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Retrospective Analyses of High-risk NPS: Integrative Analyses of PubMed, Drug Fora, and the Surface Web

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Abstract

Background: Novel psychoactive substances (NPS) can be classified based on their safety for use into low-risk and high-risk. High-risk NPS can be either lethal or poisonous. Fatalities can be either pharmacological or behavioural-induced, including suicide and homicide.

Materials and Methods: Observational analysis, including retrospective, were implemented across; Google Trends, PubMed/MedLine database; Drug Fora, and the surface web. The aim was to collect data in relation to incidents of intoxication and fatalities caused by forty-seven (47) of the most popular NPS and to infer the high-risk (hazardous) substances. Geo-mapping was also applicable. Inferential analyses were also carried out to deduct data on the different age grouping of (ab)users.

Results: Among the most popular NPS substances, nearly half of them were labelled as high-risk due to their relatively high incidence of intoxications and deaths. The substances included; DMA/DOX, MXE, Mescaline, Methylone, Crack, GHB, Benzodiazepines, NBOMe, 2C-B, DMT, Stimulants RCs, Shrooms, Ketamine, Opioids, Heroin, Meth, Speed, LSD, MDMA, and Cocaine. Many of these substances were either psychedelic or dissociative substance. Geo-mapping of use indicated that the top ten contributing countries were; Australia, Canada, United States, United Kingdom, New Zealand, Ireland, Norway, Netherlands, Switzerland, and Estonia. The contribution of the Middle East was insignificant, although data have regularly been noticed originating from Israel, Iran, and Turkey.

Conclusion: In this study, an unconventional inferential method is suggested for analysis of high-risk NPS; it is based on cross-sectional and longitudinal analysis of data. It relies primarily on data from; the surface web, Google Trends, PubMed/Medline database, and drug fora. This method is not only descriptive but also inferential for age and gender among (ab)users of a diverse array of high-risk NPS substances.

Keywords: Surface Web, Deep Web, Google Trends, Darknet, PubMed, drug fora, high-risk, intoxication, morbidity, epidemiology, retrospective, death, mortality, LSD; MDMA, Psilocybin, Ketamine, DMT

1. Background

NPS can be classified based on their safety for use into low-risk and high-risk. High-risk NPS can be either lethal or poisonous; fatalities can be either pharmacological or behavioural-induced. There have been previous attempts in the literature to study the incidence of intoxications and deaths caused by NPS via observational cross-sectional and retrospective analysis of data. This study will further explore the most popular NPS on the deep web via the Darknet and its e-markets. AlphaBay, one of the leading e-markets on the darknet, will be examined to retrieve data on the trending substances; these will be categorized as found on the e-market (Bancroft et al., 2016; Broséus et al., 2016; Van Hout et al., 2015, Wehinger et al., 2011). The NPS classification system does not depart far from the system adopted by Dargan and colleagues (Dargan, 2013; Moore et al., 2013; Nizar et al., 2015).

Current NPS-related web analytic studies are frequently based on internet snapshots, retrospective studies, reviews, and other observational analyses. To date, there are no significant interventional studies or animal models. In fact, all web analyses are purely observational, though attempts for quasi-experimental studies are emerging (Hegde et al., 2013; Van den Brink, 2012). These methods are not only highly time-consuming and requires advanced resources, including, financial, human, chemical analysis, and legislative resources, but they are also mere observations which are obsolete beyond the point of time in which they were taken (Nizar et al., 2015; Vermette-Marcotte et al., 2014; Wood & Dargan, 2014). Hence, observational and internet snapshot techniques can be considered as “endangered” methods, unless some drastic upgrades are introduced.

The upgrades should serve to reduce time and efforts, three methods are proposed; finding and targeting the most popular NPS on the web, both surface and deep web. The 2nd method is dependent on the 1st one; it includes extracting data in relation to the high-risk substances among the most popular ones (Moore et al., 2013; Schifano et al., 2015). The 3rd method implies the inclusion of data mining and knowledge discovery in databases (KDD). All these three methods should be implemented in an integrative way to extract data principally from; the predominant medical and paramedical databases, including PubMed and the Cochrane Library (1), the most popular drug fora (2) Google Trends database (3), high-rank e-markets on darknet, including AlphaBay (4), and Grams search engine (5) (Berry and Linoff, 1997; Butte and Kohane 1999; Buxton and Bingham, 2015; Martin, 2014). The aim is to reduce the efforts, in parallel with the automation principle of KDD. The traditional ways of observational web analytics are slow, consumptive, outpaced, outsourced, and may soon become obsolete.

2. Materials and Methods

The most popular classes (chemical categories) of NPS will be assessed across the darknet; these will be evaluated primarily on the AlphaBay e-market. NPS items included under each category will also be screened and scored (for the number of hits) in an aim to discover the most popular substances. These will be later visually presented in an ascending order of popularity (availability). Each individual item (NPS) will be thoroughly evaluated for safety (risks, side effects, and adverse reactions); these are expressed in the form of cases of intoxications (morbidities) and fatalities (mortalities). Precarious NPS will be labelled as red (dangerous) on a visual presentation. The screening will include shipping countries; which will expose if there are some suspicious activities in the region of the Middle East on the deep web. The mapping concept is original in relation to previous research attempts.

