Hallucinogen Related Disorders

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Definition

- ‘Hallucinogen’- misnomer. True hallucinations are atypical.
- Diverse classes of substances- no adequate definition
- Hallucinogenic drug - substance whose subjective effects are dominated by prominent alterations in perception, cognition, affect, sense of meaning, and/or sense of self
- Other psychoactive substances and prescribed medications – overlapping effects but not included in hallucinogens

Terminology associated with hallucinogens

- Psychotomimetic - similarity between hallucinogen intoxication and psychotic illness
- Psychedelic (mind manifesting)- altered state of consciousness produced by seretonergic hallucinogens
- Dissociatives- PCP and related arylcyclohexamines
- Empathogen/Entactogen – MDMA and others - feelings of emotional closeness
- Entheogens – spiritual/religious aspect of the experience

Historical Perspective

- Hallucinogens used for centuries by various local tribes
- 1943- Hoffman consumed LSD and reported its hallucinogenic properties. Used to simulate experiments by psychiatrists in 50's
- 1950's- PCP marketed as anaesthetic till 1965
- 1960's- counter-culture in USA
  - PCP entered street in San Fransisco
  - Tom Leary 'turn on, tune in, and drop out'- LSD
- 1970's- PCP epidemic
- 1980's- use of hallucinogen declined

Patterns of drug use

- Social, cultural, psychological, and biological factors determine drug taking behavior
- Recreational reasons, to enhance enjoyment.
- Enhance self-understanding, personal discovery or religious/spiritual growth
- Experiences of euphoria common; of dying or being born
- Users find experience interesting, entertaining, useful, therapeutic or spiritual
- Insight intact
- Ready availability and low cost

Epidemiology

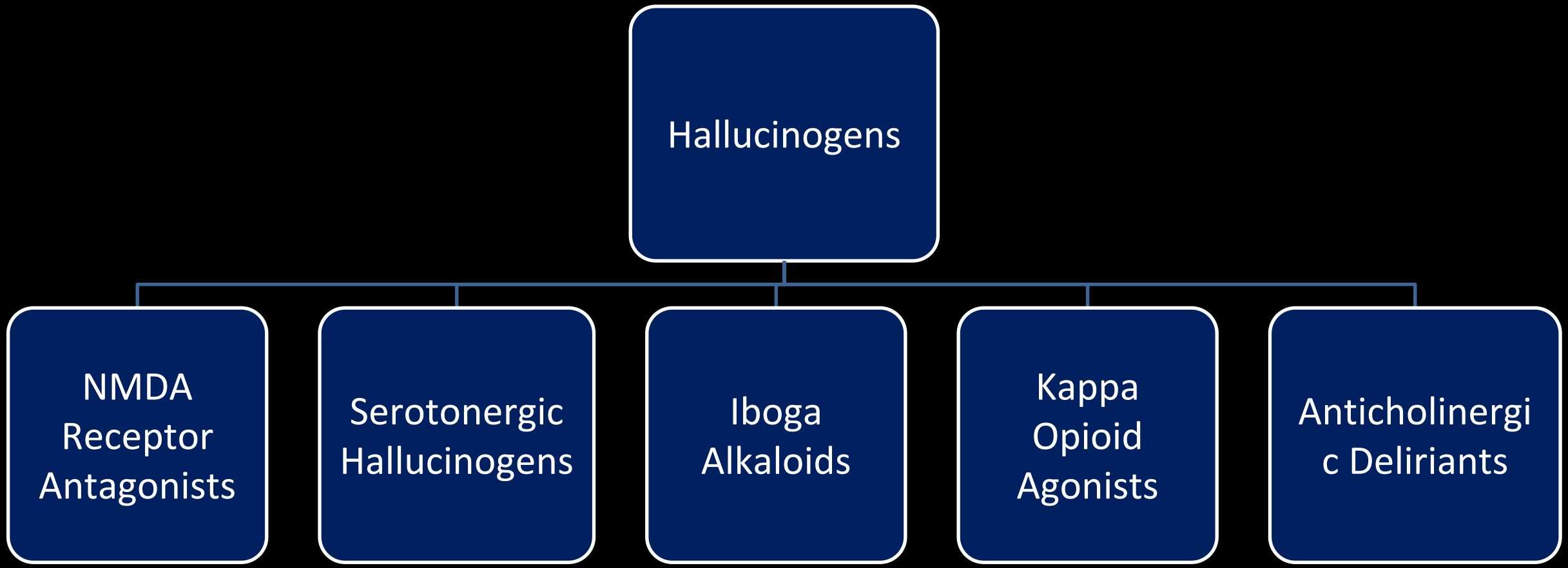
DAWN data (2011)

- Lower ED visits as compared to other substances.
- Highest for PCP (24.2/100000) followed by MDMA (7.2)
- More for males than females
- Rates are higher in the under 21 age group for the serotonergic hallucinogens
- Higher in the over 20 age group for PCP and ketamine
- Harmful patterns of use are more persistent for the NMDA antagonist drugs

Epidemiology

- Indian data
  - 0.12% prevalence in past 12 months
  - 0.03% - harmful/dependent use
  - Maharashtra, Telangana, Kerela, Delhi more common

