Online Surveillance of Novel Psychoactive Substances (NPS): Monitoring Reddit Discussions as a Predictor of Increased NPS-Related Exposures

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Abstract

Background: Novel psychoactive substances (NPS) present continuous and growing challenges for the scientific, medical, and interventional communities as emerging substances on recreational drug markets change national and international drug landscapes. NPS account for an increasing

proportion of adverse events, hospitalizations, and deaths due to increasing potency and unanticipated biological effects compared to predecessors. This study evaluated the utility of drug use forums as an early indicator or predictor of impending intoxications with potentially harmful or lethal outcomes prior to their occurrences.

Methods: Eight NPS were selected for evaluation to assess the relationship between online mentions of drugs and their involvement in toxic exposures or overdoses. Mentions on Reddit drug forum discussions were tallied and toxicology testing results from forensic investigations in the US were assessed. The selected NPS covered several subclasses and a predetermined time range (2013-2020). They included carfentanil, U-47700, eutylone, flualprazolam, *N*-ethylpentylone, 5F-MDMB-PICA, isotonitazene, and brorphine.

Results: Seven NPS (excluding 5F-MDMB-PICA) appeared in discussions on Reddit prior to their implication in poisonings or intoxications. Distinct increases and decreases in number of mentions and number of exposures were observed. For most substances (n=5, 63%), a rise in Reddit mentions was soon followed by a corresponding rise in toxicology positivity. Peak positivity for carfentanil and flualprazolam, however, preceded peak Reddit mentions.

Conclusions: This study demonstrated the utility of social media sites, such as Reddit, as a predictor for future trends in NPS-related exposures. These results provide confirmation that activity on drug use forums in the virtual world can help predict changes in exposures associated with new or re-emerging NPS in the real world. The results warrant further evaluation as a strategy for inclusion in early warning systems.

Keywords

Introduction

The drug landscape in the United States (US) and worldwide is changing continually, due in part to the rapid proliferation of novel psychoactive substances (NPS) over the past decade. NPS are defined by the United Nations Office on Drugs and Crime (UNODC) as drugs that are not listed as illegal in the United Nations Single Conventions on Controlled Substances (1961 and 1971), but which may still pose a threat to public health (UNODC, 2021). NPS drug categories encompass a broad range of substances, often referred to as "synthetic," "novel," or "designer" drugs, and includes analogues of existing controlled drugs as well as new drugs often created to mimic the effects of controlled substances (Shafi et al., 2020). From 2009 to 2020, over 1,000 different NPS drugs were reported to the UNODC Early Warning Advisory by 125 countries and territories (Tettey et al., 2020; UNODC, 2020b). As of the end of 2019, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) was monitoring at least 790 NPS throughout Europe (EMCDDA, 2020). While synthetic cathinones and synthetic cannabinoids continue to account for the largest groups of NPS reported over this period, there has also been an increase in new synthetic opioids and benzodiazepines in recent years (Tettey et al., 2020; UNODC, 2020b).

The rapidly changing market and large number of substances that consequently require monitoring pose challenges for national and international NPS surveillance efforts.

Conventional forensic chemistry and toxicology approaches may not be effective for detecting new and emerging NPS, as they are not within the scope of typical routine testing. Laboratories require specific types of analytical equipment, as well as standard reference materials, in order to be able to detect and report these new drugs and both can be difficult and expensive to obtain (Gerostamoulos et al., 2016; Peacock et al., 2019). There is a significant need to develop additional supplementary approaches to detect early indicators of changes in NPS markets, which may in turn predict potential trends in exposures, poisoning, intoxication, and/or deaths, as well as opportunities for response.

Surveillance models for NPS can include less traditional data streams (e.g., web markets, social media activity, and drug user forums) as sources that may often provide timely self-reported drug use preferences or practices (Gerostamoulos et al., 2016). European initiatives, such as the Psychonaut Web Mapping and the ReDNet projects, demonstrate how a range of internet sources can be utilized to track and anticipate fluctuations in NPS use (Corazza et al., 2013; Deluca et al., 2012). The content on these drug-related discussion forums has been shown to be useful for indicating changes and/or trends in patterns of drug use, particularly regarding early and real-time identification of the appearance of new drugs. Rhumorbarbe et al. (2019) found that nine NPS appeared on a popular drug use forum either before or at the same time as their first date of notification to the EMCDDA early warning system (Rhumorbarbe et al., 2019). However, these results may not capture the full utility of web-based data as an early identification system because listing to EMCDDA typically involves a multi-stage process initiated based on drug material testing rather than toxicology testing or confirmed use scenarios. Moreover, no prior research has paired comprehensive toxicology testing for NPS with drug use forum data – a link between such online data and potential exposures is not documented. Tangential to the work by Rhumorbarbe *et al.*, our research focused on prevalence of NPS use and chronological toxicological data relating to exposures.

The goal of this study was to determine whether online social data could serve as a monitoring system for subsequent NPS exposures or related harm, with potential future development as an early warning signal for real-time application. An advanced early warning system should include capabilities to capture a signal that is concurrent with, or even predates, the observed exposures themselves. Herein, we evaluate the link between online signal and exposures for previously prevalent NPS.

Methods

Comparison was conducted consisting of temporal trends between online drug forum mentions of specific NPS with comprehensive toxicology data generated from analysis of tens of thousands of biological specimens collected across the US, largely as part of forensic investigations. Our online data consisted of counts of substance-specific postings on the social-media website Reddit. To assess the association between online mentions and implication in exposures, data for selected NPS were queried from a chronology of NPS-related postings on Reddit drug forum discussions and comprehensive toxicology test results.

Data for eight NPS were examined spanning a wide range of subclasses and time intervals (Table 1). The drugs selected were carfentanil (a synthetic opioid), U-47700 (a synthetic opioid), eutylone (a synthetic stimulant/cathinone), flualprazolam (a new benzodiazepine), *N*-ethylpentylone (a synthetic stimulant/cathinone), 5F-MDMB-PICA (a synthetic cannabinoid), isotonitazene (a synthetic opioid), and brorphine (a synthetic opioid). These eight NPS were selected due to the knowledge that mentions existed on Reddit and toxicology cases were previously reported, providing an appropriate dataset for analysis. In addition, all eight NPS have received some level of notoriety due to prevalent involvements in adverse events and/or death.

