Global Journal of Health Science; Vol. 9, No. 11; 2017
ISSN 1916-9736 E-ISSN 1916-9744
Published by Canadian Center of Science and Education

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

Ahmed Al-Imam[1,2]

[1] Department of Postgraduate Medicine, School of Life and Medical Sciences, University of Hertfordshire, United Kingdom

[2] Department of Anatomy and Cellular Biology, College of Medicine, University of Baghdad, Iraq

Correspondence: Dr Ahmed Al-Imam, House 18/5, Al-Akhtal Street, District 318, Al-Adhamyia, 10053, Baghdad, IraQ. E-mail: tesla1452@gmail.com; a.m.al-imam@herts.ac.uk

Received: July 25, 2017 Accepted: August 17, 2017 Online Published: September 18, 2017

doi:10.5539/gjhs.v9n11p102 URL: https://doi.org/10.5539/gjhs.v9n11p102

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, also known as research chemicals and designer drugs. Hence, they are named novel (new) psychoactive substances (NPS).

Materials and Methods: This study 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 including the Middle East. However, the trends are oscillating with time with significant year-to-year changes although there was some 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 related 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 original therapeutic potential, as in the case of captagon, culminating in monumental public and economic threats. Legalising bodies should exercise tremendous and systematic efforts to counteract these threats. Database analyses can provide an accurate insight into this phenomenon that has been growing exponentially in the past decade.

Keywords: Novel Psychoactive Substances, Phenethylamine drugs, Amphetamine, Amphetamine-Type stimulants, Psychostimulant, Sympathomimetics, Captagon, Fenethylline, cardiovascular diseases, Google Trends

1. Introduction

Novel or new psychoactive substances (NPS), also known as designer drugs and legal highs, potentially poses significant 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 the communities of nations around the world (Cluver & Rheingold, 2014; United Nations Office on Drugs and Crimes, 2016). 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.

NPS can be categorized into six main groups: synthetic cannabinoids, synthetic cathinones, phenethylamines, ketamine, piperazines and plant-based substances. A seventh miscellaneous group of substances was also added later (Dargan and Wood, 2013). Despite the policies and current guidelines against the commerce and the electronic commerce (e-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 has doubled over the period 2009–2013 (United Nations Office on Drugs and

Crimes, 2016). Further, in 2013, it was estimated that almost a quarter of a billion people of age between 15-64 years used an illicit drug in 2013, which corresponds to an estimated global prevalence of 5.2% (DrugWiseUK, 2016). Similarly, the number of NPS of (ab)use reported in the European Union is increasing each year for the period 2009 to 2014 (Novel Psychoactive Treatment UK Network, 2015). In March 2015, the *European Monitoring Centre for Drugs and Drug Addiction* (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; these were produced in clandestine laboratories (DrugWiseUK, 2016). 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, is on the rise (fenethylline). Captagon, a psychostimulant and an amphetamine-type substance, is also a diffused substance in Iraq, Turkey, Iran, Jordan, Kuwait, Oman, UAE and Qatar (Al-Imam et al., 2017).

The marketing strategies of illicit drugs have significantly changed over the years. The Internet has become increasingly important as a modality of communication and trade; this method is also known as the electronic commerce or electronic trade (e-trade). The e-commerce does also take place on the anonymous deep web and the darknet e-marketplace. Additionally, potent substances can be easily purchased online, and in uncertain doses; they entail a high risk of severe poisonings, morbidity, and even sudden deaths (Krabseth et al., 2016). In the European Union (EU), forty-one novel psychoactive substances were identified for the first time in 2010, forty-nine in 2011, seventy-three in 2012, eighty-one in 2013, and thirty-seven by April 2014 via the European *Early Warning System* (Krabseth et al., 2016; World Health Organization, 2004).

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 pre-specified 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 (Jansen et al., 1998; Salton, 1991).

The literature review aimed towards; amphetamines and captagon substances (1), the collateral use of the deep web and the darknet (2), the exploitation of use of Google Trends database for the purpose of epidemiological analyses and geographic mapping (3), and the adverse reactions of amphetamines in relation to the cardiovascular system, including incidents of intoxications and fatalities (4). Priorities were given to articles; published 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* (Camanho, 2009; Merlin et al., 2009).

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 models for hypothesis testing, 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 a 95% confidence interval (95% CI). Additionally, further data were retrieved in relation to the geographic mapping of these substances. To summarise, this study is a hybrid analytic research made of a targeted systematic review of the published literature, and extrapolations based on 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* (University of Oxford, 2009).

