing strategies can be considered during stabilization and long-term treatment. Evidence suggests that doses of 24-32 mg/day of sublingual buprenorphine or extended-release buprenorphine at 300 mg may be most effective in stabilizing individuals who primarily use HPSO. Observational studies also have found reduced opioid misuse for individuals who are taking buprenorphine 24-56 mg/day over 30 months and report that individuals treated with 30-32 mg of sublingual buprenorphine were more likely to be retained in treatment at 24 weeks.[2] In addition to higher dosages (i.e., >24 mg per day), increased dosing frequency is often needed during pregnancy (i.e., between two and four times daily) to avoid withdrawal symptoms.[2]

The final clinical considerations that emerged from the report include:

- Some patients with high opioid tolerance may require buprenorphine doses >24 mg per day during the stabilization phase of treatment.
- Physiological changes during pregnancy alter buprenorphine metabolism, necessitating an adjusted buprenorphine dose and increased dosing frequency.
- Dose and frequency adjustments, psychosocial supports, and a higher level of care should be considered if individuals are unable to stabilize on < 24 mg/day buprenorphine.
- Reassessment of higher (>24 mg/day) doses should be considered once patients enter long-term treatment without ongoing use of opioids.

Key Takeaways

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[2] Weimer, M. B., Herring, A. A., Kawasaki, S. S., Meyer, M., Kleykamp, B. A., & Ramsey, K. S. (2023). ASAM Clinical Considerations: Buprenorphine Treatment of Opioid Use Disorder for Individuals Using High-potency Synthetic Opioids. Journal of addiction medicine, 17(6), 632–639. https://doi.org/10.1097/ADM.0000000000001202

[3] An example of FDA labeling language for Suboxone can be found here: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/022410s052lbl.pdf. It states "After treatment induction and stabilization, the maintenance dose of SUBOXONE sublingual film is generally in the range of 4 mg/1 mg buprenorphine/naloxone to 24 mg/6 mg buprenorphine/naloxone per day depending on the individual patient and clinical response. The recommended target dosage of SUBOXONE sublingual film during maintenance is 16 mg/4 mg buprenorphine/naloxone/day as a single daily dose. Dosages higher than 24 mg/6 mg daily have not been demonstrated to provide a clinical advantage." The petition requested, in part, that the FDA require changes to the labeling for buprenorphine transmucosal products to indicate that doses >16 mg/day have a clinical advantage compared to doses <16 mg/day.

- ✓ Buprenorphine dose and dosing frequency must be individualized based on patients' treatment needs.
- ✓ It would be wise for federal agencies to review all the evidence and appropriately revise labels, guidance, and policies, considering the increased mortality related to HPSO.

Dr. Greenwald reported on the pharmacologic rationale for high dose buprenorphine. It is well-established that, as the dose of buprenorphine is increased into the 16-32 mg/day range, there is less inter-individual variability in response. Buprenorphine, as a partial agonist, has a wider therapeutic margin than methadone, so the effective and safe region provides quite a bit of latitude. But, in circumstances where buprenorphine is discontinued, mu-receptor occupancy decreases two- to-fourfold within 24 hours. The only way to circumvent this, without divided daily dosing, is through extended-release formulations, which can achieve consistent plasma and brain concentrations of the medication.

Dr. Greenwald pointed out the dangers of focusing on the peaks rather than the troughs of buprenorphine concentration. To this end, Dr. Greenwald indicated that it is important to think about worst-case scenarios or trough levels – focusing on C_{min} concentrations, rather than C_{max} – from the standpoint of harm reduction. A number of studies have established that there are mu-receptor occupancy requirements associated with differing therapeutic thresholds in people with moderate to severe OUD.[4] Therefore, for opioid withdrawal suppression, about half of mu-opioid receptors need to be occupied but, because reactions differ among individuals, there is variability around this estimate. It also has been found that craving is actually more variable and less reliably related to mu-receptor occupancy and plasma concentrations in controlled studies.[4,6]

To block drug-liking, approximately half of an individual's mu receptors need to be occupied, but the range is wider (10-75%) because of individual variability. To block opioid seeking, about 85% of mu-receptors need to be occupied to suppress drug-appetitive motivation (drug-seeking behavior). Finally, a very large portion of mu-receptors (about 90%) must be occupied to block the respiratory depressant effects of "on-top" opioid use. For sufficient treatment of OUD and to avoid underdosing, all of the therapeutic targets need to be met, not only suppressing craving and withdrawal, but also blocking drug-seeking behavior. Higher buprenorphine plasma concentrations achieve this.

Dr. Greenwald shared the results of studies to illustrate this point, including a recent simulation study that found that higher buprenorphine concentrations can reduce fentanyl-induced respiratory depression.[5] He also provided an overview of a study recently published in the *Harm Reduction Journal* that compared higher versus lower long-term doses among people with OUD who inject drugs, showing that higher plasma concentrations of buprenorphine resulted in longer treatment retention and a significantly higher portion of those attaining abstinence up to 24 weeks.[6]

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[4] Chambers LC, Hallowell BD, Zullo AR, et al. Buprenorphine Dose and Time to Discontinuation Among Patients With Opioid Use Disorder in the Era of Fentanyl. JAMA Netw Open. 2023;6(9):e2334540. doi:10.1001/jamanetworkopen.2023.34540

[5] Olofsen E, Algera MH, Moss L, Dobbins RL, Groeneveld GJ, van Velzen M, Niesters M, Dahan A, Laffont CM. Modeling buprenorphine reduction of fentanyl-induced respiratory depression. JCI Insight. 2022 May 9;7(9):e156973. doi: 10.1172/jci.insight.156973. PMID: 35316224; PMCID: PMC9090248.

