Increased in synthetic cannabinoids-related harms: results from a longitudinal web-based content analysis

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Abstract

Background—Synthetic Cannabinoid Receptor Agonists (SCRA), also known as "K2" or "Spice," have drawn considerable attention due to their potential of abuse and harmful consequences. More research is needed to understand user experiences of SCRA-related effects. We use semiautomated information processing techniques through eDrugTrends platform to examine SCRA-related effects and their variations through a longitudinal content analysis of web-forum data.

Method—English language posts from three drug-focused web-forums were extracted and analyzed between January 1st 2008 and September 30th 2015. Search terms are based on the Drug Abuse Ontology (DAO) created for this study (189 SCRA-related and 501 effect-related terms). EDrugTrends NLP-based text processing tools were used to extract posts mentioning SCRA and

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their effects. Generalized linear regression was used to fit restricted cubic spline functions of time to test whether the proportion of drug-related posts that mention SCRA (and no other drug) and the proportion of these "SCRA-only" posts that mention SCRA effects have changed over time, with an adjustment for multiple testing.

Results—19,052 SCRA-related posts (Bluelight (n=2,782), Forum A (n=3,882), and Forum B (n=12,388)) posted by 2,543 international users were extracted. The most frequently mentioned effects were "getting high" (44.0%), "hallucinations" (10.8%), and "anxiety" (10.2%). The frequency of SCRA-only posts declined steadily over the study period. The proportions of SCRA-only posts mentioning positive effects (e.g., "High" and "Euphoria") steadily decreased, while the proportions of SCRA-only posts mentioning negative effects (e.g., "Anxiety," "Nausea," "Overdose") increased over the same period.

Conclusion—This study's findings indicate that the proportion of negative effects mentioned in web forum posts and linked to SCRA has increased over time, suggesting that recent generations of SCRA generate more harms. This is also one of the first studies to conduct automated content analysis of web forum data related to illicit drug use.

Keywords

synthetic cannabinoids; web-forums; semantic web; drug abuse ontology; NLP text processing

Introduction

Synthetic cannabinoids are a large family of chemical substances designed to reproduce specific therapeutic/psychotropic properties of cannabis. Amongst these compounds, the Synthetic Cannabinoid Receptor Agonists (SCRA) mimicking -9-tetrahydrocannabinol (THC) have attracted substantial attention due to their potential for abuse, their numerous emergency department presentations and increasing number of overdose-related cases reported in the US and in Europe (AAPCC, 2016; Bush & Woodwell, 2014; J. Cohen, Morrison, Greenberg, & Saidinejad, 2012; European Monitoring Centre for Drugs and Drug Addiction, 2013; Forrester, 2012; Riederer, 2016; Trecki, Gerona, & Schwartz, 2015). These substances belong to the Novel Psychoactive Substances (NPS) category, a heterogeneous group of substances temporarily not regulated by international legislation (Papaseit, Farré, Schifano, & Torrens, 2014; Zawilska, 2011; Zawilska & Andrzejczak, 2015). SCRA products have been available for purchase in "head shops" and through online websites since 2004 (Fabrizio Schifano, et al., 2009). SCRA were initially dissolved and sprayed onto inert vegetal material to be sold as "herbal incense", "potpourri" or "legal high" labeled as "not for human consumption" under various marketing names (e.g., "Black Mamba", "Ultimate Warrior", "Mad Hatter"). SCRA were also commercialized directly in their powder form under their chemical designation (e.g., JWH-018, MAM-CHMINACA, UR-144).

Unlike natural cannabis products (e.g., floral cannabis, hashish, marijuana concentrates), SCRA are full agonists of the endocannabinoid CB_1 and CB_2 receptors inducing a stronger neuronal response (Brents & Prather, 2014; Huffman & Padgett, 2005). This enhanced neurological response is one of the main factors contributing to a large spectrum of observed adverse effects such as increased risk of psychosis (Every-Palmer, 2011; van Amsterdam,

Brunt, & van den Brink, 2015), seizures and convulsions (Schneir, Cullen, & Ly, 2011), dependence (Zimmermann, et al., 2009), and kidney failure (Bhanushali, Jain, Fatima, Leisch, & Thornley-Brown, 2012; Centers for Disease Control Prevention (CDC), 2013; Kazory & Aiyer, 2013).

Despite legislative efforts to regulate new cannabinoids as soon as they reach the market (e.g., the U.S. government has scheduled various SCRA molecules five times in the last five years), banned SCRA are rapidly replaced by molecules presenting chemical variation(s) to bypass current legal interdictions (J. A. Cohen, 2014; Lindigkeit, et al., 2009). For example, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) has reported the emergence of 134 SCRA from the end of 2008 until end of 2014 (EMCDDA, 2015). Reported emergency department cases linked to SCRA have increased in the U.S. over the past three years (Riederer, et al., 2016). According to the American Association of Poison Control Centers (AAPCC), 7,779 calls for of synthetic cannabinoid exposures were reported in 2015 exceeding both annual cases reported in 2013 (2,668) and 2014 (3,682) (AAPCC, 2016).

