DRUG-INDUCED MOVEMENT DISORDERS

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Etiology of movement disorders

- Neurodegeneration
- Immune mediated
- Genetic factors
- Metabolic
- Toxic and drug induced
- Traumatic
- Vascular
- Infections
- Psychogenic

Drug induced movement disorders

- Parkinsonism
  - Subacute
  - Symmetrical
  - History of medications
  - Akinetic rigid
  - Tremor: atypical, postural
  - Accompanying oral-buccal dyskinesias or akathisia
- Dystonias, dyskinesias
- Chorea
- Akathisia
- Myoclonus
- Tics
- Tremor

DRUGS inducing movement disorders

- Neuroleptics
  - Butyrophenones (haloperidol, droperidol)
  - Phenotiazines (chlorpromazine, thioridazine etc)
  - Atypical neuroleptics (risperidone)
  - Benzamids (metoclopramide)
  - Dopamine depletors
    - Reserpine
    - Tetrabenazine
- Ca-channel blockers
  - Flunarizine
  - Anticonvulsants
    - Valproate
  - Antidepressants
    - Tricylic
    - SSRIs
  - Antihistamines
  - Antiarrhythmics
  - Lithium

Tardive dyskinesia

- In 15-30% of patients on long term antipsychotic treatment
- Classic tardive dyskinesia
  - Orofacial/bucco-lingual
  - Limbs, trunk
  - Rarely respiratory
  - Variants
    - Tardive tourettism
    - Tardive myoclonus
    - Tardive tremor
  - Higher risk in female; older age

Malignant neuroleptic syndrome

iatrogenic: dopamine receptor blockers/ antipsychotics; rarely – end of antiparkinsonian medication

Major criteria
- Hyperthermia
- Muscle rigidity
- Increase of creatine kinase (CK)

Confirmed diagnosis:
1) All 3 major criteria
2) 2 major and 4 minor criteria

Minor criteria
- Changes in mental status
  - Altered consciousness
  - Delirium, agitation
- Dysautonomia
  - Tachycardia
  - Unstable blood pressure
  - Tachynoea
  - Profuse sweating, salorrhoea
  - Leucocytosis

confirmed diagnosis 1985; DSM-5 Criteria 2013
Malignant neuroleptic syndrome

- Treatment: Dantrolen, Bromocriptine, benzodiazepines
- Rehydration, hypothermia
- Long term complications
  - Parkinsonism
  - Tardive dyskinesias – orobuccal, tongue
  - Dystonias
  - Cerebellar degeneration
  - Peripheral neuropathy
  - Contracts

Drug induced parkinsonism

- Etiology
  - Neuroleptic treatments in psychiatric patients on
  - Metoclopramide
  - Reserpine, tetrapenazine
  - Cinnarizine, flunarizine
  - Higher risk: older age; women
  - May worsen despite of withdrawal of the causing medication
  - Differentiating from PD
    - Non-motor symptoms – in PD more urinary symptoms, sleep disorders, hyposmia
    - SPECT normal in drug induced parkinsonism, abnormal in PD
  - 123I-MIBG scintigraphy normal in drug induced parkinsonism, abnormal in PD

Serotonin syndrome

- Caused by drugs enhancing serotonergic transmission
  - MAO inhibitors (MAO-B inhibitors very rarely)
  - Selective serotonin reuptake inhibitors (SSRI)
  - Tricyclic antidepressants
  - Opiates, amphetamines, MDMA (ecstasy), cocaine

- Core clinical features
  - Fever, tachycardia, hypertension, diarrhea
  - Myoclonus, opsoclonus, tremor, rigidity, seizures
  - Altered mental status, anxiety, agitation, delirium

Levodopa motor complications: Community-based and open studies

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Medication induced tremor

- Medication: | Tremor character
- Amantadine: | Clinically similar to essential tremor, 6–10 Hz action tremor
- Tricyclic, serotonin reuptake inhibitor, monoamine oxidase inhibitor: | Generalized action tremor, 8–11 Hz
- Tetrabenazine, Margaret: | Rest and action tremor, low amplitude and high frequency
- Citalopram: | Rest and action tremor
- Clonazepam: | Generalized action tremor, rarely cerebellar tremor, treatment with propranolol
- Valproic acid: | Postural and action tremor
- Valproate sodium: | Rest and postural tremor
- Lithium: | Rest postural tremor, irregular, not rhythmic tremor in arm/legs, treatment with primidone/bi-histidine
- Lorazepam: | Rest and postural tremor (d-7 Hz), tardive tremor as postural tremor 3–5 Hz, utterances
- Risperidone: | Low amplitude, high frequency tremor
- Phenobarbital: | High frequency, low amplitude postural tremor
- Baclofen: | Myoclonus, from 4–8 Hz to 12–15 Hz tremor

