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i) ITS RELATION TO DRUG INDUCED PULMONARY DISEASE

INTRODUCTION

DRUG ADDICTION

Drug addiction is a treatable, chronic medical disease that involves complex interactions between a person's environment, brain circuits, genetics, and life experiences.

People with drug addictions continue to compulsively use drugs despite the negative effects.

Substance abuse has many potential consequences, including overdose and even death. In this study we will learn about the short and long-term effects of drug addiction. Discover treatment options for common symptoms.

THE EFFECTS OF DRUG ADDICTION ON THE BRAIN AND THE BODY

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- Short-Term Effects
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SHORT-TERM EFFECTS

People can become addicted to any psychoactive ("mind-altering") substance. Common addictive substances include alcohol, tobacco (nicotine), stimulants, hallucinogens, and opioid painkillers.

Many of the effects of drug addiction are similar, no matter what substance someone uses. The following are some of the most common short-term effects of drug addiction.

PHYSICAL EFFECTS

Drugs can produce many short-term physical effects. These may include:

- Shallow breathing
- Elevated body temperature
- Rapid heart rate
- Increased blood pressure
- Insomnia
- Drowsiness
- Slurred speech
- Decreased or increased appetite
- Uncoordinated movements

Drug abuse can also lead to dependence and withdrawal symptoms, even in the short-term:



- **Dependence:** People can become physically dependent on a substance fairly quickly. This means they need a larger amount of that substance to get the same “high.”
- **Withdrawal symptoms:** When someone with a dependence on a drug stops using it, they can experience withdrawal symptoms, such as excessive sweating, tremors, panic, difficulty breathing, fatigue, irritability, and flu-like symptoms

DRUG ABUSE VS. DRUG ADDICTION

While the terms “drug abuse” and “drug addiction” are often used interchangeably, they're different. Someone who abuses drugs uses a substance too much, too frequently, or in otherwise unhealthy ways. However, they ultimately have control over their substance use.

Meanwhile, someone with a drug addiction abuses drugs in a way that affects every part of their life. They can't stop misusing drugs even if they want to.

MENTAL EFFECTS

Psychoactive substances affect the parts of the brain that involve reward, pleasure, and risk. They produce a sense of euphoria and well-being by flooding the brain with dopamine.

This leads people to compulsively use drugs in search of another euphoric “high.” The consequences of these neurological changes can be either temporary or permanent.

The short-term mental effects of drug abuse can include:

- Difficulty concentrating
- Irritability
- Aggression
- Angry outbursts
- Lack of inhibition
- Hallucinations

LONG-TERM EFFECTS

If drug addiction is left untreated, it can lead to a range of serious long-term effects. These are some of the most common long-term effects of drug addiction on the brain and body.

Physical Effects

Drug addiction can have serious long-term physical consequences, including major organ damage and even death.

Some of the most common long-term physical effects of drug addiction include:

- Kidney damage
- Liver damage and cirrhosis
- Various forms of cancer
- Tooth decay



- Skin damage
- Infertility
- Stroke
- Seizures
- Sexual dysfunction
- Cardiovascular problems
- Lung problems
- Overdose and death

The statistics of overdose and deaths associated with drug abuse is not well represented recently but approximately 100,000 people die from drug use. According to the WHO.

MENTAL EFFECTS

When someone continues to use drugs, their health can deteriorate both psychologically and neurologically. Some of the most common long-term mental effects of drug addiction are:

- Cognitive decline
- Memory loss
- Paranoia
- Depression
- Anxiety
- Psychosis

SIGNS OF DRUG ADDICTION

The signs of drug abuse and addiction include changes in behavior, personality, and physical appearance.

If you're concerned about a loved one's substance use, here are some of the red flags to watch out for:

- ii) Changes in school or work performance
- iii) Secretiveness
- iv) Relationship problems
- v) Risk-taking behavior
- vi) Legal problems
- vii) Aggression
- viii) Mood swings
- ix) Changes in hobbies or friends
- x) Sudden weight loss or gain
- xi) Unexplained smells on the body or clothing

DRUG ADDICTION IN MEN AND WOMEN

Men and women are equally likely to develop drug addictions. However, men are likelier than women to use illicit drugs, die from a drug overdose, and visit an emergency room for addiction-related health reasons. Meanwhile, women are more susceptible to intense cravings and repeated relapse.

