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Chapter 7

Adverse Effects of Amphetamines on Cardiovascular System: Review and Analyses of Trends

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Abstract

Background

Amphetamine and amphetamine-type stimulants are powerful physical and psychostimulants; they are Phenethylamine derivatives. The use of amphetamines can be either medicinal or illicit. Several amphetamines have been redesigned into illegal drugs of potent properties. Hence, they are named as designer drugs or novel (new) psychoactive substances.

Materials and Methods

This manuscript is a hybrid study of; data crunching and retrospective analysis of a trends database (1), and a systematic review of literature in relation to the amphetamines-induced adverse effects on the cardiovascular system (2). Google Trends database has been analysed in retrospect (2012-2017) to evaluate the attentiveness of surface web users towards amphetamine and a potent renowned amphetamine derivative known as captagon (fenethylline).

Results

Amphetamines appear to be highly popular worldwide, particularly in the developed world including North America and European countries, and to a less extent in the developing countries and the Middle East. However, the trends are oscillating with time with significant year-to-year fluctuation. However, there was a steadiness in the temporal patterns (trends), for example in 2013-2014 (p-value=0.258). Variations in the trends were found to be correlated with global events including international terrorism. The adverse effects of amphetamines were found to be highly re-

lated to the cardiovascular system with a high incidence of intoxications and deaths among substance (ab) users.

Conclusion

Several amphetamines are potent and used illicitly beyond their therapeutic potential, as in the case of captagon, culminating in momentous public and economic threats. Legalising bodies should exercise tremendous and systematic efforts to counteract the threats. Database analysis can provide an accurate insight into this phenomenon that has been growing exponentially in the past decade.

Keywords: Phenethylamine drugs; Amphetamine; Amphetamine-type stimulants; Psychostimulant; Sympathomimetics; Novel Psychoactive Substances; Captagon; Fenethylline; Cardiovascular Diseases; Google Trends; Drug-Related Side Effects; Adverse Reactions.

1. Introduction

Novel or new psychoactive substances (NPS), also known as designer drugs or research chemicals or legal highs, potentially posing health threats similar to the classic (archetypal) illicit substances; these substances (NPS) are not yet fully controlled by the United Nations drug conventions, although they do pose a serious threat to communities of nations around the world [1,2]. The rapid spread of the NPS, represents a major obstacle for the economy, policy makers, legislators, medical and paramedical professionals, and information-communication technology (ICT) personnel.

The United Nations Office on Drugs and Crime (UNODC) has identified six main groups of NPS: synthetic cannabinoids, synthetic cathinones, phenethylamines, ketamine, piperazines and plant-based substances. A seventh miscellaneous group of substances was also added later [3]. Despite the policies and current guidelines against the commerce and the electronic commerce of NPS, they continue to be highly popular and growing at an exponential rate paralleled only by the logarithmic growth in the ICT. In 2014, the UNODC via its World Drug Report indicated that the number of NPS substances have doubled over the period 2009-2013 [2]. Further, in 2013, It is estimated that almost a quarter of a billion people of age between 15-64 years used an illicit drug, which corresponds to an estimated global prevalence of 5.2% [4]. Similarly, the number of NPS of use reported in the European Union is increasing each year exponentially, for the period 2009 to 2014 [5]. In March 2015, the EMCDDA published an update on the NPS in Europe. The report divided the NPS market into several categories: legal highs, research chemicals, food supplements, designer drugs, and medicines. All produced in clandestine laboratories [4]. A tiny amount of data is known about the diffusion of NPS in the developing world, including the Middle East and the Arab world; as the current civil war and terrorism in Syria continue, the demand for illicit drugs, including the renowned substance known as captagon (fenethylline). Captagon, a psychostimulant and an amphetamine-type substance, is also a diffused substance in; Iraq,Turkey, Iran, Jordan, Kuwait, Oman, UAE and

Qatar [6].

The marketing strategies of illicit drugs have significantly changed over the years. The Internet has become increasingly important as a communication and a distribution modality; this method is also known as the electronic commerce (e-commerce) or electronic trade (e-trade). The e-commerce does also take place on the anonymous deep web and the darknet marketplace. Additionally, potent substances can be easily purchased online, and in uncertain doses, they entail a high risk of serious poisonings, morbidity, and even sudden deaths [7]. In the European Union (EU), 41 novel psychoactive substances were identified for the first time in 2010, 49 in 2011, 73 in 2012, 81 in 2013, and 37 by April 2014 via the European Early Warning System [7,8].