Except for a small number of epidemiological surveys describing SCRA use (Barratt, Cakic, & Lenton, 2013; Castellanos, Singh, Thornton, Avila, & Moreno, 2011; Caviness, Tzilos, Anderson, & Stein, 2015; Hu, Primack, Barnett, & Cook, 2011; Johnson, Johnson, & Portier, 2013; Vandrey, Dunn, Fry, & Girling, 2012; Winstock & Barratt, 2013a, 2013b), most of this literature informs either the neuropharmacology and neurophysiology of these products (Grigoryev, et al., 2011; Kavanagh, Grigoryev, Savchuk, Mikhura, & Formanovsky, 2013) or the adverse effects observed on emergency department patients (Besli, Ikiz, Yildirim, & Saltik, 2015; Bonar, Ashrafioun, & Ilgen, 2014; Johnson, et al., 2013; Tait, Caldicott, Mountain, Hill, & Lenton, 2016). Collecting information regarding SCRA patterns of use and related effects remains challenging because SCRA users are sometimes difficult to reach through conventional epidemiological surveillance methods. Furthermore, not all SCRA users who have experienced negative effects require or seek medical attention, nor were those who did receive medical attention necessarily assessed for SCRA-related symptoms (Tait, et al., 2016).

To overcome the challenges of identifying and recruiting SCRA users, we analyzed posts from web-forums dedicated to drug discussions. The last few years have seen an increased interest in the use of large-scale internet-based data as a source of information on evolving public health problems and emerging trends (Butler, et al., 2007; Daniulaityte, Nahhas, et al., 2015; Eysenbach, 2011; Lamy, et al., 2016; Lazer, et al., 2009; P. G. Miller & Sonderlund, 2010). Recent research has also demonstrated that social media analysis provides valuable information regarding new drug trends, such as the use of loperamide by opiate users to ease opiate withdrawal (Daniulaityte, et al., 2013), or changes in attitudes and behaviors of a population of synthetic cannabinoid users in Norway (Bilgrei, 2016).

In contrast to other social media platforms (such as Twitter or Instagram), Web forums allow their users to post extensive comments about their drug use, share experiences or ask questions regarding new products and trends. These websites also favor dialogue between users, who can share their thoughts, advice, and techniques on similar topics. Analysis of

such data can provide valuable information regarding effects, patterns of use, and opinions directly from the user's perspective (Miller & Sønderlund, 2010; Schifano, et al., 2006). Nevertheless, harnessing data on drug forums is a significant challenge due to the large amount of data displayed on Web forums. We used an advanced software platform, eDrugTrends (Daniulaityte, Nahhas, et al., 2015; eDrugTrends, 2015), to collect and analyze forum posts related to SCRA and their effects, and conducted a longitudinal analysis of drug-focused web-forum posts. The key aims of this study are to: 1) identify the most common SCRA-related effects discussed on Web forums; and 2) analyze how frequencies of SCRA and their effects mentioned in Web forum discussions changed from January 2008 through September 2015.

Methods

The eDrugTrends system is a semi-automated comprehensive platform resulting from collaboration between social scientists in the Center for Interventions, Treatment and Addictions Research (CITAR) and computer scientists in the Ohio Center of Excellence in Knowledge-enabled Computing (Kno.e.sis Center) (eDrugTrends, 2015). This platform is designed to extract, process, and analyze social Web data, with the current application directed towards understanding cannabis and synthetic cannabinoid-related trends from Twitter and selected Web forums.

Data Collection

Data were collected from three publicly available web-based sources: Bluelight, Forum A, and Forum B. Web forum posts were retrieved using a combination of source specific custom Web Crawlers for Forums A and B, and through direct data transfer from Bluelight. Only publicly available/viewable information was collected and stored in the eDrugTrends platform. We have collected data from the opening of the Web forums until September 30, 2015. Since synthetic cannabinoids emerged in 2008, for this analysis we used Web forum data posted between the January 1, 2008 and September 30, 2015.

Ethical considerations

The study was approved by the Wright State University IRB under exemption 4 (i.e., Exempt Human Subjects Research) as collected data are publically available. One of the three forums used in this study, Bluelight.org, has a research portal accessible from the front page of the website, which asserts Bluelight's ownership of the forum content and instructs researchers to contact Bluelight administrators to discuss proposals for research, including archival analyses. The researchers contacted Bluelight to initiate discussions regarding this project, resulting in a partnership approach involving contributions of Bluelight representatives to the eDrugTrends project. The other two forums have been anonymized because data were freely available and consent has not been obtained. Any direct quotations in this paper were adequately modified without altering their basic meaning to protect the anonymity of the Web forum users who have posted these comments from being re-identified through searching on these quotations (Roberts, 2015).

Data Processing and Drug Abuse Ontology

Data extraction is based on a domain expert-driven ontology, the Drug Abuse Ontology (DAO). The DAO is a domain-specific conceptual framework interconnecting sets (named "classes") of drug-focused lexicons initially designed for the PREDOSE project which analyzed Web forum posts mentioning buprenorphine (Cameron, et al., 2013; Daniulaityte, Carlson, Brigham, Cameron, & Sheth, 2015). One of the key benefits of using an ontology-enhanced semantic approach is the ability to identify all variants of a concept in data. For example, Daniulaityte et al. (Daniulaityte, Carlson, et al., 2015) report that for every occurrence of "buprenorphine" there were twenty-nine occurrences of its variants in other forms such as slangs (e.g., "bupe") and alternative names (e.g., "Suboxone").

