

# **Injury by Nontherapeutic Agents**

## **(Drug Use Disorder)**

Pathologic mechanisms • organ injury • clinical correlations

Cocaine • Opioids • Amphetamines • Cannabinoids • Other agents

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# Learning objectives

- Classify common nontherapeutic psychoactive agents by major molecular targets.
- Explain cocaine-related sympathetic, cardiovascular, CNS, and pregnancy effects.
- Connect opioid pharmacology, contaminants, and injection practices to distinct organ lesions.
- Distinguish methamphetamine, cannabis, hallucinogen, and related drug effects.
- Interpret characteristic clinicopathologic patterns without assuming exposure from morphology alone.

## What “drug use disorder” denotes

- Repeated or chronic use of mind-altering substances outside therapeutic or social norms.
- A disorder may progress to addiction and may be complicated by overdose.
- The textbook uses a broad, pathology-oriented framing rather than listing formal diagnostic criteria.
- Drug-related tissue injury reflects both intrinsic pharmacology and exposure circumstances.

# Drug exposure is not synonymous with use disorder

## Exposure measures

- Includes an individual who used a nonprescription drug at least once.
- Does not, by itself, establish a use disorder.
- Population exposure denominators depend on year and region.

## Use disorder measures

- Identifies a population meeting disorder criteria.
- Not interchangeable with lifetime or past-year drug use.
- Interpret source epidemiology by its specific definition.

*Historical survey estimates refer to 2021; These are not current surveillance figures.*

# Scale of global nonprescription drug exposure

UNODC figures quoted (2023 report; Year of exposure 2021)

**296 M**

People worldwide estimated to have used nonprescription drugs at least once in 2021

**5.8%**

Approximate share of people aged 15–64 years worldwide (2021)

# US exposure and disorder: Distinct denominators

Separate textbook estimates; Definitions and denominators differ

**61.2 M**

US residents who used nonprescription drugs in  
2021

**46.3 M**

US people aged  $\geq 12$  estimated to meet criteria  
for drug use disorder in 2021

# US overdose burden reported for 2023

Historical textbook statement; Not a current-year mortality update

**$\approx 107,000$**

Deaths from drug overdose in the United States  
in 2023

**$\approx 70\%$**

Approximate fraction attributed to synthetic  
opioids, mainly fentanyl

# Major classes of nontherapeutic agents

Classify by major pharmacologic effects and receptor/transporter targets

**Opioids**

**Sedative–hypnotics**

**Psychomotor stimulants**

**Dissociatives**

**Cannabinoids**

**Hallucinogens**

The class predicts some acute toxicity; Route, adulterants, and comorbidity modify tissue injury.

## Primary targets I: Opioids to stimulants

| Drug class             | Representative agents                  | Teaching target                                |
|------------------------|----------------------------------------|------------------------------------------------|
| Opioid narcotics       | Heroin; fentanyl; oxycodone            | $\mu$ -opioid receptor agonism                 |
| Sedative–hypnotics     | Barbiturates; benzodiazepines; ethanol | GABA-A receptor effects                        |
| Psychomotor stimulants | Cocaine; amphetamines; MDMA            | Dopamine transporter and serotonergic toxicity |

*Simplified targets reproduced Table 9.6; Agents can act at additional targets.*

## Primary targets II: Dissociatives to hallucinogens

| Drug class      | Representative agents      | Teaching target                  |
|-----------------|----------------------------|----------------------------------|
| PCP-like agents | Phencyclidine; ketamine    | NMDA receptor channel antagonism |
| Cannabinoids    | Marijuana; hashish         | CB1 cannabinoid receptor agonism |
| Hallucinogens   | LSD; mescaline; psilocybin | Serotonin 5-HT2 receptor agonism |

# Three broad routes to tissue injury

Distinct mechanisms may coexist in the same patient

**Drug pharmacology →  
physiologic toxicity**

**Adulterants → direct or  
foreign-body injury**

**Injection practices →  
infections**

A tissue lesion alone need not disclose which specific substance was used.

# Why route and purity matter

## Exposure route

- Intranasal cocaine → local septal injury.
- Inhaled cocaine or cannabis → pulmonary effects.
- Parenteral heroin → skin, venous, and infection-related lesions.

## Uncertain product composition

- Unknown heroin purity complicates dose estimation.
- Fentanyl substitution increases overdose risk.
- Talc, quinine, and other contaminants add their own toxicity.

## Cocaine: Forms and exposure routes

- Derived from leaves of the coca plant.
- Cocaine hydrochloride is water soluble; It may be insufflated or injected.
- The crystallized free-base form, “crack,” is heated and inhaled.
- Street products may be diluted with powders such as talc or lactose.

