Evidence-based treatment for drug misuse, with special reference to NPS; clinical and pharmacological issues

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CONFLICTS OF INTEREST; ACKNOWLEDGMENTS

- FS is both a Core Member of the Advisory Council on the Misuse of Drugs (ACMD, UK) and a member of the Specialist Advisory Group (Psychiatry) for the European Medicines Agency (EMA).

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….'SOME OLD, SOME NEW, BUT ALWAYS NASTY'…

(SCHIFANO ET AL, WORLD PSYCHIATRY, FEBRUARY 2015)

- 179 PIA/**phenethylamines**/MDMA-like drugs; amphet-type substances (fluoroamphetamine, PMA, 2C-T, 2C-B etc);
- 14 **PIA derivatives**: 'fly'; NBOMe; indanes; **benzofurans** (5; 6-APB/APDB); 'BenzoFury'
- 220 synthetic **cannabimimetics;** incl: AM-2201; AM-2233; AKB-48F
- 30 synthetic **cathinones;** incl: mephedrone; methedrone; methylone; etc
- **Novel stimulants**; aminorex derivatives; 4,4-DMAR
- A few **synthetic opiate/opioids**, such as 4-fluorbutyrfentanyl; AH-7921; IC-26; MT-45; nortilidine; W15; W18
- 3 **synthetic cocaine** substitutes: RTI 111; RTI 121; RTI 126; 'fake' cocaine/**gogaine** (lidocaine+MPA+ephedrine)
- 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, incl: 3 **GHB-like** drugs: GHB; GBL; 1,4-BD; phenibut; baclofen
- 7 **PCP-like** drugs: PCP; ketamine; methoxetamine; PCE; 3-MeO-PCP; ethylketamine; 3-HO-PCP; diphenidine etc
- 2 **piperazines**: BZP; TFMPP
- 12 **Herbs/plants/fungi/animals**: Salvia divinorum; Mytragina speciosa/kratom; Tabernanthe iboga/ibogaine; Kava Kava; Psychotria viridis/Ayahuasca; hydrangea; Magnolia officinalis; Datura stramonium; psychedelic mushrooms; bufo; sponges; flies; etc
- 11 **medicinal products**: tramadol, oxycodone, and remaining opiates/opiods; anticonvulsants (gabapentin and pregabalin); antiseptics (benzydamine); DXM; prescribing psychotropics (phenazepam/Zinnie; methaqualone; venlafaxine; olanzapine; quetiapine/Qbomb); stimulants (ethylphenidate; camfetamine); antiparkinsonian /anticholinergics: selegiline; tropicamide); chloroquine; anitretrovirals/'whoonga'; xylazine
- 6 **PIEDs**: minikikke/super strength caffeine tablets; DNP; herbal testosterone boosters/Tribulus terrestris; melanotan; cognitive enhancers (aniracetam; piracetam)

FROM: DEBORALABS.COM (ACCESSED ON SEPTEMBER 17TH, 2014)

Cannabinoids

- 5F-AB-PINACA
- 5F-ADB New
- 5F-AKB-48
- 5F-AMB
- 5F-MN-18
- 5F-SDB-005
- 5F-SDB-006
- AB-CHMINACA
- AB-PINACA Sale
- BB-22
- EG-018
- FAB-144
- FDU-PB-22
- FUB-PB-22

Stimulants

- 3,4-dimethoxy-a-PHP New
- 3-MeOMC New
- 3-MMC (crystals) New
- 4-BMC (crystals) New
- 4-CMC (crystals) New
- 4-MeO-a-PVP
- 4-MeO-PBP
- 4-MeO-PV9
- 4-MPD
- 4F-PV8
- 4F-PV9
- 4F-PVP
- 5-DBFPV New
- 5-EAPB
- a-PBT
- a-PHP New
- a-PVT
- DL-4662 New
- MDPHP
- MDPPP
- Methiopropamine
- MOPPP
- N-Methyl-2-AI
- NEB
- PV-8 (crystals

FROM: DEBORALABS.COM (2)

Dissociatives

- 3-MeO-PCP
- 4-MeO-PCP New
- **Diphenidine** New
- Methoxetamine
- Methoxphenidine New

Opioids

- MT-45

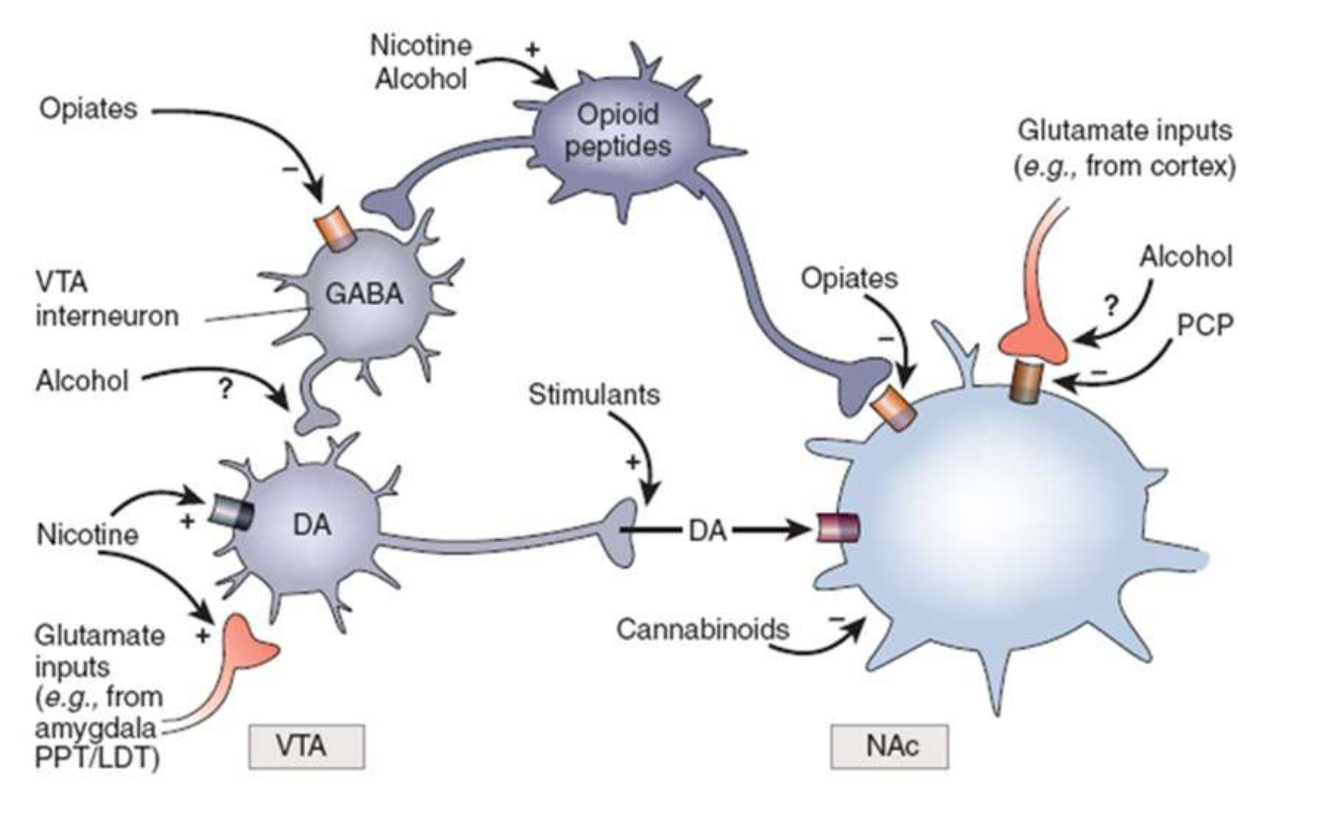
Benzodiazepine derivatives

- Diclazepam New
- Etizolam
- Flubromazepam New

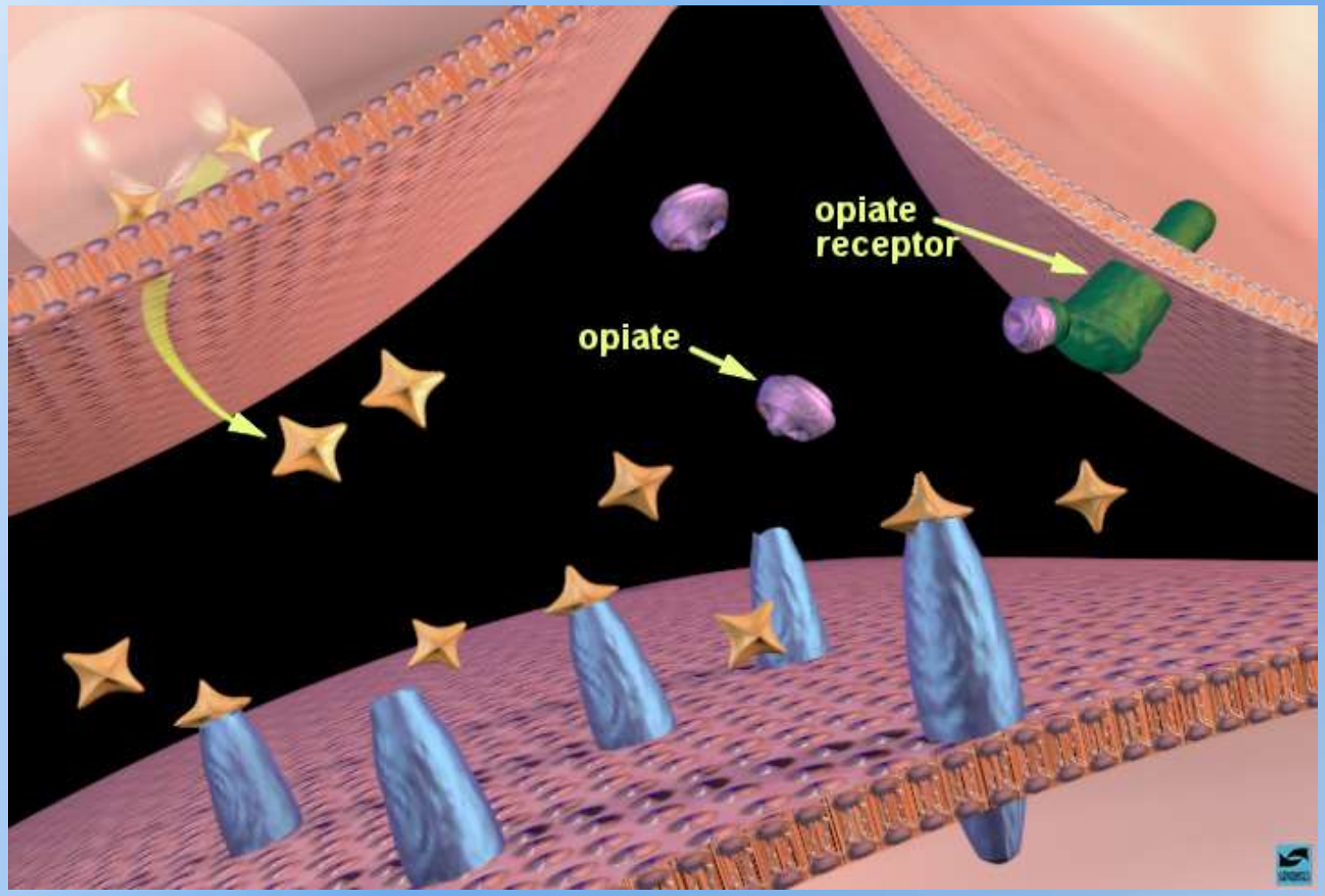
Psychedelics

- 25B-NBF
- 25C-NBF
- 25D-NBOMe
- 25E-NBOMe
- 25I-NBF New
- 25I-NBOH
- 25N-NBOMe
- C30-NBOMe

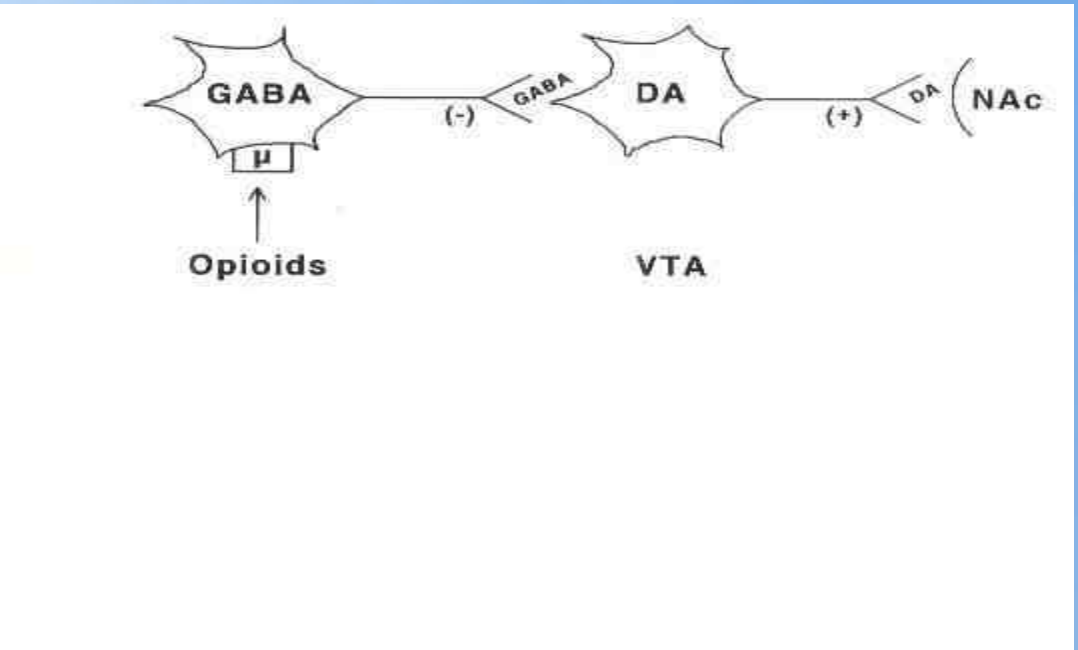
Overall summary of misusing drugs' ph. dynamics



