Introduction to Tolerance, Physical Dependence and Withdrawal

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Overview

• **Definitions**
  – Addiction, psychological dependence, physical dependence (acute and protracted), tolerance, withdrawal
    • Discrete and different phenomena that are often confused

• **Regulatory status for assessment of dependence**
  – EMA, FDA, ICH

• **Scientific insights into occurrence of dependence**
  – System level; neuronal level

• **Class-specific withdrawal syndromes**
  – Benzodiazepines, stimulants, cannabinoids, opiates, alcohol
Addiction – Word Choice Matters!

• “Addiction” is a complex, multi-faceted concept
  – Primary chronic neurobiologic disease
  – Genetic, psychosocial and environmental factors
  – Characterized by 1 or more behaviors:
    • Impaired control over drug use
    • Compulsive use, despite harm
    • Hallmark is drug craving

• Dependence can be part of addiction, but is not the same thing

• Psychological dependence
  – Drug/substance abuse, addiction, craving, relapse
  (key element is emotional need)

a: American Academy of Pain Medicine, American Pain Society, American Society of Addiction Medicine definition
Physical Dependence

• A state of neuroadaption manifested by a drug-class specific withdrawal syndrome
  – Defined following cessation of drug-taking

• Can be evidenced by appearance of withdrawal
  – Abrupt cessation of dosing
  – Rapid dose reduction
  – Decreasing bio-availability
  – Use of an antagonist

• Is an expected occurrence in all individuals in the presence of continuous use of many CNS-active drugs, particularly opioids, for days or weeks
Tolerance

• **Pharmacologic definition**
  – Resistance or decreased responsiveness to expected actions of a drug
    • Higher or more frequent dosing to achieve initial effects of drug
    • Tolerance does not imply addiction

• **Clinical definition**
  – A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug’s effects over time
Withdrawal

• The onset of a **predictable constellation of signs and symptoms** following the abrupt discontinuation of, or rapid decrease in, dosage of a psychoactive substance
  – Signs and symptoms are usually opposite of the intoxication effects of the drug

• **Withdrawal can have two phases**
  – **Acute withdrawal** begins within hours of drug cessation and gradually resolves.
    • Length of time to resolve depends on substance used
  – **Protracted withdrawal**: signs and symptoms of acute withdrawal AND non-substance specific signs and symptoms that persist, evolve or appear past the expected timeframe for acute withdrawal
Recap of Terms

• **Addiction**
  – Impaired control over drug use, compulsive drug use, *drug craving*

• **Physical Dependence**
  – Neuroadaptation to continued drug use manifested by withdrawal

• **Tolerance**
  – Higher or more frequent dosing to achieve initial effect of drug

• **Withdrawal**
  – Predictable signs and symptoms following abrupt discontinuation of drug

• **Psychological Dependence**
  – *Emotional need* for drug, for pleasurable mental effects
Focus on Physical Dependence/Tolerance

- **Power of dependence and tolerance:** S. Siegel, 1980s
  - Induced tolerance to heroin in rats in a specific context
  - Tested reaction to heroin in a different context

**Context A**

Increasing doses of heroin up to 15 mg/kg in dark-striped context

**Context B**

Saline administration in context of light stripes of different orientation on alternate days (same rats)

**Context B**

The same animals tested with 15 mg/kg heroin in Context B

Lethal in 96% of rats
Drug Dependence Is a Powerful Effect

- Development of drug dependence can be a powerful effect
  - “Situational-specific tolerance” has been demonstrated for various classes of drugs
    - Opiates, naloxone, ethanol, nicotine, pentobarbital, phencyclidine, immunoenhancing drugs, haloperidol, several benzodiazepines
  - May account for difficulty with drug rehabilitation programs away from the home “context”

- Tolerance/dependence has greater complexity than a “wash out” period or “recovery group” in a standard Tox study
  - Can result in changes in brain, peripheral nervous system, behavior that are not appreciable by histopathology or standard clinical observations
Regulatory Status

- **Preclinical and clinical assessment of tolerance/dependence is part of the abuse potential package governed by FDA, EMA and ICH regulations**
  - Required for CNS-active drugs, regardless of therapeutic indication