# Cocaine hydrochloride and crack

## Cocaine hydrochloride

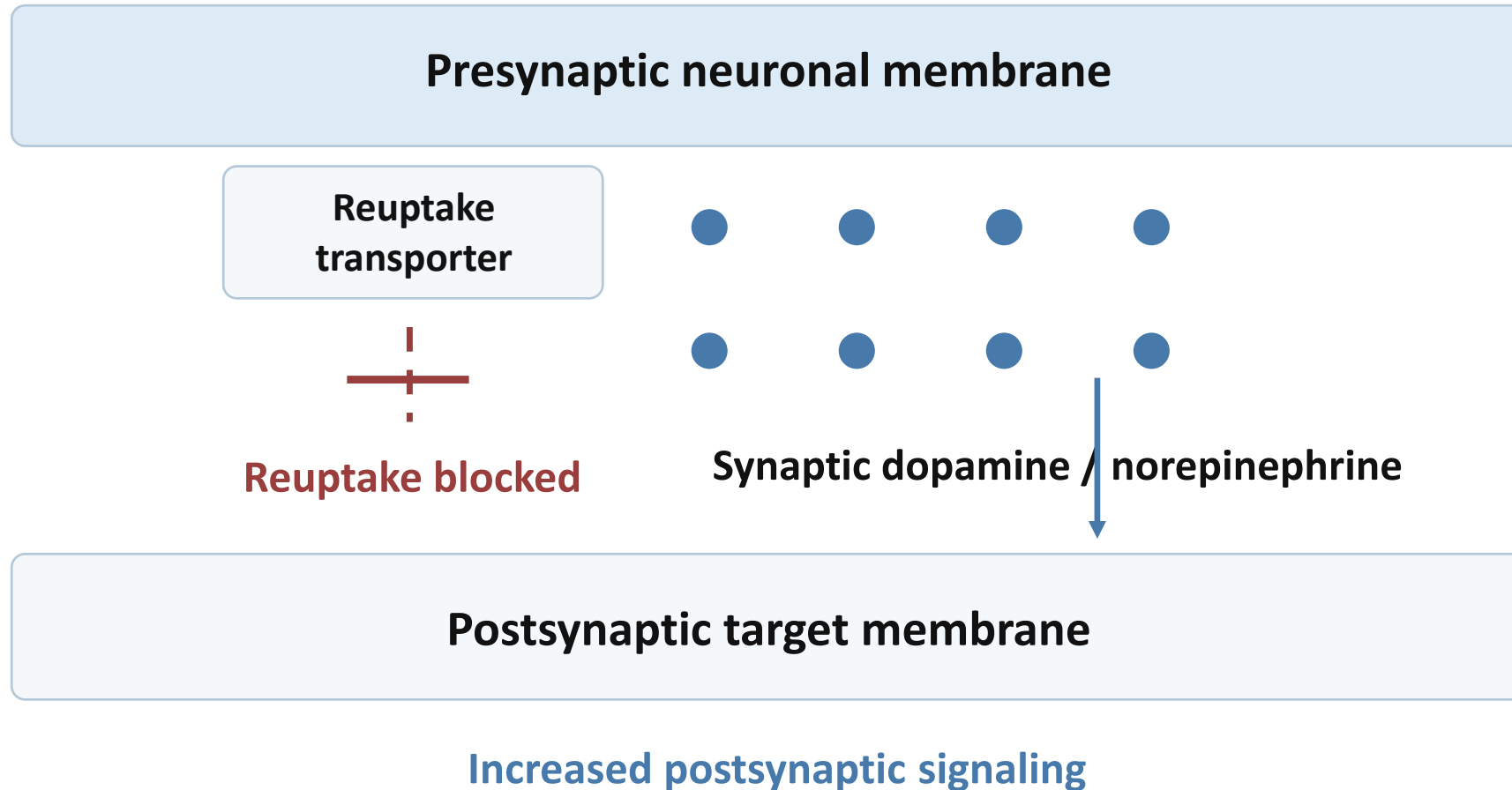
- Commonly sold as powder.
- May be taken intranasally or dissolved for injection.
- Local intranasal injury becomes relevant with repeated exposure.

## Crack cocaine

- Crystallized alkaloid inhaled after heating.
- Same essential pharmacologic actions as cocaine.
- Crack as markedly more potent.

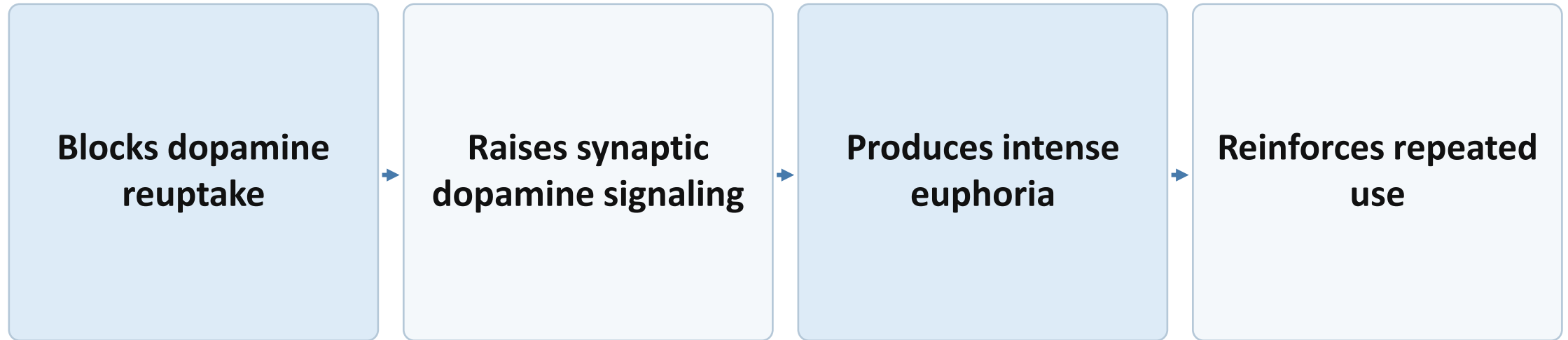
# Cocaine: Reuptake blockade at a synapse

Schematic — neurotransmitter persists because presynaptic reuptake is inhibited



# Cocaine and the mesolimbic reward pathway

Central dopaminergic action supports cocaine's strong addictive potential



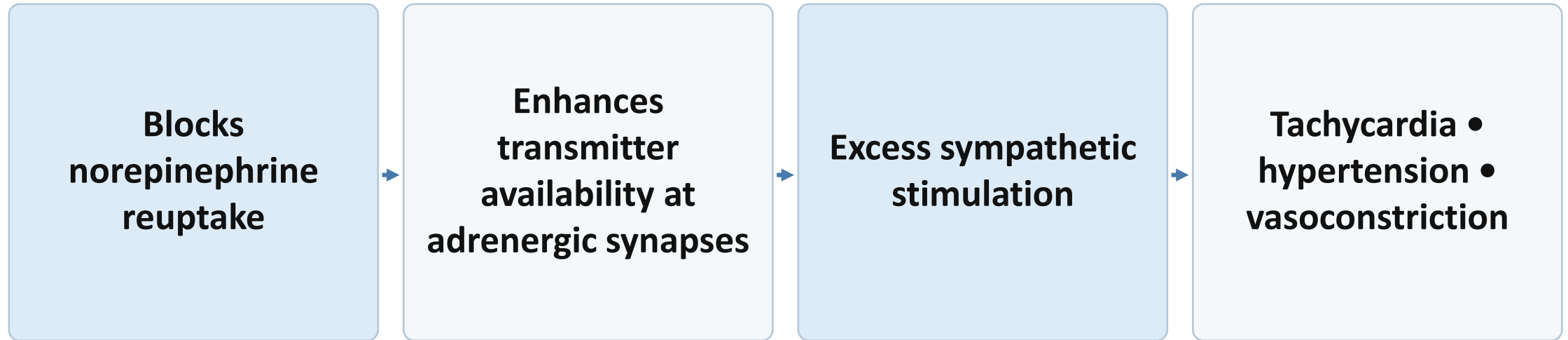
The source also describes profound craving after discontinuation.

