EURASIAN EXPERIMENT JOURNAL OF BIOLOGICAL SCIENCES (EEJBS)
ISSN: 2992-4138 ©EEJBS Publications
Volume 6 Issue 2 2025

Drug-Induced Neurotoxicity: Molecular Pathways, Clinical Manifestations, and Preventive Approaches

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ABSTRACT

Drug-induced neurotoxicity is a significant clinical and pharmacological concern, affecting both the central and peripheral nervous systems. A wide range of therapeutic agents-including chemotherapeutics, antiepileptics, antibiotics, and psychotropic medications, provoke neurotoxic effects, often as unintended consequences of long-term use, high-dose exposure, or individual susceptibility. The molecular underpinnings of neurotoxicity involve oxidative stress, mitochondrial dysfunction, disrupted calcium homeostasis, excitotoxicity, and neuroinflammation. These mechanisms ultimately compromise neuronal viability and synaptic integrity. Clinically, drug-induced neurotoxicity may manifest as cognitive dysfunction, neuropathy, seizures, encephalopathy, or psychiatric disturbances, depending on the agent involved and the neural structures affected. Early identification of neurotoxic risk factors, coupled with advances in neuroimaging, biomarkers, and pharmacogenomics, offers new opportunities for prediction and prevention. Additionally, emerging neuroprotective strategies-such as antioxidant supplementation, dose modification, and drug redesign-show promise in minimizing neurological damage. This review critically examines the current understanding of drug-induced neurotoxicity, highlighting key molecular pathways, clinical features, and innovative preventive approaches aimed at improving drug safety and neurological outcomes.

Keywords: Drug-induced neurotoxicity, oxidative stress, neuroinflammation, chemotherapeutic agents, neuroprotection

INTRODUCTION

The nervous system's vulnerability to xenobiotics, including therapeutic drugs, has been well-documented across diverse clinical settings [1]. While many pharmaceuticals are designed to exert beneficial effects on specific organs or physiological systems, unintended neurotoxic outcomes are not uncommon. These adverse effects can significantly compromise therapeutic outcomes, limit drug dosages, and impair a patient's overall quality of life. Drug-induced neurotoxicity can impact any component of the nervous system, including the central nervous system (CNS), peripheral nerves, and autonomic pathways [2]. The extent and severity of toxicity often depend on the chemical properties of the drug, the duration and dosage of treatment, and individual patient factors such as genetic makeup, age, liver and kidney function, nutritional status, and concurrent use of other medications [3]. Clinical specialties such as oncology, neurology, psychiatry, and infectious diseases frequently encounter cases of drug-induced neurotoxicity due to the use of potent agents like chemotherapeutics, antiepileptics, antipsychotics, and antibiotics [4,5]. Drugs such as cisplatin, phenytoin, chlorpromazine, and fluoroquinolones have been repeatedly implicated in various forms of neuronal injury [6]. In many cases, neurotoxicity may emerge insidiously and remain subclinical until irreversible damage occurs. Therefore, a detailed understanding of the molecular mechanisms underlying these toxic effects is essential. Such knowledge can inform the design of neuroprotective strategies, lead to the development of safer pharmacological alternatives, and promote early detection and intervention, especially in high-risk populations.

2. Molecular Pathways of Drug-Induced Neurotoxicity

2.1 Oxidative Stress and Free Radical Generation

One of the most commonly implicated mechanisms in drug-induced neurotoxicity is oxidative stress. Several drugs can either enhance the production of reactive oxygen species (ROS) or suppress intrinsic antioxidant systems such as glutathione and superoxide dismutase [7]. The accumulation of ROS leads to lipid peroxidation, protein denaturation, DNA fragmentation, and disruption of cellular homeostasis [8]. For instance, platinum-based chemotherapeutics such as cisplatin and carboplatin are known to cause significant oxidative damage in neural tissues, leading to sensory neuropathies and cognitive impairments [9].

2.2 Mitochondrial Dysfunction

Mitochondria are essential for neuronal energy metabolism and apoptosis regulation. Many neurotoxic drugs, including valproic acid and nucleoside reverse transcriptase inhibitors (NRTIs), impair mitochondrial function by disrupting the electron transport chain or inhibiting mitochondrial DNA replication [10]. These disruptions can result in decreased ATP production, increased ROS generation, and the initiation of apoptotic pathways, ultimately leading to neuronal death.

