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An assimilation of risk factors, mechanisms, and plausible measures to intercept drug induced pulmonary diseases

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Abstract

The havoc created by a plethora of drug-induced diseases in the field of medical practice is devastating. A drug being introduced for its appropriate indication simultaneously evokes the risks of unwanted adverse effects of these medications in the patients. Researchers, clinicians, pharmacists, and various national and international drug safety centres are constantly involved in the quest to identify, investigate, mitigate and document the adverse effects caused by the countless number of drugs introduced to treat a multitude of human diseases. This article is intended to summarize the different types, mechanisms, risk factors, and basic measures to manage various drug-induced pulmonary disorders and their manifestations.

Keywords: Drug-induced changes; Drug-induced lung injury; Pulmonary toxicity; Injury risk factors; Preventive measures; Mechanism of action

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Introduction

Any unintended effect of a medication clinically manifested in a patient making them vulnerable to seek medical help or necessitate hospitalization can be termed as a drug-induced disease. These unintended effects of the drug can either be anticipated or unanticipated. The drug-induced diseases can be classified into mild, moderate, severe, or lethal diseases based on the severity of the illness. The tendency of certain medications to cause serious damage to different organ systems within the human body has ultimately lead to their withdrawal from the market [1]. Drug-Induced Pulmonary disorders: Various classes of drugs such as cardiovascular medications like beta-blockers, angiotensin-converting enzyme inhibitors, anti-inflammatory agents, analgesics, chemotherapeutic agents, and antibiotics used in the treatment of a variety of disease conditions and the illicit drug use often culminates in drug toxicities out of which the diagnosis of pulmonary toxicity is a cumbersome process for the physicians [2,3]. No specific blood tests or other parameters have been identified for the diagnosis of drug-induced adverse effects on the lungs. Even the findings from chest X-rays are nonspecific. The lung function abnormalities observed in the patient can be correlated to the dyspnoeic degree and changes in the chest X-rays in such patients. Knowing the drugs that can produce adverse reactions on the lungs and knowing the predisposing factors are important for improved patient safety [4].

Types of drug-induced pulmonary injury

Alveolar Hemorrhage: Drug-induced DAH/diffuse alveolar syndrome is a path-clinical syndrome in which the alveolar spaces of the lungs are accumulated by red blood corpuscles which predominantly originates from the capillaries encircling the alveoli and rarely from the pre-and postcapillary venules secondary to drug use[4].

Bronchiolitis Obliterans Organizing Pneumonia (BOOP): Organizing pneumonia/BOOP is often an inflammatory lung response reaction. This condition is mostly subsided by the withdrawal of the causative drug or administration of a suitable corticosteroid [5].

Bronchospasm and asthma: Various therapeutic agents are known to interfere with the normal airway physiology, resulting in bronchoconstriction or asthma. The drugs that cause platelets to release cytotoxic compounds and those that alter the sensitivity to leukotrienes lead to asthmatic attacks [6,7].

Diffuse alveolar damage, ARDS: can be manifested as diffuse alveolar damage resultant from the alveolar endothelial cell and

type II pneumocyte necrosis. These patients may progress to acute respiratory distress syndrome [8].

Eosinophilic Reactions: The heterogeneous group of diseases where the causative drugs cause an elevation in the eosinophilic count within the lung parenchyma and airways is referred to as eosinophilic lung disease/reaction. This is a common allergic manifestation produced by the drug which disappears when this medication is withdrawn [9].

Pneumonitis and Fibrosis: Pneumonitis is the inflammation of the lung interstitium like the alveolar septa which in-turn, when undetected and continuously exposed to the culprit drug over few weeks may progress to end-pulmonary fibrosis.

Hypersensitivity Lung Disease: Unlike pneumonitis/fibrosis, hypersensitivity lung disease has quick onset which may occur over a few days to weeks.

Hypoventilation: Respiratory depression also termed hypoventilation has a large array of etiology. This breathing disorder when triggered by a medication manifested as slow and ineffective breathing can be restored upon stopping this medication.

Noncardiogenic Pulmonary Edema: The noncardiogenic pulmonary edema/NCPE can be precipitated within hours of exposure from a medication prescribed as part of a standard prescription or when administered in overdose. However, it can subside rapidly after the drug discontinuation.