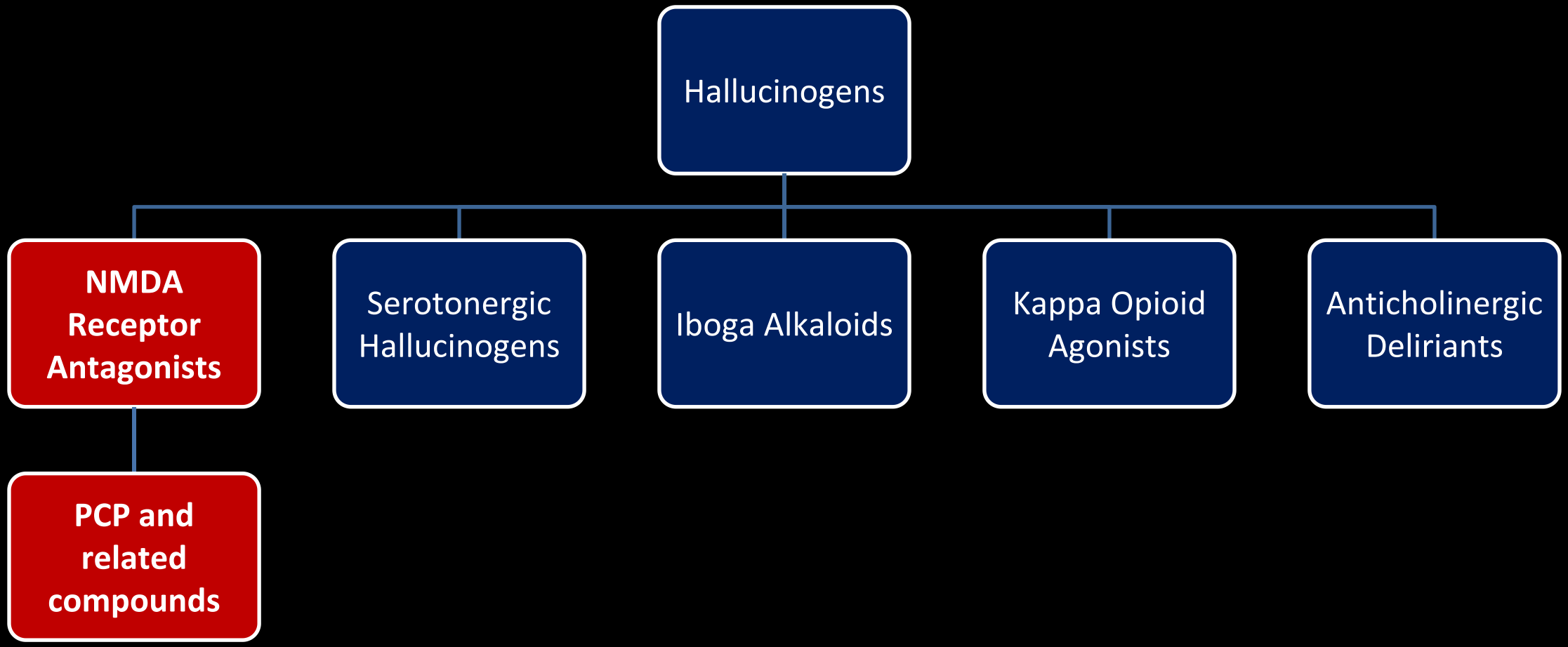
Classification



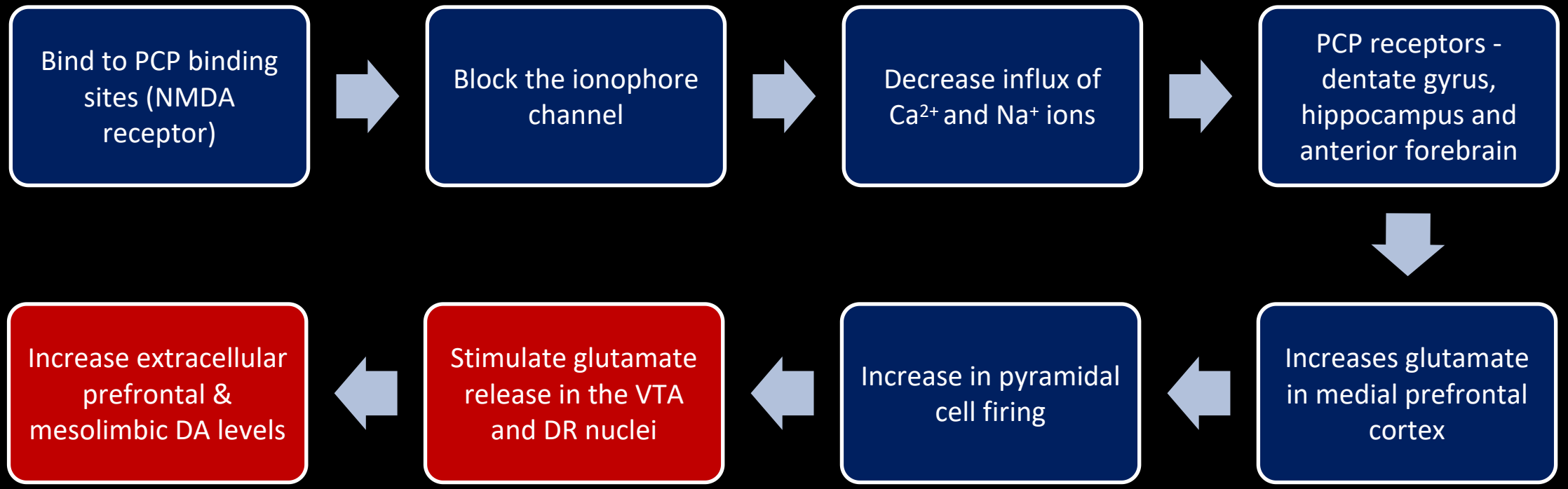
NMDA Receptor Antagonists

- PCP
- Ketamine
- Cyclohexamine
- Dizocilpine
- Dextromethorphan
- Nitrous oxide (inhalant)

Classification



Mechanism of Action



Mechanism

- DA - reinforcing effects, hyperactivity and stereotypic movements
- High doses - PCP blocks monoamine transporters, not ketamine- greater stimulation and reward with PCP
- Even higher doses - PCP blocks Na^+ and K^+ channels - seizures

Effects

- Reinforcing (animal models)
- Compulsive use (humans); lower the threshold for brain self-stimulation reward
- aka dissociatives/dissociative anesthetics - subjective mind body separation