3. Results

Amphetamines are phenethylamine derivatives; these are potent stimulants of the central nervous system (CNS) and psychostimulants (Curran et al., 2014; Dargan and Wood, 2013; Singleton et al., 2009). 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 (Li et al., 2014; Rasmussen, 2015; Seiden et al., 1993). These substances can be addictive, leading to dependence, tolerance, and withdrawal syndrome (Casey et al., 2014; Ericsson et al., 2014). Recently, an NPS substance known commercially 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 (Al-Imam, 2017a; Al-Imam, 2017b; Al-Imam et al., 2017; Katselou et al. 2016; Van Hout & Wells, 2016). 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; captagon was incriminated in Paris terror attacks in 2015 (Al-Imam et al., 2017; Kravitz & Nichols, 2016; Speckhard & Yayla, 2015).

3.1 Amphetamines and Cardiovascular Interactions

Stimulants have profound effects on the cerebrovascular systems and cardiovascular system; it may lead to congestive cardiomegaly, cardiac chambers and valvular fibrosis, and cerebral infarction and haemorrhage (Milroy and Parai, 2011). 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 (mis)using amphetamine and amphetamine-type stimulants (Hennissen et al., 2015).

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 also increase serotonin release. Histologically, the effects of amphetamines are similar to the cocaine-induced changes; those include vascular hypertrophy, interstitial fibrosis, microvascular changes (hypertrophy) 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 (Bădilă et al., 2015). Amphetamines stimulate the release of norepinephrine affecting both alpha (α) and beta (β) adrenergic receptors. Alpha-adrenergic stimulation causes vasoconstriction and an increase in the total peripheral resistance, while β-Adrenergic receptor stimulation leads to an increase in the 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 (Fitzgerald & Bronstein, 2013).

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 (Figueredo, 2011). Furthermore, amphetamine and ATS can cause an indirect stimulation of the autonomic nervous system through the release of catecholamines, dopamine, and serotonin from nerve terminals of the central and peripheral nervous systems (Fischbach, 2017). In addition, serotoninergic 5-HT(2A) receptors agonists and to a fewer extent alpha-adrenoceptors agonists can cause vasoconstriction and tissue ischemia. Therefore, those drugs can induce fibrosis of the cardiac valves leading to heart failure (Dawson and Moffatt, 2012). Moreover, the pharmacological mechanism for the vasoconstriction and consequent fibrosis was recently found to be partially attributed to the interaction of amphetamines with a specific subset of receptors known a *trace amine-associated receptors* (TAARs) which are located in blood vessels. TAARs were found to play a substantial part in mediating the cardiac toxicity (Broadley, 2010).

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 transporter. Those neurotransmitters have vasoconstrictive and growth modulating effects on smooth muscle cells leading to the development of PAH (Montani et al., 2013). Fulceri and colleagues have also found that the combination of MDMA and loud noise, as in mass recreational activities, can potentiate the effects of prolonged loud noise exposure which might explain the unexpected fatal events that happen in entertainment and rave events (Fulceri et al., 2011).

In relation to captagon, the adverse reactions mimic those of amphetamine and ATS; those 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 (Drug Enforcement Admin, 2003). Hazardous side effects include psychosis, visual distortions and hallucinations, acute heart failure, acute myocardial infarction (AMI), and epileptic fits (Shufman & Dickman, 1998; Ulucay, Kargı, & Aksoy, 2012). 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 (Shufman & Dickman, 1998). Acute myocardial infarction has been increasingly reported since the beginning of the civil war in Syria (2011), Turkey, and other regions of the Middle East (Arslan et al., 2015). The first case of AMI in association with captagon was documented in a 21-year old man (Ulucay, Kargı, & Aksoy, 2012).

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 technologies (Chen, 2012; Grams, 2016). The deep web utilises technologies which provide anonymity for users. Those 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 (Fifield et al., 2015; Prouff et al., 2014; Reid & Harrigan; 2013).

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 detailed knowledge on these substances (Al-Imam et al., 2017; Dargan and Wood, 2013). 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 (Christin et al., 2013; Van Hout et al., 2013).

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) (Bailey et al., 2006; Bancroft and Reid, 2016; Fachkha and Debbabi, 2016). 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 (Al-Imam et al., 2017; Biddle et al., 2002; Van Buskirk et al., 2016). 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* (authority) for e-markets, e-vendors, and e-customers (Dahl, 1957; Spekman, 1979; Wrong, 1980).

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* (Carrière‐Swallow and Labbé, 2013; Choi and Varian, 2012). Google trends analyses can be either retrospective or cross-sectional; these 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 (Carneiro et al., 2009; Pelat et al., 2009; Seifter et al., 2010). For instance, geo-mapping of surface web users' interest in relation to amphetamines and ATS; the attentiveness of surface web users can be analysed, using Google Trends, in connection with phenethylamine, amphetamine, and ATS, and in retrospect to provide an accurate inference on the *electronic epidemiology* (e-epidemiology) on the Internet (Carneiro et al., 2009; Seifter et al., 2010). Three specific keywords were used; *phenethylamine, amphetamine,* and *captagon*; trends analyses were done for the past five years (2012-2017) (Microsoft, 2017).