Drugs – analgesics and anesthetics

- MEPERIDINE (methadone)
  - Opioid for pain treatment
  - Rarely reported
  - Tardive, myoclonus, seizures
  - Agitation, hallucinations
  - A case of reversible parkinsonism described

- METHADONE
  - Synthetic opioid
  - Treatment of pain and opioid dependence
  - Causes rarely chorea or tremor

- PHENCYCLIDONE
  - Anesthetic, similar to ketamine
  - Eaten, snorted or injected in recreational purposes
  - Agitation, psychosis
  - Rigidity, dyskinesia, ataxia, akathisia, myoclonus

- 5-HYDROXYTRYPTIC ACID (5HT)
  - Used for treatment of narcolepsy and as a general anesthetic
  - Recreational drug
  - Overdose: myoclonus and seizures
  - Withdrawal: chorea and tremor
### ILLICIT DRUGS

<table>
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<th>Other</th>
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<td>Cocaine</td>
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<td>Methamphetamine (Meth)</td>
<td>Heroin / heroin pyrolysate</td>
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<td>Methylene-dioxy-methamphetamine (MDMA/ecstasy)</td>
<td>1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP)</td>
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<td>Cathinone (Khat)</td>
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<td>Methcathinone (Mcat)</td>
<td>γ-hydroxybutyric acid</td>
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<td>Mephedrone, methylene, ethylone, naphyrone, ...</td>
<td>Toluene</td>
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### Chemist’s Notebook Manual – receipts in Internet

- Methamphetamine – Crystal Meth, Speed
- Methcathinone – Cat, Jeff
- GHB – Liquid E, Date Rape Drug
- MDMA – Ecstasy, X
- Phencyclidine – PCP, Angel Dust
- Cocaine – Coke, Blow
- Opiates – Heroin, Codeine
- Marijuana – Weed, Bud
- Psilocybin – Shrooms, Caps
- Salvia Divinorum – Dream Herb, Salvia
- DMT & 5-MeO-DMT – Toad Venom
- Ketamine – Special K
- Dextrometorphane – DXM, Red Devil’s

### History: MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and parkinsonism

- Used in 1980ies in California intravenously as a new “synthetic heroin”
- By-product in the synthesis of MPPP
- Parkinsonism - during some months
- Similar to Parkinson’s disease:
  - Rigidity and hypokinesia
  - Gait disorder; speech disorder
  - Rarely tremor
  - Hallucinations often as initial signs
  - Levodopa treatment effective
  - Early dyskinesias and ‘on-off’ fluctuations

### Global Drug Survey

**Use of psychostimulants**

80 000 responses reported use during the past 12 months:
- 23.7% MDMA (“ecstasy”)
- 16.4% cocaine
- 11.7% amphetamine
- 7.5% “research chemicals and legal highs” (bath salts)

### Amphetamines

- Increase of dopamine, norepinephrine and serotonin release
- Amphetamine – synthesised in 1887 in Germany by Lazar Edeleanu; pharmacological use in 1929 by Gordon Alles
- Used for treatment of narcolepsy, attention deficit hyperactivity disorder, obesity, chronic fatigue
- Agitation, confusion, psychosis
- Levo- and dextroisomers

**High dosage – neurotoxic**
- Free radicals
- Excitotoxicity
- Apoptosis
- Mitochondrial dysfunction

**Neurodegeneration affecting basal ganglia**
- Neuronal loss
- Reduction of glial astrocytes
- Changes in microvasculature
Amphetamine and methamphetamine

- Increase of dopamine, norepinephrine and serotonin release
- Methamphetamine – synthesised from ephedrine in 1893
- Amphetamine – synthesised in 1887; pharmacological use from 1929 by Gordon Alles:
  - Narcolepsy, attention deficit hyperactivity disorder, obesity, fatigue
- Movement disorders may develop during abuse or abstinence
- Choreaathetosis, tremor, dystonia, araxia, gait disturbances
- Usually resolve within few days but may last longer
- Benzodiazepines or euroleptics may be of benefit

Metamphetamine/ Amphetamine and parkinsonism?

- Are chronic Meth/ Amph users at risk to develop parkinsonism?
- Do the changes reflect degenerative disorder, or are induced by the drug toxicity?
- - but
- Clinically, parkinsonism has not been described
- Reduction in DAT density is different from Parkinson disease – less extent in putamen
- - still
- Population-based cohort study in California (1990-2005): Meth/ Amph users have increased risk for PD but not cocaine users

Case

Ecstasy and parkinsonism?