An example post on Reddit about an NPS is shown in Figure 1. Geographical origins of Reddit posts are not available; however, US residents are by far the largest group of Reddit users, accounting for more than 49% (Figure 2) (Dean, 2021; Tankovska, 2021). Based on the client base of the laboratories performing toxicological analysis in this study, almost all samples originated from US based investigations. Geographical distributions of toxicology sample origins are shown in Figure 3 by specific NPS and in aggregate.

Reddit Data Collection

Reddit is a social media platform that comprises news aggregation, web content rating, and discussion pages or channels on social, societal, political, and general interest topics, including drug use (Reddit, n.d.). Posts are organized into user-created forums and bulletin boards called "subreddits" where virtual conversations take place. Originating in 2005, current estimates show a user base of over 430 million active users on Reddit (Dean, 2021; Tankovska, 2021). Reddit was selected as the drug forum of choice for this study due to prior anecdotal experience with qualitatively monitoring drug user experience self-reporting on the site and the large user base.

Online data consisted of raw counts of keywords related to the eight selected NPS that appeared on Reddit forums from 2010 to 2020, spanning one decade. We first identified specific subreddits that were likely to contain discussions of NPS, using two criteria for inclusion: 1) subreddits that contain frequent mentions of drug terms that were designated as relevant to our analysis (e.g., /r/Opioid_RCs) and 2) subreddits that self-identified, by title or description, as dedicated to drug discussion (Table 2). Among those self-identified subreddits, we distinguished three basic categories: 1) drug specific (e.g., /r/kratom, /r/cocaine), 2) dedicated to a drug class (e.g., /r/Stims, /r/opiates), and 3) general psychoactive substances (e.g., /r/researchchemicals, /r/DrugsOver30). Based on these criteria, 67 subreddits were identified for inclusion.

It is important to note that while subreddits are thematically organized, discussion in posts and comments often strays beyond the stated purpose of the community to include other topics (e.g., historical perspective, current events). Therefore, no strong assumptions can be made about the content of a subreddit's posts and comments when searching for drug keywords.

To capture a reliable measure of a drug's presence in Reddit discussions, we selected and searched only for keyword terms that refer to the specific substance directly. These

keywords can include drug names, abbreviations, and slang terms. In order to identify substance-specific keywords, we started with standard terms from drug nomenclature. Next, we used an unsupervised algorithm for keyword detection to search subreddit comments and identify additional terms referring to the same substance. The unsupervised method comprised an application of the Term Frequency-Inverse Document Frequency (TF-IDF) technique, which counted the frequency of every word in every comment to find terms that appear more often in a drug subreddit than the average subreddit (Jones, 2004; Luhn, 1957). Terms frequently used in drug subreddits were assessed manually to determine whether they were being used as alternative terms for a substance. To preserve keyword specificity, a term was only included if its mentions could be unambiguously attributed to a substance when used in drug subreddits. The keywords considered are shown in Table 1.

Keyword mentions were counted for each drug by searching all comments in every selected subreddit. Mentions were counted based on regular expression matching (non-case sensitive) of drug keywords to substrings of comment text. To minimize false positive matches, comment text was preprocessed before matching by removing URLs, as alphanumeric strings in URLs occasionally matched abbreviations included as drug keywords. Matches were aggregated to a set of comments, each identified by a unique identifier in Reddit's API. Thus, a comment was only counted once if the same substance is mentioned multiple times in the single comment's text. Comments that were counted within the same unit of time, such as a calendar month or quarter, were summed to a single count. Counts were compared over time to reveal trends in online drug mentions.

Toxicology Data Collection

Data from the analysis of toxicological samples for the presence of drugs, including the targeted NPS, were compiled from NPS Discovery at the CFSRE (Willow Grove, PA, USA) and NMS Labs (Horsham, PA, USA). NPS Discovery [www.npsdiscovery.org] is an open-access analytical drug early warning system in the US that specializes in NPS testing, data compilation, and information dissemination. NMS Labs is the largest forensic toxicology reference laboratory in the US providing national testing services in forensic toxicology and drug chemistry laboratories, with an approximate average yearly case load of more than 120,000 cases. Data were generated from comprehensive toxicological analyses performed on biological specimens submitted in suspected death and impaired driving investigations. Following analytical confirmation, drug testing results, consisting of the identity of the drugs present and the date of analysis, were output to an in-house data lake (a large repository of raw data elements). This data lake was queried to produce data tables containing the frequency of detection of specific drugs over time. The aggregate data were tallied and tabulated by year and month. First incidence of detection and identification from NPS Discovery were combined with data from NMS Labs to generate a comprehensive timeline of frequency of detection. For the purposes of this study, one toxicology detection was equivalent to one exposure case.

All methods used for NPS detections were validated in-house at NMS Labs and/or CFSRE. The detailed analytical methods for all eight drugs examined during this study (i.e., carfentanil, U-47700, eutylone, flualprazolam, *N*-ethylpentylone, 5F-MDMB-PICA,

isotonitazene, and brorphine) have been published elsewhere, or are available upon request to the authors (Krotulski et al., 2018, 2021; Krotulski, Papsun, Kacinko, et al., 2020; Krotulski, Papsun, Noble, et al., 2020; Mohr et al., 2016; Papsun et al., 2017, 2021; Tynon et al., 2017). Generally, drug screening was performed using liquid chromatography time-of-flight mass spectrometry and drug confirmation was performed by liquid chromatography tandem mass spectrometry (LC-MS/MS). For synthetic cannabinoids, testing was performed via a combination of LC-MS/MS assays due to chemical behavior. The date the drug was added to the in-house database and the reporting limit for each drug are shown in Table 1. Retrospective data-mining efforts were conducted, when possible, to determine true date of drug emergence and positivity prior to addition to toxicology testing scope (except for carfentanil, U-47700, and N-ethylpentylone).

Statistical Analysis

The number of Reddit mentions and number of related exposures were aggregated by month and quarter within each year as described above. First, data were plotted using observed values (raw counts) by month, and then trends were estimated using quarterly data. Quarterly data were used to estimate trends due to monthly data often containing multiple time points with very few cases. Joinpoint Regression (Version 4.8.0.1) was used to evaluate trends (NCI, 2020). Also known as piecewise, broken line, multi-phase, or segmented regression, Joinpoint fits weighted least-square regressions to rates on a log transformed scale (Ingram et al., 2018; Kim et al., 2000). This program also uses Monte Carlo permutation tests with a Bonferroni correction for multiple testing and identifies the best-fitting set of joinpoints within models. Joinpoints are knots in trends that indicate significant shifting points. Separate joinpoint analyses (n=16) were conducted on Reddit mentions and exposures for all eight NPS.