2. Materials and methods

This study is made of two integral components, a review of the literature and an inferential retrospective analysis of Google Trends database. A systematic review of the literature was carried out via medical and paramedical databases including; PubMed/Medline, the Cochrane Library, Embase, Scopus, CINAHL, OpenGrey, and Google Scholar. Other databases were also systematically explored including; Oxford Scholarship Online, the University of Hertfordshire Online Library, Semantic Scholar, and Sci-Hub. Accordingly, the literature review methodology covered a broad range of scholarly written articles exclusively found on the surface web, published and unpublished resources, including the Grey Literature. A list of prespecified keywords was implemented for the purpose of finding the most appropriate articles that are pertinent to the topic of amphetamine and amphetamine-type stimulants. Furthermore, boolean operators (“AND”, “OR”, “NOT”) were utilised in order to increase the specificity of the search strategy, to either narrow down or expand the number of hits retrieved from each database [9,10].

The literature review aimed at these topics; amphetamines and captagon, the collateral use of the deep web and the darknet, the exploitation of use of Google Trends database for the purpose of epidemiological analyses and geographic mapping, and the adverse reactions of amphetamines in relation to the cardiovascular system, including incidents of intoxications and fatalities. Priorities were given to articles; written in the past five years, systematic reviews and meta-analyses, randomised controlled trials (RCTs) and pragmatic RCTs, rigorous longitudinal analyses, and studies with inferential statistical analyses. The purpose of this filtering of articles is to retrieve studies of the highest attainable level-of-evidence [11,12].

The second component of this study relies on the data derived from Google Trends database, the analyses to be applied are longitudinal and retrospective in nature, and in relation to amphetamines and a particular amphetamine-derived substance known commercially as captagon. The analyses will be based on data extrapolated from millions of users of the surface

web, which is followed by the application of inferential statistical analyses of data science, particularly parametric tests, including; the Analysis of Variance and Covariance (ANOVA), Student's t-test, and z-test. The level of significance of the results was set at an alpha value of 0.05 and 95% confidence interval (95% CI). Additionally, further data were retrieved in relation to the geographic mapping of these substances. To summarise, this chapter is a hybrid analytic study made of a targeted review of literature and extrapolations based on retrospective data from Google Trends. Accordingly, the level-of-evidence is estimated to be of level-3b in accordance with the classification system imposed by the Oxford Center for Evidence-Based Medicine in 2009 [13].

3. Results

Amphetamines are phenethylamine derivatives; these are potent stimulants of the central nervous system (CNS) and psychostimulants [3,14,15]. Amphetamine and amphetamine-type stimulants (ATS) have been used widely for therapeutic purposes. For example, in treating depression, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), and as a booster of physical performance in athletes [16-18)]. The substance can be addictive, leading to dependence, tolerance, and withdrawal syndrome [19,20]. Recently, an NPS substance known as captagon (fenethylline), became widely popular for its addictive properties and its use as a powerful physiological and psychostimulant effects. Captagon can promote high physical performance and endurance, cognitive enhancement, and reduction of sleep and food requirement [6,21,22]. Therefore, it has been well-known to be used by soldiers, and even terrorist. Recently, it became well known that it was used by terrorist organisations including the Islamic State of Iraq and the Levant (ISIL), captagon was incriminated in Paris terror attacks in 2015 [6,23,24].

3.1 Amphetamines and Cardiovascular Interactions

Stimulants have profound effects on the cerebrovascular systems and cardiovascular system, leading to congestive cardiomegaly, cardiac chambers and valvular fibrosis, and cerebral infarction and haemorrhage [25]. Furthermore, Hennissen and co-authors in their meta-analytic study found that there was statistically significant increments in diastolic blood pressure, systolic blood pressure, and heart rate reported in individuals using amphetamine and amphetamine-type stimulants [26].

Amphetamine and ATS potentiate the release of catecholamines, blocks their reuptake, and interacts directly with catecholamine receptors. Further, some amphetamine and ATS metabolites inhibit monoamine oxidase (MAO) enzyme leading to a secondary increment in the plasma concentration of norepinephrine. Other metabolic derivatives may increase serotonin release. Histologically, the effects of amphetamines are similar to the cocaine-induced changes; those include vascular hypertrophy, interstitial fibrosis, microvascular changes (hypertro-

phy) of the tunica media of the arteries. Accelerated atherosclerosis has also been observed in relation to amphetamines use and misuse. In addition, amphetamines induce calmodulin activation and increase the levels of thermic shock proteins [27]. Amphetamines stimulate the release of norepinephrine affecting both alpha (α) and beta (β) adrenergic receptor sites. Alpha-adrenergic stimulation causes vasoconstriction and an increase in total peripheral resistance, while β-Adrenergic receptor stimulation leads to an increase in heart rate, stroke volume, cardiac ejection fraction, and skeletal muscle blood flow. For instance, Adderall intoxication in humans can manifest with; hyperactivity, hyperthermia, tachycardia, tachypnea, mydriasis, tremors, abnormalities in peripheral white blood cells and thrombocytopenia, hypoglycemia, and seizures [28].

