Neuropsychiatric Effects of novel psychoactive substances

Safaa Zakaria Gaballah Abdelgawad, Ghada El said Elmesallamy, Yara Mohamed Medhat, Alshaimaa Mahmoud Sami

Forensic Medicine and Toxicology Department,Faculty of Medicine, Zagazig University, Egypt

***Corresponding author:** Safaa Zakaria Gaballah Abdelgawad

Email: safaaelwakeb@yahoo.com

Abstract:

New psychoactive substances (NPSs) are a heterogenous group of psychotropic molecules and diverted pharmaceutical drugs sold worldwide as legal substitutes for controlled drugs. The neuropsychiatric consequences of NPS use are relatively unknown, although evidence of related psychotic symptoms has been described in the literatures. The most common acute symptoms were hallucinations, aggressiveness, and psychotic and bizarre behavior, related to the molecular disbalance of neurotransmitters in the central nervous systems, with different mechanisms. The lack of clear diagnostic criteria and toxicological analyses has resulted in crucial complications in psychiatric diagnoses related to NPS intoxication.

Keywords: Neuropsychatric Effects, novel psychoactive substances, Toxic Effects.

Introduction:

The increasing abuse of psychoactive drugs represents a global public health burden, as recurrent exposure to these substances cause neurodegeneration, premature ageing and negatively impact normal neurodevelopment (***1).***

According to previous studies, most brain receptor systems have been shown to mature slowly, reaching maximal levels around the age of twenty. Thus, the use of NPS might influence the neurodevelopment by inducing psychiatric disorders or other mental deficits ***(2).***

Regarding the toxic effects on the CNS, NPS were reported to be responsible for drug dependency, psychosis, long-term changes in mental health, and impairment of the psychomotor activity and cognitive performance which are category of mental health disorders (***3).***

Synthetic cannabinoid receptor agonists (SCRAs) can also induce several psychiatric disorders, including psychosis, anxiety, paranoia, visual and auditory hallucinations, delusions, aggressive and erratic conduct and seizures (4).

The risks of these toxic effects tended to increase when SCRAs were used with other psychoactive substances**.** In fact, stimulant and psychedelic NPS have been linked to neurological and cognitive impairments. Furthermore, studies using in vitro cell models or rodents indicate a variety of mechanisms that could potentially lead to neurotoxic damage in NPS users ***(5).***

Other severe neurological adverse effects, including cerebral vasculopathy, cerebral edema, and serotonin toxicity, have been associated with phenethylamine NPS. In addition, many reports have suggested various functional and structural neuronal abnormalities with the regular use of NPS. According to these findings, cannabinoids cause structural changes in the gray matter and white matter in the limbic and prefrontal areas of the brain causing cognitive impairment so many people have been involved in road accidents ***(6).***

Several previous studies that incorporated the use of bioimaging techniques have shown that the volumes of the gray matter and white matter in various regions of the brain were smaller in SCRA users**.** Considering that psychoactive drugs could induce cognitive disorders (CDs) which would increase the burden on society. Cerebral hemorrhage or ischemia might partly explain some CDs identified in psychoactive substances users **(*3*).**

Possible mechanisms of neurotoxicity

The brain is particularly sensitive to toxicity due to its high metabolic activity, limited ability to regenerate and high energy demand from neuronal functions, such as synaptic transmissions and axonal transport. Hence, toxicity leading to neuronal dysfunction or even cell death may result in irreversible damage depending on the affected (***5).***

Although the basis of such neurotoxic effects is not completely elucidated, compelling evidence has shown that dysregulation of neurotransmission, disruption of mitochondrial function and dynamics, overproduction of ROS, impairment

of neuroimmunomodulation, and epigenetic alterations are caused by many psychoactive substances (***7***).