How Addiction Is Diagnosed ?

TREATMENT

While there's no single "cure" for drug addiction, it's about as treatable as other chronic diseases. The primary ways of treating drug addiction include:



Psychotherapy: Psychotherapy, such as cognitive behavioral therapy (CBT) or family therapy, can help someone with a drug addiction develop healthier ways of thinking and behaving.

Behavioral therapy: Common behavioral therapies for drug addiction include motivational enhancement therapy (MET) and contingency management (CM). These therapy approaches build coping skills and provide positive reinforcement.

Medication: Certain prescribed medications help to ease withdrawal symptoms. Some examples are naltrexone (for alcohol), bupropion (for nicotine), and methadone (for opioids).

Hospitalization: Some people with drug addiction might need to be hospitalized to detox from a substance before beginning long-term treatment.

Support groups: Peer support and self-help groups, such as 12-step programs like Alcoholics Anonymous, can help people with drug addictions find support, resources, and accountability. There are many different ways of treating drug addiction. Forming an individualized treatment plan with the help of your healthcare provider is likely to be the most effective approach.

How Is Addiction Treated?

SUMMARY

Drug addiction is a complex, chronic medical disease that causes someone to compulsively use psychoactive substances despite the negative consequences.

Some of the short-term effects of drug abuse and addiction include changes in appetite, movement, speech, mood, and cognitive function. The long-term effects can include major organ damage, cognitive decline, memory loss, overdose, and death.

Treatment for drug addiction may involve psychotherapy, medication, hospitalization, support groups, or a combination.

CHAPTER 2

DISCUSSIONS AND RESEARCH

The lungs are a target for a variety of possible toxic substances because of their large contact surface. They can also act as a metabolism site for certain substances. Drugs can induce specific respiratory reactions, or the lungs may be affected as part of a generalized response. More than 380 medications are known to cause drug-induced respiratory diseases, the true frequency is unknown. The number of drugs, that cause lung disease, will undoubtedly continue to increase as new agents are developed.

To minimize the potential morbidity and mortality from drug-induced respiratory diseases, all health care providers should be familiar with the possible adverse effects of the medications they prescribe. The person-to-person variability of a drug response is a major problem in clinical practice and in drug development. The variability in drug response among patients is multifactorial, including extrinsic factors like environmental aspects and also genetic and intrinsic factors that affect the disposition of a certain drug.

Drug-induced lung injury may involve the airways, lung parenchyma, mediastinum, pleura, pulmonary vasculature, and/or the neuromuscular system. The most common form of drug-induced lung toxicity is drug-induced interstitial lung disease (DILD). Oral and parenteral routes of drug administration are most frequently cited as causing DILD; however, nebulized and intrathecal administration have also been implicated. Pulmonary drug toxicity may result from a direct or indirect drug effect. Direct effects may be either idiosyncratic or due to a toxic reaction of the drug or one of its metabolites.

Recognition of drug-induced lung disease, however, is difficult because the clinical, radiological, and histological findings are nonspecific. The connection with drug use and the development of related inflammatory damage or idiosyncratic toxicities is hard to recognize and objectify, especially in those cases using multiple drugs.

RISK FACTORS FOR DILD

The likelihood of developing adverse pulmonary effects secondary to drugs remains largely unpredictable and idiosyncratic. Patients likely to develop DILD are those receiving chemotherapy, those with inflammatory conditions such as rheumatoid arthritis and inflammatory bowel disease, and those receiving concurrent multiple toxic agents. Some of the known risk factors are as follows:

- i) Age
- ii) Sex
- iii) Ethnicity
- iv) Dose
- v) Oxygen
- vi) Drug Interaction
- vii) Underlying Lung Disease
- viii) Radiation



CAUSES OF DILD

The major representatives of DILD include cytotoxic, cardiovascular, anti-inflammatory, antimicrobial, biological agents and miscellaneous drugs.

