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AN OVERVIEW ON NEUROTOXIC AGENTS

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Abstract:

Neurotoxicology is the science that deals with the adverse effects of naturally occurring and synthetic chemical agents on the structure or function of the nervous system. Many industrial and recreational solvents can cause neurotoxicity. Pharmaceutical neurotoxicity is very common and may be iatrogenic or self-initiated. Vinca alkaloids and taxols are at high risk for neurotoxicity. : International validations authorities such as OECD, EURL, ECVAM, and ICCVAM have not reviewed or validated any non-animal method or alternative testing strategy for assessing neurotoxicity. Thus, regulatory authorities have not accepted any non-animal method or alternative testing strategy for neurotoxicity testing.Most morphological changes such as neuropathy (a loss ofneurons), axonopathy (a degeneration of the neuronal axon),myelinopathy (a loss of the glial cells surrounding the axon),or other gliopathies, would be considered adverse, even if structural and/or functional changes were mild or transitory. Neurotoxicity canalso occur as a result of indirect effects, such as damage to hepatic or cardiovascular structures, or because of interference with the endocrine systems. Some chemicals may have multiple modes of action and may affect the nervous system both directly and indirectly. Forexample,some halogenated compounds may interact directly with brain cells, and also affect the development of the nervous system by altering thyroid hormone homeostasis. Encephalopathy, movement disorders, visual system impairment, psychiatric and behavioural disorders are some of the common complications associated with neurotoxic agents

Key Words: *Neurotoxic agents, Encephalopathy, nervous system, neuropathy...*

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NEUROTOXINS:

Neurotoxicity has been defined as "any adverse effect on the chemistry, structure or function of the nervous system, during development or at maturity, induced by chemical or physical influences"[1]. An adverse effect is "any treatmentrelated change which interferes with normal function and compromises adaptation to the environment"[2.] Thus, most morphological changes such as neuropathy (a loss ofneurons), axonopathy (a degeneration of the neuronal axon), myelinopathy (a loss of the glial cells surrounding the axon), or other gliopathies, would be considered adverse, even if structural and/or functional changes were mild or transitory. Neurotoxicity canalso occur as a result of indirect effects, such as damage to hepatic or cardiovascular structures, or because of interference with the endocrine systems. Some chemicals may have multiple modes of action and may affect the nervous system both directly and indirectly. Forexample,some halogenated compounds may interact directly with brain cells, and also affect the development of the nervous system by altering thyroid hormone homeostasis[3,4]

EPIDEMIOLOGY:

Carbon monoxide: *Carbon monoxide poisoning* is responsible for approximately 50,000 visits to the emergency department annually and results in about 1,200 deaths per year in the United States[5].

Sulfide, cyanide, and azide: In 2016, the Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS) reported 670 cases of *hydrogen sulfide* exposure and 198 cases of *cyanide exposure*[6]. There were no data reported for exposure to azides.

Ethanol: In the National Epidemiologic Survey on Alcohol and Related Conditions III, the 12-month and lifetime prevalence of alcohol use disorder based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5) definition among adults in the United States were 13.9% and 29.1%, respectively.[7] According to the Centers for Disease Control and Prevention (CDC), excessive alcohol consumption contributed to over 87,000 adult deaths in the United States from 2006 to 2010, with 44% due to chronic conditions and 56% due to acute conditions.[8]

Methanol: *Methanol toxicity* is uncommon and usually results from consumption of adulterated alcoholic beverages. In one study, exposure to methanol alone (excluding methanol mixtures in automotive and cleaning products) was reported in 526 cases[6]

Solvents: Many industrial and recreational solvents can cause neurotoxicity. Carbon disulfide, N-hexane, and toluene are some of the more common industrial solvents. In 2016, 464 cases of toluene diisocyanate exposure were reported by the NPDS.[6] No data were reported for carbon disulfide and N-hexane exposures.

Pharmaceutical agents: Pharmaceutical neurotoxicity is very common and may be iatrogenic or self-initiated

METALS:

Metals have been known to be neurotoxic for centuries.

Contamination of groundwater with arsenic has been associated with epidemics of *arsenic poisoning* in some parts of south Asia.[9]In 2016, the NPDS identified 769 exposures of arsenic poisoning in the United States. Increased awareness of *lead toxicity* over the past decades and regulations regarding the use of lead-based paints has decreased the incidence of lead toxicity. However, lead toxicity still occurs. In 2016, the NPDS reported cases of 43 lead exposures.[6] in more recent years, contamination of drinking water in Flint, Michigan, resulted in increased lead exposure among adult and pediatric residents ("Flint water crisis"). Manganese toxicity/manganism is rare but accounted for 128 exposures in the United States in 2016.[6]

List of Neurotoxic agents[10]