Discovering life-threatening NPS will be thorough and systematic; it will rely on a hybrid of evidence from; surface web (1) media and social media networks (2), drug fora reports (3), medical and paramedical databases (4), and Google Trends database (5). Hence the study is considered as a mixed-breed observational study of retrospective analyses and multiple internet snapshots. The databases will be cross-checked in an attempt to eliminate duplicate reporting of cases of intoxications and deaths. PubMed/Medline will be the principal representative of medical and paramedical databases (Sayers et al., 2015). Filters in medical and paramedical databases will be used to include manuscripts of; case reports (1), case series (3), reviews (4), and systematic reviews (5); duplicate reporting of incidents in literature databases will be avoided. Data extracted from the documented cases of intoxications and fatalities will include; date of incidence, gender, age, geographic location or country, the number of incidents, and the outcome. The outcome of each incident includes; intoxication (1), suicide (2), homicide (3) pharmacological fatality (4), and Behavioural fatality (5). The date of occurrence of an incident will be the actual date. However, if that information was not available, the date of publication (of the manuscript) will be considered as an alternative. These tabulated data will be later analysed using descriptive and inferential statistics. An alpha value of 0.05 and confidence interval of 95% (95% CI) was considered as the cutoff limit for statistical significance. Tests will include independent student’s t-test and the analysis of variance and covariance (ANOVA). The aim is to test if the age and gender are uniquely specific to a particular substance. This study is to be considered as an evidence-based review for the most popular and risky NPS based on data extracted from the surface web with a particular interest in drug fora and PubMed database. These comprehensive and systematic reviews can be used in future studies for more integrative analyses with the darknet and its e-markets. Attention will also be directed towards the Middle East. The statistical analyses were carried out via *Microsoft Excel 2016*.

3. Results and Discussion

The adopted classification system of NPS will be the same as found on the AlphaBay e-market, in which NPS are categorised into (Figure 1); Dissociative substances (2%), Prescription-related and medicinal (5%), Psychedelics and Hallucinogens (7%), Benzodiazepines (8%), Opioids (9%), Empathogens (16%), Stimulants (18%), and Cannabis and Cannabinoids (35%). Apparently, cannabis and hashish, including cannabinoids and cannabimimetic, were ranked 1st. The high popularity of cannabis and cannabinoids seems to be concordant with data already retrieved from Google Trends database. The internet snapshot of AlphaBay e-market made it possible to further analyse the advertised NPS in relation to risks and hazards which are represented by the incidents of intoxications and fatalities induced by NPS (ab)use all over the world. The majority of these events were found either in literature databases, and Erowid drug forum (Erowid, 2017). However, other drug fora have also contributed (Bluelight.org, 2016; Drugs-forum.com, 2016; Officialbenzofury.net, 2016; Reddit.com, 2016).

