FDA DOCUMENTATION FOR THE GENERIC CLEARANCE, "DATA TO SUPPORT SOCIAL AND BEHAVIORAL RESEARCH AS USED BY THE FOOD AND DRUG ADMINISTRATION" (0910-0847)

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TITLE OF INFORMATION COLLECTION: An Exploratory Assessment of Substances Used as Adjuncts or Alternatives to Prescription Opioids

DESCRIPTION OF THIS SPECIFIC COLLECTION

1. Statement of Need:

The FDA is committed to ongoing efforts to help enhance the safe and appropriate use of prescription opioids, and considers the misuse and abuse of substances used as alternatives and adjuncts to them to be a public health concern. Misuse and abuse of and addiction to opioids are well-documented. This situation is increasingly urgent. According to data collected from the 2017 National Survey on Drug Use and Health, "an estimated 2 million Americans misused prescription pain relievers for the first time within the past year, which averages to approximately 5,480 initiates per day."[1] While considerable data exist about the extent of opioid misuse, abuse and addiction, a better understanding is needed about the impact of other substances that may be used in addition to or as a substitute for prescription opioids. Of particular interest based on discussion occurring on social media and online forums and other research being conducted are the following substances: gabapentinoids, benzodiazepines, the plant kratom, and cannabidiol.

There is increasing clinical evidence that at least three categories of substances put users at risk when taken along with an opioid: gabapentinoids (e.g., Lyrica), benzodiazepines or BZDs, (e.g., Xanax, Ativan) and the plant kratom. Concomitant use of any of these substances with a prescription opioid can reduce respiration to dangerously low levels. Preliminary evidence also suggests that concomitant use of these substances may create a synergistic effect, increasing the bioavailability of the opioid as measured by its presence in the bloodstream.

There is also mounting evidence that gabapentin is associated with an increased risk of opioid-related death in people who are prescribed opioid painkillers. For example, the authors of a 2017 study found that "the combination of gabapentin and opioid exposure was associated with a 49% higher risk of dying from an opioid overdose than opioid use alone.[2] In fact, former FDA Commissioner Dr. Scott Gottlieb has said, "The opioid crisis is taking many new and unpredictable turns… One relates to the possible risk of misuse and abuse of gabapentinoids… Gabepentinoid misuse and abuse may be growing, both when taken alone and when taken with opioids, benzodiazepines or other central nervous system depressants."[3]

Similarly, there is an increasing body of medical literature documenting the risk of taking an opioid and a BZD simultaneously.[4] All prescription opioids and all BZDs now contain the following Boxed Warning, FDA's most prominent warning: "Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death." According to the National Institutes of Health, "more than 30 percent of overdoses involving opioids also involve benzodiazepines."[5] For these reasons, "FDA is warning patients and their caregivers about the serious risks of taking opioids along with benzodiazepines…"[6]

Although kratom is not currently an illegal substance, it can have psychotropic and even deadly effects and is readily available on the internet."[7] Even alone, kratom has been associated with depressed breathing, up to and including acute respiratory distress syndrome.[8] Gottlieb recently said, "As the scientific data and adverse event reports have clearly revealed… kratom [is] an opioid. And it's an opioid associated with novel risks because of the variability in how it's being formulated, sold and used recreationally…"[9]

Another substance of concern when used in conjunction with or as a substitute for prescription opioids is cannabidiol, or CBD. According to an FDA press release, "FDA continues to be concerned at the proliferation of products asserting to contain CBD that are marketed for therapeutic or medical uses although they have not been approved by FDA."[10] Several studies have indicated that consumers are using CBD-containing products as a substitute for prescription opioids with or without medical supervision. There is some evidence that cannabis products with high levels of CBD may be being used as a treatment for opioid use disorder[11]

As a result, this project involves using qualitative research in the form individual in-depth interviews with people who have sought treatment for their use of one of these four substances along with or as a substitute for a prescription opioid. These interviews will explore participants' attitudes, perceptions, and behaviors related to use of these substances. FDA has contracted and is working with Mark Herring Associates, Inc. (MHA) to carry out this study.

