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Trends in Novel Psychoactive Substance Use and the Impact of Irish Legislative Efforts

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Abstract

Introduction

Novel Psychoactive Substances (NPS) are emerging at increasingly rapid rates, creating unpredictability in drug markets and ineffective drug policies. Ireland has a drug-induced mortality rate greater than three times the European average and the highest rate of NPS use. Given the scarcity of published literature, the National Advisory Committee on Drugs has recommended trends in NPS use be studied in order to facilitate appropriate public health measures.

Objectives

To critically evaluate the published literature on NPS and establish the health risks associated with their use, trends in drug-induced fatalities, and the efficacy of legislative policies in reducing NPS consumption.

Methods

A systematic search of Medline and PubMed was completed based on pre-defined inclusion criteria, and relevant studies were selected for comprehensive analysis.

Results

Clinical experiences of NPS abusers predominantly involved neurological or psychological symptoms, coupled with cardiovascular effects. While the overall prevalence of NPS presentations in Europe remains low, fatal overdoses were primarily attributed to acute overdose and commonly involved ingestion of synthetic cathinones. Legislation in 2010 resulted in decreased rates of recent and problematic NPS use, along with higher rates of negative user experiences. No significant displacement towards established illicit drugs was reported.

Conclusion

This systematic review has demonstrated the current state of knowledge regarding NPS within an Irish context. The trends in NPS prevalence and toxicity are important considerations for the development of effective drug monitoring or enforcement strategies. This knowledge is further relevant for emergency physicians and forensic pathologists in order to make accurate medical assessments.

Introduction

The term novel psychoactive substance (NPS) encompasses those psychoactive substances not prohibited under the UN Convention on Narcotic Drugs, which are often designed to mimic the effects of illicit drugs[1]. To circumvent legal restrictions, they are often mislabeled as 'research chemicals', 'bath salts', or 'not fit for human consumption'[2]. NPS are emerging and being reformulated at increasingly rapid rates, creating unpredictability in drug markets and ineffective drug policies[1]. By 2016, the EU Early Warning System on New Psychoactive Substances was monitoring over 560 substances, with 70% emerging in the preceding five years[3]. The most commonly reported NPS are the synthetic cannabinoids (39.3%), synthetic cathinones (16.6%), and phenylethylamines (14.1%)[2].

The emergence of NPS in Ireland was noted in 2005 with the rise of 'legal highs' sold in headshops, which at the time complied with Irish law [4]. With their products rapidly gaining popularity, it was estimated that by 2010 the number of headshops had risen to one per 45,000 people. In response, the Irish government implemented two legislative controls in 2010 by i) amending the Misuse of Drugs Act to cover over 100 NPS, and ii) introducing the Criminal (Psychoactive Substances) Act[5]. While the regulations succeeded in curtailing the headshop supply route, availability through street and online markets has contributed to continued use of NPS among many users[4]. 'Darknet' cryptomarkets, encrypted networks isolated from the visible Internet, have particularly changed the model of illegal drug importation and distribution by utilizing anonymized transactions and delivery via legitimate couriers[6]. Research indicates a significant increase in online drug transactions in recent years, accounting for two-thirds of all darknet market activity[7].

In the "Youth Attitude on Drugs" report, Ireland was found to have the highest self-reported NPS use at 16% lifetime prevalence, whereas the majority of EU countries reported levels at or below 5%[8]. The national drug-induced mortality rate in adults was found to be 71 deaths per million in 2014, greater than three times the European average[9]. Current literature highlighting the specific contribution of NPS to drug fatalities, however, is limited mainly to case reports[10]. Despite anecdotal accounts, the published data on the effects and toxicity of NPS are scarce due the recent emergence of the phenomenon and the speed at which new compounds are formulated[11]. Expert concerns center on short term impacts such as paranoia and heightened aggression, injection-related bacterial infections, and particularly the deterioration of mental health in the form of suicidal ideation and acute psychosis[4]. In light of these findings, one of the key recommendations of the National Advisory Committee on Drugs is further research into the shifting patterns of drug consumption, with particular focus on the surveillance of local trends, the monitoring of online NPS sourcing, and the evaluation of harm reduction strategies[10-11]. These steps would contribute to a pragmatic public health approach, critical for the identification of emerging risks and development of appropriate evidence-based responses.