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 a maximum 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 e-trade activities of the substance by some extremist organisations including (Al-Imam et al., 2017; Marazziti, 2016; Van Hout & Wells, 2016). 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 on a year-to-year basis 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). Additional analyses, using regression models, revealed the presence of some degree of a positive 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 (same months) of the year in both 2013 and 2014.

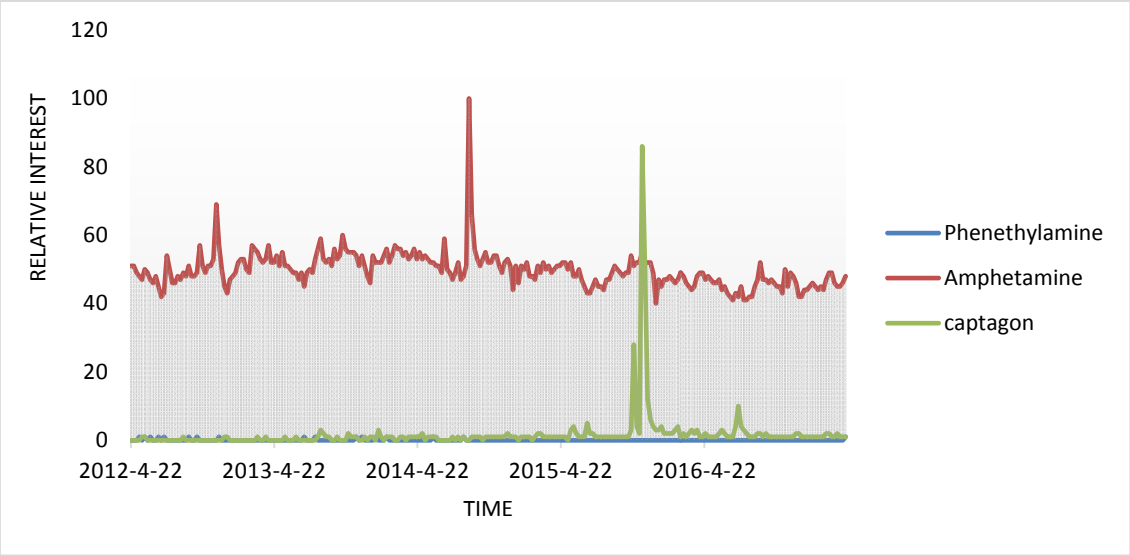

Figure 1. The Attentiveness of Surface Web Users in; Phenethylamine, Amphetamine, and Captagon

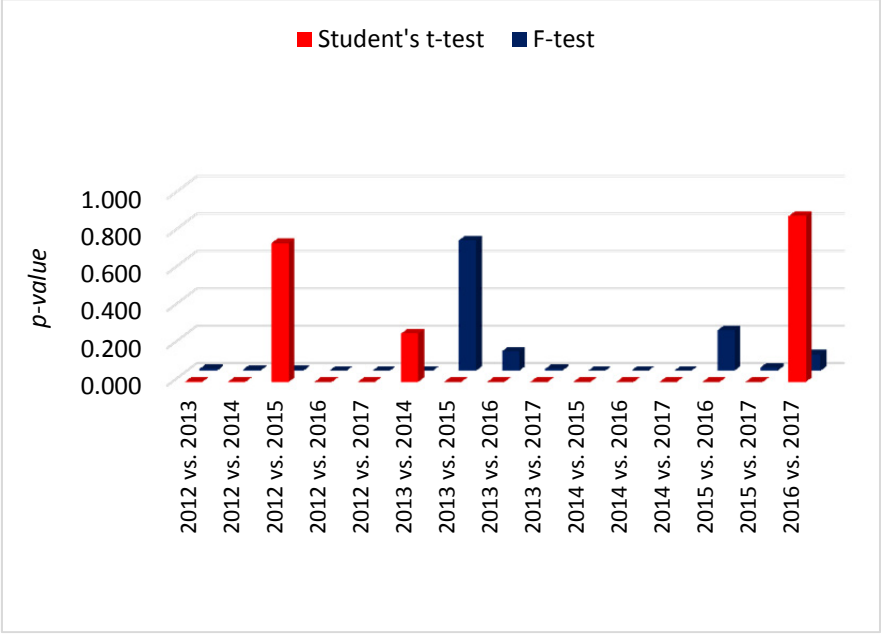

Figure 2. Inferential Statistics: Attentiveness of Web Users in Amphetamine in 2012-2017

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 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 one-seventh of the entire geo-map.