2.3 Calcium Dysregulation and Excitotoxicity

Drugs that influence neurotransmitter systems or ion channels can cause excitotoxic damage by allowing excessive calcium influx into neurons [11]. This is especially true for substances affecting glutamatergic signaling, such as ketamine and certain antiepileptics [11]. Overactivation of NMDA receptors leads to sustained intracellular calcium accumulation, activation of proteases and endonucleases, and eventual cell lysis [12].

2.4 Neuroinflammation

Another crucial contributor to drug-induced neurotoxicity is neuroinflammation. Several drugs activate microglia and astrocytes, triggering the release of proinflammatory cytokines such as IL-1β, TNF-α, and IL-6 [13]. These mediators create a toxic environment that amplifies oxidative stress, disrupts the blood-brain barrier, and promotes chronic neural injury. Methamphetamine and interferon therapies have been shown to elicit such inflammatory responses [14,15].

2.5 Disruption of Neurotrophic Factors

Neurotrophic factors are essential for neuronal survival, growth, and synaptic plasticity [16]. Certain drugs, particularly when used chronically, may suppress the synthesis or activity of these factors. For example, long-term corticosteroid use has been associated with reduced levels of brain-derived neurotrophic factor (BDNF), which is critical for hippocampal integrity [17]. This reduction contributes to neuronal atrophy, impaired neurogenesis, and cognitive decline commonly observed in steroid-treated patients.

3. Clinical Manifestations

Drug-induced neurotoxicity can present with a wide range of clinical manifestations, depending on the type of drug involved, the duration and dosage of exposure, the specific neural structures affected, and the patient's baseline neurological status [6]. These manifestations may be acute or delayed and range from subtle cognitive changes to severe and potentially irreversible neurological impairments. Recognition of these patterns is critical for timely intervention and to minimize long-term consequences.

3.1 Central Nervous System (CNS) Effects

The central nervous system is particularly susceptible to adverse drug reactions due to its high metabolic demand and limited regenerative capacity [18]. CNS manifestations often include seizures, which may occur with medications such as isoniazid, bupropion, and theophylline, especially at toxic levels [19]. Delirium and acute confusional states are commonly associated with anticholinergic agents, opioids, benzodiazepines, and corticosteroids [20]. Cognitive impairment, particularly with long-term use of sedatives, antiepileptics, or corticosteroids, may mimic or exacerbate conditions such as dementia. A well-known example is "chemo brain" or chemotherapy-induced cognitive dysfunction, commonly reported by cancer survivors [21]. This condition encompasses memory lapses, attention deficits, and executive dysfunction. Additionally, encephalopathy—marked by altered mental status, disorientation, and lethargy—can result from drugs like cefepime, metronidazole, or valproic acid, especially in patients with renal impairment or concurrent systemic illness [22].

3.2 Peripheral Nervous System Effects

The peripheral nervous system is frequently affected by neurotoxic drugs, leading to a spectrum of sensorimotor deficits. Chemotherapy-induced peripheral neuropathy (CIPN) is among the most extensively studied complications, particularly with agents such as paclitaxel, vincristine, oxaliplatin, and bortezomib [23]. Patients often report tingling, numbness, burning sensations, and neuropathic pain, typically in a glove-and-stocking distribution [23]. These symptoms can significantly impair motor function, gait stability, and dexterity. In some cases, motor neuropathies may occur, leading to muscle weakness and atrophy [24]. Neuropathic symptoms may persist long after discontinuation of the offending agent, sometimes becoming permanent and severely affecting quality of life.

Less commonly, autonomic neuropathies may develop, resulting in symptoms such as orthostatic hypotension, gastrointestinal dysmotility, or urinary dysfunction [25]. Fluoroquinolones, certain antiretroviral drugs, and high-dose pyridoxine are additional examples of agents associated with peripheral neurotoxicity [26].

