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Dear Readers,

Welcome to the fourth installment in the third season of the IYNA Journal! We greatly appreciate your readership, continued or new. We have worked hard at producing more high-quality articles for everyone to read and encouraging a growing number of high school students from around the world to submit their neuroscience findings, research, and/or interviews to the journal. We’ve hand-picked a special few to showcase in this month’s journal.

We have been receiving many wonderful articles from you guys. It is clear how much the journal is improving as we progress into the new year. We would just like to thank everyone who has submitted articles to this issue and prior issues alike. Without your dedication and hardwork, we would not be able to spread the word about the amazing diversity in subject matter that neuroscience, and neuroethics specifically, has to offer. With that being said, here are some previews of the essays published this month:

Shaun Konganda gives an overview of Down Syndrome, Maha Kirmani sheds light on potential epilepsy treatments, Alex Rahal presents sciatica, Francesca Venditti examines schizophrenia, Unaiza Naeem talks about savant syndrome, Shambhavi Chaturvedi evaluates treatments for Parkinson’s Disease, and Kaitlyn Ramesh delves into benzodiazepines and their links to dementia.

We would like to recognize all of our dedicated editors for helping us make this issue the success that it is. You can see all of their names and positions on our Contributors page. If you have any questions, comments, or suggestions for us, please feel free to contact us at info@youthneuro.org. We hope you enjoy reading this issue as much as we enjoyed editing it!

Best Regards,
Sojas Wagle - IYNA Journal Editor-In-Chief
Aayush Setty - Managing Editor
Anita Singh - Senior Editor
Kareena Thakur - Senior Editor
Annie Pan - Senior Editor
Christine Zhou - Head of Assembly
Down Syndrome: An Overview
Shaun Konganda

Abstract

Down Syndrome is a disorder currently afflicting 250,000 people in the United States according to the U.S. National Library of Medicine [1]. Down Syndrome is thought to be a childhood disorder, characterized by flat facial features and intellectual disability. Current research has found that Down Syndrome has been linked to many genetic and environmental causes and risk factors as well as to other diseases such as Alzheimer’s Disease. In addition, advancements in medicine and technology allow for new, safe techniques in prenatal diagnosis such as amniocentesis and chorionic villus sampling [2]. In order to alleviate the debilitating effects of Down Syndrome, new techniques and treatments such as chromosomal inactivation and psychoactive drugs are being developed [3].

Genetic and Environmental Causes and Risk Factors

Down Syndrome is thought to be linked to a variety of genetic and environmental factors. The most defining feature of Down syndrome is the extra copy of Chromosome 21, explaining a type of Down Syndrome known as Complete Trisomy 21. In addition, a part of Chromosome 21 can be translocated to other chromosomes, causing a type of Down Syndrome known as Translocation Trisomy 21 [2]. The final type of Down Syndrome is Mosaic Trisomy 21, which tends to have less severe symptoms compared to the other types of Down Syndrome [5].

The overall cause of Down Syndrome is an error known as nondisjunction. In normal cell division, the pair of chromosomes are split so that there is a chromosome for each daughter cell. However, errors in cell divisions can lead to nondisjunction where one daughter cell may receive the pair of chromosomes, while the other daughter cell does not receive any chromosomes [5]. During fertilization, if one of the gametes (sperm or egg) has an extra Chromosome 21, then the zygote will develop into a child with Complete Trisomy 21. The other type of Down Syndrome is Translocation
Trisomy 21, in which a part of Chromosome 21 is “stuck” on another chromosome during cell division [5]. Finally, Mosaic Trisomy 21 is a rare form of Down Syndrome where not all of the cells have an extra Chromosome 21 [2]. Known as mosaicism, the error may occur early in fetal development after fertilization of a normal sperm and egg or some of the cells may lose the extra Chromosome 21 that was present during conception [5].

The largest genetic risk factors include being a carrier of a genetic translocation of Down Syndrome or having a previous child with Down Syndrome [6]. The largest environmental risk factor is the advanced maternal or paternal age, but generally older women (above the age of 35) are more likely to have a child with Down syndrome since older eggs are prone to improper chromosome division [5].

Prenatal Diagnosis

In the past, prenatal diagnosis for Down Syndrome used the mother’s blood, which was an invasive procedure; however, modern technology allows for two new, safer tests: chorionic villus sampling (CVS) and amniocentesis [2]. In a CVS, some cells from the placenta are removed and analyzed in a laboratory in order to diagnose the fetus. In amniocentesis, a sample of amniotic fluid surrounding the fetus is removed via a needle and the fetal chromosomes are analyzed. These techniques aid the diagnosis of a fetus for Down Syndrome, having a low risk for miscarriage [7].