- **Standard package includes**
  - Assessment of reinforcing or rewarding properties of substance
    - Preclinical self-administration, drug discrimination
    - Clinical study in recreational drug users
  - Assessment of dependence potential of substance
    - Preclinical tolerance/withdrawal study
    - Clinical study in recreational drug users
    - Specifics of how to design preclinical study covered in later talks

- **Data used, along with other relevant information, for scheduling and labeling**
2. Types of Animal Abuse Potential Studies

• Dependence Potential
  
  “Tests for tolerance and physical dependence examine the responses to repeated administration of a drug. Repeated doses over a wide range are needed to attain the same effects observed at starting doses or, as an alternative, to avoid symptoms of withdrawal or “bad feelings” ”.

(red text added for emphasis only)
FDA Proposed Decision Tree: 20 Steps

Nonclinical

7 Animal drug discrimination study
   Is compound similar to comparator drug of abuse?

8 Animal Self administration study
   Is compound rewarding or reinforcing?

9 Physical dependence study
   Does compound produce tolerance or withdrawal syndrome?

Early Clinical

11 Abuse AEs in healthy volunteers (Phase 1)
   Does drug cause abuse-related AEs in healthy subjects?

12 Abuse AEs in patients (Phase 2)
   Does drug cause abuse-related AEs in patients?

13 Incorporate physical dependence in humans
   Does drug cause physical dependence in humans?

Late Clinical

15 Abuse study in recreational drug users
   Does drug produce rewarding/reinforcing effects in humans?

16 Abuse AEs in patients (Phase 3)
   Does drug cause abuse-related AEs in larger number of patients?
• **Section 4.2.2 Studies Investigating Withdrawal Syndrome and the use of data on tolerance**

  – “…Non-clinical studies may provide more systematic insight in withdrawal phenomena. Specific considerations…are:
    
    • The dose, frequency and duration of treatment…
    
    • Careful definition of endpoints (behaviour, body temperature, body weight, food intake)…
    
    • Observations should be …long enough and with a frequency sufficient to detect all signs of withdrawal…”

• “…tolerance reveals an aspect neuroadaptation and may contribute to the development of dependence. However, tolerance is not regarded as a robust marker…”
Section 15 NONCLINICAL ABUSE LIABILITY

“Three types of studies are often completed to evaluate the potential for abuse liability: drug discrimination, self-administration of the compound, and an assessment of withdrawal. When conducted, studies of drug discrimination and self-administration are generally stand-alone. Assessments of withdrawal can sometimes be incorporated within the design of the reversibility arm of a repeated-dose toxicity study.”

(red text added for emphasis only)
Mechanisms of Tolerance and Withdrawal

Repeated CNS-active drug administration can produce neuroadaptive changes in the brain

- These changes are often opposite to the intoxicating effects
  - Example: drug produces hyperthermia; adaptive effect = hypothermia
  - Can off-set the “high” to maintain homeostasis

Increasing doses of heroin up to 15 mg/kg in dark-striped context

The same animals tested with 15 mg/kg heroin in Context B
Lethal in 96% of rats
Opponent Process Theory of Addiction

- Opponent Process theory – psychological and neurologic model used to explain a wide range of behaviors
- Solomon and Corbit (1974) applied it to drug tolerance and withdrawal
  - $a$ process = drug effect, for example euphoria
  - $b$ process = body’s compensatory response, for example dysphoria

Initial drug experience: euphoria
Notice time offset for $b$ process

Repeated drug administration: $b$ process becomes larger and the delay period shorter. Experience is now short spike of euphoria followed by less pleasurable experience and dip into dysphoria, which = withdrawal
Neuroplasticity

• Collier (1965) hypothesized that a similar phenomenon (opponent processes) occurred at the neuronal level
  – Hypothesis revised and explored by many others

• Receptor numbers could be changed by constant exposure to a psychoactive drug: physiological homeostasis at the cellular level
  – Down-regulation of receptors in response to an agonist drug (opiate)
  – Up-regulation of receptors in response to an antagonist (caffeine)
  – Alterations in neuronal function, not just number, can also occur in response to drugs
Psychoactive drugs such as opiates stimulate the mesolimbic dopamine (DA) system (pathway shown in blue), starting in the VTA which releases DA into the nucleus accumbens and prefrontal cortex producing pleasurable feelings.