[6] Greenwald, M. K., Wiest, K. L., Haight, B. R., Laffont, C. M., & Zhao, Y. (2023). Examining the benefit of a higher maintenance dose of extended-release buprenorphine in opioid-injecting participants treated for opioid use disorder. Harm reduction journal, 20(1), 173. https://doi.org/10.1186/s12954-023-00906-7

Key Takeaways

- ✓ Higher plasma buprenorphine concentrations offer important pharmacologic and therapeutic benefits, and concentration is preferred over the dose of buprenorphine. Concentration is a pivotal determinant of therapeutic efficacy. Higher buprenorphine concentrations can safely produce biological leverage for behavior change and harm reduction.
- ✓ There is a need to focus on worst-case scenarios by ensuring there are sufficient minimum concentrations at the drug's trough level, and not focus so heavily on peak concentrations, which overestimate therapeutic benefit.
- ✓ Sublingual kinetics involve significant drops in concentration across the 24-hour cycle leading to periods when therapeutic efficacy is sub-optimal. Divided sublingual dosing is a compromise but also increases patient burden. Extended-release formulations can ensure more consistent, higher concentrations, which some patients may need for maximum benefit.
- ✓ While clinical judgement is still needed, higher concentrations offer more certain benefits for a higher proportion of patients to address all major aspects of OUD.

Dr. Gordon began his presentation with a quick overview of the Department of Veterans Affairs (VA), which is the largest addiction treatment system in the United States. There has been a major push by the VA to address opioid use disorders within the confines of primary care, mental health, and even pain clinics. They are seeing increased use of buprenorphine and have been working to decrease barriers and increase access to quality care. As a result of the recommendations of the joint VA/Department of Defense Guidelines for Pain - that buprenorphine may be the preferred agent for chronic pain among patients on chronic prescription opioid pain medication - the VA is seeing an increasing number of people transitioning to buprenorphine for pain control.

The VA has done very well in improving access to medications to treat OUD (MOUD) –about 48% of those with OUD are treated with MOUD, with approximately 20,000 patients on buprenorphine. Between 2006 and 2018 there was a dramatic increase in the amount of care that included buprenorphine, and increasingly the VA is helping people stay retained in buprenorphine treatment for several years. Retention rates at six months exceed 70%. Traditionally, most people receive 28-30 days of the medication, a lot of doses of which are high and are provided long-term. As noted in a recent study published in *Drug and Alcohol Dependence*, the highest daily dose in the VA, between 2006 and 2019, was 32 mg/day. The most common daily dose is 16 mg/day. The percentage of people on doses higher than 24 mg/day increased between 2006 and 2019, with about 8% of people on higher doses in 2019.[7]

[7] Gordon, A. J., Saxon, A. J., Kertesz, S., Wyse, J. J., Manhapra, A., Lin, L. A., Chen, W., Hansen, J., Pinnell, D., Huynh, T., Baylis, J. D., Cunningham, F. E., Ghitza, U. E., Bart, G., Yu, H., & Sauer, B. C. (2023). Buprenorphine use and courses of care for opioid use disorder treatment within the Veterans Health Administration. Drug and alcohol dependence, 248, 109902. https://doi.org/10.1016/j.drugalcdep.2023.109902

Key Takeaways

- ✓ Within the VA healthcare system, the percentage of patients prescribed buprenorphine doses higher than 24 mg has been increasing since 2013. This has been facilitated by recent changes to joint VA/Department of Defense Guidelines for Pain.
- ✓ A proliferation of extended-release buprenorphine preparations has been seen. Many patients are receiving both these and sublingual formulations. The VA expects more patients will be receiving higher doses of extended-release formulations.
- ✓ There has been an increase in high dose buprenorphine initiation in the Emergency Department (ED), particularly in people with fentanyl exposure.
- ✓ The VA is reducing administrative barriers to increase access to buprenorphine. Since 2018 there has been no criterion for use, so clinicians can prescribe buprenorphine in a patient-centered manner. However, VA clinicians are held to state licensure requirements. There are five states that currently have restrictions, complicating prescription of buprenorphine doses in excess of 16 mg / day. This has caused some problems in those VA settings where providers are part of those state systems.

Dr. Bach's presentation focused on buprenorphine dosing in Canada. While Canada's health system is different from that of the U.S., each province has its own regulatory environment and recommendations. In general, however, Canada offers more flexibility to prescribe buprenorphine, and there is no prior authorization requirement for insurance. In British Columbia, about 25,000 people are on some form of opioid treatment, and methadone is the most common form of MOUD. The monograph for buprenorphine-naloxone in Canada states that a single daily dose should not exceed 24 mg. However, clinical guidelines in various provinces offer different guidance, with softer language often used, allowing for some flexibility. Clinical guidelines in British Columbia and Ontario, for instance, do suggest that doses up to 32 mg can be considered. A recent study shows that there are substantial increases in the percentage of patients in British Columbia who are being prescribed ≥24 mg/day as a long-term dose over the past 8 years (1% in 2014 to 8% in 2021). This trend is expected to continue.

Dr. Bach discussed an observational study out of Ontario that looked at trends in prescribing extended-release buprenorphine in 2020-2022; almost 20% of individuals who received 3 doses were continued on the 300 mg dose.[8] Twenty-nine percent of those who were reduced to the 100 mg dose ended up increasing back to the 300 mg dose at some point during their treatment course.

Key Takeaways

- ✓ When comparing clinical guidelines, there are no significant differences in the use of high dose buprenorphine between Canada and the U.S., but prescribing higher doses is becoming an increasingly common practice in Canada.