Symptoms

Down Syndrome is usually characterized by brachycephaly (flatter and shorter facial features) and intellectual disability. However, many other problems that accompany Down Syndrome include heart defects, auditory and visual disturbances, hypotonia (weak muscle tone), digestive problems, hormonal imbalances, developmental and behavioral problems, and memory deficits [2]. Some gastrointestinal medical conditions include gastroesophageal reflux disease (stomach acid flows into the esophagus) and celiac disease (gluten intolerance); in addition, 15% of Down Syndrome patients have an underactive thyroid gland, causing hypothyroidism. Unfortunately, a small percentage of children with Down Syndrome have leukemia as well [1]. Down Syndrome also leads to slower speech and language development and behavioral deficiencies such as...
attention problems and obsessive-compulsive disorder (OCD). Additionally, a majority of adults with Down Syndrome will experience early-onset Alzheimer’s Disease by the age of 50 [9].

Chromosome 21 contains the gene coding for the amyloid precursor protein (APP), which is cleaved into amyloid-beta plaques; if the plaque is soluble, it would aggregate in the brain and become toxic. APP toxication is seen in both Alzheimer’s Disease and Down Syndrome patients. With an extra copy of Chromosome 21, it is speculated that carrying an extra copy of the APP gene may be a risk factor for dementia in Down Syndrome patients [2].

Treatments and Current Research

Although there is no definite treatment for Down Syndrome, researchers and specialists work together to fight the health problems of Down Syndrome patients. One way to improve the physical and mental abilities of Down Syndrome patients is to use therapies and early occupational programs, which can help these young individuals who may be struggling in school [10]. The type of therapies that currently exist include physical therapy, speech-language therapy, occupational therapy, emotional therapy, and behavioral therapy. Many Down Syndrome patients use amino acid supplements to affect brain activity, but poorly controlled clinical trials have led to the drugs having some side effects [3]. However, newer psychoactive drugs are currently being developed and tested such as antioxidants, which may be used as a possible treatment for dementia [3]. Most of these newer treatments target the hippocampus, the main area that is affected, since it is believed that poor connectivity between hippocampal neurons is a key factor linked to the intellectual disability in Down Syndrome [2].

One study suggests the use of chromosomal inactivation. Researchers took a gene that is used to inactivate a female’s second X chromosome (known as a Barr Body) and spliced it into stem cells with three copies of the 21st chromosome [2]. The inactivation gene muted the expression of genes on the extra 21st chromosome [2]. This model is currently used to test for cellular changes or complications and it may be used for clinical trials in the future [2].

Final Words

As the hundreds of thousands of Down Syndrome patients continue to live in America, scientists have developed treatments to increase these patients’ lifespans and prevent many health problems associated with Down Syndrome. Hopefully, the use of chromosomal inactivation and the development of new drugs will create a brighter future for Down Syndrome patients all over the world.

References


An Overview of Epilepsy: A Seizure Disorder
Maha Kirmani

Introduction
Epilepsy is classified as a seizure disorder derived from the brain. Epilepsy is diagnosed when a patient receives two or more recurring seizures that weren’t influenced by previous neurological trauma [i]. While epilepsy is classified as a seizure disorder, not all seizures are derived from epilepsy. These seizures can be induced by infections, traumas, or fevers. The disorder brings the individuals many life challenges. An epileptic may have difficulty driving, operating machinery, or playing sports. We will discuss the history of, types of, and the causes of epilepsy, and its modernized surgical treatments.

History of Epilepsy
Epilepsy is a well-known disorder both in historical and modern contexts, even being referenced in the Bible. History indicates that the Babylonians were the first people group to record occurrences of epilepsy in their society. They believed the seizures were derived from demonic possession of the individual and the different types of seizures signified the presence of a diverse array of demons.

In 400 BC, the Greeks also recorded incidents of epilepsy within this society and classified the disorder as the “sacred disease”. They believed epilepsy was a curse bestowed on the individual by the goddess Selene. The legend dictated that the afflicted one would spend a night in her temple and wait for the deity to summon them in their dreams, where she would then tell them how to remove the curse.

The Romans treated epileptics poorly and often isolated them from society. They also initiated the first treatment for epileptics, which involved providing them blood of a recently murdered individual. Gladiators were the preferred sacrifices[i].

Types of Epilepsy
There are two common epileptic seizures: generalized seizures and tonic-clonic seizures. A generalized seizure involves a sudden discharge of neurons on both sides of the brain. The origin is
localized, but the neural dysfunction spreads to other regions fairly quickly. There are many types of generalized seizures. The tonic-clonic seizure usually occurs when there is a large discharge of neurons in both cerebral hemispheres [3]. This seizure often encompasses convulsions and can cause the individual injury if they aren’t in a safe place.

Another generalized seizure is the atonic seizure. This specific seizure causes the person to fall down, due to loss of muscle tone.

A partial seizure is another type of epileptic seizure. There are two main partial seizures: simple partial seizures and complex partial seizures. Simple partial seizures are short seizures that make the patient experience unusual sensations in an olfactory, visual, or auditory capacity. During complex partial seizures, patients may experience olfactory or visual hallucinations, sudden recall of memories, and sensations of Déjà vu [2].