Definite high risk	Moderate to significant risk	Uncertain of minor risk	Negligible or doubtful risk
Vinca alkaloids (Vincristine)Taxols (paclitaxel, docetaxel, cabazitaxel)	Amiodarone (Cordarone) Arsenic Trioxide Auranofin (Ridaura) Aurothioglucose (Solganal) Bortezomib (Velcade) Brentuximab Vedotin Cetuximab Ciprofloxacin (Cipro) Cisplatin & Oxaliplatin Colchicine (extended use) Dapsone Didanosine (ddI, Videx) Dichloroacetate Disulfiram (Antabuse) Eribulin Mesylate (Halaven) Fluoroquinolones (oral and injectable antibiotics) (2) Gemifloxacin (Factive) Gold salts Ipilmumab Ixabepilone (Ixempra) Leflunomide (Arava) Lenolidomide Levofloxacin (Levaquin) Lomefloxacin (Maxaquin) Mefloquine (Lariam) Metronidazole/Misonidazole (extended use) (Flagyl) Moxifloxacin (Avelox) Nitrofurantoin (Macrodantin, Furadantin, Macrobid) Nitrous oxide (inhalation abuse or Vitamin B12 deficiency) Nivolumab Norfloxacin (Noroxin) Ofloxacin (Floxin) Pembrolizumab Perhexiline (not used in U.S.) Pertuzumab Pomalidomide Pyridoxine (mega dose of Vitamin B6) (see NIH Fact Sheet) Sparfloxacin (Zagam) Stavudine (d4T, Zerit) Suramin Thalidomide Trovafloxacin (Trovan) Zalcitabine (ddC, Hivid)	5-Fluoracil (Adrucil) Adriamycin Almitrine (not in U.S.) Atorvastatin (Lipitor) Chloroquine Cytarabine (high dose) Ethambutol Etoposide (VP-16) Fluvastatin (Lescol) Gemcitabine (Gemzar) Griseofulvin (Grifulvin, Fulvicin) Hexamethylmelamine (Hexalen) Hydralazine (Apresoline, Apresazide, Marpres) Ifosphamide (Ifex) Infliximab (Remicade) Interferon Alfa Isoniazid (INH) Lansoprazole (Prevacid) Lithium (Lithobid, Eskalith) Lovastatin (Mevacor, Altocor) Omeprazole (Prilosec) Penicillamine (Cuprimine, Depen) Phenytoin (Dilantin) Podophyllin resin Sertraline (Zoloft) Statins Tacrolimus (FK506, ProGraf) Zimeldine (not in U.S.)	Allopurinol (Zyloprim, Aloprim) Amitriptyline (Elavil) Chloramphenicol Chlorprothixene (Taractan) Cimetidine (Tagamet) Clioquinil Clofibrate (Atromid) Cyclosporin A (Sandimmune, Neoral) Enalapril (Vasotec) Gluthethimide Phenelzine (Nardil) Propafenone (Rythmol) Sulfonamides Sulphasalzine (Azulfidine) Sulfathiazole Sulphamethoxazole Sulfisoxazole

NEUROTOXIC AGENTS	MAXIMUM TOLERATED DOSE
Vincristine	2mg/m2
Paclitaxel	250mg/m2
Docetaxel	100mg/m2
Amiodarone	2.2 gm
Cisplatin	6mg/kg
Colchisine	6mg
Dapsone	100mg
Disulfiram	500mg
Levofloxacin	750mg
Metronidazole	4 gm
Nitrofurantoin	200mg
Pyridoxine	100mg
Thalidomide	200mg
Chloroquine	1gm
Hydralazine	300mg
Lithium	1800mg
Methanol	56.2 gm
Arsenic	1mg/kg
Toulene	625mg/kg
Hydrogen sulfide	20ppm

TOXICITY STUDIES CONDUCTED ON ANIMALS AND HUMANS:

Animal studies: Neurotoxicity testing for regulatory purposes is based on in vivo animal test methods. Four Organisations for Economic Co-operation and Development (**OECD**) Test Guidelines (TGs) describe in vivo neurotoxicity studies. Delayed Neurotoxicity of Organophosphorus Substances Following Acute Exposure, TG 418, involves a single oral dose to hens, which are then observed for 21 days. Primary observations include the hen's behavior, weight, and gross and microscopic pathology. Delayed Neurotoxicity of Organophosphorus Substances: 28-day Repeated Dose Study, TG 419, involves daily oral dosing of hens with an organophosphorous pesticide for 28 days followed by biochemical and histopathological assessments. Neurotoxicity Study in Rodents, TG 424, involves daily oral dosing of rats for acute, subchronic, or chronic assessments (28 days, 90 days, or one year or longer). Primary observations include behavioral assessments and evaluation of nervous system histopathology.