Figure 3. Geo-mapping: Phenethylamine (above), Amphetamine (middle), and Captagon (below)

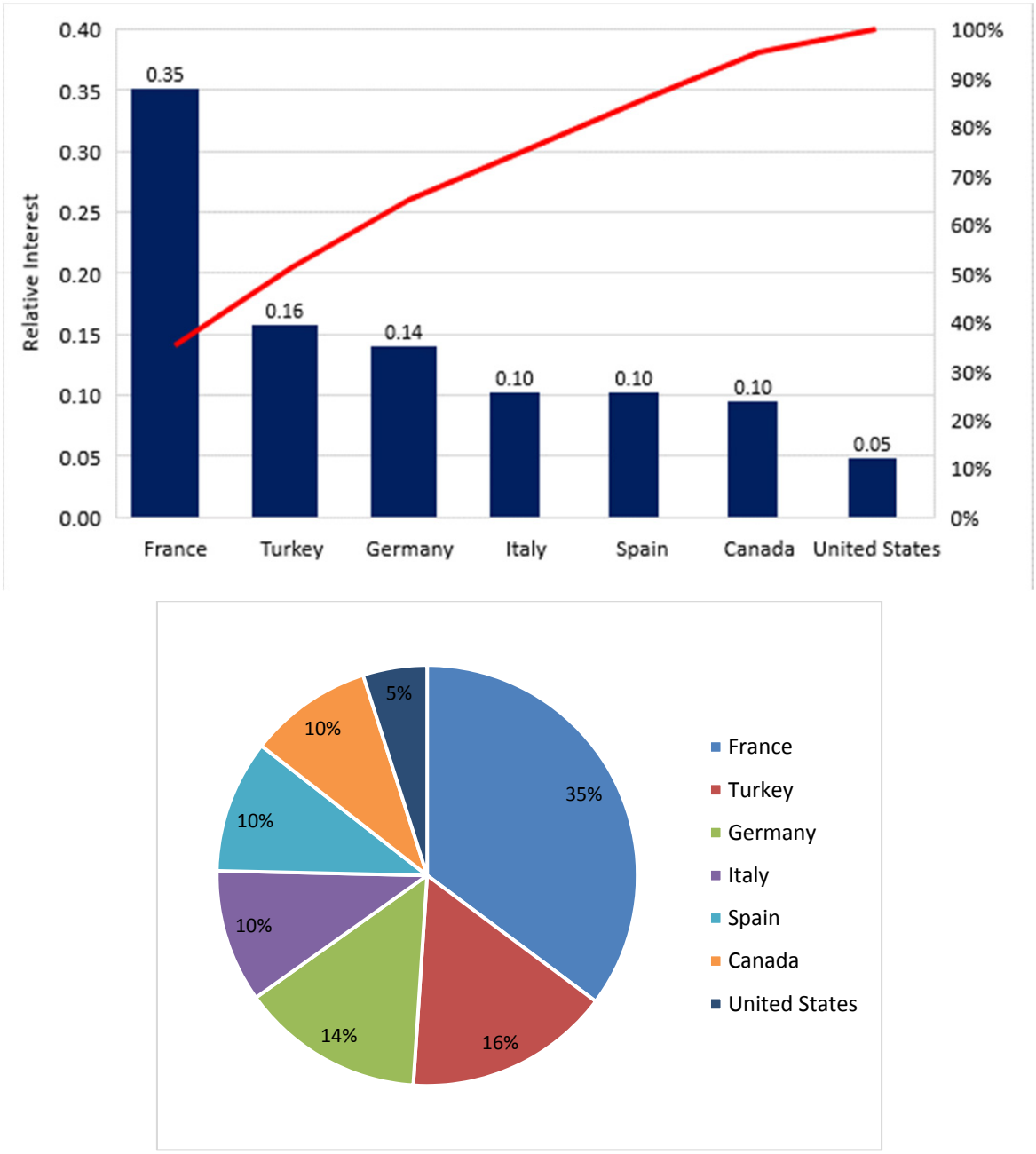

Figure 4. Geo-mapping of Captagon: Pareto Chart (above), and Pie Chart (below)

A summative geo-mapping for all three substance categories (Figure 5) has shown that the top ten 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 accounted. On the other hand, countries from the Middle East and the Arab world contributed to 2.3%; those countries 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 versus captagon (R^2=0.017). To summarise, amphetamines appear to be interesting for surface web users from the developed world, including some states of the former USSR (Soviet Union). On the other hand, countries from the developing countries, including the Middle East and Arabic world, contributed minimally.

