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Review Article

Medication-induced neurotoxicity: Adverse reactions to drug therapy

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The drug-based treatment methods which have revolutionized modern medicine are vital in effective medical practice. While the use of drug therapy has benefited multitudes since its inception, it is imperative to note the consequences of chronic substance administration. Synthetic medications such as antibiotics, cancer-treating agents, and psychoactive modifiers are all linked to drug-induced neurotoxicity in patients. This results in adverse reactions that significantly increase morbidity, and in some cases, mortality. The potential implications associated with the use of select drugs within each corresponding class will be discussed. Examples of these select medications and their clinical intervention mechanisms are reviewed, and a recently published case report will be introduced for analysis of clinical presentation respective to each category. Analysis of literary review demonstrates correlation and causation between neurotoxicity and chronic medication use. These findings warrant cautionary administration of drugs in clinical practice, and call for increased research in efforts to advance recognition of drug-induced neurotoxicity in patients.

Key words: Neurotoxicity, psychopharmacology, psychophysiology, drug therapy, substance induced neurotoxicity, antibiotics, cancer-treatment therapy, psychoactive drugs, neuronal modification, adverse drug effects, pathogenesis, psychosis, neurotransmission, cefepime, blinatumomab, phendimetrazine

INTRODUCTION

Balance—this is what has been the goal of holistic medicine since the genesis of medical practice. The human body is a complex system dependent on interrelation and harmony, and if a single element is disturbed, the consequence is not expressed exclusively. Even before birth, development occurs through a self-regulatory process that stabilizes internal environments. The body is constantly seeking a state of equilibrium, which is ultimately impossible if the connection between body and mind is ignored; manipulation of one will certainly elicit change in the other. This has been emphasized since the days of Hippocrates, and remains a pillar for many modern physicians of today. However, the development of synthetic medication and emerging methods of drug-based practice tend to overlook interdependence throughout the body as a whole. While these drugs have had a monumental impact towards effective condition management, it is spurious to expect that direct physiological interference of any sort will have no effect on neurological health. This is clearly illustrated by the development of adverse neurological effects upon the use of intensive therapeutic medications. The synthetic substances in question are identified to cause changes that are potentially detrimental to neurological wellness, especially in the case of chronic use. As total health is conditional to the balance of all the body's systems, a call is made for further research and effectuation of these findings in clinical settings. This paper will discuss adverse neurological effects of antibiotics, cancer- treatment drugs, and psychoactive medications in efforts to encourage further understanding of the matter. Additionally, this review presents case manifestations of drug-induced neurotoxicity in hopes that these highlights may promote symptom recognition in clinical settings.

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LITERATURE REVIEW

Antibiotic-induced neurotoxicity

Antibiotics are among the most frequently utilized medications in drug therapy. They have provided benefits that have enhanced the future of medicine since their discovery in the 19th century. The development of such a resource has proved useful in quickly slowing, killing, and preventing the occurrence of disease infection. However, although many microbes were susceptible to the anti-bacterial agents available, there were some that were not responsive to these naturally-occurring substances. Moreover, many of the microbes that

were once sensitive to such substances eventually developed resistance through evolutionary mutation. Scientists had a strong foundation given the pre-existing anti-microbial available; they simply needed to make a few adjustments. Thus, the development of synthetic, man-made antibiotics began. Soon after, there seemed to be a perfectly feasible cure for any bacterial infection presented. This remains true today, so it is hardly surprising that antibiotics are the most commonly prescribed treatment within clinical settings.

While the advantages of antibiotics are substantially valued, research shows that the drugs may elicit considerable neurotoxic adverse effects (Bazzazi et al., 2018). In the 20th century, scientists became conscious to the neurotoxic symptoms that manifested in association with anti-microbial drugs. Since then, numerous studies have emerged in order to recognize, understand, and address antibiotic-induced neurotoxicity. The conspicuous engrossment of physicians and scientists with this topic rightfully highlights the severity of the situation, as substantial morbidity and mortality are demonstrated by the findings. Manifestations of antibiotic neurotoxicity may vary, and are influenced by the class of antibiotics in question.

