The e-psychonaut drugs' psychopharmacology

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Abstract:
The focus here was on the pharmacological and clinical pharmacological issues pertaining to the vast range of drugs (e.g., synthetic cannabimimetics; synthetic opioids; novel stimulants; novel psychedelics; PCP/ketamine-like compounds; prescribed medicinal compounds; and popular psychotropic herbs/plants) discussed by Internet-based, new/novel psychoactive substances (NPS) enthusiasts, 'e-psychonauts'. Currently ongoing related *in silico* studies, followed by further *in vitro* and *in vivo/*preclinical studies, will hopefully provide important findings in terms of which molecules within each given NPS class may present with higher levels of receptor affinities, and hence clinical potency. Understanding the pharmacological characteristics/potency of those novel recreational molecules will hopefully help in predicting related NPS diffusion, morbidity, and possible lethality data.

Key words: e-psychonauts; psychopharmacology; addiction; new psychoactive substances; novel psychoactive substances; NPS; drug abuse

Introduction

The market for new/novel psychoactive substances (NPS) is on the rise, arguably facilitated by the ongoing Covid-19 pandemic [1]. The web is playing a major role in shaping this unregulated market [2-4], and users are being attracted by these drugs due to both their intense psychoactive effects and likely lack of detection in routine drug screenings [5]. Overall, NPS are defined as new narcotic/psychotropic drugs which are not controlled by the United Nations' 1961 Narcotic Drugs/1971 Psychotropic Substances Conventions, but which may pose a public health threat [6]. The term 'novel' can also express something which is: a) *newly created; b)* a compound that *has come back into fashion* after a period of absence from the recreational drug scene; c) *a known NPS molecule being used in an innovative or unusual way*, hence presenting with a 'novelty' appeal [7]. Conversely, 'new' can include a failed pharmaceutical or an old patent which has been 'rediscovered' and marketed for its potential use as a 'recreational' substance.

E-psychonauts

E-psychonauts are those individuals aiming to experience self-induced altered states of consciousness in an attempt to investigate their own mind, whilst possibly addressing spiritual questions, through a direct experience [8]. The typical key-skills of e-psychonauts include high levels of pharmacological/pharmaceutical knowledge of psychoactives; and a strong desire to share/disseminate online their 'on drug' experiences. Psychonauts have been schematically defined as either a) '*mind navigators*', where the use of drugs is carried out in order to explore the frontiers of the mind, typically preferring a range of entheogens/plant substances conferring the user a divine experience; or b) '*chemicals' experimenters'*; e.g., researchers/experimenters of novel chemicals in order to document the drug's effects and to assess whether it is safe for others to use [2-4].

Searching for e-psychonauts' drugs

An approach aiming at describing what is being discussed online by the web-based NPS enthusiasts 'e-psychonauts' [2] has been considered as potentially useful to identify in advance NPS availability, marketing and diffusion. In fact, the online NPS scenarios, with their related concerns, typically predict the real-life NPS scenarios [3-4]. To facilitate the process of early recognition of the increasing dissemination of NPS online and the variability of information sources, our research group has implemented the use of a crawling/navigating software (i.e. NPSfinder®), which was designed to automatically scan the open/surface web for new/novel/emerging NPS. This is meant to map on a 24/7 basis the large variety of psychoactive molecules mentioned/discussed within a range of major and representative online psychonaut web sites/fora. As of today,

some 4,335 unique NPS molecules, ranked in a dozen categories [5], have been included in the NPSfinder® database [9]. Overall, the pharmacological characteristics of this vast range of molecules is quite complex and diversified, implying a range of neurotransmitter pathways [10]. However, a clear knowledge of these issues may be relevant for the clinician, to be able to implement an appropriate treatment and management plan for those clients presenting with an acute/subacute/chronic NPS intake.

Aims and objectives

The aim of this study was to provide an overview of the pharmacological and clinical pharmacological issues related to the several hundred, or indeed few thousands, of e-psychonauts' most popular drugs. We focussed here in particular on the following NPS classes: synthetic cannabimimetics; synthetic opioids; novel stimulants; novel psychedelics; PCP/ketamine-like compounds; prescribed medicinal compounds; and popular psychotropic herbs/plants.