2. Intended Use of Information:

As part of FDA's ongoing efforts to help enhance the safe and appropriate use of prescription opioids, these interviews offer participants the opportunity to provide diverse and in-depth input and reactions in their own language, which will help FDA identify trends related to the use of these substances, and help ensure that we have elicited a range of information related to decision-making and behaviors about these four substances in conjunction with or as an adjunct to prescription opioids.

The findings from this qualitative exploratory study will be used to inform FDA's understanding of the uses of these four substances and help determine the need for additional research and/or next steps. As such, the findings will not be used for the purposes of making policy or regulatory decisions.

3. Description of Respondents:

We will conduct 140, 60-minute interviews with people seeking treatment for a substance use disorder regarding their use of a gabapentinoid, a benzodiazepine, kratom and/or a cannabidiol (CBD) along with or as a substitute for a prescription opioid (for simplicity to be called "opioids" going forward in this document).

Exhibit 1. Interview Segmentation

Cohort	Cohort Size	Cohort Description
Cohort #1	~35 respondents	Have used opioids in the last 12 months and have also used gabapentin as an adjunct to or as a substitute for an opioid
Cohort #2	~35 respondents	Have used opioids in the last 12 months and have also used a benzodiazepine as an adjunct to or as a substitute for an opioid
Cohort #3	~35 respondents	Have used opioids in the last 12 months and have also used kratom as an adjunct to or as a substitute for an opioid
Cohort #4	~ 35 respondents	Have used opioids in the last 12 months and have also used CBD as an adjunct to or as a substitute for an opioid

The participants will be those receiving inpatient or outpatient treatment from centers across the U.S., which MHA will recruit through collaboration with the National Association of Addiction Treatment Providers (NAATP). NAATP is a consortium of more than 900 independent addiction treatment centers with a nationwide presence and is committed to research on substance use disorders. MHA will interview those currently receiving inpatient and outpatient treatment for use of opioids and other substances in 10 different facilities within NAATP's network. In order to maximize the diversity of the participant population, the 10 sites for these interviews will be selected in conjunction with NAATP staff based on several considerations, including the opioid overdose death rate by state as reported by the Centers for Disease Control and Prevention, geographic distribution across the U.S., patient demographics, and the range of treatment services offered. A structured screener developed by FDA and MHA will be used by NAATP staff in each of the 10 treatment locations to identify those who meet the eligibility criteria and are willing to participate (See **Attachment A: Interview Screening Questionnaire**). This screening will include asking potential participants which prescription opioids they have used. Since there are so many opioid names to remember, participants will be provided worksheet containing a complete list of prescription opioids, listed by both their brand and generic names, to use as a memory aid (See **Attachment B: Prescription Opioids**). Given a similar abundance of brand and generic names of benzodiazepines, participants will be provided a worksheet containing a complete list of these drugs to use as a memory aid (See **Attachment C: Benzodiazepines**). Individuals who have worked for the Department of Health and Human Services, a pharmaceutical company or a market research firm will be ineligible. MHA will provide a briefing session for staff at each treatment facility regarding use of the screener, qualifying respondents to participate in the study, and protecting participant and document confidentiality.

4. Date(s) To Be Conducted and Location(s):

The interviews will be conducted as soon as possible after OMB and IRB approvals have been obtained. MHA will conduct interviews either onsite at the 10 treatment centers and/or remotely using an online interview platform depending on the situation with COVID at that

time. MHA will work with FDA to attempt to achieve sociodemographic and geographic diversity among participants.

5. How the Information Is Being Collected:

These interviews will be collected in-person and/or remotely using an online platform depending on what is needed as a result of the situation with COVID-19 to ensure the health and safety of participants, treatment center staff, and the two MHA interviewers. Each interview will last about 60 minutes.

Specifics for In-person Interviews

The in-person interviews will be conducted in private offices at each of the 10 treatment centers across the country by one of two trained MHA interviewers. MHA will ensure that respondents' interviews cannot be seen or heard by passersby or by center staff. This in-person strategy will enable us to engage a diverse and hard-to-reach population. At each of the 10 sites, MHA will spend two days in the treatment facility to complete ~14 interviews, which, to the extent possible, will be about evenly split among users of each the four substances.

