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DEI DIPARTIMENTI E DEI SERVIZI DELLE DIPENDENZE

Le nuove frontiere della psichiatria: gli psichedelici degli psiconauti

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Special thanks to Damicom srl; A Vento, MD. PhD; L Orsolini, MD; D Arillotta, MD

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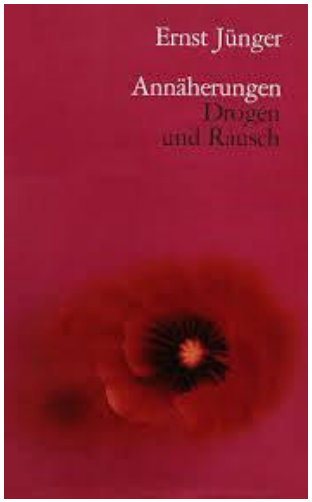
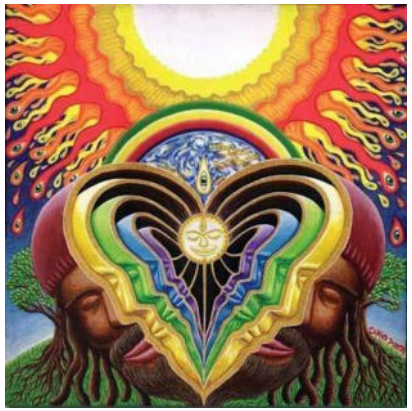
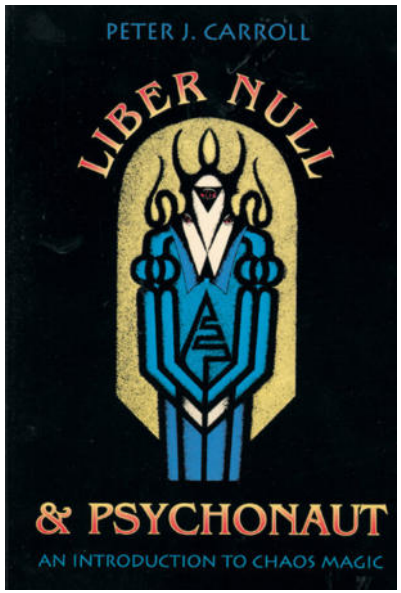
PSYCHONAUTS and e-PSYCHONAUTS: self-appointed shamans?

DEFINITION AND ORIGIN OF THE TERM



Jünger (1970). Introduces the word 'Psychonaut' to describe individuals who took psychoactive drugs with the intention of achieving greater knowledge of what he called the 'inner universe', 'Psychocosmos'.





P.J. Carroll (1987) describes in his book 'Psychonaut', the experimental use of meditation, rituals and DRUGS as tools to reach the state of 'psychonaut' in the exploration of consciousness.

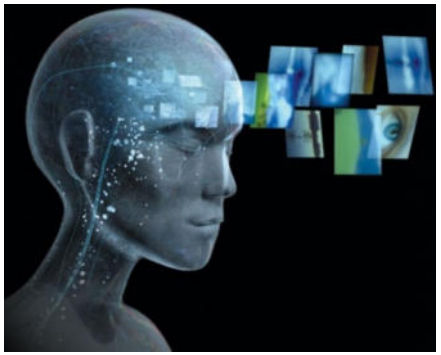
E-PSYCHONAUTS' FEATURES

PERSONAL KEY-SKILLS

- Open-mindedness to the exploration of the inner 'soul' (*usually, but not only, by means of psychotropic drugs*)

- A sense of community and sharing own experiences (detailed trip reports with dosage, combined drugs, clinical and psychological effects, etc.) in a manner similar to the '*specified culture of group of the druggies'* (Anzieu, 1976)

- Open-mindedness and availability to take part in scientific research discuss about research topics ("chemical researchers")



- An attitude to the *exploratory activity in response to novel stimulation* and an *impulsive decision maker* (possibly high levels of *Novelty Seeking* scale scores at the *Temperament and Character* Inventory by Cloninger??)