Simultaneously, pre-existing risk factors play a key role in the potential development of neurotoxic symptoms. In a recently published clinical review, antibiotic neurotoxicity was demonstrated in patients who are advanced in age. Symptomatic appearances increased in older individuals with renal dysfunction, as well as any former neurologic conditions (Bhattacharyya et al., 2014).

As antibiotics differ in their composition and mechanisms of action, expressions of neurotoxic symptoms are hardly uniform across all of the classes. However, there are trends pertaining to drug-induced neurotoxicity within each class. Betalactams, which encompass the most commonly used antibiotics, are the first class to be associated with neurotoxicity in patients. Notably, cephems and penams are the two most neurotoxic antibiotics of the class. Cephems refer to subgroups known as cephalosporins and cephamycins, which are derived from a particular fungus known as Acremonium. Although these drugs have a naturally-derived base, they are biosynthetically modified to effectuate their method of action. The goal of this class is to inhibit the synthesis of bacterial cell walls, and thus interfere with bacterial production. While these antibiotics are effective in their bactericidal properties, they are associated with adverse drug reactions. Beta-lactams elicit disruptions within the nervous system, leading to adverse effects such as seizures, hallucinations, myoclonus, encephalopathy, and peripheral neuropathy (Hurkacz, et al., 2021).

Similarly, another broad-spectrum, synthetic antibiotic class known as fluoroquinolones share a similar list of adverse neurotoxic effects. Among these two drugs, encephalopathy is the most common symptom exhibited, often demonstrated by agitation and psychosis among patients. These antibiotics presumably induce clinically-diagnosed encephalopathy through direct toxic effects, or by causing seizures that catalyze alterations in mental states (Bhattacharyya et al., 2014). The risk of encephalopathy increases in patients with pre-existing renal conditions, especially acute renal failure. However, cases of antibiotic- induced encephalopathic expression has been reported in patients with normal renal function (Bhattacharyya et al., 2014). Further expression of adverse neurotoxic effects involves the clinical manifestation of peripheral neuropathy, which involves symptoms of paresthesia, sensory impairment, and motor weakness—as well as myoclonus, which is categorized as a "Tourette-like syndrome" (Hurkacz et al., 2021).

Pathogenesis

The manner in which antibiotics can damage the nervous system relies on the path taken by a specific drug or its metabolites. In the case of antibiotics, it is likely that the drugs are incorporated into neurons through retrograde axonal transport or peripheral axonal uptake. This can lead to immense disturbances in neurotransmitter functionality, and even synthesis. The neurotransmitters involved may fail to be effectively released from neuronal terminals, which render them unable to effectively transmit the appropriate signals throughout the nervous system. This was studied among Beta-lactam and fluoroquinolone antibiotics, and results indicated the drugs induced inhibitory effects on Gamma-Amino Butyric Acid (GABA) transmission (Bhattacharyya et al., 2014). This is crucial, as GABA is the principle inhibitory neurotransmitter in the central nervous system. This discovery explains the occurrence of seizures among those exhibiting antibiotic-induced neurotoxicity, as disruption of GABA's inhibitory functionality will induce unregulated excitatory neurotransmission. Further adverse reactions involving sensory and motor disruption are potentially attributed to drug metabolites that hinder energy production. A disturbance in neuronal ATP production harbors neurotoxic effects that mirror hypoxia, hypoglycemia, or ischemia. In severe cases, this can lead to events such as ion-dependent apoptosis of nerve cells (Hurkacz, 2021).

2022 Case report: Antibiotic-induced neurotoxicity in a 74-year-old patient

A recently-published clinical case report addressed the neurotoxic adverse effects of Cefepime, a beta-lactam cephem. A 74-year-old woman presented to the emergency room complaining of a painful foot ulcer. The patient had pre-existing risk factors, such as type 2 diabetes and chronic kidney disease. As discussed previously, these factors, combined with her advanced age, are predisposing factors of adverse neurotoxic effects when taking antibiotics. Upon examination of the patient, the physicians discovered the ulcer had progressed, and detected an area of exposed tendon with nearly necrotic tissue at the base. Immediately, the necessary laboratory parameters were done, and the results clearly indicated severe infection. This was confirmed by performance of an MRI scan, and a subsequent wound culture. The patient was admitted for treatment of bone infection, and was placed on an antibiotic regimen that included cefepime, as well as supportive pain management. On the second day of the patient's admission, she was found in an overtly confused and delirious state. As she was a diabetic, her glucose levels were assessed. As they appeared to be near the lower range, the proper efforts were made, and the levels were quickly stabilized. However, a few hours later, the patient demonstrated increased confusion,