[8] Iacono, A., Wang, T., Tadrous, M., Campbell, T., Kolla, G., Leece, P., Sproule, B., Kleinman, R. A., Besharah, J., Munro, C., Doolittle, M., & Gomes, T. (2024). Characteristics, treatment patterns and retention with extended-release subcutaneous buprenorphine for opioid use disorder: A population-based cohort study in Ontario, Canada. Drug and alcohol dependence, 254, 111032. https://doi.org/10.1016/j.drugalcdep.2023.111032

- ✓ Data do not show significant safety concerns of higher buprenorphine doses. One 2020 paper looking at toxicology of overdose deaths in British Columbia between 2015-2017 showed that of almost 2,000 overdose deaths fewer than five deaths involved buprenorphine.[9]
- ✓ Canadian data regarding improved outcomes at higher (>24 mg) sublingual doses are lacking, but comparisons by serum levels obtained with buprenorphine extended-release formulation suggest that, for at least some, higher doses are very much preferred in practice.
- ✓ A key research gap is identifying best practices in the current fentanyl era.

PANEL – New and Original Data on the Use of High Dose Buprenorphine

Moderator: *Wilson Compton, MD, Deputy Director, National Institute on Drug Abuse, NIH*

Panelists: *Kun Zhang, PhD, Division of Overdose Prevention, National Center for Injury Prevention and Control, CDC; Bradley D. Stein, MD, PhD, Director, Opioid Policy, Tools, and Information Center (OPTIC); Senior Physician Policy Researcher, RAND Corporation; Michelle Lofwall, MD, Professor, Departments of Behavioral Science and Psychiatry, University of Kentucky*

Dr. Zhang's presentation focused on the association between buprenorphine initiation doses and retention in treatment for OUD among patients in the U.S., between 2020 and 2022. The study used a large national, all-payor prescription database to examine the relationship between the buprenorphine initiation dose and treatment retention. Before presenting findings, Dr. Zhang reviewed the study design and the IQVIA pharmacy claims database, which includes 93% of retail pharmacy prescriptions dispensed yearly in the U.S. and all payment types, including cash. The database also identifies all buprenorphine prescriptions provided for the treatment of OUD. The cohort included individuals who initiated buprenorphine treatment between January 1, 2020, and September 30, 2021. In addition, individuals received at least 7 consecutive days of medication for initiation, plus stabilization. Treatment retention was defined as coverage without a gap of over 60 days.

The cohort consisted of approximately 734,000 patients, 56.5% of whom were male and 43.5% of whom were female. The median age was 38 years and mean treatment duration was approximately 9 months, while the median duration of treatment was approximately 4 months. The most common initiation daily dose for the cohort was 13-16 mg/day (40% of the sample), followed by 30% receiving 1-8 mg/day, 16% receiving 17-24 mg/day, 12% receiving 9-12 mg/day, and only 2% receiving >24 mg/day. The study found that groups with shorter retention had more patients on 1-8 mg/day, while groups with longer retention had more patients on 17-24 mg/day. Dr. Zhang cautioned that the longer retention among patients on higher doses also could be due to the fact that the longer someone stays in treatment, the higher likelihood that the dosage will be increased. In this way, observational data does not speak to dynamic changes in treatment during or after buprenorphine initiation. The results also showed that the groups with longer retention tended to have more patients on the maximum 7-day moving average daily dose of 17-24 and >24 mg. In short, the longer a patient is in treatment, the more likely their daily dose is increased or that the individual receives concurrent buprenorphine prescriptions.

[9] Health Canada, Public Health Agency of Canada, and U.S. Department of Health and Human Services. Canada-U.S. Joint White Paper: Substance Use and Harms During COVID-19 and Approaches to Federal Surveillance and Response. Ottawa, Ontario; Washington, D.C.: U.S. Department of Health and Human Services, Office of the Assistant Secretary for Health, 2022.

Dr. Zhang also discussed treatment retention by buprenorphine dose. This analysis confirms that higher daily doses result in better treatment retention. Among the 1-8 mg/day patients, 50% were no longer in treatment at ninety days; whereas, among the highest dose group (17-24 mg/day and >24 mg/day) the 50% mark was not reached until 160 days. There were limitations to the study, including the fact that the data were from retail pharmacies only, the data did not include extended-release buprenorphine prescriptions or other forms of treatment, and relatively few patients were prescribed >24mg.

Key Takeaways

- ✓ A daily buprenorphine dose higher than 8 mg/day is associated with a higher likelihood of longer retention in care. The dose-response relationship holds when adjusting for additional patient and treatment characteristics.
- ✓ The highest daily dose categories (17-24 mg & >24 mg) are associated with the highest likelihood (HR+0.79, HR+0.78) of remaining in care; however, the model did not find that these two data points significantly differed from each other.
- ✓ Lack of insurance is still a potential barrier for better retention in treatment, as the adjusted model showed cash-pay had the highest likelihood (HR-1.38) for short retention.

Dr. Stein's presentation focused on better understanding the landscape of high dose buprenorphine prescribing through exploring two analytic scenarios: patterns of high dose buprenorphine prescribing and the relationship between high dose buprenorphine prescribing and outcomes such as health care utilization. The first analysis used the IQVIA pharmacy claims database to identify high dose buprenorphine prescriptions. The analysis sought to explore the overall rate of high dose prescriptions and variations by patient, prescriber, and county characteristics and the extent to which high dose buprenorphine prescribing was driven by a small number of clinicians. The second analysis used 2016-2020 OPTUM claims data, primarily commercially insured individuals, and Medicare enrollees. In that analysis, analysts created different buprenorphine dose tiers and examined the relationship between dose and outcome, including ED visits and in-patient stays.