## **Cocaine dependence: Craving is central**

- Euphoria and neurologic stimulation promote repeated administration.
- Physical dependence is described as generally limited.
- Psychological withdrawal and craving can be severe.
- Cravings can be particularly intense in early abstinence and recur long afterward.

# Cocaine amplifies sympathetic neurotransmission

Peripheral catecholamine effects explain characteristic cardiovascular toxicity



# Cocaine: Four linked acute responses

## Heart rate

Tachycardia increases myocardial oxygen demand.

## Vasculature

Peripheral and coronary vasoconstriction alter blood flow.

## Pressure

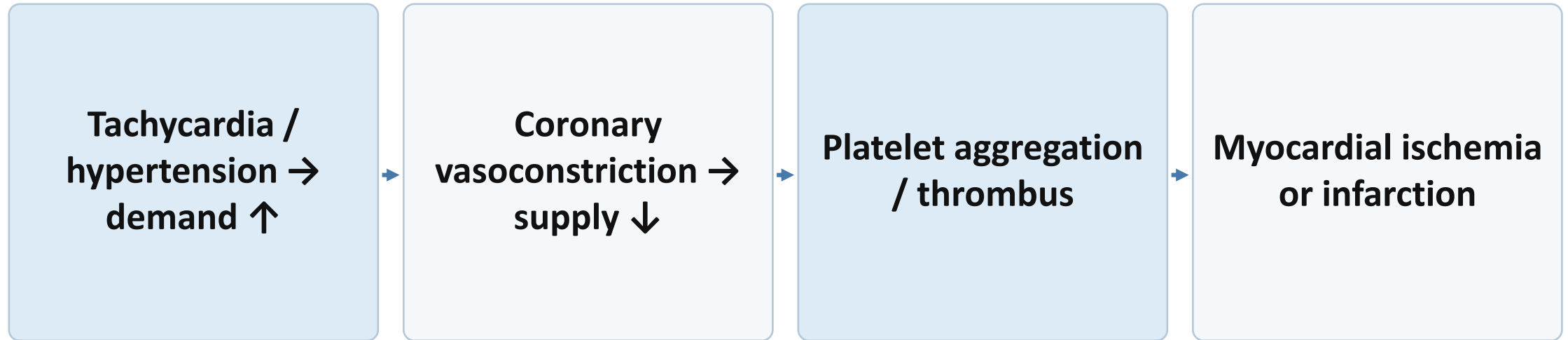
Systemic hypertension raises cardiovascular stress.

## Platelets

Increased aggregation supports thrombosis and ischemia.

# Myocardial ischemia: Demand–supply mismatch

Cocaine creates concurrent demand and supply stresses



## **Cocaine-associated coronary thrombosis**

- Cocaine can increase platelet aggregation and thrombus formation.
- Coronary vasoconstriction simultaneously reduces perfusion.
- The interaction can produce ischemia even without a preexisting fixed obstruction.
- Myocardial infarction is a major possible outcome.

# Arrhythmia: Converging mechanisms

## Adrenergic mechanism

- Enhanced sympathetic activity increases cardiac excitability.
- Tachycardia and hypertension accompany the catecholamine effect.

## Myocardial electrical mechanism

- Cocaine can disrupt  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Ca}^{2+}$  transport.
- Electrical instability may produce lethal arrhythmias.

## **Cocaine toxicity may be unpredictable**

- Severe cardiovascular effects are not necessarily proportional to dose.
- Fatal events may occur in first-time users at a typical mood-altering dose.
- Cigarette smoking may amplify coronary vasospasm risk.
- No clinical presentation should be considered benign solely on presumed exposure amount.

# Cocaine: Vascular and myocardial endpoints

## Cardiac

- Myocardial ischemia or infarction.
- Lethal arrhythmia.
- Chronic dilated cardiomyopathy.

## Cerebrovascular

- Hypertension-associated stress.
- Cerebral hemorrhage.
- Cerebral infarction.

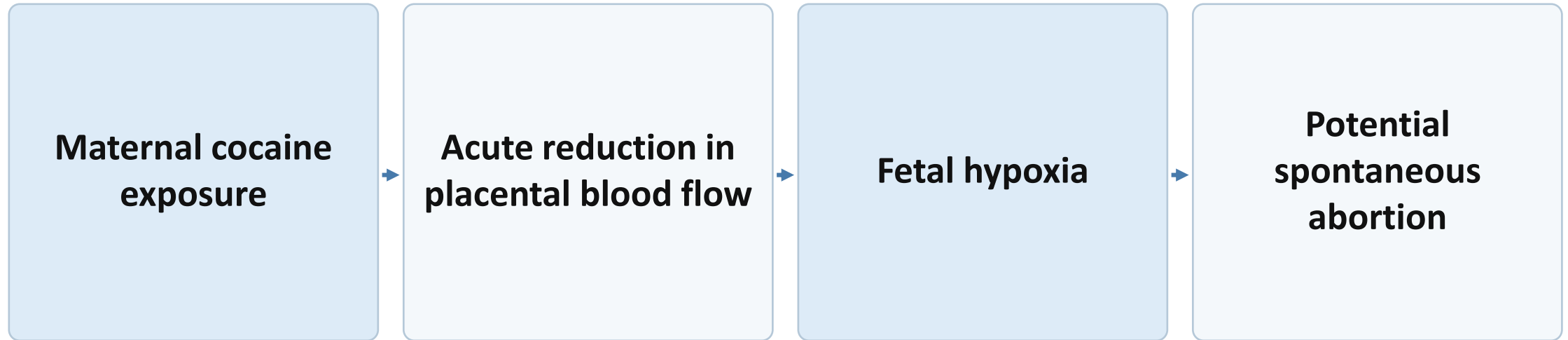
*Cerebral endpoints also appear in the captioned effects Figure 9.14.*

## **Acute cocaine injury of the CNS**

- Hyperpyrexia is an important acute manifestation.
- Altered dopaminergic temperature-regulation pathways are implicated.
- Seizures may occur during acute toxicity.
- Neurobehavioral effects also include euphoria and paranoia.