The DAO was extended and refined for the eDrugTrends project (eDrugTrends, 2015) by encompassing and classifying words and expressions specific to cannabis and synthetic cannabinoids. Hence, the first phase included identifying specific SCRA terminology such as chemical denominations, commercial names and slang terms, and updating the DAO for the new research objectives. These search terms were drawn from the scientific literature, and names of "spice" products were collected from online retail shops (e.g., Ghcmarijuana; OrganicSpiceBlend). Next, the DAO was populated with general medical terms and slang expressions representing physical/psychological effects induced by drugs. These terms were based on the medical literature describing drug use consequences and extended with common denominations and/or slang terms for each of the existing medical terms. For example, the medical terms "bruxism" has been associated with the common denomination "jaw clenching" and the slang term "teeth grinding." Drug effect expressions frequently contain a mention of a body part or a specific organ (e.g., "head", "legs" or "lungs") with a combination of adjectives and/or present/past participles describing the symptoms (e.g., "heart racing", "upset stomach", "nasty cough"). Hence, a Natural Language Processing algorithm was developed to inductively extract such expressions in posts by using the NLTK (i.e., Natural Language ToolKit) package from the Python computational language (Bird, Klein, & Loper, 2009; van Rossum, 1990).

Based on 4000 random posts, terms referring to organs/body parts were first recognized by comparing each word in the post with effect terms listed in the DAO and "tagged" as entities of interest. Secondly, the contextual words surrounding the tagged organ/body part were collected to recreate expressions. Relevant extracted expressions were manually selected and added to the index of effect-related terms already populating the DAO. Based on the scientific literature and the content of websites selling SCRA, the DAO was populated with 189 SCRA-related terms (cf. Supplementary material 1), which brings the total of substance denotations and slang terms contained in the DAO to 497. The DAO also indexes 501 effects and associated slang terms as search terms (cf. Supplementary material 2) based on medical literature concerning drug use, the domain-expert knowledge of the CITAR team, and expressions extracted using the NLP algorithm.

Content analysis

Content analysis focused on quantitative word frequency analysis and concept cooccurrence analysis. To extract relevant posts, the following post search queries were performed: first,

posts containing at least one mention of SCRA based on DAO searched terms were extracted. Next, SCRA-related posts that mentioned other types (or type) of substances were removed by processing a negative query (SCRA-related terms AND NOT other drug-related terms) to ensure that effects described in one post were linked to SCRA and not to another drug or to a combination of substances (herein designated as SCRA-only). Third, SCRA-only posts were processed further to identify frequencies of different effect mentions. This analysis was based on the search terms referring to potential drug effects indexed in the DAO. Effect-related terms belonging to the same group were encompassed in a common category; for example, "anxiety", "anxious", "anxiety attack", and "panic attack" were grouped under the common category "Anxiety." A "fuzzy" query based on Damerau-Levenshtein edit distance was used to collect misspelled effect terms (Damerau, 1964; Levenshtein, 1966). This edit distance allows misspelled words, such as "siezure" instead of "seizure", be captured by our query.

Trend Analysis

To examine changes over time, the following data were recorded for each month of data collection: (1) the number of drug-related posts ("Posts"); (2) of these, the number that mentioned an SCRA-related term ("SCRA Posts"); (3) of these, the number that mentioned no terms related to any other drugs ("SCRA-Only Posts"); (4) of these, the number that mentioned any SCRA-related effect ("SCRA-Only Effect Posts"); (5) of these, the number that mentioned any of the seven most commonly mentioned SCRA effects based on our content analysis (anxiety, euphoria, high, nausea, overdose, seizure, and hallucination) ("Frequent Effect Posts"); and (6) the numbers of posts mentioning each of the seven most frequent effects ("Individual Effect Posts"). We have limited our results to categories representing more than 2% of the effects mentioned in posts to present the most frequent effects discussed by forum users.

The following proportions were computed for each month:

- SCRA Posts, SCRA-Only Posts, SCRA-Only Effect Posts, and Frequent Effect Posts, each as a proportion of Total Posts

- SCRA-Only Posts, SCRA-Only Effect Posts, and Frequent Effect Posts, each as a proportion of SCRA Posts

- SCRA-Only Effect Posts and Frequent Effect Posts, each as a proportion of SCRA-Only Posts

- Frequent Effect Posts as a proportion of SCRA-Only Effect Posts

- Individual Effect Posts, each as a proportion of SCRA-Only Posts

- Individual Effect Posts, each as a proportion of Frequent Effect Posts

Time trends for these 24 proportions were estimated using generalized linear regression (Pinheiro & Bates, 2006) without assuming a linear trend; rather, time was modeled via a restricted cubic spline function (Devlin & Weeks, 1986) with four knots. The model was fit using the RMS and NLME packages in R 3.3.1 (Harrell, 2016; Pinheiro, Bates, DebRoy, & Sarkar, 2016; R Core Team, 2016), with knots at the 5th, 33rd, 67th, and 95th quantiles of the

time distribution (05/2008, 09/2010, 01/2013, and 05/2015). For each of the 24 outcomes, the null hypothesis of no time trend was tested using a 3 d.f. Wald test comparing the spline fit to a flat trend. Adjustment for multiple testing across the 24 tests was done via the Hommel procedure (Hommel, 1989) in SAS PROC MULTTEST (SAS, 2010) to preserve a familywise $\alpha = 0.05$ Type I error rate. Individual p-values are presented as Hommel-adjusted (HA) p-values.