The first analysis found that only 2% of the total buprenorphine prescriptions were high dose (>24 mg), and 26% of all buprenorphine prescribers wrote at least one high dose prescription, with 85% of high dose prescriptions being written by 10% of practitioners. When looking at payment sources for the high dose versus non-high dose prescriptions, over a quarter of the high dose prescriptions were cash pay or self-pay at the pharmacy, compared to only 7% of the non-high dose prescriptions. In addition, the analysis showed that 4% of active prescribers wrote 83% of all high dose prescriptions. These clinicians tended to be in more urban communities and in counties where there are a greater than median percentage of residents of color and fatal overdoses. The majority of clinicians responsible for these high dose prescriptions were primary care practitioners, followed by psychiatrists and pain specialists.

The second analysis used 2016-2021 OPTUM data to identify individuals with new buprenorphine treatment episodes. Individuals were assigned to a dose tier based on the highest dose they reached for 2 or more weeks. Relatively few individuals reached the high dose buprenorphine tier (>24 mg), with most individuals in the 16-24 mg, 8-16 mg, and 1-8 mg ranges. It is important to remember when looking at the data that it is a relatively small number at the high dose tier. The analysis controlled for multiple factors, including age, gender, race/ethnicity, date of initiation, pre-existing diagnoses, visits to

emergency departments or inpatient treatment, etc. The median treatment duration for all tiers was 270 days. The analysis showed that individuals in the >24 mg tier had a longer period before seeking ED/in-patient treatment. It is also interesting that, although little difference between tiers was seen early on, the differences started increasing at about six months after reaching that tier and increased even more at one year out. Additionally, individuals with pre-existing OUD and mental health diagnoses were significantly more likely to require ED or in-patient care sooner.

Key Takeaways

- ✓ There is a tendency for high dose buprenorphine prescriptions to be paid for by cash or self-pay as opposed to other forms of insurance.
- ✓ A relatively small number of prescribing clinicians are the source of high dose prescriptions.
- ✓ Individuals with pre-existing OUD and mental health diagnoses were significantly more likely to require ED or in-patient care sooner than those without co-occurring conditions. Even controlling for these factors, individuals receiving stable buprenorphine dosages above 24 mg had a longer period after being stabilized at the highest dose before receiving inpatient care or ED services compared to individuals stabilized at lower dosage tiers.

Dr. Lofwall presented on the first 30-day dose of buprenorphine for OUD treatment and the subsequent association with mortality over the year. She began her presentation with some background, including the observation that some patients are limited to sublingual maximum doses of 16-24 mg/day due to payor limits and/or state policies/regulations. It is also notable that the long-acting injectable buprenorphine products produce higher maximum serum concentrations after a single dose than daily sublingual buprenorphine; however, there is limited information available about the association between the sublingual dose in the early stages of treatment and subsequent risk of death. The study Dr. Lofwall reported on used the Kentucky All Schedule Prescription Reporting program and Kentucky death certificate records to focus on the association between the average daily dose of sublingual buprenorphine for OUD in the first 30 days of treatment and incidence of death at one-year follow-up.[10] Individuals were classified as urban or rural based on zip code. The cohort included patients initiating sublingual buprenorphine between January 2017, and November 2019, and dose was categorized into three groups: less than/equal to 8 mg/day, greater than 8 mg to 16 mg/day, and greater than 16 mg/day. They followed just under 50,000 patients for 365 days after the first 30-days. The breakdown of the first 30-day mean sublingual buprenorphine dose showed: 21.1% at ≤8 mg/day, 49.2 % at >8 mg to ≤16 mg/day, and 29.7% at >16 mg/day (including 1.9% at >24 mg). At the 365 days follow-up, 686 patients had died, including 33.1% opioid-involved overdose deaths and 66.9% from other causes. There were 131 patients that had switched to long-acting injectable buprenorphine doses. A higher dose of buprenorphine during the first 30 days was associated with lower risk of mortality, with doses greater than 16 mg/day having the lowest risk.

[10] Lei, F., Lofwall, M. R., McAninch, J., Adatorwovor, R., Slade, E., Freeman, P. R., Moga, D. C., Dasgupta, N., Walsh, S. L., Vickers-Smith, R., & Slavova, S. (2024). Higher First 30-Day Dose of Buprenorphine for Opioid Use Disorder Treatment Is Associated With Decreased Mortality. Journal of addiction medicine, 10.1097/ADM.0000000000001300. Advance online publication. https://doi.org/10.1097/ADM.0000000000001300

Key Takeaways

- ✓ People with opioid use disorder have significant medical/psychiatric comorbidities, so treating those conditions may also help prevent mortality. Not all mortality is due to opioid-involved overdose.
- ✓ Receiving ≤8 mg/day of buprenorphine was associated with an elevated risk of mortality versus those receiving ≥16 mg/day.
- ✓ FDA labeling indicates 16 mg/day as the recommended target dose, and sometimes regulators and state medical boards interpret this as a maximum dose. This complicates prescribing greater than 16 mg/day in some cases.
- ✓ The findings suggest potential benefits of a higher first 30-day transmucosal target dose in reducing mortality using real-world data. This study was limited by its observational design and focus on a single state.
- ✓ Since few patients were receiving >24 mg/day, there is a question about whether there would be further mortality reduction with higher doses or if a plateau effect would be observed.
- ✓ There is a need to prioritize research to better understand the dose response curves and clinically relevant public health outcomes.

General Discussion

Ricardo Ruis asked about use of buprenorphine after an overdose. Dr. Lofwall responded that there have been case reports of people giving buprenorphine and naloxone sublingual in the field, particularly after a heroin overdose. These reports have been published and demonstrated efficacy. Dr. Andrew Herring cited a case study by Dr. Zimani with rodents who received methadone after overdose reversal. Dr. Nguemeni shared that naloxone's relatively short half-life, compared to many opioids, requires many overdose survivors to be hospitalized on IV naloxone to prevent a return to respiratory depression. In such cases, buprenorphine may be helpful because of its longer acting properties. He also suggested that, barriers aside, buprenorphine buccal film is faster acting and would be best versus a sublingual formulation of buprenorphine. Dr. Compton added that this touches on some of the clinical implications of Dr. Stein's work on hospitalization, or lack of hospitalization, following higher dose buprenorphine. It was noted that this is observational data.