Causes

Epilepsy is most commonly a result of head injuries, stroke, brain tumor, and infections such as meningitis. About 50%-70% of the cases of epilepsy are idiopathic. Brain damage derived from traumatic head injuries may leave a “scar” on the brain and the location of the scar is normally where the epileptic seizures start [3]. There is no defined cause for epilepsy as many factors can trigger the disorder. Epilepsy can be triggered by a lack of sugar, stress, and even lack of sleep.

Treatment Options

Vagus Nerve Stimulation: VNS is an adjunctive (add-on) therapy. It is primarily utilized for those who suffer from drug-resistant epilepsy. This therapy implants a device located on the left side of the chest. The device is a pacemaker-like generator that is programmed to stimulate the vagus nerve. This device is woven around the vagus nerve to lessen the number of seizures. VNS therapy is beneficial for epilepsy, as it can reduce the number of seizures for an epileptic and enhance their quality of life [4].

Responsive Neurostimulation

Responsive Neurostimulation treats uncontrolled partial-onset seizures. This innovation provides neurostimulation, actively monitors brain signals, and provides stimulation for abnormal electrical events. RNS is usually known as the pacemaker for the brain. This device is implantable and is connected to two small lead wires that are placed in up to two areas of the brain where the seizures start. RNS is a relatively new advancement that could aid many epileptics. While this
treatment is not considered a cure for epilepsy, it reduces the number of seizures for most patients [6].

**Stem Cell Therapy**

Stem cells are cells that haven’t differentiated, that, when injected, can replicate and differentiate into the cells it’s surrounded by. Stem cells are utilized to replace damaged tissues. There is great potential for stem cells in treating epilepsy, as they can replace abnormal cells that cause epilepsy [7]. This advancement is still in its early stages and is currently being experimented on rats.

**Eslicarbazepine Acetate-Aptiom (Brand Name)**

Aptiom is an anticonvulsant that decreases nerve impulses that cause pain and seizures. It is used specifically for partial-onset seizures. This drug has a stronger mechanism of action meant for patients whose treatments haven’t been effective. There are a variety of drugs that are anti-convulsant, but Aptiom is one of recent drugs that have been released as an anticonvulsant.

**Surgeries**

There are three main surgical options for people with epilepsy:

- **Temporal lobe surgery** removes the brain tissue from where the seizure started. This operation involves removal of the cortex of the temporal lobe, amygdala, and the hippocampus.
- **The other type of surgery for epileptics is called Corpus Colostomy.** This surgery operates on both left and right cerebral hemispheres. It is performed so that when the patient suffers from a seizure, the seizure cannot spread throughout the whole brain.
- **The last surgery for epileptics is called Hemispherectomy.** This surgery removes only one cerebral hemisphere. This surgery is not as common as the other surgeries because more risk factors are involved. While these surgeries all have a given risk, they have all successfully decreased seizures in epileptics.

**Conclusion**

Epilepsy is a disorder that affects about 65 million people in the world presently. But, as the research progresses, the potential for improved treatment also increases, leading to better quality of life for all those affected by it.
Glossary [8]

Babylonians: A resident of ancient civilization Babylonia

Neurons: A nerve cell that sends nerve impulses

Cerebral hemispheres: The two parts of the cerebrum (left and right) in the brain of a vertebrate

Stroke: The result of which a clot forms in a blood vessel in the brain.

Brain tumour: Abnormal cell forms to become a tumor in the brain

Meningitis: An infection that infects the membranes covering the brain and spinal cord

References


A Brief Overview of Sciatica

Alex Rahal

Introduction

Sciatica results from complications within the sciatic nerve. The sciatic nerve is the largest nerve in the human body, starting in the lower back and traveling down the legs. This nerve controls the muscles located in the back of the knee and lower leg, which in turn maintains sensory perception in the back portion of the legs. Damage to this crucial nerve can result in a set of symptoms known as sciatica, which results in numbness, tingling, or even pain in the back and legs; however, the symptoms occur regularly on only one side of the body [2]. This article will examine the symptoms, methods of diagnosis, treatments, and prevention techniques of sciatica, perhaps one of the most influential conditions in modern-day America.

Symptoms

Although sciatica is relatively unknown among the majority of citizens in America, its reach and effect is widespread in the nation. According to Harvard Health Publishing, nearly 40% of all people will experience sciatica at one point in their life [2]. Due to its wide reach among the American populace, with nearly 3 million reported cases each year, information about sciatica, including its symptoms, is becoming more accessible to those afflicted with this condition [2].

Sciatica is associated with a wide range of symptoms, ranging from a simple weakness in the leg to a burning pain. Sciatic pain radiates from the lower back through the leg and down to the foot. The pain associated with sciatica comes in different forms, ranging from a small ache to sharp jolts of pain; such pain often occurs on only one side of the body. This pain can often render it difficult for the affected person to move their legs or stand up. Furthermore, feelings of pain and discomfort can be intensified with coughs or sneezes [3]. In extreme cases, sciatica can lead to loss of bowel or bladder function [4]. However, not all cases of sciatica yield such dire consequences. Some of sciatica’s symptoms can be mild. Examples include a tingling sensation or numbness. Multiple symptoms of sciatica may be present in some patients; pain, numbness, and tingling could all occur simultaneously in different portions of the leg.