OPIATES' BINDING TO OPIATE RECEPTORS IN THE NUCLEUS ACCUMBENS: INCREASED DOPAMINE RELEASE



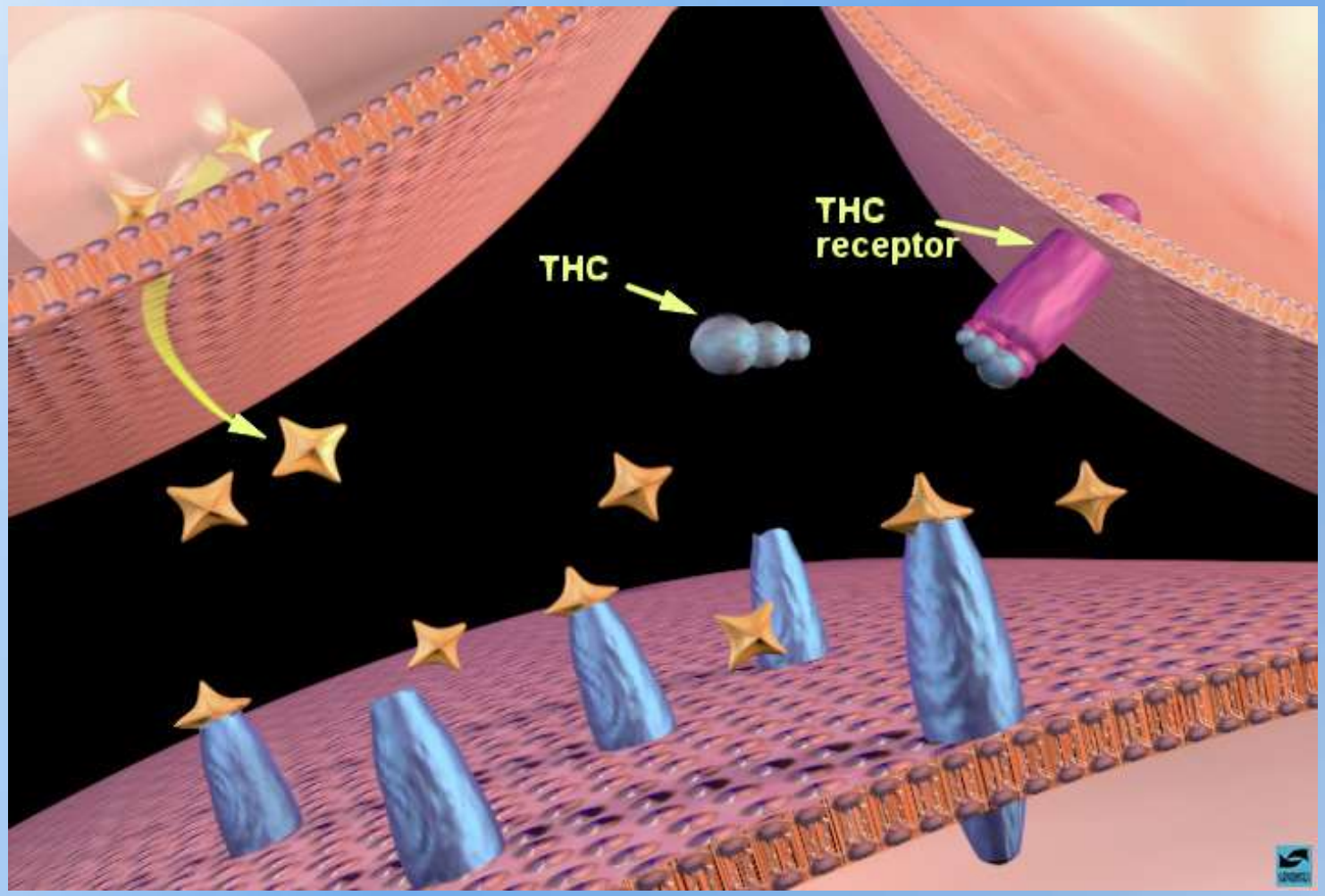
DA NEURONS IN THE VTA AND OPIOIDS



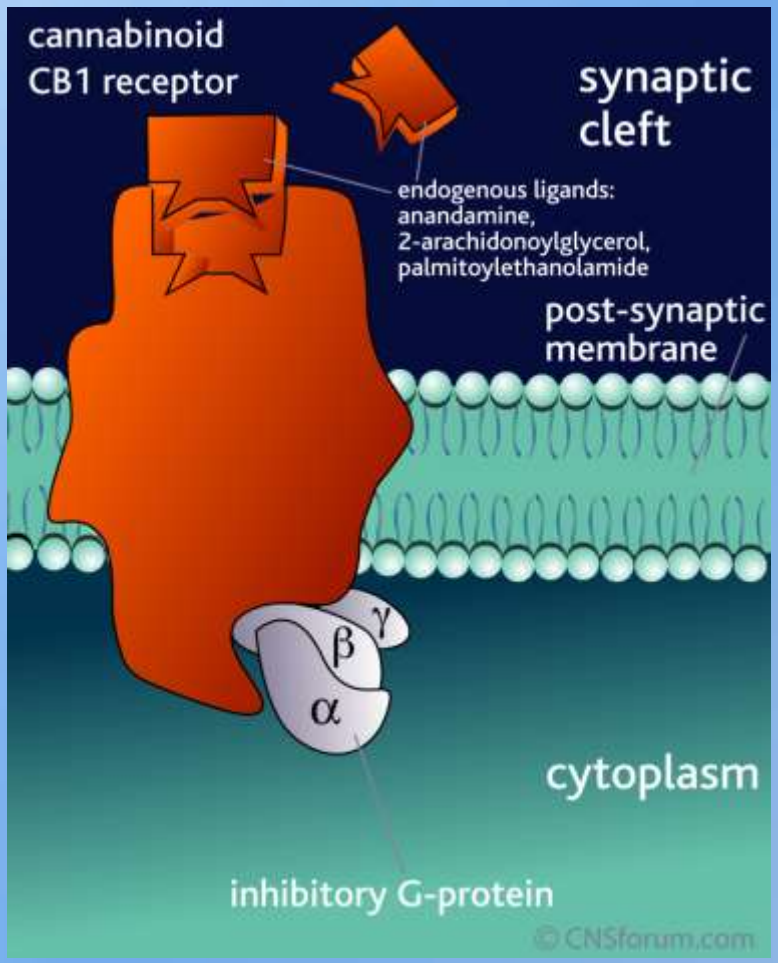
Schematic illustration of the way in which DA-containing neurons in the ventral tegmental area (VTA) are excited by opioids. GABA-containing interneurons are hyperpolarized by opioids acting at p-receptors. This results in decreased (-) GABA release and increased (+) firing and DA release of DA-containing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

THC BINDING TO THC RECEPTORS IN THE NUCLEUS ACCUMBENS: INCREASED DOPAMINE RELEASE; THE ROLE OF ANANDAMIDE AND 2-AG IN MODULATING DA RELEASE /PROTECTING FROM THE EMERGENCE OF PSYCHOTIC DISTURBANCES

THC INDUCES DOPAMINE RELEASE IN THE SHELL OF NUCLEUS ACCUMBENS ACTING ON CB1 RECEPTOR. THIS EFFECT MAY BE INDIRECT AND MEDIATED IN PART BY CANNABINOID REGULATION OF ENDOGENOUS OPIOID SYSTEMS IN THE VTA

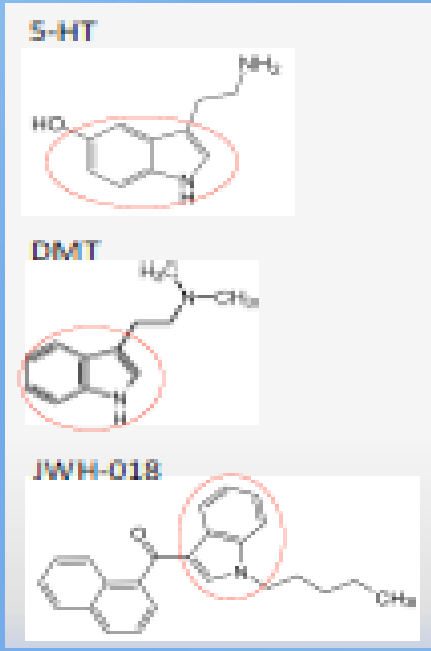


CB1 RECEPTOR



SYNTHETIC CANNABIMIMETICS

- Most SC are **CANNABIMIMETIC INDOLES**

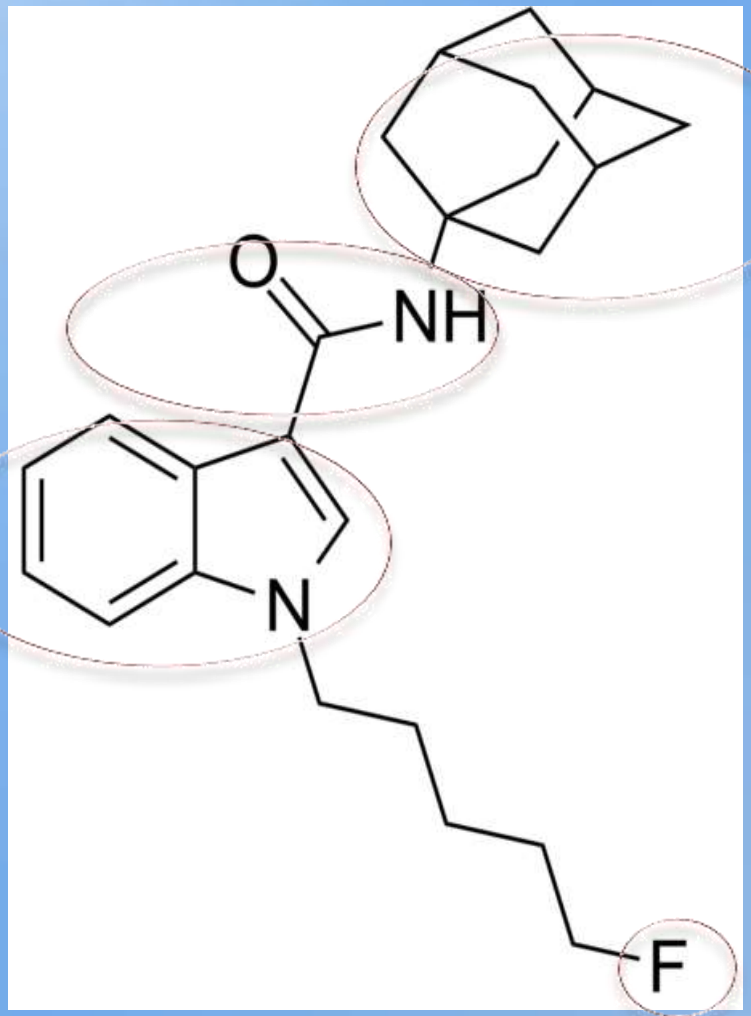


- **SEROTONIN SYNDROME**

SYNTHETIC CANNABIMIMETICS;

IS STS-135 A POLY-SUBSTANCE PER SE?