Methods

Electronic database searches were performed, using Medline (EBSCO) and PubMed, to identify published studies which address the objectives of the systematic review. The following search strategy was employed:

("Novel psychoactive substance" OR "new psychoactive substance" OR "legal high" OR "synthetic cathinone" OR "synthetic cannabinoid" OR "bath salts")

AND

(("Toxic*" OR "risk" OR "abuse" OR "fatal*" OR effect) OR (prevalence OR use) OR (legislat*)).

The keywords for NPS terminology were formulated based on reference to Hohmann et al.[2], given the lack of consistency in the terms used by researchers, lawmakers, and drug users.

When evaluating studies regarding the trends in NPS prevalence and response to legislation, this review aimed to retrieve research in the context of the Irish population as these parameters are highly influenced by local settings, NPS access, and demographic variables[1]. Given the limited nature of research overall in this field[10], this priority may not be achieved and literature involving international settings with strong research methodology will be selected in these cases. Indeed, the terms "Irish" or "Ireland" were not included in the search strategy as this severely limited the results retrieved when initially attempted. The preference of Irish settings for studies pertaining to the adverse effects of NPS will not be applied as rigorously given that adverse drug reactions are less prone to these national influences[12]. Additionally, literature studying larger NPS drug categories will be preferentially selected over studies involving specific single drugs.

This review will seek to select studies with strong research methodologies to provide a more solid foundation on which to appraise the current state of knowledge. Unfortunately, it has been reported that information on NPS primarily originates from case reports and case series[13], but these will not be selected where more suitable research is retrieved. Based on the rapid rate of reformulation of NPS, recent literature is preferable but a timeframe of 2010-2019 will be employed in the search strategy since 2010 represents the introduction of Irish NPS legislation, and studies shortly following this timeframe may be important for analyzing the impact of regulation on NPS consumption. Based upon the criteria outlined, inclusion and exclusion criteria for screening articles were defined.

Inclusion Criteria	Exclusion Criteria
- Original research article - Research aims involving NPS toxicity, use or prevalence, fatalities, or legislation - Published between 2010-2019 - English language - Available as free full text - Human studies - Study population representative of the general population or active NPS users - Studies on NPS drug categories (in preference over single drug studies; if available)	- Case reports or case series - Systematic or narrative reviews - Meta-analyses or evidence summaries - Governmental or organizational publications - Conference proceedings - Animal studies - Solely toxicological analysis - Solely paediatric population - Population not reflective of general population (i.e. solely prison population, solely psychiatric patients)

Application of these inclusion and exclusion criteria to the initial results obtained in PubMed and Medline (EBSCO) resulted in 361 studies screened through title or abstract, followed by 35 full text articles reviewed for eligibility, after which 10 articles were included in the systematic review (Figure 1).