- Hallucinogen effects (visual/true), sensory changes, altered thought process, labile/inappropriate affect, anxiety & paranoia
- Intoxication with PCP - unpredictable violent behaviour, nystagmus, ataxia, HTN, tachycardia & muscular rigidity.

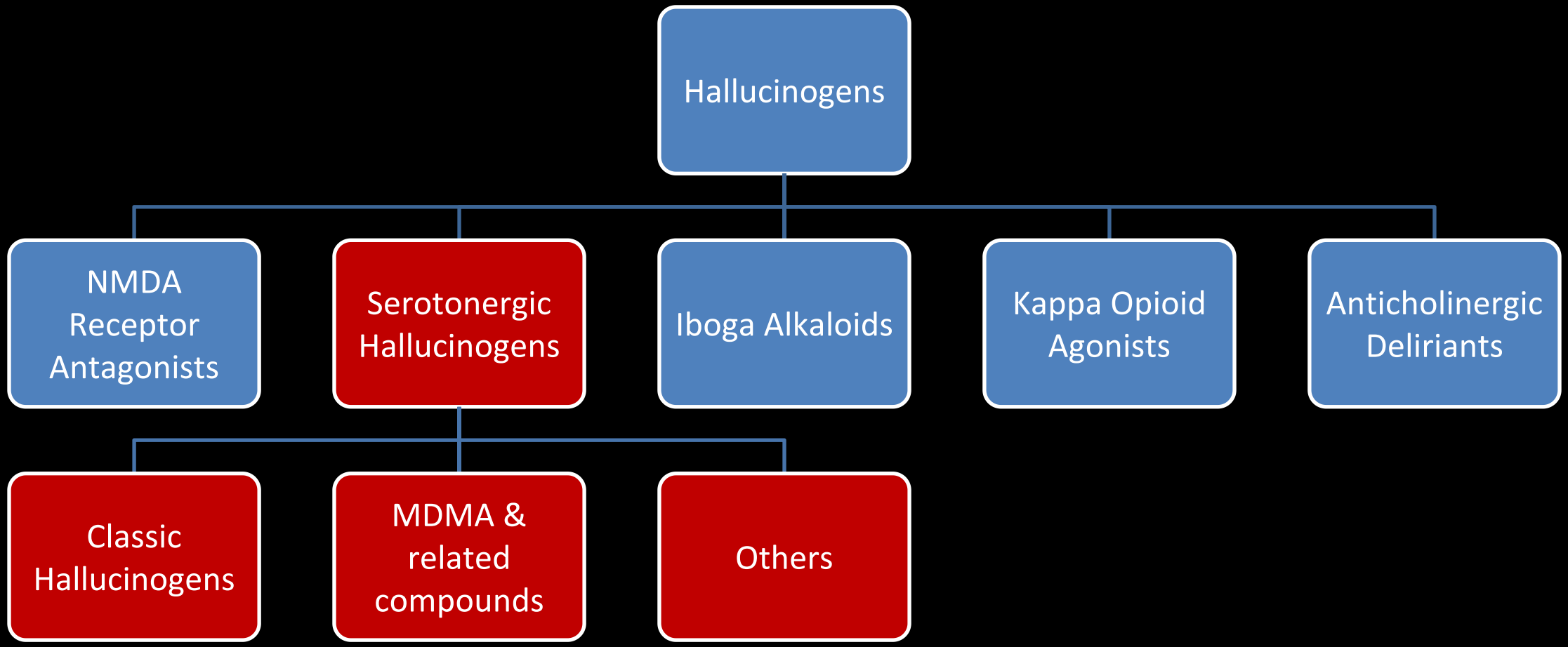
Pharmacokinetics

- Duration of effects - drug, dose and route
- PCP- sniffed/snorted. Street dose- 5 mg
- Ketamine- ingeted/snorted/injected. Street dose- 200-300mg
- $T_{1/2}$ of PCP - 20 hours (variable), lipid soluble; accumulates in fat
- $T_{1/2}$ of Ketamine - 2 hours.
- Metabolism - hepatic
- Withdrawal (primates) - vocalizations, bruxism, oculomotor hyperactivity, diarrhea, piloerection, somnolence, tremor & seizures