STS-135



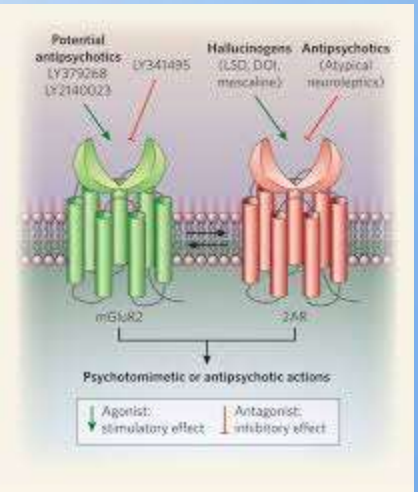
NMDA antagonist

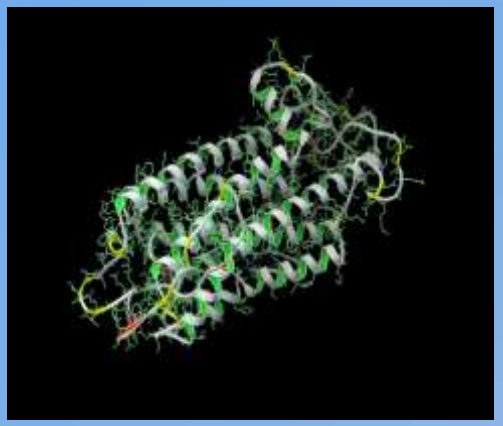
CB-rs ligand

Indole
5HT-rs ligand

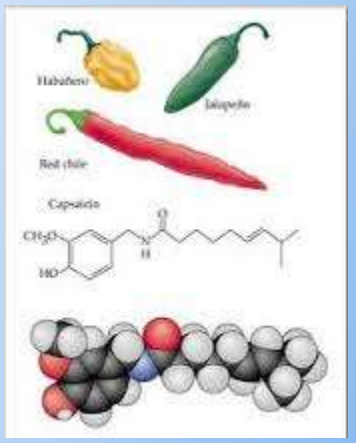
Fluorination

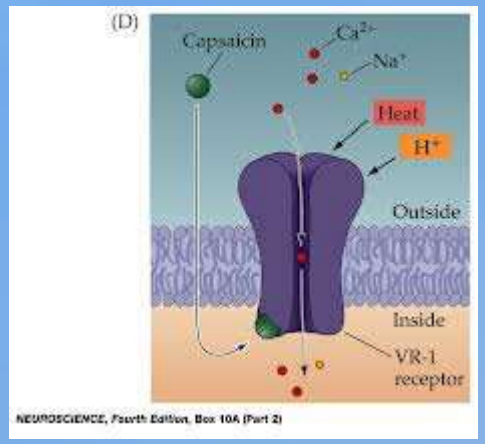
THE 5-HT2A RECEPTOR

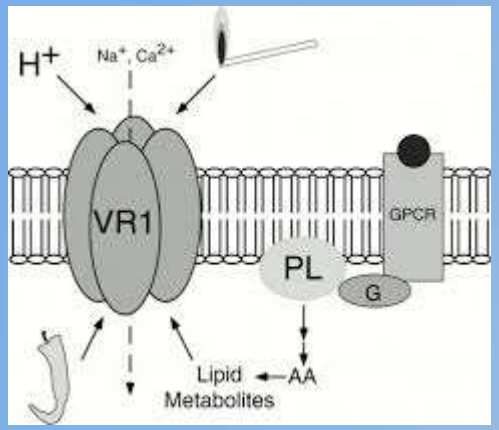




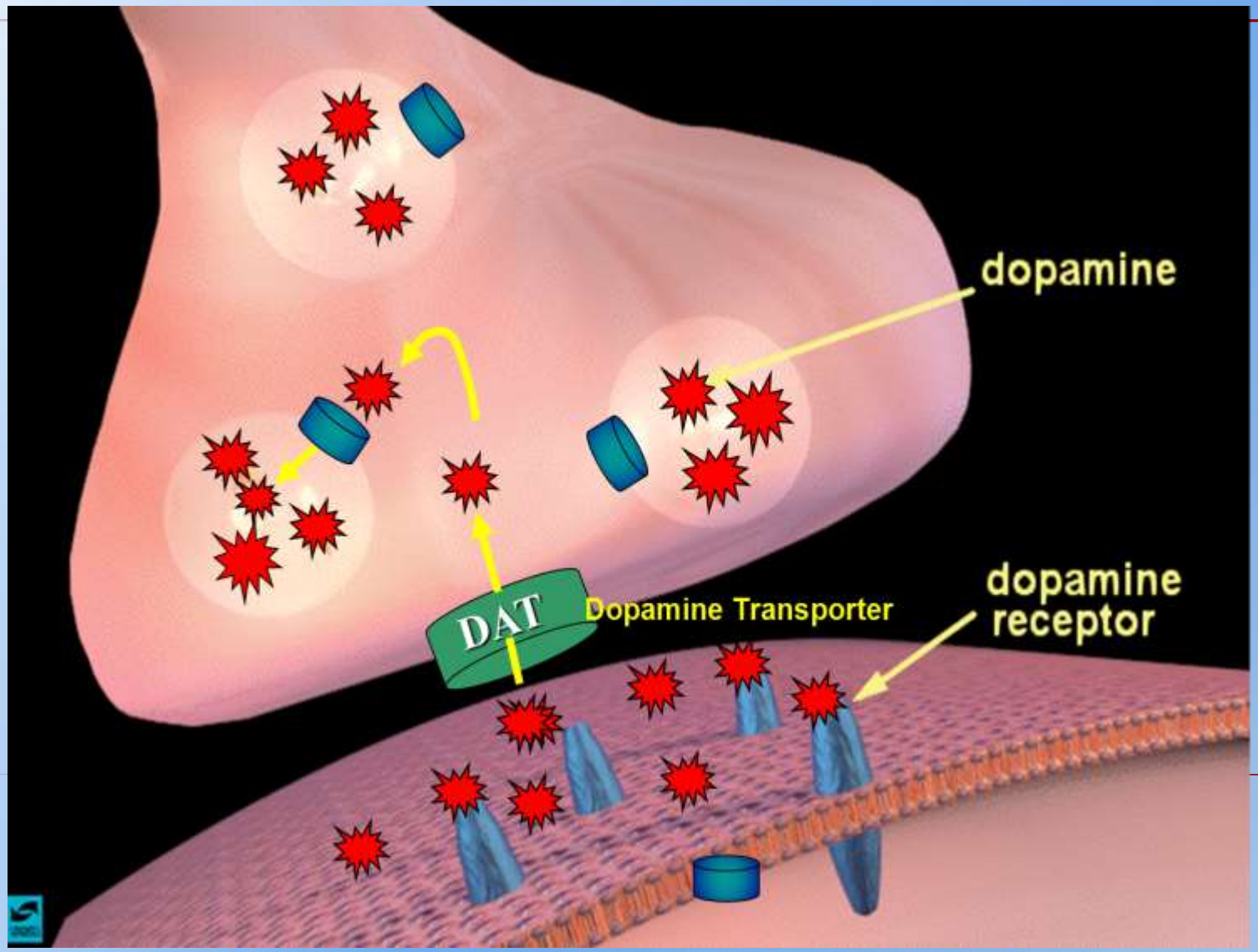
THE VANILLOID RECEPTOR



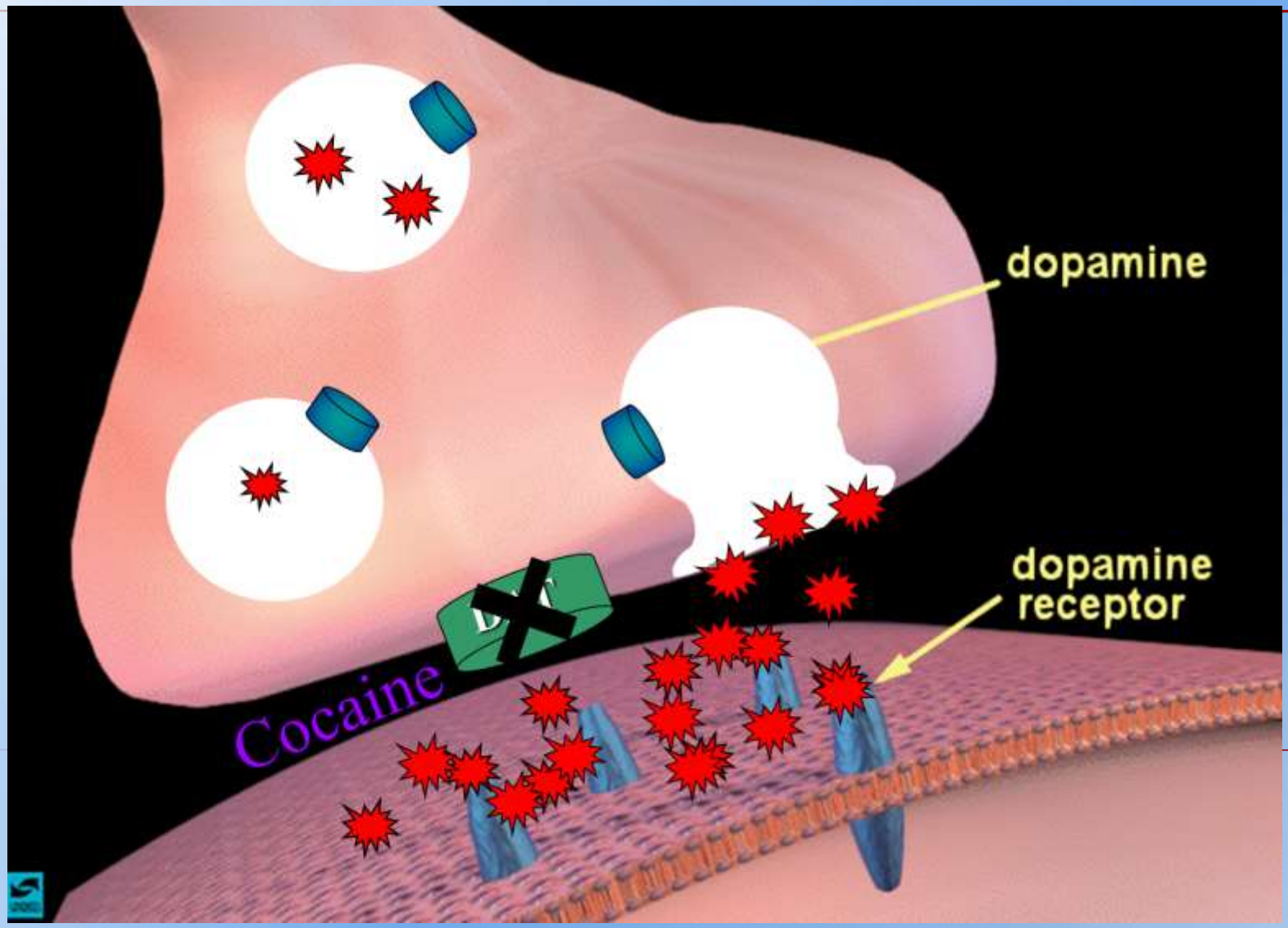




Mechanism of action of cocaine/most synth cathinones/1



Mechanism of action of cocaine/most synth cathinones/2



Cocaine

Street names: coke, charlie C, white, percy, snow, toot

Routes of administration: sniffing and snorting

Dose	Physical effects	Psychological effects
Low to moderate dose	Loss of appetite Dry mouth Tachycardia Hypertension	Euphoria Sense of well-being Increased self confidence Sense of superiority
Excessive doses	Convulsions Heart failure Respiratory arrest Exhaustion	Anxiety Irritability Insomnia Depression

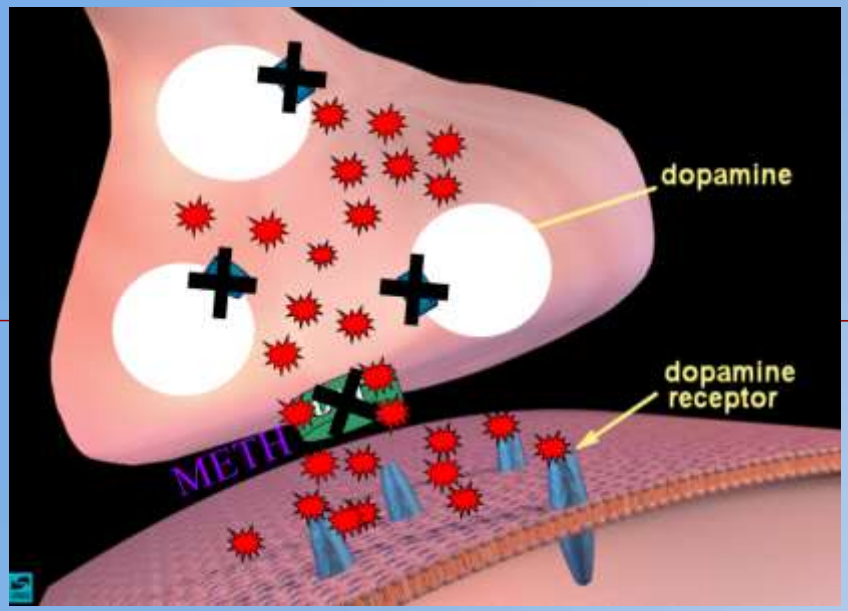
Withdrawal symptoms
Craving
Drug seeking behaviour
Irritability
Nausea
Depression

ECSTASY

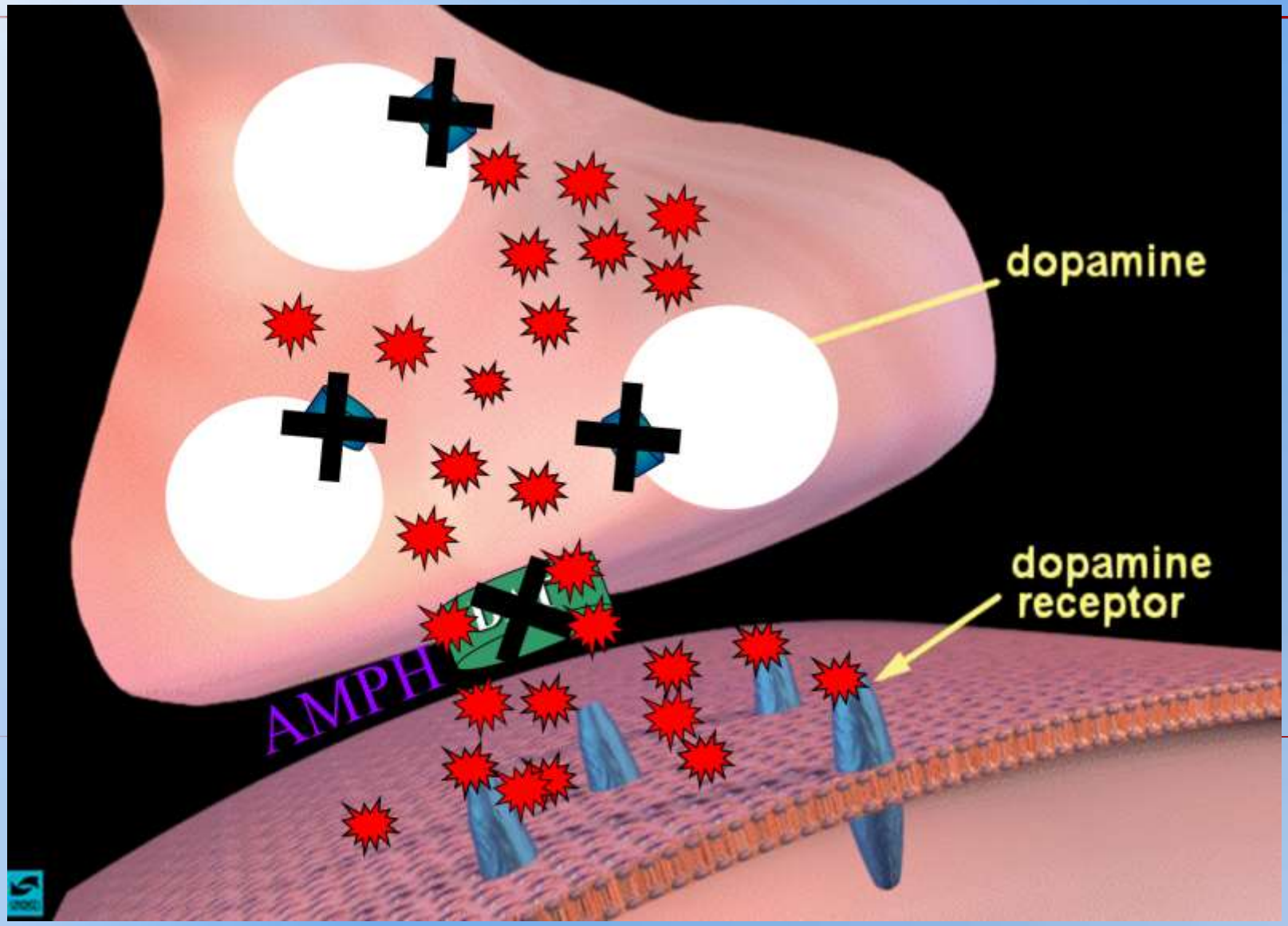
Street names: E, adam, XTC, love doves (tablets, capsules, powder)

Routes of administration: swallowing, snorting, injection

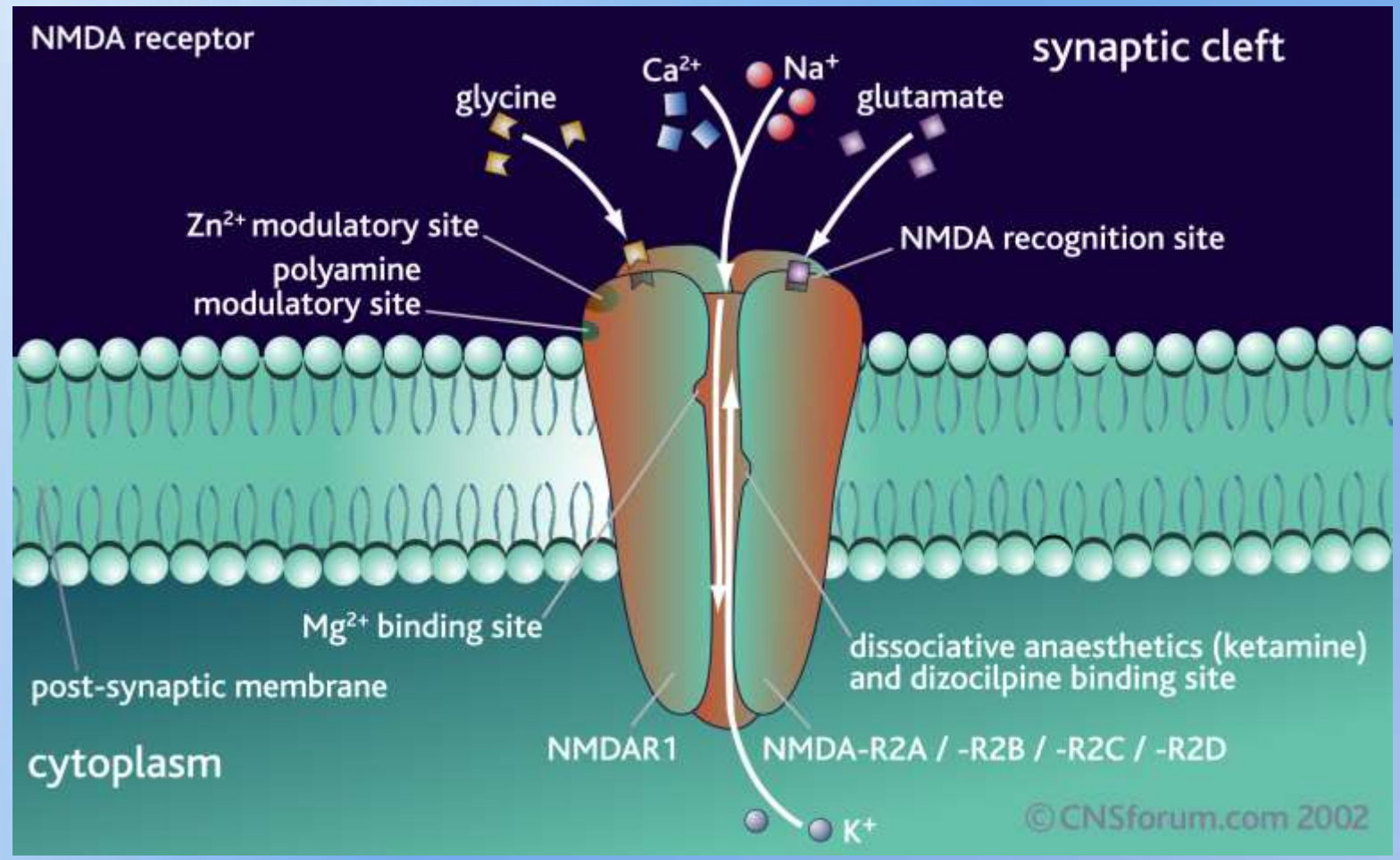
Physiological effects	Psychological effects
Increased physical energy	Euphoria
Increased heart rate	Empathy
Increased body temperature	Increase in emotion energy
Increased blood pressure	Increased ability to interact with others