MHA will make a high-quality digital audio recording of each interview. Each day, these recordings will be transferred from the digital recorder to a dedicated computer maintained by MHA that has full encryption capability. These digital audio recordings will not be shared by MHA with any NAATP staff or management or with FDA. This data will be backed up to an external hard drive that can be accessed only with a numeric keypad on the cover of the hard drive. Hard copies of consent forms, meeting notes and all other hand-written information will remain in the personal possession of the MHA researchers throughout each site visit and will then be transferred to locked filing cabinets that only MHA researchers will be able to access. A verbatim transcript of each interview will be completed, and any names or other personally identifiable information will be removed.

Specifics for Remote Interviews using an Online Platform

In-person interviews are preferred and were planned for; however, given the continuing concerns about the transmission of the coronavirus and the need to social distance and wear face-coverings/masks for protection, we may instead need to conduct some or all of the interviews remotely using an online interview platform that supports interaction between the interviewer and the participant via a webcam. The platform will also have audio recording capabilities and allow participants to view documents on the screen if needed. To mirror the in-person experience as closely as possible, the participant and the interviewer will be able to see each other. To help ensure participant privacy, NAATP has agreed that each of the 10 site facilities will provide access to a secure office with a computer with a webcam and internet where each participant is able to participate in the individual interview. MHA will hire an online platform vendor that will work with staff at each facility to test the platform in advance of the interviews and will provide technical support to the participants during the interviews if needed. MHA will work with the treatment centers to ensure these online conversations cannot be seen or heard by their staff or others. However, if the coronavirus situation worsens, making participation at the facility unsafe, these remote interviews using the online platform may be conducted instead from participants' homes. If the interviews are conducted from participants' homes, the platform vendor will work with each participant to test the platform in advance of

the interview and will provide similar technical support. Neither FDA nor the treatment center staff will have access to this online platform during the interviews. Online platform employees record an Oath of Confidentiality every quarter and also sign a confidentiality agreement. The Quarterly Oath helps each employee remember their personal responsibilities to safeguard all data and PII and to follow required protocols.

MHA will download the audio recordings from the online platform at the end of each interview onto a secure computer accessible only by MHA project staff. The company will transcribe the audio recordings and provide a verbatim transcript of each interview, removing any names or other personally identifiable information before they are provided to MHA. The company will delete the audio and recordings associated with this study once MHA provides them with a written request to do so.

MHA will save the transcripts to a secure computer and/or external hard drive that can be accessed only with a numeric keypad on the cover of the hard drive. Only MHA project staff will have access to this computer/hard drive. Hard copies of consent forms, meeting notes and all other hand-written information will remain in the personal possession of the MHA researchers and transferred to locked filing cabinets that only MHA researchers will be able to access.

Information Collection Processes for Both Options

The staff at each treatment facility will make appointments for each interview as part of the screening process. At the time the interview is scheduled, the treatment center staff will also provide each participate with an informed consent form to read and sign prior to participation **(See Attachment D: Consent Form)**. The consent form will describe the purpose of the study, how the information will be collected, benefits and risks to participation, confirmation of audio recording, the right to refuse or withdraw, the voluntary nature of participation, and the amount and type of the honorarium. The form will also describe the procedures in place to protect confidentiality: nondisclosure of personally identifiable information (PII), the inability to link individual responses to PII, reporting in aggregate such that individuals cannot be identified by name, storage of study documents and information, and eventual destruction of study files, including audio recordings (see Section 6 for additional details on confidentiality procedures). Contact information for the MHA Project Director and the external IRB will be provided. For the in-person interviews, MHA will collect the hard copy of the consent forms from the treatment facility screening staff prior to arriving at the facility. For the online interviews, either the facility's recruiting staff or the participant will take a photo of or scan each signed consent form and email it to MHA prior to the interviews. No one will be allowed to participate in an interview without MHA receiving a signed consent form in advance. The treatment center staff at each facility will remind each participant of his/her interview the day before the interview either in-person, email or a text message based on each participant's preference **(See Attachment E: Reminder Language).**

The interviewers will use a semi-structured guide developed by FDA and MHA to facilitate the discussions and ensure that all major topics of interest are addressed **(See Attachment F: Interview Guide).** The interviewers will start each conversation by introducing themselves, explaining the ground rules, and reviewing key points from the informed consent, including related to audio recording that will not be shared with FDA or any treatment center staff. After addressing these items, the interviewer will move on to the discussion questions.