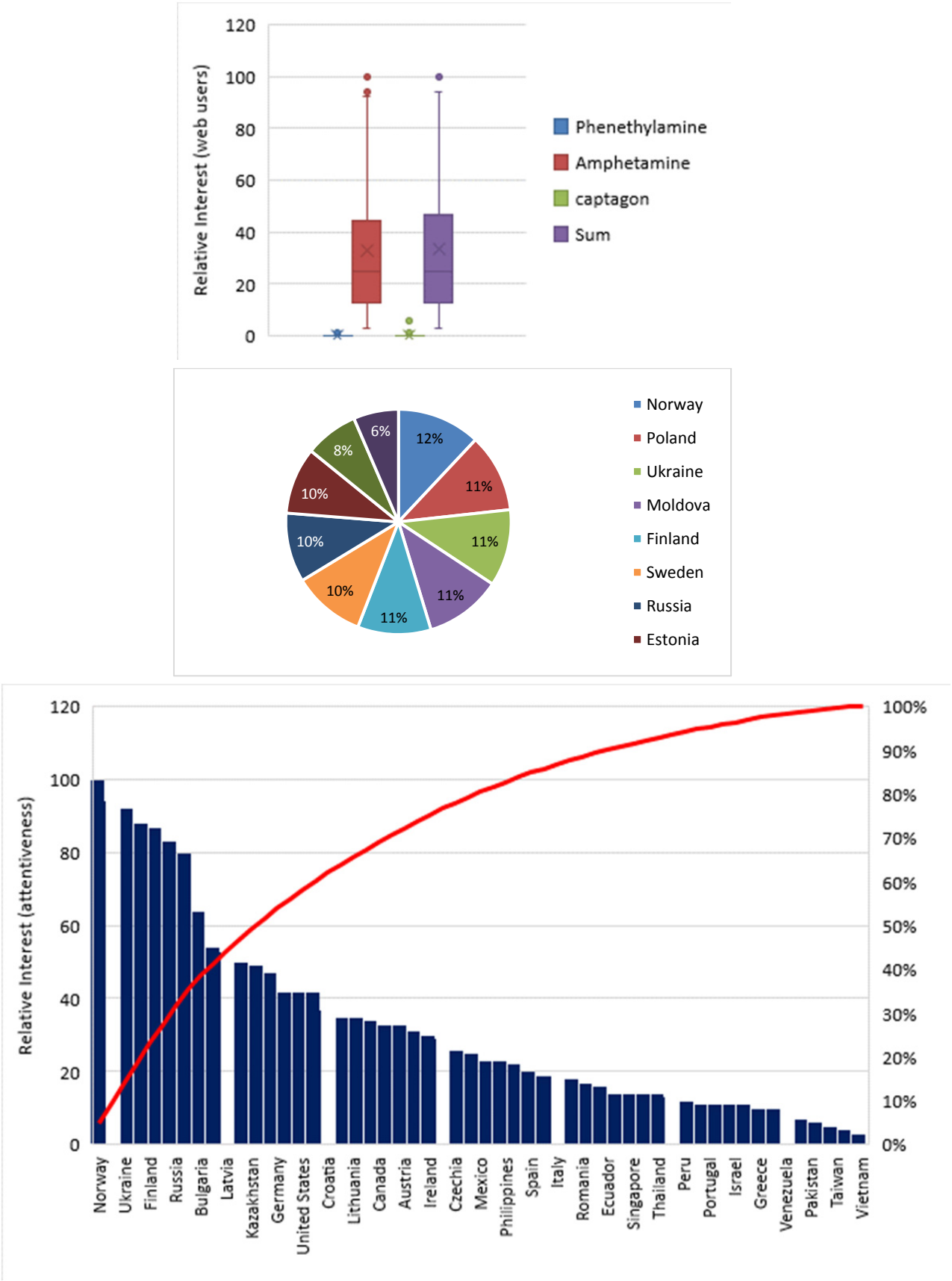

Figure 5. Summative Geo-mapping: Boxplot (above), Pie Chart (middle), and Pareto Chart (below)

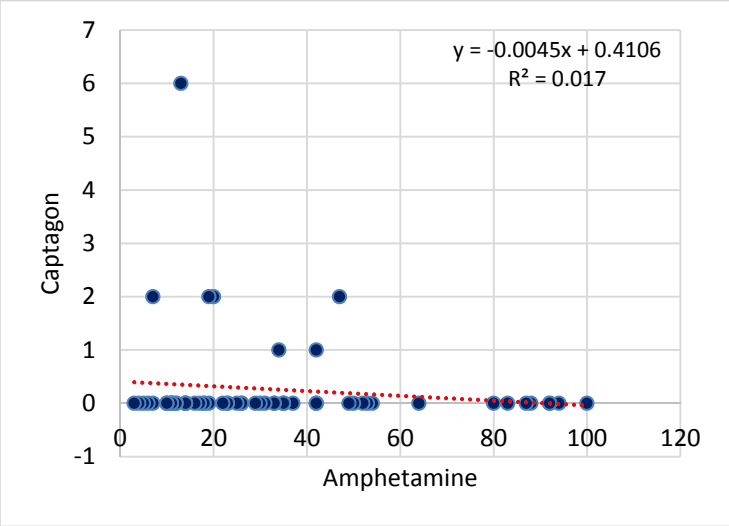

Figure 6. Inferential Statistic via Regression Analysis: Geo-mapping of Amphetamine vs Captagon