Mechanism of action of amphetamines/PIAs/other stimulants



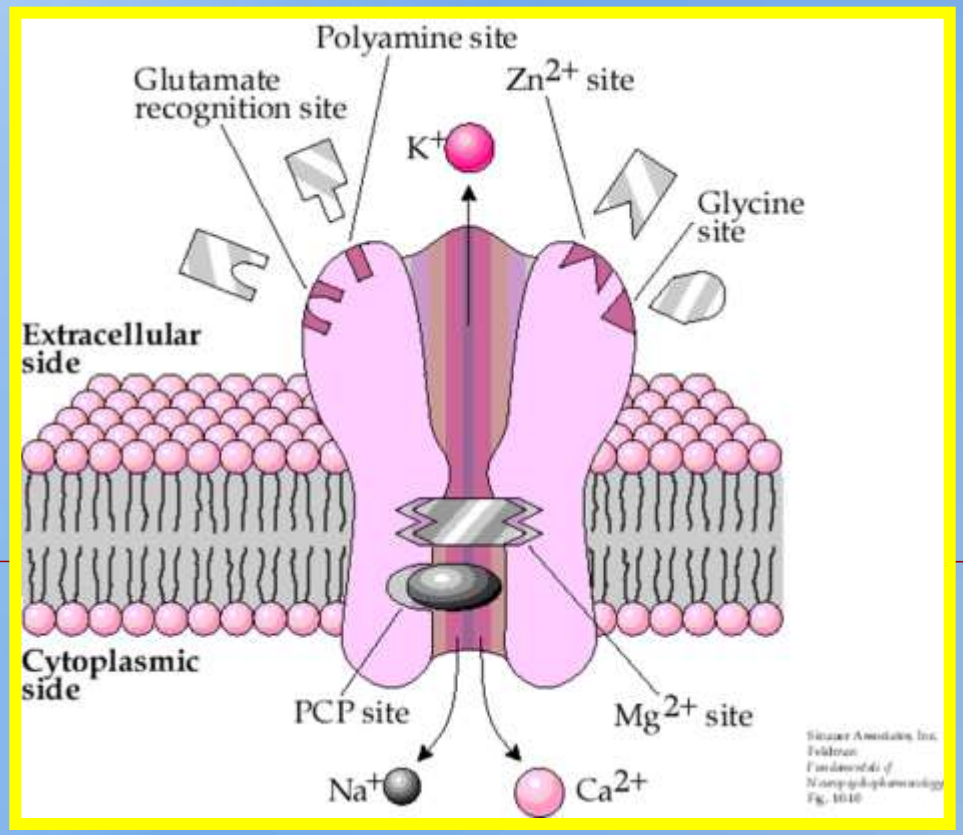
PCP-LIKE DRUGS; NMDA RECEPTORS' NON COMPETITIVE ANTAGONISTS



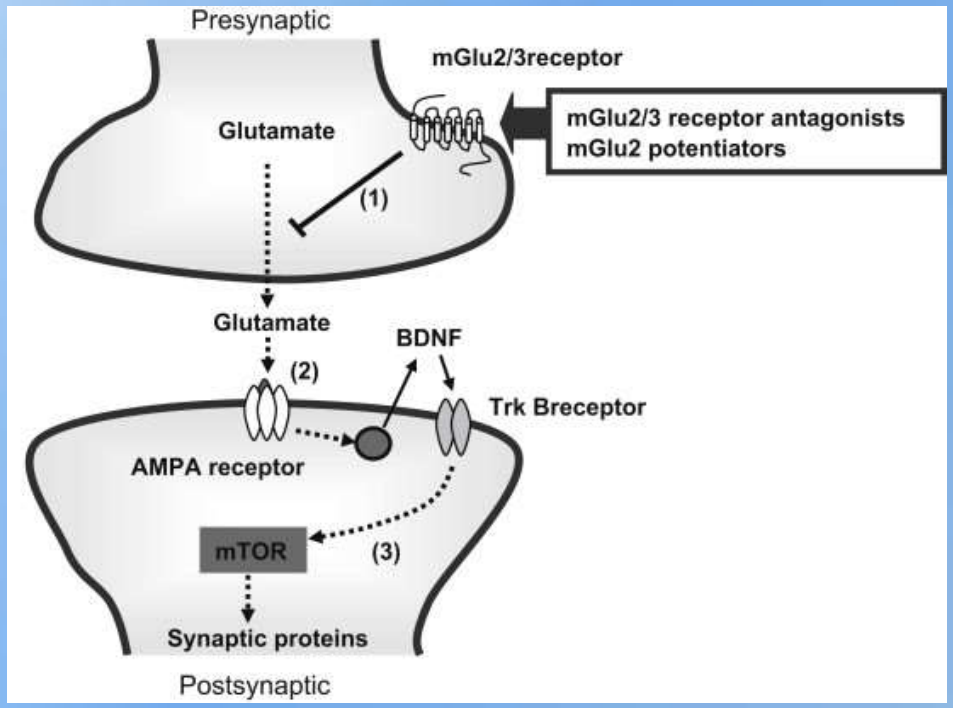
Ketamine and Phencyclidine

- Street names of ketamine: special K, super K, green, vitamin K (powder or liquid)
- Routes of administration of ketamine: inhalation, injection, drinking

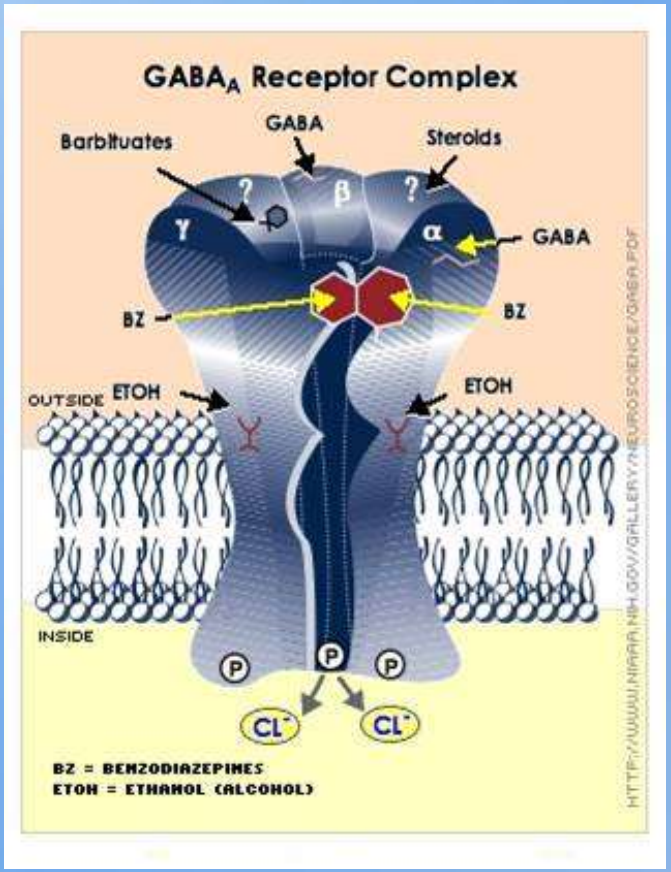
- Street name of PCP: angel dust (tablets, capsules, powders)
- Routes of administration of ketamine: swallowing, smoking, sniffing, injection



PCP-LIKE DRUGS; MGLU2/3 RECEPTOR ANTAGONISTS

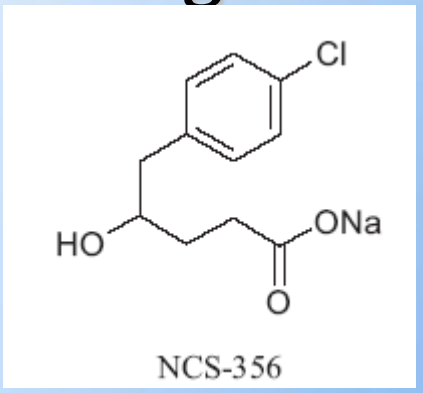


$GABA_A$ RECEPTOR

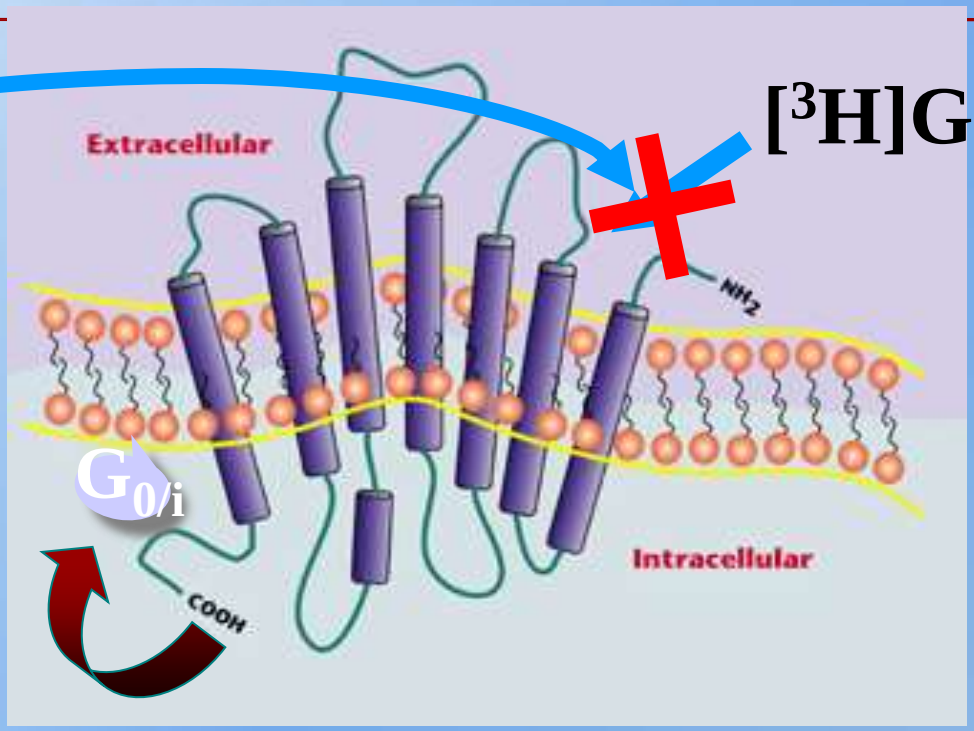


GHB RECEPTOR

NCS382 antagonist



NCS-356



K_{d1}=30-580 nM
High affinity GHB binding site

K_{d2}=2,3-16 µM
Low affinity GHB binding site

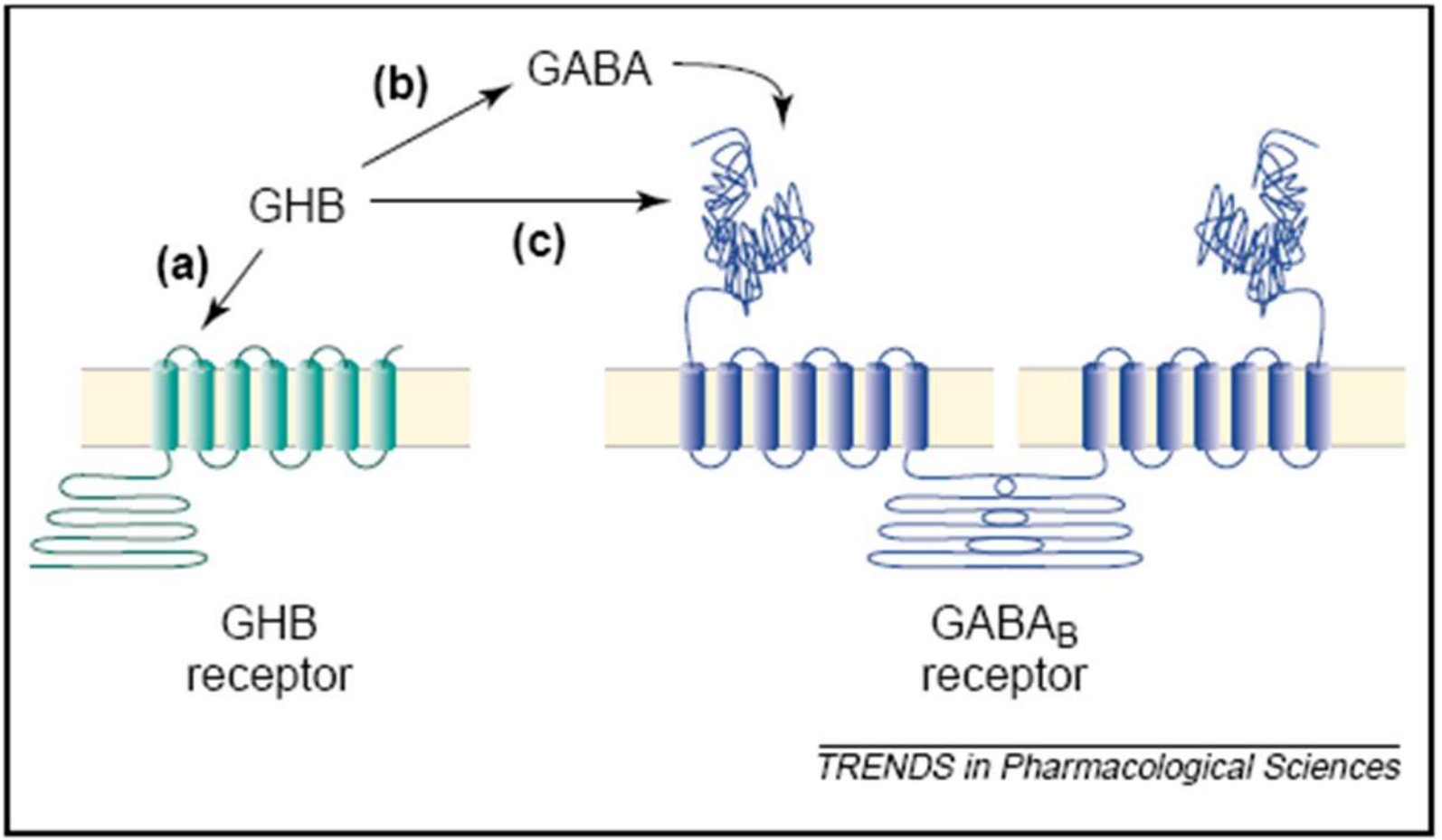


Figure 1. γ-Hydroxybutyric acid (GHB) has multiple mechanisms of action in the brain. **(a)** Physiologically relevant concentrations (1–4 μM) of GHB activate at least two subtypes of the GHB receptor: NCS382-sensitive and -insensitive subtypes [11]. **(b)** In addition to binding to the GHB receptor, at supra-physiological concentrations (high micromolar to low millimolar) a sufficient quantity of GHB might be metabolized to GABA, which then activates the $GABA_B$ receptor [7]. **(c)** At supra-physiological levels, GHB itself might bind to the $GABA_B$ receptor [12].

Nicotine

Main psychoactive Ingredient of tobacco

Routes of administration: smoking, chewing

Psychological effects
Increased pleasure
Mood regulator
Reduced aggression
Increased performances
Increased anxiety
Increased depression

	Physiological effects	Psychological effects
Withdrawal symptoms	Nausea Drowsiness Headache Constipation	Craving Inability to concentrate Anger Irritability

Nicotine regulation of the DA system

Ventral tegmental area

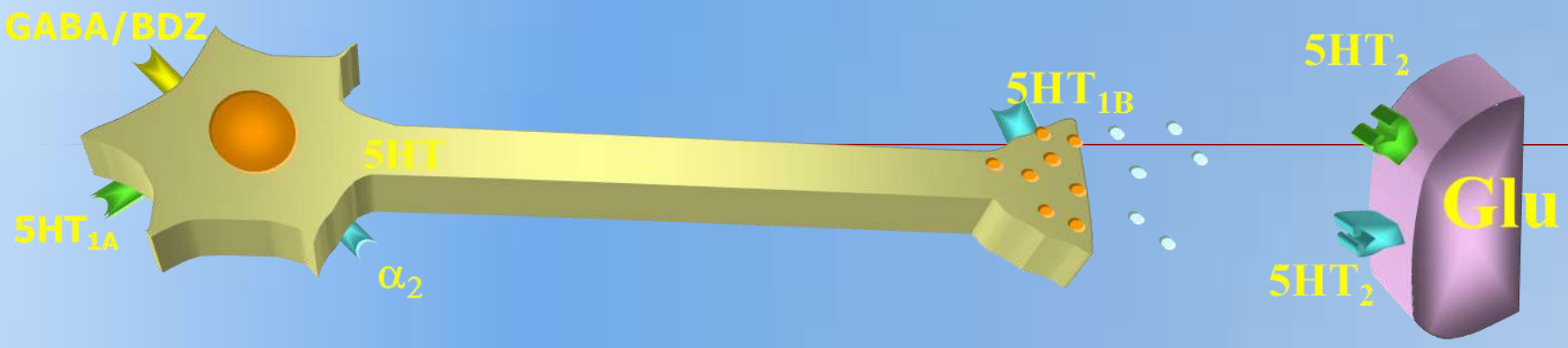
Nucleus accumbens

Lysergic acid dietylamide (LSD)

Liquid, tablets, capsules, blotting paper

Routes of administration: swallowing, sniffing, injection, smoking

Physical effects	Psychological effects
Dilated pupils	Distorted perceptions
Lowered body temperature	Hallucinations
Nausea	Anxiety
Vomiting	Depression



RISK OF PSYCHOPATHOLOGICAL DISTURBANCES/PSYCHOSIS AND INVOLVEMENT OF THE FOLLOWING PATHWAYS/RECEPTORS….