The heart is a target organ of injury for numerous chemicals including prescription and non-prescription chemical compounds. Pathologic mechanisms of chemical-induced cardiomyopathies include; direct toxic effects, neurohormonal activation, alteration of calcium homoeostasis, oxidative stress, modulation of cardiac gene expression, and apoptosis [29]. Furthermore, amphetamine and ATS lead to indirect stimulation of the autonomic nervous system through the release of catecholamines, dopamine, and serotonin in nerve terminals of the central and peripheral nervous systems [30]. In addition, serotoninergic 5-HT(2A) receptors agonists and to a fewer extent alpha-adrenoceptors agonists, including amphetamines, can cause vasoconstriction and tissue ischemia. Therefore, those drugs can induce fibrosis of the cardiac valves leading to heart failure [31]. Moreover, the pharmacological mechanism for the vasoconstriction and consequent fibrosis was recently found to be partially attributed to amphetamines interaction with a specific subset of receptors known as trace amine-associated receptors (TAARs) which are located in blood vessels. TAARs were found to play a substantial part in mediating the cardiac toxicity [32].

Amphetamines and cocaine are also considered to be risk factors for pulmonary arterial hypertension (PAH). Methamphetamine and amphetamines act more potently on norepinephrine and dopamine transporters and to a less extent on serotonin transporters. Those neurotransmitters have vasoconstrictive and growth modulating effects on smooth muscle cells leading to the development of PAH [33]. Fulceri and colleagues have also found that the combination of MDMA and loud noise, as in recreational mass events, can potentiate the effects of prolonged loud noise exposure which might explain the unexpected fatal events that happen in recreational situations [34].

In relation to captagon, the adverse reactions mimic those of amphetamine and ATS; these include; an increase in heart rate (tachycardia), body temperature, respiration and blood pressure as well as extreme depression, neurological excitation, lethargy, sleep deprivation, heart and blood vessel toxicity, and malnutrition in case of chronic substance misuse [35]. Hazardous side effects included: psychosis, visual distortions and hallucinations, acute heart

failure, acute myocardial infarction (AMI), and epileptic fits [36,37]. High-risk adverse effects that are also incompatible with war (combat) zones requirements include psychosis, visual distortions and hallucinations, acute heart failure, acute myocardial infarction (AMI), and epileptic fits [36]. Acute myocardial infarction has been increasingly reported since the beginning of the civil war in Syria (2011), the Middle East and in Turkey [38]. The first case of AMI in association with captagon was documented in a 21-year old man [37].

3.2 The Deep Web and the Darknet

The deep web, also known as the invisible web, seems to be the most important for the e-commerce activities of illicit substances including NPS. This is due to the anonymity granted in this division of the internet, and the use of anonymous payment system [39,40]. The deep web utilises technologies which provide anonymity for users. These technologies include: the use of specific browsers (Tor Browser, Grams search engine), login credentials specific to each e-market, secure routing protocols, virtual private networks (VPN), Internet Protocol Masking (IP masking), and Bitcoin payment system [41-43].

By the end of 2015, more than 700 NPS had been reported by a large number of countries in the world. Synthetic cathinones; synthetic cannabinoids; phenethylamines; and psychedelics account for the greater number of these substances. This thriving growth was facilitated and promoted by the online drug culture which finds its expression; in chat rooms, drug fora, blogs, and e-markets, on both the surface web and the deep web. The deep web, with high-level of anonymity, has progressively modified the NPS phenomenon into a virtual one. The rapidly evolving changes in the NPS online markets (e-markets) constitutes a major challenge to the provision of detailed knowledge on these substances [44-46].

The deep web represents the online content which is not indexed by the standard search engines (including Google, Yahoo, MSN, etc.). Novel psychoactive substances are promoted on the deep web in a plethora of e-markets. The e-markets of the deep web can also hold several illicit activities in relation to child pornography, human trafficking and slavery, unethical medical experimentations, human organs' trade activities, and other crimes including terrorism [47,48].