Pharmacological and clinical pharmacological considerations of e-psychonauts' drugs

Synthetic cannabimimetics (SCs)

Although tetrahydrocannabinol (THC) is a partial (cannabinoid) CB1/CB2 receptor agonist, SCs contained in so-called 'Spice' products are typically full-efficacy agonists with very high affinity for these receptors [11]. Furthermore, the effects of THC in cannabis are modulated by the presence of other phytocannabinoids such as cannabidiol (CBD) and cannabivarin (CBDV), with these 'moderating' molecules not being identified in 'Spice' products [12-13]. Several SCs have been found to interact with a range of non-cannabinoid receptors, including 5-hydroxytryptamine (5-HT), nicotinic acetylcholine, glycine, and/or ionotropic glutamate (*N*-methyl-D-aspartate, NMDA), clearly contributing to the final 'Spice' effects [14]. A range of more recent SC compounds incorporate indole-derived moieties, as components of the structure or as substituents. Indoles are structurally similar to serotonin/5-HT; hence, they can activate 5-HT receptors thereby increasing the risk of serotonin syndrome in SC misusers [12-13]. The recent trend in SC fluorination, commonly applied in medicinal chemistry, may increase the compounds' lipophilicity, hence promoting their absorption through biological membranes/blood brain barrier, possibly enhancing overall SC toxicity [14]. Finally, 'Spice' products typically contain a range of different SCs in a single preparation.

Consistent with their pharmacodynamics' activities, SC acute intoxication may be associated with tachycardia, hypertension, visual/auditory hallucinations, mydriasis, agitation/anxiety, hyperglycaemia, dyspnoea/tachypnoea, and nausea/vomiting [15]. Serious cardiological (e.g., dysrhythmias, cardiac arrest, chest pain, and myocardial infarction)

and neurological (e.g., nystagmus, seizures, encephalopathy, coma, and stroke) issues have been reported as well [10]. The occurrence of psychotic issues ('Spiceophrenia) [12-13] has been reported (Table 1).

Novel synthetic opioids (NSOs)

Over the last few years, there has been an increase in the appearance of novel synthetic opioids (NSOs) on the recreational drug market. Fentanyl, fentanyl analogues, and the remaining opioids present as partial/full agonists, and with different affinity levels, at the mu, delta, and kappa opioid receptors. Indeed, fentanyl potency is considered to be 50–100 times that of morphine [16]. NSOs (n=426) recently identified by our research group have included two ohmefentanyl, with a putative potency 6,300 x morphine [17], and seven carfentanyl, characterized by a putative potency about 10,000 x morphine [18], analogues identified. Carfentanyl has been reported in association with a number of fatalities. Due to their high potency, their continued use and abuse may induce tolerance, with the risk of overdose and death being elevated [16; 19] (Table 1).

Novel stimulants: synthetic cathinones and psychedelic phenethylamines

The synthetic cathinones category covers in excess of 180 different molecules [20]; these drugs show structural similarities to amphetamines, whilst being mostly inhibitors of the serotonin (SERT), dopamine (DAT), and noradrenaline (NET) transporters. Synthetic cathinones can be further sub-categorised as: (1) cocaine/3,4-methylenedioxy-substituted cathinones, e.g., butylone): these act as inhibitors at SERT, DAT, and NET, and as serotonin releasers; (2) methamphetamine-like (*N*-alkylated or ring-substituted cathinones, e.g., buphedrone): these act as inhibitors at SERT, DAT, and NET, and as DA releasers; and (3) pyrovalerone-like cathinones (*N*-pyrrolidine cathinones e.g., MDPV [3,4-methylenedioxypyrovalerone]): these are very potent at DAT and do not induce any monoamine substrate release (for a thorough review, see [21]) (Table 1).

Novel psychedelic phenethylamines' derivatives: these compounds are still the most popular for e-psychonauts [9], being overall grouped as MDMA/ecstasy derivatives. These molecules, related to the so-called 2C-, include both: 2C-B/2,5-dimethoxy-4-bromophenethylamine/'Nexus'/'pink cocaine'; 2C-D (2,5-dimethoxy-4-methylphenethylamine), and 2C-E (2,5-dimethoxy-4-ethylphenethylamine); and the *N*-methoxybenzyl/NBOMe series drugs [5; 10; 21]. Indeed, those molecules which present with high 5-HT/DA ratios (e.g., MDMA; 2C- and 2D- series drugs; benzodifurans such as 3C-bromo-dragonfly; and others) may be considered proper entactogenic substances. Conversely, high DA/5-HT ratios might predict a strong stimulant experience [10] (Table 1).