# Cocaine in pregnancy: Placental perfusion

The source also links chronic maternal exposure with impaired fetal neurologic development.



# Cocaine: Route-specific chronic injury

## Nose

Intranasal exposure can cause nasal septal perforation.

## Lung

Inhaled cocaine smoke can reduce diffusing capacity.

## Heart

Chronic cocaine use can be associated with dilated cardiomyopathy.

## CNS

Craving may persist after discontinuation.

## **Cocaine-induced septal damage: Morphology**

- Repeated intranasal exposure is associated with perforation of the nasal septum.
- This is a local structural lesion, not simply a transient pharmacologic effect.
- History of intranasal exposure provides the essential etiologic context.
- The supplied text does not provide a specific histologic diagnostic pattern.

## **Cocaine-related chronic cardiomyopathy**

- Dilated cardiomyopathy is identified among chronic consequences.
- It is distinct from the acute coronary ischemia and arrhythmic pathways.
- In an individual with cardiomyopathy, drug history is important for attribution.
- The provided excerpt does not specify pathognomonic histology for cocaine exposure.

# Cocaine: Clinicopathologic integration

| Organ/system   | Mechanism / exposure                     | Characteristic effect               |
|----------------|------------------------------------------|-------------------------------------|
| Cardiovascular | Catecholamines; coronary tone; platelets | Ischemia, infarction, arrhythmia    |
| CNS            | Dopaminergic effects                     | Hyperpyrexia; seizures              |
| Placenta/fetus | Reduced placental blood flow             | Fetal hypoxia; pregnancy loss       |
| Airway/nose    | Inhalation; insufflation                 | Reduced gas transfer; septal injury |

## **Case: Chest pain after cocaine exposure**

### **Clinical vignette (hypothetical)**

A young adult develops acute chest pain and marked tachycardia after cocaine use. No prior coronary disease is reported.

**What two mechanisms jointly make myocardial ischemia plausible?**

## Opiates and opioids: Terminology

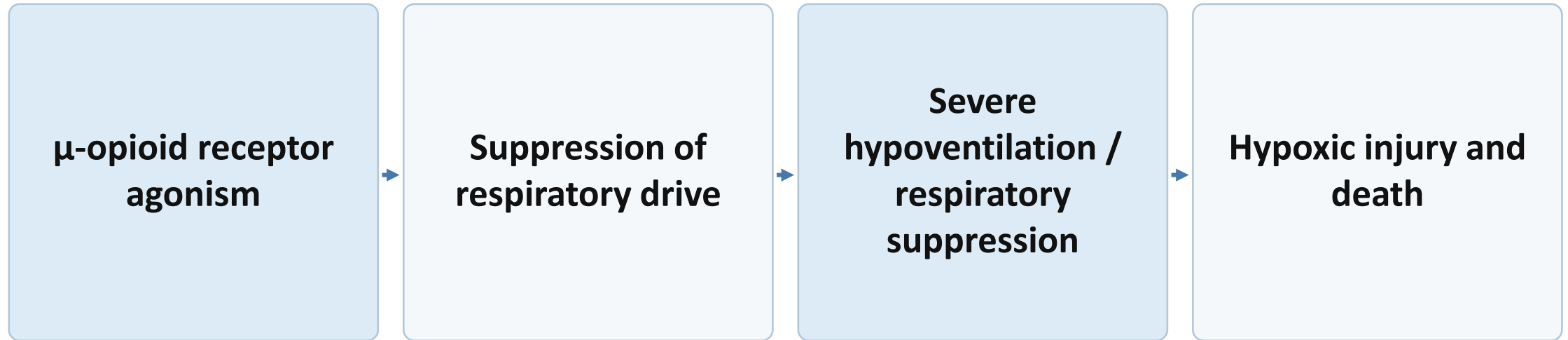
- Opiates are naturally occurring substances obtained from poppy plants, such as morphine.
- “Opioids” encompasses related derivatives and synthetic agents.
- Prescription opioids may also be used nontherapeutically.
- Heroin and fentanyl because of severe public-health injury.

## Representative opioids in the source

| Group                   | Examples                                    | Key context                                               |
|-------------------------|---------------------------------------------|-----------------------------------------------------------|
| Poppy-derived / related | Morphine; heroin                            | Heroin is an illicit derivative related to morphine       |
| Prescription opioids    | Oxycodone; hydrocodone; tramadol; methadone | Therapeutic use does not preclude nontherapeutic exposure |
| Potent synthetic opioid | Fentanyl                                    | Illicit substitution or mixing can be fatal               |

# Opioid toxicity: Principal fatal pathway

The most emphasized immediate fatal mechanism is respiratory suppression



## **Illicit fentanyl intensifies overdose risk**

- Fentanyl is highly potent and can be mixed with or replace other drugs.
- Exposure may be unrecognized by the individual using the substance.
- Those without opioid tolerance are particularly vulnerable to profound respiratory suppression.
- Appropriate medically supervised fentanyl use is distinct from uncontrolled illicit exposure.

# Opioid deaths: Direct versus accompanying mechanisms

## Primary pharmacologic effect

- Profound respiratory depression is emphasized as the usual cause.
- Delayed reversal allows progression to serious hypoxic injury.