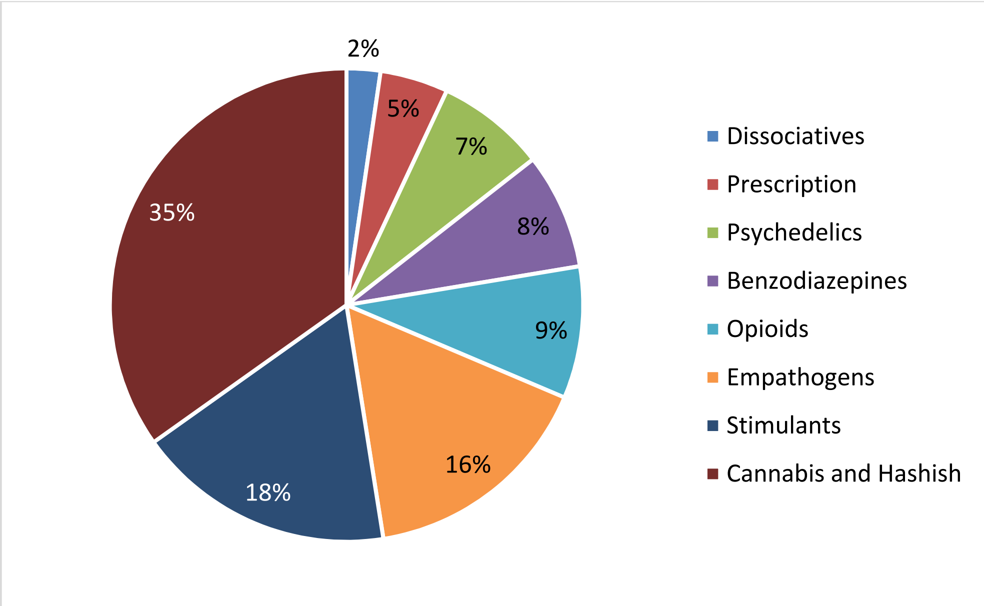

Figure 1. Most Popular Categories of NPS on AlphaBay e-market on the Deep Web

A total of forty-seven (47) substances were found to be advertised on AlphaBay (Figure 2), including; LSA, 2-FA, DMA/DOX, Topical and Others (of Cannabis and Hashish), Prerolls (of Cannabis and Hashish), MXE, Mescaline, MDA, Pressed Pills (Stimulants), Other RCs (Psychedelics), Methylone and BK, Synthetic (Cannabis and Hashish), Others (Dissociatives), Crack, Shakes (Cannabis and Hashish), GHB, RCs (Benzodiazepines), NBOMe, 2C-B, Seeds (Cannabis and Hashish), DMT, Powders (Benzodiazepines), Other RCs (Stimulants), Others (Psychedelics), Edibles (Cannabis and Hashish), Shrooms, Others (Benzodiazepines), Others (Empathogens), Ketamine (Dissociatives), Others (Opioids), Adderall and Vyvanse, Fentanyl and RCs (Opioids), Others (Stimulants), Heroin, Meth, Speed, Others (Cannabis and Hashish), Pills (Opioids), LSD, Concentrates (Cannabis and Hashish), Prescription, Pills (Empathogens), MDMA, Cocaine, Pills (Empathogens), and Buds and Flowers (Cannabis and Hashish).

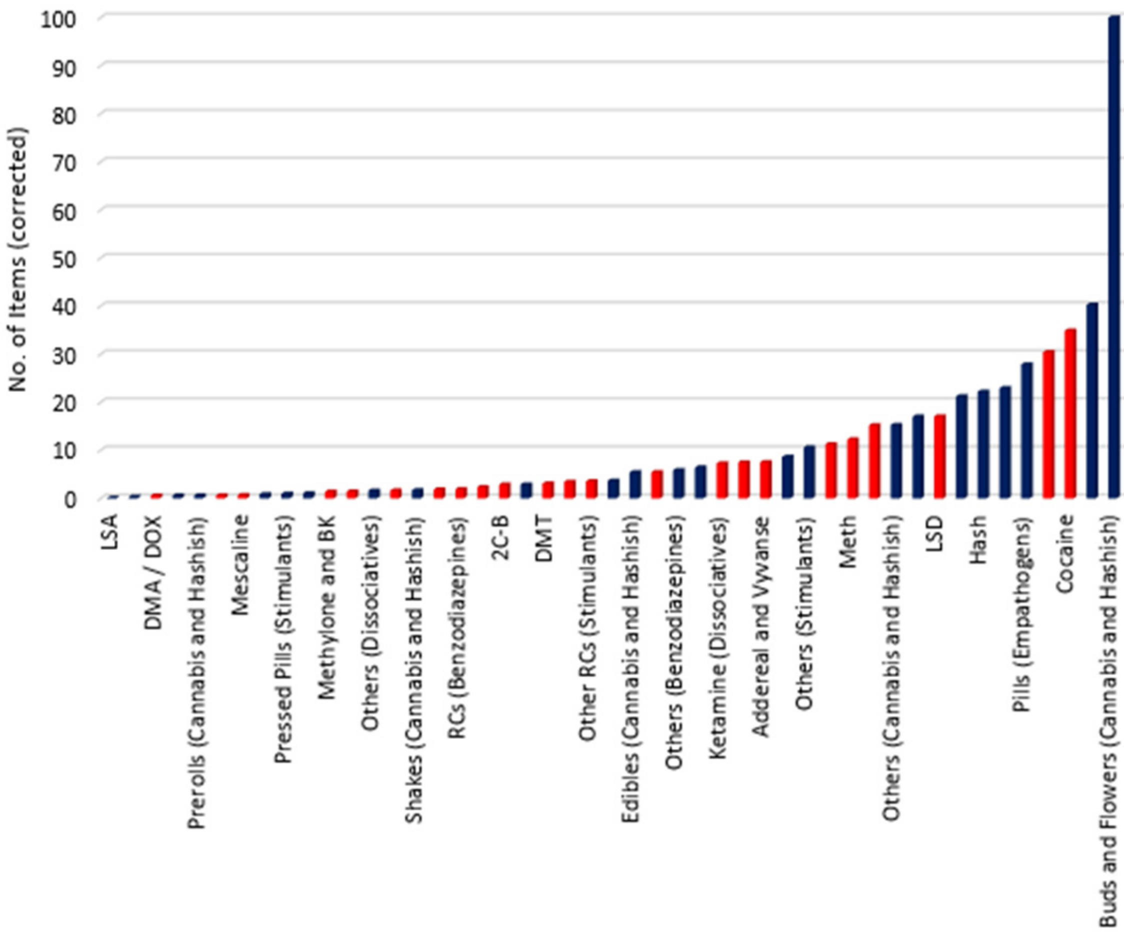

Figure 2. The Most Popular NPS Items on AlphaBay; Risky Items are Color-coded as Red