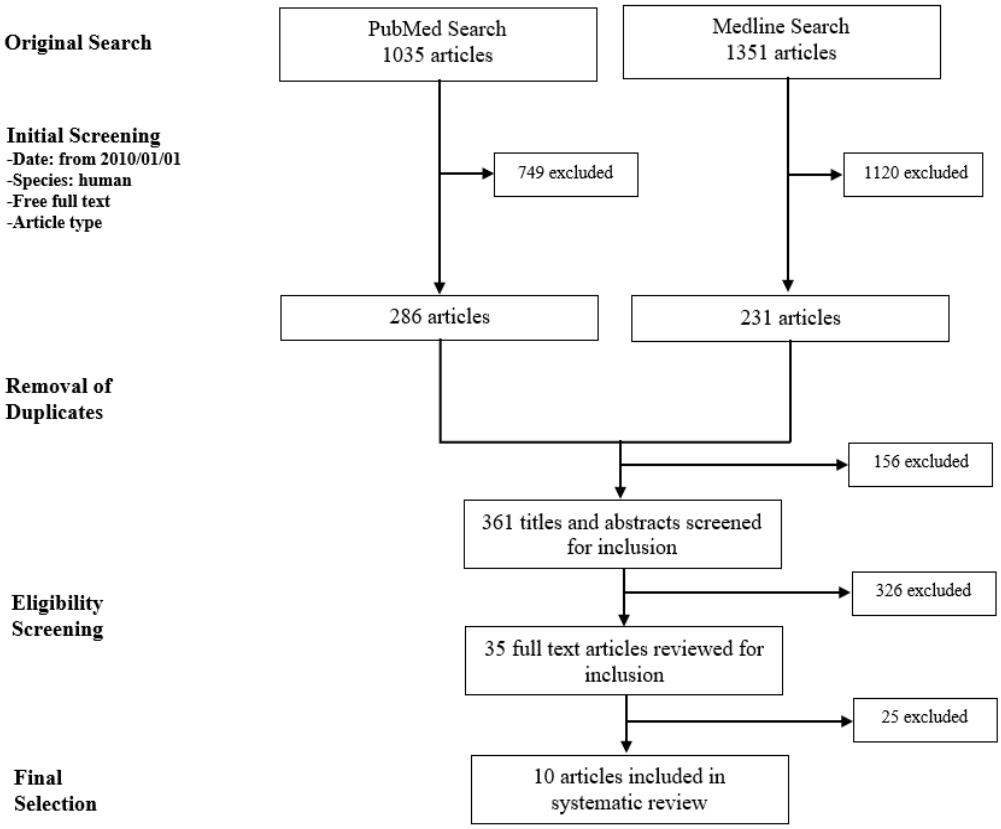
Results

Toxicity Associated with NPS Consumption

The clinical experience and demographic characteristics associated with NPS toxicity were analyzed in three multicenter surveys[14-16] and an epidemiological case-control study[17] (Table 2). While a population survey within Ireland was not obtained, the demographic profile of users reporting acute toxicity was highly concordant among the surveys despite large geographic and societal variation (Netherlands[14], Japan [15], and US[16]). The majority of NPS abusers across studies were male (>75%) and less than 30 years old. Clinical symptoms reported on admission were predominantly neurological and psychological, with high levels of agitation, hallucination, confusion, and nausea[14-16]. Cardiovascular symptoms often presented during acute toxicities, with tachycardia and hypertension consistently identified across the studies and reflective of published literature in other jurisdictions[18]. Mechanisms of action for most NPS remain uncertain, however the sympathomimetic syndrome has been proposed for many NPS categories, particularly synthetic cathinones [16]. Inhibition of membrane catecholamine transporters is suspected to result in reuptake inhibition, and initial animal studies concur[19]. Further complications to acute toxicities occurred in the form of major organ complications (i.e. liver injury, rhabdomyolysis) and harmful behaviours (i.e. suicide attempts, traffic accidents)[15-16]. Importantly, the severity of adverse effects and harmful behaviours was noted to increase with time and prolonged consumption[15].

The epidemiological study focused on one particular health risk, HIV infection, however was included as it represented a vulnerable population specific to Ireland[17]. Prompted by an

Figure 1
Study Identification and Selection.



outbreak identified by the Department of Public Health, the study provided the first evidence of an association between HIV in the homeless and injection of a synthetic cathinone, 'snow blow'. Higher risk scores were associated with females, chaotic drug users, daily injectors, and multiple NPS consumption[17].