- 38 years man
- Heavy use of ecstasy for 12 years
- Rapidly progressive parkinsonism
- Poor effect of medication and DBS
- 19 years man
- Used 6 month use of MDMA
- Tremor and parkinsonism
- Antiparkinsonian medication - poor effect

Methylphenidate (MPH, MPD)

- Psychostimulant used for the treatment of
  - Attention-deficit hyperactivity disorder (ADHD)
  - Narcolepsy
  - Postural orthostatic syndrome
  - Weight control
- Recreational drug
- May induce chorea, tics, dyskinesias
- British National Formulary (2011: p. 246)
  - Indications: ADHD, narcolepsy (adult and children)
  - Side-effects of MPH: tics, movement disorders

Methcathinone (Mcat) / ephedrine

- Used as antidepressant 1930-1940
- Amphetamine-like effect
- Abused as a ‘designer’ psychostimulant
  - Sudafed tablets (pseudoephedrine)
  - Boiling water
  - Potassium permanganate
  - Acetic acid
- 10-20 injections per day
- Estimated daily load of
  - manganese: 60-180 mg
  - Mcat: 400-1200 mg
**Mcat abusers and manganism**
- Clinical syndrome develops during months-years
  - Parkinsonism: bradykinesia
  - Limb and face dystonias
  - Dysarthria, hypophonia
  - Gait disorder, postural instability, falls
- Severity varies greatly
- Unresponsive to levodopa
- May worsen despite drug discontinuation

**Neurological complications of psychostimulants**

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<td>MDMA (Ecstasy)</td>
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<td>Methylenedioxane</td>
<td>Anxiety, hyperactivity, stereotypical movements</td>
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<td>Cathinone</td>
<td>Tremor; Memory disorder; depression, psychosis, insomnia</td>
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**Cocaine**
- Alkaloid coca-plant leaves – South American indigenous chewed
- Described in the 16th century; isolated 1855 by German chemist Friedrich Gaedcke
- Neuropathological investigation: α-synuclein levels in DA cells elevated
- ‘Crack dancing’ – smokable cocaine
- In chronic cocaine abuse
- Reversible choreoathetoid limb movements or akathisia
- Orofacial dyskinesias
- Rarely: neuroleptic malignant syndrome following to delirium

**Heroin**
- Intravenous heroin
  - Euphoria followed by dream-like state
  - Overdose
    - coma, respiration depression
    - brain anoxia, ischaemia
  - Borderzone infarction
    - Tremor, rigidity, myoclonus, dystonias, ballism, ataxia, cognitive impairment, oculogyric crises
  - MRI: gray matter lesion in basal ganglia
  - Section: bilateral cystic infarcts in gl. pallidum

**Heroin pyrolysate – ‘chasing the dragon’**
- Heroin pyrolysate ‘chasing the dragon’ – inhalation, heating the drug on metal foil
- Spongiform encephalopathy
  - Ataxia, dystonia, myoclonus, chorea
  - Apathy, confusion
  - Spastic paraparesis or tetraparesis
  - Pseudobulbar palsy
  - Late stages – parkinsonism
- Neuropathology
  - Spongiform degeneration of deep white matter
  - Vasculitis, loss of oligodendrocytes, axonal reduction, astrogliosis

**Plants with psychedelic effects**
- Peyote cactus (*Lophophora williamsii*)
  - Contains mescaline
  - Dyskinesia, chorea
- Angel trumpet flower (genus *Datura*)
  - Contains tropane alcaloids
  - Blurred vision, speech disorder, hallucinations
  - Chorea, ballism, ataxia, seizures
- Kava kava (*piper methysticum*)
  - Contains kavapyrones
  - Ceremonial beverage in the Pacific and Australia
  - Muscle relaxation, anaesthesia, anxiolytic
  - Choreoathetosis, dystonias, parkinsonism
Conclusions

Drug induced movement disorders can represent MEDICAL EMERGENCIES
• Neuroleptic malignant syndrome
• Serotonin syndrome
• Toxic conditions due to illicit drugs

Variable phenotypic manifestations
• Suboptimal treatment
• No preventive treatments
• The most important – avoiding exposure

• Amanita muscaria
• Hallucinogens: muscimol, ibotenic acid
• Oswald Schmiedeberg - Dept of Materia Medica in Tartu, 1847-1867
  – Described muscarine and its antagonism with atropine – a basis for the theory about antagonism of poisons and antidotes
  – Proved that nerve endings can be pharmacologically selectively influenced: founded pharmacology of synaptic transmission