("[...] *simply tripping out on your favourite drug every now and then does not make you a psychonaut. You have to be interested in new experiences. If you do it too much, it's not new, it's just a habit[...]").*

E-PSYCHONAUTS' FEATURES

SOCIO-DEMOGRAPHIC FEATURES

- Age. Mainly Youngsters (age ranging from 15 to 35 yy; 3 peak ages: 18, 19, 20)
- Gender. Mainly Males (*Probably female group underestimated??)*
- Ethnic group. Caucasians and White → Hispanic/Latino subjects -→ Asian cultures
- Employment status. Mainly good employment levels (i.e. software engineer, office worker, university PhD, teacher, etc.)
- Level of education. At least a University qualification (i.e. Chemistry, Mathematic, Psychology, Philosophy, Engineering and Computer Sciences)
- Countries. U.S.A., U.K., Australia/New Zealand (English→Spanish→French and German)

E-PSYCHONAUTS' FEATURES

TYPOLOGY

❖The 'Chemicals' experimenters":
who *test the chemicals in order to document the drug's effects* and to assess whether it is safe for others to use. These subjects perceive themselves as doing it in the name of "*psychedelic research*".

❖The 'Navigators of the mind":
who *use drugs in order to explore the frontiers of the mind* in the name of "*psychonautism"* as means to spiritual, interpersonal and psychological revelations.

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NPS.finder

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NPS FINDER

NPS.Finder® is a Damicom/Rome based crawling/navigating software, designed to automatically scan a 9-language range of psychonaut web sites/fora for new/novel/emerging molecules.

eg. *Bluelight, Erowid, isomerdesign, etc*.

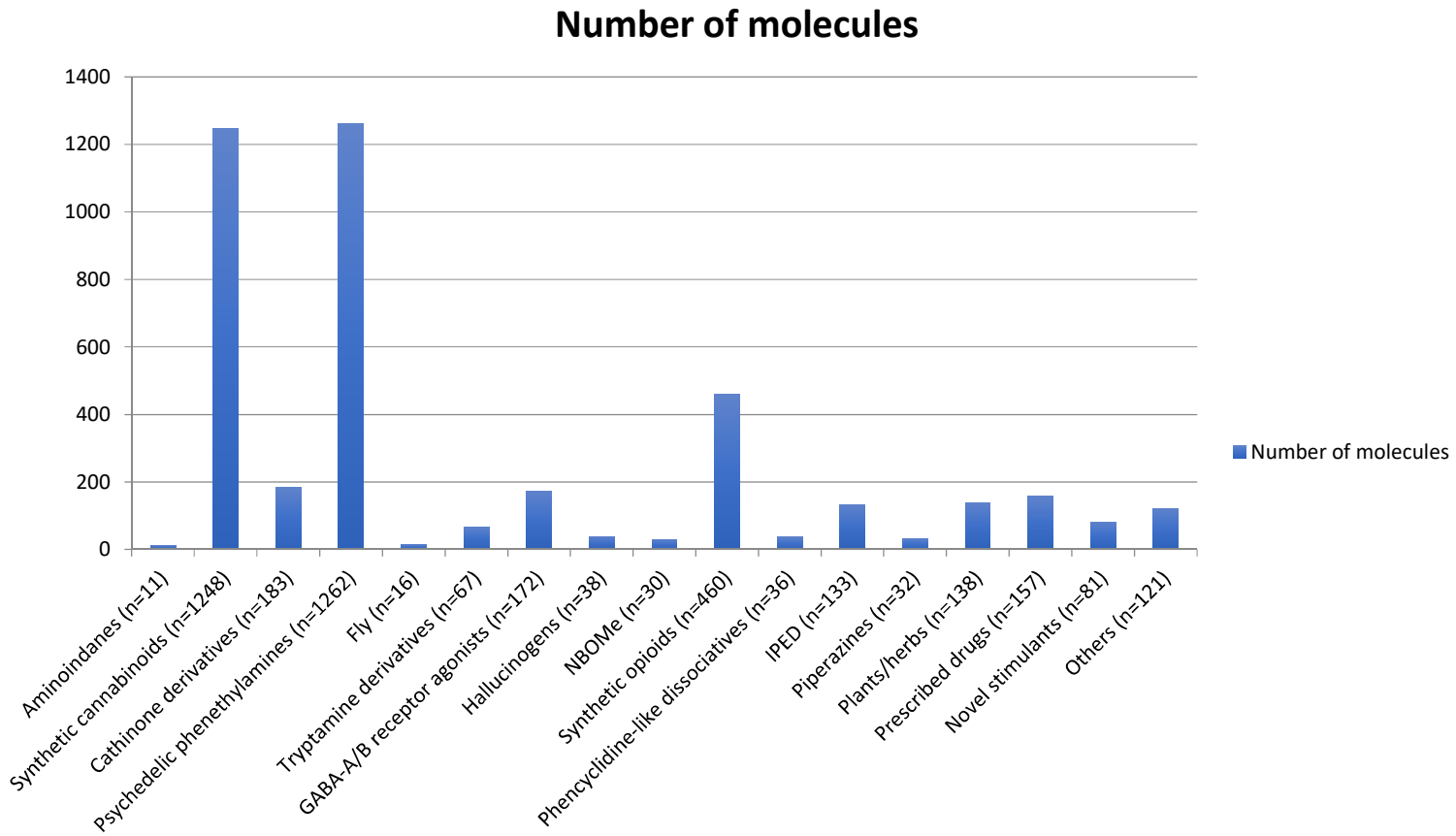
After about 27 months of web crawler activities, the number of substances identified is >6,000;