- DA (agonists)
- CB1; vanilloid (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 antagonists' behavioural effects*

GABAPENTINOIDS (E.G. PREGABALIN AND GABAPENTIN) CLINICAL INDICATIONS

(SCHIFANO, CNS DRUGS, 2014)

Pregabalin identified within the 30 most prescribed medications in the USA in 2011; pregabalin approved for:

1. **epilepsy (partial seizures)**
2. **neuropathic pain**
3. **generalised anxiety disorder**
4. In the USA further approved for **fibromyalgia and post-herpetic neuralgia** .

Prescribed off-label for a range of clinical conditions,

1. **bipolar disorder;**
2. **alcohol/narcotic withdrawal states;**
3. **attention-deficit/hyperactivity disorder;**
4. **restless legs' syndrome;**
5. **trigeminal neuralgia;**
6. **non-neuropathic pain disorders** .

Gabapentin approved for: **adjunctive treatment of complex epilepsy; post-herpetic neuralgia** in adults . In the UK, the molecule is indicated for the treatment of both **partial seizures and peripheral neuropathic** pain

GABAPENTINOIDS' INCREASING INTAKE RATES AND RELATED FATALITIES

- In the UK, pregabalin and gabapentin prescribing has increased, respectively, by 350 and 150% in just 5 years.

- In parallel with this, there is an anecdotally growing black market, with gabapentinoids being allegedly available without prescriptions through online pharmacies.

- Pregabalin and gabapentin first emerged in the UK mortality databases in 2006 and have shown an increasing trend since then in respect of being implicated in death. Indeed, most gabapentin victims (e.g. two-thirds in 2012) were not being prescribed with the molecule (Corkery et al, 2014)

GABAPENTINOID PHARMACODYNAMICS/CLINICAL PHARMACOLOGICAL ISSUES

- **Gabapentinoids decrease central neuronal excitability by binding to the auxiliary a2-d protein/subunit of voltage-gated calcium channels on neurons.** The entry of calcium ions into neurons allows the process of vesicle fusion with cell membrane/release of neurotransmitters. Hence, potent binding of pregabalin/gabapentin at the calcium channel of hyperexcited neurons results in a reduction in the release of excitatory molecules

- Pregabalin and gabapentin are thought to possess GABA-mimetic properties as well through both modulation of GABA metabolism and reversal of neuronal/glial amino acid transporters, with GABA being released

- Gabapentinoids may somehow present with **direct/indirect effects on the dopaminergic 'reward' system as well**

PREGABALIN VS. GABAPENTIN

- With a relatively short half-life of about 6 h, gabapentinoids are mostly ([98 %) excreted unchanged in the urine, with a **urine specimen being positive for pregabalin for up to 5–6 days after intake** in subjects with normal renal function.
- **Pregabalin binding affinity for the a2-d subunit, and potency, is six times more than that of gabapentin**
- Orally administered **pregabalin is absorbed more rapidly than gabapentin,** with maximum plasma concentrations attained within 1 h as opposed to 3–4 h.
- Absolute **bioavailability of gabapentin drops from 60 to 33% as the dosage increases** from 900 to 3,600 mg/day, while the **absolute bioavailability of pregabalin remains at 90%** irrespective of the dosage .
- This may explain as well why **pregabalin is anecdotally perceived as more 'powerful'** by drug misusers .

GABAPENTINOID POTENTIAL FOR MISUSE; THE AVAILABLE EVIDENCE (GENERAL POPULATION SURVEYS)

- At the time of marketing authorisation, the addictive liability levels of pregabalin were assessed to be low. However, findings' generalizability was limited by the therapeutic/limited dosages chosen and the population selected (e.g. non-drug-abusing volunteers).

- In a UK-based, anonymous, 1,500-respondent, online survey, Kapil et al. (2014) compared misuse of baclofen, gabapentin and pregabalin. **Respondents' self-reported lifetime prevalence of gabapentin misuse (1.1 %) was similar to pregabalin (0.8 %) and baclofen (1.3%),** in contrast with an alleged lifetime prevalence of cocaine and cannabis use, respectively, of 8.1 and 28.1%. Frequency of misuse of these molecules was monthly in 37% of cases and between once per month and once per week in 50%.

GABAPENTINOID POTENTIAL FOR MISUSE; THE AVAILABLE EVIDENCE

(ADDICTION CLINICS' SURVEYS)

- **Pregabalin was detected in 12.1 % (n = 15) of urine samples from opiate-addicted subjects attending a German addiction clinic.** None of these patients were suffering from any of the indications for pregabalin prescribing, with most having confirmed that they had acquired pregabalin illicitly

- Baird et al. carried out a questionnaire-based survey **in 6 Scottish substance misuse clinics; 22% (29/129) of respondents admitted to abusing gabapentinoids**, with 38% (11/29) of these clients abusing these molecules to potentiate the 'high' they obtained from methadone.

- In Tayside/Scotland, **gabapentin/'gabbies' is available at the price of £1 per 300-mg** tablet, and may be used as a 'cutting agent' in street heroin.

- **Pregabalin is widely traded in prisons**

QUALITATIVE OVERVIEW OF A RANGE OF ONLINE POSTS/NOTES/OBSERVATIONS

- A range of experiences may be associated with **gabapentin abuse, including: euphoria, improved sociability and a marijuana-like 'high'/relaxation**. A sedative/'opiate buzz' and psychedelic/MDMA effects are being reported as well.
- Taken in combination with gabapentin: cannabis; alcohol; SSRIs; LSD; amphetamine; GHB
- **Pregabalin considered an 'ideal psychotropic drug'** to achieve specific mindsets, including: **alcohol/GHB/benzodiazepine-like effects mixed with euphoria**; to achieve entactogenic feelings/**disassociation**; and to cope with opiate/opioid withdrawal.
- Misuse of **pregabalin, at dosages up to 20 times higher** than the maximal dosage indicated, mostly seems to occur **orally, but intravenous, rectal ('plugging'), smoking and 'parachuting'** (emptying the content of the capsule into a pouch) self-administration techniques are also being reported
- Pregabalin is reportedly taken in combination with: alcohol/gabapentin/benzodiazepines; THC/LSD/Salvia divinorum; heroin/opiates; and amphetamines/synthetic cathinones .
- **Abrupt/rapid discontinuation of high dosages** of pregabalin is reportedly associated with withdrawal signs/symptoms: **insomnia, nausea, headache or diarrhoea**.
- **Tolerance may reportedly develop fairly rapidly** to quickly wear off upon drug cessation

GABAPENTINOIDS AS A TREATMENT FOR ADDICTION?

- Pregabalin may present with beneficial effects for both alcohol withdrawal symptoms and alcohol relapse prevention
- Pregabalin has been shown to be effective in the withdrawal phase of both benzodiazepine and opiate detoxification, with valuable effects on cue- and stress-induced cocaine relapse .
- Similarly, gabapentin has been indicated for the treatment/management of opiates; cannabis , behavioural and alcohol addictions

MISUSE AND ABUSE OF PREGABALIN AND GABAPENTIN: CAUSE FOR CONCERN? (1)

- Some of the issues identified here may be a cause for concern, and these include: the **complex gabapentinoid pharmacodynamics**, possibly including the involvement of drug reward pathways; the **increasing prescription levels** over time

- **Pregabalin has been approved** in Canada and the USA since **2005**, and approval by the EU Commission to treat generalised anxiety disorder was received in **2006.** Yet, **the debate regarding abuse and dependence did not appear in the medical literature before 2010.**

- Similarly, remaining prescription drugs with misuse potential (e.g. benzodiazepines; z-hypnotics) were considered 'safe' for many years before their addictive liability levels were identified . This may be because of pre-marketing clinical trials typically involving the administration of carefully controlled, daily therapeutic dosages.

- **The real potential of misuse of the index molecule more properly appreciated only when a large number of clients, who will involve vulnerable individuals, are exposed to the drug.**

MISUSE AND ABUSE OF PREGABALIN AND GABAPENTIN: CAUSE FOR CONCERN? (2)

- Gabapentinoid experimenters are profiled as individuals with a history of recreational polydrug misuse, who self-administer with dosages clearly in excess (e.g. up to 3–20 times) of those that are clinically advisable.

- Physicians should carefully evaluate for a possible previous history of drug abuse, whilst being able to promptly identify signs of pregabalin/gabapentin misuse and provide possible assistance in tapering off the medication.

TRAMADOL HYDROCHLORIDE

Discovered in Germany in 1970s; tramadol acts as a

1. μ-opioid receptor agonist
2. 5-HT releasing agent
3. NA reuptake inhibitor
4. NMDA receptor antagonist
5. 5-HT2C receptor antagonist

- These serotonergic-modulating properties give it the potential to interact with other serotonergic agents increasing the risk of serotonin toxicity when tramadol is taken in combination with SSRIs

- Tramadol increase in 5-HT levels may be associated with improvement in depressive and OCD symptoms..

- Tramadol is converted to O-desmethyl-tramadol, ('Krypton'), two to four times more potent than tramadol itself

TRAMADOL DEPENDENCE AND TOLERANCE

- Only limited international efforts to control abuse of tramadol at an international scale. In 2007, China took vigorous measures against tramadol marketing; this was associated with eventual decreasing levels of misuse in the general population

- Long-term use of high tramadol dosages may be associated with physical dependence and a withdrawal syndrome.

- Withdrawal symptoms: composed of both typical opiate-like withdrawal symptoms and others, related to its effects on 5-HT/NA re-uptake. The atypical withdrawal symptoms may include those of SSRI discontinuation syndrome, such as: anxiety, depression, severe mood swings, aggressiveness, brain "zaps", electric shock-like sensations throughout the body, paresthesias, sweating, palpitations, restless legs syndrome, sneezing, insomnia, vivid dreams or nightmares, micropsia and/or macropsia, tremors, headache

Year	Number of mentions of tramadol	Deaths where tramadol was implicated	% of implicated deaths where tramadol was the “sole agent” (number)	% of implicated deaths where tramadol was NOT prescribed or “not known”(number)	Year	Number of mentions of tramadol	Deaths where tramadol was implicated	% of implicated deaths where tramadol was the “sole agent” (number)	% of implicated deaths where tramadol was NOT prescribed or “not known”(number)
1998	2	2	50% (1)	0% (0)	1998	2	2	50% (1)	0% (0)
1999	9	12	8% (1)	33% (4)	1999	9	12	8% (1)	33% (4)
2000	9	10	30% (3)	70% (7)	2000	9	10	30% (3)	70% (7)
2001	29	33	15% (5)	58% (19)	2001	29	33	15% (5)	58% (19)
2002	19	19	21% (4)	53% (10)	2002	19	19	21% (4)	53% (10)
2003	38	37	22% (8)	41% (15)	2003	38	37	22% (8)	41% (15)
2004	55	45	36% (16)	67% (30)	2004	55	45	36% (16)	67% (30)
2005	61	53	34% (18)	62% (33)	2005	61	53	34% (18)	62% (33)
2006	85	76	25% (19)	68% (52)	2006	85	76	25% (19)	68% (52)
2007	96	82	17% (14)	62% (51)	2007	96	82	17% (14)	62% (51)
2008	97	80	21% (17)	61% (49)	2008	97	80	21% (17)	61% (49)
2009	123	98	18% (18)	61% (60)	2009	123	98	18% (18)	61% (60)

KRATOM (*MYTRAGINA SPECIOSA*)

Historical use

Leaves CHEWED as an opiate substitute and stimulant in Thailand and South-East Asia (Thailandia, Malaysia, Borneo and New Guinea)

Street names:
Kratom, Ketum, Kakuam, Ithang, Thom, Mambog

ROA: chewed, smoked, brewed (tea, extract)

Several cases of **deaths reported**

Also found in ***Krypton*** herbal incense

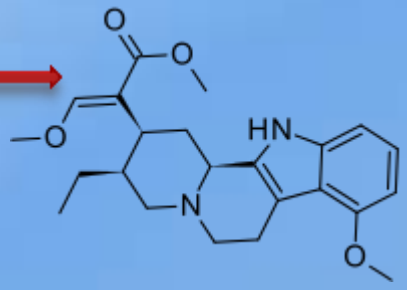
CONTRADICTORY EFFECTS

↑↑↑doses → ❖ opiate-like sedation '***opiate-like dreamy reverie***'

↓↓↓doses → ❖ coca-like stimulation (alertness, energy, euphoria)

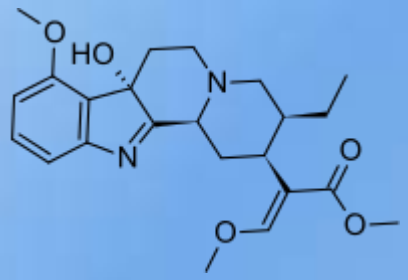
KRATOM LEAVES CONTAIN:

1) **Mytragynine (or Biak-Biak)**



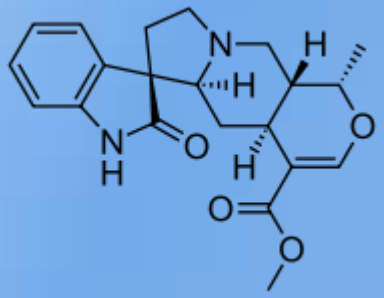
Partial agonist: μ-receptors, δ-opioid-receptors

2) **7-HO-mitragynine**



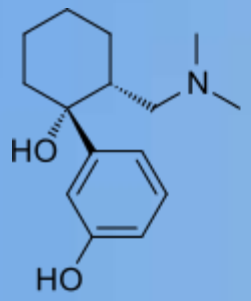
30-fold more potent μ-opioid agonist than 1) ↑

3) **Mitraphylline**

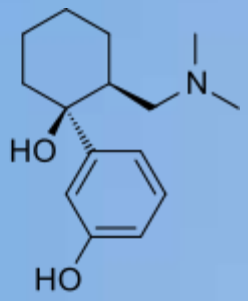


Agonism on **μ-and δ-opioid-receptors** as well as **NMDA-antagonist**

4) **O-desmethyltramadol**



(1*R*,2*R*)-O-DSMT

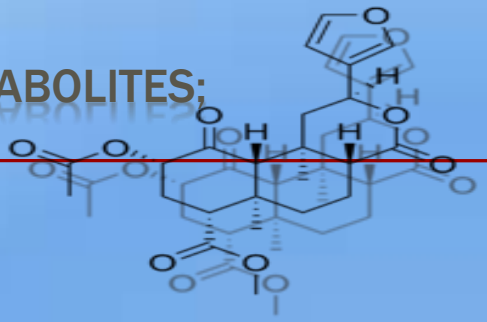


(1*S*,2*S*)-O-DSMT

NAUCLEA LATIFOLIA SM.