agitation, and delirium. The patient was unable to follow any instruction given by medical personnel, and reportedly, "just said her name in response to any question". Physicians reviewed a necessary report of healthy glucose levels, as well as normal MRI and CT scan results. The patient appeared to have no direct malady attributing to her disrupted mental state. Shortly after, she appeared to develop extreme rigidity in all four extremities. The deterioration of her condition was rapid, severe, and unjustified by her affliction. Once all efforts seemed to be made, her behavior was attributed to polypharmacy, and the frequency of all pain medication was decreased. Still and all, the patient's condition continued to decline. By the eighth day of her admission, she was not able to speak, she appeared pale and fatigued, and her breathing was reportedly quite labored. Finally, this was the turning point, as cefepime toxicity was clinically diagnosed. The medication was stopped, and she was placed on a milder antibiotic. Less than 24 hours later, the patient had improved drastically. She was coherent, responsive, and completely comfortable. She had no further episodes during her stay (Sharma et al., 2022).

This case report highlights the jarring under-recognition of antibiotic-induced neurotoxicity. While it is a difficult diagnosis to make—as symptoms can manifest in overt forms—it must be considered in modern medicine, especially among the treatment of elderly patients with renal complications. This report also emphasizes the need for increased research endeavors in this regard, as all efforts must be made in an attempt to decrease the morbidity attributed to this phenomenon.

DISCUSSION

Chemotherapy-induced neurotoxicity

In the early days of chemical warfare, nobody considered that the development of nitrogen mustard bombs would eventually contribute to anti-cancer therapeutic agents. However after World War II, when scientists began to study the manner in which the toxic gas functions, an unexpected benefit of the weaponized gas was discovered. After noticing a drastic drop in leukocytes within rabbits that were injected with the chemical, medical researchers began presenting analogs of mustard gas as effective methods in the treatment of lymphoma (Falzone et al., 2018). Since then, the development and utilization of chemotherapeutic drugs have been the epitome of cancer treatment. While they are notorious for their many characteristic side effects, such as immune system deficiency, nausea, vomiting, and hair loss, these drugs are also associated with cognitive disruption, such as direct and indirect neurotoxicity.

Chemotherapy-induced neurotoxicity results from the disturbance of both the central and peripheral nervous system. These agents, widely known as being efficient methods of cancer treatment manifest symptoms of neurotoxic malady such as enteric neuropathy, neuropathic pain, and a phenomenon referred to as chemo brain (Was et al, 2022). Like many drugs, there are differing classes of chemotherapeutic medications, and their distinction depends on the respective mechanism of action. In this paper, the following two classes will be discussed relating to their association with adversely induced neurotoxicity: Mitotic inhibitors and alkylating agents.