of these, 4,335 unique molecules have been included in the database and about 1,700 (29%) of the remaining molecules resulted to be false positives duplicates. An update being carried out at present

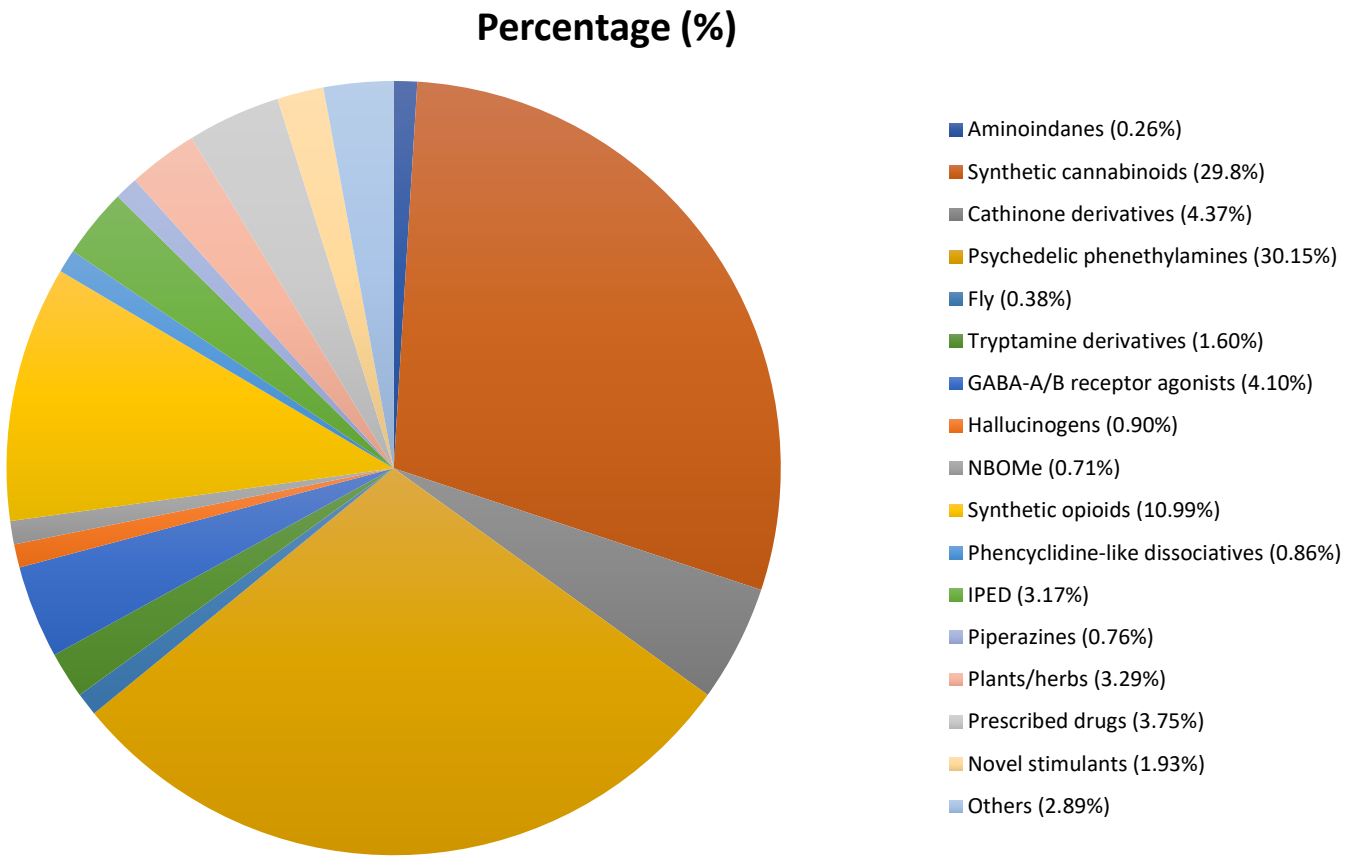
Most popular molecules:

- Psychedelic phenethylamines (around 30%)
- Synthetic cannabimimetics (around 30%)
- Novel synthetic opioids (around 11%)

Current findings; n=4,335 NPS identified



Results


Percentage (%)
Aminoindanes (0.26%)
Synthetic cannabinoids (29.8%)
Cathinone derivatives (4.37%)
Psychedelic phenethylamines (30.15%)
Fly (0.38%)
Tryptamine derivatives (1.60%)
GABA-A/B receptor agonists (4.10%)
Hallucinogens (0.90%)
NBOMe (0.71%)
Synthetic opioids (10.99%)
Phencyclidine-like dissociatives (0.86%)
IPED (3.17%)
Piperazines (0.76%)
Plants/herbs (3.29%)
Prescribed drugs (3.75%)
Novel stimulants (1.93%)
Others (2.89%)

...the few thousands of different NPS currently available...

- 179 PIA/**phenethylamines**/MDMA-like drugs; amphet-type substances (fluoroamphetamine, PMA, 2C-T, 2C-B etc);
- **PIA derivatives**: 'fly'; **NBOMe**; indanes; **benzofurans** (5; 6-APB/APDB; EAPB); 'BenzoFury'
- **lysergamides** such as LSA, 1P-LSD, ALD-52, ETH-LAD, Pro-LAD, AL-LAD, LSZ and LSD-like structures
- Up to 1,300 synthetic **cannabimimetics;** incl: **BB-22; FPB-22;** AKB-48F; AM-2201; AM-2233;
- >180 synthetic **cathinones;** incl: mephedrone; methedrone; methylone; **alpha-PVP** etc
- **Novel stimulants**; aminorex derivatives; **4,4'-DMAR**
- **Synthetic opiates/opioids**, such as >20 fentanyls (e.g. **carfentanil);** AH-7921; IC-26; MT-45; nortilidine; W15; W18; **U-47700, U-48800,** U-51,754
- **synthetic cocaine** substitutes: RTI 111; RTI 121; RTI 126; 'fake' cocaine/**gogaine** (lidocaine+MPA+ephedrine); '**el blanco**' (ethylphenidate and benzocaine)
- 64 **tryptamine** classical derivatives and 5 **tryptamine derivatives** such as 5-Meo-DALT; AMT; 5-Meo-AMT etc
- 126 **psychedelic phenethylamines/stimulants** from the Shulgin Index (2011); about *1,300 molecules being* covered; including DMAA
- GABA-A/GABA-B agonists: 3 **GHB-like** drugs: GHB; GBL; 1,4-BD; phenibut; baclofen; 50 **designer bdz** (phenazepam)
- **PCP-like** drugs: PCP; ketamine; methoxetamine; PCE; 3-MeO-PCP; ethylketamine; 3-HO-PCP; diphenidine, MXP etc
- **piperazines**: BZP; TFMPP
- **Herbs/plants/fungi/animals**: **Salvia divinorum**; Mitragyna speciosa/**kratom**; Tabernanthe iboga/ibogaine; Kava Kava; Psychotria viridis/Ayahuasca; hydrangea; **Magnolia officinalis**; Datura stramonium; psychedelic mushrooms; bufo; sponges; flies; etc
- **medicinal products**: tramadol, oxycodone, and remaining opiates/opiods; anticonvulsants (gabapentin and **pregabalin**); antiseptics (benzydamine); **DXM**; **venlafaxine/'baby XTC'; bupropion; olanzapine; quetiapine/Qbomb**); stimulants (ethylphenidate; camfetamine); antiparkinsonian /anticholinergics: selegiline; tropicamide); chloroquine; anitretrovirals/'whoonga'; xylazine
- **IPEDs**: minikikke/super strength caffeine tablets; DNP; **3-FPM; clenbuterol**; herbal testosterone boosters/Tribulus terrestris; melanotan; sexual enhancers (medicines; herbal products); cognitive enhancers (aniracetam; piracetam; **modafinil**)