- *African peach, Pincushion tree*
- *Stem bark, leaves, roots and fruits: anti-epileptic, anti-malaria, pain relief etc.*
- Root bark: natural source of the synthetic opioid **TRAMADOL**

HERBAL COMPOUNDS; DATURA PRODUCTS; IBOGAINE & METABOLITES; MESCALINE; SALVIA DIVINORUM



- Salvia divinorum
- Aka: *Ska Pastora, Shepherdess' Herb, yerba de Maria, Magik Mint*

- Active costituent: Salvinorin A (k opioid receptor agonist)
- Intense and short acting hallucinogenic plant.
- Intake: smokable (pipe, bhong)

- Historical use: shamanic inebriant (Mexico)

SCELETIUM TORTUOSUM

- *Channa, Canna, Kanna, Kou, kougoed ('something good to chew'), kauwgoed*
- Ancient South African plant used:
  - by **warriors** after the battles Vs fear and depression
  - by **Hottentots** as vision-inducing narcotic plant (roots **chewed**)
  - by bushmen during the **eland/antelope hunt** (sacred animal, also called Kanna)
  - by indigenous people for **toothache or abdominal pain** (colic in **infants**)
  - by **shepherds** walking long distances in arid areas as an appetite suppressant

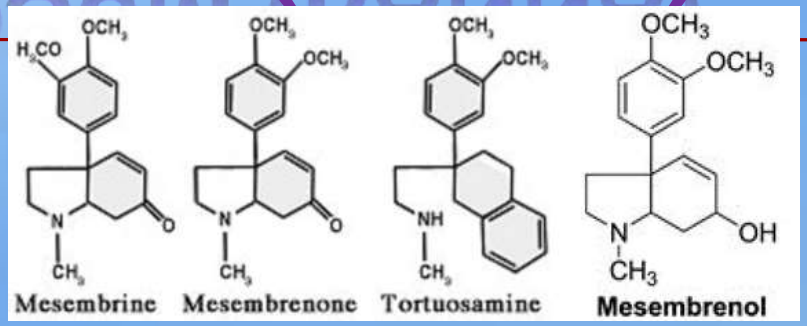
SCELETIUM TORTUOSUM (KANNA)

- Inebriating sedative, mood-enhancer, appetite suppressant, anxiolytic

- Intake: traditionally chewed (dried material); oral ingestion (juices; tea, infuses, in milk etc.); inhaled as a snuff or smoked (also with C. sativa)
- Doses: 20 mg (if inhaled); 50-150 mg (chewed); >200 mg (oral intake)
- Sold as extract, dried herb, powdered herb, tincture, tea bags or seeds

SCELETIUM TORTUOSUM (KANNA)

CHEMISTRY/PHARMACOLOGY



- Alkaloids
  - **Mesembrine** (↑↑selectivity for 5-HT transporter; Ki=1.4nM)
  - **Mesembrenone** (dual inhibitor of 5-HT transporter [Ki=27nM] and PDE4)
  - **Mesembrenol** (inhibitor of 5-HT transporter [Ki=62nM])
  - **Tortuosamine**

- **Desired Effects**
  - Euphoria, empathy; sexual stimulation,
  - mood enhancement, appetite suppressant, anxiolytic

  Side effects:
  - tachycardia, elevated blood pressure, headache, insomnia, sedation, slight nausea, anxiety
  - **WARNING!!!** In combination with MAOI and SSRI (Serotonergic Sdr)

AYAHUASCA

From Quechuan language, '***Vine of the Souls***'

- ***Street names***: Huasca; Yagé; Brew; Daime; Pharma-huasca; The Vine; The Tea; La Purga ('*the purge is the trip experience related*')

Psychedelic South American brew

Shamanic practices

EFFECTS

- Dose-dependent
- Strong visual effects (snakes, big cats, insectoid aliens, etc.)
- Healing properties; powerful mind-altering entheogenic effects
- Euphoria, connectedness to the universe etc.

SIDE EFFECTS

- (most common) vomiting and/or diarrhoea
- Flu- or food poisoning-like symptoms
- Imbalance, paranoia, fear, etc.

AYAHUASCA: components

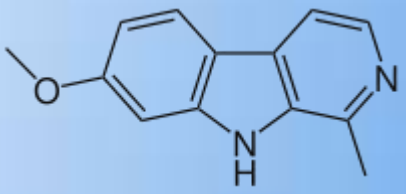
1) **BANISTERIOPSIS CAAPI VINE**

- ✓ **Harmine (or *Telepathine*)**
- ✓ **Harmaline**
- ✓ **Tetrahydroharmine**
  (weak SSRI)

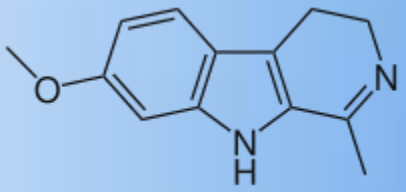
- ✓ **B-carboline Harmala alkaloids**
- ✓ **Reversible MAOI-A**

→ Anti-parasitic/bactericidal etc.

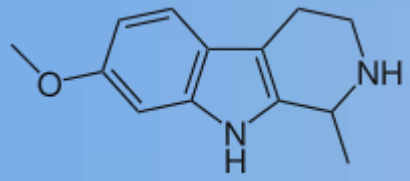
→ Purgative (GI tract)



Harmine



Harmaline



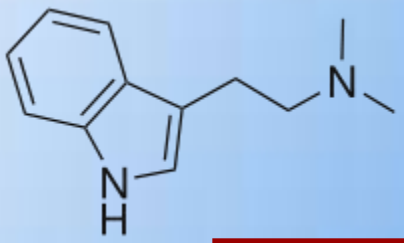
Tetrahydroharmine

AYAHUASCA: components

2) **DMT source**

- ***Psychotria viridis***
- *Diplopterys cabrerana*

etc.



MAOI-A allows DMT to be orally active➔effective

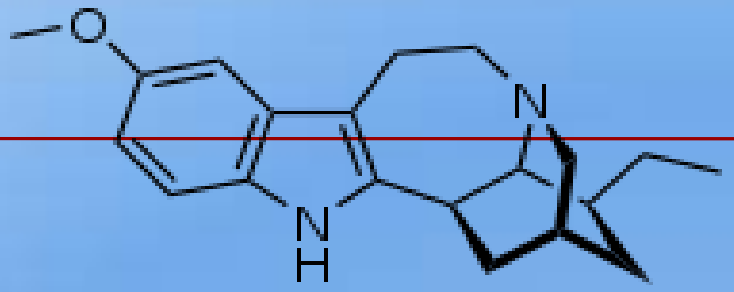
Fatalities!!!

IBOGAINE (Tabernanthe iboga)

- monoterpine indole alkaloid extracted from the **root bark** of the African shrub **T. iboga** (‘*le bois sacre*’)

- Ceremonial use in the **Bwiti religion**
- Anti-addiction agent in detoxification from opiates
- Ibogaine-containing extract was sold as an antidepressant in France (1939) [**Lambarene**]
- **Strong, long-lasting psychedelic** with **dissociative properties**
- **oneirogen** (dreamlike effect)

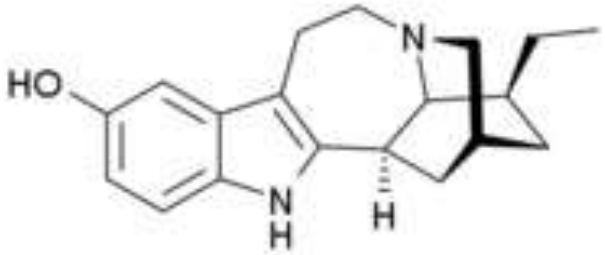
IBOGAINE



- ❖**K-opioid** receptor AGONIST
- ❖Non competitive **5-HT2A** receptor AGONIST
- ❖Non competitive **DAT** inhibitor
- ❖**NMDA** receptor ANTAGONIST

CYP450

NORIBOGAINE



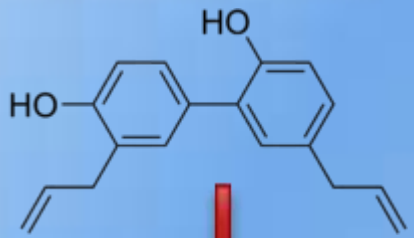
- ❖ ↑↑ potent as SSRI
- ❖ moderate k-opioid-R antagonist
- ❖ weak μ-opioid-R antagonist/weak partial agonist

MAGNOLOLS/CALLISTEMON

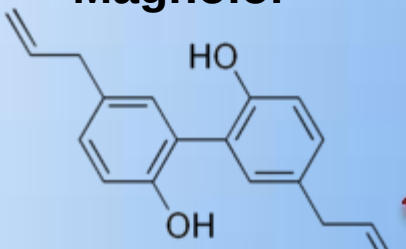
- Large use in Chinese and Japan medicine (constipation; headache; asthma etc.)
- Anxiety-reducing activity; weight-loss aid
- Main constituents

MAGNOLIA BARK EXTRACT

Honokiol



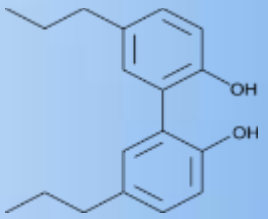
Magnolol



weak CB2 agonist

Both GABA-A agonists

Tetrahydromagnolol

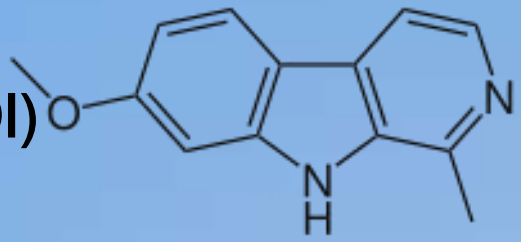


CB2 agonist

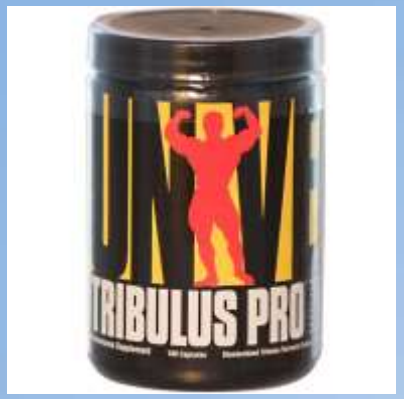
Reported to contain also phenibut (GABA-B)

TRIBULUS TERRESTRIS

- Also called '***Puncture vine***', ***Caltrop; Tribolo; Goat's head***
- Active costituent: **B-carboline Harmine (MAOI)**



- Alternative to Ayahuasca?
- Aphrodisiac



- Performance enhancer supplement

DATURA STRAMONIUM

- *Jimson weed, Mad Apple, etc.*
- ***Native to Asia, West Indies***
- ***Historically described as a toxin, popular for its mind-altering properties*** (Homer's Odyssey, Shakespeare's Hamlet, etc.)
- Hallucinogen, deliriant and euphoric (atropine, hyoscine, hyoscyamine)
- oral (seeds, teas) or smoking

- **WARNING!! Serious illness** (fatal medullary paralysis, arrhythmias, cardiovascular collapse)/**deaths** (***anticholinergic activity***)

Sacred plant in India (favourite of the ***Hindu god Shiva Nataraja***)

RHODIOLA ROSEA

- *Arctic root, roseroot, golden root*
- *Historical use in medicine:*
  - *Physical strength, endurance (Vikings)*
  - *Cold, flu (oriental brew)*
  - *Cancer, TBC (Mongolians) etc.*
- Taken to potentiate tryptamines
- Inhibition MAO-A and MAO-B

SPICE DRUGS

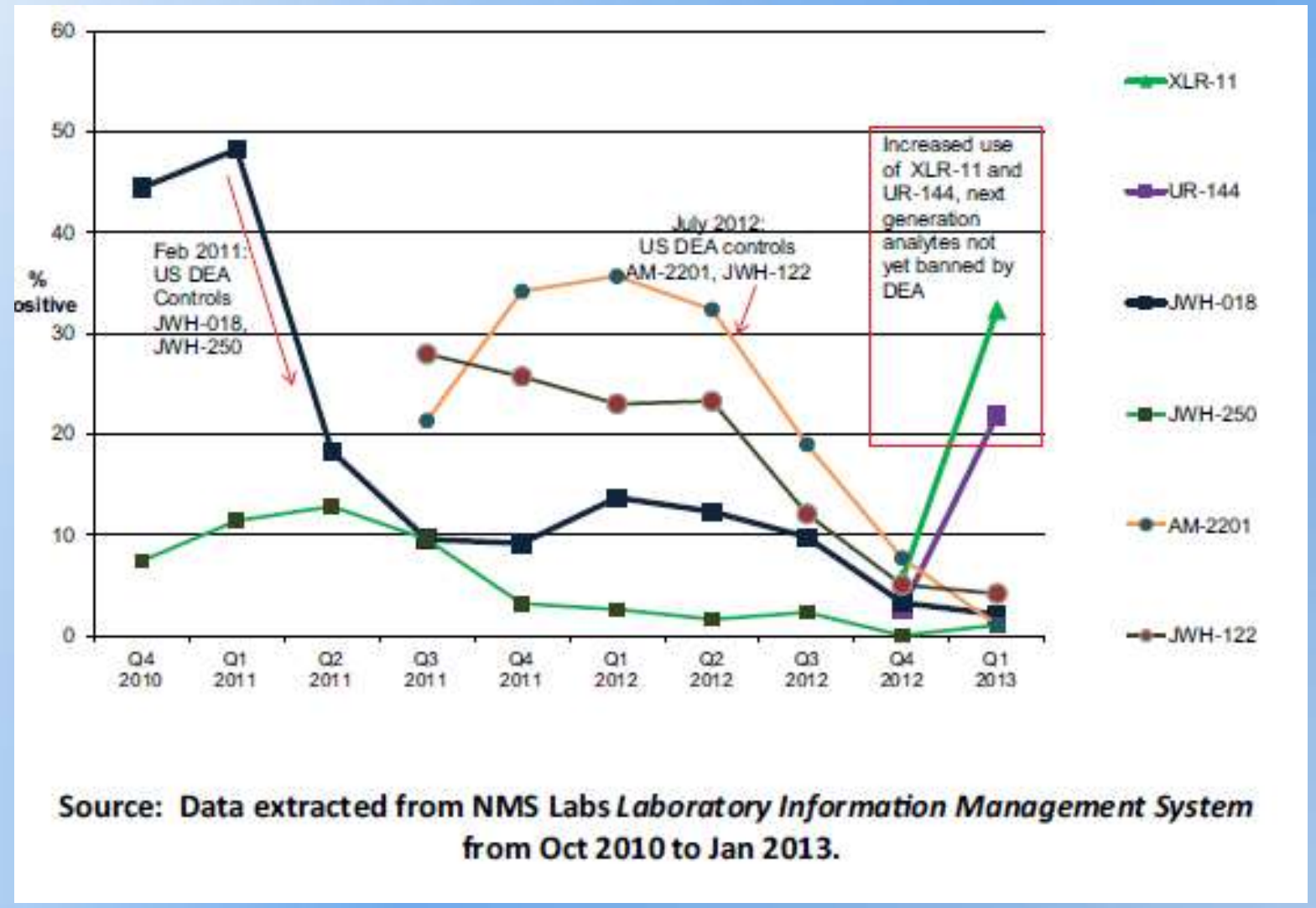
- Smokable poly-cannabimetics designer drugs
- Appeared in or around 2004; now more than 220 compounds, in many different available combinations and brands
- Sold as ‘fake cannabis’ but DIFFERENT PHARMACOKYNETICS, PHARMACODYNAMICS and TOXICOLOGY

- Schifano, F., Corazza, O., Deluca, P., Davey, Z., et al. Psychoactive drug or mystical incense? Overview of the online available information on Spice products. *International Journal of Culture and Mental Health, 2009.*
- » Mustata, C., Torrens, M., Pardo, R., Perez, C., The Psychonaut Web Mapping Group., & Farre, M. (2009). Spice drugs: Cannabinoids as new designer drugs [Spanish]. *Adicciones, 21(3),* 181- 186.
- » Papanti, D., Orsolini, F., Francesconi, G., Schifano, F. (2014). ‘Noids’ in a nutshell: everything you (don’t) want to know about synthetic cannabimimetics. *Advances in Dual Diagnosis* , in publication.