Results

Data extraction

The eDrugTrends platform collected a total of 19,823,726 drug-related posts (Bluelight: 1,558,832; Forum A: 18,170,129; Forum B: 94,765) written by 67,841 forums users. Forum users were identified by their unique ID serial for each forum. Counting users by their forum ID implies that (a) one individual could create several accounts in a web-forum and s/he will be considered as several different "forum users"; (b) the same individual will be identified as different users across several forums. Our geolocation data remain partial as drug-focused Web forum users are not generally inclined to reveal their country of residence and because Forum B does not display any location field for users. Aggregate data provide by Bluelight indicate that the majority of their users are located in the U.S (61.9%), followed by U.K (10.9%), Canada (5.6%), Australia (4.6%), Germany (1.4%), and Netherlands (0.9%). Data extracted from Forum A publically displayed user profiles also indicate that most of users are geolocated within the U.S (52.1%), followed by U.K (19.5 %), Canada (5.1%), Ireland (3.3%), Australia (2.9%), Netherlands (2.3%), and Germany (1.5%).

The extracted data covered the time period from 01/01/2008 until the 09/30/2015. Out of the total 19,823,726 posts, 45,163 (0.22%) were SCRA-related posts (Bluelight (n=8,254), Forum A (n=9,271), and Forum B (n=25,981)) posted by 5,468 users (12.88% of all Web forum users). We then isolated posts only mentioning SCRA (and no other drugs of abuse), reducing the number of posts to a total of 19,052 (Bluelight: n=2,782; Forum A: n=3,882; Forum B: n=12,388) from 2,543 users (3.7% of all Web forum users). Among the 19,052 posts, 5,160 posts (27.1%) posted by 1,281 users (50.9% of users that posted SCRA-only posts) contained at least one mention of one of the 501 effect-related terms indexed in the DAO. Feeling "High" appeared to be the most common effect mentioned in SCRA-only posts (43.2%, n=2,155), followed by "Hallucinations" (11.2%, n=560), "Anxiety" (9.4%, n=470), "Overdose" (6.2%, n=307), "Euphoria" (5.7%, n=286), "Seizures" (5.4%, n=267), and "Nausea" (4.9%, n=246) (see examples in Table 1). The effect categories, associated search terms, and results of the frequency analysis are presented in Table 2.

Longitudinal analysis

Even after adjusting for multiple testing, all but three of the 24 trends were statistically significant (cf. Table 3). For brevity, we present specific results only for trends in the following nine proportions: SCRA-Only Posts per Post, Frequent Effect Posts per SCRA-Only Effect Post, and each of the seven Individual Effect Posts as a proportion of SCRA-Only Posts.

The percentage of SCRA-only posts out of the total number of collected posts steadily decreased from about 0.425% in January 2008 to 0.055% in September 2015 (HA p < 0.0001; see Figure 1). Of these SCRA-only posts, the proportion mentioning at least one of the seven most frequently mentioned effects also decreased, from about 20% in January 2008 to 16% in September 2015 (HA p = 0.0305; see Figure 2).

The longitudinal analysis of changes over time in individual SCRA-related effect mentions reveals disparities within the seven most frequently mentioned effects (see Figure 3). Although "High" remains the predominant mentioned effect, the proportions of mentions of "High" (HA p = 0.0030) and "Euphoria" (HA p < 0.0001) each continuously decreased between January 2008 and September 2015. In contrast, mentions of "Seizure" sharply increased over the same time (HA p < 0.0001). "Overdose" (HA p < 0.0001) and "Anxiety" (HA p = 0.0013) trends displayed a sawtooth pattern, increasing through 2010, then decreasing through 2013, and finally slightly increasing again from 2014 to September 2015. Posts mentioning "Nausea" (HA p < 0.0001) increased through 2013, but sharply decreased thereafter. Mentions of "Hallucination" increased through 2012 before plateauing until the end of the data collection period; however, after adjusting for multiple testing, this trend was not significantly different from no change over the entire period (HA p = 0.1497).

These results indicate that SCRA-related effects that are perceived as positive (i.e. "High" and "Euphoria") have decreased since 2008, while "negative" effects (i.e. "Nausea", "Seizure", "Anxiety", and "Overdose") have increased over the same period (although mentions of "Nausea" are on the decline).

Discussion

To the best of our knowledge, this study is the first to evaluate the frequency and trends of effects associated with SCRA use based on web-forum data. Our analysis shows that the proportion of drug-related posts mentioning at least one SCRA and no other drug has consistently decreased since 2008 without completely disappearing. The most frequent categories of effects mentioned in SCRA-only posts are "High," "Hallucinations," "Anxiety," "Euphoria," "Nausea," "Overdose," and "Seizure." These types of SCRA-related effects are consistent with the effects described by ER patients in the literature (Derungs, et al., 2013; Tait, et al., 2016): for example, gastrointestinal symptoms such as nausea and vomiting (Banerji, Deutsch, & Bronstein, 2010; Bozkurt, Umut, Evren, & Karabulut, 2014; Fattore & Fratta, 2011; Forrester, Kleinschmidt, Schwarz, & Young, 2011; Freeman, et al., 2013; Gugelmann, et al., 2014; Heath, Burroughs, Thompson, & Tecklenburg, 2012; Heltsley, et al., 2012; Hermanns-Clausen, Kneisel, Hutter, Szabo, & Auwärter, 2013; Hermanns-Clausen, Kneisel, Szabo, & Auwärter, 2013; Hopkins & Gilchrist, 2013; McQuade, Hudson, Dargan, & Wood, 2013; Schneir, et al., 2011; Simmons, et al., 2011; Tofighi & Lee, 2012; Vearrier & Osterhoudt, 2010), anxiety (Benford & Caplan, 2011; Castellanos, et al., 2011; J. Cohen, et al., 2012; Control & Prevention, 2013; Every-Palmer, 2011; Glue, et al., 2013; Harris & Brown, 2013), hallucinations (Auwärter, et al., 2009; Castellanos, et al., 2011; J. Cohen, et al., 2012), and seizures (Harris & Brown, 2013; Hermanns-Clausen, Kneisel, Hutter, et al., 2013; Hermanns-Clausen, Kneisel, Szabo, et al.,

2013; Lapoint, et al., 2011; Schneir, et al., 2011; Vearrier & Osterhoudt, 2010) have been reported in several clinical research and emergency department reports.

