Opioids

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There has been **no greater disruption** of modern civilizations as the insidious havoc brought upon them by the **addictive potential** of **opioid compounds** and their derivatives.

From the **introduction of opium into China** in the 17th century, resulting in the undermining of its organized system, to the modern-day pharmaceutical **production of synthetic narcotic analgesics**, these **compounds** have **infiltrated urban** and **rural** societies.

Today, **narcotic addiction** permeates **all socioeconomic classes**, from economically underserved communities to affluent neighborhoods to the U.S. **armed forces**.

Among the substances **most** frequently involved in **toxic human** exposures**, analgesics, with or without narcotic components**, account for **14%** and **11.7%** of all adult and human exposures, respectively.

The **increase** is largely **due to** the **illicit** use of prescription **pain relievers** such as **oxycodone and hydrocodone**.

These compounds are **not** necessarily **obtained only** through illicit **drug dealing** (street drugs), **but** their **supply** is **abundant due to** fraudulent and illegitimate **prescriptions**, as well as in the course of overprescribing practices.

Health care professionals are **also** particularly **vulnerable** to the **addictive** potential of **narcotics**, principally **due to easy accessibility**.

Initial narcotic ingestion is often an **unpleasant experience**.

Patients usually **complain** of nausea, dizziness and muscular weakness.

With **continued use**, individuals build **tolerance** to the **unpleasant adverse reactions** in **preference to** the **euphoric** effects.

Opioid compounds are ingested orally in **tablet** or **capsule** form, the most **common method** of **administration** (considering both therapeutic and illicit drug use).

As greater tolerance develops, ingesting the **same amount** of drug does **not produce euphoria** as initially experienced, **necessitating** either **higher doses** or an **alternate**, more immediate **method of administration**.

This includes **rendering** the **tablets to a powder**, or using a reformulated powder form, for **nasal insufflation** (snorting), for **injection subcutaneously** (skin popping) or intravenously.

Classification

By definition, **opiates**, as **a class**, exert their **pharmacological effects** at **opioid receptors**, whereas **opioids** are **alkaloid** extracts of the **opium poppy**.

Opium, the **parent crude** form of the naturally occurring compounds, is derived from the **milky exudates** of the unripe capsule **of** *Papaver somniferum L.* (**opium poppy**).

The **plant** is **cultivated** in the **Mediterranean** and **Middle East** regions, **India** and **China**.

About **two dozen alkaloids**, of which **morphine occupies** about **10%**, are formed primarily in various cells of the plant.

Interestingly, the very **small seeds** of the plant **do not contain** opium.

Few pharmacological and toxicological **differences** exist between the **classes**.

Some **pharmacokinetic properties**, however, **distinguish** the **compounds**, especially among the many **narcotic derivatives**.

Mechanism of Toxicity

The mechanism of opiate toxicity is an **extension** of its **pharmacology** and is directly **related** to **interaction** with stereospecific and saturable binding sites or **receptors** in **central nervous system tissues**, including the cerebrum, limbic system, basal ganglia and brain stem.

These **receptors** are **classified according** to the empirical **observations** noted for the variety of **opioid effects**.

The **opioid receptors** are **biologically** active **sites** of **several endogenous ligands**, including the **two** pentapeptides, **methionine-enkephalin** and **leucine-enkephalin**.

Three receptor classes have been identified:

1. **Compounds** that selectively **bind** to the ***μ-receptor*** exhibit **morphine-like** analgesia, euphoria, respiratory depression, miosis, partial gastrointestinal inhibition and sedative effects.

2. **Narcotic antagonists** such as pentazocine, nalorphine and levorphanol appear to **bind** to the ***k-receptor***, **although** analgesia, sedation, delusion, hallucinations, GI inhibition and miotic effects **still persist**.

3. **Pentazocine** and **nalorphine** are **also** described as having **affinity** for the ***δ-receptors*** although **this binding** is primarily **associated** with **dysphoria** and **mood changes**.

Toxicokinetics

Morphine is **rapidly absorbed** from an **oral** dose, and from intramuscular and subcutaneous **injections**.

Peak plasma levels occur at 14 to 60 minutes and 14 minutes, respectively.

Morphine is **metabolized extensively**, with only **2% to 14% excreted** as the **parent molecule**, while **60% to 80%** is **excreted** in the urine as the **conjugated glucuronide**.

Heroin is rapidly **biotransformed** first to **monoacetylmorphine** and **then** to **morphine**.

Both heroin and monoacetylmorphine **disappear rapidly** from the blood (t½=3 minutes, 5–10 minutes, respectively).

Thus, **morphine** levels **rise slowly**, **persist longer**, and **decline slowly**.