James Berry directed a question to Dr. Greenwald about trough levels of buprenorphine that may not reflect receptor saturation in the brain. To this end, trough levels may not be as important as average levels or peak levels of the medication. Dr. Greenwald responded that it is known that there is a recirculation from adipose tissue stores into the central compartment that will prolong the agonist actions of buprenorphine. However, that potentially will delay the inevitable, since the rate of egress from the brain is slower. Since we live in a world of HPSOs, peak plasma or peak brain concentration is less important than trough levels of buprenorphine.

Adaku Ofoegbu added that buprenorphine has a high binding affinity for the mu-opioid receptor. Therefore, if buprenorphine and fentanyl are competing for a receptor, it is most likely that buprenorphine is going to kick fentanyl off the receptor and make it difficult for fentanyl to bind. This is why it is important to have someone on buprenorphine. In her work with Dr. Chapman, she has seen that

patients want to be stabilized and need higher doses because often they are ultrarapid metabolizers for CYP3A4, the major metabolizing enzyme for buprenorphine. When patients are able to receive a stable dose of buprenorphine, they are less likely to have other substances in their urine.

PANEL – Qualitative Data and Implementation Insights

Moderator: *Yngvild K. Olsen, MD, Director, Center for Substance Abuse Treatment, SAMHSA*

Panelists: *Edward Chapman, MD, Washington, DC; Melissa Weimer, DO, MCR, Associate Professor, Yale University, and internal medicine physician and addiction medicine specialist; Gail D'Onofrio, MD, Chief of Emergency Services, Yale New Haven Hospital & Addiction Specialist; Mr. Larry Bing, Leadership Council for Healthy Communities, and Mr. Kevin Hargrove, patients of Dr. Chapman; Jade Waits, peer recovery specialist, Boulder Care and in recovery; and Tyler Mischley, Harm Reduction Michigan and currently taking buprenorphine.*

Dr. Olsen introduced the session, which focused largely on those who are on the ground, prescribing buprenorphine in a variety of settings, and on those who are prescribed buprenorphine as part of their treatment. Dr. Olsen started the discussion by asking how frequently the practitioners on the panel are prescribing or recommending high dose buprenorphine and if they have noticed any trends or patterns in their practice.

Dr. D'Onofrio stated that in the ED they always start with at least 8 mg of buprenorphine and then progress, as per patient need, up to what is required to suppress withdrawal symptoms – generally around 8-16 mg at initiation. They also offer "induction on your own" for patients not in withdrawal at the time they appear in the ED. In those cases, they give patients instructions and tell them to start at 8 mg and go up to 16 or 24 mg if needed. They also explain why the patients might want to use a higher dose. They always give at least 16 mg for the days until patients can find ongoing care. In their state, they can give out five days of medication, which allows patients to start treatment as they await an appointment with their care provider. Dr. D'Onofrio's team started thinking about higher doses of buprenorphine based on Dr. Herring's research that found often patients couldn't get the medication through their pharmacy. Dr. Herring found that if he gave 24 mg for initiation, the patient could wait up to three days before seeing a practitioner. The team has begun to do that; for instance, if someone is incarcerated for the weekend they will give 24 mg. They have published retrospectively on patients who have received high doses (≥24 mg) and found it was very safe. They are hoping to study this more and have a grant from the NIDA CTN to study inductions up to 24 mg, with a control of 8 mg, in a double blind trial.

Dr. Weimer reported that because they have a lot of options in the hospital setting, they treat patients according to their individual needs and tolerance. When considering buprenorphine, individuals provided with the high dose initiation approaches are typically those who have a shorter length of stay and need to be stabilized quickly. For those individuals, because there is a concern for precipitated withdrawal, many are stabilized with full agonist opioids for a period of 24 to 48 hours, then are stopped and allowed some amount of withdrawal, before being given the higher doses starting at 16-24 mg as an initial dose. Sometimes they will follow that the same day with injectable extended-release buprenorphine. Again, each patient is different, but among patients who are using HPSO, they have not had any patients who have stabilized on less than 16 mg, and most need a higher dose. Use of other substances can make the transition more challenging.

Landis Lum asked Dr. Weimer how many doses of sublingual buprenorphine-naloxone or buprenorphine she would give patients before prescribing 300 mg extended-release buprenorphine. Dr. Weimer responded that they give 24 mg sublingual buprenorphine, making sure patients are tolerating it well, waiting about two hours, and then following it with the injectable formulation. (i.e., giving a "loading" dose). Patients have responded well to this protocol. They are fortunate to have a warm handoff with community partners, and they provide a lot of education to their patients about the first month, even after getting the injectable buprenorphine, because they find many of them need concomitant sublingual buprenorphine. They sometimes send them with additional sublingual buprenorphine. The hospital has been financially supporting use of the injectable buprenorphine formulation so they can avoid billing the patient's insurance. That is key because some people get the buprenorphine injection and start having withdrawal during that first month because the buprenorphine level isn't yet at a steady state. Consequently, they say it isn't working. They need to be told that it is working, but it takes time, and patients should be educated about when to get their next injection. A lot of education is necessary to reassure patients.