The decrease of SCRA-related posts echoes the decrease of SCRA consumption observed over the past few years in the countries from where most of the Web forums users are geolocated (U.S. (Johnston, Miech, O'Malley, Bachman, & Schulenberg, 2015), U.K (U.K Home Office, 2016), Australia (Sutherland, et al., 2016)). Our longitudinal analysis demonstrates that positive effect (i.e., "High" and "Euphoria") proportions continuously decreased since 2008. In contrast, the proportion of negative effects grouped under the categories "Nausea," "Seizure," "Anxiety," and "Overdose" have increased during the same period. We are unaware of another study investigating the variations of SCRA-related effects over time. However, our results are consistent with the qualitative analysis Norwegian Web forum data of Bilgrei (2016) that demonstrated how the opinion of forum users gradually changed from an "initial attractiveness" in late 2007, to "ambivalent opinion" in late 2008/ early 2009, to finally become a "communal rejection" thereafter, mainly because the number of negative effects overweighed the number of positive effects over time (Bilgrei, 2016).

The "overweighing" proportion of negative effects described by Bilgrei and the increased proportions of negative effects we observed could be explained by the constant and frequent changes in the SCRA molecules available on the drug market (J. A. Cohen, 2014; Lindigkeit, et al., 2009). Over the last eight years, despite the successive administrative bans, illicit SCRA manufacturers have continuously introduced new SCRA molecules on the market (J. A. Cohen, 2014). At least three "generations" of SCRA (Fattore & Fratta, 2011; Shanks, Behonick, Dahn, & Terrell, 2013; Shanks, Dahn, Behonick, & Terrell, 2012) have succeeded each other since the first administrative ban early 2009 for several European countries (UK Statutory Instrument, 2009) and on March 1, 2011 in the U.S. (Drug Enforcement Administration, 2016). 2013-2015 drug seizure data from NFLIS (National Forensic Laboratory Information System) indicate that first generation (e.g., JWH-018, JWH-073, JWH-250) and second generation molecules (e.g., JWH-122, XLR11, UR-144) were either not seized or were on the decline, while the number of seizures of third generation of SCRA (e.g., FUBINACA, AB-CHMINACA, MAB-CHMINACA) were on the rise. These data suggest that new generation of SCRA have become increasingly available on the drug market in contrast with banned molecules which tend to recede over time (Drug Enforcement Administration, 2016). The latest generation of SCRA (e.g., CHMINACA, FUBINACA) displays increased endocannabinoid CB_1 and CB_2 receptor affinities compared to the previous generations (Aung, et al., 2000; Franz, Angerer, Moosmann, & Auwärter, 2016; Iversen, 2015; Labay, et al., 2016; Uchiyama, Kawamura, Kikura-Hanajiri, & Goda, 2013; Wiley, et al., 2015), which means that, at the same dose, the third generation SCRA induce stronger reactions and, in turn, increase the risks of harm. Users are more likely to use higher than necessary doses because they are not properly informed regarding the type and potency of the higher affinity SCRA, especially while smoking "herbal blends", as the substances sprayed on inert materials have changed in composition or molecular structure following administrative bans. Thus, an unintended consequence of these administrative bans appears to have been the introduction of more potent SCRA molecules in the drug market (Iversen, 2015; Reuter & Pardo, 2016), leading the remaining population of SCRA users to experience more negative outcomes. In turn, the deterrent effects inherent in the

higher potency of newer generations of SCRA may have induced a diminution in SCRA use as observed by Bilgrei (Bilgrei, 2016) among Norwegian Web forum users.

Our study illustrates the potential to collect useful epidemiologic information by harnessing web-forum social data and how monitoring emerging NPS for harmful effects using Web forum content analysis can inform public health professionals. The Natural Language Processing techniques developed for this study allow extending inductively the number of relevant expressions describing effects.