## Additional severe effects

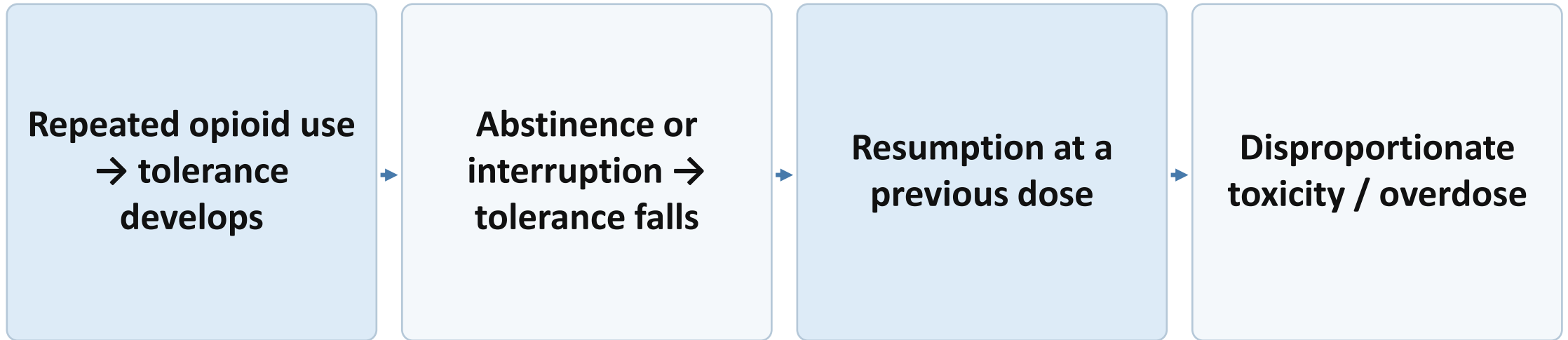
- Cardiac arrhythmia or cardiac arrest.
- Severe pulmonary edema.
- Unknown drug content makes overdose risk less predictable.

## **Naloxone: Mechanism-based reversal**

- Naloxone is an opioid receptor antagonist.
- It can rapidly reverse opioid-induced respiratory suppression if administered in time.
- Reversal does not erase other exposure-related complications, such as infection or tissue injury.
- The Robbins passage supports the reversal principle but not a detailed dosing protocol.

# Lost tolerance increases overdose vulnerability

The textbook explicitly cites loss of tolerance during incarceration as an example.



# **Why heroin-related tissue injury is heterogeneous**

These mechanisms can occur together; Pathology may reflect more than heroin itself.

**Pharmacologic  
opioid toxicity**

**Adulterants /  
cutting agents**

**Hypersensitivity to  
contents**

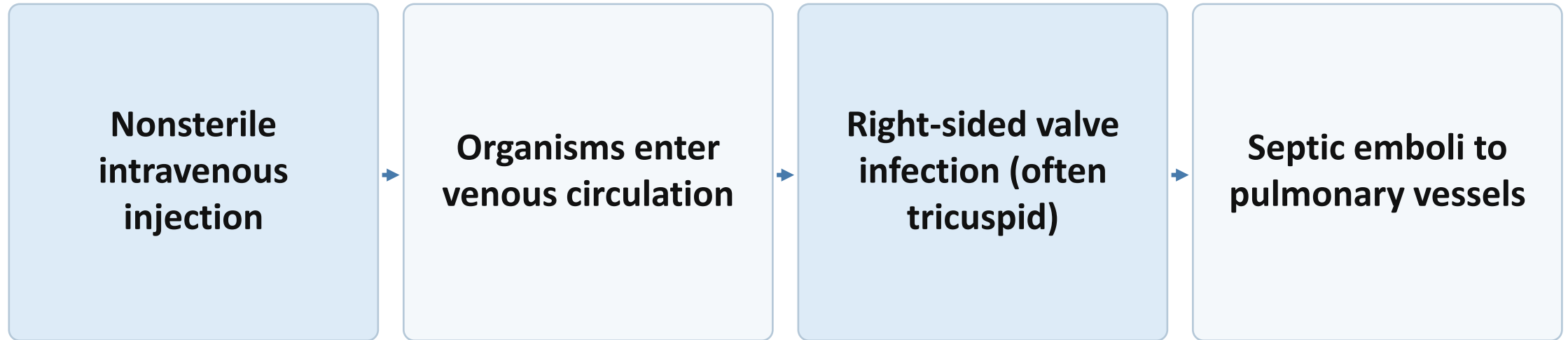
**Contaminated  
needles and  
injection**

## **Opioid-related pulmonary edema**

- Moderate to severe pulmonary edema is described after heroin use.
- Edema can accompany severe overdose and sudden death.
- Pulmonary complications also include infection and embolic disease.
- Do not interpret edema alone as specific proof of opioid exposure.

# Injection-associated tricuspid endocarditis

*Staphylococcus aureus* is highlighted as a frequent cause.



## **Infections associated with injection drug use**

- Skin and subcutaneous tissue infections may accompany injection.
- Right-sided infective endocarditis is a characteristic serious complication.
- Viral hepatitis is transmitted by needle sharing.
- HIV infection has also been linked to contaminated injection equipment.

# Heroin use: Characteristic organ involvement

## Skin / veins

Cellulitis, abscesses, ulceration; Scarring and thrombosed veins.

## Heart valves

Right-sided, often tricuspid, infective endocarditis.

## Lung

Edema, septic emboli, abscess, or foreign-body reaction.