☒ ***Dysregulation of neurotransmission:***

The principal mechanisms of action of NPS overlap with traditional drugs of abuse. Stimulant and psychedelic NPS both mediate their psychoactive effects by interacting with monoaminergic targets. Stimulant NPS act as inhibitors or substrates of norepinephrine, dopamine, and serotonin (5-HT) transporters (NET, DAT, and SERT, respectively) ***(8).***

Potential neurotoxic effects of NPS can be expected due to increased neurotransmitter levels, enhanced functional activity at the respective receptors, or direct cellular toxicity leading inhibition of neurogenesis. Furthermore, the pharmacological similarity of some NPS to traditional drugs with known neurotoxic potential suggests that such NPS may be neurotoxic as well ***(5***).

NPS most potently interact with serotonergic receptors and mediate their mind-altering effects mainly through agonism at serotonin 5-hydroxytryptamine-2A (5-HT2A) receptors. Excessive intra synaptic 5-HT originates from increased presynaptic release, reuptake inhibition, or monoamine oxidase (MAO) inhibition. Furthermore, serotonergic overstimulation in the brain may be the result of 5-HT receptor agonism or antagonism (***9***).

The affinity of NPS at different 5-HT receptor subtypes and transporter selectivity therefore allows estimations of the risk for serotonin toxicity and its severity ***(5).***

The combination of stimulant NPS with other serotonergic agents, such as SSRIs, SNRIs and monoamine oxidase inhibitors (MAOIs) increases the risk of serotonin toxicity ***(10).***

Importantly, serotonin toxicity can consequently lead to a variety of non-neurological clinical sequelae, such as SIADH. Rhabdomyolysis may occur as a result of hyperthermia or increased motor activity due to excessive 5-HT levels ***(11).***

☒ ***Oxidative stress:***

There is a strong correlation between neurotransmitter load and oxidative stress. One of the most important pathways leading to sustained production of reactive

oxygen species (ROS) the massive drug-induced release of monoamines from neuronal storage vesicles and subsequent metabolism by monoamine oxidase (MAO) producing H_2O_2 interacts with transition metal ions to form toxic hydroxyl radicals. Cytotoxicity, mitochondrial dysfunction, oxidative stress and activation of apoptosis pathway may potentially contribute to neurotoxicity of stimulant NPS in addition to altered neurochemistry ***(5).***

The maintenance of the mitochondrial integrity and function is crucial for cell survival especially the neuronal homeostasis. Hence, to ensure unimpeded mitochondrial function, various mitochondrial defense mechanisms have evolved. Such mechanisms include ROS scavenging, degradation of faulty mitochondrial proteins, and turnover of organelles (***12)***.

Excessive ROS production following stimulant use can lead to oxidative damage of the mitochondria, initiating an intracellular cascade increased intracellular Ca2+ concentrations resulting in neurotoxicity. Also ROS can potentially react with transition metal ions such as iron via the Haber-Weiss/Fenton reaction, forming highly reactive hydroxyl radicals causing per oxidative damage at pre-synaptic membranes (13).

Additionally, superoxide anions may react with nitric oxide, producing the neurotoxin peroxynitrite, which can damage cellular DNA and proteins through its interaction with thiol groups. The antioxidative defense system of the brain comprises of the enzymatic and non-enzymatic antioxidant system ***(14).***

Subsequently, ROS accumulation can lead to opening of the mitochondrial permeability transition pore (mPTP) and release of cytochrome c into the cytoplasm, followed by caspase activation and apoptosis (***15).***

☒ ***Glial cell activation***

Recently, various evidence has shown that exposure to different types of drugs of abuse greatly affects glial cells (microglia and astrocytes), leading to notable alterations in morphology, gene expression, and function. Additionally, activation of microglia caused by drugs leads to the production of proinflammatory cytokines, chemokines, and colony-stimulating factors (CSFs), potentially causing neurotoxicity, neurodegeneration, or cognitive impairment ***(16).***

Exposure to THC or synthetic cannabinoids results in changes in glial cells and brain cytokine production, indicating the important involvement of the endocannabinoid system in neuro-inflammation. ***(17)***.