4. Conclusion

The growth of NPS industry, including the trade activities and its links to international terrorism, are reaching unprecedented levels. The e-commerce phenomenon of amphetamines seems to be highly prevalent in the western countries of the developed world, principally in 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 were also reported from the developed world. Furthermore, a considerable proportion of those events is related to the adverse pharmacological effects in relation to the cardiovascular system. Unless some 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 Eastern and Arabic countries (1), incorporation of efficient use of data science and advanced web analytics (2), compulsory training in relation to the disciplines of information science and basic neuroscience (3), validation and incorporation of data mining techniques and real-time analyses of databases (4), inclusion of the rarely-used experimental studies including; quasi-experiments, RCTs, pragmatic RCTs, and animal modelling (5), enhancement of the internet snapshot techniques (6), and the full exploitation of trends databases of the surface web (7).

Competing Interests Statement

There are no conflicts of interest to be declared.

Source of Funding

This study was entirely self-funded.

References

Al-Imam, A. (2017a). Could Hallucinogens Induce Permanent Pupillary Changes in (Ab) users? A Case Report from New Zealand. *Case Reports in Neurological Medicine*, 2017. https://doi.org/10.1155/2017/2503762

Al-Imam, A. (2017b). The relation between cerebral dominance and visual analytic skills in Iraqi Medical students, a cross sectional analysis. *Journal of the Anatomical Society of India, 66*(1), 42-43. https://doi.org/10.1016/j.jasi.2017.08.136

AL-Imam, A., Santacroce, R., Roman‐Urrestarazu, A., Chilcott, R., Bersani, G., Martinotti, G., & Corazza, O. (2017). Captagon: use and trade in the Middle East. *Human Psychopharmacology: Clinical and Experimental*, 32(3).

Al-Imam, A., Simonato, A. P., & Corazza, O. (2016). Haloperidol, an old antipsychotic with potential use by NPS

users in Iraq. *Research and Advances in Psychiatry*, *3*(3), 81-84. Retrieved from https://www.rapjournal.eu/materiale_cic/948_3_3/8031_haloperidol/article.htm

Arslan, M. M., Zeren, C., Celikel, A., Ortanca, I., & Demirkiran, S. (2015). Increased drug seizures in Hatay, Turkey related to civil war in Syria. *International Journal of Drug Policy, 26*(1), 116-118. https://doi.org/10.1016/j.drugpo.2014.04.013

Bădilă, E., Hostiuc, M., Weiss, E., & Bartoş, D. (2015). Illicit drugs and their impact on cardiovascular pathology. *Romanian Journal of Internal Medicine, 53*(3), 218-225. https://doi.org/10.1515/rjim-2015-0029

Biddle, P., England, P., Peinado, M., & Willman, B. (2002, November). The darknet and the future of content protection. In *ACM Workshop on Digital Rights Management* (pp. 155-176). Springer, Berlin, Heidelberg.

Broadley, K. J. (2010). The vascular effects of trace amines and amphetamines. *Pharmacology & therapeutics, 125*(3), 363-375. https://doi.org/10.1016/j.pharmthera.2009.11.005

Camanho, GL., (2009). Level of Evidence. *Revista brasileira de ortopedia, 44*(6), IFC1.

Carneiro, H. A., & Mylonakis, E. (2009). Google trends: a web-based tool for real-time surveillance of disease outbreaks. *Clinical infectious diseases, 49*(10), 1557-1564. https://doi.org/10.1086/630200

Carrière‐Swallow, Y., & Labbé, F. (2013). Nowcasting with Google Trends in an emerging market. *Journal of Forecasting, 32*(4), 289-298. https://doi.org/10.1002/for.1252

Casey KF, Benkelfat C, Cherkasova MV, Baker GB, Dagher A, Leyton M. Reduced dopamine response to amphetamine in subjects at ultra-high risk for addiction. *Biological psychiatry, 76*(1), 23-30. https://doi.org/10.1016/j.biopsych.2013.08.033

Chen, H. (2012). Dark Web research overview. In *Dark Web* (pp. 3-18). Springer New York. https://doi.org/10.1007/978-1-4614-1557-2_1

Choi, H., & Varian, H. (2012). Predicting the present with Google Trends. *Economic Record, 88*(s1), 2-9. https://doi.org/10.1111/j.1475-4932.2012.00809.x

Christin N. (2013). Traveling the Silk Road: A measurement analysis of a large anonymous online marketplace. In *Proceedings of the 22nd international conference on World Wide Web 2013 May 13* (pp. 213-224). ACM. https://doi.org/10.1145/2488388.2488408

Cluver, J. S., & Rheingold, A. A. (2014). *Handbook of Clinical Psychopharmacology for Therapists*.