Similar to the 2C- series drugs, both the 'fly' and the NBOMe series present with characteristics of both the hallucinogen and psychostimulant categories [21]. All NPS belonging to the so-called 'fly' series, with the

term referring to their molecular structure resembling an insect, and particularly 'Bromo-DragonFly'/'B-fly' (1-[4-Bromofuro{2,3-f}{1}benzofuran-8-yl]propan-2-amine), have been described as powerful and long-lasting drugs, with ill-health effects lasting for up to three days [10; 21]. The NBOMe compounds' market has recently increased in parallel with the declining availability of the lysergic acid diethylamide (LSD). These molecules produce similar effects to LSD but possess a higher potency [10].
All these serotonergic agents may induce a serotonin syndrome, hepatic toxicity, and modifications of endocrinological function [22] (Table 1).

Novel psychedelics: tryptamines and lysergamides
Apart from psychedelic phenethylamines, hallucinogens also include tryptamines/N,*N*- dimethyltryptamine (DMT)-like and lysergamides/LSD-like drugs. All of them share the same pharmacodynamic activities, e.g., agonism/partial agonism of the 5-HT2A, 5-HT2C, and 5-HT1A receptors. LSD displays high affinity for further 5-HT receptor subtypes including 5-HT1B, 5-HT1D, 5-HT7, and 5-HT6 [21]. Mescaline may present with the lowest, and LSD the highest, potency hallucinogen activity [10]. Other transporters/receptors implicated in the effects of tryptamines include the vesicular monoamine transporter 2 (VMAT2), sigma-1 receptors, SERT, and trace amine-associated receptors (TAAR; for a thorough review, see [10]).
Tryptamine derivatives continue to appear on the online drug market as NPS [10; 21]. They include: 5-MeO-DALT (N,*N*-diallyl-5-methoxytryptamine); 5-MeO-AMT (5-methoxy-α-methyltryptamine); 4-AcO-MET (4-acetoxy-*N*-methyl-*N*-ethyltryptamine); and many others. Tryptamines are typically metabolised by monoamine oxidase (MAO), and hence will need to be sniffed, smoked, or injected to increase their bioavailability. Tryptamines include as well naturally occurring molecules found in plants, fungi, or in the skin of various species of toads (for a review, see [21; 23]).
LSD look-alike drugs include: lysergic acid 2,4-dimethylazetidide (LSZ); 1-propionyl-d-lysergic acid diethylamide hemitartrate (1-PLSD); and D-lysergic acid amide (LSA, known as 'Morning Glory seeds'); 1-acetyl-N,*N*-diethyllysergamide (ALD-52, known as 'Orange Sunshine Acid') and many others [5; 10; 21].
Consistent with their complex pharmacodynamics, overall psychedelics' subjective effects include: mild stimulation, visual hallucinations, alterations in sensory perception enhanced depersonalisation, and anxiety/panic. The effects of hallucinogens are usually dose-dependent, highly context-dependent, and user-specific. Long-term effects may include the onset of a hallucinogen-persisting perception disorder (HPPD; [24] (Table 1).

Phencyclidine (PCP)-like substances

PCP-like drugs (e.g., including ketamine, methoxetamine and a few dozens of others) hallucinogenic effects are related to central NMDA receptor antagonism; 5-HT2A agonism; and high affinity for mu/delta/sigma opioid receptors [5; 25]. Subjective effects (e.g., 'K-hole') include dissociation from both the setting and the body, auditory/visual hallucinations, unusual thought content, euphoria and visual distortions [10]. Its related risks may include trauma, drowning, death from hypothermia, traffic accidents [5], and severe urinary dysfunction issues [22] (Table 1).

Prescription medications

A range of prescribed medications are currently being used recreationally as NPS, typically at high or super-high dosages (Table 1).

GABAergics: A few hundreds of NPS belonging to the benzodiazepine (BDZ) class have recently appeared on the street/online/virtual markets and are known as *'exotic'* or *'designer' benzodiazepines* [9; 26]. They were either tested, but not approved, as medicinal compounds or are derivatives of currently prescribed BDZs. Although only very little related pharmacology and toxicity knowledge is available, a few dozens of them seem to present with high/very high potency levels [27].