Diagnosis

To diagnose a patient with sciatica, doctors will often order their patients to conduct many activities to test their muscle strength and record their pain. Activities, such as raising one leg at a time or rising from a squatting position, are often used to test for sciatica. If the patient truly does
have sciatica, their pain should worsen, making it easier for their doctor to diagnose them [3]. Many machines are also used in sciatica’s diagnosis, including X-Ray, Magnetic Response Imaging (MRI), and Electromyography (EMG). All of these methods allow doctors to determine, what, if any, causes of sciatica are present. This includes herniated disks and bone spurs (the overgrowth of a bone), which cause sciatica when they pinch the sciatic nerve [4]. Once a patient is diagnosed with sciatica, their doctor can assign a wide variety of treatments.

Treatments and Prevention

After a patient is fully diagnosed with sciatica, their doctor often prescribes medications such as anti-inflammatories. Medicinal treatments under this category include Ibuprofen, muscle relaxants, narcotics, and tricyclic antidepressants, all of which are designed to mitigate the pain caused by sciatica [3]. In limited cases, doctors may inject corticosteroids into the affected area, which reduces inflammation around the nerve [4]. In the past, bed rest was the recommended remedy for mild cases of sciatica. However, this is no longer seen as a suitable treatment, as a paper by B.W. Koes, a professor from the Department of General Practice at the University of Medical Center Rotterdam, M.W. van Tulder, a professor of health technology assessment at VU Medical Center, and W.C. Peul, a neurologist, indicates. Koes, Tulder, and Peul recommend more physical activities compared to bed rest. “A few hours of bed rest may provide some symptomatic relief but does not result in faster recovery,” the study indicated [7]. In some extreme cases, surgery may be conducted to remove a portion of the bone spur or herniated disk that irritates the sciatic nerve when it is the cause of extreme weakness or worsening pain [4].

Figure 1 depicts the spine’s vertebrae and discs. In a herniated disk, a portion of the nucleus, the soft center pushes through a crack in the annulus [4].
While there are many treatments for sciatica, avoiding it entirely is much simpler and appealing. Although not all causes of sciatica can be prevented, including degenerative disc disease, pregnancy, and even age, the majority of causes can be prevented by taking simple precautions [6]. For example, obesity can increase the stress on the spine, which can lead to sciatica. In addition, diabetes increases the risk of nerve damage due to its effect on the body’s use of blood sugar. By managing and maintaining a healthy weight, these contributors to sciatica can be mitigated. In addition, prolonged stillness in one position (particularly sitting) can contribute to the appearance of sciatica. Good posture, which relieves the spine of stress, serves as an effective countermeasure to this neurological disorder. Another way to prevent sciatica is regular exercise, which strengthens the muscles in the back and abdomen, which in turn strengthens the spine. Finally, avoiding smoking products can prevent the degeneration of the spinal discs, which also contributes to the prevalence of sciatica [6]. Many of these precautions not only help prevent sciatica, but also other degenerative physical conditions, increasing the likelihood of living a longer, healthier, and happier life.

Conclusion

Sciatica’s reach and effects on American citizens is unparalleled by most conditions. Every person should have a deep understanding of this condition, its symptoms and diagnosis process, and the steps needed to prevent sciatica altogether. Medical treatments to sciatica have been steadily advancing throughout the years, including a rice-sized pellet injected near the inflammation, reducing pain caused by sciatica. As medical knowledge continues to expand, newer treatments such as this will become more common and sciatica may lose its painful influence in America.
References


Schizophrenia: An Overview
Francesca Venditti

Abstract
Schizophrenia is a chronic, neurological, and multilateral condition that affects the behavior, emotions, and thoughts of a person [1]. Patients with this disorder are usually detached from reality, losing touch with aspects of their lives [1]. While schizophrenia is not “as common as other mental disorders, the symptoms can be very disabling” [5]. They can also affect daily functioning and other parts of life [2]. There are positive, negative, and cognitive symptoms that can potentially result from schizophrenia. Some drugs can treat certain symptoms well, and there are more treatments being developed, like clozapine and aripiprazole.