Dr. Nguemeni asked if in the event patients are going to experience withdrawal during the initial days, would she consider giving them supplemental sublingual buprenorphine? Dr. Weimer responded that they would give additional sublingual buprenorphine of 8 mg. She would not use buccal buprenorphine since the dose is not sufficient to treat OUD. They use buccal buprenorphine for their low dose initiations, but that would be the only case. Dr. Lum added that it sounds like they would need additional sublingual buprenorphine even after the 300 mg of extended-release buprenorphine if there is precipitated withdrawal. Dr. Olsen added that the idea of "front loading" might be interesting to study. Dr. Weimer emphasized that they are not always giving the injectable. Dr. D'Onofrio added that they give 7-day subcutaneous buprenorphine under a protocol and have given it to over 850 patients across 29 sites nationwide. They do not use any sublingual buprenorphine lead-in and have had only 4 or 5 precipitated withdrawal events. This is less than 1% of the study population. They don't need to do the sublingual buprenorphine lead-in and, in fact, it could be harmful because of the rapid upslope. The advantage of the 7-day injectable buprenorphine is that it gradually increases in the bloodstream and enables them to use it at very low rates. It is a great opportunity for individuals to initiate and then receive extended-release buprenorphine.

Dr. Chapman reported that Washington DC is an outlier, with 46% of their population being African American. However, 85% of overdose deaths are among African Americans, with 20% from fentanyl in 2015 to 98% as of today. Heroin use today is rarely seen. In the past six weeks, he also has had 26 patients test positive for xylazine in addition to fentanyl. About two-thirds of patients who come into Dr. Chapman's office on fentanyl have tried buprenorphine that was not prescribed to them. Dr. Olsen pointed out that this is another example of the differences and uniqueness of locations and populations. This affects what can be done in hospital settings versus EDs, and outpatient settings.

Dr. Herring highlighted the importance of trying to maximize the benefits of any one health care interaction, whether in the ED, hospital, EMS, or clinic. That is where the loading concept comes in, basically never taking any potential interaction for granted and using that moment to rapidly get patients to treatment to decrease opioid cravings.

Mr. Bing shared that most of his clients are senior citizens and homeless. He also mentioned that his clients are given generic buprenorphine-naloxone, which he believes does not work well among those

who are exposed to fentanyl compared to proprietary preparations of buprenorphine-naloxone. He shared that he has had clients who were switched to generic buprenorphine-naloxone and returned to substance use. The Department of Behavioral Health has been trying to get pharmacies to dispense the original buprenorphine-naloxone. Most of his clients have been using opioids long-term and need high doses of buprenorphine to suppress craving. He also emphasized that when administering the medication for addiction treatment protocol they have to take into consideration mental health, homelessness, and other conditions. The need for prior authorization is also an issue. In his opinion, buprenorphine-naloxone will not keep someone from overdosing; rather, it keeps the person feeling well. He also said that he supports higher doses of buprenorphine because when clients leave and are stressed about where they will sleep, etc., the higher dose helps calm them. He also agreed with Dr. Chapman that he does not see heroin use anymore, but instead fentanyl that is sometimes mixed with other substances.

Dr. Olsen emphasized the insurance issues Mr. Bing brought up, whether prior authorization or the use of generic medications, as well as the social determinants of health that influence care, as topics for discussion.

Mr. Hargrove responded to Dr. Herring's discussion of high dose buprenorphine and possible detriment to patients. He discussed Dr. Chapman's procedure when treating patients, which begins with a complete physical examination. He also mentioned the pain medications that he was given for various injuries when in the hospital. After the physical examination Dr. Chapman started him on a low dose of buprenorphine-naloxone, but his addiction to codeine was so severe that he continued to have positive tests for codeine since his cravings hadn't subsided. Therefore, Dr. Chapman increased the dose incrementally, which resulted in Mr. Hargrove decreasing his use of pain medications. He also emphasized that buprenorphine-naloxone does not give the patient euphoria; instead, it brings the patient back to normalcy so they can interact with family and friends and deal with life.

Ms. Waits emphasized the importance of considering access to education and uplifting Black and Brown communities, as well as focusing on the clinical needs. Ms. Waits recognized that there have been some great outcomes with higher dose buprenorphine. On a personal level, it is important to remember this is not one-size-fits-all and that individuals are coming with different tolerance to opioids, desires for treatment, and needs. She also echoed the systemic barriers, particularly cost and the need for practitioners to obtain prior authorization, because waiting time can change the person's perspective of care or return them to use. She also pointed out the trauma some patients feel seeking care if they have had negative experiences with practitioners. She shared a patient's initial experience in the ED seeking care that had unfortunately been more negative due to stigma, but also not being able to access treatment with ease. Not all EDs are equipped with an addiction specialist or have the medications immediately available. Patients can get a referral at the ED to a provider, but the wait time can be critical. The need for rapid access to medication across clinical environments is critical. More education also is needed to combat stigma among clinical providers. Conversations about the benefits of naloxone are not always shared with the public, so stigma persists, particularly around asking for buprenorphine-naloxone in a pharmacy line. This can cloud the patient's own view of their care.

Mr. Mischley spoke about difficulties in trying to find a provider in rural Michigan. He would have to drive 3 hours just to see a practitioner, who then wanted him to come back within a week or two. He would get pulled over in small towns by police who did not believe that they were going to a doctor. When he was younger, he had insurance so it was easier finding a doctor, but he also felt that some

doctors took advantage of the insurance by requesting expensive tests. Mr. Mischley also discussed that buprenorphine should potentially have better bioavailability. Additionally, it was noted that sublingual buprenorphine damages patients' teeth. Mr. Mischley also identified the importance of appropriately managing those long-term buprenorphine patients who also have severe and/or chronic pain. This is a growing problem that needs to be addressed with appropriate guidance and education.

Dr. Chapman pointed out that Mr. Hargrove's Medicare Advantage plan changed and reduced his dose of buprenorphine from 32 mg to 24 mg, which he tolerated for a couple of months. He bought illicit buprenorphine on the streets that included fentanyl and suffered an overdose. This was successfully reversed and, by calling the insurance company, he convinced them to increase Mr. Hargrove's dose. Dr. Chapman also highlighted that the HHS Inspector General published a report in May, showing that during the COVID-19 pandemic, buprenorphine's presence in overdose deaths didn't change, remaining at about 2%. This speaks to MOUD's low rates of diversion.