MECHANISM OF TOXICOLOGY IN DILD

The mechanism of DILD is not fully understood. Pulmonary toxicology can be divided in two broad categories based on the route of exposure to the offending agent. Alveolar and bronchial epithelial cells may be injured by inhalation of a drug or through the vasculature system. Various reasons may be put forward to explain why certain drugs cause toxicity specifically in the lungs:

- (1) Some substances reach higher cell or tissue concentrations in the lung than in other organs.
- (2) A specific pattern or extent of bioactivation occurs in the lung.
- (3) The consequences of bioactivation are lung specific.

Furthermore, some foreign compounds may accumulate preferentially in lung tissue.

Lung injury that is induced by pneumotoxic agents gives rise to alveolitis and oedema. In response to injury to the lung parenchyma, there is an immediate requirement to initiate tissue repair and restore barrier function. Acute injury may progress to chronic inflammation and eventually lead to fibrotic change that ultimately interferes with gas exchange. Chemotherapeutic drugs can additionally cause a direct toxic reaction, and direct toxicity usually occurs over time before manifesting clinically induced pulmonary fibrosis.

Most chemicals do not cause cell toxicity directly; usually some form of biotransformation is required for chemical agents to cause cell injury. This biotransformation process may increase the toxicity of chemicals by producing reactive metabolites. If these reactive metabolites are not readily removed by enzymatic or nonenzymatic reactions, they may cause cell injury and death.

The concept that some drugs may cause oxidative stress and that their toxicity may be enhanced by the (therapeutic) administration of oxygen is of paramount importance in clinical settings. A disturbance of oxidant/antioxidant system homeostasis may occur. The resulting toxic oxygen species depletes the reducing equivalents and generates oxidative stress.

DIAGNOSIS AND PROCEDURES

The diagnosis of DILD is mainly one of exclusion and requires the meticulous ruling out of all other possible causes. Unfortunately, therapeutic agents that cause DILD are often used to treat disease that can result in diffuse interstitial lung changes.

It is, therefore, frequently difficult to determine if pulmonary abnormalities are related to the underlying disease or due to the medication. Discontinuance of the offending agent is often followed by spontaneous improvement, whereas failure to appreciate the causal relationship between the drug and the pulmonary disease can lead to irreversible lung injury or death.

The diagnosis of DILD is usually based on several criteria:

- (1) A history of drug exposure with correct identification of the drug, its dose, and its duration of administration.
- (2) Clinical, imaging and histopathological patterns which are consistent with earlier observations with the same drug.
- (3) Exclusion of other lung disease.



- (4) Improvement following discontinuation of the suspected drug and
- (5) Recurrence of symptoms on rechallenge, but rechallenge can be hazardous.

CLINICAL SIGNS AND SYMPTOMS/ PHYSICAL EXAMINATION

Many of the DILD have similar clinical features and are not easily distinguished on examination. Time to onset is from a few days to years and is unpredictable. The onset of the disease may be progressive over a few weeks, with isolated fever followed by the insidious development of respiratory symptoms, or the onset may be abrupt. Acute pneumonitis secondary to drug therapy can present with acute breathlessness occurring over several hours or days.

Fever, rash, wheeze, and peripheral eosinophilia are features of these reactions. The chronic form of the disease manifests as decreased exercise tolerance mainly as a result of progressive dyspnea. In the case of pulmonary hemorrhage, patients usually present with hemoptysis, dyspnea, hypoxemia, and acute anemia. It is also important to be aware that DILD may be enhanced by other factors such as age, impaired renal function, smoking and radiation therapy.

The physical findings of DILD are nonspecific. Physical examination reveals crackles on respiratory examination and may include digital clubbing. Signs of pulmonary hypertension with right ventricular dysfunction, such as lower-extremity edema or jugular venous distention, can occur late in the course and are not helpful in diagnosing a specific DILD.

LABORATORY STUDIES

In general, laboratory analyses do not help in establishing the diagnosis. The white blood count may show increased eosinophils in cases of drug-induced pulmonary eosinophilia.

However, the absence of peripheral eosinophilia does not exclude a diagnosis of drug-induced eosinophilic pneumonia.

In the case of HP, peripheral eosinophilia may be present. Testing for antinuclear antibodies, anti-cytoplasmic antibodies and anti-glomerular basal membrane autoantibodies is essential to classify drug-induced DAH (autoimmune *vs* non-autoimmune), and to separate drug-induced DAH from DAH related to a naturally occurring systemic illness, for example the determination of anti-cytoplasmic antibodies may be appropriate for the drug PTU.