Schifano, Orsolini et al. 2015; Schifano, 2015; Schifano, Orsolini et al., 2016; Schifano et al., 2016; Chiappini and Schifano, 2019; Schifano et al, 2020)

Novel psychoactive substances of interest for psychiatry

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Novel psychoactive substances include synthetic cannabinoids, cathinone derivatives, psychedelic phenethylamines, novel stimulants, synthetic opioids, tryptamine derivatives, phencyclidine-like dissociatives, piperazines, GABA-A/B receptor agonists, a range of prescribed medications, psychoactive plants/herbs, and a large series of performance and image enhancing drugs. Users are typically attracted by these substances due to their intense psychoactive effects and likely lack of detection in routine drug screenings. This paper aims at providing psychiatrists with updated knowledge of the clinical pharmacology and psychopathological consequences of the use of these substances. Indeed, these drugs act on a range of neurotransmitter pathways/receptors whose imbalance has been associated with psychopathological conditions, including dopamine, cannabinoid CB1, GABA-A/B, 5-HT2A, glutamate, and k opioid receptors. An overall approach in terms of clinical management is briefly discussed.

Key words: Novel psychoactive substances, legal highs, smart drugs, research chemicals, substance abuse, dual diagnosis, psychedelic phenethylamines, synthetic cannabimimetics, phencyclidine-like drugs, cathinones, tryptamines

(World Psychiatry 2015;14:15–26)

EXPERT REVIEW OF CLINICAL PHARMACOLOGY, 2016
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REVIEW

Novel psychoactive substances: the pharmacology of stimulants and hallucinogens

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ABSTRACT

There are increasing levels of concern relating to the rapidly evolving novel psychoactive substances/NPS and web markets' scenarios. The paper aims at providing an overview of the clinical pharmacological issues related to some of the most popular NPS categories, e.g. stimulants and hallucinogens. NPS intake is typically associated with the imbalance of a complex range of neurotransmitter pathways/receptors, namely: dopamine; cannabinoid/CB1; and 5-HT_{2A}. The intake is almost invariably undetectable with standard screening tests. Hence, it may frequently occur that the acute management of NPS misusers will need to focus on decreasing levels of both self/outward-directed aggression and agitation. Benzodiazepines may be considered as first line treatment. Alternatively, propofol and/or antipsychotics can be administered. Focus will be as well on treatment of possible rhabdomyolysis and hyperthermia. Indeed, future studies should inform better tailored management/treatment strategies.

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KEYWORDS
Novel psychoactive substances; synthetic cannabimimetics; synthetic cathinones; hallucinogenic drugs; phenethylamines; psychiatric disturbances; drug misuse