FDA social scientists will NOT listen to the interviews. MHA will debrief the FDA Project Advisory Group regularly, discussing any issues that arise related to logistics, etc., after completing the interviews from the first site and regularly.

The digital audio recordings will be used by the online platform provider to create electronic transcripts of each interview; the audio recordings will not be shared with FDA or any NAATP staff. The recordings, electronic transcripts, signed consent forms, and all other written information will be saved on MHA computer hard drive that can be accessed only by MHA project staff using a numeric keypad.

6. Confidentiality of Respondents:

Several procedures to protect participants' confidentiality will be implemented, including the following:

1. Only treatment center staff doing the screening will have access to each facility's participants' full names and contact information; FDA will have access only to de-identified screening data.
2. The informed consent form covers several aspects related to confidentiality. At the beginning of each interview, the interviewer will remind each participant of this information. If a participant discloses his/her first name, last name or other PII, this information will be redacted from the transcripts before they are provided to FDA.
3. FDA issued a Certificate of Confidentiality, which provides an additional layer of protection for participants and their study information and documents. The FDA issued the COC so that MHA cannot be required to disclose any identifiable, sensitive information collected about as a part of this study in a lawsuit or legal proceeding. They are also prevented from releasing participants' study information without their consent.
4. Only two authorized MHA staff will conduct the interviews either remotely using an online platform, in private offices that will be locked and posted with do-not-enter signs or in the privacy of the participants' home. If remote interviews occur with participants staying in the treatment centers, MHA will work with the treatment centers to provide separate space for participants to participate in these remote interviews and to ensure that these conversations cannot be seen or heard by others.
5. Only the interviewers will participate in the interviews or have access to the audio recordings of them. Neither FDA nor treatment center staff will be able to access the offices/online platform during the interviews. Only FDA project research staff will be provided the de-identified transcripts.
6. There will be no link between the data collected and the participants' identities. FDA will not have the full names or any contact information for any of the participants.
7. All screener and interview data will be analyzed and reported in aggregate.
8. At both FDA and MHA, access to project data and materials will be limited to only research staff working on the project who have been granted access by the FDA project officer or MHA project director.
9. All study documents and files will be stored on password-protected computers at FDA and/or MHA and destroyed within 5 years of the study's end date.

7. Amount and Justification for Any Proposed Incentive:

Paying participants with a token of appreciation for their contribution to a study is a common practice in public health. Expressing appreciation for someone's contribution to research helps to reinforce the trust that is essential to the relationship between investigators and participants.[12,13]

Research involving participants who abuse substances is often hindered by low rates of recruitment. Research suggests that monetary payment or remuneration can be an effective strategy to overcome this obstacle.[14,15] Low rates of recruitment are problematic because they may raise concerns related to distributive justice, and racial, ethnic, and gender representation.[16] In addition, multiple studies have determined that people known to abuse substances should be compensated the same as non-users.[16] As part of a randomized controlled trial, Festinger et al. [17,18] found that neither the type (cash versus a gift card) nor the amount ($70, $100, $130, or $160) of incentives to adults in outpatient substance use disorder treatment programs increased feelings of coercion.

Therefore, the treatment center will provide each participant a $50 Visa gift cards as a token of appreciation for their willingness to provide feedback as part of this critical project. The treatment center will either hand deliver or mail the gift card to the participants at the completion of the interviews. The $50 token of appreciation is impacted by a number of variables for this project, including the following:

- Recommendation from the NAATP
- 60 minutes length of the interview
- Specifications that each participant has to meet to qualify to participate

In addition, the proposed incentive amount of $50 is lower than the $100-$150 market rates cited by recruitment firms. It is in line with the average hourly wage of employees on private nonfarm payrolls calculated by the Bureau of Labor Statistics (BLS) to be $30.04 in April 2020 (https://www.bls.gov/news.release/empsit.t19.htm). Based on this hourly amount, the estimated 100 minutes participants would spend on this study, including time for screening (15 minutes), testing the platform (10 minutes), participation in the interview (60 minutes), and the request to log in 15 minutes early to confirm technical operation, would amount to $50.16.