Results

Table 3 presents respective dates of several critical time points (i.e., online mentions, first reported exposure, intent to schedule, temporary scheduling) for each of the eight NPS included in the study. Figure 4 depicts total monthly recorded online mentions and exposures, as well as respective calculated trend lines, across a multi-year period.

Carfentanil

Carfentanil was first mentioned on Reddit in February 2013. To begin, mentions were relatively rare but significantly increased by late 2015 through late 2016 (β=0.87, SE=0.38, P=0.031). Mentions continued to rise in a nonsignificant manner to a peak occurring in May 2017 (n=215 mentions). Mentions significantly decreased in a staggered manner from 2017 through 2020 (β=−0.05, SE=0.01, P<0.001). Up to the end of 2020, mentions of carfentanil continued to appear on Reddit. With respect to exposures, carfentanil was first detected in October 2016 – 44 months after its first Reddit mention. Detection of carfentanil in toxicological cases in the US rose quickly early on to high levels, with the peak occurring in January 2017 (n=87 cases). This peak in exposures data preceded the peak in Reddit mentions by four months. Through 2017, the number of exposure cases began to significantly decline, especially in the last quarter of 2017 (β=−0.44, SE=0.08, P=0.001),

and reached a nadir in late 2018 and early 2019. However, there was another increase (which approached significance) in exposure cases through late 2019 (β=0.32, SE=0.15, P=0.074), followed by a nonsignificant decrease through the rest of the year. A small number of cases containing carfentanil continued to be reported through the end of 2020.

U-47700

U-47700 was first mentioned on Reddit in November 2014. Mentions increased through early 2016 (β=0.75, SE=0.11, P<0.001), and continued to increase (non-significantly) to a peak of 441 mentions in September 2016. The number of mentions significantly decreased throughout 2017 (β=−0.33, SE=0.06, P<0.001), and there was a less steep significant decrease beginning in early 2018 (β=−0.05, SE=0.02, P=0.044). U-47700 was first detected in an exposure in the US in October 2016 – 23 months after its first mention on Reddit. The number of cases significantly increased after its first detection (β=0.25, SE=0.10, P=0.034) and reached a peak in August 2017 (n=82 cases). This peak for exposures was 11 months after the peak in Reddit mentions. The number of cases significantly decreased (β=−0.60, SE=0.16, P=0.004) through late 2018, and there was a nonsignificant decline in cases thereafter. In 2020, U-47700 was rarely detected, fluctuating between zero and a handful of cases each month.

Eutylone

Eutylone was first mentioned on Reddit in February 2015. Mentions remained sparse through early 2018 and mentions slowly increased through May 2020 with a peak of 41 mentions (β=0.35, SE=0.03, P<0.001). Mentions began to decrease through the end of the year, but not in a significant manner. Eutylone was first detected in an exposure in the US in May 2019 – 51 months after its first mention on Reddit. The number of exposure cases increased across 2019 and 2020, but this increase only approached statistical significance (β=0.34, SE=0.15, P=0.064). Eutylone continued to be detected in toxicology cases throughout 2020. Increase in exposures reached a peak in July 2020 (n=40 cases), which was two months after the peak in Reddit mentions.

Flualprazolam

Flualprazolam was first mentioned on Reddit in August 2015. Mentions remained infrequent until a significant increase was observed in 2017 lasting through January 2018 (β=1.26, SE=0.52, P=0.042). Mentions remained stable through late 2019 and significantly increased through early 2020 (β=0.42, SE=0.15, P=0.025), reaching a peak in June 2020 (n=795 mentions). Mentions significantly decreased after early 2020 (β=−0.32, SE=0.14, P=0.046). Flualprazolam was first detected in the US from a single exposure in April 2018 through retrospective data-mining efforts – 32 months after its first Reddit mention. Thereafter, flualprazolam remained undetected until it re-emerged in June 2019. Cases involving this NPS increased through its peak in May 2020 (n=166 cases; β=0.86, SE=0.14, P<0.001), which was one month before the peak in Reddit mentions. The number of exposure cases significantly decreased throughout the rest of 2020 (β=0.97, SE=0.29, P=0.015). Flualprazolam continues to be detected in exposure cases, but less frequently than during peak positivity.

N-Ethylpentylone

N-Ethylpentylone was first mentioned on Reddit in April 2016. Mentions increased through April 2018 with 29 mentions that month (β=0.23, SE=0.09, P=0.021). Mentions significantly decreased in a staggered manner thereafter (β=−0.13, SE=0.05, P=0.016). *N*-Ethylpentylone was first detected in an exposure in the US in August 2017 – 16 months after its first mention on Reddit. The number of cases peaked in September (n= 5 cases) – 5 months after the peak in Reddit mentions. There was a significant decrease in cases thereafter (β=−0.56, SE=0.11, P<0.001). *N*-Ethylpentylone was detected only three times in early 2020, and not detected in the last six months of that year.

5F-MDMB-PICA

5F-MDMB-PICA was first mentioned on Reddit in September 2018. Mentions remained somewhat rare thereafter, but significantly increased across 2019 and 2020 (β=0.29, SE=0.07, P=0.002). Peak in Reddit mentions occurred in August 2020 (n=10 mentions). 5F-MDMB-PICA was first detected in an exposure in the US in June 2018 – 3 months before the first Reddit mention. The number of cases increased through early 2019 (β=0.60, SE=0.20, P=0.024) with a peak in January 2020 (n=35 cases). This peak in exposures preceded the peak in Reddit mentions by seven months. The number of cases decreased in a staggered manner with the trend only approaching significance (β=−0.15, SE=0.06, P=0.051). A handful of cases involving 5F-MDMB-PICA continue to appear in forensic casework in the US, but the synthetic cannabinoid market has shifted to new drugs with greater positivity.

Isotonitazene

Isotonitazene was first mentioned on Reddit in January 2019. Mentions significantly increased through early 2020 (β=0.62, SE=0.13, P=0.017) and peaked in February 2020 with 57 mentions. Mentions decreased thereafter in a nonsignificant manner. Isotonitazene was first detected in an exposure in the US in September 2019 – 8 months after its first mention on Reddit. Cases increased in a nonsignificant manner through March 2020, peaking at 38 cases. This peak succeeded the peak in Reddit mentions by three months. The number of cases decreased throughout the rest of 2020 in a nonsignificant manner. By the end of 2020, few cases involving isotonitazene were detected.