Curran, C., Byrappa, N., & Mcbride, A. (2004). Stimulant psychosis: systematic review. *The British journal of psychiatry, 185*(3), 196-204. https://doi.org/10.1192/bjp.185.3.196

Dahl, R. A. (1957). The concept of power. *Systems Research and Behavioral Science, 2*(3), 201-215. https://doi.org/10.1002/bs.3830020303

Dargan, P., & Wood, D. (Eds.). (2013). *Novel psychoactive substances: classification, pharmacology and toxicology*. Academic Press.

Dawson, P., & Moffatt, J. D. (2012). Cardiovascular toxicity of novel psychoactive drugs: lessons from the past. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 39*(2), 244-252. https://doi.org/10.1016/j.pnpbp.2012.05.003

Drug Enforcement Administration (DEA). (2003). *Fenethylline and the Middle East. A brief summary*. Springfield, VA: DEA.

DrugWiseUK. NPS Come of Age: A UK overview. Available at http://www.drugwise.org.uk/nps-come-of-age-a-uk-overview/ (accessed 14 June 2016).

Ericsson, E., Bradvik, L., & Hakansson, A. (2014). Mortality, causes of death and risk factors for death among primary amphetamine users in the Swedish criminal justice system. *Substance use & misuse, 49*(3), 262-269. https://doi.org/10.3109/10826084.2013.825921

Fifield, D., Lee, L. N., Egelman, S., & Wagner, D. (2015). Tor's Usability for Censorship Circumvention. In *Workshop on Hot Topics in Privacy Enhancing Technologies*.

Figueredo, V. M. (2011). Chemical cardiomyopathies: the negative effects of medications and nonprescribed drugs on the heart. *The American journal of medicine, 124*(6), 480-488. https://doi.org/10.1016/j.amjmed.2010.11.031

Fischbach, P. (2017). The role of illicit drug use in sudden death in the young. *Cardiology in the Young, 27*(S1),

S75-S79. https://doi.org/10.1017/S1047951116002274

Fitzgerald, K. T., & Bronstein, A. C. (2013). Adderall®(amphetamine-dextroamphetamine) toxicity. *Topics in companion animal medicine, 28*(1), 2-7. https://doi.org/10.1053/j.tcam.2013.03.002

Fulceri, F., Ferrucci, M., Lenzi, P., Soldani, P., Bartalucci, A., Paparelli, A., & Gesi, M. (2011). MDMA (ecstasy) enhances loud noise‐induced morphofunctional alterations in heart and adrenal gland. *Microscopy research and technique, 74*(9), 874-887.

Grams. Search the darknet. Available at http://grams7enufi7jmdl.onion/ (accessed 14 June 2016).

Hennissen, L., Bakker, M. J., Banaschewski, T., Carucci, S., Coghill, D., Danckaerts, M., ... & Nagy, P. (2017). Cardiovascular effects of stimulant and non-stimulant medication for children and adolescents with ADHD: a systematic review and meta-analysis of trials of methylphenidate, amphetamines and atomoxetine. *CNS drugs*, 1-17.

Jansen, B. J., Spink, A., Bateman, J., & Saracevic, T. (1998, April). Real life information retrieval: A study of user queries on the web. In *ACM SIGIR Forum* (Vol. 32, No. 1, pp. 5-17). ACM. https://doi.org/10.1145/281250.281253

Katselou, M., Papoutsis, I., Nikolaou, P., Qammaz, S., Spiliopoulou, C., & Athanaselis, S. (2016). Fenethylline (Captagon) Abuse–Local Problems from an Old Drug Become Universal. *Basic & clinical pharmacology & toxicology, 119*(2), 133-140. https://doi.org/10.1111/bcpt.12584

Krabseth, H. M., Tuv, S. S., Strand, M. C., Karinen, R. A., Wiik, E., Vevelstad, M. S., ... & Vindenes, V. (2016). Novel psychoactive substances. *Tidsskrift for den Norske laegeforening: tidsskrift for praktisk medicin, ny raekke, 136*(8), 714-717. https://doi.org/10.4045/tidsskr.15.1278

Kravitz, M., & Nichols, W. (2016). A Bitter Pill to Swallow: Connections between Captagon, Syria, and the Gulf. *Journal of International Affairs, 69*(2), 31.

Li, J., Hou, L., Du, P., Yang, J., Li, K., Xu, Z., ... & Li, X. (2014). Estimation of amphetamine and methamphetamine uses in Beijing through sewage-based analysis. *Science of the Total Environment, 490*, 724-732. https://doi.org/10.1016/j.scitotenv.2014.05.042

Marazziti, D. (2016). Psychiatry and terrorism: exploring the unacceptable. *CNS spectrums, 21*(2), 128-130. https://doi.org/10.1017/S1092852916000031

Merlin, T., Weston, A., & Tooher, R. (2009). Extending an evidence hierarchy to include topics other than treatment: revising the Australian'levels of evidence'. *BMC medical research methodology, 9*(1), 34. https://doi.org/10.1186/1471-2288-9-34

Microsoft. Google Trends. Available at https://trends.google.com/trends/explore?q=Phenethylamine,%2Fm%2F0_0j,captagon (accessed 19 April 2017).