## Kidney

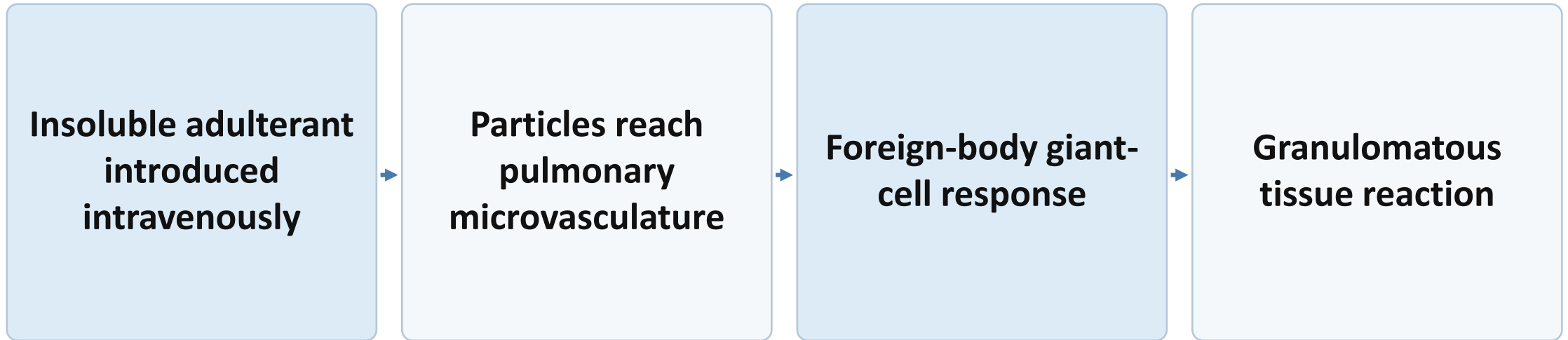
Amyloidosis and focal segmental glomerulosclerosis.

## **Skin: Acute and chronic injection findings**

- Acute changes include subcutaneous abscesses, cellulitis, and ulcerations.
- Repeated intravenous injection can scar the skin and hyperpigment vein tracks.
- Thrombosed veins are a further consequence of recurrent injury.
- These changes indicate an exposure pattern rather than an agent-specific chemical fingerprint.

# Talc embolization: Foreign-body lesion

Schematic mechanism; Birefringent talc particles visible by polarized light.



## **Foreign-body granulomas: Evidence in tissue**

- Adulterant particles can produce foreign-body granulomas, especially in lungs.
- Talc may be visible as crystalline material under polarized light.
- Particles can lie within multinucleated foreign-body giant cells.
- Granulomas may also involve spleen, liver, and regional lymph nodes.

# Kidney pathology with heroin use

## Amyloidosis

- May occur secondary to recurrent skin infections.
- Can lead to proteinuria and nephrotic syndrome.

## Focal segmental glomerulosclerosis

- Also associated with heroin use.
- Can cause proteinuria and nephrotic syndrome.

*These are associations, not a specific etiologic diagnostic test.*

## Opioid complications: Mechanism determines lesion

| Injury mechanism                    | Potential morphologic outcome         | Exposure context       |
|-------------------------------------|---------------------------------------|------------------------|
| Respiratory suppression             | Hypoxic consequences; pulmonary edema | Overdose               |
| Injection infection                 | Tricuspid endocarditis; abscesses     | Contaminated injection |
| Adulterant particles                | Foreign-body granulomas               | Particulate exposure   |
| Recurrent infections / renal injury | Amyloid disease or FSGS               | Chronic exposure       |

## **Case: Multiple pulmonary nodules in an injector**

### **Clinical vignette (hypothetical)**

A patient with recurrent injection drug use has fever, a new tricuspid vegetation, and multiple lung lesions consistent with infected emboli.

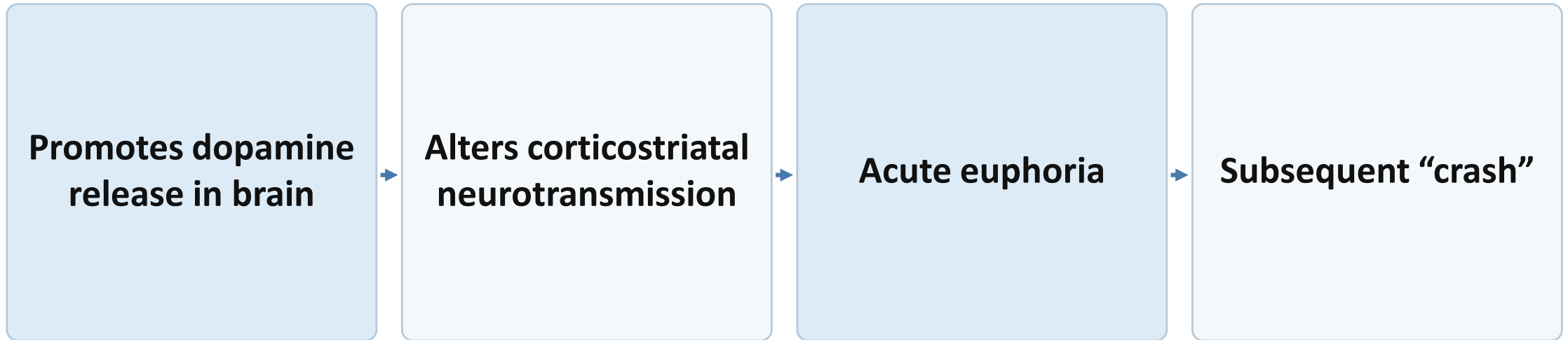
**What is the most direct path from right-heart infection to pulmonary injury?**

## **Methamphetamine: Drug class and potency**

- Methamphetamine is closely related to amphetamine.
- It is a potent addictive psychomotor stimulant.
- Stronger CNS effects than those of amphetamine.
- Injection is one reported mode of methamphetamine use.

# Methamphetamine and the dopamine pathway

Robbins also describes reduced glutamate release at corticostriatal synapses.



# Methamphetamine: Immediate versus prolonged effects

## Acute neurobehavioral pattern

- Intense euphoria.
- A post-use crash.
- Altered cortical–striatal signaling.

## Long-term presentation

- Confusion and violent behavior.
- Paranoia and hallucinations.
- Psychosis may occur with prolonged use.