Repeated drug exposure causes drug target receptors (e.g. opioid receptors) to become less sensitive to stimulation.

Increasing amount of drug is required to stimulate the VTA to release enough DA to stimulate cells.
Opiates also act to suppress the locus ceruleus (LC), which produces noradrenaline (NA).

Less LC stimulation results in decreased NA, causing the symptoms of sleepiness, decreased respiration, lowered blood pressure.

Repeated exposure to opiates causes the LC to increase their basal level of activity to compensate.

Opiates counteract this increase so the person feels “normal”.

During withdrawal, opiates are not present to offset the increased release of NA.

Higher levels of NA cause symptoms of jitteriness, anxiety, muscle cramps.
## Acute Withdrawal Timeframes

<table>
<thead>
<tr>
<th>Substance</th>
<th>Withdrawal Time Human</th>
<th>Withdrawal Time Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>5-7 days</td>
<td>1-2 days</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>1-4 weeks</td>
<td>&gt;3 days</td>
</tr>
<tr>
<td>Cannabis</td>
<td>5 days</td>
<td>≥96 h</td>
</tr>
<tr>
<td>Nicotine</td>
<td>2-4 weeks</td>
<td>4-14 days</td>
</tr>
<tr>
<td>Opiates</td>
<td>4-10 days</td>
<td>72 h</td>
</tr>
<tr>
<td>Stimulants</td>
<td>1-2 weeks</td>
<td>1 week (brain slice)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 days (cocaine)</td>
</tr>
</tbody>
</table>

- Protracted withdrawal is difficult to assess in humans and rats
Alcohol Withdrawal Syndrome

**Humans**
- Anxiety
- Excess sweating
- Tremors
- Dehydration
- ↑ HR and BP
- Insomnia (1-3 years!)
- Nausea & vomiting
- Diarrhea
- Agitation
- Headache
- Seizures

**Rats**
- Tail stiffness
- Muscle spasms
- Rigid body posture
- Tremors
- ↑ HR and BP
- Piloerection
- Sensory hyper-reactivity
- Diarrhea
- Seizures
Opiate Withdrawal Syndrome

- **Humans**
  - Anxiety
  - Nausea & vomiting
  - Hot and cold flushes
  - Sweating
  - Muscle cramps
  - Diarrhea
  - Watery nasal/ocular discharge

- **Rats**
  - Irritability
  - Yawning/stretching
  - Wet dog shakes
  - Jumping
  - Head bobbing
  - Sweeping tail movements
Stimulant Withdrawal Syndrome

- **Humans**
  - Agitation
  - Irritability
  - Depression
  - Increased sleeping
  - Increased appetite
  - Muscle aches

- **Rats**
  - Increased food intake
  - Increased startle response
  - Increase ultrasonic vocalizations (anxiety)
  - Head shakes
  - Tremor
  - Ptosis
  - Chewing
Summary

• **Dependence causes neuronal and systemic alterations in the brain that are revealed when drug administration ceases**
  – Changes are usually opposite in nature to drug effects and offset a drug’s effects to maintain the body at homeostasis
  – Cessation of drug administration expresses the altered state, which is experienced as withdrawal symptoms

• **Class-specific withdrawal syndromes are defined for the classes of commonly abused drugs**
  – Human and rat syndromes are similar within a drug class
Conclusions

• Physical dependence and tolerance are important indicators of potential abuse liability
  – Tolerance may be an expected result of repeated administration of CNS-active drugs; does not always indicate addiction

• Preclinical evaluation of dependence and defining the withdrawal syndrome, if it exists, can indicate a potential issue for the human population
  – For volunteers, clinical population and recreational drug users

• Assessment of dependence is more complex and nuanced than periodic evaluation of rodent clinical signs during recovery following a standard tox study