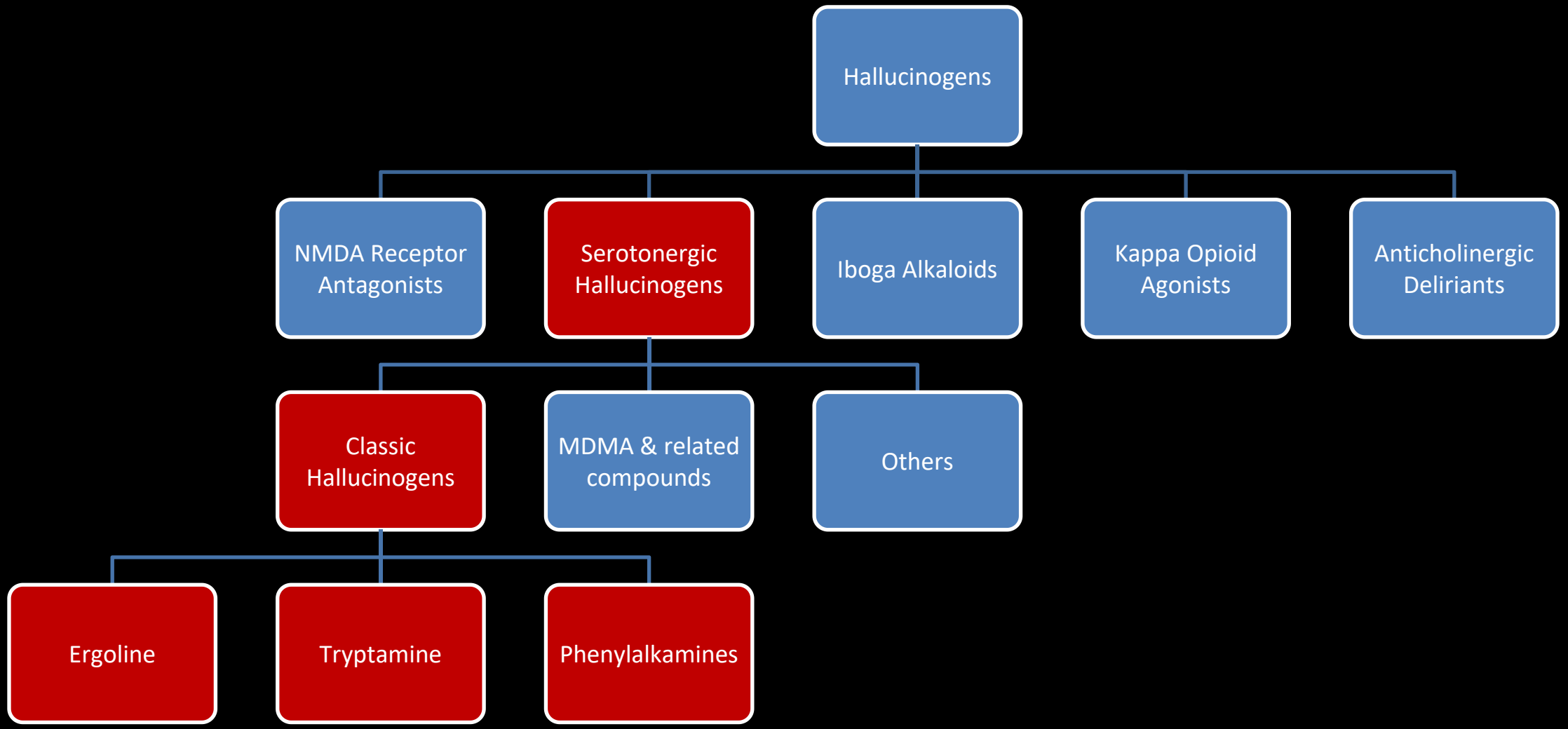
NMDA Receptor Antagonist Model of Psychosis

- 1959- PCP intoxication model
- Ketamine studies- negative and cognitive symptoms similar to SCZ even more than positive symptoms
- Inhibits prepulse inhibition
- Olney and Farber model of glutamate exitotoxicity.