Based on literature review and data retrieved from the drug fora, hazardous substances included nearly two dozens of susbtances, including (ascending order of popularity); DMA/DOX, MXE, Mescaline, Methylone, Synthetic Cannabinoids, GHB, Benzodiazepines, NBOMe, 2C-B, DMT, Stimulants research chemicals (RCs), Shrooms, Ketamine, Opioids, Adderall and Vyvanse, Heroin, Meth, Speed, LSD, MDMA, and Cocaine and crack. Out of these, only fourteen (14) NPS will be analysed, via literature review and drug fora, for incidents of intoxications and deaths. It was found that these events can be categorised into; poisoning, chronic morbidity, near-death event, pharmacological fatality, behavioural fatality, suicide, automutilation, and homicide. Incidents reported from the region of the Middle East were absent except for; MDMA (Iran, Turkey, and Israel), DMT and Ayahuasca (Iran, and Turkey), and PCP (Israel). The lack of reporting of incidents from the Middle East, represents either real (true positive) lack of incidents or under-reporting of incidents (false negative); it is very likely that the 2nd reason is the most plausible due to the lack of; professional training in the field of NPS and addictions, research facilities, diagnostic and therapeutic procedures relevant to the discipline of NPS (Al-Imam et al., 2016; Al-Imam et al., 2017; Al-Imam, 2017a; Al-Imam, 2017b; Wood et al., 2014). In fact, the level of reporting from Israel goes in compliance with this justification, as Israel is the most developed and technologically advanced country in the entire region of the Mediterranean Sea.

The majority of the incidents took place in the developed world, particularly in the US, UK, Western Europe and Scandinavia including Germany and the Netherlands, Poland, Australia, Canada, and Japan. This goes in compliance with data extracted from Google Trends. There were also fewer reports from Latin (South) American and East Asia, including; MDMA (China), Psilocybin (Japan), Ketamine (China, Republic of Korea), DMT and Ayahuasca (Brazil, Colombia, and Peru), NBOMe (China), Methylone (Japan), 2C-B (Japan), and Adderall-Vyvanse (China). However, it seems that Meth-Speed (methamphetamine) is an NPS unique for East Asia; incidents were highly reported in China, Japan, Malaysia, and Thailand.

It is also apparent that the majority of these events were reported in male victims rather than females. In fact, almost two-thirds of incidents were reported in men; Most of the incidents were reported within the past ten years although some documented incidents may go back in time as far as the 1950s, as in the case of LSD (Table 1). In relation to age, the majority of victims were adults in the 2^{nd}, 3^{rd}, and 4^{th} decades of life. However, exceptional case of extremes of age, pediatric or advanced age groups, also occurred in; LSD (US), MDMA (Iran, Slovenia, and Australia), Ketamine (US and UK), DMT and Ayahuasca (UK, Turkey, Netherlands, Czech Republic, and Peru), PCP (US and Israel), MXE (UK), GHB (France, Switzerland, US, and Italy), 2C-B (US), Adderall-Vyvanse (Japan), Meth-Speed (China, US, and Japan), and Mescaline-Peyote (US and Germany). These unique age groups of incidents were also evident as statistical outliers on box plot presentation (Figure 3). Descriptive statistics were implemented to conclude the age groups (mean +/- standard deviation) for those risky substances, these were; 25.3 +/- 3.2 (LSD), 23.8 +/-7.6 (MDMA), 22.7 +/- 6.9 (Psilocybin), 29.4 +/- 9.8 (Ketamine), 33 +/- 14.2 (DMT and Ayahuasca), 31.8 +/- 10.1 (PCP), 18.3 +/- 3.6 (NBOMe), 26.7 +/- 6.3 (DMA-DOB), 27.2 +/- 7.2 (Methylone), 28.6 +/- 15.3 (GHB), 27.5 +/- 8.7 (2C-B), 23.4 +/- 11.5 (Adderall-Vyvanse), 35.8 +/- 11.2 (Meth-Speed), and 24.4 +/- 10.7 (Mescaline-Peyote).

Table 1. Incidents of Death due to LSD (acid)

	Date	Gender	Age	Location	Number of Death	Outcome
1	1985	M	25	UK	1	Pharmacological fatality?
2	1977	M	34	US	1	Pharmacological fatality?
3	1972	F	20	US	8	Near-death, Pharmacological fatality
			19			
			28			
			33			
		M	39			
			29			
			28			
			28			
4	1969	F	20	US	1	Suicide?
5	1953	M	43	US	1	Homicide (CIA assassination), suicide?
6	-1967	M, F	Not documented (ND)	US and Canada	19	Attempted suicide
					4	Attempted homicide
					11	Successful suicide
					1	Successful homicide
					9	Suicidal intentions
7	1956 1957	ND	ND	US	2	Psychotherapy-induced suicide
8	1988	M	14	Canada	1	Behavioural fatality
9	1989	M	18	US	1	
10	2002	M	16	UK	1	
11	2008	M	17	US	1	
12	2007	M	26	US	1	
13	2007	M	19	US	1	