3.3 Psychiatric Symptoms

Drug-induced psychiatric manifestations are diverse and may include mood disturbances, psychosis, behavioral changes, and suicidality. Corticosteroids are notorious for inducing mood swings, mania, irritability, and even steroid-induced psychosis, particularly at high doses or with prolonged use [27]. Interferon-alpha, often used in the treatment of chronic hepatitis and some cancers, is associated with depressive symptoms, anxiety, and cognitive disturbances [28]. Similarly, certain antidepressants and mood stabilizers may paradoxically exacerbate anxiety or induce mania, especially in patients with underlying bipolar disorder [29]. Antipsychotic drugs, particularly first-generation agents like haloperidol or long-term use of second-generation antipsychotics, are linked with extrapyramidal symptoms such as dystonia, akathisia, and parkinsonism [30]. Tardive dyskinesia, a serious and often irreversible movement disorder characterized by repetitive, involuntary facial or limb movements, is another potential long-term complication [31]. Furthermore, some antiepileptic drugs (e.g., levetiracetam, topiramate) and varenicline, a smoking cessation aid, have been associated with agitation, depression, or suicidal ideation, warranting close psychiatric monitoring during treatment [32]. In clinical practice, it is essential to maintain a high index of suspicion for drug-induced neurotoxicity, particularly when new neurological or psychiatric symptoms arise during pharmacotherapy. Timely drug discontinuation or dose adjustment, along with symptomatic management and referral to neurology or psychiatry when appropriate, can mitigate adverse outcomes. Early recognition and individualized risk assessment are vital components of effective neurotoxicity management in both inpatient and outpatient settings.

6. Preventive Approaches and Neuroprotective Strategies

Preventing drug-induced neurotoxicity requires a multifaceted strategy that integrates pharmacological caution, proactive patient management, and the use of emerging biomedical tools. These approaches aim to minimize risk, detect early signs of neurotoxicity, and preserve neurological function without compromising therapeutic efficacy.

6.1 Pharmacological Modifications

One of the most practical and widely used strategies to reduce neurotoxicity is modifying the pharmacological regimen. This includes lowering the drug dosage, extending infusion times to reduce peak plasma concentrations, or switching to less neurotoxic alternatives. For instance, liposomal formulations of doxorubicin are designed to minimize central nervous system penetration and thereby reduce neurotoxic risk while maintaining anticancer efficacy [33]. Similarly, substituting oxaliplatin with less neurotoxic agents in chemotherapy protocols can help reduce the incidence of peripheral neuropathy in cancer patients [34].

6.2 Antioxidants and Adjunct Therapies

Adjunctive treatment with antioxidants and cytoprotective agents has shown considerable potential in experimental and clinical settings. Compounds like N-acetylcysteine, alpha-lipoic acid, vitamin E, and glutathione help neutralize reactive oxygen species, thereby mitigating oxidative stress-induced neuronal injury [35]. These agents are increasingly being studied as co-therapies, particularly with drugs known to induce mitochondrial dysfunction and free radical damage. Early evidence suggests they may attenuate symptoms and promote neuronal recovery.

6.3 Personalized Medicine

The use of pharmacogenomics to tailor drug selection and dosing is a promising approach to prevent neurotoxicity. Genetic variations in enzymes such as TPMT, CYP2C19, and efflux transporters like ABCB1 influence how individuals metabolize or transport drugs [36]. Screening for these polymorphisms before initiating treatment can help identify high-risk patients and guide safer therapeutic choices.

6.4 Monitoring and Patient Education

Regular neurological assessments, including baseline and follow-up evaluations, are essential for early detection of drug-induced neurotoxicity. Patient education on recognizing and reporting neurological symptoms such as numbness, confusion, or mood changes enables prompt clinical response. Clinicians should remain vigilant, particularly when initiating high-risk medications in vulnerable populations.

CONCLUSION

Drug-induced neurotoxicity encompasses a broad spectrum of molecular mechanisms and clinical syndromes. While unavoidable in some cases, a deeper understanding of the pathways involved and the implementation of preventive strategies can significantly reduce the burden of neurological side effects. Moving forward, interdisciplinary research, improved diagnostics, and precision medicine approaches will be essential to safeguarding the nervous system while ensuring therapeutic efficacy.

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Alberta Jeanne N. Drug-Induced Neurotoxicity: Molecular Pathways, Clinical Manifestations, and Preventive Approaches. EURASIAN EXPERIMENT JOURNAL OF BIOLOGICAL SCIENCES, 6(2):36-40.