Codeine is **extensively metabolized**, primarily to the **glucuronide conjugate**.

About **10% to 14%** of a dose is **demethylated** to **form morphine** and **norcodeine conjugates**.

Therefore, **codeine**, **norcodeine** and **morphine** in free and conjugated forms **appear** in the **urine** after **codeine ingestion**.

Mechanism of Toxicity

Clinical signs and symptoms correlate with the **highest concentrations** of **binding sites** in **CNS** and other tissues.

The limbic system, thalamus, corpus striatum, hypothalamus, midbrain, and spinal cord have the highest concentrations.

Analgesia appears to affect **spinal** ascending and descending tracts, **extending** up to the **midbrain**.

Mood, **movement**, and **behavior** correlates with interaction with receptors in the **basal ganglia**, while **mental confusion**, **euphoria**, **or dysphoria** alter neuronal activity in the **limbic system**.

Hypothalamic effects are responsible for **hypothermia**.

Miosis is thought to **occur** from **μ-receptor stimulation**.

Signs and Symptoms of Clinical Toxicity

The clinical presentation of the opioid is characterized by **CNS depression** (including coma), **miosis** and **respiratory depression**.

Miosis is generally an **encouraging sign** since it suggests that the **patient** is **still responsive**.

Respiratory depression is a **result** of **depressed brain stem** and **medullary respiratory centers**, responsible for maintenance of normal rhythm.

μ-receptor agonists **depress respiration** in a **dose-dependent manner,** and can **lead** to **respiratory arrest** within **minutes**.

Fifty percent of **acute opioid overdose** is **accompanied** by a **noncardiogenic pulmonary edema** responsible for the **majority** of **fatalities**.

The condition involves **loss of consciousness** and **hypoventilation**, probably resulting from hypoxic, stress-induced, pulmonary capillary fluid leakage.

Peripheral effects include **bradycardia**, **hypotension** and **decreased GI motility**.

Urine output also **diminishes** as a **consequence** of **increased** antidiuretic hormone (**ADH**) secretion.

Clinical Management of Acute Overdose

Maintenance of **vital functions**, including **respiratory** and **cardiovascular** integrity, is of **paramount importance** in the clinical **management** of **acute opioid toxicity**.

Gastric lavage and induction of **emesis** are effective **if** treatment is instituted **soon after ingestion**.

It is **possible** to **reverse** the **respiratory depression** with **opioid antagonists**.

Naloxone is a pure **opioid antagonist**.

Naloxone is also **indicated** in the **diagnosis** of suspected **acute opioid overdose**.

Depending on the **extent** of **narcotic overdose**, a **continuous infusion** of **naloxone** may be required, **especially** in the presence of **opioids** with **longer half-lives**, such as **propoxyphene** or **methadone**.

As **respiration improves**, **naloxone**, which has a **half-life** of **60 to 90 minutes**, may be **discontinued** and **resumed**, as **necessary**.

If there is **no response** after **10 mg** of **naloxone**, concomitant ingestion with **other depressants** is likely.

It should be noted that **naloxone** is of **little benefit** in reversing **noncardiogenic pulmonary edema**.

Naltrexone is also a pure **opioid antagonist** available as oral **tablet** dosage form **only**.

A **50-mg** dose of **naltrexone blocks** the pharmacological **effects** of **opioids** by **competitive binding** at **opioid receptors**.

It is **also** indicated in the **treatment** of **alcohol dependence**.

Naltrexone has been noted to induce **hepatocellular injury** when **given** in **excess**.

Nalmefene, available in 1mg/mL and 100µg/mL ampoules, is **indicated** for the **complete** or **partial reversal** of **natural** or **synthetic** opioid effects.

It is a 6-methylene **analog** of **naltrexone**.

Nalmefene has been **associated** with **cardiac instability**, **although** this reaction **appears** to be the **result** of **abrupt reversal** of **opioid toxicity.**

Several drugs have **agonist** activity at some receptors (**k**) and **antagonist** activity at other (**μ**) receptors.

Nalbuphine is a potent analgesic with narcotic **agonist** and **antagonist** actions.

Other mixed **agonist-antagonist** compounds are **designated** as **partial agonists**, such as **butorphanol**, **buprenorphine** and **pentazocine**.

These compounds are **potent analgesics** and **weakly antagonize** the effects of **opioids** at the **μ-receptor**, while **maintaining** some **agonist properties** at the **k**- and **δ**-receptors.

Tolerance and Withdrawal

The Department of Mental Health and Substance Dependence at the World Health Organization (WHO), in collaboration with the U.S. National Institute on Drug Abuse (NIDA), defines several terms important in understanding drug abuse and the phenomena of tolerance and withdrawal.