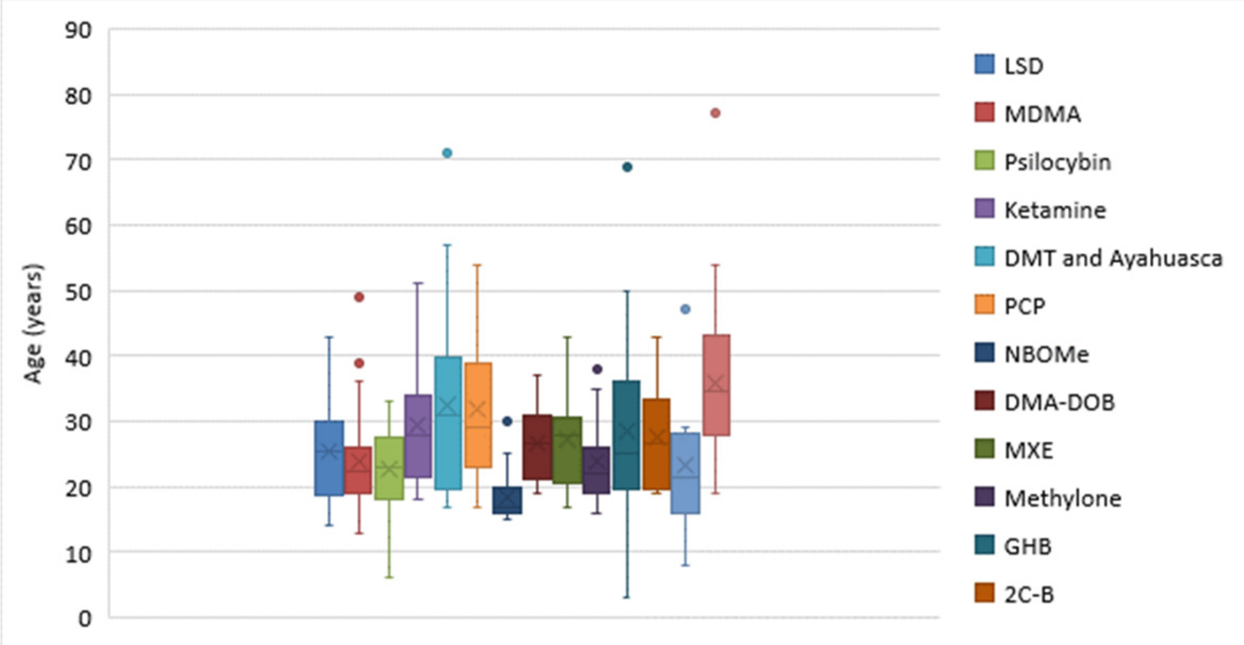

Figure 3. Boxplot Presentation: Age (years) of Incidents Related to High-risk Substances.

The descriptive statistics for age grouping are discrete enough to show substance-to-substance uniqueness in relation to incidents of intoxication and deaths. However, further inferential statistics were also applied using ANOVA test and t-test. The analysis of variance (ANOVA) revealed a significant difference (*p-value*<0.001) in age among (ab)users of high-risk NPS. There seems to be a unique age group of incidents due to some high-risk NPS, these include; LSD, MDMA, Psilocybin, DMT, PCP, NBOMe, and Adderal. Analysis with Student's t-test (independent) showed a significant difference between; LSD and DMT (*p-value*=0.029), LSD and PCP (0.016), LSD and NBOMe (0.001), LSD and Meth (<0.001), MDMA and Ketamine (0.026), MDMA and DMT (0.008), MDMA and PCP (0.001), MDMA and NBOMe (<0.001), MDMA and MXE (0.032), MDMA and Meth (<0.001), Psilocybin and Ketamine (0.015), Psilocybin and DMT (0.005), Psilocybin and PCP (0.001), Psilocybin and NBOMe (0.012), Psilocybin and MXE (0.020), Psilocybin and Meth (<0.001), Ketamine and NBOMe (<0.001), Ketamine and Methylone (0.032), Ketamine and Meth (0.021), DMT and NBOMe (<0.001), DMT and Methylone (0.009), DMT and Adderal (0.047), PCP and NBOMe (<0.001), PCP and DMA (0.075), PCP and MXE (0.041), PCP and Methylone (0.005), PCP and Adderal (0.005), NBOMe and DMA (0.010), NBOMe and MXE (<0.001), NBOMe and Methylone (0.002), NBOMe and GHB (0.003), NBOMe and 2C-B (0.024), NBOMe and Meth (<0.001), DMA and Meth (0.001), MXE and Meth (<0.001), Methylone and Meth (<0.001), GHB and Meth (0.033), 2C-B and Meth (0.036), Adderal and Meth (0.010).