Whilst presenting with a common mechanism of action with BDZ, zopiclone/zaleplon/zolpidem (*'Z-drugs'*) appeared on the market as their safe substitutes due to receptor selectivity and improved pharmacokinetic properties. However, their idiosyncratic routes of administration and high-dosage intake may well increase the risk of Z-drugs' misuse and withdrawal issues [28].

Finally, γ-hydroxybutyric acid (*GHB; 'liquid ecstasy'*) intake is associated with both increased central DA levels and activation of GABAA/-B receptors [29]. In the UK, some 159 GHB/γ-butyrolactone (GBL)-associated fatalities, mostly related to the 'chemsex' scenarios [30-31], were identified; most (79%) were accidental and GHB/GBL alone was implicated in 37% of cases [32].

Remaining e-psychonauts' GABAergic drugs include the web-based dietary supplement phenibut/'PB'; when ingested at high dosages, it acts as an GABA-A/B receptor agonist, whilst stimulating DA/5HT neurotransmission as well. Its use may rapidly lead to dependence; withdrawal signs/symptoms may include visual and auditory hallucinations [28].

Gabapentinoids: Whilst both pregabalin and gabapentin are widely being reported as being misused, pregabalin presents with higher risk due to its rapid absorption, faster onset of action, and higher potency [28]. Pregabalin is a known inhibitor of α2δ-subunit-containing voltage-dependent calcium channels, with its potent binding reducing the release of excitatory molecules (e.g., glutamate, NA, and substance P, but not DA), acting against aberrant neuronal stimulation (for a thorough commentary, see [33]). In rats, conditioned place preference was, however, induced only with high intraperitoneal (but not oral) pregabalin doses, restricting the ability to develop a substantial addictive power [34].

Accordingly, patients reported a euphoric high ('liking'; [35]) only when using supratherapeutic/mega (e.g., 1,500-12,000 mg) pregabalin dosages [36]. Finally, pregabalin may counteract opioid withdrawal whilst presenting also with potentiating effects when given to mice with existing opioid levels [37]. Consistent with this, gabapentinoids are being typically misused in combination with opiates/opioids [33]. Overall, mortality, physical dependence, and the propensity to cause depression of the central nervous system, especially when used in combination with opioids and sedatives, were harms identified both for pregabalin and gabapentin [35-36].

Antidepressants (ADs): Out of all ADs, the cathinone derivative bupropion and venlafaxine have emerged as increasingly being reported by e-psychonauts as possessing a misuse potential [28]. Stimulant effects of bupropion have been reported with high/very high dosages and with oral, nasal, and intravenous use. This is associated with its action as a selective inhibitor of both NA and DA reuptake [38]. At mega dosages, venlafaxine ('baby XTC' [39]) can be misused as well, and the occurrence of a withdrawal syndrome may be a significant issue [40]. Overall, this is consistent with desvenlafaxine, being an inhibitor of NA transporter activities, further increasing the rate of DA turnover in the prefrontal cortex [40].

Antipsychotics (quetiapine, olanzapine, clozapine): When snorting high-dosage crushed quetiapine ('Susie Q') tablets, there may be a 'high'. This may be associated with both increased levels of DA in the nucleus accumbens (NAc) and D2 receptor blockade, although norquetiapine-related NA reuptake blockade; 5-HT7 antagonist properties and sigma receptor activation may contribute to its misuse liability (for a commentary, see [41]). Olanzapine high-dosage consumption has been anecdotally reported as the 'ideal trip terminator/modulator', possibly due to its related activity on GABA-A receptors, hence the associated sedation and rewarding glutamatergic stimulation of the ventral tegmental area DAergic neurons [42]. Finally, although difficult to be interpreted, misuse/abuse cases of clozapine ingestion as an NPS have been described [43].

Loperamide: Within the over-the-counter medication abuse scenario ("pharming"; [1]), the anti-diarrhoeal loperamide has increasingly been reported [28]. It acts as a potent mu-opioid receptor agonist, albeit with predominantly peripheral activity on the myenteric plexus. At therapeutic (2-16 mg) dosages, loperamide does not exert cross-central opioid effects due to its low availability and P-glycoprotein-mediated outflow at the blood-brain barrier. However, at high dosages (50–800 mg), it is associated with an opiate-like euphoric state ('lope high'; 'poor man's methadone'; for an overview, see [44]). Loperamide toxicity effects of concern include: gastrointestinal (e.g., nausea, vomiting, constipation), central nervous system (e.g., respiratory depression), and cardiovascular (e.g., syncope; ventricular dysrhythmias; electrocardiogram alterations;

such as prolonged QTc, QRS widening, and torsades de pointes) effects [45-46].