SYNTHETIC CANNABIMIMETICS

- More than one/two SC in each Spice product
- The same batch can have different compounds
- Different batches can have the same compound
- Concentration of SC highly variable/HOT-SPOTS
- Presence of other NPS in Spice Products

The ‘eternal recurrence’ of SC



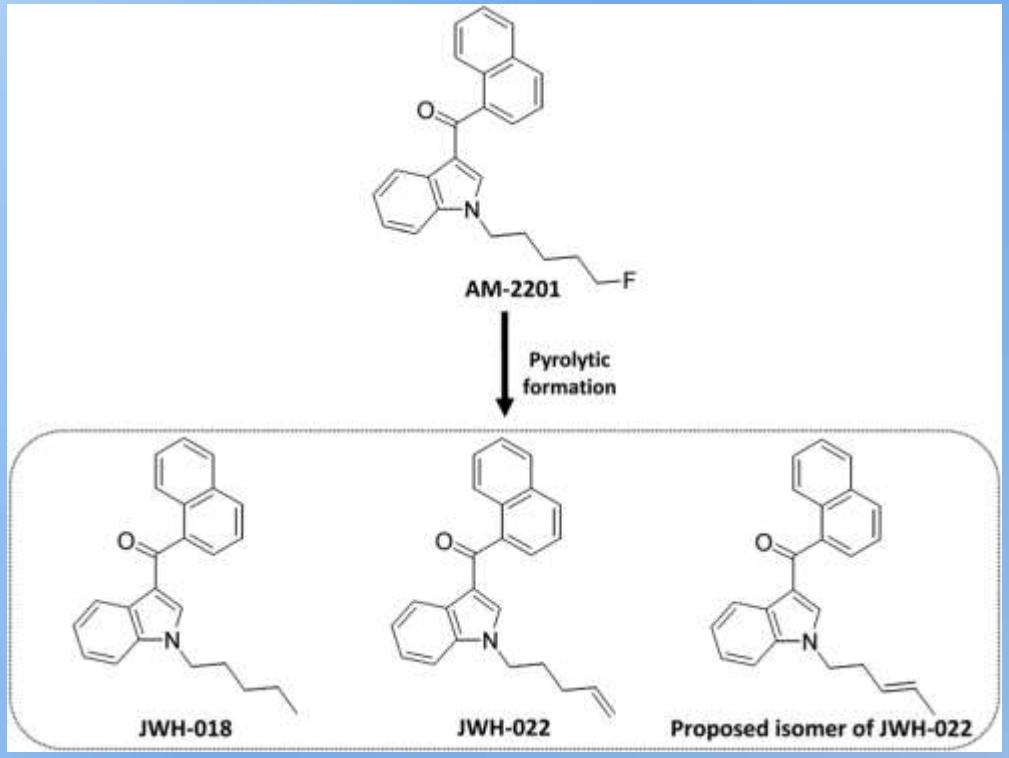
Source: Data extracted from NMS Labs *Laboratory Information Management System* from Oct 2010 to Jan 2013.

SYNTHETIC CANNABIMIMETICS

- LITTLE MODIFICATIONS RESULT IN LARGE DIFFERENCES IN METABOLISM AND PHARMACODYNAMICS
- Substitution ring/side chain: AM 694; AM 2201
- Modification side chain: AM 1220; AM 2233
- Replacement of specific groups: AB-001; AB-1248
- Other variations: CB-13; UR-144
- Most recent: AB-PINACA; AB- A-836,339; AB-FUBINACA

SYNTHETIC CANNABIMIMETICS; PHARMACOKINETICS

- PYRROLISIS leads to the formation of further active compounds



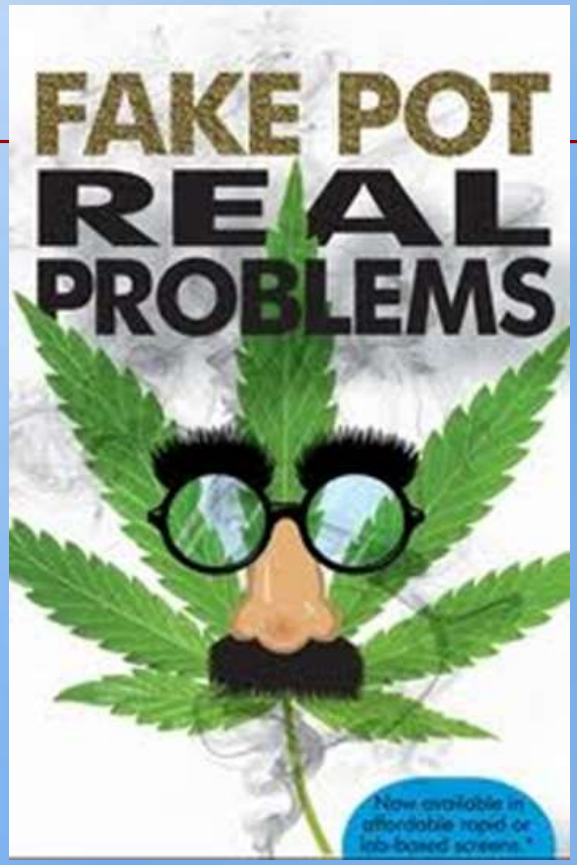
SYNTHETIC CANNABIMIMETICS; PHARMACOKINETICS

- DRUG-DRUG INTERACTIONS: Spice frequently contain *combinations* of SC, hence relative potency of single compounds increased
- ACTIVE METABOLITES: metabolism of JWH-018 and AM-2201 leads to the generation of CB-1rs high affinity metabolites

SYNTHETIC CANNABIMIMETICS VS THC

- SC full agonists on CB-rs; THC partial
- No CBD in Spice products
- Lower receptor occupancy for CB1 activation required for comparable signaling effects for SC vs THC

Vomiting
Seizures
Tachycardia
Mydriasis
Hypertension
Confusion
Restlessness



Anxiety/ Panic attack

Tachypnoea

Hyperglycaemia

Hypokaliemia

Acute kidney injuries

DEATH

?

- **Delusions/Paranoia**
- **Disorganized thought**
- **Visual (!) and auditory hallucinations**
- **Short and long (!!) standing psychosis**

SPICE DRUGS' PSYCHIATRIC EFFECTS

- Acute psychoactive effects: changes in mood, anxiety, perception, thinking, memory, and attention
- Adverse effects: anxiety, agitation, panic, dysphoria, psychosis, bizarre behaviour
- Possible involvement of 5-HT2A receptors
- Psychosis outcomes associated with Spice ('**SPICEOPHRENIA**') provide additional data linking cannabinoids and psychosis.

USE OF METHADONE

- Methadone is the currently preferred drug of choice for the treatment of opioid dependence in many countries, including the UK.

- Methadone dominates the substitute opiate-prescribing market in the UK, accounting for perhaps 90% of it. Within the EU the number of addicts being treated with methadone increased seven-fold between 1993 and 2000.

- Such use of the drug has increased as its advantages have become widely recognised: reduction of criminal activity, costs of crime and illicit drug use by opiate addicts; improving social integration and employment prospects and reducing the morbidity and mortality of opiate users.

METHADONE DIVERSION AND DRDS

- Diversion may be a factor in many methadone-related fatalities. At least three-fifths of deaths associated with methadone in England and Wales are accounted for by the use of methadone which may have been illicitly obtained.

- Rates as high as 75% have been reported in Scotland

PHARMACOKINETICS (1)

- Methadone appears in the blood stream within 30 minutes of being taken orally and has a bio-availability of between 70% and about 90%. It takes 2 to 4 hours for it to reach peak plasma concentrations.

- Methadone has a long but variable plasma half-life. Mean estimates of this have varied from 15 to 55 hours but it is usually assumed to be 24 hours.

- In some drug-naïve persons, a single dose can have clinical effects up to 72 hours in duration. When methadone is the principal source of death it is likely that death will occur a few hours following its consumption.

PHARMACOKINETICS (2)

Metabolism

- Methadone is widely distributed amongst tissues. It is highly bound to tissue proteins, perhaps in the range 60% to 90%; this may help to explain its cumulative effect and slow elimination. The main binding protein in plasma is α1-acid glycoprotein.

- Methadone is chiefly metabolised in the liver, where it undergoes N-demethylation and cyclisation, and appears to be eliminated unconjugated.

- The major metabolites of methadone (EDDP and EMDP) are widely considered to be pharmacologically inactive.These metabolites are excreted in the faeces (via bile) and urine together with any unchanged methadone.

PHARMACOKINETICS (3)

Factors affecting methadone metabolism

- Drug users with severe liver damage may have decreased ability to metabolise opioids. For example, one study found the period of terminal half-life to be 18.8 hours in those with healthy livers and 35.5 hours for those with chronic liver disease.

- Methadone takes two to three weeks to induce itself, and thus the hepatic enzyme systems (which convert methadone to its metabolites) of new methadone users will therefore take longer to clear methadone from their bodies.

- It has been shown that the metabolism of methadone is very slow in individuals who have just started titration with the drug and/or are methadone-naïve. The drug accumulates from one dose to the next. This, clearly, poses a risk of overdose especially during the initial phase of MMT

PHARMACOKINETICS (4)

- There may be *genetic variability* in the response of a sub-group of individuals to the drug and their metabolism of it, making them more susceptible to overdose. There can be great variation between individuals in the accumulation and clearance of methadone from their bodies. Bioavailability has been reported to vary between 41% and 99%, its half-life to vary between 4 and 91 hours, and its rate of clearance from the body has been reported to vary by a factor of almost 100.

- Eap *et al* have distinguished three types of metabolisers in respect of a genetic polymorphism of cytochrome P450 2D6 which assists in the processing of methadone - poor (zero functional gene), extensive (one or two functional genes) and ultra rapid (three or more functional genes).

- The cytochrome P450 3A4 enzyme system (CYP3A4) is the principal agent responsible for metabolising methadone. The other main enzymes responsible are CYP 2D6 and CYP 1A2.

METHADONE TITRATION

- Methadone should only be administered following a thorough clinical assessment of opiate/opioid dependence and current level of drug consumption. There is now widespread agreement that for outpatient stabilisation the initial dose of methadone will be less than 30 mg.

- The Department of Health *Orange Guidelines* (DH, 1999) and the *European Methadone Guidelines* recommend that where tolerance to opioids is high the normal dose will be between 25-40 mg and that where tolerance is low or uncertain an appropriate dose would be between 10-20 mg.

METHADONE INDUCERS

- The metabolism of methadone can be affected by interactions with other medications such as phenytoin, carbamazepine, rifampicin, fluconazole and some protease inhibitors. These types of drugs cause induction of the CYP3A4 enzyme and an increase in the metabolism of methadone and thus a decrease in its concentration.

- The concurrent administration of drug inducers such as benzodiazepines, barbiturates and opiates with methadone may result in significantly lower plasma levels of the drug.

METHADONE INHIBITORS

- Ketoconazole and erythromycin may (because they inhibit the metabolism of methadone) enhance the risk of overdose in susceptible people if taken concurrently. Fluoxetine can increase plasma concentration of methadone, as can other selective serotonin reuptake inhibitors such as fluvoxamine. These act as substrates or inhibitors of the CYP3A4 enzyme.

- Other interactions have been reported. Of particular importance are monoamine oxidase inhibitors (MAOIs). These can prolong and potentiate methadone's respiratory depressant effects. Used with opioids including methadone, MAOIs may cause fatal hypotension and coma Other centrally acting agents enhance the general depressant effects of methadone through synergism; these include alcohol, barbiturates, phenothiazines and tranquillisers.

ADVERSE EFFECTS

- lightheadedness, dizziness, anorexia, nausea and vomiting, dry mouth and sweating.
- Similar to other opioids, methadone toxicity can cause drowsiness and hypotension.
- True intolerance to methadone is considered to be most unusual: if, very rarely, an allergic reaction occurs alternative drugs can be used in treatment of dependence

METHADONE DRDS

- As a synthetic opioid, methadone causes death in a similar way to heroin

- The signs of overdose associated with methadone include deep respiratory depression, unusually loud snoring, pin-point pupils, hypotension, circulatory failure, pulmonary oedema and coma.

METHADONE DRDS

- Almost exclusively, deaths associated with methadone also involve a cocktail of drugs (such as alcohol, and benzodiazepines i.e. diazepam, nitrazepam, etc.)

BASIC CLINICAL ADVICE FOR PRESCRIBERS....

- methadone's longer half-life means that it stays in the body longer than other opioids and thus plasma levels build up quicker than might be realised.
- The metabolism of methadone is very slow in those who have just entered MMT compared to those who have been fully induced and have attained steady-state levels.
- The lack of complete cross-tolerance between methadone and other opioids means that those entering MMT may have lower tolerance to methadone than they might suppose, and thus initial dosages could be too high.

CLINICAL ISSUES

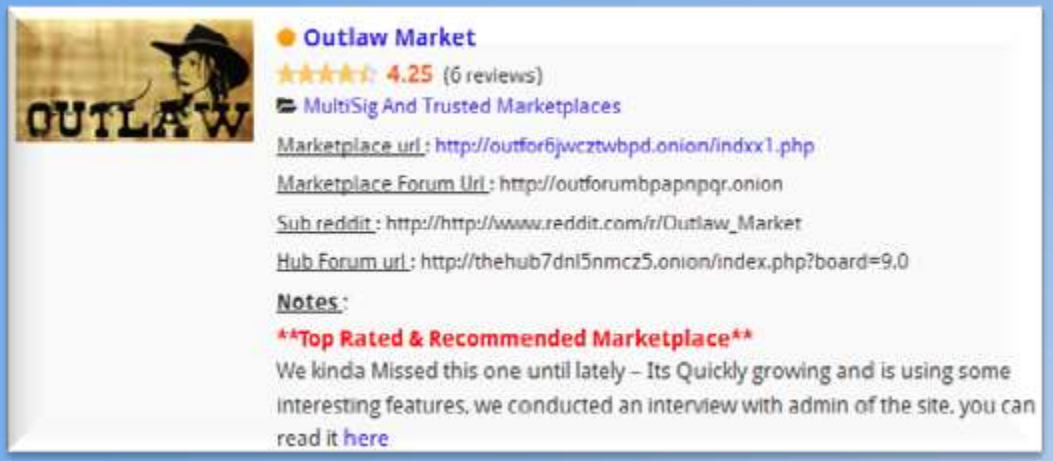
- Prescribers and treatment programme managers need to be aware of and communicate to those who are opioid dependent or who are entering into MMT the dangers of using methadone following loss of tolerance and the resumption of illicit drug use.
- This is particularly important to get over to those leaving prison or residential detoxification programmes.
- There should be regular monitoring of patients' compliance with treatment plans.