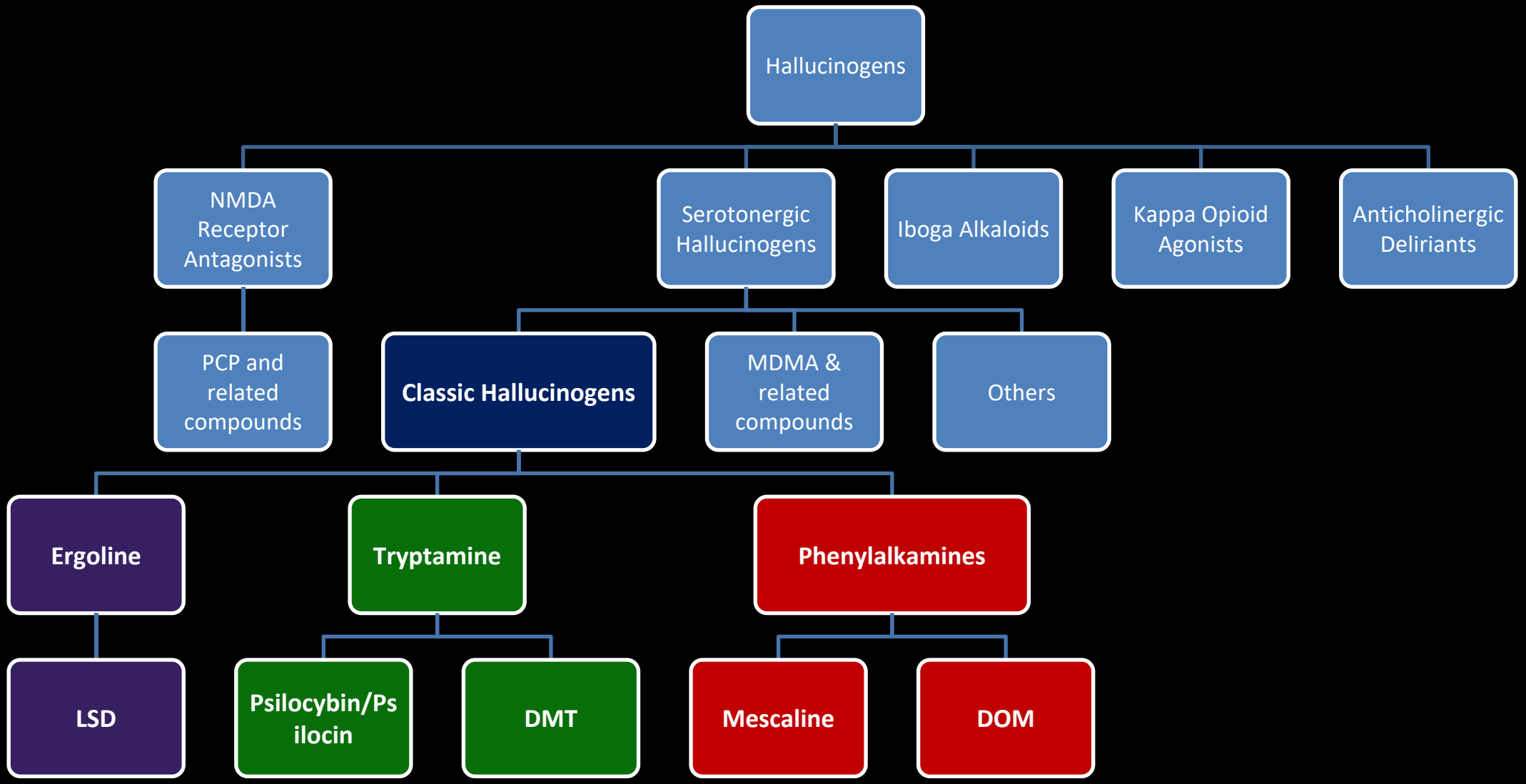
Seretonergic hallucinogens



Seretonergic hallucinogens



Seretonergic hallucinogens



Serotonergic Hallucinogens

- Naturally occurring or synthetic

1. Classic Hallucinogens – agonist/partial agonist at 5-HT_{2A} receptor
2. Psychotic-like symptoms
3. Evidence of seretonergic involvement in SCZ

Effects

- Similar effects, differ in time course, potency, mode of use
- Psychological effects: mental state, preparation & intention of user, drug and dose taken, environment (personal ,archetypal or spiritual themes)
- Somatic effects: chills, tremor, unsteadiness, nausea with(out) vomiting, xerostomia, paresthesias, blurred vision, PR & BP elevated, anorexia
- Sensory effects: alteration in perception of shape, size, and color, time and the illusion of movement; eyes closed - vivid imagery, synesthesia, true hallucinations uncommon
- Affect : changes rapidly & frequently; Anxiety and catharsis, bliss/joy/peace
- Depersonalization, derealization, and paranoia

Ergoline (LSD)

- Indole structure within a complicated 4-ring molecule.
- High potency
- Dose currently used- 25mcg to 50 mcg. Decline in adverse effects
- LSD - tablets, liquid, powder, gelatin squares, and “blotter acid”,sugar cubes, chocolates
- Onset <60 minutes, peak @ 3-4 hours, total duration of action 8-10 hours.

Ergoline (LSD)

- Higher doses - more intense symptoms and signs
- Death by LSD toxicity - unknown
- Rapid psychological tolerance to LSD, resolves within a week of abstinence
- Cross-tolerance b/w mescaline, psilocybin, and LSD occurs

Tryptamines

- Structurally resembles serotonin
- Psilocybin/psilocin and DMT

- Psilocybin
  - Mushrooms
  - Intermediate potency
  - Shorter duration of action (4 to 6 hrs)
  - Mild to moderate headache upto 24 hrs of use
  - Ooty in India

n,n –dimethyltryptamine (DMT)

- Orally inactive d/t rapid metabolism by MAO-A
- Route- parenteral/sniffing
- 25 mg - instantaneous, intense 20-minute hallucinogenic episode
- Loss of reality sense, intense visual experiences, terrifying, overwhelming, otherwordly
- Tolerance unremarkable
- Ayahuasca- MAOIs (harmala alkaloids) + DMT (leaves of Psychotria viridi)- shamanic rituals- 4 hrs effect- purging