Trends in NPS Prevalence and Fatal Cases

Observed patterns in NPS consumption were assessed through cross-sectional database analyses[20-21] and retrospective forensic casework studies[22-23] (Table 2). Reporting from 16 European monitoring centres, including two Irish districts, demonstrated low overall prevalence of NPS in drug-related emergency presentations, between 0-2.8% monthly, with higher frequencies for traditional recreational drugs or misused prescription medicines[21]. The most frequently reported NPS in European users were synthetic cathinones, particularly mephedrone and methedrone. The Australian database, in contrast, found a shift in most reported drug from mephedrone in 2010 to 2C-x phenylethylamines in 2013, demonstrating volatility of drug markets and the influence of local factors on drug consumption[20]. NPS users were more likely to source drugs through online markets, which has been corroborated elsewhere and believed to reflect preferences for avoiding threats of violence[24]. NPS users were further associated with younger age of first drug use, higher consumption frequency, and perceptions of traditional street drugs as lower quality[20]. These individual characteristics may be key factors in users' decisions to continue or increase NPS consumption.

Regarding fatal NPS cases, the leading cause of death reported in forensic casework studies was acute drug toxicity, particularly with synthetic cathinones[22-23]. Knowledge regarding the pathophysiology of these adverse events, however, is severely constrained. Pathological findings commonly reported were cardiac ischaemia and cerebral hypoxia[21,23], which may be explained by chronic vasoconstriction elicited by NPS, leading to artery stenosis[25]. Traumatic injuries are also important contributors to NPS fatalities, with relative high prevalence of fatal hangings, mechanical suicide (i.e. asphyxia, falls), and homicide[22]. Post-mortem drug

concentrations varied widely, prohibiting the establishment of 'fatal ranges' for commonly encountered NPS.

Efficacy of Legislation in NPS Regulation

The changes to NPS use and accessibility following Irish legislation in 2010 were assessed through a cross-sectional[26] and qualitative study[27] (Table 2). While significant changes to lifetime prevalence were not detected post-legislation, this period demonstrated lower rates of recent NPS use and decreased problematic practices[26]. Such reductions are consistent with short-term results following similar bans in other countries[28-29]. While use of all NPS categories remains higher than desired by legislators and health advocates, the research has found that post-ban polydrug use fell among NPS users and there was no large displacement towards established illegal drugs as some expected[26].

In parallel, the qualitative study revealed that mephedrone users in the post-legislative timeframe noticed shifts in their 'high' experiences[27]. 'New' negative effects with continued mephedrone use were noticed, commonly described as more serious mood changes, depression, or anger. During interviews, participants did not link the legislative controls and media reporting to their decreased NPS use, yet their attitudes toward the safety and perceived health risks of these substances became more critical. These changes were often attributed to negative personal or peer experiences[27], however the influence of these public health initiatives should be critically assessed. Concerns also grew among users about potential contaminants and mixed agents following legislation, given the need to utilize street markets. Corresponding with these user considerations, other small-scale post-legislative studies in Ireland report reductions in various NPS detection rates[30-31]. Despite the limited scope of the qualitative study, it provides insight into the perceptions of NPS users following changes to drug accessibility, important for the development of future legislative proposals.

Discussion

The analysis of ten original research articles has provided insight into the current state of the literature regarding novel psychoactive substances. Despite variability in the geographic context of the studies, the clinical experiences of NPS abusers were consistent with predominant neurological or psychological symptoms, coupled with cardiovascular effects of tachycardia and hypertension[14-16]. The mechanism remains unclear for most drugs, but the studies and further literature support the sympathomimetic syndrome[2,19]. This knowledge is important in application to emergency physicians, where recognition of the syndrome despite negative drug screens can help with faster delivery of appropriate care. Similarly, associations of toxicity with major organ complication and harmful self-behaviours[15-16] should be considered when evaluating patient risk and therapies. Population surveys are common in this research area, most likely due to feasibility, however their application is accompanied by certain limitations. Marginalized populations, such as the homeless, prisoners, or youth, are often underrepresented in such surveys[1]. The health risks to which NPS users are exposed will remain a difficult topic of research given the inherent subjectivity of drug effects, the lack of information about NPS interactions with other illicit substances, the lack of certainty in contents of drugs consumed, and rapid altering of NPS molecular structures to bypass regulation constantly setting researchers behind[13].