LIST OF HIDDEN MARKETPLACES (TOR & I2P)

Accessed 27-05-2014 on Tor browser (www.deepdotweb.com)

- **Invite/Referral only markets**:
  requested invite code or
  a referral link in order to register

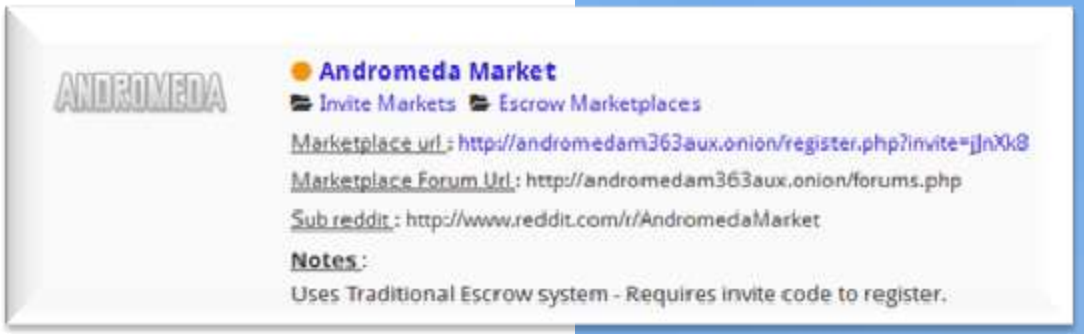
- **Multisig or Trusted:**
  use of multisig transactions
  or marketplaces who have
  displayed great conduct over
  a long period of time with no
  security issues at all; minimal
  reports about scamming/technical issues



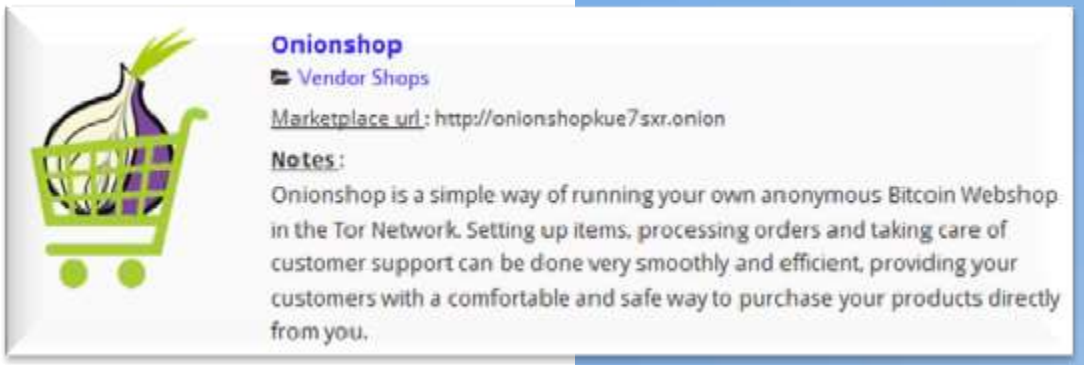
LIST OF HIDDEN MARKETPLACES (TOR & I2P)

Accessed 27-05-2014 on Tor browser (www.deepdotweb.com)

- **Escrow marketplaces**:
  using regular escrow & FE



- **Vendor shops**:
  not marketplaces but vendors who opened their own WBs



- **Marketplaces for specific languages/countries**

Finnish: Silkkitie url: http://silkkitiehdg5mug.onion (Finnish Silk Road) Forum (Hub): http://thehub7dnl5nmcz5.onion/index.php?board=37.0
French: French Dark Place 2.0: http://ruzh5shkcme2tpfk.onion
French: Scion: http://kva4nqylqvrdzhkk.onion
Polish: Torepublic Market: URL: http://nco5ranerted3nkt.onion/forum/market.php Forum: http://nco5ranerted3nkt.onion/forum/
Russian: Ramp Url: http://ramp2bombkadwvgz.onion
Russian: Hydra Market – Russian Version url: http://hydraruehsdjjfud.onion/register/ktgvv60br5et

LIST OF HIDDEN MARKETPLACES (TOR & I2P)

Accessed 27-05-2014 on Tor browser (www.deepdotweb.com)

- **New markets & under construction**:

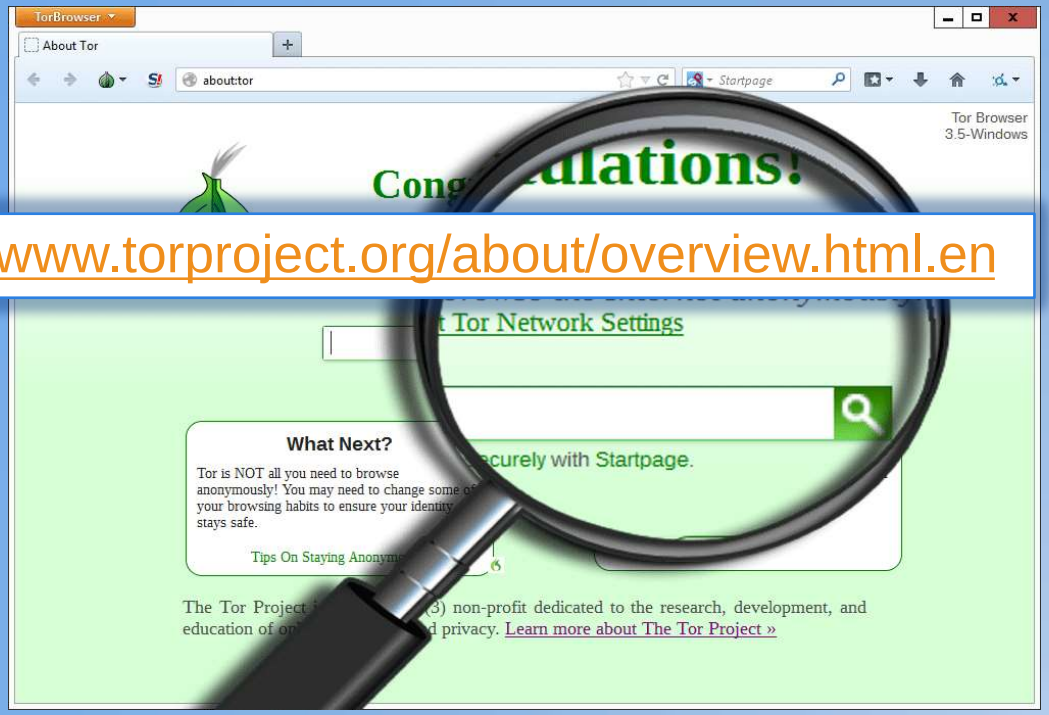
New Marketplaces (Either new or we have no reviews about them)
Silk Street Url: http://silkr2xyqsu73qhh.onion
Underground Market Url: http://unground6baopdio.onion Forum: http://vxcwhb4lzqltfauq.onion/
TOM Marketplace url: http://tom3j5jkjl7327oc.onion Forum: http://tomf2fo56wthggwk.onion/
AdMagz: http://admagzkknk3luzak.onion/ (Free Classifieds)
deepzon: http://deepzondhyl3yaro.onion
DarkNetServices: http://darknet4x3hcv5zp.onion/ (DNS Hosting and vendor shop services)

Under construction:
"The Shop" – No url so far.

- **Misc links**: link to helpful WBs related to the dark marketplaces (i.e. Bitrated, Schared Coin, Bitcoin, etc.)
- **Dead/Scam Marketplaces links**

What is the Tor Browser?

- **Free software**
- **Open network that helps you defend against traffic analysis and allows confidential business**
- **Internet path so making it harder to track what sites/services you use**
- **The PERFECT PLACE for finding hidden marketplaces (on firearms, guns, pornography, paedophilia, and also ILLEGAL DRUGS)**
- **The only way to access to the dark web market**

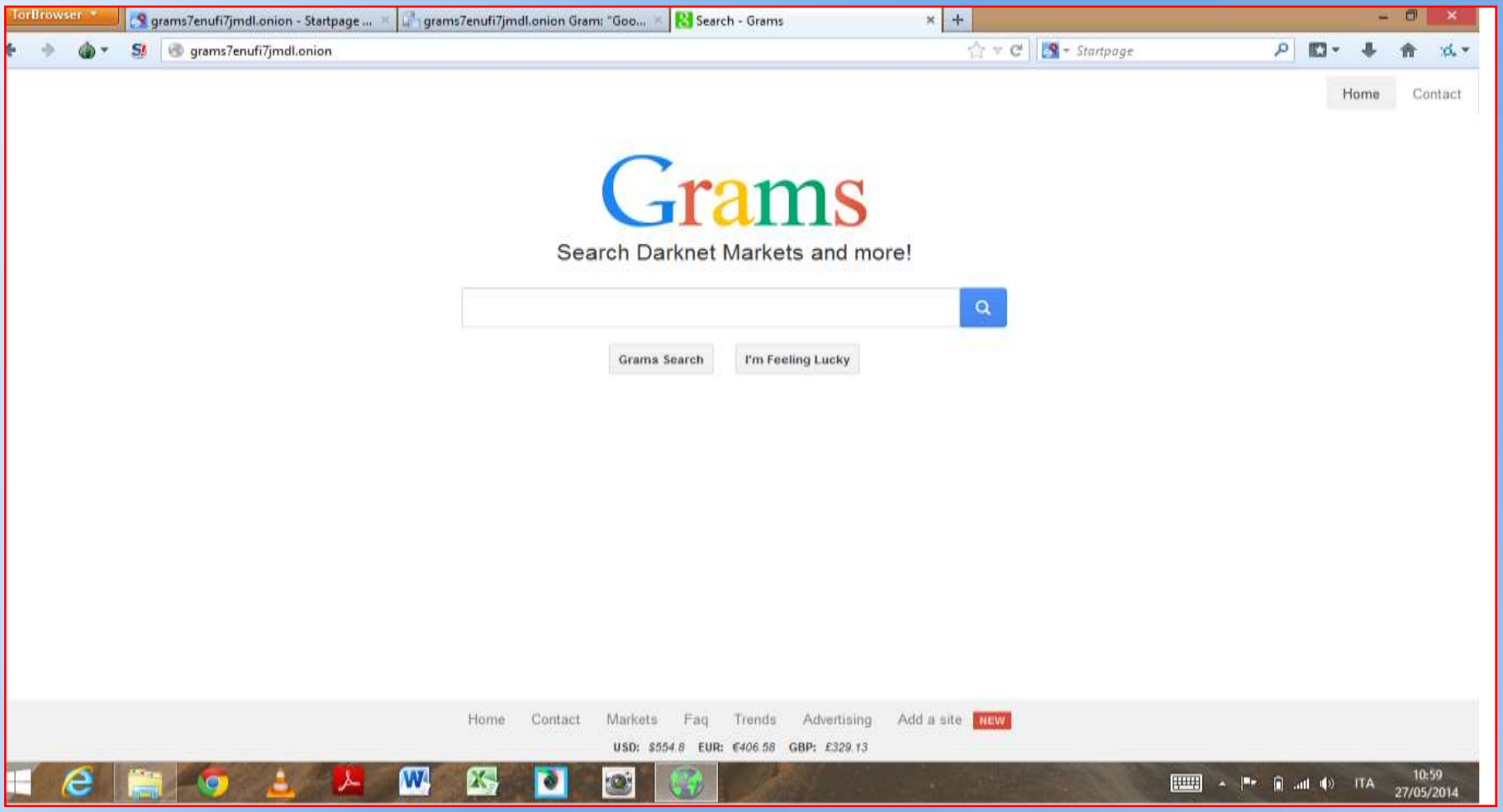


More information here: https://www.torproject.org/about/overview.html.en

What is bitcoin ?

- A peer-to-peer payment system (**Satoshi Nakamoto**, 2009)
- A decentralized virtual currency (not associated with banks or system of detecting money transfer, etc.)
- A crypto-currency used for ILLEGAL ACTIVITIES
  - Obfuscate online transactions
  - *"the currency of choice for seedy online activities"*
  - Anonymity and security for your business

And finally…Google clone makes it easy to search for drugs/guns on the Dark Web



Accessed 27-05-2014 on Tor browser (http://grams7enufi7jmdl.onion/)

Grams: offers from 14-04-2014

TorBrowser

cocaine - Grams

grams7enufi7jmdl.onion/results

Startpage

Grams Beta

cocaine

Home Contact Markets FAQ

Currency
BTC USD EUR GBP
Sort
Relevance Price▲ Price▼ New

Searching
1776 Agora ADM BlackBank C9 EVO SilkRoad TPM

About 1244 results for 'cocaine' (0.5832 seconds)

News

22-04-14
Another New Market!

We Just added the 1776 Market. This market makes multi-sig transactions easy.
Read more at DeepDotWeb (clearnet)

EZ Test Cocaine Combo Pack SALE

k5zq47j6wd3wdvjq.onion/listing/2284 **Evolution**

This listing is for three **cocaine** EZ Tests Free Shipping Included are the following three EZ Tests 1 EZ Test **Cocaine** For Positive identification of **Cocaine** 1 EZ Test **Cocaine** Purity How Strong is your **Cocaine** 1 EZ Test **Cocaine** Cuts How Clean is your Coke What is it cut with These tests are available individually or buy the combo and save

Vendor EZTest **Price** Ƀ0.07906206 **Location** United States

3 Grams Of Cocaine

silkroad6ownowfk.onion...tems/3-grams-of-cocaine **Silk Road 2**

3.00 Gram Of **Cocaine** From **Cocaine** Cowboy CC Good sociable **cocaine**. United Kingdom and N.Ireland delivery only. Same stuff i was selling on SR SMP and Tormarket.. Check out my vendor profile for description. Thanks for looking.

Vendor Cocaine Cowboy **Price** Ƀ0.493888 **Location** United Kingdom

3 gram 80 purity cocaine

agorahooawayyfoe.onion/p/sq6WyorK6k **Agora**

description Hello welcome to my shop I Will Provide You With **cocaine** the best there is Pure

And who are the E-Psychonauts?

Not the recent videogame

Not a British electronic band

…but the virtual psychedelic researchers, the drug/psychedelic Nerds and maybe the new Shamans

- The virtual users/abusers of psychedelics and especially NPS
  - Self-exploration, pseudo-religious and spiritual purposes
  - Sense of community and sharing own experiences (detailed trip reports with dosage, combination drugs, clinical and psychological effects, etc.)
  - looking for, and trying out, NPS with total lack of available data re: their potential effects through a self-exploration process in A SIMILAR WAY OF THE OLD SHAMANIC TICES

❖**The 'Chemicals' experimenters":** who test the chemicals in order to document the drugs' effects 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.

EUropean-wide, **M**onitoring, **A**nalysis and knowledge **D**issemination on **N**ovel/**E**merging p**S**ychoactive**S**

(**EU-MADNESS**):

integrated EU NPS monitoring & profiling to prevent health harms and update professionals

EC – funding awarded of € 635,215.

Started 1 April 2014 & lasts 24 months.

Principal Investigator – Professor Fabrizio Schifano

http://ec.europa.eu/justice/newsroom/files/c%282013%29_8313_dpip_annexes_en.pdf

Participants – Institutions

Dept of Pharmacy, University of Hertfordshire
St George's, University of London
Semmelweis University, Hungary
European Institute of Health Promotion, Italy
Anti-Drugs Department, Italy
Università Politecnica delle Marche, Italy
Cagliari University, Italy
National University for Distance Learning (UNED), Spain
Kliniken/ Institut der Universität Duisburg-Essen Klinik für abhängiges Verhalten und Suchtmedizin, Germany
University of Edinburgh
University "G.d'Annunzio", Italy
IMIM (Hospital del Mar Medical Research Institute), Spain

Work streams

- WS1 - led by John Corkery; collaborators from UK, Hungary, Italy
- WS2 - led by Dr. Jacqueline Stair with support from Dr. Stewart Kirton, Prof. Mire Zloh (all UH), with Prof Raffaele Giorgetti (Italy)
- WS3 - led by Dr Colin Davidson, St George's University of London (SGUL), with Prof Gaetano di Chiara (Italy) and Prof Emilio Ambrosio (Spain)
- WS4 - led by Dr Colin Davidson with Mrs Christine Goodair (SGUL), with partners in Scotland (Prof Simon Maxwell), Germany (Prof. Norbert Scherbaum), Italy (Prof Giovanni Martinotti and Professor Raffaele Giorgetti), and Spain (Prof Magi Farré)

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