8. Questions of a Sensitive Nature:

The questions concern participants' use of prescriptions opioids and other substances as adjuncts or alternative to them and as such are likely similar to the kinds of questions they are routinely asked to answer as part of their substance abuse treatment. However, participants will be told at the beginning of the interview that they may skip any question that they do not want to answer and may stop participating at any time without penalty, and this information will also be stated in the informed consent document each participant will receive and agree to in advance.

9. Description of Statistical Methods:

Once the interviews are completed, MHA will use the transcripts created from the audio recordings of all interviews, along with the discussion guide and researchers' notes as the data for analysis. MHA will examine this qualitative data to identify emerging themes. The two interviewers will develop a codebook based on initial readings of their notes and a subset of the transcripts. This codebook will be provided to FDA for review and approval. MHA will then use the qualitative analysis software QSR International's NVivo 12 to assist in the organization, identification, and analysis of these themes. NVivo is ideal for managing large amounts of data and allows analysts to link external information, such as participant characteristics obtained through screeners, to qualitative data. The two interviewers will enter the transcript data from seven interviews into NVivo 12 and will each code the data independently using the approved code book. To assess the degree of agreement between the two coders, interrater reliability will be calculated using the kappa coefficient, which is a statistical measure that accounts for the amount of coder agreement expected to occur by chance. A kappa value of .80 or higher represents excellent agreement among the coders. Should the kappa coefficient be less than .80, the two coders will discuss discrepancies and revise the codebook with FDA input. The two coders will then individually code an additional 5 transcripts and recalculate the kappa coefficient. This process will continue until a kappa coefficient of greater than .80 is reached. After a .80 kappa coefficient is achieved, the complete set of transcript data will be coded in NVivo according to the updated final codebook.[19, 20] At this point in the analysis, the research team will note regularities, patterns, and other explanations in the data.[21] This analytic approach will allow us to determine the knowledge, attitudes, perceptions, decision processes, behaviors, etc. are occurring and to identify whether any of these elements differ by substance or other factors. The findings will be summarized in a report.

BURDEN HOUR COMPUTATION *(Number of responses (X) estimated response or participation time in minutes (/60) = annual burden hours):*

Type/Category of Respondent	No. of Respondents	Participation Time (minutes)	Burden (hours)
Screening/People who have sought treatment for substance abuse	280	15	70
Interviews/People who have sought treatment for substance abuse	140	60	140
TOTAL			**210**

REQUESTED APPROVAL DATE: August 15, 2020

NAME OF PRA ANALYST & PROGRAM CONTACT:

Ila S. Mizrachi
Paperwork Reduction Act Staff
Ila.Mizrachi@fda.hhs.gov
Tel: 301-796-7726

Paula Rausch PhD, RN
Project Officer, Associate Director, Research and Risk Communications
Office of Communications
Paula.Rausch@fda.hhs.gov
(301) 325-4662

FDA CENTER: Center for Drug Evaluation and Research

REFERENCES

[1]National Institute on Drug Abuse (NIDA). (2018, December 13). *Misuse of Prescription Drugs*. Retrieved from https://www.drugabuse.gov/publications/research-reports/misuse-prescription-drugs on 2020, January 21.

[2]Gomes, T., Juurlink, D. N., Antoniou, T., Mamdani, M. M., Paterson, J. M., & van den Brink, W. (2017). Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case-control study. PLoS medicine, 14(10), e1002396. doi:10.1371/journal.pmed.1002396

[3]Food and Drug Administration (FDA) [Commissioner Gottlieb, S.] (2018). *Public Workshop on Strategies for Promoting the Safe Use and Appropriate Prescribing of Prescription Opioids*. National Press Club, Washington, DC.