The most commonly used drugs in treating breast, ovarian, and lung cancer are chemotherapeutic agents that are defined as mitotic inhibitors. This class of anti-cancer medications also effectively treat cases of leukemia and lymphoma, if administration begins early enough. As indicated by their name, these drugs alter mitosis by inducing alterations of mitotic spindle function, and even formation (Was et al., 2022). A prime example regarding this class is Vincristine (VCR), which inhibits mitosis by critically interacting with tubulin during metaphase. Although VCR is effective in damaging tumoral tissue, it bears neurotoxicity as a main side effect (Diouf et al., 2021). The adverse effects of the drug create for a major doselimiting toxicity, which primarily manifests as peripheral neuropathy. Moreover, anti-cancer drugs known as alkylating agents are also regarded as neurotoxicity-inducing agents. This class of chemotherapeutics treats the same cancers as mitotic inhibitors, but additionally treats Hodgkin's disease, sarcoma, and multiple myeloma. This class involves the earliest chemotherapeutic agents discovered, such as the nitrogen mustards previously mentioned. These drugs boast an impressive mechanism of action that effectively damages DNA by adding alkyl groups to the guanine base. This completely inhibits the molecule's ability to link properly, but instead produces strand crosslinks (Was et al., 2022). Consequently, the DNA strands begin to break, and the cancer cell will eventually die. Oxaliplatin (OXL) platinum compounds are especially associated with colorectal cancer treatment, commonly used in conjunction with 5fluorouracil (5- FU) and leucovorin (LV) (Gondinho, 2020). Neurotoxic effects of OXL outweigh the anti-cancer properties it holds, as the adverse reactions lead to significant morbidity that promotes treatment discontinuation. While this drug also manifests neurotoxic abnormalities characterized by peripheral neuropathy, it involves a certain side effect that creates a life of pain for patients. OXL notably decreases action potential amplitude, which increases distal latency. When this occurs, it causes a feeling that mirrors electric shock. Further, it leaves behind sensations of paresthesia, burning, and tingling. These sensations commonly occur in the hands and feet, but are reported as orofacial pain as well (Makker et al., 2017).

A common complaint of cancer patients under chemotherapeutic treatment is the term chemobrain. This term is often used to describe the typical neurotoxic effects of chemotherapy as a whole, and the cognitive impairment exhibited since the beginning of treatment. These impairments can take the form of cognitive deficits such as difficulty concentrating, impaired learning, and diminished memory. Chemobrain is also commonly associated with the presence of frequent mood swings, as well as depression, fatigue, and insomnia. Furthermore, symptoms can branch into more sever manifestations, such as seizures, dementia, and even stroke (Was et al., 2022).

While a call must be made for further research efforts in order to entirely understand the neurotoxic effects involved, prior patient assessment studies have illuminated the striking incidence rates of chemotherapy-induced neurotoxicity among cancer patients. Accordingly, recent publications of these randomized studies exhibit rates that border 100%, and the data illustrates a positive correlation between incidence and

cumulative dosage (Seretny et al., 2014).

Pathogenesis

Although the drugs mentioned share peripheral neuropathy as the main neurotoxic symptom reported, the pathogenesis of Chemotherapy-induced neurotoxicity is specific to the treatment given—notably, the composition and mechanism of the drug.

In the case of VCR, the previously mentioned mitotic inhibitor, adverse neurotoxic effects are attributed axon degeneration. The microtubule destabilization mechanism responsible for the anti-cancer properties of VCR occurs through direct cellular binding with the drug, but research indicates this is not what triggers neuropathic symptoms (Poruchynsky et al., 2008). Accordingly, the drug will not induce neurotoxic effects when bound to the cell body, but rather when bound to the axon. Upon VCR making contact with the axon, degeneration will begin to occur. This information begs the question: If the drug functions properly at the cellular level, what is the neurotoxicity-inducing property which allows it to reach and degenerate the axon? The answer resides in the ability of VCR to alter excitability of the peripheral neurons (Diouf et al., 2021). Once this occurs, homeostasis of the calcium ion is disturbed, leading to an alteration in vital ion channels. This causes neuroinflammation that incites membrane remodeling of neurons, loss of myelinated fibers, and consequently, axon degeneration (Carozzi et al., 2015).

Platinum alkylating agents such as OXL also induce disruption of axonal excitability and disturbances within ion channels. However, these agents are also characterized by their specific ability to impair mitochondrial function and increase oxidative stress. By doing this, the destruction of neuronal and glial cells ensue (Was et al., 2022). An additional effect of this chemotherapeutic agent is the subsequential cell death that occurs due to mitogen-activated protein kinases, which can also be attributed to atypical elevations of oxidative stress (Carozzi et al., 2015). Neuroinflammatory ramifications in response to the mentioned disruptions also lead to the phenomena known as chemobrain, as central nervous system degeneration begins to ensue debilitating symptoms of cognitive impairment (Was et al., 2022).