Dr. Olsen asked practitioners in this session about potential barriers to prescribing high dose buprenorphine. In particular, Dr. Olsen was interested in insurance issues and FDA labeling. She asked how practitioners might be interpreting some of the guidance from the federal agencies regarding dose, and how they perceive insurance companies are interpreting that information. In response, Mr. Bing emphasized the importance of trust in dealing with this population. Dr. Nguemeni asked if it is worth reconsidering the utility of naloxone in common formulations since it serves no purpose. The main reason naloxone was added to buprenorphine was to prevent people from injecting it, but at this point much of that is actually contributing to harm, and people are not remaining on their medication. Dr. Beverlyn Settles-Reaves shared that one of the key factors is the continued existence of silos and barriers between patients, their providers, and individuals who support patients. Communication is key to eliminating stigma. No one sees the big picture, so if everyone worked better as teams rather than in silos those barriers could be broken down.

PANEL – Identifying Barriers to Accessing High Dose Buprenorphine and Potential Solutions

Moderator: *Wilson Compton, MD, Deputy Director, National Institute on Drug Abuse (NIDA), National Institutes of Health (NIH).*

Panelists: *Susan C. Winckler, RPh, Esq., CEO, Reagan-Udall Foundation, FDA; Andrew Herring, MD, Emergency Medicine, co-founder, CA Bridge, and director of the Bridge Clinic, The Wilma Chan Highland Hospital, Oakland, CA; Anne Burns, BSPharm, RPh, American Pharmacists Association (APhA); Shari M. Ling, MD, Deputy Chief Medical Officer, Centers for Medicare and Medicaid Services (CMS); Max Jordan Nguemeni Tiako, MD, MS, medical resident at Brigham and Women's Hospital/Harvard Medical School in Internal Medicine-Primary Care, and addiction medicine researcher.*

Dr. Winckler spoke about payor policy underlying high dose buprenorphine. Her research looked at 20 commercial payors as well as Medicare Part D plans and State Medicaid coverage. They also spoke directly to some payors. Payor policy doesn't directly change what could be dispensed but does influence financial contributions from the individual and/or an insurer. At a high level, Medicaid and commercial plans provide broad coverage of buprenorphine and related products. Medicare and commercial insurance offered on the health exchanges are a little different. There is broad access in all programs to generic formulations. Such access drops off among Medicare and health exchange

populations; generally there is coverage for buprenorphine but under different conditions, including prior authorization and dose/quantity limits.

Among commercial insurance plans, there is very little need to obtain prior authorization, but there are almost universal dose restrictions. Most commercial payors have a cap at 24 mg/day, with the rationale that they are sticking to the FDA label. Several of the commercial payors still talked about the DATA waiver, which was rescinded in 2023, indicating that there remains a gap in education about the change in that requirement. In Medicare, there is virtually no prior authorization requirement, but there are a number of quantity limits. In Medicaid, there are some prior authorizations requirements and a similar situation regarding the quantity limits. Therefore, coverage for high dose buprenorphine is limited across all carriers. Some payors also have a counselling requirement.

Her research also captured some qualitative data. The payor community is seeking clarity on what the right dose might be across different contexts. The answers are not as clear-cut as the payors would like to see. Payors need to understand that there isn't much guidance regarding the right dose of buprenorphine for any one patient. Indeed, they apply a quite rigid and structured approach to their current coverage of buprenorphine.

Key Takeaways

- ✓ If a patient does benefit from more than 24 mg/day of buprenorphine, that individual often has to make a financial contribution to their care, even if they have health insurance.
- ✓ Most Medicaid plans and commercial payors have a dose limit of 24 mg/day for generic buprenorphine and buprenorphine/naloxone products, and this is set to the FDA label.
- ✓ They did hear clearly that payors would welcome further data on dose and the optimum length of treatment. There is stigma that needs to be overcome but also a willingness to learn about what can be improved.

Dr. Compton then led a panel discussion, beginning with a question, primarily directed to Ms. Burns, regarding the role that pharmacies and the American Pharmacists Association (APhA) could play in facilitating appropriate access for patients who would benefit from high dose buprenorphine.

Ms. Burns noted that federal efforts to look at buprenorphine dispensing at pharmacies are equally important as efforts to expand prescribing. A major consideration is the need for appropriate education and communication with pharmacists and other healthcare providers about the acceptability of using high dose buprenorphine, as well as efforts to normalize the practice. Pharmacists in dispensing roles face a lot of barriers. There is trepidation about the DEA closing a pharmacy down if they feel they are not doing their due diligence in keeping controlled substances from being diverted. She mentioned the findings regarding the role of drug Distributors that have emerged from the opioid multi-district litigation. There are three major companies that have had injunctions placed against them. As part of the opioid settlement, there are a lot of requirements that Distributors must meet that could impact pharmacies. Most importantly, Distributors have instituted "red flags" to monitor and report suspicious orders and can block the pharmacy's ability to fill prescriptions for controlled substances. Buprenorphine, unfortunately, is included in the high-risk, controlled substance list. This applies to both the mono and combination products. Patients paying for buprenorphine with cash are also considered "red flags."

One pharmacy Ms. Burns spoke with dispenses buprenorphine to telehealth patients and cannot order a controlled substance from any of the three major wholesalers. They are able to obtain buprenorphine from a small wholesaler in their area. Trying to get buprenorphine out of "suspicious order formulas" would make pharmacists much more comfortable with dispensing the medication. Prior authorization and insurance issues are also barriers. There are also pricing and payment issues for buprenorphine that cause some pharmacies to choose not to dispense it because they can't break even.