[4]Jones, J. D., Mogali, S., & Comer, S. D. (2012). Polydrug abuse: a review of opioid and benzodiazepine combination use. *Drug and alcohol dependence*, *125*(1-2), 8–18. doi:10.1016/j.drugalcdep.2012.07.004

[5]NIDA. (2018, March 15). *Benzodiazepines and Opioids.* Retrieved from https://www.drugabuse.gov/drugs-abuse/opioids/benzodiazepines-opioids on 2020, January 21

[6]FDA. (2016, August 31). *New Safety Measures Announced for Opioid Analgesics, Prescription Opioid Cough Products, and Benzodiazepines.* Retrieved from https://www.fda.gov/drugs/information-drug-class/new-safety-measures-announced-opioid-analgesics-prescription-opioid-cough-products-and
on June 8, 2020.

[7]NIDA. (2019, April 8). *Kratom*. Retrieved from https://www.drugabuse.gov/publications/drugfacts/kratom on 2020, January 21

[8]Jaliawala, H.A., Abdo, T., & Carlile, P.V. (2018) Kratom: A Potential Cause of Acute Respiratory Distress Syndrome. *American Journal of Respiratory and Critical Care Medicine*, 197, A6604.

[9] FDA [Commissioner Gottlieb, S.](2018, February 6). *Scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse* [Press Statement]. Retrieved from: https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-scientific-evidence-presence-opioid-compounds

[10]FDA. (2019). *FDA regulation of Cannabis and Cannabis-Derived products: Questions and answers.* Retrieved from https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd
on 2020, January 21

[11]Wiese, B., & Wilson-Poe, A. R. (2018). Emerging Evidence for Cannabis' Role in Opioid Use Disorder. *Cannabis and cannabinoid research, 3*(1), 179–189. doi:10.1089/can.2018.002213

[12]Grady, C. (2005). Payment of clinical research subjects. *J Clin Invest, 115*(7), 1681–1687.

[13]Emanuel, E.J., Wendler, D., & Grady, C. (2000). What makes clinical research ethical? *JAMA, 283*(20), 2701–2711.

[14]Collins, A. B., Strike, C., Guta, A., Baltzer Turje, R., McDougall, P., Parashar, S., & McNeil, R. (2017). "We're giving you something so we get something in return": Perspectives on research participation and compensation among people living with HIV who use drugs. *The International journal on drug policy*, *39*, 92–98. doi:10.1016/j.drugpo.2016.09.004

[15]Festinger, D. S., & Dugosh, K. L. (2012). Paying substance abusers in research studies: where does the money go?. *The American journal of drug and alcohol abuse*, *38*(1), 43–48. doi:10.3109/00952990.2011.563337

[16]Souleymanov, R., Kuzmanović, D., Marshall, Z. *et al.* (2016). The ethics of community-based research with people who use drugs: results of a scoping review. *BMC Med Ethics 17*, 25. doi:10.1186/s12910-016-0108-2

[17]Festinger, D., Marlowe, D., Croft, J., Dugosh, K., Mastro, N., Lee, P., & Patapis, N. (2005). Do research payments precipitate drug use or coerce participation? *Drug and Alcohol Dependence* 78(3), 275–281.

[18]Festinger, D.S., Marlowe, D.B., Dugosh, K.L., Croft, J.R., & Arabia, P.L. (2008). Higher magnitude cash payments improve research follow-up rates without increasing drug use or perceived coercion. *Drug Alcohol Depen, 96*, 128–135.

[19]Weinberger, M., et al. (1998). Can raters consistently evaluate the content of focus groups? *Social Science and Medicine, 46*: 929-933.

[20]Hruschka, D.J., Schwartz, D., Cobb-St John, D., DeCaro, E., Jenkins, R., & Carey, J.W. (2004) “Reliability in coding qualitative data: Lessons learned from HIV behavioral research.” *Field Methods, 16*:3, 307-331.

[21]Miles, M. B., & Huberman, A. M. (1994). Qualitative data analysis: An expanded sourcebook (2nd ed.). Sage Publications, Inc.