Pleural disease: A pleural disease induced by a drug should be suspected in any patient with idiopathic pleural abnormality clinically characterized by pleuritic chest pain, pleural effusion, or pleural thickening without infiltration of the parenchyma [10-13].

Pneumothorax: Pneumothorax is the abnormal presence of air in the pleural space which can either be primary or secondary. The latter can sometimes be associated with various drugs. However, it is quite a dilemma to determine the causal nature of this association [14].

Pulmonary–Renal Syndrome: The clinical manifestations of pulmonary-renal syndrome of drug-induced origin include hemoptysis without any other obvious etiology and these manifestations can be temporarily ceased by adequate pharmacological therapy along with the withdrawal of the suspected drug [10].

Mechanism of drug-induced pulmonary injury

The 4 primary mechanisms behind drug-induced pulmonary toxicity include

Oxidative stress: Certain drugs lead to the formation of a large number of free radicals and singlet oxygen, which can damage the epithelium and endothelium. E.g. Nitrofurantoin [15,16]

Direct cytotoxic damage to the lung parenchyma: Immunosuppressants exert direct cytotoxic parenchymal injury. Destructive effects on the DNA of epithelial cells are also possible, such as that seen with bleomycin [17].

Accumulation of phospholipids in macrophages and alveolocytes: Leading to their accumulation in the distal respiratory tract. This mechanism underlies lung lesions observed in amiodarone lung injury [18] and exogenous lipoid pneumonia.

Immune-mediated reactions: This mechanism can involve a wide range of drugs, such as sulfanilamides, hydralazine, monoclonal antibodies to tumour necrosis factor-alpha, and other biological drugs [19,20]

Risk Factors

The occurrence of adverse pulmonary effects secondary to drugs remains largely unpredictable and idiosyncratic.

Age: Both extremes of age (i.e. childhood and old age) are associated with an increased risk of drug toxicity [21].

Sex: Most of those affected have been elderly and most have been females. There is no scientific evidence yet supporting the view that gender influences the risk of DILD.

Ethnicity: There may be racial differences in the incidence of DILD [22]. Genetic polymorphisms may help explain why some groups of patients have the expected response to pharmacotherapy whereas others experience toxicity or therapeutic failure

Dose: In several cases, such as therapies with amiodarone, bleomycin, or BCNU (carmustine), the dose is a risk factor for a drug to cause ILD [23]. Physicians should keep in mind this possibility and adjust the dose required for the patient.

Oxygen: Lung tissue is vulnerable to the toxic effects of oxygen and thereby causes oxygen damage [24].The lungs are equipped with an extensive antioxidant network to protect the lung from tissue damage by reactive oxygen species. This network may be insufficient and this situation of inadequate protection is called oxidative stress.

Drug Interaction: Proper monitoring of the drugs taken concomitant should be done. Drugs from the same therapeutic class may induce a similar pulmonary toxicity pattern. Eg: Hazardous associations have been reported with the co-administration of cisplatin and bleomycin [20], which can increase the risk of bleomycin-induced interstitial lung disease.

Radiation: Radiation can injure the lung by DNA damage and radiation therapy in combination with chemotherapy may be synergistic [25].

Underlying Lung Disease: Pre-existing lung disease as an important risk factor [26].

Basic measures in preventing pulmonary drug toxicity

- Treatment is stopping the drug that is causing pulmonary disease and managing the pulmonary symptoms [27].
- Doses of causative agents should be adjusted to decrease the risk of drug-induced pulmonary disease [28].
- Smoking cessation.
- Control of other chronic underlying lung diseases
- Prompt treatment of concomitant respiratory infections.
- Glucocorticoid therapy has been observed beneficial in gas

exchange and reversal of radiographic abnormalities in some drug-induced pulmonary toxicity [29].

- Patients with severe lung toxicity and irreversible fibrosis may be considered for lung transplantation [30].
- Pulmonary function tests especially diffusing capacity of the lungs for carbon monoxide [DL_{CO}]), the 6-minute walk test, and chest radiographs are recommended to monitor the course of the disease in case of long term management and also in patients who are about to begin or already taking drugs with pulmonary toxicities [27].