An expert working group of the International Life Sciences Institute (ILSI) Risk Science Institute published a series of four reports in 2008 "to assess the lessons learned from the implementation of standardized tests for developmental neurotoxicity in experimental animals"[11] These reports covered the following topics: need for positive control studies[12]; understanding variability in study data[13]; statistical issues and appropriate techniques[14]; and interpretation of DNT effects[15].

Human studies: International validations authorities such as OECD, EURL ECVAM, and ICCVAM have not reviewed or validated any non-animal method or alternative testing strategy for assessing neurotoxicity. Thus, regulatory authorities have not accepted any non-animal method or alternative testing strategy for neurotoxicity testing.Major considerations for progress in replacing animals in neurotoxicity testinghave been developed[16, 17].

MECHANISM AND PATHOPHYSIOLOGY

The nervous system is exceptionally complex and goes through a prolonged period of development characterised by cellular migration and differentiation, and synaptic pruning. The basic structures of the brain are formed in stages and the successful completion of one stage is totally dependent on the successful completion of all former stages.[18]Thus, chemical disruption of any of the underlying processes during development can have profound structural and functional (including behavioural) consequences for the rest of the life of the animal, human or non-human. Also important are the features of mature neuronal

cells and their interconnecting circuits. Neurones are post-mitotic, and so the consequences of a cell's death cannot be repaired by the proliferation of surviving cells. They are very active cells and have a high metabolic demand, servicing dendritic trees that may be very large (for example, in the Purkinje cells of the cerebellum) or axons that are very long (as in motor neurones) via highly effective systems for moving metabolites between the cell body and its dendrites and axons (retrograde and anterograde axoplasmic transport). The neurone is, therefore, exquisitely sensitive to anoxia or hypoglycaemia.

Finally, cells with long processes are vulnerable to attack at numerous sites—cell body, dendrites, axon, myelin sheath, node, terminal synaptic expansion, etc. Thus, the mature nervous system is remarkably vulnerable to toxin induced damage, and because any damage may disrupt the extensive communication systems that characterise the brain, neurotoxins have the capacity to affect gait and posture, the special senses, behaviour and cognition, and produce a complex pattern of clinical signs and symptoms. In the adult, the nervous system is protected by the blood–brain and blood–axon barriers. These act effectively to retard the transfer of charged and large molecular weight compounds from circulation to nervous tissue, but do not provide protection against lipid soluble agents or against toxins that damage and render porous the blood–brain barrier. The very young are much more vulnerable to most neurotoxins than the adult. Numerous neurotoxins can gain entry to the young via placenta or breast milk, and although the efficiency of transfer may be low, exposure by these routes may extend over many weeks and months.

Sometimes a metabolic step is involved in actually enhancing toxicity—for example; n-hexane is transformed into 2, 5-hexanedione and the formation of the active oxons from some organophosphates. Sequestration, particularly into plasma lipids, proteins, or body lipids, etc, may act as a "sump" from which slow release enables detoxification and excretion without the expression of clinical disease. If the rate of accumulation exceeds the rate of sequestration, metabolism and excretion, then toxic effects may be expressed.

Environmental stressors associated with Parkinson's disease, such as paraquat and MPTP, may act in part by eliciting senescence and SASP expression by glial cells in the aging brain, thereby contributing to the characteristic decline in neuronal integrity that occurs in the disorder.[19]

The mechanism of methamphetamine neurotoxicity involves dopamine receptors[20]

People infected with HIV, even those treated with antiretroviral therapy, often exhibit mild or severe neurological problems defined as HIV-associated neurocognitive disorders (HAND). HIV impairs neuronal plasticity, which is dependent on the availability of brain-derived neurotrophic factor (BDNF) that acts through Trk and p75NTR receptors.[21]

Mn is necessary for maintaining proper function and regulation of many biochemical and cellular functions. Accumulation of Mn in the substantia nigra, globus pallidus and striatum induces neurotoxicity resulting in a neurological brain disorder referred to as manganism. Its toxicity is associated with disruption of the GGC between astrocytes and neurons with disruption of astrocytic Gln uptake, release and metabolism. In addition, astrocytes have aberrant Gln replenishment/transport upon Mn exposure, with subsequent increase in extracellular Glu.[22]

Axonal lesions similar to those found in neurodegenerative diseases including amyotrophic lateral sclerosis (ALS) can be induced by a number of toxic chemicals that induce axonopathies characterized by accumulations of neurofilaments located in axonal swellings at varying distances from the somata. Γ-diketone is formed from the occupationally relevant agents, n-hexane and methyl-n-butyl ketone, by microsomal activity.[23]