Phenylalkylamines

- Mescaline & DOM (STP)
- Structurally similar to amphetamine
- Mediated by activity at 5-HT_{2A} receptor

- 2,5-dimethoxy-4-methylamphetamine
  - Synthetic analog of Mescaline
  - Potent amphetamine with hallucinogen properties
  - Popular for a brief period in the 1960s
  - Appears to have disappeared from the illicit market

Mescaline

- Least potent; active hallucinogenic alkaloid in Peyote and San Pedro cactii (peyote buttons)
- 1st structurally characterized hallucinogen (1919)
- Sacramental and ritual use- mexicans and native americans
- Cactus consumption a/w more nausea and vomiting; bitter taste
- Slow onset, longer duration of action (10-12 hours)
- Low potency- lower safety index
- Dose > 500mg : Autonomic hyperstimulation

Equivalent Dose

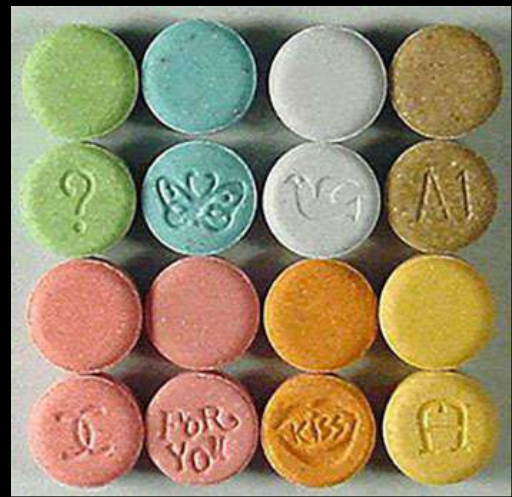
1.5 µg/kg dose of LSD

225 µg/kg of Psilocybin

5 mg/kg of Mescaline

MDMA and related compounds

- Structurally similar to mescaline and DOM
- Mechanism- presynaptic induction of serotonin release, 5-HT2A stimulation, reuptake inhibitor
- Effects :
  - Feelings of closeness and love, acceptance toward others with little alteration in sense perception/thought process
  - Stimulant, increased tolerence to painful negative emotions- psychotherapy adjunct in PTSD
- Self inhibiting metabolism- overdose risk
- Greater potential for compulsive use



MDMA and related compounds

- Somatic effects - increase in BP, PR and temp.
- A/E - Trismus and bruxism
- High doses - muscle stiffness & rhabdomyolysis
- Overdose - seizures and cardiorespiratory collapse
- Psychological effects- positive emotional tone, closeness, empathy and euphoria; strong releases of negative emotion, anxiety and paranoia can occur uncommonly

Other Serotonergic Hallucinogens

- Newer hallucinogens with novel structures with strong LSD-like effects but greater toxicity
- Bromo-DragonFLY: agonist at 5-$HT_{2A, 2B, and 2C}$ receptors; active in doses <1 mg, effects last for several days.
- 25I-NBOMe: agonist at 5-HT_{2A} receptor; active in doses of <1 mg.
- 2C-B- combine aspects of classic hallucinogen effects and entactogen effects.
- More toxic, caused fatalities d/t overdose (high potency)

Iboga Alkaloids (Ibogaine)

- Ibogaine -root of the tabernanthe iboga
- Medicinal and spiritual use in west africa
- Hallucinogen at ~ 400-1500 mg dose
- Intense and unpleasant hallucinogenic experiences ~ 2-3 days
- Action- 5HT2 and 5HT3 receptors, inhibits the serotonin transporter, NMDA, mu, kappa and sigma opioid, and muscarinic and nicotinic cholinergic receptors.
- Antiaddictive properties- heroin dependence treatment
- Cardiotoxic

Kappa Opioid Agonists (Salvia divinorum)

- Salvia (sage plant) leaves used traditionally in Mexico tribe
- Active component - Salvinorin A - extremely potent hallucinogen (4.5 µg/kg when smoked)
- Similar effects and duration to smoked DMT, binds to the opioid kappa receptor
- Effects: classic hallucinogens + dissociative effects + impaired recall
- No physiological effects
- Risk- damaging experiences, self-harm or violence under intoxication

Anticholinergic Deliriants

- Nightshade family plants- shamanic and witchcraft practice
- DSM-5: jimsonweed – “ethnobotanical hallucinogen”
- Jimsonweed, henbane, and belladonna – used for hallucinogenic properties
- Contain atropine and scopolamine

Anticholinergic Deliriants

- High dose synthetic - benztropine and diphenhydramine - similar effects
- Anticholinergic effects - dry mouth, mydriasis, blurred vision, increased HR, decreased sweating, hyperthermia, seizures, and occasionally, death.
- True hallucinations and delirium (disorientation, agitation, grossly impaired cognition and memory, and fluctuating mental status)

Hallucinogen-induced Psychiatric Disorders

Phencyclidine and Other Hallucinogen Intoxication

Phencyclidine Intoxication

Diagnostic Criteria

A. Recent use of phencyclidine (or a pharmacologically similar substance).
B. Clinically significant problematic behavioral changes (e.g., belligerence, assaultiveness, impulsiveness, unpredictability, psychomotor agitation, impaired judgment) that developed during, or shortly after, phencyclidine use.
C. Within 1 hour, two (or more) of the following signs or symptoms:

   Note: When the drug is smoked, "snorted," or used intravenously, the onset may be particularly rapid.