Despite these findings, this study has several limitations. Although little is known about the population of SCRA users, the population of web-forum users is not necessarily representative of the general population of SCRA users in any country. Several newspapers articles (Doward, 2015; Karlamangla, 2016; Thompson, 2016) and a scientific paper (Nolan, Allen, Kunins, & Paone, 2016) have described an increased number of ER presentations in the population of homeless due to the consumption of SCRA in the past few years, and these populations are not likely to be represented in web-forum populations. Other limitations are inherent to the field of Internet-based research. Although our findings are consistent with trends and results of other research and reports, by focusing on keywords and not on the whole post text, only mentions of keywords were captured without the possibility to ensure direct relationships between SCRA and identified effects. Our semantic approach involving use of Drug Abuse Ontology and Natural Language Processing techniques was targeted to alleviate this limitation. Second, our current approach does not allow differentiating effects mentioned as the report of self-experienced effects, witnessed in other users, or part of a more general discussion. Because this latter possibility could potentially amplify the proportions of effects mentioned in the total number of posts, our future work will develop a classification of posts by type of communication to increase the precision of this method. Third, by limiting our analysis to posts containing only SCRA and no other drugs, we have potentially missed some frequent effects; users frequently compare the effects of one substance with another, for example, comparing the withdrawal linked to SCRA to heroin withdrawal. Fourth, this analysis did not compare the effects of SCRA in powder form versus effects induced by "herbal blend" or e-liquid as not all users specify which form of SCRA they were using. Fifth, it is unclear if these increases are related to immediate effects induced by SCRA or if long-time users are discussing their past experiences while sharing their opinions with other forum users. Sixth, our users' geolocation data are only partial making difficult to deduce accurately the correlation between negative effects and SCRA generations as the administrative bans starting dates vary from country to country. Finally, the most frequent effects described in this study, as well as in the literature, are short-term effects. Long-term effects remain unknown at the moment and require further research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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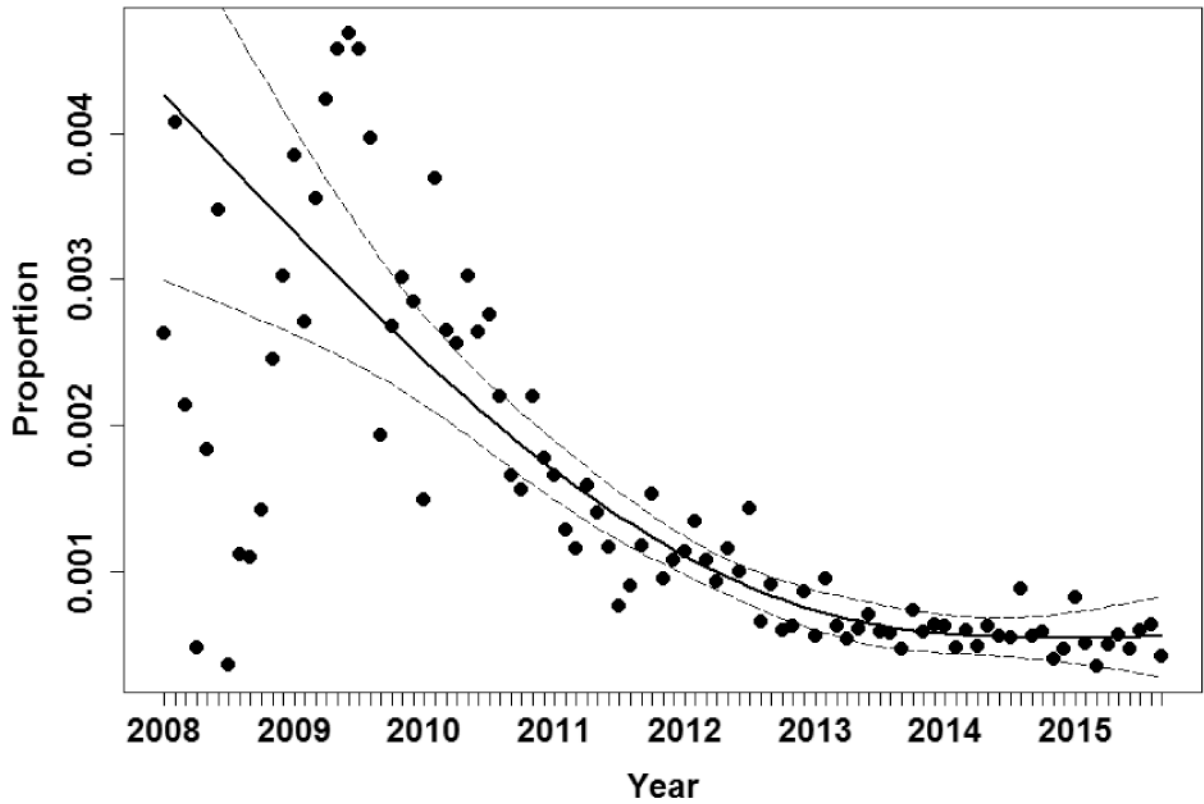
Figure 1.
Proportion of all posts ("Posts") that mention SCRA but not other drugs ("SCRA-Only Posts") (January 1, 2008 to September 30, 2015) (solid line = estimated mean, dotted lines = 95% confidence interval for the mean)
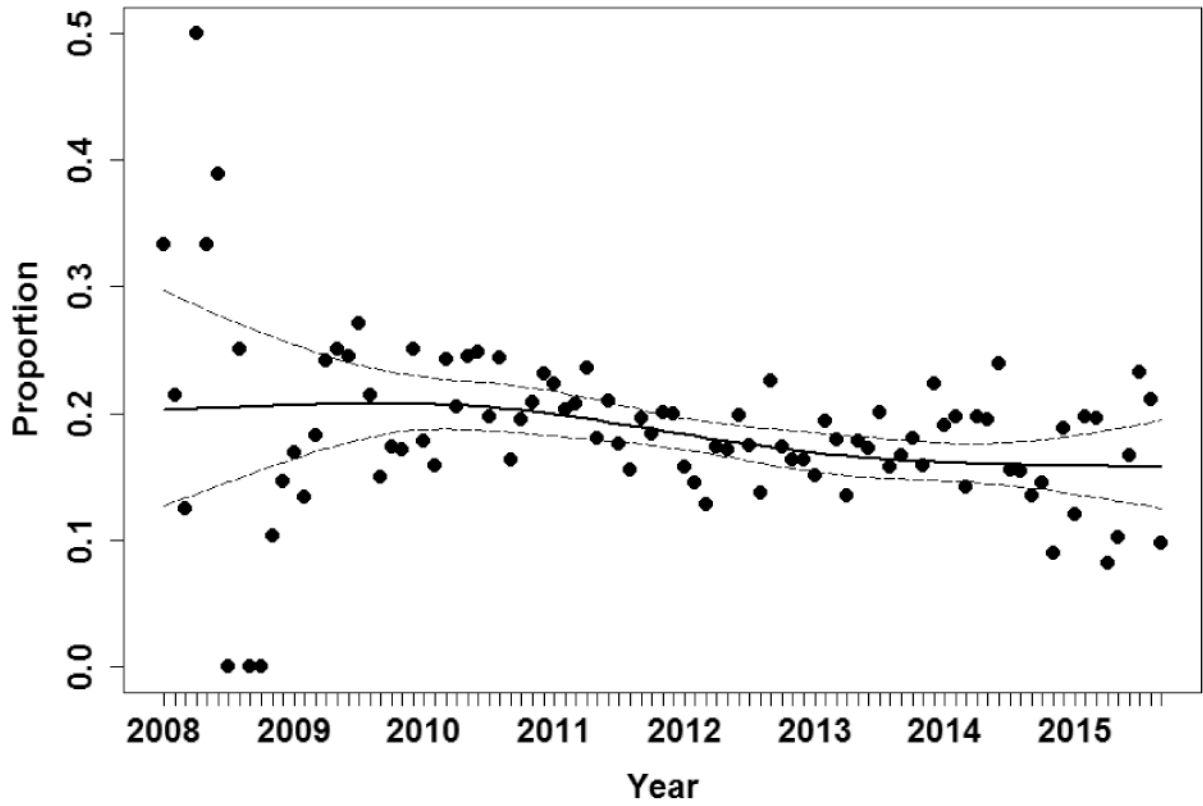
Figure 2.
Proportion of SCRA-Only Posts mentioning at least one of the seven most frequently mentioned effects ("Frequent Effect Posts") (January 1, 2008 to September 30, 2015) (solid line = estimated mean, dotted lines = 95% confidence interval for the mean)
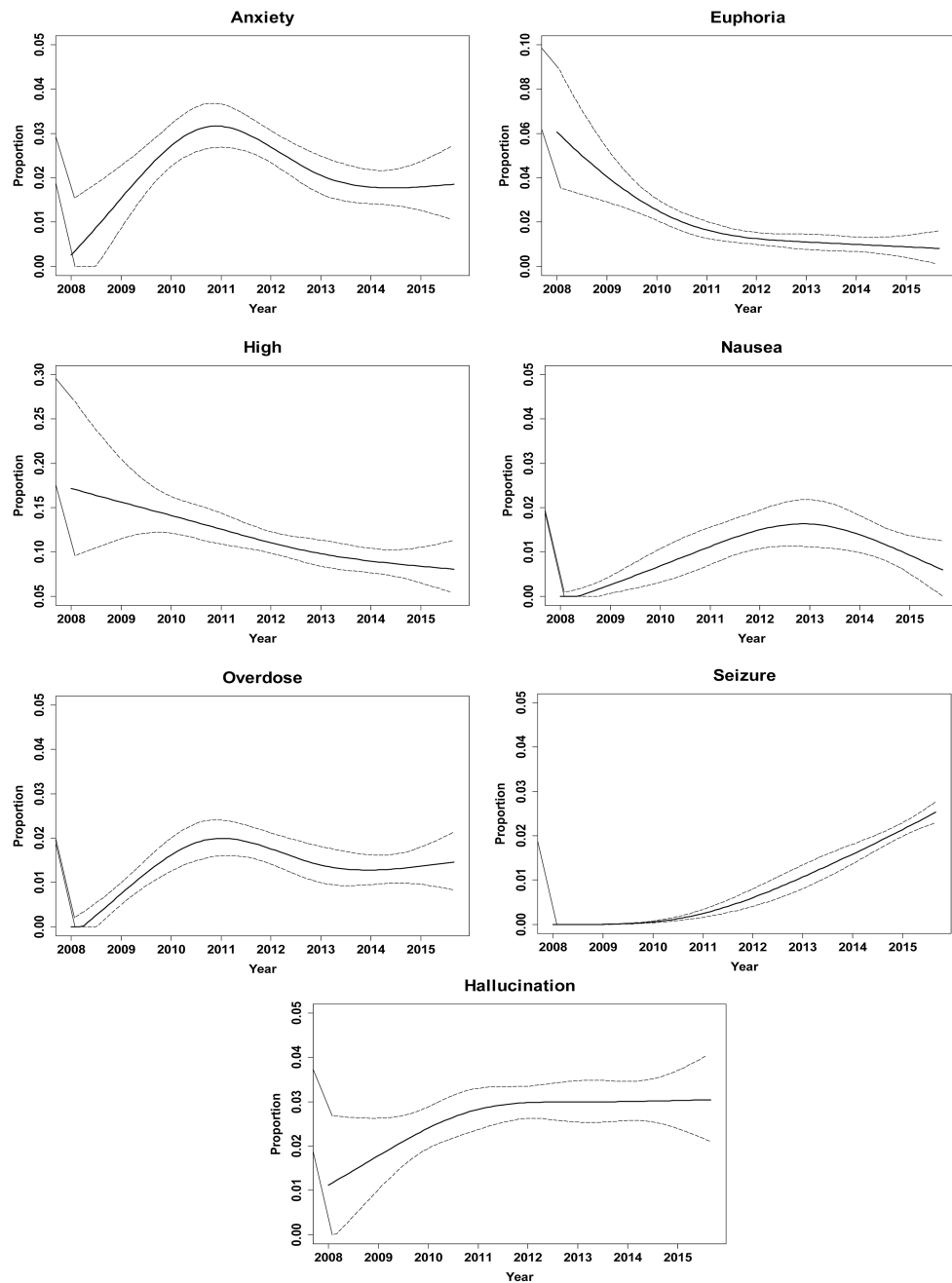
Figure 3.
Proportion* of SCRA-Only Posts mentioning each of the seven most frequently mentioned effects (January 1, 2008 to September 30, 2015) (solid line = estimated mean, dotted lines = 95% confidence interval for the mean)