Various drug-induced lung diseases, causative agents, their mechanism, and management techniques are discussed in **Table 1.**

Table 1: Drug-induced pulmonary diseases.

DRUG INDUCED PULMONARY DISEASE	MOA	CAUSATIVE DRUGS	COMMENTS & MANAGEMENT
Pneumonitis and Fibrosis	Apparent dose-dependent relationship with symptoms	Amiodarone, beta-blockers, busulfan, bleomycin, carmustine, ciprofloxacin, hydralazine, adalimumab, methotrexate, lomustine, nitrofurantoin, oxygen, radiation, statins, sulfasalazine, tamoxifen, and thalidomide [10]	Discontinuation of the drug.
	Diffuse fibrosing alveolitis induced by a variety of toxic chemicals [31].		Systemic corticosteroids are administered at a prednisolone dose of 40–60mg/day [33].
	It has also been proposed that immunologic mechanisms may play a role in the development of pulmonary fibrosis(bleomycin) [32].		Monitoring DLCO (Carbon monoxide diffusing capacity) is recommended only for patients taking drugs associated with a high incidence of pulmonary fibrosis [28].
Hypersensitivity Lung Disease	Hypersensitivity pneumonitis	Pravastatin, lovastatin, and simvastatin [34-36]	Discontinuation of the drug and treatment with oral corticosteroids led to rapid improvement [10]
	Interstitial pneumonitis, granulomatous hypersensitivity	Ticlopidine, Ciprofloxacin [37], Sirolimus [38], Ampicillin, bupropion, carbamazepine, cytarabine, cephalosporins, cytarabine [39], erythromycin, interferon alfa, methotrexate, NSAIDs, nitrofurantoin, penicillin, phenytoin, sulfonamides,trimethoprim-sulfamethoxazole [40]	Severe cases may need respiratory support; high doses of systemic steroids may be required. Usually a starting dose of prednisone at 1 mg/ kg body weight
Noncardiogenic Pulmonary Edema	Immediate anaphylaxis and delayed reactions,Altered capillary permeability [41]	Sympathomimetics [42,43], narcotics [44], salicylates, carbamazepine, cytarabine, erythromycin, hydrochlorothiazide, IV radiographic contrast agents, methotrexate, protamine, tamoxifen, and tumor necrosis factor [45,46]	Resolves quickly or 2-3 weeks after discontinuation of the drug involved [10,41].,Diuretics are indicated for patients with fluid overload.,Oxygen should be administered only in cases of hypoxemia,Inotropic agents in case of hypotension and evidence of reduced organ perfusion. (1st line: dobutamine) [47]
Bronchospasm and asthma	Not clearly understood. Probably an imbalance of pro-inflammatory and anti-inflammatory eicosanoids due to altered reaction to COX inhibition.,Beta -receptor blockade,	Aspirin [48],	Avoidance of aspirin Aspirin desensitization Acetaminophen, meloxicam, or celecoxib may be used instead of aspirin.
	Anaphylaxis (IgE-mediated)	Beta-blockers [49],	Ipratropium 17 mcg/ bronchospasm inhalation 2 to 3 puffs every 6 h
	Increased concentrations of acetylcholine leading to cholinergic stimulation	Bromelin	
	Unknown. Fluctuating estrogen levels may sensitize mast cells.	Neostigmine [50,51]	Patients with a respiratory condition such as asthma or COPD should inform providers of their condition.28
	Anaphylactoid mast-cell degranulation	Estrogen [52,53]	
	Precipitation of IgG antibodies	Meperidine [54,55]	
	Three proposed mechanisms: 109 anaphylaxis; 91 sulfur dioxide–induced cholinergic reflex, and 110 decreased sulfite oxidase concentrations.	Methyldopa [56]	