Brorphine

Brorphine was first mentioned on Reddit in February 2019 and mentions significantly increased through early 2020 (β=0.84, SE=0.19, P=0.022) with a peak in mentions in February 2020 (n=81 mentions). There was a staggered nonsignificant decrease thereafter. This NPS was first detected in an exposure in the US in July 2020 – 17 months after its first mention on Reddit. Given that this compound was not detected in exposures until mid-2020, accurate counts could not be finalized and trends could not be estimated as the time period ended in December 2020. Brorphine continued to be detected in toxicology cases into 2021, with seeming peak positivity occurring in late 2020; however, the lifecycle of brorphine is not yet complete.

Discussion

For seven out of the eight NPS assessed, online mentions preceded observed exposures with gaps between 8 months and >4 years. The overall shape of the two curves in each group reveal striking similarities for most NPS; peaks in online mentions were typically followed, in fairly close succession, by peaks in exposures. With the exception of 5F-MDMB-PICA, online discussion appeared to predict later exposures to a surprisingly high degree. However, the results are not uniform across substances with variability in the time between online mentions and exposures, with at least one substance (5F-MDMB-PICA) showing no clear relationship and exposures preceding online mentions.

While these results show promise with respect to the overall utility of online monitoring for early detection, the observed variability across NPS sub-classes suggests that individual substances should be interpreted in a manner which accounts for time-specific factors and influences. Factors influencing NPS emergence and detection are complex, as this broad category of drugs is continually evolving. We considered the results of each substance individually and discuss possible factors that may have influenced the observed data, including US market trends, drug scheduling, temporal events, and/or international considerations.

Carfentanil

Carfentanil is a potent analogue of the narcotic analgesic fentanyl (George et al., 2010). Carfentanil was the oldest NPS evaluated during this study. As such, the state of NPS drug testing and knowledge about NPS were vastly different in 2016 compared to the time of analysis (2021). Carfentanil differs from other substances evaluated during this study as it was a well-known and well-characterized drug and was scheduled prior to its introduction on the illicit drug market (Leen & Juurlink, 2019; Papsun et al., 2017; WHO, 2017). Early notoriety of carfentanil was fueled by its involvement in the Moscow theater hostage crisis in 2002 (Riches et al., 2012) – some Reddit mentions gathered included reference to this event.

Due to toxicity, carfentanil was scheduled by the US Drug Enforcement Administration (DEA) in 1988 (DEA, 2018a). Reddit mentions of carfentanil began appearing in 2013 (not solely related to Moscow), followed by exposures in the US reported in 2016. Based on this information, the Schedule II status of the drug in the US may not have prevented carfentanil from being distributed and recreationally used or impacted its lifecycle. Rather, the decline in carfentanil positivity appears to be linked to international control, and specifically a ban implemented by China in March 2017. Beginning in early 2017, a decline in US exposure cases was observed. We hypothesize that the large wane in carfentanil positivity could be due, at least in part, to supply reduction decisions after adverse events, or possibly due to educational and harm reduction efforts leading to the substance not being preferential or being used with caution. Nevertheless, carfentanil continues to appear less frequently in exposures each year.

The overall lag time between the emergence of carfentanil on drug use forums and its detection in exposure cases was up to 44 months. When examining substantial rises in the

data, mentions began a sharp upward trend after May 2016 and for exposures this occurred immediately after carfentanil was added to testing procedures in October 2016 (data-mining not available). This gap was approximately five months. A gap in these data can be expected due to delays between time of death, autopsy, and toxicology testing, which can generally take between one to three (or more) months depending on jurisdiction. The prolonged gap of five months for carfentanil and the quick spike in exposure cases was likely linked to developing scientific practices, administrative delays external to our laboratories, and some inexperience with new high potency synthetic drugs.

Based on our experience in the US, the emergence carfentanil in the drug supply created great concern in public health and public safety circles. Some law enforcement agencies and testing laboratories were hesitant to handle cases (powders and even biological samples) suspected of containing carfentanil. Reference material manufacture was delayed due to implementation of safety precautions for handling this highly potent drug, followed by delays in importation of the drug if purchased from outside the US. Toxicology laboratories were required to obtain high analytical sensitivity, sometimes requiring the development of new and improved testing methods. It should be noted that NMS Labs serves as a reference laboratory for other toxicology laboratories seeking novel drug confirmations, so case numbers could also have been impacted if partnering toxicology laboratories did not have adequate analytical sensitivity during in-house screening. In culmination, these factors likely led to delays in testing and reporting of carfentanil in exposure cases.

In summary, first mentions of carfentanil on Reddit preceded initial confirmed exposure events as evaluated by carfentanil detection in this post-millennial opioid crisis. Peak exposures and mentions were roughly correlated. Overall, Reddit discussions were a predictor for future carfentanil exposures.

U-47700

U-47700 was not truly a "new" drug when it was first discovered in the recreational drug supply in the US beginning in 2016. Pharmaceutical patents existed for U-47700 dating back to the 1970s (Cheney et al., 1985; Szmuszkovicz, 1978). This information published in research literature may have allowed clandestine chemists and drug experience-seekers to have realistic expectations of potential euphoric effects. Mentions of U-47700 on Reddit were in-part linked to the expanding opioid crisis in the US, as some were searching for the next new "legal high". At that time, the role of drug use forums were still developing, and, from our review, U-47700 was likely the first drug for which people turned to forums to share information.

As U-47700 was emerging, laboratories were beginning to recognize the need for rapidly adding capabilities to testing methodologies. U-47700, however, belongs to a different opioid subclass than fentanyls, with an unfamiliar chemical structure and analytical profile. This created additional challenges for laboratories in recognizing the drug as an opioid, appreciating its significance in death investigations, including it in analytical scope, and differentiating it from other related drugs (e.g., AH-7921). There was a 23-month gap between first mentions of U-47700 on Reddit and detection in first exposure cases. When examining the substantial increase in mentions vs. exposures, an approximate 12-month gap

was visualized. Many factors could have influenced this time lag, several of which were previously mentioned for carfentanil and likewise valid for U-47700.

In the US, the DEA filed intent to schedule U-47700 in September 2016, about a month after an initial surge in exposures (DEA, 2016b). U-47700 was officially placed in Schedule I in November 2016; however, no impact was observed. Conversely, the number of exposure cases continued to increase (DEA, 2016c). Around mid-to-late 2017, the number of U-47700 exposure cases began to decline more dramatically. In April 2018, the DEA placed U-47700 under Schedule I indefinitely. No clear impact was directly related to national control; however, it appears that international control may have impacted US-based exposure events. Specifically, China implemented a ban on U-47700 in July 2017.

