Cocaine Related Disorders

Outline

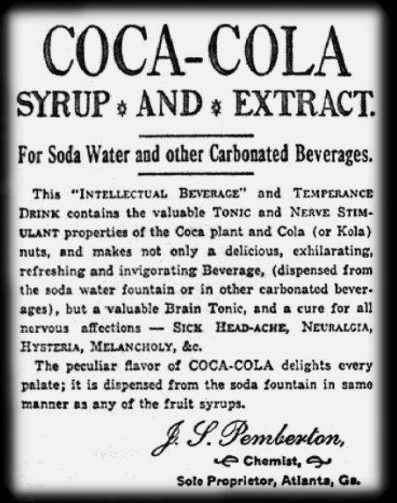
- Introduction & history
- Epidemiology
- Comorbidities
- Etiology
- Routes of administration
- Nosology and disorders
- Adverse effects
- Management

Introduction

- Cocaine - naturally occurring alkaloid found within the leaves of coca plant *Erythroxylon coca* and *E. novogranatense*

History

- High mountain ranges of South America ~1500 yrs.
- Spanish invaders initially prohibited, then controlled distribution to rule locals – brought back to Europe
- 1855 – Friedrich Gaedecke extracted active constituent
- 1859 – Albert Niemann coined the term “Cocaine”
- 1880 – local anaesthetic
- 1884 – Freud – study on pharmacological effects
- Medical tonics, soft drinks – exaggerated, patently false claims
- Cocaine addiction, linked with crime



History

- 1910 – US President William Taft – cocaine – national threat
- 1914 - Harrison Narcotic Act – nonmedical use of cocaine banned; “underground” use until the 1970s
- 1970s – increased use; “soft” drug, curiosity
- 1980s – increased production, lower price – epidemic – 9x increase in medical emergencies; 11x increase in deaths
- Mid-1980s – “crack” – cheap, ready-to-smoke
- 1985 – 5.7 million active users (3%)
- 1986-87 – 20% fall; 1992 – 66% fall
- Change in glamourous position (addiction, overdose deaths, crime)

Epidemiology

- Lifetime cocaine use (US, 2013) – 37 million (1.5M last month; 4.7M last yr.); 18-25 yr. old (2x)
- New users in 2013 – 601,000
- Prevalence – 1.5M (2003) to 855,00 (2013)
- Average age of onset – 20.4 years
- M:F = 2:1
- Ranks 4th (14%) after alcohol (21%), marijuana (17.5%) and heroin (16.3%) in SUD admissions
- India - Cocaine (0.10%)

Comorbidities

- Epidemiological Catchment Area Study:
  - lifetime prevalence rate of non-substance related mental disorder – 76% (11x)
  - Alcohol abuse/dependence – 85%
- Higher rates of major depression and ADHD in treatment seeking pts

Psychiatric Diagnosis	Current Disorder	Lifetime Disorder
Major depression	4.7	30.5
Cyclothymia/hyperthymia	19.9	19.9
Mania	0.0	3.7
Hypomania	2.0	7.4
Panic disorder	0.3	1.7
Generalized anxiety disorder	3.7	7.0
Phobia	11.7	13.4
Schizophrenia	0.0	0.3
Schizoaffective disorder	0.3	1.0
Alcoholism	28.9	61.7
Antisocial personality disorder	32.9	32.9
Attention-deficit disorder		34.9

(Adapted from Rounsaville BJ, Anton SI, Caroll K, et al. Psychiatric diagnoses of treatment-seeking cocaine abusers. *Arch Gen Psychiatry.* 1991;48:43.)

Etiology

1. Genetic
2. Sociocultural
3. Learning and conditioning
4. Neuropharmacology

Genetic Factors

- Monozygotic twins – higher concordance rates than dizygotic twins
- Equal contribution of genetic factors and unique, unshared environmental factors
- Genes implicated:
  - dopamine-β-hydroxylase
  - dopamine transporter
  - D2 dopamine receptor

Sociocultural

- Important for initial use, continuation and relapse
- Excessive use in countries where cocaine is readily available
- Different economic opportunities influence certain groups

Learning & Conditioning

- Reinforcers (“rush”)
- Environmental cues become associated with euphoric state - can precipitate craving & withdrawal
- Stimuli activate brain regions for episodic and working memory (EEG arousal)
- Increased metabolic activity- amygdala, parahippocampal gyrus, dorsolateral prefrontal cortex - correlates with craving