It seems that these incidents of intoxications and death were highly reported in relation to psychedelics (Hallucinogens). Therefore, additional analyses were implemented based on data retrieved from Google Trends (Figures 4 to 6) for the period from the beginning of 2012 to the end of 2016. The analysis included the most famous psychedelics including; Lysergic acid diethylamide (LSD), MDMA, Psilocybin, Phencyclidine (PCP), Ketamine, N,N-Dimethyltryptamine, Dextromethorphan, Peyote, Ayahuasca, Salvia divinorum, Ergine, NBOMe, AL-LAD, alpha-Methyltryptamine, 2,5-Dimethoxy-4-bromoamphetamine, and TMA-6 (Dargan, 2013; Psychedelic.com, 2017). Based on ANOVA test, it was found that there is a significant difference (*p-value*<0.001) in relation to the popularity of all these psychedelics among users of the surface web. Hence, statistical testing with Student's t-test (paired) was implemented. The trends were highly oscillating; there was no pattern, apart from increments in the trends during the holidays in developed countries, specifically during Christmas and the New Year holidays (Bellis et al., 2007; Halpern & Mechem, 2001; Lai et al., 2013). LSD (rank 1st) and MDMA (rank 2nd) appeared to be the most popular psychedelics on the surface web, while Psilocybin, Phencyclidine, Ketamine, and N,N-Dimethyltryptamine were of comparable popularity. Geographic mapping (Figure 7) revealed that these substances were highly sought out by developed countries. The top ten countries were; Australia (1st), Canada (2nd), United States, (3rd), United Kingdom, New Zealand, Ireland, Norway, Netherlands, Switzerland, and Estonia; the Middle East accounted for a minute fragment of 3% only. Middle Eastern countries and Arabic countries included (descending order); Israel (1st), Iran (2nd), Morocco, UAE, Turkey, Egypt, and Saudi Arabia.

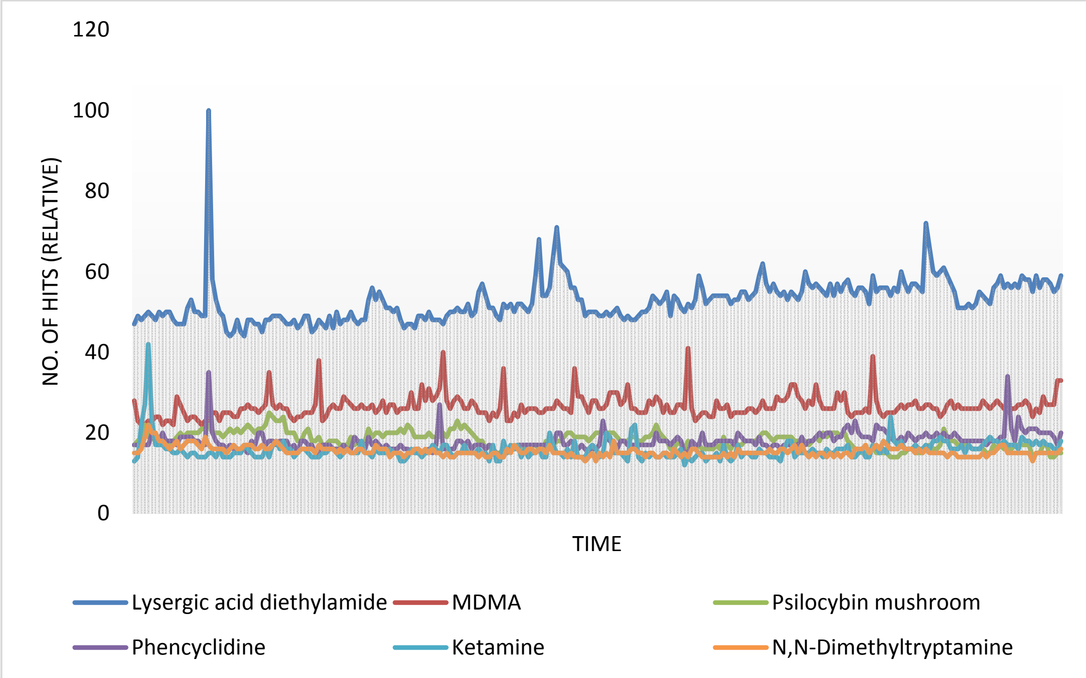

Figure 4. Google Trends of Psychedelics (2012-2016): Lysergic acid diethylamide, MDMA, Psilocybin, Phencyclidine, Ketamine, and N,N-Dimethyltryptamine