The darknet is a vital component of the deep web; its e-marketplace is a huge virtual place where several illicit activities exist including the NPS electronic trade (e-trade) [49-51]. Dozens of e-markets are active on the darknet e-marketplace, including; Hansa, Darknet Hero League, AlphaBay, Agora, Nucleus Market, Majestic Garden, Real Deal Market, Oasis, Abraxas, Outlaw Market, Middle Earth, Silkkitie, Oxygen, Tochka Market, and Arsenal [6,52,53]. Those e-markets can be systematically analysed and thoroughly mapped not only for NPS e-trade activities, but also from a social science perspective, the aim is to analyse and categorise the basis of power for; e-markets, e-vendors, and e-customers [54-56].

3.3 Google Trends Analyses: Amphetamine and Amphetamine-Type Stimulants

The popularity and the epidemiology of (ab)use of amphetamines and ATS can be inferred with high accuracy via the web, specifically the surface web by means of trends databases including *Google Trends* [57,58]. Google trends analyses can be either retrospective or cross-sectional. The analyses are highly accurate, as they are based on extrapolation of data from millions of users of the web (surface web). Furthermore,extrapolations can be geographically mapped (geo-mapped) for a particular region of the world. For instance, geo-mapping of surface web users' interest in relation to amphetamines and ATS [59-61]. The attentiveness of surface web users can be analysed, using Google Trends, in relation to phenethylamine, amphetamine, and ATS, and in retrospect to provide an accurate inference on the *electronic epidemiology* (e-epidemiology) on the Internet [59,61]. This can be inferred by using three specific keywords; *phenethylamine, amphetamine,* and *captagon* in the past five years (2012-2017) [62]. It seems that amphetamine was much more popular than both phenethylamine and captagon (Figure 1). The attentiveness was more oscillating with time in case of amphetamine and captagon, while interest in phenethylamine was steadier and almost represent a baseline superimposed on the x-coordinate (Figure 1). Interest in amphetamine reached amaximum in August 2014 and to a lesser extent (smaller peak) in November 2012. On the other hand, interest in captagon reached a maximum in November 2015, while a lower peak can be noticed in July 2016. These events have been correlated with terror attacks around the world, and the substance e-trade by extremist organisations including ISIL [6,22,63]. The relative interest of surface web users was as follows (mean +/- standard deviation); phenethylamine (0.07 +/- 0.25), amphetamine (49.73 +/- 5.25), and captagon (1.68 +/- 6.44). The trends of amphetamine were found to be the highest and the most oscillating (Figure 1). Accordingly, inferential statistics,using student's t-test (Figure 2), confirmed that the trends were significantly variable year-to-year with an exception for; 2012 versus 2015 (*p-value*=0.743); 2013 versus 2014 (p=0.258), and 2016 versus and 2017 (p=0.888). Further analysis, using regression models (Figure 2), revealed the presence of some degree of linear correlation (R^2 score=0.015) between the trends in 2013 and 2014, it means that the surface web users were attentive around the same time of the year (months) in 2013 when compared to 2014.

The top related queries by surface web users included; *phenthylamine drugs, pehnthylamine, phenegran, amfetamina, moc energy amfetamin, moc energy amfetamina, captagon isis, isis, captagon daesh, captagon syria, captagon effet, captagon efectos, and, isis drug*. Geo-mapping (Figure 3). It seems that phenethylamine is geo-mapped primarily in the United States (US), while amphetamine was geo-mapped in 61 countries, including (highest to lowest frequency); Norway, Poland, Ukraine, Moldova, Sweden, Finland, Russia, Estonia, Bulgaria, and Belarus. On the other hand, captagon was geo-mapped (Figure 4) into seven countries only; France (35%), Turkey (16%), Germany (14%), Italy (10%), Spain (10%), Canada (10%),

and US (5%). France represented a statistical outlier possibly due to the correlation with international terrorism and terrorist attacks concentration in the country, while Turkey was the only country from the Middle East representing approximately 1/7th of the entire geo-map. A summative geo-mapping for all three substance categories (Figure 5) has shown that the top contributing countries are Norway (5%), Poland (5%), Ukraine, (5%), Moldova (5%), Finland (4%), Sweden (4%), Russia (4%), Estonia (4%), Bulgaria (3%), and Belarus (3%). Norway, Poland, Ukraine, and Moldova represented statistical outliers of the geo-map. The top countries contributed to 41.1% of the global geo-mapping. Other countries contributed to another 40% these included; Latvia, Australia, Kazakhstan, Denmark, Germany, Bosnia and Herzegovina, United States, Switzerland, Croatia, Serbia, Lithuania, Chile, Canada, United Kingdom, Austria, Netherlands, Ireland, Slovenia, Czechia, New Zealand, and Mexico. On the other hand, countries from the Middle East and the Arab world contributed to 2.3%. It included; Iran (0.8%), Israel (0.5%), Saudi Arabia (0.5%), and Turkey (0.4%). Furthermore, an additional regression analysis (Figure 6) showed the absence of a positive linear correlation in between the geo-mapping of amphetamine and captagon (R^2=0.017). To summarise, amphetamines appear to be important for surface web users from the developed world, including some states of the former USSR (Soviet Union), while the developing countries, including the Middle East and Arabic world, contributed minimally. Further analyses are required for the deep web, but these are beyond the scope of this chapter.