Research in a European context has revealed low overall prevalence of NPS in emergency presentations, averaging 1%[21]. The most frequently reported were the synthetic cathinones, however volatility of these preferences in time and space was noted[20]. The associations of NPS users with younger age of first drug use, greater frequency of consumption, and preference for online markets[20,24] are important considerations when tailoring prevention and rehabilitation programs. Frequent involvement of synthetic cathinones in fatal cases reveals the necessity to keep toxicological screens updated

for these compounds to facilitate accurate pathological determinations. There is also need for pathologists to be aware of the common findings of ischaemia and cerebral hypoxia [21,23] when assessing suspected cases.

A major source of information on NPS prevalence is found in non-scientific publications such as governmental or agency reports[32-34], which were not included per systematic review methodology. These publications provide population-wide data at regular intervals, important for tracking the implementation of national health strategies, but in turn avoid important peer-review processes. Certain researchers bypass these processes due to the lengthy processing times, preferring to quickly disseminate to the general public. Scientific publications of survey studies can often suffer from small sample sizes, self-reporting errors, and memory biases[14]. Whether assessing normal use or fatal events, it is recommended that information on NPS be triangulated from all relevant sources[7], which may include emergency departments, forensic institutions, and poison control centres[14]. In forensic cases, the influence of post-mortem redistribution is particularly important when determining the contribution of drugs to death[35-36].

The 2010 regulations were associated with decreased rates of recent and problematic NPS use[26], which is consistent with data from other countries[28-29]. Importantly there was not a significant displacement towards established illegal narcotics. In terms of user perceptions, users noticed greater rates of negative effects with continued use[27], which may reflect effective public health initiatives or rise of potential contaminants in altered drug markets. Criticism of NPS bans without supplementary measures has been raised, as evidence of small reductions does not necessarily indicate that easy access to these drugs has been negated[37-38]. Current research does not provide rationale for Ireland to alter the current prohibitionist approach[26], but an important negative consequence is that compounds which became controlled limited academic research given the burdens of licensing requirements[39]. It is recommended provisions for research be provided in future legislation.

Conclusion

The issue of NPS is a major concern for governments across Europe, therefore knowledge of the trends in their prevalence and toxicity are important considerations for the development of effective drug monitoring or enforcement strategies. The synthesis of this information is further necessary for emergency physicians and forensic pathologists to make accurate clinical judgements.

This literature review has demonstrated that clinical experiences of NPS abusers are consistent despite geographic variability, however the mechanisms underlying these adverse effects remain unclear. Despite low overall prevalence of NPS use across the continent, the association of synthetic cathinones with fatal overdose remains a concerning trend in the published data. Meanwhile, legislation implemented by the Irish government has resulted in decreased rates of problematic use without significant displacement towards other illegal narcotics.

This review is limited by the exclusion of case reports and governmental publications, which produce meaningful insights into NPS trends but do suffer from a lack of strong research methodology. The rapid reformulation of these substances, inherent to current drug markets, creates challenges in keeping literature updated and relevant. High levels of polysubstance use are a confounding variable in the studies cited as the determination of specific agents contributing to death is impeded. Lastly, the prevalence of NPS in fatalities may be underrepresented as post-mortem toxicology for every autopsy is not currently feasible.

Allowing for these limitations, this review is nonetheless able to provide a comprehensive overview of the public health issues surrounding novel psychoactive substances. Given the scarcity of systematic data, the authors agree with

recommendations to develop a centralized national database for the collection of emergency department data[11]. The insights provided by such a database would aid public health agencies to understand the harm caused by existing and newly developed substances. The authors further recommend that future research in this field focus on the analysis of recent trends in drug fatalities within an Irish context. Such data will provide a better understanding of the vulnerable populations and specific health risks unique to this demographic population, enhancing efforts to implement appropriate and proactive harm-reduction strategies.

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