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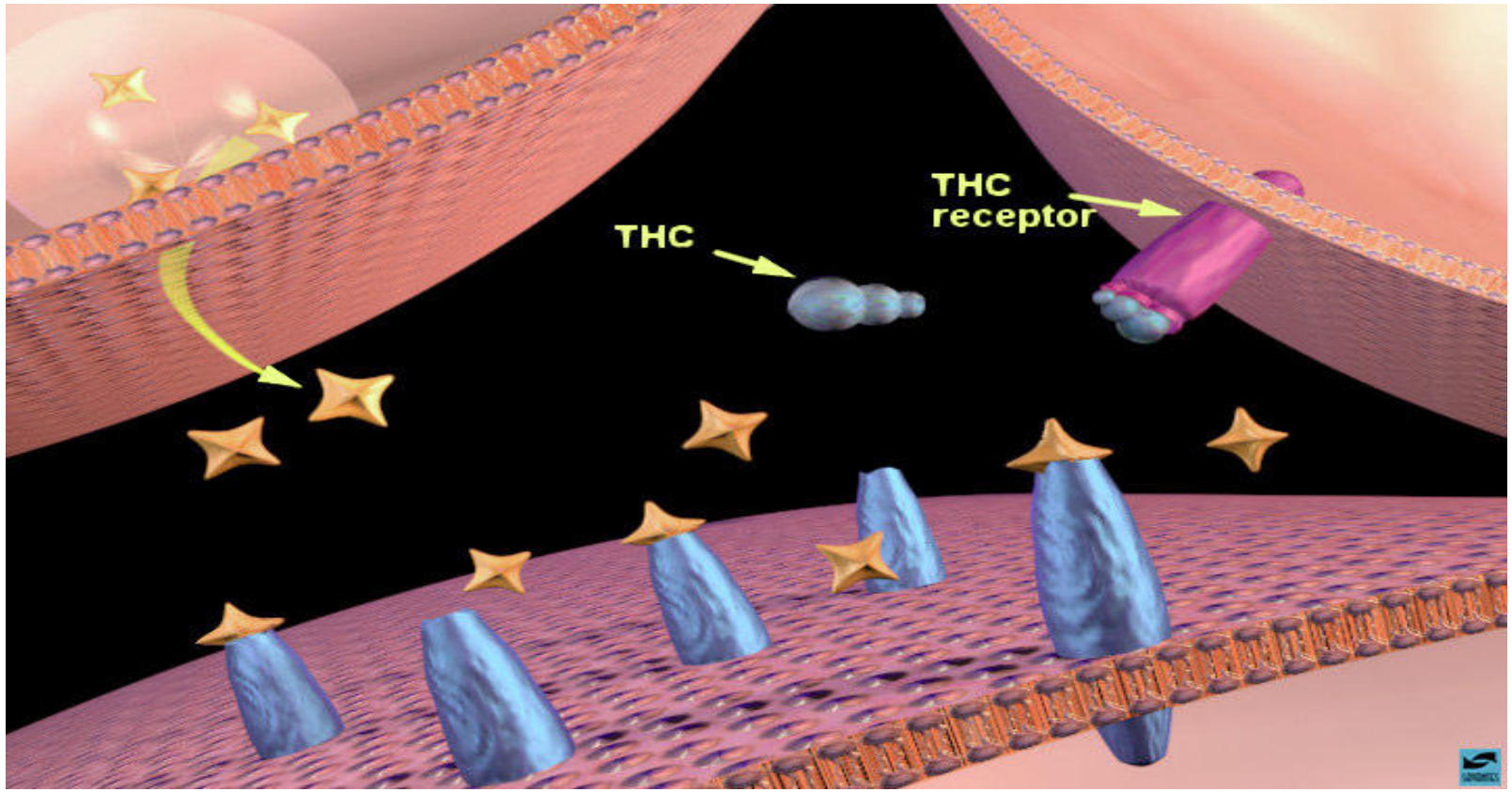
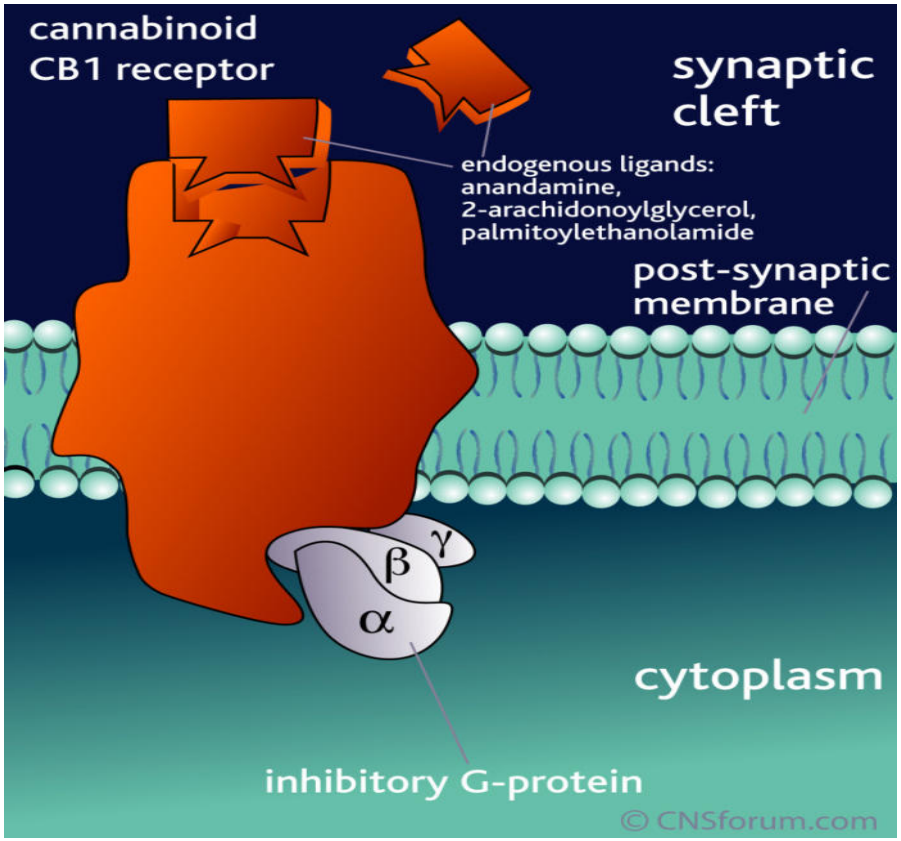
DA neurons in the VTA and opioids

