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

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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 drugsis 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 areneurotoxic. There is need to discover some methodto reduce their toxicity and to avoid the chronic use of these medications.

Keywords: *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 neurotoxicity[1]. 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 system[2].

Neurotoxicity is a major side effect of many chemotherapeutic drugs used for the treatment of many diseases, including tumors.Toxicitycan 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 life[3].

Such effects are usually cause spontaneously fade, asdoses are high then chances of neurotoxicity are also high[4]. If these drugs are used at high therapeutic levels for longtime, the plasticity of the neurons is affected badly, and the damage becomes irreversible sometimes[5].

Neurotoxicity is one of the main reasons of drug withdrawal, and the biological experimental method of evaluating neurotoxicity are time taking and arduous. Many Anti-biotic, Analgesic are also showed their neurotoxicity due to their cytotoxic and neurochemical disturbing mechanisms [6].

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.

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Table 1: 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	Ifosfamideinhibits 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 explained[7]. Bortezomib showed the severe neurotoxicity through apoptosis in PC12 cells. It imparts neurotoxicity regardless of cell density[8]. 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 effect[9].

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 organs[10]. 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 dysfunctionare also among its neurotoxic mechanisms[12]. 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 toxicity[13].

Carboplatin: Carboplatin is widely used agent to treat the various types of cancer. However, anumber of severe side effects induced by the nonspecific binding of platinum drugs tonormal tissues limit their clinical use[14]. 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 abnormalgeneration of DNA adducts is occurred. Mostly due to Alterations in voltage-gatedsodium channel kinetics, Calcium chelation and Potassium channel blockade[3]. Peripheral neurotoxicity is a main toxicity that afflicts up to 90% of patients with colorectal cancer which are taking oxaliplatincontaining 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, andsarcoma[18]. It is Pro-drug, that after bioactivation, inhibits the DNA functions and cause cell death[3]. 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 stress[19].

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-Flurouracil[20]. Maximum doses and combined use of 5-FU with interferon alpha increases the neurotoxicity. Itimpairs 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 cells[22]. 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 compounds[23].

Methotrexate: Methotrexate is a folic acid antagonist for the treatment ofcancer and rheumatoid arthritis because of its high potency and efficacy[24]. It inhibits the enzyme dihydrofolate reductase which interference with DNA synthesis, DNA repair, protein synthesis, cellular replication, lipids and cause autonomic neuropathy[25]. 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 neurotoxicity[27]. Possible adverse neurological effects based on the occurrence of neurological signs (altered mental status, depressed concentration of consciousness, aphasia, myoclonus, asterixis, confusion, seizure, dystonia [28].

Nandrolone decanoate with Cannabis: These are Psychoactive drugs. Polydrug use among adolescence is a widespread activity and has enhanced in the last some years[29]. 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 rats[30].

Tramadol: Tramadol is a synthetic analogue of codeine that is prescribed for the treatment of moderate pains as an analgesic[31]. It has alsosome side effects including emotional instability and anxiety. it triggersastrogliosisand microgliosis along with neuronal death in the prefrontal cortex[32]. 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 response[33].

Cathinones N-Ethylhexedrone and buphedrone: N-Ethylhexedrone and buphedrone are emerging synthetic cathinones[34].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 abnormalities[35].

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 method to overcome the neurotoxic effects of all these drugs.

Source of Support: We acknowledge USM (Universiti Sains Malaysia) fellowship scheme support for Muhammad Irfan Bashir.

Conflict of Interest: No any conflict of interest

Ethical Declaration: This is a review article so there is no need to get its ethical approval.

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