   1. Vertical or horizontal nystagmus.
   2. Hypertension or tachycardia.
   3. Numbness or diminished responsiveness to pain.
   4. Ataxia.
   5. Dysarthria.
   6. Muscle rigidity.
   7. Seizures or coma.
   8. Hyperacusis.

D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance.

Other Hallucinogen Intoxication

Diagnostic Criteria

A. Recent use of a hallucinogen (other than phencyclidine).
B. Clinically significant problematic behavioral or psychological changes (e.g., marked anxiety or depression, ideas of reference, fear of "losing one's mind," paranoid ideation, impaired judgment) that developed during, or shortly after, hallucinogen use.
C. Perceptual changes occurring in a state of full wakefulness and alertness (e.g., subjective intensification of perceptions, depersonalization, derealization, illusions, hallucinations, synesthesias) that developed during, or shortly after, hallucinogen use.
D. Two (or more) of the following signs developing during, or shortly after, hallucinogen use:

   1. Pupillary dilation.
   2. Tachycardia.
   3. Sweating.
   4. Palpitations.
   5. Blurring of vision.
   6. Tremors.
   7. Incoordination.

E. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance.

Clinical Features

- acutely altered mental status and behavioral changes following ingestion of a drug.
- Common - Acute anxiety, agitation, inappropriate/labile affect, visual illusions and hallucinogens, and paranoia or other delusions
- Characteristics features vary by class

PCP and related intoxication

- Somatic symptoms
- Behavioral disinhibition, agitation, panic, rage, aggression, and exaggerated reactions to environmental stimuli, delirium, frank hallucinations and delusions
- Hyperexcitability, hypertension, hyperthermia
- Hypertensive crisis - cerebral hemorrhage, Respiratory arrest, coma, and death
- Ketamine intoxication - less malignant presentation; medical complications are less common- tachycardia, anxiety and HTN

Classical Hallucinogens

- Mild physiological effects- Marked mydriasis ,Mild-to-moderate elevation in BP and PR
- Fully oriented less likely to be confused or show severe cognitive, verbal, or motor impairment
- Anxiety & panic; “losing their minds.”
- Other seretonergic hallucinogens- HTN, tachycardia, seizures, hyperpyrexia, elevated creatine kinase, vasoconstriction (tissue necrosis) and deaths
- Ibogaine- Resembles classic hallucinogen intoxication but greater degree of dissociation and confusion similar to PCP

MDMA

- Does not usually cause thought disorder, paranoia, disorganized behavior, or aggression
- Serotonin syndrome- hyperthermia, rigidity, hyperreflexia, seizures, rhabdomyolysis, renal failure
- High doses – hallucinogen-like effects
- Delirium may be present

Salvia and Anticholinergics

- Similar to PCP intoxication
- Salvia intoxication unlikely to be seen in clinical setting due to short action duration
- Anticholinergics – true hallucinations as part of delirium

Pathology and Laboratory Examination

- Urine toxicology – PCP and MDMA
- Screen for other drugs
- Serum/urine/gastric samples - specific mass spectrographic analysis
- Palm test

Differential Diagnosis

- Psychosis
- Delirium
- Stimulant intoxication
- Sedative and alcohol withdrawal
- History, toxicology screening to rule out and differentiate
- Observation- more than 12 hrs, consider other causes
- Nystagmus (especially rotary), ataxia, and hypertension is relatively specific for PCP intoxication.

Course and Prognosis

- Uncomplicated hallucinogen intoxication resolves spontaneously (<12 hours) except DOM and ibogaine
- Complete recovery from PCP intoxication within 24-72hrs
- Hallucinogen-induced disorders after intoxication uncommonly seen

Treatment

- Largely supportive, monitor mental status
- Reassurance and calm safe environment, Minimal sensory input
- Activated charcoal- PCP and MDMA
- BZDs - Agitation, seizures, and HTN
- Antipsychotics – mild intoxication, use with caution, can worsen symptoms
- PCM – Hyperthermia, cooling measures
- IV fluids and diuretics – rhabdomyolysis
- MDMA-May require ICU admission for cardiac monitoring and monitoring of vital signs

Phencyclidine Use Disorder and Other Hallucinogen Use Disorder

- The DSM-5 and ICD-10 criteria for PCP use disorder and other hallucinogen use disorder are identical to those for all other classes of substances, with the exception that the criterion for withdrawal does not apply
- Lifetime prevalence: 0.6-1.7%
- 5% users develop dependence
- 7.8% of adult current users & 17% of adolescent current users = hallucinogen use disorder

Phencyclidine Use Disorder and Other Hallucinogen Use Disorder

- Reward mechanism doesn’t play role except in PCP and possibly MDMA
- No withdrawal syndrome recognized
- Low frequency of use, fewer adverse consequences and no loss of control.
- Effects- neurotoxicity- MDMA and PCP
- Investigation- Urine, blood or hair analysis ,PCP - urine (up to 8 days)