	Not clearly understood. Probably an imbalance of pro-and anti-inflammatory eicosanoids due to altered reaction to COX inhibition.	Sulfites [28],NSAIDs [28,57]	
Systemic Lupus Erythematosus	Slow acetylators with genetic deficiency of N-acetyltransferase are at a higher risk of DIL, especially from procainamide and hydralazine [58]	Hydralazine [58,59], isoniazid, phenytoin, procainamide, and sulphonamides, chlorpromazine, ethosuximide,Quinidine [60]	Symptoms rapidly resolve with discontinuation of the offending agent, and the length of time to recovery is shortened by corticosteroid administration [10]
Bronchiolitis Obliterans Organizing Pneumonia(BOOP)	Small airway inflammation, granulation tissue formation	Busulfan, gold salts, penicillamine, ridesdronate, sulfasalazine [10],Bleomycin, Radiation, Methotrexate Mitomycin-C Cyclophosphamide Cocaine [61]	Cessation of the medication or treatment with corticosteroid therapy results in resolution of symptoms and radiographic abnormalities for most patients [62].
Alveolar Hemorrhage	Immune or hypersensitivity reaction to a medication, an injury to the alveolar-capillary basement membrane, or a coagulation defect that was induced by the medication [63]	Gefitinib [64], anticoagulants [65,66], clopidogrel, cyclosporine, epoprostenol [67], fibrinolytics	Discontinuation of the drug, empiric high-dose methylprednisolone, and supportive care [10].
Eosinophilic Reactions	Eosinophilic pleural effusion	Diltiazem [68],	Symptoms resolve upon withdrawal of the offending agent [10].
	Eosinophilic pneumonia	Venlafaxine,Duloxetine, daptomycin [69]	
Hypoventilation	Induce and/or prolong neuromuscular blockade.	Glucocorticoids, calcium channel blockers, aminoglycosides,alcohol, sedatives, narcotics, and hypnotics	Caution should be used when administering any of these agents to patients with myasthenia gravis [10]
Pulmonary–Renal Syndrome	Often auto- immune-mediated aggravated by causative drugs	Penicillamine, hydralazine[3,10]	Pulse dose of methylprednisolone, followed by 1 mg/kg of prednisone gradually tapering the dose [3].
Pneumothorax	Chemotherapy-induced lysis of sub-pleural tumor deposits, the progression of subpleural tumor deposits due to lack of efficacy [16]	Propofol, Colfosceril, Poractant Alfa, Beractant, Nitric Oxide, Pentamidine, Alglucosidase Alfa, Carmustine, Dacarbazine, Bleomycin, Gefitinib, Docetaxel, Bevacizumab, Vinblastine, Epoprostenol, Actinomycin-D, Busulfan [70]	Withdraw the drug.,Supplemental oxygen: If the pneumothorax is very small,Needle aspiration: A needle attached to a syringe will be inserted into the chest cavity to remove air via suction.,Percutaneous chest tube drainage, Open chest thoracotomy may be required [17].
Cough	Induced by bradykinin, substance P, and agents that are degraded by ACE. They accumulate in the upper respiratory tract or lung when the enzyme is inhibited [71].	ACE Inhibitors [72]	Nebulized cromolyn(800 mcg/ inhalation, 2 puff four times daily) sodium may be an effective form of therapy when it is necessary to keep these patients on an ACE inhibitor [28],Alternative therapy includes angiotensin-receptor blockers (ARBs) or antihypertensive agents [72]
Pleural disease	(1) hypersensitivity or allergic reaction;	Chemotherapeutic agents, Nitrofurantoin (acute), Bromoocriptinie Dantrolene Methysergide, L-tryptophan, Drug-inducing SLE, Tocolytics Amiodarone, Esophageal variceal sclerosing agents, Interleukin-2	Drug discontinuation and corticosteroid ,treatment in more severe cases.Drug therapy withdrawal should be a considered [73,74].
	(2) direct toxic effect;		
	(3) increased oxygen free radical production;		
	(4) suppression of the antioxidant defenses; and (5) chemical-induced inflammation.		

Conclusion

The incidence of drug-induced lung injury is much more than the expected rates of incidences. Over 400 drugs are known to cause pulmonary damage. However, drug-induced lung diseases are not considered as a primary focus of an adverse drug event and are often overlooked compared to drug-induced kidney and liver injury. In most cases, early recognition is a necessity since detrimental lung injury can be progressive and fatal. The health care team should be vigilant of any new-onset pulmonary symptoms in a patient without other obvious attributable causes. Since the diagnosis of the drug-induced lung injury is cumbersome, the health care providers must be aware of the common drugs prone to cause lung injury, their mechanism of injury, and the associated risk factors to initiate adequate management strategies in such patients.

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