Schematic illustration of the way in which DA-containing neurons in the ventral tegmental area (VTA) are excited by opioids. GABA-containing interneurons are hyperpolarized by opioids acting at p-receptors. This results in decreased (-) GABA release and increased (+) firing and DA release of DA-containing neurons in the VTA towards the nucleus accumbens (NAc).

…and what about cannabis? (2)



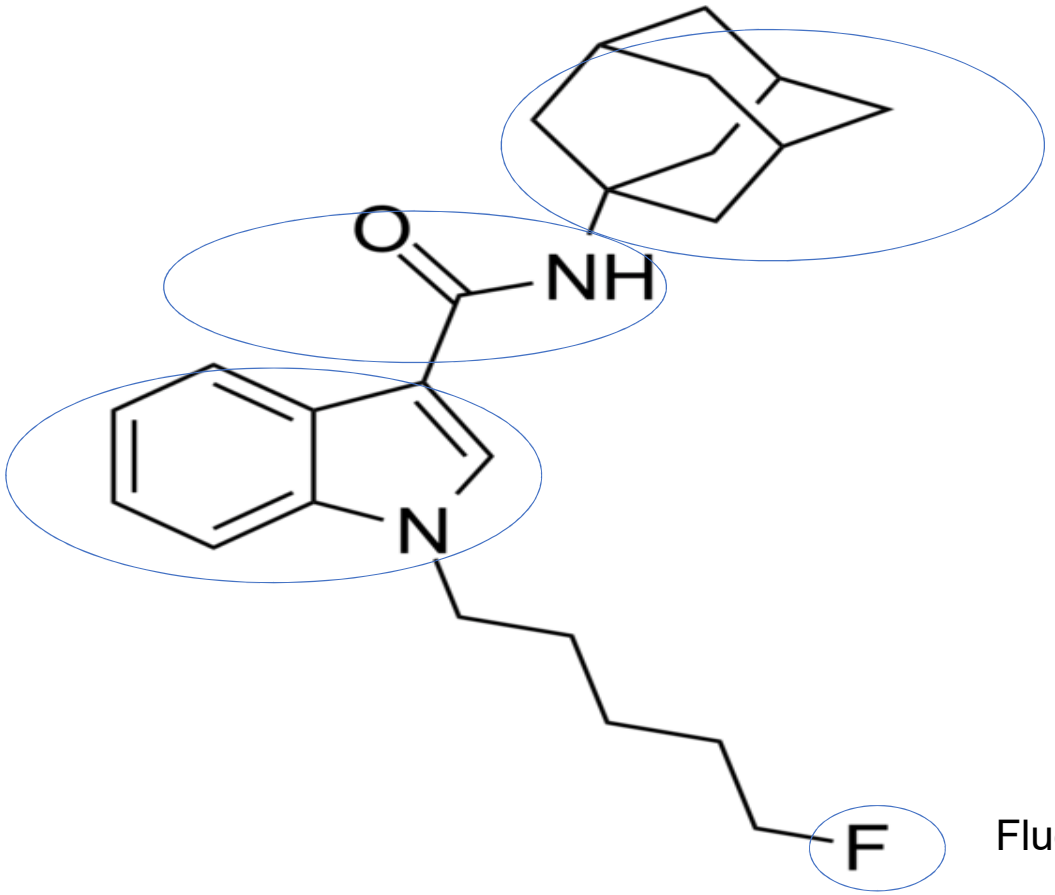
CB1 receptor



SYNTHETIC CANNABIMIMETICS;

Is STS-135 a poly-substance per se?