4. Conclusion

The growth of NPS industry, including the trade activities and its links to international terrorism, are reaching unprecedented levels primarily in the region of the Middle East. The e-commerce phenomenon of amphetamines seems to be highly prevalent in the western countries of the developed world, primarily; the US, UK, Italy, Canada, Scandinavia, and western Europe. On the other hand, the contribution of the Middle East and Arabic country to the e-trade phenomenon seems to be minimal; it can be described as infinitesimal especially when juxtaposed to those of the developed countries from the European Union and the United States.

The vast majority of incidents related to intoxications and deaths are also reported from the developed world. Furthermore, a considerable proportion of these events is related to pharmacological adverse effects in relation to the cardiovascular system. Unless some reasonable efforts and ingenious upgrades of the current research methodologies are achieved, the NPS trade and e-trade will ever continue to be on the rise, leading to more incidents of intoxications, morbidities, and mortalities, including cardiovascular-related one.

Research enhancements should aim at; increasing the quality and quantity of studies in the poorly-mapped developing countries including Middle East and Arabic countries, incor-

poration of efficient use of data science and advanced web analytics, compulsory training in relation to the disciplines of data science and basic neuroscience, validation and incorporation of data mining techniques and real-time analyses of databases, inclusion of the rarely-used experimental studies including; quasi-experiments, RCTs, pragmatic RCTs, and animal modelling, enhancement of the internet snapshot techniques, and full exploitation of trends databases of the surface web.

5. Figures

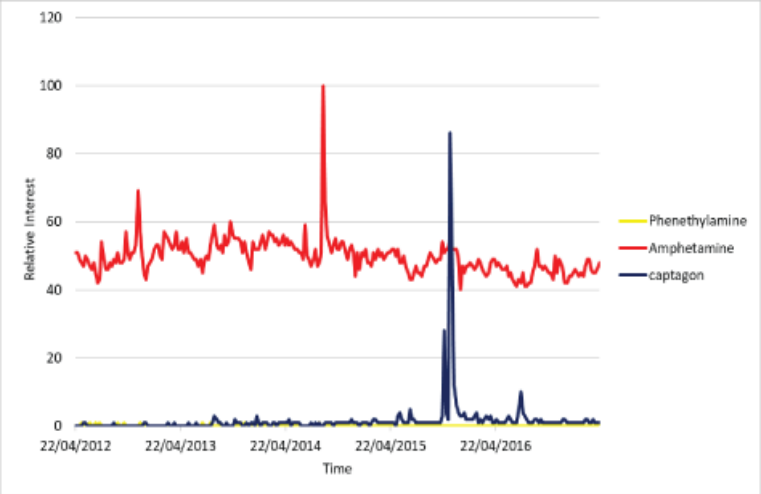


Figure 1. The attentiveness of surface web users in; Phenethylamine, Amphetamine, and Captagon.