2019 Case report: First published clinical report of severe neurotoxicity in a cancer patient administered blinatumomab and intrathecal chemotherapy

Despite the fact that chemotherapy-induced neurotoxicity has been recognized for years, no other published case reports have ever highlighted the severity of the adverse neurological reactions which occur. In the Journal of Oncology Pharmacy Practice, Jason Chen, Dat Ngo, and Joseph Rosenthal have documented the condition of a patient undergoing a treatment regimen of blinatumomab administration, alongside simultaneous intrathecal chemotherapy.

The 26-year-old male suffered from Acute Lymphoblastic Lymphoma (ALL), which involves the unregulated production of naive lymphoblast cells. The patient received an initial diagnosis of his condition 19 years prior, and fulfilled three years of chemotherapeutic treatment. Although treatment was completed, the patient suffered a central nervous system bleed induced by a thrombotic event. Consequently, seizures ensued after this event, and continued to occur sparingly throughout the following years. Regardless of past treatment completion, the patient relapsed nearly 20 years later. In this instance, the findings were isolated to the central nervous system, as physicians discovered blasts in his cerebrospinal fluid. These findings aligned with corresponding indications, as the patient reported seizures of increased frequency and intensity six months beforehand. Appropriate and personalized treatment was completed in the following three years, but diagnosis of a second relapse was made solely a year later.

The patient was primarily put on a seven-day regimen of blinatumomab, and received triple intrathecal chemotherapy that consisted of methotrexate, cytarabine, and hydrocortisone. The first drug, blinatumomab, operates by binding of surface proteins specific to B and T-cells. Normal B-cells freely express the CD19 antigen, until down regulation of expression occurs at the point of terminal differentiation. Therefore, this drug uses this antigen to recognize cancerous B-cells, as their expressions of CD19 indicate they are pre-mature lymphoblasts. Once the B-cells are recognized, the CD3 antigen is utilized to activate associated T-cells. This activation allows for the creation of a synapse between the fighter T-cell and cancerous B-cell, whereby the T-cell releases cytolytic proteins and inflammatory cytokines that incite apoptosis. In turn, the lysis of multiple target cancer cells is achieved within the bloodstream. On the other hand, the patient simultaneously received a triple intrathecal therapy, which refers to the delivery of hydrocortisone and two more chemotherapeutic drugs: Methotrexate and Cytarabine.

Methotrexate is a chemotherapy agent used to inhibit immune responses in cases of unregulated lymphocyte production. Cytarabine is commonly used in the treatment of leukemia, typically alongside other agents. It functions as an antimetabolite drug, conducive to the inhibition of DNA synthesis (National Center for Biotechnology Information, 2022). These drugs were directly injected into the cerebrospinal fluid using an Ommaya reservoir. During days 1-7, the patient remained stable upon administration of blinatumomab, and his dosage was increased by more than triple on day 8. Simultaneously, he was also receiving triple intrathecal therapy on days 4, 8, and 11. While the treatment appeared to be effective in lowering the levels of his white blood cell count, neurotoxic symptoms acutely manifested on day 12. The patient displayed confusion and disorientation, delayed speech, and mild hypoxia. Although blinatumomab was immediately discontinued, his condition rapidly declined. The following day, the patient developed urinary and fecal incontinence alongside total verbal and non-verbal unresponsiveness. Upon brain imaging, physicians could not conclude the patient was suffering from cerebral thrombosis. Additionally, an MRI was conducted to visualize the circle of Willis, which emerged with no specific malady. Therefore, chemotherapy-induced neurotoxicity was clinically diagnosed, and he was removed from all chemotherapeutic agents. The patient was placed on palliative care regimens including his antiepileptic medications and a nasogastric tube for nutritional support. During this time, he showed improvement in mental cognition, and was

eventually discharged to complete rehabilitation elsewhere. In the following six months, the patient exhibited significant cognitive improvement, and was able to carry out his basic activities (Chen et al., 2019).