Sts-135



Risk of psychopathological disturbances/psychosis and involvement of the following pathways/receptors....

- DA (agonists)
- CB1 (partial/full agonists)
- 5-HT2A (agonists)
- Glutamate: NMDA and mGlu2/3 (antagonists)
- Mu, delta, and k opioid (agonists)

Clozapine *: CB1 receptor antagonism; delta agonism; 5-HT2A antagonism; mGlu2/3 agonism*

Aripiprazole*: D2 partial agonist; 5-HT(2A) antagonist; counteracting the NMDA-R antagonist behavioural effects*

Opioids in NPS Finder:

quantitative and qualitative analysis

(Arillotta et al, Front Neurosci. 2020)

Further suggestions from the psychonauts' world (1)

- 6-Methylenedihydrodesoxymorphine: a potent μ-opioid agonist, *80x stronger than morphine*.
- BDPC alias Bis(2,4-dinitrophenyl)carbonate or bromadol: studies assigned a value of *504 times the potency of morphine* for the more active trans-isomer. BDPC/bromadol (Ki = 1.49 nM for MOR)
- Cyclazocine: it is a KOR agonist and MOR partial agonist, and also has high affinity for the DOR. *psychotomimetic, dysphoric, and hallucinatory* effects.
- Cyprenorphine: mixed agonist–antagonist effects at opioid receptors, like those of buprenorphine. However the effects are somewhat different, as it produces *pronounced dysphoric and hallucinogenic effects* which limit its potential use as an analgesic.
- O-desmethyltramadol/Krypton: considerably *more potent as μ-opioid agonist compared to tramadol*. It also shows comparatively far lower affinity for the δ- and κ-opioid receptors. It is also an antagonist of the serotonin 5-HT2C receptor, at pharmacologically relevant concentrations, via competitive inhibition.
- Embutramide: potent opioid analgesic and sedative drug that is structurally related to methadone. Presents with a very narrow therapeutic window; used for euthanasia of a range of different animals; been reported as being *used for suicide by people with access to the drug*.

Further suggestions from the psychonauts' world (2)

- Levallorphan: as an *agonist of the κ-opioid receptor* (KOR), can produce severe mental reactions.
- Levomethorphan (note dextromethorphan as well): potent agonist of all three of the opioid receptors, μ, κ (κ1 and κ3 but notably not κ2), and δ, as an *NMDA receptor antagonist, and as a serotonin-norepinephrine reuptake inhibitor*. Can produce dysphoria and psychotomimetic effects such as dissociation and hallucinations.
- Levorphanol: Relative to morphine, lacks complete cross-tolerance and possesses greater intrinsic activity at the MOR and shows a *high rate of psychotomimetic side effects* such as hallucinations and delusions.
- Nalorphine: an antidote according to ATC classification. Side effects such as dysphoria, anxiety, confusion, and hallucinations, and for this reason, is no longer used medically. It act at the μ-opioid receptor (MOR) where it has antagonistic effects, and at the *κ-opioid receptor* (KOR) (Ki = 1.6 nM; EC50 = 483 nM; Emax = 95%) where it exerts *high-efficacy partial agonist/near-full agonist* characteristics.

Qualitative analysis

The 10 most popular molecules include:

BDPC, bromadol, Krypton, U-family, W-family, levallorphan, levomethorphan, levorphanol, metopromide, oxpheneridine, piperidylthiambutene.

Next steps

- Better characterize **miscellaneous** molecules (the ones not yet known to UNODC, EMCDDA) and the **fentanyl** derivatives
- Investigate further the binding affinities (especially regarding **MOR** and **KOR**)
- Exploring more in depth the user's **experiences** from the psychonauts' fora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Thanks!!
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