

An Updated Review on Some Neurotoxic Pharmacological Agents Along with their Neurotoxic Mechanisms

Muhammad Irfan Bashir¹, Nur Hidayah Kaz Abdul Aziz², Dzul Azri Mohamed Noor³

¹ Researcher, ²Scientist, Discipline of Pharmacology, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Minden 11800, Penang, Malaysia, ³Scientist, Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Minden 11800, Penang, Malaysia

Abstract

This review will provide the vital information about some pharmacological agents which are Neurotoxic. Through this update, Anti-cancer, Anti-bacterial, Analgesic, Psychoactive drug and Anabolic steroid medication are reported briefly regarding their neurotoxic mechanisms. In this review all information regarding neurotoxic drugs is collected from 2020 published work by Web of science, Scopus, PubMed and Google Scholar. It is concluded that all these drugs which the part of our study are neurotoxic. There is need to discover some method to reduce their toxicity and to avoid the chronic use of these medications.

Key Words: Neurotoxic, Pharmacological agents, Anti-cancer, Analgesic, Antibacterial

Introduction

Several types of drugs have side effects on brain, some are minimal, and some are toxic. Toxic effects of drug on brain can cause irreversible brain damage sometimes which are very dangerous for mental health, as any living organism can lose its life due severe neurotoxicity¹. In routine treatments we don't know about some drugs which we are taking has negative impact on our mental health as well as on our nervous system².

Neurotoxicity is a major side effect of many chemotherapeutic drugs used for the treatment of many diseases, including tumors. Toxicity can compromise the quality of life of patients. As per previous reports 84.4% of patients which were affected by lymphoma and treated with chemotherapeutic agents developed a serious neuropathy regarding sensory organs and

43.8% showed polyneuropathy, causing a significantly dangerous for the quality of life³.

Such effects are usually cause spontaneously fade, as doses are high then chances of neurotoxicity are also high⁴. If these drugs are used at high therapeutic levels for long time, the plasticity of the neurons is affected badly, and the damage becomes irreversible sometimes⁵.

Neurotoxicity is one of the main reasons of drug withdrawal, and the biological experimental methods of evaluating neurotoxicity are time taking and arduous. Many Anti-biotic, Analgesic are also showed their neurotoxicity due to their cytotoxic and neurochemical disturbing mechanisms⁶.

In this updated review, adverse effects of some drugs that cause neurotoxicity are explained individually. These updates are collected from recently published work in 2020. Among these drugs, anti-cancer, anti-bacterial, Analgesic, Psychoactive drug and Anabolic steroid medication are reported briefly. Table 1 is showing summarized report regarding some neurotoxic drugs with their mechanism.

Corresponding Author:

Muhammad Irfan Bashir

E-mail: mirfanbashir786@gmail.com

Discipline of Pharmacology, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Minden 11800, Penang, Malaysia

Table1: Neurotoxic Drugs with mechanisms

Drug	Class	Neurotoxic Mechanism	Year of Publish
Bortezomib	Anti-cancer	Apoptosis in PC12 is a cell line derived from a pheochromocytoma of the rat adrenal medulla, that have an embryonic origin from the neural crest that has a mixture of neuroplastic cells and eosinophilic cells.	2020
Doxorubicin	Anti-cancer	It Interact with nuclear DNA and impairing expression of proteins synthesis, involved in mitochondrial functions	2020
Cisplatin	Anti-cancer	It also interreacts with DNA, forms crosslinks in between chains and induces apoptosis. It can cause Central and Peripheral neuropathy	2020
Carboplatin	Anti-cancer	Inhibition of the DNA repair pathways, generation of DNA adducts in brain cells	2020
Oxaliplatin	Anti-cancer	Alterations in voltage-gated sodium channel kinetics ,Potassium channel blockade, Calcium chelation and sensory axonal nerve damage	2020
Ifosfamide	Anti-cancer	Ifosfamide inhibits the DNA functions and induces cell death.	2020
5-Fluorouracil	Anti-cancer	Interferences with DNA synthesis; inhibits of thymidylate synthase; blocks of thymidine formation	2020
Novel Methcathinones	Psychoactive drug	Mitochondrial toxicants whose toxicity is increased by shifting the temperature from 37 to 40.5 °C (Hyperthermia)	2020
Methotrexate	Anti-cancer	Inhibition of the enzyme dihydrofolate reductase; interference with DNA synthesis, DNA repair, cellular replication, protein synthesis, lipids and myelin metabolism. motor and autonomic neuropathy)	2020
Cefepime	Anti-Bacterial	Cross the blood brain barrier and cause depressed concentration of consciousness, confusion, aphasia, asterixis, myoclonus, dystonia, seizure in 23.2% population.	2020
Nandrolone decanoate	Anabolic steroid medication	Oxidative stress, inflammation, and intrinsic and extrinsic apoptosis in the hippocampus and PFC of rats	2020
Cannabis	Psychoactive drug	Apoptosis in the hippocampus and PFC of rats	2020
Tramadol	Analgesics	It can trigger the microgliosis and astrogliosis along with neuronal death in the prefrontal cortex	2020
N-Ethylhexedrone and buphedrone	Novel Psychoactive Substances	Neuro-microglia dysfunctionalities	2020

Bortezomib

Bortezomib is an anti-tumor agent that inhibits 26S proteasome degrading proteins. While apoptotic transcription activation in response to bortezomib has also been observed, mechanisms regarding influence on gene silencing mediated regulation by non-coding RNAs remain not fully explained⁷. Bortezomib showed the severe neurotoxicity through apoptosis in PC12 cells. It imparts neurotoxicity regardless of cell density⁸. Some studies also showed that, highest cytotoxicity in low cell density, bortezomib more frequently cause major peripheral neuropathy, only few of studies have reported the effective strategy to prevent its side effect⁹.