Addiction involves compulsive **psychoactive drug use** with an **overwhelming involvement** in the securing and using of such drugs.

The **withdrawal syndrome** occurs as a result of **sudden** or **abrupt discontinuation** of the **substance**.

Compulsive drug use involves the **psychological need** to procure and use drugs, often referred to as **craving**.

In this case, the uncontrollable drive to obtain the drugs is necessary to maintain an optimum state of well-being.

Habituation refers to **psychological dependence**.

Physiological dependence involves the **need** for **repeated administration** to **prevent** the **withdrawal syndrome**.

In fact, with repeated **chronic** dosing, **seizure threshold** for opiate **narcotics** is **elevated**, **threatening** the precipitation of **seizure upon withdrawal** (rebound effect).

With **repeated administration**, addicted individuals **necessitate greater amounts** of drug **to achieve** the **desired effect**.

Conversely, the **euphoric effect** is **markedly diminished** with **continued use** of the **same amount** of drug.

Since various **pharmacological effects** on **different organ** systems are **not uniformly distributed**, **tolerance** is **not evenly demonstrated**.

While a **diminished effect** continues with **progressive tolerance**, the **increasing doses** threaten induction of **respiratory depression**.

Increased metabolism and adjustment to the sedative, analgesic, and euphoric effects are proposed as possible mechanisms for the development of tolerance that is, the physiological drive to achieve homeostasis.

Depending on the **drug** and the intensity and **severity** of the **addiction**, the **withdrawal syndrome** is precipitated **hours after** the **last narcotic dose**, with **peak intensity** occurring at about **72 hours**.

The **intensity** of the **syndrome** is **greatest with** heroin, followed by morphine and methadone.

Heroin withdrawal is characterized by acute, **sudden symptoms** of **greater vigor**, while **methadone withdrawal** is distributed over **7 to 10 days** and is of **lower intensity**.

The development of **muscle spasms** has come to **define** the **syndrome**, commonly **known** as **“kicking the habit”.**

Although the **syndrome** is **rarely fatal**, **administration** of an **opioid** at **any time** and at relatively **low doses** during withdrawal **alleviates the condition**.

Casual, habitual, uncontrolled use of prescription narcotics often follows the “**medical addict**.”

The **cyclic behavior** is characterized by **excessive use** of the drugs **followed** by a **period of abstinence** and is **often** accompanied by **subtle signs and symptoms of withdrawal**.

The **withdrawal** experience in **this case** is often **indistinguishable** and unrecognizable **by both patients and health care professionals** and **may** be **mistaken** with **other** low grade indicators.

For **example**, within **24 hours after** the **last opioid dose**, patients **may experience** anxiety, irritability, abdominal cramps, diaphoresis, insomnia and joint pain.

Nevertheless, these are **warning signs** of the **development of tolerance and withdrawal** and should be deemed, understood, and accepted as a **chronic disease**.

Characterization of the Opioid Withdrawal Syndrome

Stage	Time after last dose	Signs and symptoms
Anticipatory	3–4 hr	Withdrawal fear, craving, compulsive drug-seeking behavior
Early withdrawal	8–12 hr	Lacrimation, sweating, listless behavior, anxiety, restlessness, stomach cramps
	12–16 hr	Restless sleep, nausea, vomiting, mydriasis, anorexia, tremors; cold clammy skin, fever, chills; compulsive drug-seeking behavior
	48–72 hr	Peak intensity; tachycardia, hypertension, hypothermia, piloerection (goose bumps, *cold turkey*), muscle spasms; continued nausea, vomiting, dehydration, compulsive drug-seeking behavior; risk of cardiovascular collapse
Protracted abstinence	6 mo	Stimulus-driven cravings, anorexia, fatigue, bradycardia, hypotension

Clinical Management of Addiction

The risks and benefits of traditional medical detoxification associated with the use of **methadone and narcotic antagonists** are presented.

Although methadone treatment programs have **shown** some **success** in **opioid detoxification**, significant **progress** in therapeutic intervention has **resulted** more **recently** using **buprenorphine**.

Buprenorphine is the **first opioid drug approved** under the Drug Addiction Treatment Act (DATA) **for** the **treatment** of **opioid dependence** in an office-based setting.

The drug, a **partial opioid agonist**, is dispensed **for outpatient** use and administered **sublingually**, sometimes **in combination with naloxone**, the full opioid antagonist.

The antagonist **blocks μ-receptors**, thus **precipitating** the **withdrawal syndrome**.

Buprenorphine reduces illicit opioid use and helps patients remain in treatment programs by increasing availability of treatment options, **suppressing symptoms of opioid withdrawal**, and **decreasing cravings for opioids**.


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