# **Methamphetamine: Interpreting psychiatric injury**

- Long-term use may lead to psychosis with paranoia and hallucinations.
- Behavioral and cognitive manifestations are prominent.
- Co-occurring substance use and mental illness are common in the described population.
- Psychosis is a clinical manifestation; The supplied excerpt does not provide a specific brain histologic lesion.

# **Cannabis: Material and principal psychoactive agent**

- Marijuana derives from leaves of *Cannabis sativa*.
- $\Delta^9$ -tetrahydrocannabinol (THC) is the main psychoactive constituent emphasized.
- Cannabinoid effects are associated with CB1 receptor signaling.
- Nontherapeutic smoking and aerosolized THC exposure are discussed separately.

# Acute cannabis effects: Multisystem profile

## Perception

Heightened sensory impressions and altered perception of time.

## Behavior

Euphoria, relaxation, laughter, or increased appetite.

## Motor control

Impaired coordination and psychomotor performance.

## Cardiovascular

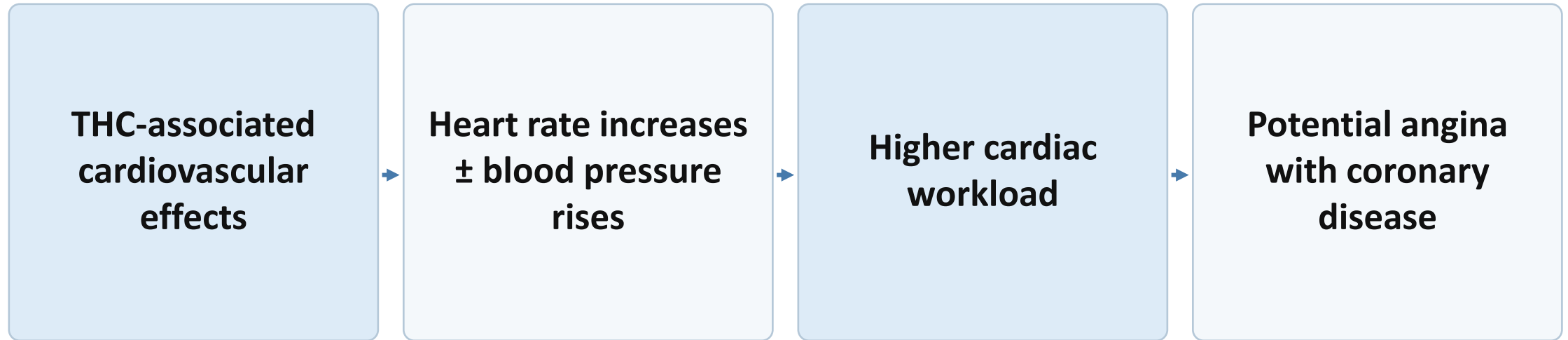
Increased heart rate; Sometimes increased blood pressure.

# **Cannabis impairs psychomotor judgment**

- Acute use may distort sensory perception and motor coordination.
- With continued use, impaired estimation of time, speed, and distance is described.
- The resulting judgment deficits can contribute to motor-vehicle accidents.
- Clinical impairment and morphologic injury are not interchangeable concepts.

# Cannabis and ischemic symptoms in susceptible hearts

Robbins specifies risk in individuals with preexisting coronary artery disease.



## **Smoking cannabis: Airway consequences**

- Chronic smoking is associated with laryngitis, pharyngitis, and bronchitis.
- Cough, hoarseness, and asthma-like symptoms can occur.
- Mild but significant airway obstruction is described.
- The smoke contains several carcinogens also encountered in tobacco smoke.

# Inhaled cannabis: Combustible smoke versus aerosol

## Smoked cannabis

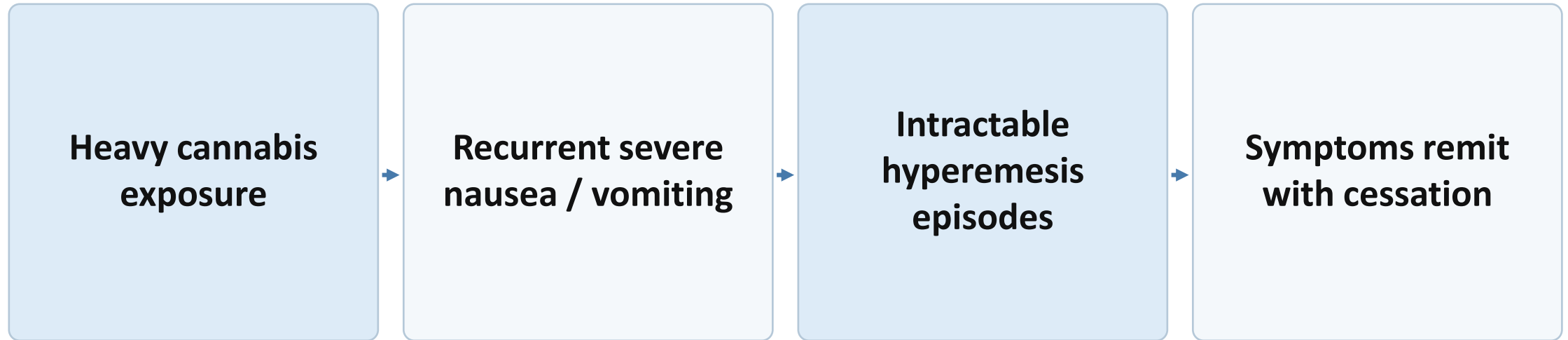
- Respiratory irritation and obstructive airway effects.
- Smoke-associated tar and carcinogen exposure.

## Aerosolized THC products

- Severe lung injury has been associated with some vaping products.
- Robbins raises possible adulterant involvement; Causation is not universally established.

# Cannabis hyperemesis syndrome

Paradoxical gastrointestinal presentation despite recognized antiemetic uses.



# **Cannabis withdrawal and use disorder**

- Some individuals develop problematic cannabis use with dependence.
- Reported withdrawal includes mood changes and sleep difficulties.
- Symptoms may persist for up to approximately two weeks in the source.
- Variable definitions and uncertainty around addiction estimates.