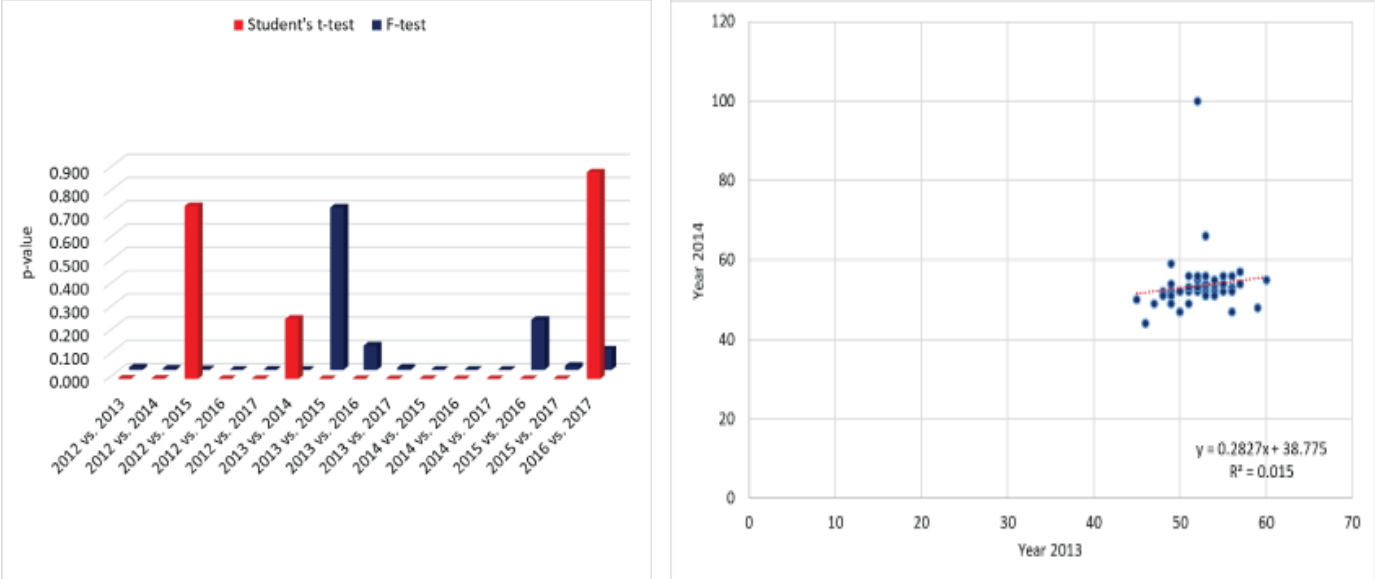


Figure 2. Inferential Statistics: Attentiveness of web users to Amphetamine in 2012-2017 (above), and Linear Regression for 2013 vs. 2014 (below).

Figure 3. Geo-mapping of interest in Phenethylamine (above, blue), Amphetamine (middle, red), and Captagon (below, yellow-brown).