The *in vivo* experiments, performed by exposing pregnant/lactating mice to MeHg, showed long-term behavioural changes in the male offspring that presented depression-like behaviour associated with a lower expression of brain-derived neurotrophic factor (BDNF) mRNA in the hippocampal dentate gyrus associated with epigenetic changes at the BDNF promoter IV[24]

NEUROTOXICITY RISK FACTORS:

- Increased CNS permeability
- Intrathecal administration
- Renal failure
- Prior CNS disease
- Older age
- Excess dosage
- Immunocompromized
- Cystic fibrosis
- Myasthenia gravis[25]

COMPLICATIONS:

May be expressed in the central, the peripheral and the autonomic nervous systems, and in skeletal muscle. They are often associated with pain, changes in the special senses of taste and smell, as well as changes in visual acuity and hearing.

Encephalopathy: The transition from acute (mild) to chronic (severe) encephalopathy with associated loss of cognition and psychomotor function is relatively uncommon,but has been seen following acute severe poisoning by domoic acid, aluminium, cadmium, and lead and following chronic abusive use of alcohol or organic solvents.

Disorders of movement Cerebellar dysfunction, characterised by ataxia, intention tremor, and loss of coordination is best known as a feature of chronic exposure to mercury

Visual system Damage to the eye is usually caused by the direct action of a toxic or corrosive substance on the cornea and conjunctiva, or the loss of transparency of the lens associated with the formation of cataracts Nystagmus may be a complication of overuse of a variety of therapeutic agents such as phenytoin and the aminoglycoside antibiotics.

Skeletal muscle Damage to skeletal muscle is relatively uncommon. Most toxicological problems of skeletal muscle result from actual denervation. Skeletal muscle regenerates rapidly following removal of the causative agent. The most serious acute clinical problem associated with rhabdomyolysis is the risk of acute renal failure.

Psychiatric and behavioural disorders Patients complaining of neurotoxic syndromes frequently report that they are depressed, anxious, and forgetful. Psychiatric abnormalities are relatively mild, but major problems of dementia and a parkinsonism/dementia syndrome have been associated with aluminium toxicity, a cerebellar ataxia with dementia with lithium overdose.[26]

SPECIAL PRECAUTIONS TO BE TAKEN

- Always read medication labels carefully and take prescription medications only as directed. Keep all medications in their original packaging.
- Avoid drugs of any kind unless advised by a doctor.
- Always inform your doctor or other health professional of a previous overdose.
- Do not stockpile unnecessary drugs. Return them to the pharmacist if you no longer need them.
- Keep all drugs and poisons locked away in a safe secure place and out of reach of children.
- Be cautious when taking different drugs or substances (including alcohol) at or around the sametime as they can interact negatively and increase the risk of overdose.[27]

ROLE OF PHARMACIST

The toxicological problems caused by acute ingestion of drugs are becoming more numerous in this present era of a drug-oriented society. The prevention and treatment of these various toxicological problems require a better coordination of our health manpower resources. The pharmacist, as a drug specialist, often overlooked in the past, can play an important role in the development of a specialized health care team. A number of hospitals are developing satellite pharmacies in emergency rooms to provide both specific clinical and traditional dispensing pharmacy services for that area. One of the first functions of the pharma-cist would be the identification of the particular ingested material, not only through the gross examination of the product, but the specific analysis of the ingested material. This ability has been acquired by the pharmacist through his training in analytical and medicinal chemistry. Following identification of the expected poison, the therapy again can have an input from the pharmacist. Through the control of drugs in the emergency room, especially if a unit dose system is in operation, he can help provide accurate drug therapy for the patient[28].Also educates patients on their medications to maximize their safe use and maintains routine follow up with patients.

CONCLUSION:

Neurotoxicity is considered as major cause of neurodegenerative disorders. Scientific research is required to claim about potential neurotoxins, as they do not have safe limit. More attention is needed on its effect on developing fetus, growing infants and long term exposure to neurotoxins in man either from natural origin or by a chemical moiety which is developed for a disease or disorder.

ABBREVIATIONS:

OECD-Organisation for Economic Co-operation and Development
EURL-European Union Reference Limited
ECVAM-European Centre for Validation of Alternative Methods
ICCVAM-Interagency Coordinating Committee on Validation of Alternative Methods

NPDS-National Poison Data System
DSM-5 – Diagnostic and Statistic Manual of Mental Disorders 5th Edition
CDC-Center for Disease Control and prevention
TG-Test Guidelines
ILSI-International Life Science Institute
DNT-Dinitrotoluenes
SASP-Senescence Associated Secretory Phenotype
BDNF-Brain-derived Neurotrophic Factor
P75NTR-Neurotrophin receptor p75
ALS-Amyotrophic Lateral Sclerosis
Gln-Glutamine
Glu-Glucose
MeHg-Methylmercury

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