This case report is a fundamental example of the debilitation caused by chemotherapy- induced neurotoxicity. The significance of this report is that it represents the lack of understanding regarding this phenomenon. As this was the first published case report of the matter, there was no data literature that resembled this patient's scenario, and thus a lack of understanding his condition. His symptoms were entirely unexpected, as Blinatumomab's molecular characteristics do not support its ability to cross the blood-brain barrier. However, the neurotoxic symptoms displayed by the patient in this report indicate the drug had managed to implement its harsh effects within the central nervous system. Additionally, evaluation illustrated that the patient's neurological damage was made significantly worse by the additive use of simultaneous intrathecal chemotherapy. Researchers of clinical therapy must apply instances like this into drug therapy examination, as inquiry and investigation will allow for efficient patient treatment.

Psychoactive drug-induced neurotoxicity

Psychoactive substances are perhaps the most obvious contributors to any potential development of neurotoxicity. These chemical substances are directly involved in nervous system alteration, and are often utilized to achieve an explicit goal of mental state manipulation. A psychoactive substance can describe a wide array of drugs existing in many different capacities. For example, the term may be used to describe prescribed stimulants utilized in clinical treatment of ADHD, but it may also refer to illegal substances taken for recreational purposes. Additionally, a drug that is characteristically psychoactive does not consequentially imply it is addictive (Hartney, 2020). The drugs relevant to this discussion will be physician- prescribed psychoactive medications used for therapeutic clinical treatment. Among the commonly prescribed psychoactive medications are antipsychotics, SSRI Anti-depressants, and stimulants. These drugs are used to treat schizophrenia and mania, clinical depression or anxiety, and Attention Deficit Hyperactive Disorder (ADHD), respectively (National Alliance on Mental Illness, 2022). These disorders all involve chemical imbalances within the brain, and are thus administered in order to manage the effects of neurological dysregulation. Psychoactive drugs are often very effective when used as long-term treatment, especially when combined with psychotherapy in the appropriate cases (Hirschfeld, 2001).

While these substances undoubtedly enhance the quality of life for many patients, prolonged utilization of these drugs can incite adverse neurological symptoms. Additionally, these symptoms can develop into significant calamities, potentially leaving patients with an overall lower quality of life. Converging association of these drugs may incorrectly suggest they exert influence on patients uniformly, but the sequential outcome of each drug—intended or adverse—is attributed to the nature of the disorder in question.

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), psychosis is a symptom aleatory to a spectrum of neuropsychiatric disorders. It is fundamentally characterized by impaired perceptions of reality, notably requiring the presence of delusions and/or hallucinations (American Psychological Association, 2013). The most severe representations of psychosis characterize schizophrenic disorders, which involve visual or auditory hallucinations (Arciniegas, 2015). Treatment of psychosis—namely in the form of schizophrenic manifestations—was the initial motive behind the development and administration of antipsychotic medications. In the late 20th century, however, atypical antipsychotics emerged with promising evidence of their efficiency. Due to this, administration of the drugs no longer solely pertained to treating schizophrenia, but was approved as effective treatment for a variety of mood disorders (Voineskos et al., 2020). The ability of antipsychotics to treat these disorders lies in their regulation of abnormal dopamine production through blocking the D2 and D3 receptors. As psychotic disorders are traced to increased levels of dopamine transmission, patients demonstrate diminished symptoms as early as the beginning days of treatment (Kapur et al., 2006).

Contrastingly, Selective Serotonin Reuptake Inhibitors (SSRIs) are psychoactive drugs that regulate through increasing neurotransmission levels. Low transmission of serotonin is associated with a wide array of conditions, such as major depressive disorder, generalized anxiety disorder, bipolar depression, Obsessive-Compulsive Disorder (OCD), and eating disorders such as bulimia nervosa (Chu et al., 2022). As this is not a comprehensive list of conditions that are U.S. FDA-approved to be treated by SSRIs, it is no surprise the drugs are of the most common pharmacotherapeutics prescribed to manage mood disorders. The mechanism attributing to their avail begins at the presynaptic nerve terminal, where the drug hinders binding of the serotonin transporter. As the neurotransmitter is unable to bind to the protein, the reuptake process will not occur and more serotonin will be left in the synaptic cleft. As a result, serotonergic transmission is substantially improved (Meyer et al., 2019).