Positive Symptoms
Symptoms of schizophrenia can appear in different categories. They can range from hallucinations, disordered thinking and behavior, feelings of fright and paranoia, and delusions [2] [3]. Positive symptoms of schizophrenia are “psychotic behaviors not generally seen in healthy people,” including agitated, irregular movements, hallucinating, and unusual ways of thinking or delusions [1]. Most often positive symptoms are associated with losing touch with reality or abnormally interpreting reality [1]. Delusions are the most common symptoms seen in patients with schizophrenia. These patients most likely have “false beliefs that are not based in reality,” causing them to believe that, for example, there is an imminent disaster about to occur, someone is trying to harm them, they are famous, or they are being watched [2]. Hallucinations, while they are not the same as delusions, are quite similar. Most of the time, hallucinations “include a person hearing voices, seeing things, or smelling things others can’t perceive” that usually seem entirely real to schizophrenia-afflicted people [4]. Out of all hallucinations, hearing voices appears to be the most common in a lot of patients [2]. Movement disorders, where the patient shows abnormal, child-like or
excessive movement, affect the body. Since the movement is not goal-based, it becomes difficult to complete tasks [2]. Bodily behaviors related to this include “resistance to instructions, inappropriate or bizarre posture, a complete lack of response, or useless and excessive movement” [2]. On the other hand, negative symptoms strongly affect a patient’s ability to manage their emotions.

Negative Symptoms

Negative symptoms involve effects that directly inhibit a patient’s abilities, and disrupt their normal, emotional and habitual behavior [1][4]. These symptoms include the “flat affect,” less pleasure in everyday life (avolition), difficulty with starting and finishing activities, and reduced speech (alogia) [1]. The “flat affect” includes reduced emotional expression, through either diminished or lack of facial expression and tone of voice [1]. Traditionally, these negative symptoms have been seen as resistant to treatments, responding to only “pharmacologic and social interventions” [5]. Schizophrenic patients with negative symptoms have impaired function at school, work, their relationships with close relatives or friends deteriorates, and personal interest lessens, yielding to “dampening influences of anhedonia, apathy, and inattention” [5]. Since active psychosis leads to hospitalization in most psychotic patients, treatments aim to reduce or eliminate positive symptoms, but even these treatments barely restore functional capacity [5]; negative symptoms are challenging to treat because of “their modest therapeutic response, pervasiveness, and diminution of patients’ quality of life” [5]. Besides affecting emotional and mental health, schizophrenia can also cause various cognitive difficulties for patients.

Cognitive Symptoms

Cognitive symptoms of schizophrenia vary from patient to patient. Some may have more severe cognitive impairments, like loss of memory or “other aspects of thinking,” as a result of the disorder in comparison to other disorders [1]. Symptoms that fall under this category include poor executive function, or the ability to process events and make decisions based on the information, trouble with concentration or focusing, problems with working memory, or “the ability to use information immediately after learning it” [5]. A more severe case of cognitive schizophrenia might include dementia. Like the negative symptoms, cognitive symptoms may only be noticeable after “dominance of psychotic episodes or positive symptoms have either been controlled with medication or diminished with age” [6]. Over time, the subtle cognitive symptoms may gradually worsen to a note-worthy point. For
example, where once reading a book was a pleasurable and intellectual activity, a schizophrenic patient may blankly stare at its pages as it is upside down, without noticing the words [6]. Typically, schizophrenic symptoms must be reported by familial connections, as patients themselves may have no idea that they are ill. Studies have found a relationship between the onset of schizophrenia and dementia in old age, although some prove that the “cognitive dysfunction in schizophrenia to be relatively stable,” suggesting that schizophrenia may or may not be related to exacerbated cognitive decline over time [6]. Treatments for cognitive symptoms are not specific, although “it has been argued that there are chemical and structural Alzheimer-type changes that take place in the brain from long term antipsychotic treatment” [6]. However, many patients with schizophrenia also have pre-existing abnormalities such as “a comparatively reduced brain or cerebral volume and larger than normal structures known as ventricles” [6]. Schizophrenic patients, as a whole, may have a range of symptoms, but there are multiple causes and risk factors that may lead to contracting schizophrenia in the first place.

Causes and Risk Factors

Several factors heighten the chances of contracting schizophrenia. While most are genetic, others can be environment-based [1]. Although schizophrenia does run in some families, scientists have found that different genes may augment the risk of schizophrenia as opposed to a single gene [1]. However, interactions with the environment “are necessary for schizophrenia to develop,” including exposure to viruses, poor nutrition before birth, complications during birth, and psychosocial factors [1]. Changes during puberty could trigger psychotic symptoms because of genes or because of a difference in brain chemistry and structure [1]. Faulty connections from imbalanced neurotransmitters, like dopamine and glutamate, as well as from brain development problems at birth [1]. In addition, mind-altering substance use “during teen years and young adulthood can increase the risk of schizophrenia...the younger and more frequent the use, the greater the risk” [4]. Just as there are various causes and factors, diagnosing a patient with schizophrenia can be difficult due to the differences between patients.