Neuropharmacology

- Competitive inhibitor of dopamine reuptake by dopamine transporter
- Increases dopamine in synaptic cleft; activation of D1 and D2 Rs
- Blocks reuptake of NE and serotonin
- Decreased cerebral blood flow and glucose use
- Behavioural effects lasts for 30-60 mins; requires repeated dose
- Highly potent positive reinforcer of behaviour – psychological dependence
- Tolerance, sensitivity and physiological dependence

Neuropharmacology

- PET scans during craving – high activation of the mesolimbic dopamine system
- D2 Rs mesolimbic dopamine system – increased activity during craving
- PET – drop in neuronal activity with a decreased ability to receive dopamine over 18 months after withdrawal
- Chronic use - metabolic dysfunction in frontal and orbitofrontal cortex

Pharmacodynamics

- Smoking + IV use – most rapid pharmacological & subjective onset of action & termination
- Cocaine-induced euphoria – a/w rate of increase in serum level
- Half life – 50-90 minutes
- Rapidly metabolized by liver and serum esterases to benzoylecgonine and ecgonine methyl ester; no biological activity
- Cocaine + alcohol – ethyl cocaine (cocaethylene) - cocaine-like pharmacologic and subjective effects, longer half-life, more toxic
- 1-5% excreted unchanged in urine, rest metabolites
- Urinary benzoylecgonine – 2-3 days

Routes of Administration

- Oral/injection/absorption via nasal and buccal membranes/inhalation
- Cocaine hydrochloride - water-soluble form (snorting/injection)
- “Freebase” cocaine inhalation – immediate absorption and rapid onset
- Cocaine + sodium bicarbonate = “crack” (freebase + impurities)




Routes of Administration

- Smoking of intermediate product, cocaine sulphate (coca paste, pasta basica, basuca) – contaminated with solvents
- Addition of sedatives/opioids to modulate the stimulant and toxic effects
- IV heroin + cocaine = speedball (euphorigenic)
- Cocaine + alcohol – modulate “cocaine high” and “dysphoria”




ICD-10

- F14 - Mental and behavioural disorders due to use of cocaine
- F1x.0 Acute intoxication
  - .00 Uncomplicated
  - .01 With trauma or other bodily injury
  - .02 With other medical complications
  - .03 With delirium
  - .04 With perceptual distortions
  - .05 With coma
  - .06 With convulsions
  - .07 Pathological intoxication
- F1x.1 Harmful use
- F1x.2 Dependence syndrome
  - .20 Currently abstinent
  - .21 Currently abstinent, but in a protected environment

ICD-10

- F1x.3 Withdrawal state
  - .30 Uncomplicated
  - .31 With convulsions
- F1x.4 Withdrawal state with delirium
  - .40 Without convulsions
  - .41 With convulsions
- F1x.5 Psychotic disorder
  - .50 Schizophrenia-like
  - .51 Predominantly delusional
  - .52 Predominantly hallucinatory
  - .53 Predominantly polymorphic
  - .54 Predominantly depressive symptoms
  - .55 Predominantly manic symptoms
  - .56 Mixed

ICD-11

- **6C45.0** Episode of harmful use
- **6C45.1** Harmful pattern
  - **6C45.10** Episodic
  - **6C45.11** Continuous
  - **6C45.1Z** Unspecified
- **6C45.2**Cocaine dependence
  - **6C45.20** Current use
  - **6C45.21** Early full remission
  - **6C45.22** Sustained partial remission
  - **6C45.23** Sustained full remission
  - **6C45.2Z** Unspecified

Associated with:

- **6C45.3** Intoxication

DSM-5

- Stimulant Use Disorder
- Stimulant intoxication
- Stimulant withdrawal
- Stimulant-induced psychotic disorder
- Stimulant-induced bipolar disorder
- Stimulant-induced depressive disorder
- Stimulant-induced anxiety disorder
- Stimulant-induced obsessive-compulsive disorder
- Stimulant-induced sleep disorder
- Stimulant-induced sexual dysfunction

Cocaine Use Disorder

1. Large quantity/longer duration
2. Desire/unable to cut down
3. Time spent
4. Craving
5. Difficulty at work/school/home
6. Social/IPR conflicts
7. SOF impairment
8. Usage in hazardous conditions
9. Ignoring harmful effects
10. Tolerance

≥ 2 within 12 months

Severity

- Mild: 2-3 Sx;
- Moderate: 4-5 Sx;
- Severe: ≥ 6 Sx

Remission:

- Early (3-12 mths)
- Sustained (≥ 12 mths)