# Cannabis: Potential therapeutic value and harm

## Potential medical applications in source

- Relief of chemotherapy-associated nausea.
- Pain reduction in selected difficult chronic conditions.
- Approved cannabis-derived or related prescription products exist.

## Nontherapeutic-associated harms

- Impaired coordination and driving judgment.
- Airway symptoms or possible vaping-associated injury.
- Cannabis hyperemesis and withdrawal in some users.

## **Phencyclidine and ketamine: Dissociatives**

- PCP and ketamine are described as related anesthetic agents.
- Both are listed among phencyclidine-like nontherapeutic drugs.
- Robbins Table 9.6 emphasizes NMDA receptor channel antagonism.
- Therapeutic ketamine derivatives are a separate medically supervised context.

## Other agents: Representative classes

| Class / group        | Examples                          | Source-described risk / effect                     |
|----------------------|-----------------------------------|----------------------------------------------------|
| Hallucinogens        | LSD; mescaline; psilocybin        | Altered mood, affect, thought                      |
| MDMA / ecstasy       | 3,4-Methylenedioxymethamphetamine | Possible serotonergic depletion with prolonged use |
| Synthetic cathinones | “Bath salts”; related to khat     | Stimulant group, limited chronic-outcome data      |
| Dissociatives        | PCP; ketamine                     | NMDA channel antagonism                            |

## **LSD: Acute perceptual and behavioral hazard**

- LSD is described as a potent hallucinogen.
- Acute effects on mood, affect, and thought may be unpredictable.
- Behavior can be bizarre or dangerous during intoxication.
- The supplied excerpt does not specify a diagnostic tissue lesion for LSD exposure.

## **MDMA: Longer-term effects remain uncertain**

- MDMA is a psychomotor stimulant also known as ecstasy.
- Robbins raises possible depletion of CNS serotonin after chronic use.
- Potential consequences include sleep problems, depression, anxiety, and aggression.
- Use “may” and “potential” for this association; Source emphasizes knowledge gaps.

## **Therapeutic investigation is not equivalent to safety**

- Ketamine derivatives are used therapeutically for severe depression in selected settings.
- Clinical trials have investigated hallucinogens for certain psychiatric conditions.
- The source reports initial short-term benefit in selected populations.
- Controlled clinical use should not be conflated with unregulated exposure.

## Across classes: Mechanism predicts acute phenotype

| Agent class     | Primary pathway in Robbins                  | Major acute clinical concern             |
|-----------------|---------------------------------------------|------------------------------------------|
| Cocaine         | Dopamine / norepinephrine reuptake blockade | Sympathetic excess; seizures; ischemia   |
| Opioids         | $\mu$ -opioid agonism                       | Respiratory suppression                  |
| Methamphetamine | Dopamine release                            | Euphoria, crash; neurobehavioral effects |
| Cannabinoids    | CB1 agonism                                 | Altered perception and coordination      |
| Dissociatives   | NMDA channel antagonism                     | Dissociative psychoactive effects        |

## Across classes: Recognizable organ injury patterns

| Agent / exposure                     | Organ pattern                                   | Causal interpretation               |
|--------------------------------------|-------------------------------------------------|-------------------------------------|
| Cocaine                              | Myocardial infarction; septal perforation       | Vascular tone / intranasal exposure |
| Injected heroin                      | Tricuspid endocarditis; septic pulmonary emboli | Contaminated injection              |
| Heroin with insoluble cutting agents | Pulmonary foreign-body granulomas               | Particulate embolization            |
| Cannabis smoke                       | Chronic airway irritation                       | Repeated inhalational exposure      |
| Methamphetamine                      | Psychosis / behavioral change                   | Neurotransmitter dysfunction        |

# A useful differential: Ischemia versus respiratory failure

## Cocaine pattern

- Sympathetic activation predominates.
- Tachycardia, vasoconstriction, thrombosis.
- Acute ischemia or arrhythmia is plausible.

## Opioid pattern

- Central respiratory suppression predominates.
- Hypoventilation and hypoxia drive mortality.
- Coexisting infection or adulterant injury may be present.

# Case: Abrupt collapse after unknown drug ingestion

## Clinical vignette (hypothetical)

A person becomes profoundly unresponsive with markedly depressed breathing after taking a substance of uncertain composition.

**Which drug class and reversible fatal pathway should be considered?**

## **Case: Chronic intranasal exposure**

### **Clinical vignette (hypothetical)**

A patient has a perforated nasal septum and a history of repeatedly insufflating a stimulant powder.

**Which source-described drug and route-specific injury fit this pattern?**

## **Case: Recurrent emesis in a heavy cannabis user**

### **Clinical vignette (hypothetical)**

A person with heavy cannabis use experiences repeated episodes of severe vomiting and reports resolution after stopping exposure.

**Which syndrome explains this clinical association?**

# Four principles for pathology interpretation

## Pharmacology

Identify the receptor or transporter mechanism of acute toxicity.

## Route

Ask whether nasal, inhaled, or injection injury adds local pathology.

## Composition

Adulterants and fentanyl substitution can change the injury pattern.

## Association

Use morphology plus history; Avoid assuming lesions uniquely identify a drug.

## Core clinicopathologic synthesis

- Cocaine combines reward-pathway effects with severe cardiovascular and CNS injury.
- Opioid mortality is dominated by respiratory suppression; Injecting introduces infections and particulate lesions.
- Methamphetamine and hallucinogens may produce substantial neurobehavioral toxicity.
- Cannabis can cause psychomotor impairment, airway effects, hyperemesis, and withdrawal in some individuals.
- Attribution requires exposure history and a mechanism compatible with the observed lesion.

## Primary reading and source boundaries

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Chapter 9, Environmental and Nutritional Diseases, printed pages 386–389.
- Injury by Nontherapeutic Agents; Cocaine; Opioids and Opiates; Amphetamines; Marijuana; Other Drugs.
- Source-derived historical epidemiology is explicitly labeled by year.
- Conceptual diagrams are original PowerPoint shapes, not reproduced textbook illustrations.