TREATMENT

The primary goal of treatment is to suppress the inflammatory response and prevent the deposition of fibrotic tissue. The management strategy depends on the severity of the disease.

In the first step, the medication should be withdrawn and the treatment of DILD consists appropriately managing of pulmonary symptoms, after other possibilities are eliminated and DILD is highly suspected.

Ideally, symptoms should remit, and management includes supportive care. Acute episodes of drug-induced pulmonary disease usually disappear 24–48 hours after the drug has been discontinued, but chronic syndromes may take longer to resolve. Because hypoxemia is common in DILD, supplemental oxygen therapy is often prescribed.

Because many patients with DILD are treated with immunosuppressive medications and are at some modest increased risk for the development of infections, patients with DILD should receive a pneumococcal vaccine and a yearly influenza virus vaccine. Furthermore, tuberculosis may be associated with anti-tumor necrosis factor monoclonal antibody therapy.



PROGNOSIS

Prognosis of acute DILD may be satisfactory if the diagnosis is performed early. Therefore, a full recovery could be achieved. On the other hand, failure to recognize a drug-mediated lung disease can lead to significant morbidity and mortality.

The prognosis is variable and depends on the specific drug and underlying clinical, physiologic, and pathologic severity of the lung disease. Typical complications of DILD are pulmonary fibrosis and respiratory failure requiring mechanical ventilation.

Unfortunately, if the initiating injury or abnormal repair from injury is not halted, progressive tissue damage can lead to worsening physiologic impairment and even death.



CHAPTER 3

RECOMMENDATIONS, CONCLUSIONS AND REFERENCES

RECOMMENDATIONS

Therefore, it is important for physicians to be familiar with iatrogenic diseases for which their patients are at risk. Despite better appreciation of DILD, patients may still die from acute or chronic DILD. DILD is preventable to a certain extent, and sources of improvement include better information to patients, avoidance of certain drugs in allergic patients, and earlier diagnosis. Serial lung function testing is still considered useful in patients on bleomycin, less so in those on amiodarone or methotrexate.

CONCLUSIONS

Many types of lung injury can result from medicines. It is usually impossible to predict who will develop lung disease from a medicine.

Types of lung problems or diseases that may be caused by medicines include:

- Allergic reactions -- asthma, hypersensitivity pneumonitis, or eosinophilic pneumonia
- Bleeding into the lung air sacs, called alveoli (alveolar hemorrhage)
- Swelling and inflamed tissue in the main passages that carry air to the lungs (bronchitis)
- Damage to lung tissue (interstitial fibrosis)
- Drugs that cause the immune system to mistakenly attack and destroy healthy body tissue, such as drug-induced lupus erythematosus
- Granulomatous lung disease -- a type of inflammation in the lungs
- Inflammation of the lung air sacs (pneumonitis or infiltration)
- Lung vasculitis (inflammation of lung blood vessels)
- Lymph node swelling
- Swelling and irritation (inflammation) of the chest area between the lungs (mediastinitis)
- Abnormal build-up of fluid in the lungs (pulmonary edema)
- Build-up of fluid between the layers of tissue that line the lungs and chest cavity (pleural effusion)
- Abnormal pressure of the arteries that bring blood to the lungs (pulmonary hypertension)

Many medicines and substances are known to cause lung disease in some people. These include:

- Antibiotics, such as nitrofurantoin and sulfa drugs



- Heart medicines, such as amiodarone
- Chemotherapy drugs such as bleomycin, cyclophosphamide, and methotrexate
- Street drugs

Symptoms

Symptoms may include any of the following:

- Bloody sputum
- Chest pain
- Cough

- Fever

- Shortness of breath
- Wheezing

Exams and Tests

The health care provider will perform a physical exam and listen to your chest and lungs with a stethoscope. Abnormal breath sounds may be heard.

Tests that may be done include:

- Arterial blood gases
- Blood test to check for an autoimmune disorder
- Blood chemistry

- Bronchoscopy
- Complete blood count with blood differential
- Chest CT scan
- Chest x-ray
- Lung biopsy (in rare cases)
- Lung function tests
- Thoracentesis (if pleural effusion is present)

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