In the treatment of Attention Deficit Hyperactivity Disorder (ADHD) and narcolepsy, psychostimulants known as amphetamines are administered. The cause behind the characteristic symptoms of these neurodivergent disorders is theorized to be "deficient catecholaminergic activity in multiple neural circuits that (are necessary for) cognitive functioning" (Meyer et al., 2019). Therefore, amphetamines are prescribed due to their ability to activate the transmission of catecholamines—particularly dopamine (DA) and norepinephrine (NE). In a manner that resembles the approach of SSRIs, although less specified, amphetamines inhibit the reuptake of catecholamines, allowing for an increase in the extracellular levels of DA and NE. However, these drugs also go a step further by directly releasing catecholamines. This mechanism involves entry of the drug molecule into the nerve terminals, where it incites dopamine to be released into the cytoplasm. Dopamine will float freely within the cell before it is reversely expelled into the extracellular fluid by its transporter (Meyer et al., 2019). At this point, the DA floating throughout the is at a substantially high level, and the typical

stimulating effects of amphetamines are felt. It is important to note that amphetamine drugs are highly dose-specific, yet have fervent addictive effects. While therapeutic effects are felt most profoundly within the appropriate dosage range of each patient, drug tolerance develops quite quickly in the case of abuse (Ailakis, 2014). This is especially common in utilizing stimulants in short-term treatment regimens for obesity, as patients who desire to lose weight may take higher-than-prescribed doses to refrain from eating. Dose administration that is significantly higher or lower than the determined appropriate range will not be as effective in disease treatment. In actuality, it can induce adverse—even paradoxical—effects towards the patient.

Pathogenesis

While antipsychotic medication is effective in treating the symptoms of psychosis in patients, dopamine receptor inhibition is not without various clinical implications. Research indicates the same mechanism that allows for the active treatment of psychotic disorders is also responsible for adverse neurological developments such as parkinsonism, Tardive Dyskinesia (TD), and Neuroleptic Malignant Syndrome (NMS) (Meyer et al., 2019). The ability of these drugs to block dopamine receptors mirrors the effects of dopamine insufficiency in Parkinson's disease, notably a loss of voluntary movement, akathisia, and excess cholinergic neural activity. This is due to the absence of sufficient dopamine, which has inhibitory effects on the cholinergic cells. The cholinergic neurons are now excessively active, causing symptoms of disordered movement, as seen in Parkinsonism and TD. In fact, in a study of 362 psychiatric patients treated with therapeutic antipsychotics for a prolonged period of time, nearly 70% of patients will develop TD. Although these findings well establish the neurological toxicity antipsychotics induce within the central nervous system, these substances also pose significant dysregulation in the autonomic nervous system. The converging anticholinergic reactions of the drugs create adverse effects such as those characterized by NMS. This includes rapid heart rate, fluctuation in blood pressure, difficulty urinating, decreased gastric motility, and significant sedation. NMS is a potentially lethal disease if not diagnosed early and combatted with immediate treatment (Meyer et al., 2019).

SSRIs are known for their high specificity in inhibiting serotonin uptake. Thus, they are relatively safer and more tolerable than drugs that inhibit the reuptake of dopamine or norepinephrine. This is not to say that SSRIs do not have side effects on the central nervous system, however. These adverse reactions may present as insomnia, sexual dysfunctions, minor extrapyramidal systems—mainly in the form of tremors, and a phenomenon reported as emotional blunting. Vast selectivity for receptors 5-HT2A, 5-HT2C, 5-HT3 and 5-HT4 can cause stimulatory effects that promote the dysfunction of transmission, leading to the neurotoxic outcomes mentioned (Marazziti et al., 2019).