Diagnosis

Schizophrenia, as it appears to vary between patients, is not easily diagnosable. In addition to an overall lack of awareness, there may be different causes for a patient’s schizophrenia, making the disease difficult to diagnose [4]. Moreover, drug use can sometimes cause a person to have “schizophrenia-like symptoms” but not necessarily schizophrenia [4]. Schizophrenia is usually thought of as a late-onset disorder, with symptoms showing between the ages of 16 and 30 [1]. Nevertheless, children can also be diagnosed with schizophrenia. Only about “1 in 40,000” children have it, “compared to 1 in 100 in adults” [7]. Often, persistently hearing voices “saying derogatory things about him or her, or...conversing with one another, talk[ing] to himself or herself, star[ing] at scary things—snakes, spiders, shadows—that aren’t really there, and show[ing] no interest in friendships” may be signs of schizophrenia in children of 7 years or older [7]. Although there is no lab test or specific procedure to diagnose schizophrenia, “a health care provider who evaluates the symptoms and the course of a person’s illness over six months can help ensure a correct diagnosis”
after ruling out other possible factors, like a brain tumor or other psychiatric illnesses [4]. A person must have two or more symptoms of schizophrenia “in the context of reduced functioning,” including “delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, or negative symptoms [4].” The most prominently recognized symptoms leading to diagnosis of schizophrenia are mainly delusions and hallucinations [4][8]. Early identification can “improv[e] a person’s chances of managing the illness, reducing psychotic episodes, and recovering” [4]. However, because patients are usually unaware of their illness, it “often falls to family or friends to get them help” [2]. Once recognized, schizophrenia can be treated with methods from therapy to drugs.

Treatments

Unfortunately, there is no cure for schizophrenia so far. Treatments, however, can be used to reduce symptoms of schizophrenia. These treatments include: antipsychotics, “taken daily in pill or liquid form... [or as] injections that are given once or twice a month,” psychosocial treatments, “coping skills” patients use after finding a medication that works, and coordinated specialty care, which “integrates medication, psychosocial therapies, case management, family involvement, and supported education and employment services” [5]. Besides these three treatments, the National Institute of Mental Health (NIMH) launched a research project in 2008 called Recovery After an Initial Schizophrenia Episode (RAISE). Its overall aim is to use “coordinated specialty care treatment in the earliest stages of the disorder...to reduce the likelihood of long-term disability that people with schizophrenia often experience and help them lead productive, independent lives” [1]. Nami.org also writes that treatments include “antipsychotic medications, psychotherapy, such as cognitive behavioral therapy and assertive community treatment and supportive therapy, [and] self-management strategies and education” [4]. In general, typical, or “first generation,” antipsychotic medications can block dopamine, a chemical which is responsible for basic feelings and communication between control centers in the brain, and “inhibi[t] the ability for control centres and cells in the brain to send or receive signals” [6]. Newer and atypical, or “second generation,” drugs act more selectively in blocking dopamine and can also affect serotonin, a chemical associated with feelings of happiness or love, “pathways in the brain” [6]. Serotonin is also responsible for feelings of anxiety and depression. A new drug called aripiprazole is the “new hope” that, “instead of blocking receptors, is what is known as a ‘partial agonist’ thus stimulating certain receptors and increasing activity” [6]. As previously stated, many positive symptoms respond well to treatment, while “negative and cognitive ones are not as well treated” [6]. On the other hand, an alternative drug treatment called clozapine may “remain[n] the only drug with proven efficacy in patients who are poor or partial responders” [9]. It also seems, according to research, to help schizophrenic patients in reducing suicidal behaviors, but many clinicians hesitate to use it due to “perceived risks and the burden of blood monitoring” [9].

Conclusion

Schizophrenia is not just about patients you’ve never met. They could be your neighbors, family members, schoolmates, teachers, coaches, and colleagues. 1 in 100 people have schizophrenia, and it’s likely that you, if you have not already, someone with schizophrenia in your lifetime.
Luckily, science is constantly evolving and growing. Going into the future, genetic engineering could be a revolutionary way to treat patients with schizophrenia. New technology and a renewal of interest in the field of scientific research will be beneficial in promoting the development of treatments for schizophrenia, amongst other disorders. While the developments will take time and research, “the promise of further discoveries in genetics leading to new treatment targets and better predictors of treatment response (both therapeutic and adverse) is enormously exciting” [9]. A cure for schizophrenia or similar illnesses may even be discovered, what with the thrilling prospects that genetic engineering provides. Meanwhile, funding scientific research is a large part of fueling the efforts to treat schizophrenia. In the future, these treatments will hopefully prove more effective and provide patients with new possibilities for recovery.

References


Savant Syndrome
Unaiza Naeem

Abstract
“Savant”, or ‘knowledgeable person’, is derived from the French word ‘saviour’ meaning ‘to know’ [1]. It was Dr. J. Langdon Down who, 125 years ago, described savant as a distinct condition. Savant syndrome occurs when a person with below-average intelligence displays a special talent or ability in a specific area. The term autistic savant is frequently heard as forms of developmental conditions such as autism are present[2]. As Dr. David Hiles of De Montfort University aptly states, “A savant has extraordinary memory but with a great defect in reasoning power” [3].