Milroy, C. M., & Parai, J. L. (2011). The histopathology of drugs of abuse. *Histopathology, 59*(4), 579-593. https://doi.org/10.1111/j.1365-2559.2010.03728.x

Montani, D., Seferian, A., Savale, L., Simonneau, G., & Humbert, M. (2013). Drug-induced pulmonary arterial hypertension: a recent outbreak. *European Respiratory Review, 22*(129), 244-250. https://doi.org/10.1183/09059180.00003313

Novel Psychoactive Treatment UK Network (NEPTUNE). Guidance on the Clinical Management of Acute and Chronic Harms of Club Drugs and Novel Psychoactive Substances. Available at http://neptune-clinical-guidance.co.uk/wp-content/uploads/2015/03/NEPTUNE-Guidance-March-2015.pdf (accessed 14 June 2016).

Pelat, C., Turbelin, C., Bar-Hen, A., Flahault, A., & Valleron, A. J. (2009). More diseases tracked by using Google Trends. *Emerging infectious diseases, 15*(8), 1327. https://doi.org/10.3201/eid1508.090299

Prouff, E., Rivain, M., & Roche, T. (2014, February). On the practical security of a leakage resilient masking scheme. In *Cryptographers' Track at the RSA Conference* (pp. 169-182). Springer, Cham. https://doi.org/10.1007/978-3-319-04852-9_9

Rasmussen, N. (2015). Chapter two-amphetamine-type stimulants: the early history of their medical and non-medical uses. *International review of neurobiology, 120*, 9-25. https://doi.org/10.1016/bs.irn.2015.02.001

Reid, F., & Harrigan, M. (2013). *An analysis of anonymity in the bitcoin system. In Security and privacy in social networks* (pp. 197-223). Springer New York. https://doi.org/10.1007/978-1-4614-4139-7_10

Salton, G. (1991). *Developments in automatic text retrieval. science*, 974-980. https://doi.org/10.1126/science.253.5023.974

Seiden, L. S., Sabol, K. E., & Ricaurte, G. A. (1993). Amphetamine: effects on catecholamine systems and behavior. *Annual review of pharmacology and toxicology, 33*(1), 639-676. https://doi.org/10.1146/annurev.pa.33.040193.003231

Seifter, A., Schwarzwalder, A., Geis, K., & Aucott, J. (2010). The utility of "Google Trends" for epidemiological research: Lyme disease as an example. *Geospatial health, 4*(2), 135-137. https://doi.org/10.4081/gh.2010.195

Shufman, E., & Dickman, M. (1999). Fenethyllin psychosis: description of two cases. *Israel journal of psychiatry and related sciences, 36*(2), 129-131.

Singleton, J., Degenhardt, L., Hall, W., & Zabransky, T. (2009). Mortality among amphetamine users: a systematic review of cohort studies. *Drug and Alcohol Dependence, 105*(1), 1-8. https://doi.org/10.1016/j.drugalcdep.2009.05.028

Speckhard, A., & Yayla, A. S. (2015). Eyewitness accounts from recent defectors from Islamic State: Why they joined, what they saw, why they quit. *Perspectives on Terrorism, 9*(6).

Ulucay, A., Kargi, C. A., & Aksoy, M. F. (2012). Acute myocardial infarction associated with Captagon use/Kaptagon kullanimi ile iliskili akut miyokart enfarktusu. *The Anatolian Journal of Cardiology (Anadolu Kardiyoloji Dergisi), 12*(2), 182-186.

United Nations Office on Drugs and Crimes. World Drug Report 2016. Available at http://www.unodc.org/wdr2014/ (accessed 14 June 2016).

University of Oxford. Center for Evidence Based Medicine. Available at http://www.cebm.net/ (accessed 16 March 2017).

Van Buskirk, J., Roxburgh, A., Bruno, R., Naicker, S., Lenton, S., Sutherland, R., ... & Burns, L. (2016). Characterising dark net marketplace purchasers in a sample of regular psychostimulant users. *International Journal of Drug Policy, 35*, 32-37. https://doi.org/10.1016/j.drugpo.2016.01.010

Van Hout, M. C., & Bingham, T. (2013). 'Silk Road', the virtual drug marketplace: A single case study of user experiences. International *Journal of Drug Policy, 24*(5), 385-391. https://doi.org/10.1016/j.drugpo.2013.01.005

Van Hout, M. C., & Wells, J. (2016). Is Captagon (fenethylline) helping to fuel the Syrian conflict?. *Addiction, 111*(4), 748-749. https://doi.org/10.1111/add.13262

World Health Organization. (2003). *Neuroscience of psychoactive substance use and dependence*.

Wrong, D. (2017). *Power: Its form*s, *bases and uses*. Routledge.