Cocaine Intoxication

A. Recent use
B. Behavioural/psychological changes
C. ≥ 2 after use:
    1. Tachy/Bradycardia
    2. Pupillary dilatation
    3. BP changes
    4. Chills/perspiration
    5. Nausea/vomiting
    6. Weight loss
    7. PMA agitation/retardation
    8. Muscular weakness, respiratory depression, chest pain,

Cocaine Withdrawal

A. Cessation/reduction in cocaine use
B. Dysphoric mood + ≥ 2:
    1. Fatigue
    2. Unpleasant dreams
    3. Insomnia/hypersomnia
    4. Increased appetite
    5. PMA increased/decreased
C. SOF impairment
D. Not attributable to other causes

Cocaine Withdrawal

Phases:

1. Crash – depression, anhedonia, irritability, sleep disturbances
2. Intense craving, anxiety, agitation, suicidal ideation
3. Varying levels of agitation, anxiety, alternating anorexia and hyperphagia, fatigue, and anhedonia over next 4-6 weeks

Cocaine-induced Psychotic Disorder

- Brief paranoia common (50-70%)
- Diagnosis reserved for cases where symptoms exceed the quality or severity characteristic of cocaine intoxication
- Longer duration/larger quantities/routes of administration
- ADHD pts. at increased risk
- Genetic predisposition
- Tactile hallucinations (cocaine bugs/formication/Magnan syndrome) – a/w excoriation of skin
- Inappropriate sexual behaviour, homicidal tendencies

Cocaine Intoxication Delirium

- Higher doses
- Shorter time
- Cocaine + other substances (opiates, amphetamines, alcohol)
- Pre-existing brain damage

Other cocaine-induced disorder

- Cocaine-induced psychotic disorder
- Cocaine-induced bipolar disorder
- Cocaine-induced depressive disorder
- Cocaine-induced anxiety disorder
- Cocaine-induced obsessive-compulsive disorder
- Cocaine-induced sleep disorder
- Cocaine-induced sexual dysfunction
- Cocaine intoxication delirium

Diagnosed only when symptoms sufficiently severe to warrant independent clinical attention

Medical Complications

Direct toxic effects:

- CVS – Hypertension, angina pectoris, MI, arrhythmias
- CNS – Cerebrovascular haemorrhage, seizures (3-8%), acute dystonia, tics, migraine-like headache
- Respiratory – Respiratory depression, pneumothorax, acute lung injury, pulmonary edema

Medical Complications

Direct toxic effects:

- Other – Hyperpyrexia, Loss of libido, affects reproductive function, gynaecomastia (males), galactorrhoea, amenorrhoea, infertility (females)
- Cocaine use in pregnancy – “crack babies” (congenital malformations in foetus and perinatal cardiovascular and cerebrovascular disease in mother)

Medical Complications

Complication related to route of administration:

- Infections – HIV, hepatitis B & C, endocarditis, cellulitis
- Nasal – Mucosal congestion/ulceration, perforated nasal septum
- Others – Burns, lung injury

Laboratory Investigations

- Metabolites detected in blood (acute), urine (relapse), hair, sweat, saliva
- May be detectable for up to 2 weeks
- CT/MRI/ECG/cardiac enzymes/CXR/blood cultures

Treatment

Detoxification:

- OPD setting – withdrawal rarely requires specific intervention
- Withdrawal Sx – uneventful recovery within 1-2 weeks
- Social, psychological and biological strategies (cocaine & -ve reinforcement)
- Hospitalization to remove from social settings
- Frequent urine testing to monitor abstinence
- Relapse prevention therapy - CBT

Treatment

Psychosocial Therapies:

- Involves individual, group and family modalities
- Contingency management and CBT
- Individual: dynamics leading to use, perceived +ve effects, alternate methods
- Group: Narcotics Anonymous – share strategies
- Family: F/M responses to pt's past harmful behaviour, changes to make pt stay off drug

Treatment

Network Therapy:

- Office-based treatment
- Individual + group therapy (family & peers)
- Psychodynamic + CBT approaches
- Group used as a therapeutic network, joining pt and therapist at intervals – provides cohesiveness and support, promote compliance

Treatment

Pharmacological measures

- No single drug for decreasing use and dependence and relapse
- DA agonists/antagonists ineffective
- 5-HT reuptake inhibitors ineffective
- Supportive care (short term BZD/anti-psychotics)
- (?) Dextroamphetamine, modafinil, desipramine (comorbid depression), disulfiram, topiramate
- Pre-existing ADHD/mood disorder: Methylphenidate, Lithium

Treatment

Immunotherapy:

- Therapeutic vaccine to induce antibodies to cocaine
- Reduce reinforcing effects of cocaine
- 2 genetic variations: low level expression of dopamine-beta-hydroxylase and polymorphism of OPRK1 kappa opioid Rs – a/w better response

Treatment

Others:

- Butyrylcholinesterase – selective hydrolysis of cocaine
- Vigabatrin – attenuates increase in DA in extracellular nucleus accumbens and drug seeking behaviour

Treatment

TABLE 14.2 Highlights of pharmacologic Rx for cocaine addiction

Therapeutic goal	Pharmacologic class (agents)	Comments/caveats
Reduce brain exposure to ingested cocaine ▪ Increase metabolism of cocaine ▪ Prevent passage across blood–brain barrier	▪ "Super" cholinesterases derived from bacterial species. ▪ Mutant human butyrylcholinesterases with increased activities. ▪ Immunotherapy(ies): passive (autocatalytic antibodies) and active immunization (norcocaine linked with cholera B toxin)	▪ Modified enzymes seem promising for emergency management of overdoses/ immunologic risks appear minimal. ▪ Immunotherapies show great promise because they have no abuse potential, but the immunologic response is variable and can be overcome by increased dosing; ethical concerns.
Agonist (replacement) therapies retain some aspects of cocaine's effects using drugs with reduced abuse potential or less toxicity	▪ Oral cocaine (tea, tablets) ▪ Available psychostimulants, DA and 5-HT augmenting agents (methylphenidate, dextroamphetamine, disulfiram, modafinil, levodopa, PLA287, ondansetron) ▪ DA selective and nonselective monoamine uptake inhibitors (RTI-336 and NS2359, bupropion)	▪ Reported beneficial effects in clinical trials have been highly variable, often contradictory; interpretation of results, confounded by impact on comorbid psychiatric and psychological issues ▪ Even in the case of drugs with apparently low abuse potential there is concern that DA augmenting agents may perpetuate or prevent extinction of reinforcement effects of cocaine
Relapse prevention ▪ Reduce perception of cocaine euphoria ▪ Relapse triggered by drug-associated environmental cues ▪ Relapse triggered by reintroduction of a "priming" dose of cocaine ▪ Relapse triggered by stressful conditions	Cannabinoid-1 (CB-1) receptor antagonists (rimonabant; AM 251) ▪ DA (D1) receptor agonists (dihydrexidine and benzazepine derivatives) ▪ DA (D2) antagonists (olanzapine, aripiprazole) ▪ DA (D3) receptor agonists (BP897) and antagonists (NGB2904) ▪ GABA receptor agonists (baclofen, topiramate) ▪ GABA uptake inhibitors and other GABA system modulators (tiagabine, vigabatrin) ▪ Glutamate antagonists, partial agonists and other GLU-modulators (JNJ 16567083, MTEP, disulfiram, N-acetyl cysteine) ▪ Kappa-opioid receptor agonists (dynorphin; U62066) ▪ Opiate-like receptor (ORL-1) agonists (nociceptin) ▪ CRF-1 receptor antagonists (CP154,526 and DMP695) ▪ Orexin receptor antagonists	▪ Available CB-1 receptor antagonists are promising but may have limited tolerability given widespread effects on mechanisms of pleasure perception (e.g., the anorexant rimonabant). ▪ D1 receptor agonists show promising preclinical results, but poor bioavailability, lack of receptor selectivity, and short t½ are significant challenges ▪ Antipsychotic class D2 antagonists have produced unconvincing benefits in clinical trials with instances of worsening reported ▪ D3 receptor modulators of great interest given selective expression of D3 in the limbic system. ▪ Several GABA system modulators have entered advanced clinical trials with results that are generally moderate and contradictory; these drugs may have additional benefits as anxiolytics. ▪ GLU receptor modulators are in early clinical testing; selectivity issues are a major challenge given the fact the GLU is the predominant excitatory neurotransmitter of the CNS ▪ Study of genetically determined differences in endogenous opioid receptors, components of the HPA axis, and other neuromodulatory peptides have been fertile sources of potential therapeutic intervention
Treat psychiatric comorbidity	▪ Antidepressants (SSRIs) ▪ Anxiolytics ▪ Psychostimulants for ADHD	▪ Pharmacologic treatment of comorbid psychiatric conditions undertaken with caution in early stages of recovery

Summary

- Strong stimulant
- 2nd most illegally used drug after cannabis
- Highly addictive with various adverse effects
- Acts by inhibiting reuptake of dopamine, serotonin and NE
- Mild withdrawal state
- Psychosocial therapies > pharmacological therapies

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Thank You