*The scales were chosen to highlight the shape of each trend rather than the magnitude of the proportions. If plotted on a scale from 0% to 100%, trends in rare side effects would not be visible. Thus, not all figures have the same vertical scaling.

Table 1

Examples of SCRA effects mentioned in web-based forums.

High:

"My Trip Report on JWH-018 is like, a good example of being super high. I'm high on JWH-018 at the moment, and I'm really good."

Hallucinations:

"I love psychedelics and would consider myself a happy and experienced tripper but the trip I got from K2 was the worst trip that I have ever experienced. No connections with reality, I couldn't remember who I was, thought I was living in a post-apocalyptic world. Vomit everywhere. My buddy told me that my lips went blue. Visibly, I was shaking and was unable to move, kept asking who I was, who they were."

Anxiety:

"After smoking spice, I experienced depersonalization…. I hated it and it was intense and… I ended up in the ER, having a panic attack."

Euphoria:

"I made a very tiny rolled joint, approximatively 75mg, and I had effects much milder than last night. I had a head rush for about 2-3mins, then sober up in a relaxed state."

Nausea:

"My friend got too high from that stuff and it was one of the scariest thing I've ever witnessed. He was screaming and begging for an ambulance, sweating alot, crying, afraid, and was vomiting for over a couple of hours."

Overdose:

"I blacked out and overdosed while throwing up and convulsing on K2. I was stupid and changed to another type and blacked out one more time. That crap is Fucking evil. I will never do that again."

Seizure:

"I was hooked on spice for about a year back in 2010. Lost my voice from smoking it too much and was shoplifting after I sold every games and BluRay I had. I never allowed myself to buy the pure chemical because I had 3 seizures before because of that. One of those seizures let me 3 days in a coma and I ended up with severe amnesia I waste about 10 months of my life due to that stuff."

Table 2

Frequencies of effects mentioned in SCRA-only posts (n=19,052)

Effects	Searched Terms	N (Percentage)
High	high *, stoned, "headrush"	2155 (43.2%)
Hallucination	trip, tripping, hallucinating, visual distortions, hearing things, time dilatation, psychedelic	560 (11.2%)
Anxiety	anxiety, panic attack, anxious, anxiety attack	470 (10.2%)
Euphoria	euphoric, euphoria, rush, buzz, bliss	286 (5.7%)
Nausea	nausea, vomiting, threw up, puking, vomit, throwing up, puke, throw up, vomited	250 (4.9%)
Overdose	overdose, od, overdosed, oded, od's	307 (6.2%)
Seizure	seizure, seizures **	267 (5.4%)

*
 Terms such as "too high", "high dose", "high temperature", and "high amount" were removed from the query to ensure more accurate results relative to this search term.

**
 To avoid confusion with law enforcement seizures, posts containing mention of "border", "custom", or "DEA" were removed.

Table 3

Results of trend analysis

Test #	Proportion	Raw p-value	P-value after multiple comparisons adjustment	
1	Frequent Effects (% of all posts)	<.0001	<.0001	
2	Any Effect (% of all posts)	<.0001	<.0001	
3	SCRA-Only Posts (% of all posts)	<.0001	<.0001	Figure 1
4	SCRA Posts (% of all posts)	<.0001	<.0001	
5	Frequent Effects (% of SCRA posts)	<.0001	<.0001	
6	Any Effect (% of SCRA posts)	<.0001	<.0001	
7	SCRA-Only Posts (% of SCRA posts)	<.0001	<.0001	
8	Frequent Effects (% of SCRA-only posts)	0.0076	0.0305	Figure 2
9	Any Effect (% of SCRA-only posts)	0.0001	0.0008	
10	Frequent Effects (% of any effect posts)	0.7909	0.7909	
11	anxiety (% of frequent effects)	0.0003	0.0019	
12	euphoria (% of frequent effects)	<.0001	<.0001	
13	high (% of frequent effects)	0.0007	0.0034	
14	nausea (% of frequent effects)	<.0001	<.0001	
15	overdose (% of frequent effects)	0.0179	0.0536	
16	seizure (% of frequent effects)	<.0001	<.0001	
17	hallucination (% of frequent effects)	0.0002	0.0013	
18	anxiety (% of SCRA-only posts)	0.0002	0.0013	Figure 3
19	euphoria (% of SCRA-only posts)	<.0001	<.0001	Figure 3
20	high (% of SCRA-only posts)	0.0006	0.0030	Figure 3
21	nausea (% of SCRA-only posts)	<.0001	<.0001	Figure 3
22	overdose (% of SCRA-only posts)	<.0001	<.0001	Figure 3
23	seizure (% of SCRA-only posts)	<.0001	<.0001	Figure 3
24	hallucination (% of SCRA-only posts)	0.0749	0.1497	Figure 3