In summary, first mentions of U-47700 on Reddit preceded initial confirmed exposure events involving U-47700. Peak exposures and mentions did not appear to be well correlated, with exposures shifting later in time. Overall, Reddit discussions were a predictor for future U-47700 exposures.

Eutylone

First synthesis of eutylone dates back to the 1960s (Ingelheim et al., 1967). Eutylone emerged in the recreational drug supply in 2014 (EMCDDA, 2014). As such, it is not surprising that eutylone first appeared in Reddit (an international platform) mentions as early as 2015. However, at the time, there was no market for this new stimulant in the US as ethylone, methylone, and alpha-PVP continued to dominate. Eutylone did not emerge in the US until years later when prior synthetic cathinones (e.g., butylone, dibutylone, N-ethylpentylone) were scheduled and removed from the market. This historical perspective makes it difficult to evaluate the long timespan between first Reddit mention and exposure cases (51 months). For eutylone specifically, the evaluation of peak positivity is a much better indicator, as this feature was closer in time (approximately 2 months apart) for mentions and exposures, respectively. As of December 2020, eutylone was not scheduled in the US and exposure cases continued to appear.

In summary, first mentions of eutylone on Reddit preceded initial confirmed exposure events, however, the timeframe for these initial events is skewed. Peak exposures and mentions appeared to be correlated, tracking nearly identical trajectories. Overall, Reddit discussions were a predictor for future eutylone exposures, and eutylone appears to be a more controlled example for how Reddit mentions can predict a rise in exposures when the laboratory is testing for the substance well before its emergence (added to testing assays roughly 3 years prior to first case).

Flualprazolam

Flualprazolam was first synthesized and studied in the 1960s, but not marketed for therapeutic use (Hester, 1976; Hester et al., 1971). Unlike other NPS subclasses in the US, benzodiazepines are generally not scheduled or scheduled in lower tiers. Between 2016 and 2019, the US benzodiazepine market was heavily gripped by etizolam. This could help explain the lag between Reddit mention and exposure cases. However, as flualprazolam

emerged and proliferated in the US, both Reddit mentions and exposure cases increased, seemingly synchronously.

As of December 2020, flualprazolam was not federally scheduled in the US. However, it appears international control may have impacted the presence of flualprazolam in exposure cases in the US. In March 2020, the United Nations Commission on Narcotic Drugs voted to place flualprazolam under international control following recommendation by the World Health Organization Expert Committee on Drug Dependence (UNODC, 2020a; WHO, 2019). The ruling was set into effect in November 2020. The decline in both Reddit mentions and exposure cases began in mid-2020.

In summary, first mentions of flualprazolam on Reddit preceded initial confirmed exposure events involving flualprazolam. Initial increases among discussions preceded exposures by about 2 years, but this could be due to international availability and consumption preceding those in the US. Peak exposures and mentions appeared to be well correlated, tracking nearly identical trajectories. Overall, Reddit mentions were a predictor for future flualprazolam exposures, albeit delayed but in sync with the "second Reddit surge".

N-Ethylpentylone

First synthesis of *N*-ethylpentylone dates back to the 1960s (Ingelheim et al., 1967). *N*-Ethylpentylone first emerged in the recreational drug supply in 2016 in Europe (EMCDDA, 2016). This date corresponds with the emergence of *N*-ethylpentylone on Reddit in 2016 and more closely with exposure cases in 2017. This improved association (compared to eutylone) is likely due to scheduling actions opening a void in the market with space for a new stimulant drug. *N*-Ethylpentylone was scheduled in the US in August 2018, followed by the decline of exposure cases beginning around September 2018.

In summary, first mentions of *N*-ethylpentylone on Reddit preceded initial confirmed exposure events involving *N*-ethylpentylone. Increased discussions were observed over time, but no clear initial spike was observed. The proliferation of *N*-ethylpentylone in exposure cases tracked a similar trajectory as Reddit mentions. Overall, Reddit discussions were a predictor for future *N*-ethylpentylone exposures.

5F-MDMB-PICA

Literature involving 5F-MDMB-PICA date back to 2016 as part of exploratory efforts to study and predict new cannabinoid drugs (Banister et al., 2016). The synthetic cannabinoid subclass is vastly different from other NPS subclasses, one reason being their naming conventions. Preferred names use an alphanumeric code linked to structural components. This unfortunately complicates factors related to the communication of these drugs. Reddit mentions for 5F-MDMB-PICA were rare between 2018 and 2020, yet it was the most commonly encountered synthetic cannabinoids in 2020 (NPS Discovery, 2019). We hypothesize this is linked to naming complexities, as it is more common to find street names or brands like "K2" or "Spice" used for communication.

5F-MDMB-PICA was federally scheduled in the US in April 2020, with initial announcement in December 2019 (DEA, 2019). A noticeable decline in the number of

US exposures occurred following this action. Conversely, the majority of Reddit discussion occurred after scheduling action, which could be explained by increased awareness and more common encounters via internet browsing.

In summary, 5F-MDMB-PICA behaved differently from the other NPS examined. First confirmed exposure events involving 5F-MDMB-PICA preceded mentions on Reddit. No substantial increase in discussion was observed, and no clear peak in mentions. Proliferation of 5F-MDMB-PICA in exposure cases increased in 2018 and through 2019. Drug scheduling action appears to have played a role in the decline of exposure cases in 2020, and possible slight increase in online mentions as well. Overall, Reddit discussions were not a predictor for future exposures involving 5F-MDMB-PICA.

Isotonitazene

Isotonitazene began emerging among the recreational drug supply in 2019. Its synthesis and pharmacological action were previously reported in the 1950s (Hoffmann et al., n.d.; Hunger et al., 1957). The closely related analogue etonitazene was also characterized during these studies and eventually scheduled in the US (DEA, 2016a). First mentions of isotonitazene on Reddit coincide with the era after passage of core structure scheduling of fentanyl related substances in the US, which was placed into effect in February 2018 by the DEA (DEA, 2018b). A subsequent decline in fentanyl analogue availability was observed. As it became clear that fentanyl analogues were disappearing, the market was forced to turn to other "new" or "legal" NPS opioid subclasses.

Based on prior experience with synthetic opioids, some laboratories (including ours) were well prepared for the introduction of new potent opioids into the drug supply. Detections of isotonitazene in exposure cases rose coinciding with the initial substantial rise in Reddit mentions. As the months progressed, the number of exposure cases fell sharply while Reddit discussion persisted. Isotonitazene was scheduled in the US in August 2020, with notification of intent published as early as June 2020. This action was based on timely information available regarding death investigations involving isotonitazene (Krotulski et al., 2019; Krotulski, Papsun, Kacinko, et al., 2020). The decline in isotonitazene exposures began around April 2020. It is unclear the exact cause that triggered this decline.