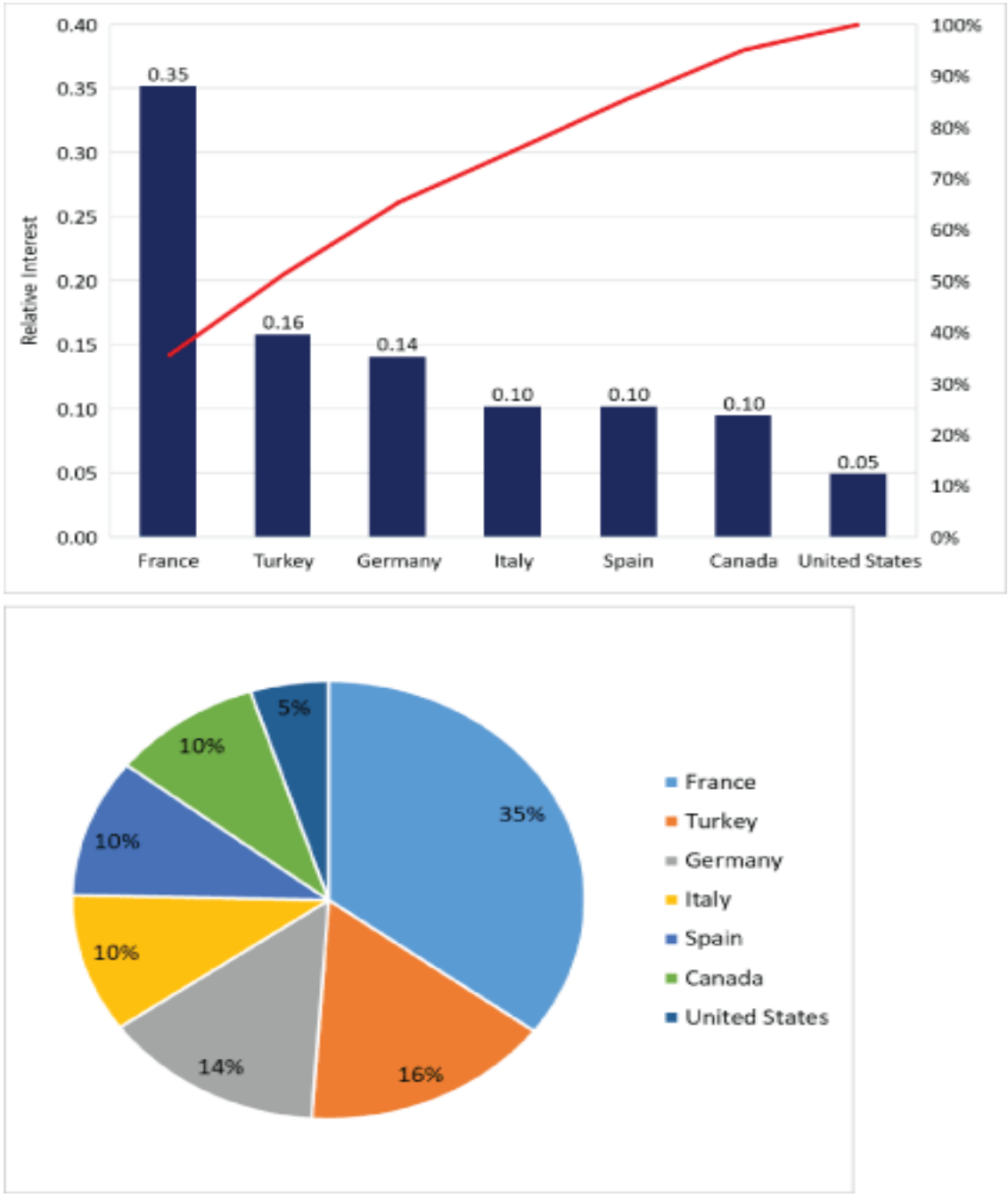
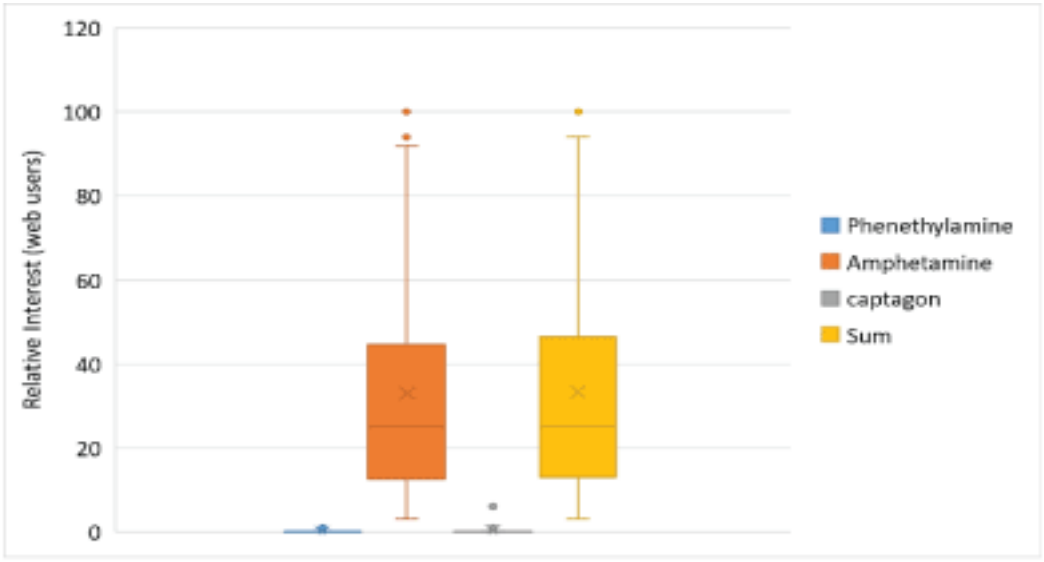
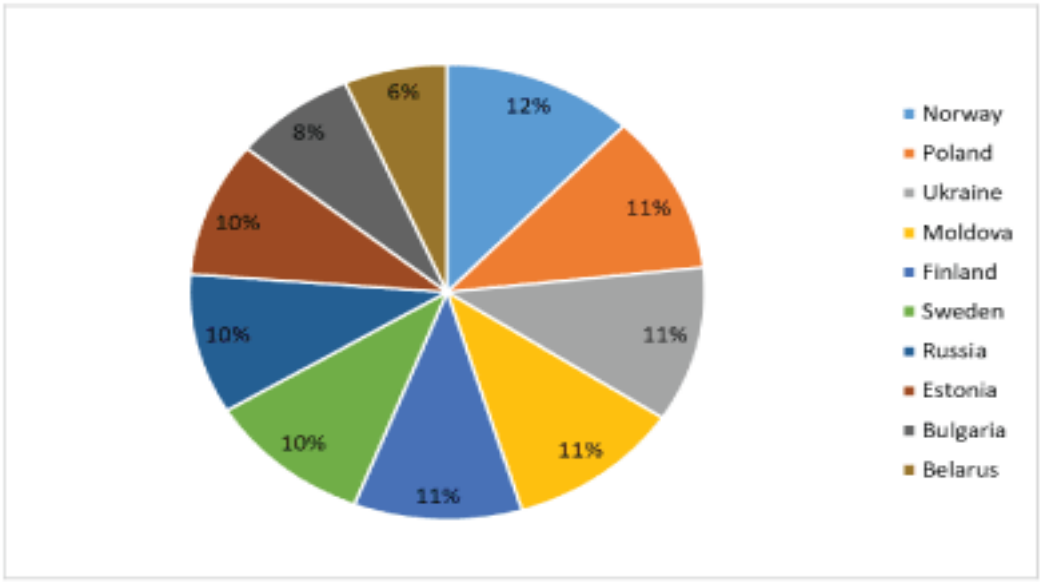


Figure 4. Geo-mapping of Captagon: Pareto Chart (above), and Pie Chart (below).