Finally, the neurotoxic effects of psychostimulants are perhaps the most dire, as the drug has a high chance of being abused even when administered therapeutically. When presynaptic catecholamines are released by these drugs, postsynaptic receptors respond by triggering a signaling cascade in the brain. This cascade can induce specific gene repression that is essential in regulating protein expression—namely ΔFosB. As this protein is able to accumulate in the neuron, it alters the mesolimbic pathway in a manner that incites structural changes within the brain. In turn, this will result in extreme dependency on the drug. Often times in long-term clinical administration, tolerance is rapidly developed, warranting increased dosage (Nestler et al., 2012). This is grave, as chronic use of these drugs are shown to trigger a dismal, acute development of neurotoxicity that can result in the manifestation of extreme mental disorders, as well as various adverse psychophysical symptoms. Adverse neurotoxic effects of these drugs have presented as catatonia, muscle rigidity and involuntary movement, cognitive impairment, and seizures. Moreover, chronic users of stimulant medication are at an inclined risk of developing disorders such as schizophrenia, anorexia, and bipolar disorder (Ailakis, 2014). Psychostimulant substances consequentially induce these adverse reactions by causing various forms of behavioral and neurochemical plasticity—with both these changes occurring concurrently with one another. Primarily, the reason behind negative manifestations of psychostimulant-induced neurotoxicity is due to altered striatal dopamine signaling and a vastly sensitized dopamine response within the nucleus accumbens. Accordingly, this ensues structural changes in the synapses, such as a significant increase in dendrites and dendritic spine density (Olsen, 2011). Furthermore, chronic administration eventually results in a permanent depletion of both dopamine and tyrosine hydroxylase, and dopamine transport proteins within the dorsal striatum. As a result, axon fibers are damaged, ultimately leading to significant neuron death (Meyer et al., 2019).

2021 Case report: Phendimetrazine-induced persistent psychosis

In this report, a middle-aged woman was admitted to the hospital through efforts of her husband and son. She had no history of past psychiatric abnormality, yet she presented as grandiose and elated, demonstrating delusional and disorganized behavior such as intrusive behavior and flight of ideas. She mentioned having auditory hallucinations after week-long insomnia, and she persistently reiterated that she was a mathematician—she would solve equations out loud in rushed and muddled speech. Upon prescription investigation, it was discovered that she was prescribed a CNS stimulant known as phendimetrazine (35 mg). A drug similar to amphetamine, it stimulates the central nervous system. In turn, it then triggers the sympathetic nervous system and results in appetite suppression (PubChem, 2022). According to her family, she began demonstrating this behavior upon beginning her use of this medication. Furthermore, she was reportedly taking more than 20 pills per day, but was persuaded to stop by her family 6 days before her presentation to the hospital (Vartak et al., 2021).

In this case, the patient displayed evident neurotoxic-induced psychosis due to abuse of this psychostimulant. The 35 mg dosage is intended to be taken 2-3 times daily, resulting in a total daily intake of 105 mg. Further, the maximum threshold permitted of the immediate-release tablets are 70 mg taken 3 times daily. This allows for a maximum of 210

mg daily before the occurrence of toxic effects (Drugs.com, 2022). The patient in this case report was reported to be taking above 700 mg everyday—more than triple the maximum dosage. It is plausible that her acute development of psychotic symptoms appeared so rapidly due to extreme deregulation of dopaminergic transmission. The patient remained hospitalized for 9 days, which is a full week longer than the average stay of 3 days for substance-related psychosis. In fact, her 9 day stay aligned directly with the average length of hospitalization for individuals with primary psychotic diseases (Vartak et al., 2021). Upon undergoing a treatment regimen of benzodiazepines and aripiprazole to address her insomnia and stimulant-induced psychosis, respectively. On her final day, she had completed 7 days of medical treatment and 13 days abstinent from phendimetrazine. She no longer displayed symptoms of psychosis and mania, although irritability lingered. Upon discussing her mental state with the family, she was discharged.

This report highlights the importance of caution in regards to stimulants and their proclivity for abuse, and reinforces the principle of psychoactive drugs having the strong affinity for the development of severe neurotoxicity. Additional benefits of this report include the successful therapeutic measures for stimulant-induced psychosis, which can be utilized in future research and treatment.

CONCLUSION

Medication-induced neurotoxicity is a phenomenon that is overlooked— potentially seen as a collateral effect of drug therapy. Although synthetic medications have made effective treatment easier, faster, and overall more convenient, they have the potential to incite detrimental neurological effects. These adverse reactions can intensify patient morbidity, thus significantly degrading the quality of life. Therefore, a call for research has been made in this article. The adverse signs of neurotoxicity in patient treatment must be recognized and addressed, and a deeper understanding of mechanisms that may incite drug-induced neurotoxicity must be sought out.

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