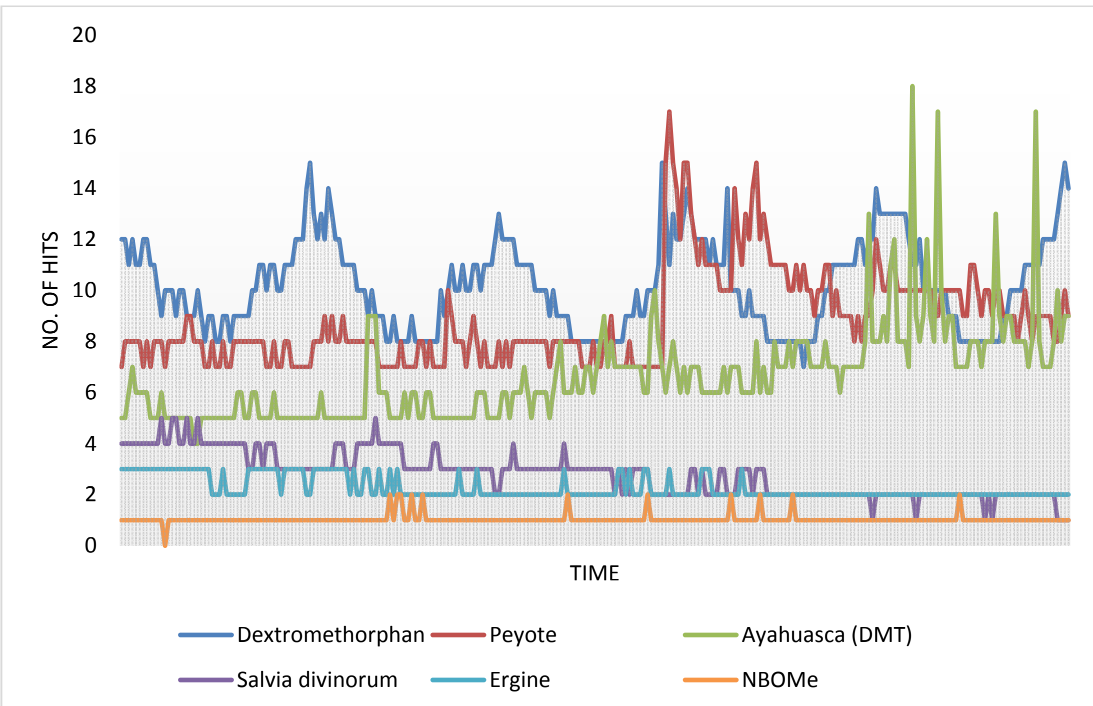

Figure 5. Google Trends of Psychedelics (2012-2016): Dextromethorphan, Peyote, Ayahuasca, Salvia divinorum, Ergine, and NBOMe

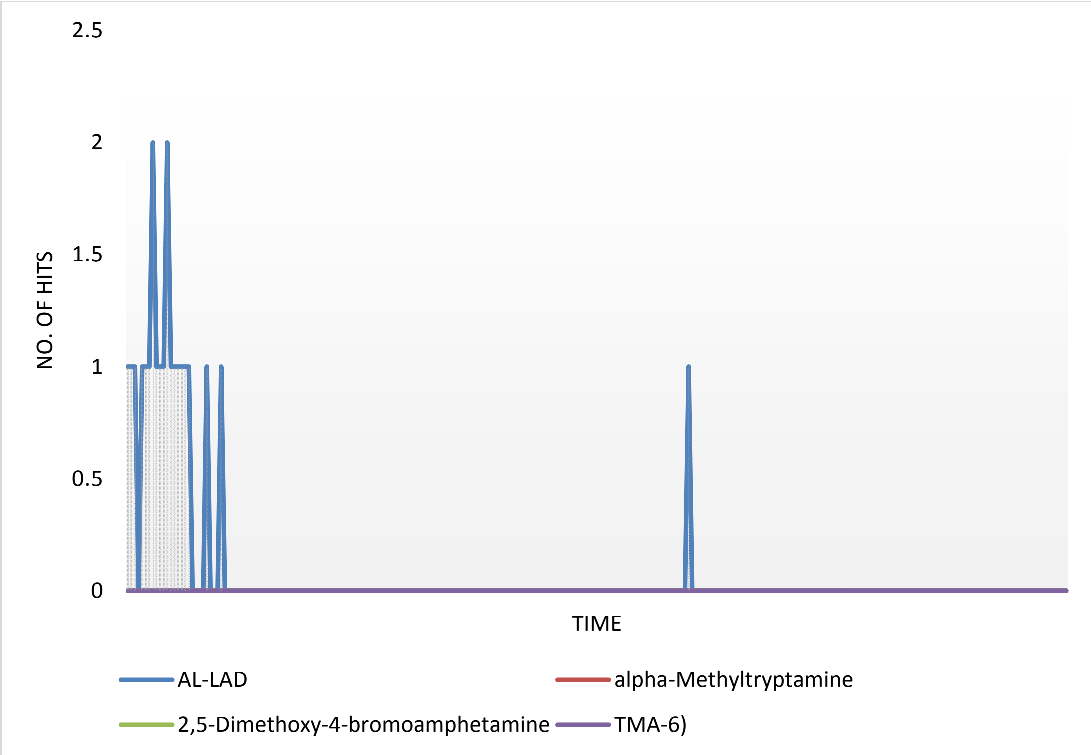

Figure 6. Google Trends of Psychedelics (2012-2016): AL-LAD, alpha-Methyltryptamine, 2,5-Dimethoxy-4-bromoamphetamine, and TMA-6