What Is It?
Savant syndrome is a rare but remarkable condition in which persons with developmental disabilities, including autistic disorder, brain injury, or brain disease have some spectacular “islands” of skill or ability that stand in jarring, marked contrast to overall handicap [4]. The condition can be congenital (genetic), can be acquired later in childhood, or can begin even in adulthood. The savant skills co-exist with or are superimposed upon various developmental disabilities including autistic disorder, or other conditions such as mental retardation, brain injury. The extraordinary skills are always linked with prodigious memory of a special type, exceedingly deep, but very narrow. Savant skills are characterized by its domain-specificity, enhanced memory capability, and excessive focus on low-level perceptual processing. In addition, impaired integrative cognitive processing such as social cognition or executive function, restricted interest, and compulsive repetition of the same act is observed in savant individuals [5].

Causes and Risks
Some researchers think that savants may have some brain injury or abnormality on the left side of the brain, the side which controls language, or to other areas of the brain which control abstract thinking. While this may be true for some savants, others show normal electrical activity in the brain when they are tested [6]. Another explanation involves left brain injury with right-brain compensation. The two brain hemispheres do tend to have specialized functions and the skills most often seen in savants are those associated with the right hemisphere, and those most lacking are those associated with the left hemisphere. Several cases studied thus far document left hemisphere damage on CT and MRI scans, and those imaging studies are also correlated with corresponding left-sided deficits on detailed neuropsychological testing. PET studies have also shown particular
defects in the left hemisphere function in autistic persons, with confirming left-sided findings on neuropsychological tests. A theory that offers plausible explanations for savant abilities states that pneumo encephalograms demonstrated left hemisphere abnormalities, particularly in the left temporal lobe areas. Supportingly, in a study of seventeen autistic patients, fifteen of the seventeen patients had left hemisphere abnormalities and four had savant skills in music or mechanical interest areas. In addition to left-brain injury and right brain compensation, in the savant, it is postulated that there is corresponding damage to the higher-level cognitive or semantic memory circuitry, with enhanced compensatory function in the lower level, more primitive, habit or procedural memory circuitry. This results in reliance on the characteristic automatic memory. Such left-brain damage/right brain compensation, coupled with semantic memory damage and procedural memory compensation, produces then the emergence of right-brain skills coupled with automatic memory typically and characteristically seen in savant syndrome [7].

Some experts suspect that developmentally disabled savants have inherited two separate genes, one for mental retardation and one for the special ability; however, only some savants have family histories that contain special skills. Some researchers have speculated that autistic or developmentally disabled persons may receive only a limited amount of sensory stimulation. This low level of stimulation might be due to biological causes or because such people are sometimes ignored by others and live in relative isolation. According to this theory, the resulting boredom could lead to the development of super-intense concentration levels as seen in savants that normal people are unable to achieve. However, this accounts for only some savants. Another theory holds that since savants cannot think abstractly, they come to rely entirely on concrete thinking, channeling all of their mental energy into one form of expression, be it art or calendar calculating [6]. Certain risks associated with the syndrome is a family history of having the savant condition, mental illness in the family, prematurity in infants where the gestation period is less than 35 weeks, parent’s maturity (Father: over 49, Mother: over 40). Different investigations have related the abilities of the savants with chromosome 15 associated alterations, as in the case of the Prader-Willi syndrome. Asperger’s syndrome in the family is also included as a risk [8].

Demographics

Only an estimated one out of every 2,000 developmentally disabled people living in institutions can be called a savant. It is known that the rate of savant syndrome is as much as six times higher among males than among females [6]. The left hemisphere normally completes its development later than the right hemisphere and is thus subjected to prenatal influences, some of which can be detrimental, for a longer period. In the male fetus particularly, circulating testosterone, which can reach very high levels, can slow growth and impair neuronal function in the more vulnerable, exposed left hemisphere, with actual enlargement and shift of dominance favoring skills associated with the right hemisphere. A ‘pathology of superiority’ was postulated, with compensatory growth in the right brain as a result of impaired development or actual injury to the left brain [2].
Characteristics of the Syndrome

Savant skills often appear in an individual very suddenly, rather than developing over time; the abilities are fully formed and don’t increase as the savant grows older. Savant skills disappear just as suddenly as they appeared and do not seem to require their total attention. Many can play a piece of music, draw a picture, or make complex mathematical calculations while their mind appears to be elsewhere. They seem to exercise their talents without conscious effort, as if some part of their brain, unconnected to the rest, operates automatically. A savant who, given any date in the past hundred years, could say what day of the week it fell on, might not be able to perform simple tasks like tying his shoes or catching a bus. The skills of savants appear to be almost robot-like. For example, a musical savant may be able to reproduce a complex musical piece after hearing it once, but if the original rendition contains a mistake, the savant will repeat that mistake. Further, they do not appear to be able to reason about what they are doing. For instance, a savant who can read and perfectly memorize a book containing the complete works of Shakespeare, even to the point of being able to recite a specific page of text when given a page number, probably cannot explain what those plays and poems mean [6].