Exposure to Meth leads to activation of microglia, resulting in the release of pro-inflammatory cytokines, leading to drug-induced behavioral changes that can be reduced by regulating activated glial cells. Certain researchers demonstrated that the toxicity caused by Meth was associated with a significant increase in GFAP levels, particularly in the striatum that known to be particularly susceptible to the harmful effects of Meth ***(18).***

☒ ***Dopamine neurotoxic cycle:***

Several in vitro and in vivo studies showed that dopamine is neurotoxic mainly due to its high oxidizability. After enzymatic or non-enzymatic oxidation, dopamine may induce oxidative stress in dopaminergic neurons and surrounding cells (***5).***

This mechanism potentially contributes to the toxicity of dopaminergic NPS. The brain is highly sensitive to oxidative stress due to its high concentration of polyunsaturated fatty acids, the high oxygen consumption, and the presence of transition metals ***(19).***

The dopamine concentration in the synaptic cleft is regulated by release, reuptake, and inactivation mechanisms. If not appropriately sequestered into vesicles, cytosolic dopamine can even after reuptake produce toxic intermediates, quinones, and reactive oxygen species (ROS) by autoxidation, metabolism, and enzymatic reactions ***(20).***

Quinones are highly redox-active molecules that may be further oxidized to cyclic aminochromes and, if not polymerized to form melanin, are toxic to nerve endings. Conjugated to glutathione, quinones may form a glutathionyl adduct that can react with more glutathione and protein thiols resulting in glutathione depletion and formation of protein adduct ***(21).***

Notably, quinones may covalently modify and subsequently inactivate the enzyme tyrosine hydroxylase and DAT, thereby inhibiting dopamine synthesis und reuptake ***(15)***.

☒ ***Tau protein dysfunction***

Tau protein could maintain neuronal cytoskeleton stabilization. Studies suggested that Tauopathy (tau phosphorylation) is involved in NPS-induced cognitive disorder and different psychoactive substances may act by affecting the balance between kinases and/or phosphatases in the metabolic pathway of tau. NPS usage is associated with greater tau concentration in the brains of young users. The level of p-tau in any region of brain is significantly related to duration of practice ***(22).***

A study suggested that hippocampal accumulation of phosphorylated tau would lead to abnormal mitochondrial kinetics, changes of mitochondrial structure and function, and hippocampal based learning and memory deficits (***23).***

☒ ***Immune modulation:***

There is accumulating evidence that immune modulation plays a key role in the development of some psychoactive substances' neurotoxicity**.** Normally, the blood-brain barrier (BBB) has different functions; the most relevant is protecting the brain against immune system elements. Upon destruction of BBB immune system will access the brain and destroy the brain for any reason that normally causes immune system activation ***(24).***

☒ ***Sympathomimetic over stimulation***

Various acute neurological adverse effects have been reported as a consequence of stimulant NPS use, often in combination with sympathomimetic toxicity. However, patients often present with polydrug intoxications, which typically prevents the attribution of the observed toxicity to a specific NPS (***8***).

The parafluorinated amphetamine analog 4-fluoroamphetamine (4-FA) has been linked to severe headache, reduced level of consciousness, coma, convulsions, and cerebral hemorrhage. Similarly, synthetic cathinones have been associated with headache, tremor, seizures, cerebral edema, and stroke (***25)***.

All of these symptoms were observed in poly drug users as well as in users that did not combine 4-FA with other substances. The observed toxicities may be explained by a combination of oxidative stress resulting from drug metabolism and increased catecholamine levels that may provoke vasoconstriction and micro vascular dysfunction. In vitro, 4-FA predominantly interacts with NET and DAT, which supports this hypothesis (***26).***

☒ ***Other contributing factors:***

- Hyper thermic conditions have been shown to further increase the mitochondrial superoxide production and to decrease the oxygen consumption rate following methcathinone derivatives exposure in differentiated SH-SY5Y cells ***(27).***
- Furthermore, contributing factors, such polydrug intoxication, metabolic predisposition, and user susceptibilities, may render NPS substantially more neurotoxic than might be expected from studies in cell lines or rodents (***5).***
- Environmental factors may also determine the neurotoxicity of psychoactive substances. For example, there is accumulating evidence suggesting that cannabinoid use may induce epigenetic changes, including DNA modifications (e.g., acetylation/deacetylation, methylation, phosphorylation), that may trigger neurological adverse effects ***(7***).

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