Dr. Compton asked Dr. Nguemeni to spotlight two or three priority challenges that he has been addressing. Dr. Nguemeni focused on structural issues - in addition to dosing issues, he emphasized differences between the states, particularly insurance companies, "playing doctor." He agrees that buprenorphine needs to be rescheduled so pharmacies aren't under as much of a microscope from the DEA, but even if it isn't rescheduled, he feels that it is important to phase out the naloxone component in buprenorphine combination products. Law enforcement also was raised as an issue because there is a fear at the pharmacy level of police officers arresting people even if they have a buprenorphine prescription. Asking people to show their prescription is an issue in an age where e-prescribing is often required.

Dr. Compton asked Dr. Herring what safeguards or concerns have emerged that require consideration. Dr. Herring responded that a significant component of why buprenorphine works is that it is rewarding, and that is okay. But this can be exploited, so not thinking about this issue is not the correct thing to do. If enforcement agencies use common sense regarding what a pill mill might look like, this allows practitioners to be somewhat more liberal with their prescribing and distribution. California's success in clamping down on pill mills has allowed Dr. Herring to run a low threshold, high dose practice.

Dr. Stein responded to Dr. Herring that he doesn't see the cash only pill mills in national data. There is a predisposition for people who prescribe high dose buprenorphine to tolerate more cash payments than other prescribers, but it's rare for that to be more than 40-50% of their practice. He then asked Dr. Nguemeni about potential unintended consequences of buprenorphine prescribers who may not increase buprenorphine doses out of concern for diversion and misuse. Would getting rid of formulations with naloxone, until the perspectives of the broader prescribing community can be changed through education, have the unintended consequence of moving people away from buprenorphine prescribing? Dr. Nguemeni responded that with all policy changes there is a risk of negative impacts. There is evidence that the mono product works, and when people express concerns about diversion they may be misguided – practitioners need to root out the police officer in themselves. If harm reduction is a concern, then don't phase out the naloxone version but at least make it clear that it's okay to prescribe one or the other.

Dr. Chapman shared that in DC, overdose statistics in 2022 showed 461 deaths, the second highest per capita death rate in the country. Among these deaths, only ten individuals had buprenorphine in their systems, and only 24 had methadone in their systems. They, therefore, know that medication is not being diverted.

Dr. Settles-Reaves asked the panel about the cash payment issue with pharmacies, and what level of cash payment is common. Most of her patients can't afford much and do have a $5-$6 copay. Secondly, she echoed Dr. Chapman's comments that a majority of the overdoses were in individuals not in treatment or who had returned to use. If a patient comes up short with their buprenorphine the first thing

the staff often think is that they sold it. The reality could be that the patient suffered a trauma and increased the dose to help deal with it.

Mr. Bing then asked Dr. Winckler why generics are so popular now, since he feels they are not as effective in treating those who have previously used fentanyl. Dr. Winckler replied that often a pharmacy doesn't have a choice as to whether they dispense a generic version of a medication. As soon as a generic alternative is available at a lower price, except in very rare circumstances, that is the version that is approved by the insurance company. In some cases, the brand name might not even be available anymore.

Dr. Compton completed the discussion by asking each panelist: "If you had a magic wand to tackle one key obstacle to improve access to higher than 24 mg of buprenorphine right now, what would it be and why?"

Dr. Ling spoke about spreading expertise, skills, and knowledge on how to better manage people and treatments that best address the needs of individuals. Acknowledge that the system is very dynamic and complex, and the landscape is shifting. First, think about what the workforce needs to be able to do to provide better care, not just people who already have the expertise and training, but to think more broadly. Second, understand the realities and be able to look at them though a data lens.

Ms. Burns wanted to remove buprenorphine from the Department of Justice (DOJ), DEA, and wholesaler monitoring lists for controlled substances and reduce stigma. Structural stigma filters down from the Department of Justice to the DEA, to insurance companies and health plans. We need to start treating buprenorphine differently in order for healthcare providers across the spectrum to feel more comfortable with expanding access.

Dr. Herring added that there are a whole series of algorithms that are governing "who gets what." He doesn't have any idea how to influence those algorithms because the work is happening behind closed doors and affecting people on a large scale. Secondly, hospitals are able to easily walk away from treating people with OUD. There needs to be rigorous health institution certification standards and a way to prevent systems from abandoning patients, which is happening in most hospitals in the United States. So, the big wish is an actual mandate that says if you are discovered to have people with OUD in your health system who are not offered buprenorphine or methadone, you are sanctioned.

Dr. Nguemeni stated that "we need to disempower the DEA the best we can." In his opinion, a lot of the rules coming out of the DEA are not evidence-based and create an artificial scarcity of medications that people need beyond just buprenorphine, as well as a lot of fear generally.

Dr. Winckler concluded with if it's really a magic wand, let's eradicate stigma.

CLOSING REMARKS

Dr. Compton emphasized the importance of continuing discussion with colleagues and for those in the federal government to use the wisdom from this meeting to influence policies and practices.

Dr. Olsen reiterated some of the meeting's main points, including continuing to address the ever-present issue of stigma and the role of buprenorphine in treating OUD, as well as continuing to work together to address the many barriers that the meeting identified. She emphasized the growing body of evidence in

support of higher dose buprenorphine, its safety profile, and need. Dr. Olsen also pointed out that it is essential to use evidence to inform guidelines, policies, and programs. In addition, she emphasized the importance of hearing from providers and patients as well as researchers about how they use buprenorphine. The pharmacy perspective is also critical.

Dr. Sokolowska emphasized the importance of publishing data regarding high dose buprenorphine, since it is critical to have it in the public domain. This is so that the FDA and other agencies can review it and take appropriate action.

APPENDIX A
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