Doxorubicin

Doxorubicin is the most potent anthracycline antibiotics used for treatment of multiple cancer types including breast cancer therapy. But its efficacy is limited by fatal toxicities associated with therapy causing damage to normal tissues and organs¹⁰. It interacts with nuclear DNA, altering the pair base sequence and preventing the topoisomerase-II-mediated DNA repair mitochondrial DNA, impairing expression of proteins involved in mitochondrial functions^{3,11}.

Cisplatin

Cisplatin is an anti-cancer drug it interreacts with DNA, forms crosslinks between chains and induces apoptosis. Central or Peripheral neuropathy. 50–85% score of sensory and sensorimotor neuropathy. Oxidative stress, generation of DNA adducts, apoptosis, mitochondrial dysfunction are also among its neurotoxic mechanisms¹². Cisplatin also react with RNA but the ration of modified molecules to the total number of the same molecular species in the cell is much higher in the case of DNA molecules, binding of this agent to the DNA is the main cause of its toxicity¹³.

Carboplatin

Carboplatin is widely used agent to treat the various types of cancer. However, a number of severe side effects induced by the nonspecific binding of platinum drugs to normal tissues limit their clinical use¹⁴. This drug is also involved in Inhibition of the DNA repair pathways, generation of DNA adducts and cause severe neurotoxicity^{3,15}.

Oxaliplatin

Oxaliplatin is involved in acute neuropathy upon exposure to chronic peripheral neuropathy, in which sensory axonal nerve abnormal generation of DNA adducts is occurred. Mostly due to Alterations in voltage-gated sodium channel kinetics, Calcium chelation and Potassium channel blockade³. Peripheral neurotoxicity is a main toxicity that afflicts up to 90% of patients with colorectal cancer which are taking oxaliplatin containing therapy^{16,17}.

Ifosfamide

Ifosfamide is an alkylating agent used in the treatment of various solid tumors, including small cell lung cancer, testicular cancer, cervical cancer, and sarcoma¹⁸. It is Pro-drug, that after bioactivation, inhibits the DNA functions and cause cell death³. Chloroacetaldehyde (metabolite responsible for neurotoxicity) inducing many damages to the mitochondrial respiratory chain depletion of glutathione level in central nervous system and also creating oxidative stress¹⁹.

5-Fluorouracil

This drug also reacts with DNA synthesis and inhibits of thymidylate synthase which blocks the thymidine formation. Seldomly sensorimotor polyneuropathy is observed during treatment with 5-Fluorouracil²⁰. Maximum doses and combined use of 5-FU with interferon alpha increases the neurotoxicity. It impairs the urea cycle and permits an accumulation of ammonia a transient stagnation of 5-FU catabolites induces neurotoxicity. This drug can increase the cellular thiamine metabolism, inducing a thiamine deficiency^{3,21}.

Novel Methcathinones

These are mitochondrial toxicants whose toxicity is increased by transferring the temperature from 37 to 40.5 °C. It can cause apoptosis and necrosis among brain cells²². The activation of proper defense mechanisms like autophagy is necessary to prevent the cell dysfunction and cell death. Mitochondrial toxicity, which is accentuated by hyperthermia, represents an important mechanism of the neural toxicity of these compounds²³.

Methotrexate

Methotrexate is a folic acid antagonist for the treatment of cancer and rheumatoid arthritis because of its high potency and efficacy²⁴. It inhibits the enzyme dihydrofolate reductase which interference with DNA synthesis, DNA repair, protein synthesis, cellular replication, lipids and cause autonomic neuropathy²⁵. Aseptic meningitis occurs in 10–50% of patients due to influence of this drug. Disturbances of myelin metabolism, inhibition of glucose metabolism, oxidative stress^{3,26}.

Cefepime

Cefepime is an antibacterial drug belongs to cephalosporins, previously its concentrations were determined in 584 individuals. Among 319 individuals with available through concentrations included, the overall incidence of neurotoxicity was 23.2% (74 of 319 individuals). Maximum cefepime plasma trough concentrations were significantly associated with risk of neurotoxicity²⁷. Possible adverse neurological effects based on the occurrence of neurological signs (altered mental status, depressed concentration of consciousness, aphasia, myoclonus, asterixis, confusion, seizure, dystonia²⁸.

Nandrolone decanoate with Cannabis

These are Psychoactive drugs. Polydrug use among adolescence is a widespread activity and has enhanced in the last some years²⁹. Most nandrolone decanoate abusers combine its use with cannabis. Abuse of both drugs conferred larger neurotoxic effects than either drug alone that were at least partially attributed to inflammation, oxidative stress, and apoptosis in the hippocampus and prefrontal cortex of brain in rats³⁰.

Tramadol

Tramadol is a synthetic analogue of codeine that is prescribed for the treatment of moderate pains as an analgesic³¹. It has also some side effects including emotional instability and anxiety. it triggers astrogliosis and microgliosis along with neuronal death in the prefrontal cortex³². Behavioral problems and cognitive function impairment are other side effects of tramadol. Previous results indicate that tramadol is responsible for neurodegeneration in the prefrontal cortex through

activation of neuroinflammatory response³³.

Cathinones N-Ethylhexedrone and buphedrone

N-Ethylhexedrone and buphedrone are emerging synthetic cathinones³⁴. Small information about their negative effects within central nervous system. These drugs showed in vivo/in vitro neurotoxicity's but enhanced specific N-Ethylhexedrone induced behavioral and neuro-microglia abnormalities³⁵.

Conclusion

Due to reported neurotoxic mechanisms of all discussed drugs in this review, it is concluded that long term use of these medication can cause brain damaged. There is need to find some methods to overcome the neurotoxic effects of all these drugs.

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