Isotonitazene differed from that of carfentanil and U-47700 was its lifecycle. Mentions and exposures to carfentanil and U-47700 spanned 3-5 years, while those for isotonitazene spanned only one year (albeit lingering mentions persisted into 2021). This exemplifies the nature of the NPS opioid landscape in 2016 vs. 2020 – shorter lifecycles possibly due to better drug testing practices and public health and safety response.

In summary, the timeline between first mention and first exposure was dramatically decreased for isotonitazene compared to other NPS reported herein, a likely link to better intelligence and more aggressive drug testing efforts. First mentions of isotonitazene on Reddit preceded initial confirmed exposure events involving isotonitazene. Peak exposures and mentions of isotonitazene occurred close in time, following similar trajectories. Overall, Reddit mentions were a predictor for future isotonitazene exposures.

Brorphine

Brorphine was largely unfamiliar when it emerged for sale and on drug forums. Brorphine shares some structural similarity with fentanyl but is not widely considered a fentanyl analogue. It appears brorphine was first discovered in 2018, but related analogues date back to the 1960s (Janssen, 1967; Kawamoto et al., 1999; Kennedy et al., 2018). Brorphine emerged subsequent to the scheduling of isotonitazene, yet Reddit discussions preceded this market shift. The time delay in peak mentions and exposure cases could be due to the overall migration of the NPS opioid market away from fentanyl analogues towards more esoteric opioids. As some were seeking the next new opioid, brorphine may have sparked interest but there was no supply to meet the potential demand (isotonitazene was dominating this front, similar to the relationship between eutylone and *N*-ethylpentylone). Our laboratories were prepared and equipped to detect brorphine when Reddit mentions first increased but an increase in exposure cases did not occur until mid-2020. The DEA filed intent to schedule brorphine in the US in December 2020 citing timely data regarding mortality. December 2020 marked the end of our data collection period so subsequent trends were not recorded (however, we can report that brorphine positivity declined in early 2021) (Krotulski, Fogarty, Papsun, et al., 2020; Krotulski, Papsun, Noble, et al., 2020).

In summary, first mentions of brorphine on Reddit preceded initial confirmed exposure events involving brorphine. Initial increased discussions preceded exposures in the US by about 6 months. Overall, Reddit discussions were a predictor for future brorphine exposures.

Limitations

A few limitations should be noted for this study. There is the inherent lag time between exposures and the testing of biological samples creating the potential for an unknown gap. Due to the nature of forensic practices and logistical processes, a delay of up to one month or more could be common for time between ingestion of a new substance and toxicology testing and/or reporting. These factors are often unknown and could not be included as part of our assessment.

Retrospective data-mining was implemented in 2018, and as such was not in place when carfentanil, U-47700, and *N*-ethylpentylone first emerged in exposure cases in 2016. This means the first emergence of these three NPS could have been missed prior to inclusion in the toxicology testing scope. However, it is important to note that national and international trends do not suggest that would be an appreciable amount of time.

The geographical origins and distribution of cases examined during toxicology testing may be limiting. All cases originated from the US while Reddit mentions are global. NPS trends can differ internationally, so these results cannot be applied to other countries without further evaluation. Additionally, cases were not tested from all jurisdictions within the US (although the coverage was extensive). Some local discrepancies may be present if sub-populations were missed.

Future Work

The results of this study will help propel future work and the authors have identified areas for additional research related activities in six ways. First, the current study examined Reddit as the only drug use forum. Future studies should include additional forums and user interfaces. Second, this study only examined data from exposure cases from CFSRE and NMS Labs. Future studies might consider the consolidation of additional national or international data for comparison, if available. Third, geographical difference may be worth investigating to examine implications internationally, nationally among other countries, or regionally within specific jurisdictions associated with high incidence of specific drug use (e.g., Midwest US and NPS opioids). Fourth, this study specifically focused on substances present in both Reddit mentions and exposure cases. Future studies should examine NPS that do not appear in one of these data sources but are present in the other to identify pitfalls and/or improved strategies.Fifth, future work may also include the assessment of seized drug material trends and their correlation with mentions and/or exposures. Finally, future research is currently being conducted to monitor online vendor websites and their availability of NPS. In many cases, Reddit mentions are derived from individuals finding new drugs for sale online and then inquiring about or describing their identity or effects among subreddits. We hypothesize that online recreational drug suppliers may even be a predictor for increased Reddit mentions.

Conclusions

All NPS evaluated during this study were mentioned on Reddit and appeared in exposure cases in the US. Carfentanil, U-47700, eutylone, flualprazolam, *N*-ethylpentylone, isotonitazene, and brorphine appeared in discussions on Reddit prior to their implication in exposure cases; 5F-MDMB-PICA was the exception. The timeframe (mean 5.2 months, median 5 months, range 1-11 months, n=5) between peak mentions and peak exposures varied. Distinct increases and decreases in data were observed for both mentions and exposures for most drugs. In some cases, a dramatic rise in Reddit mentions was followed by a rise in exposure cases within only a few short months. In other cases, there was a long delay between increase in mentions and increase in exposures, in most part due to external factors affecting the drug market and marketing. This study demonstrates the usefulness of monitoring mentions of specific drugs on Reddit as a predictor for future increases in NPS-related exposures.

Financial Disclosure

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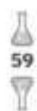
Highlights

- Timelines of NPS mentions on Reddit were compared to comprehensive toxicology data.

- Seven of eight evaluated NPS were mentioned online prior to emergence in exposure cases.

- Peak mentions generally preceded peak exposure, indicating usefulness as a predictor.