Herbal highs; Salvia divinorum; Mitragyna speciosa; Ayahuasca
Although there is a vast range of 'herbal highs' being commented by the e-psychonauts, the most popular plants include (Table 1):
Salvia divinorum ("Sally-D"): Its current use includes smoking or chewing the dried leaves containing salvinorin A and B, both kappa-opioid receptor agonists [47]. At high dosages, time distortion, vivid imagery and empathogenic effects have been anecdotally reported [5].
Mitragyna speciosa (*Kratom*): its leaves contain mitragynine, mitraphylline, 7-hydroxymitragynine and *O*-desmethyltramadol. Mitragynine ("biak-biak") is a partial agonist of the mu/delta opioid receptors. Mitraphylline acts both on mu/delta opiate receptors and as an NMDA receptor antagonist, whilst 7-hydroxymitragynine is a mu-opioid agonist 30-fold more potent than mitragynine [5]. *Kratom* may be smoked or brewed or ingested as an extract. Users report either an opiate-like sedation, particularly at higher dosages, or a cocaine-like stimulation at lower dosages [48]. Regular use may lead to dependence and opioid-like withdrawal symptoms upon discontinuation [47]; many related fatalities have been reported [48], typically in association with other substances and/or in individuals with pre-existing health issues.
Ayahuasca: This is a decoction made of both DMT (N,*N*-dimethyltryptamine/'Dimitri')-containing *Psychotria viridis* together with *Banisteriopsis caapi*, whose beta carbolines harmala alkaloids possess reversible MAOI-A properties, hence allowing DMT to be orally bioavailable. Ayahuasca effects are characterized by powerful entheogenic experiences, intense visual hallucinations, paranoid ideation and euphoria, associated with vomiting and/or diarrhoea [5; 47].

Conclusions

A thorough and updated overview of the pharmacological activities relating to a range of novel recreational drugs, including misusing medications, has been provided here. Overall, these activities revolve around the imbalance of a range of neurotransmitter pathways/receptors, including: a) increased central DA levels; this is associated with the intake of most of these substances, including novel psychedelic phenethylamines; synthetic cathinones; and novel stimulants in general; b) cannabinoid CB1 receptor activation, achieved with synthetic cannabimimetics; c) 5-HT2A receptor activation, reported with psychedelic phenethylamines; recent tryptamine and lysergamide derivatives; and hallucinogenic plants/fungi; d) antagonist activity at NMDA receptors, described with phencyclidine-like dissociatives; and e) k-opioid receptor activation, typically associated with *Salvia divinorum* intake [5].
It is difficult for both Accident and Emergency Department clinicians and mental health professionals to keep up to date with the growing number

of NPS being made available from a constantly growing drug scenario [49], and this may be a reason for concern. Indeed, standard toxicology tests can identify just a few misused molecules and only expensive, lengthy, screening tests carried out in specialised settings are able to identify the vast range of NPS available [9]. Conversely, it has recently been suggested that the pattern of use of these NPS substances, e.g., synthetic cannabinoids, is often sporadic, and that perhaps the frequency of somatic and mental side effects prevent an addictive use in many cases of subjects experimenting with these drugs [50].
To improve accuracy and provide a thorough evaluation of NPS pharmacology, further research should focus on an integrative model in which web-based analyses will be combined with more advanced research approaches. From this perspective, our currently ongoing related quantitative structure–activity relationship (QSAR), docking, *in silico* studies will hopefully provide important findings in terms of which NPS molecules, within a given class (e.g., novel synthetic opioids; novel benzodiazepines; [27]) will present with higher levels of receptors' affinities, and hence clinical potency. These data, taken from selected molecules, could then be used to plan further *in vitro* and *in vivo/*preclinical studies. Clinicians should be regularly informed about the range of NPS; their intake modalities; their psychoactive sought after-effects; the idiosyncratic psychotropics' combinations; and finally their medical; psychobiological; and psychopathological risks [22].

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