Phencyclidine Use Disorder and Other Hallucinogen Use Disorder

- Differentiate from other substance use
- Short duration, self limiting course
- Incidence rate near zero over the age of 50
- No specific treatment (psychosocial)

Hallucinogen Persisting Perception Disorder

Hallucinogen Persisting Perception Disorder

Diagnostic Criteria **292.89 (F16.983)**

A. Following cessation of use of a hallucinogen, the reexperiencing of one or more of the perceptual symptoms that were experienced while intoxicated with the hallucinogen (e.g., geometric hallucinations, false perceptions of movement in the peripheral visual fields, flashes of color, intensified colors, trails of images of moving objects, positive afterimages, halos around objects, macropsia and micropsia).

B. The symptoms in Criterion A cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The symptoms are not attributable to another medical condition (e.g., anatomical lesions and infections of the brain, visual epilepsies) and are not better explained by another mental disorder (e.g., delirium, major neurocognitive disorder, schizophrenia) or hypnopompic hallucinations.

HPPD

- Rare condition of Re-experience perceptual effects, causing distress or impairments in functioning
- More common in males
- Spontaneous/triggered by stress, anxiety, exercise or other drug
- Episodic/constant
- Visual illusions and hallucinations common
- Depersonalization and derealization symptoms
- Auditory and other sensory distortions
- D/D – flasback, visual epilepsy, migraine, delirium, dementia, schizophrenia, hypnopompic hallucinations, PTSDs and other hallucinogen-induced disorders.

Course & Prognosis and Treatment

- 50% patients symptoms resolve within 5 years.
- Persist for decades in some cases
- Worsened by stimulant drugs, marijuana, fatigue, exercise, and infections
- Supportive psychotherapy and CBT
- Drugs effective: BZDs, Phenytoin, Clonidine, Naltrexone

PCP and other Hallucinogen-induced Psychotic Disorders

- DSM-5: syndrome meeting criteria for a psychotic episode that
  - has its onset during or shortly following use of a hallucinogen
  - persists beyond the usual period of action of the drug
  - is not better accounted for by another psychotic disorder or other psychiatric, neurological, or medical disorder
- Sufficiently severe to cause significant impairment and/or distress

Diagnosis and Clinical Features

- PCP-induced psychosis resembles schizophrenia
- Other hallucinogens: Younger age at onset, visual hallucinations, more depression, family history of mood disorder
- More mood swings, euphoria, grandiosity, hyperreligiosity, and multimodal hallucinations, and positive symptoms
- If mood symptoms more prominent, consider hallucinogen-induced mood disorder.

Pathology and Laboratory Examination, Differential Diagnosis

- Urine drug screens to confirm recent ingestion of hallucinogens (for PCP and MDMA)
- D/D – Schizophrenia and other primary psychotic disorders
- Hallucinogen-induced intoxication
- Consider primary psychotic disorder if symptoms persist beyond 4-8 weeks

Course and Prognosis and treatment

- Highly variable
- Intoxication - resolving rapidly completely
- Symptoms persist for weeks, despite aggressive treatment
- PCPs – antipsychotics and BZDs
- Other hallucinogens - antipsychotic medications, lithium, anticonvulsants, ECT, benzodiazepines, and antidepressants
- Controlled trials are lacking

Phencyclidine and other Hallucinogen-Induced Bipolar Disorder

- Manic, hypomanic, or mixed episode during/soon after hallucinogen intoxication
- Mood symptoms common, usually transient and fluctuating
- Atypical antipsychotics, BZDs, and mood stabilizers
- Resolves within days to weeks on stopping
- Consider primary BPAD if symptoms beyond 4-8 weeks

Phencyclidine and other Hallucinogen-induced Depressive Disorder

- Depressive episode during/soon after hallucinogen intoxication.
- aka bad trips; usually resolve with acute effects of the drug
- Evaluation and management of suicide risk
- May exacerbate a pre-existing mood disorder; unlikely as PCP and Ketamine have antidepressant activity

Phencyclidine and other Hallucinogen-Induced Anxiety Disorders

- Anxiety episode during/soon after hallucinogen intoxication.
- Clinically significant anxiety common during intoxication with Salvia and many of the classic hallucinogens.
- Full-blown panic attacks can occur.
- Self-limiting, but distressing
- Reassurance, calm and safe environment
- Oral/parenteral BZDs

Phencyclidine and other Hallucinogen-Induced Intoxication Delirium

- Disturbances in attention and cognition
- Diagnosis depends on severity of the neurocognitive symptoms.
- Uncommon, may occur in severe intoxication (Except MDMA and
- Conservative management
- Activate charcoal
- Anticholinergic delirium - supportive care and BZDs.
- Avoid antipsychotics and physostigmine

Summary

- Hallucinogen use is mainly for recreational/spiritual purposes
- Cheaper, easily available
- Use is on the rise, reversal of decline
- Lack of epidemiological studies – fewer cases reported
- Newer drugs pose a challenge in the diagnosis and treatment
- Conservative management
- Therapeutic use research- alcoholism, existential distress, mood and anxiety disorders, PTSD, ASD

References

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Thank you