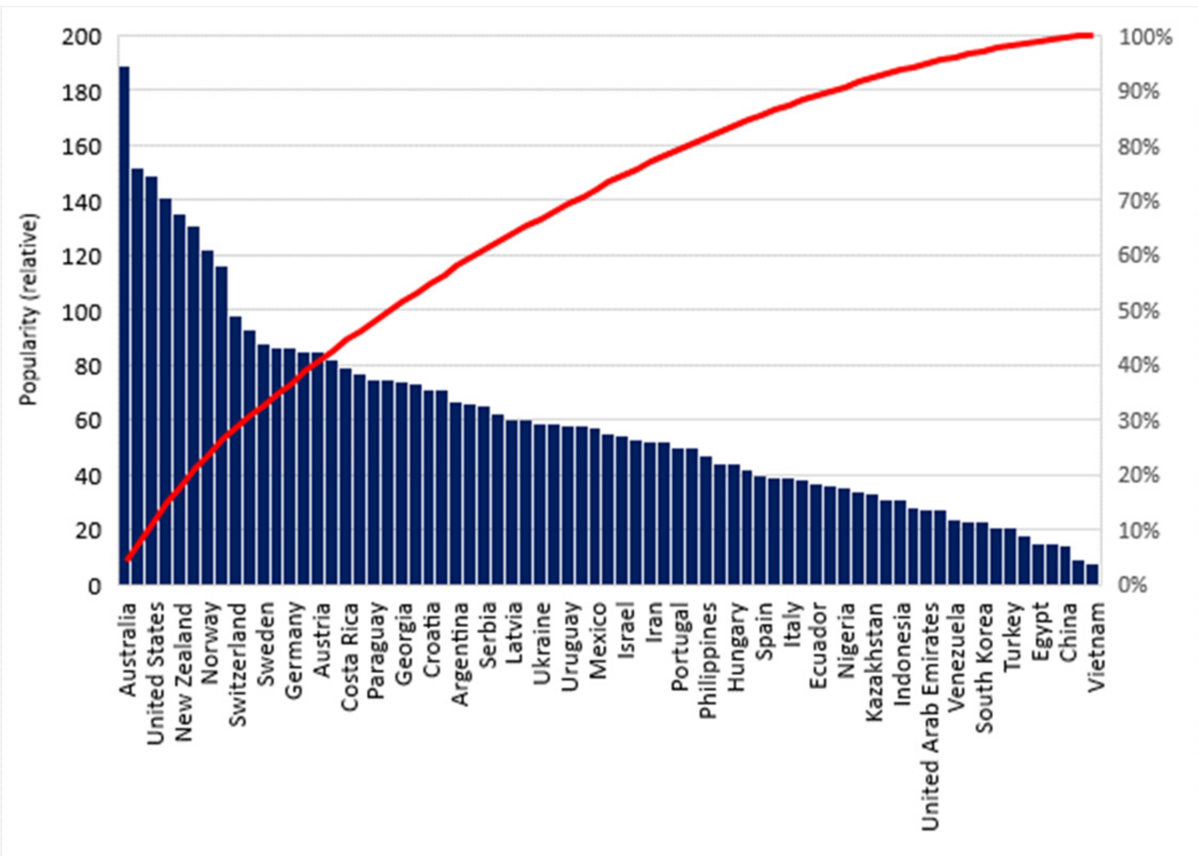

Figure 7. Google Trends: Geo-mapping of the Most Popular Psychedelics

4. Conclusion

The explosive nature of the diffusion of NPS and research chemicals is unparalleled, particularly on the deep web, due to the factor of anonymity. Perhaps the best way to augment the efficacy of observational web analyses, including internet snapshot technique, is to categorise these substances based on their popularity. The popular NPS will be easier to track and analyse; the purpose is to get the best results in the case of limited manpower and financial resources. At the same time, this technique will always keep pace with the major health and economic threats by keeping the casualties and collateral damage (patients and money) to a minimum. In this analysis, it was shown that three categories of NPS were always in the lead; cannabis and cannabimimetic, stimulants, and empathogens. However, it is critical to know that the attractiveness of these chemicals to customers (popularity) can be changeable through time. This has been confirmed by the oscillating nature of the trends (Google Trends) in the past five years. Therefore, the monitored substances should be upgraded on a regular basis possibly via the use of knowledge discovery in databases (KDD; data mining techniques can provide automatic updates on the most popular NPS.

The use of the two techniques combined can have a significant effect on the way NPS are studied, leading to higher accuracy, and reduction of time and efforts. The NPS industry is a profitable business led by several “smart” individuals and criminal organisations. Those keen members should be counteracted with inventive methods and designs to put this escalating e-trade phenomenon to some retreat. Furthermore, to date, the e-trade was found to be almost exclusive to the developed countries; the Middle Eastern and Arabic countries are contributing microscopically to the overall phenomenon on the deep web. However, Israel and Iran contributed the most. Data from the surface web (including Google Trends) and deep web were in harmony. In summary, the internet analytic methods should keep the focus on the e-markets active within the developed world, in addition to some of the Far East Asian countries; Japan, China, Thailand, and Malaysia.

Competing Interests Statement

The authors declare that they have no competing or potential conflicts of interest.

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