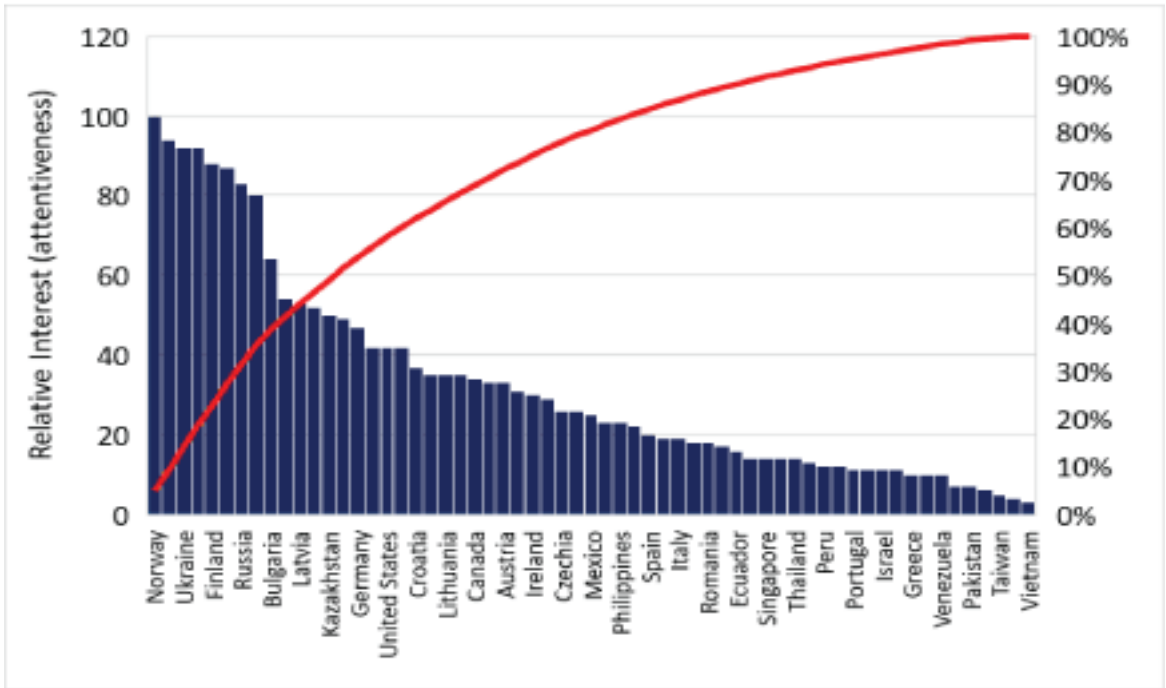


Figure 5. Summative Geo-mapping: Boxplot (above), Pie Chart (middle), and Pareto Chart (below).

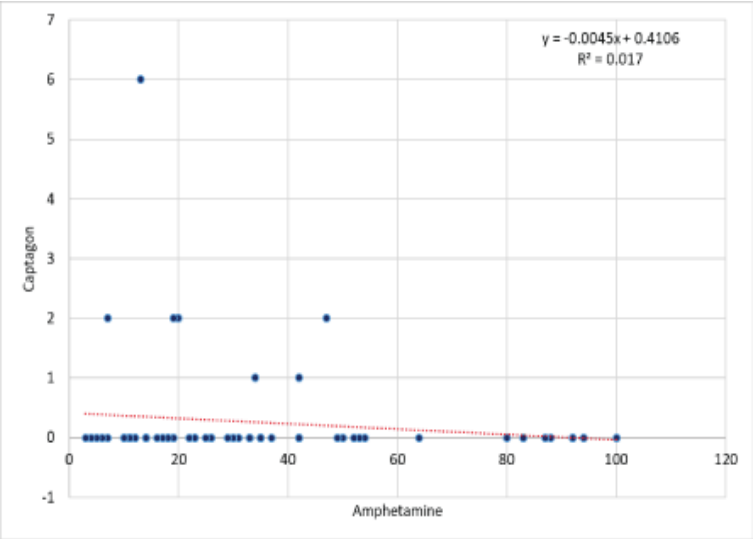


Figure 6. Inferential Statistic via Regression Analysis: Geo-mapping of Amphetamine vs. Captagon.

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