- Exposure events generally tracked similar yet delayed trajectories vs. mentions.
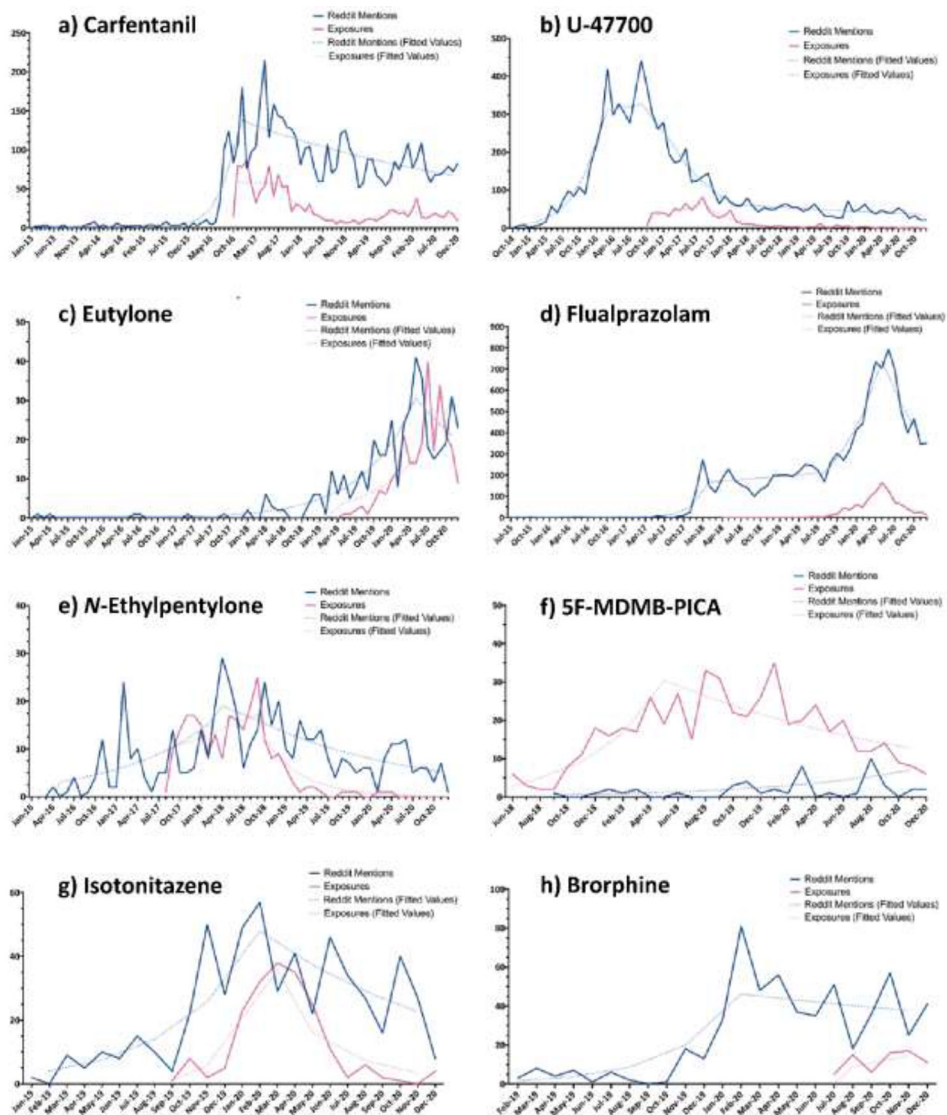
Figure 1:
Reddit post mentioning isotonitazene and soliciting feedback (from January 2019).
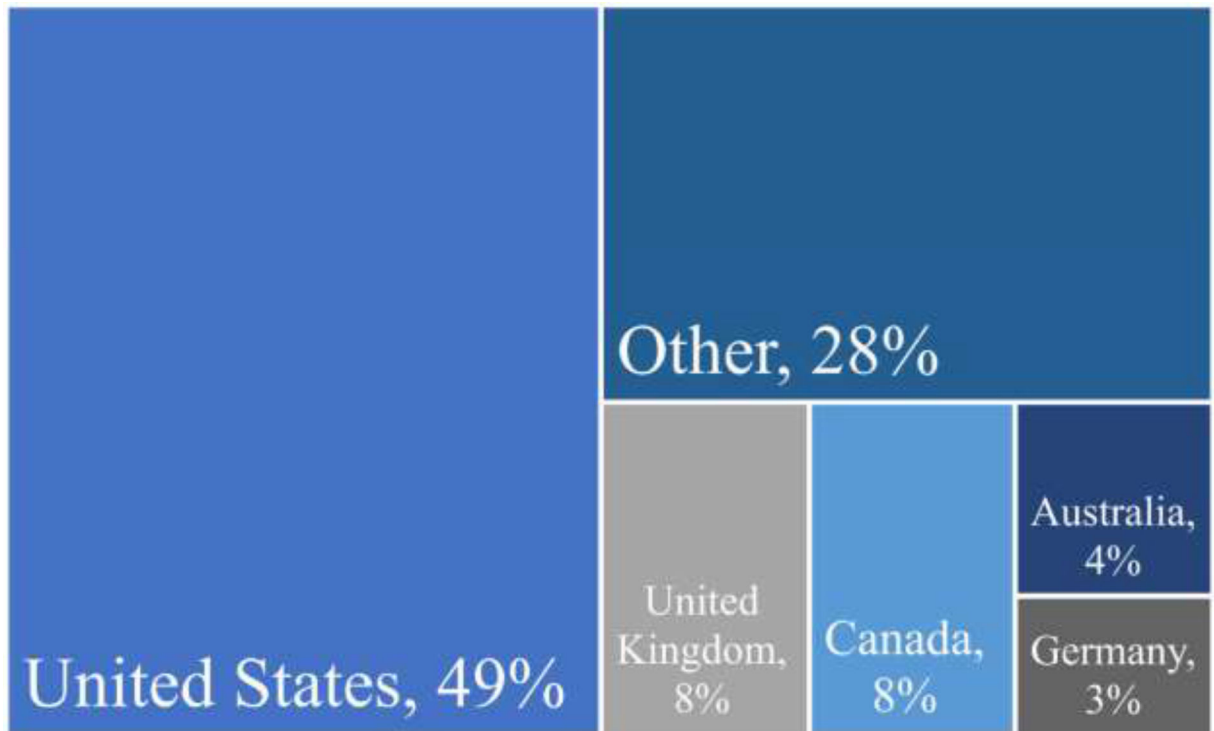
Figure 2:
Reddit traffic by country based on available statistics (as of December 2020). The "other" category includes the combined traffic from many countries (not reported individually).
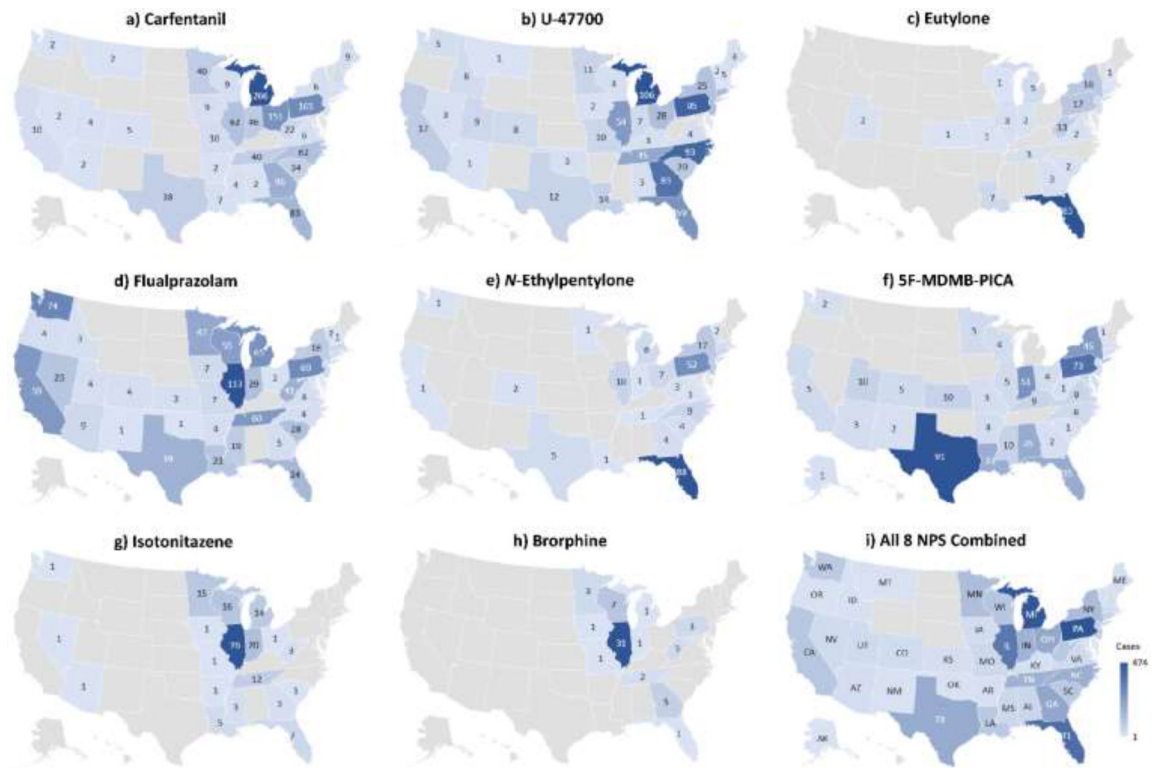
Figure 3:
Geographical distribution of toxicology sample origins for cases involving a) carfentanil, b) U-47700, c) eutylone, d) flualprazolam, e) *N*-ethylpentylone, f) 5F-MDMB-PICA, g) isotonitazene, and h) brorphine, as well as i) a combined map for all cases included in this study demonstrating national landscape.

Figure 4:
Plot of Reddit mentions and exposure cases (x-axis) over time (y-axis), including statistical modeling, for a) carfentanil, b) U-47700, c) eutylone, d) flualprazolam, e) *N*-ethylpentylone, f) 5F-MDMB-PICA, g) isotonitazene, and h) brorphine.

Table 1:

Characteristics of the eight NPS evaluated during this study.

Name	Drug Class	Synonyms	Reddit Keywords	Date Added to Toxicology Test*	Analytical Cutoff
Carfentanil	Opioid	Carfentanyl	"carfent"	October 2016	0.1 ng/mL
U-47700	Opioid	N/A	"u4", "u-4", "u47", "U- 44770", and "47700"	October 2016	0.2 ng/mL
Eutylone	Stimulant	N-ethyl butylone, bk- EBDB	N/A	March 2016	5 ng/mL
Flualprazolam	Benzodiazepine	N/A	"flualp"	October 2018*	2 ng/mL
N-Ethylpentylone	Stimulant	Ephylone, bk-EBDP	"ephylone"	May 2017*	10 ng/mL
5F-MDMB-PICA	Cannabinoid	MDMB-2201	N/A	March 2018*	0.1 ng/mL
Isotonitazene	Opioid	N/A	N/A	September 2019*	0.1 ng/mL
Brorphine	Opioid	N/A	N/A	September 2019*	0.1 ng/mL

*
Retrospective data-mining was performed to ensure drug positivity was not missed prior to included in toxicology testing scope.

Table 2:

Drug subreddits included for keyword monitoring, categorized by name and discussion topic.

Category	Subreddit Names
Drug-Specific	r/1P_LSD, r/2cb, r/4acodmt, r/adderall, r/afinil, r/ambien, r/AMT, r/Ayahuasca, r/cocaine, r/cripplingalcoholism, r/DMT, r/DPH, r/dxm, r/fentanyl, r/ketamine, r/kratom, r/LSA, r/LSD, r/MDMA, r/MemantineHCl, r/mescaline, r/meth, r/PCP, r/phenibut, r/PsilocybinMushrooms, r/Salvia, r/shroomers, r/shrooms
Drug Class-Specific	r/benzodiazepines, r/dissociatives, r/DissonautUniverse, r/gabagoodness, r/microdosing, r/noids, r/opiates, r/Opioid_RCs, r/PsychedelicMessages, r/Psychedelics, r/PsychedSubstance, r/Psychonaut, r/RationalPsychonaut, r/Stims, r/treedibles, r/trees, r/tryptonaut
Other/General Discussion	r/AnAnswerToHeal, r/AskDrugNerds, r/askdrugs, r/aves, r/bestoferowid, r/CurrentlyTripping, r/druganalytics, r/druggardening, r/DrugNerds, r/Drugs, r/DrugShowerThoughts, r/DrugsOver30, r/erowid, r/ObscureDrugs, r/ReagentTesting, r/researchchemicals, r/samelevel, r/TheDrugClassroom, r/TheeHive, r/tripreports, r/TripSit, r/TripTales

Table 3:

Timeline for emergence of select NPS with respect to online mentions and exposures, as well as US drug scheduling actions.

Drug	First Mention (Reddit)	First Exposure (Toxicology)	Intent to Schedule (US)	Temporary Schedule (US)
Carfentanil	2/2013	10/2016	1/1988	10/1988
U-47700	11/2014	10/2016	9/2016	11/2016
Eutylone	2/2015	5/2019	*Not Scheduled*	
Flualprazolam	8/2015	4/2018	*Not Scheduled*	
N-Ethylpentylone	4/2016	8/2017	6/2018	8/2018
5F-MDMB-PICA	9/2018	6/2018	12/2018	4/2019
Isotonitazene	1/2019	11/2019	6/2020	8/2020
Brorphine	2/2019	7/2020	12/2020	*Pending*