While measured IQ levels in savant syndrome are most often below 70, a low measured IQ score, or “mental retardation” either as a symptom or separate disorder, is not what determines whether a person is or is not a savant. Thus, a low IQ score, while often present in savant syndrome, is not necessarily the case in all instances, and it is not a finding essential or requisite to savant syndrome. Some savants do score in the normal or superior range on commonly used IQ tests, or at least on some of the subtests that make up the overall IQ test battery [9].

Types of Savants

Savant syndrome can be congenital or acquired. Congenital savant syndrome means savant skills present from birth or emerging in early childhood with conditions such as early-onset and late-onset ASD, other developmental disorders, intellectual disability, Williams syndrome, agenesis of the corpus callosum, tuberous sclerosis, hypopituitarism, or other brain disorders as the underlying disability. Acquired savant skills appear, when none were previously present, in neurotypical individuals following brain injury or disease, stroke, dementia or any other central nervous system (CNS) incident later in infancy, childhood or adult life. Savant abilities that emerge, are sometimes at a prodigious level [4]. The astonishing new abilities in the acquired savant are mostly in music [10].

Allan Synder, a neuroscientist at the University of Sydney has followed acquired savants intently. In research conducted in 2012, Synder and his colleagues gave 28 volunteers a geometric puzzle that has stumped laboratory subjects for more than 50 years. The challenge was to connect nine dots, arrayed in three rows, using four straight lines without retracing a line or lifting the pen. None of the subjects could solve the problem. The team then attached electrodes to the heads of subjects and used painless direct electrical currents to temporarily immobilize the left anterior temporal lobe. At the same time, they stimulated areas in the right anterior temporal lobe, making
the neurons associated with creativity more likely to fire. This time more than 40 percent of the participants solved the problem. This experiment supports the theory that acquired savants blossom once brain areas normally held in check have become unfettered, meaning that savants can access raw sensory information normally off-limits to the conscious mind [11].

Another new category in this syndrome is the “sudden savant”. According to Darold A. Treffert, a psychiatrist who is actively engaged in research over the subject tells that “I have 14 such cases now. Ten are female and four are male. Age of onset of the new skill averages 47.2 years. The new skill was art, painting or drawing in nine cases; mathematics or calendar-calculating in four; music in one. These cases came to my attention via unsolicited emails by people seeking explanations or advice from internet searches” [10]. An ordinary person has an unanticipated, spontaneous epiphany like a moment where the rules and intricacies of music, art or mathematics, for example, are experienced and revealed, producing almost instantaneous giftedness and ability in the affected area of skill sets. Because there is no underlying disability such as that which occurs in congenital or acquired savant syndromes, technically sudden savant syndrome would be better termed sudden genius [10]. Some features of the sudden are that the skill has an abrupt onset with no prior interest in or talent for the newly acquired ability. There is no obvious precipitating event or CNS injury or disease. There is a fear of the gift and obsessive-compulsive disorder (OCD) is evidence of losing one’s mind, and a tendency to hide the new ability from others rather than display it. The new skill is accompanied by an obsessive-compulsive (OCD) component; there is the overpowering need to play music, draw or compute. Also, sudden savants work hard at improving their craft [12].

An interesting case of the sudden savant syndrome is of the 28-year-old gentleman from Israel who describes his epiphany moment when he suddenly could play like a well-educated pianist. He knew most of what is taught in music theory. As he writes “I suddenly realized what the major scale and minor scale were, what their chords were and where to put my fingers in order to play certain parts of the scale. I was instantly able to recognize harmonies of the scales in songs I knew as well as the ability to play melody by interval recognition” [13].

Range of Skills

Considering all the abilities in the human repertoire, it is interesting that savant skills generally narrow to five general categories: music, usually performance, most often piano, with perfect pitch, although composing in the absence of performing has been reported as has been playing multiple instruments, art (usually drawing, painting or sculpting), calendar calculating mathematics, including lightning calculating or the ability to compute prime numbers, and mechanical or spatial skills, including the capacity to measure distances precisely without the benefit of instruments, the ability to construct complex models or structures with painstaking accuracy or the mastery of map-making and direction-finding. Other skills have been
reported less often, including prodigious language facility; unusual sensory discrimination in smell, touch or vision including synesthesia; perfect appreciation of passing time without the benefit of a clock; and outstanding knowledge in specific fields such as neurophysiology, statistics or navigation. In Rimland’s (1978) sample of 543 children with special skills, musical ability was the most frequently reported skill followed by memory, art, pseudo-verbal abilities, mathematics, maps and directions, coordination, calendar calculating and extrasensory perception. Hyperlexia, which is distinguished by precocity rather than the age-independent level of skill, has also been frequently reported in autism [1].

Generally, a single special skill exists but, in some instances, several skills exist simultaneously. It was noted that the incidence of multiple skills appeared to be higher in savants with autism than in savants with other developmental disabilities. Whatever the special skill, it is always associated with a prodigious memory. Some observers list memory as a separate special skill; however, prodigious memory is an ability all savants possess cutting across all the skill areas as a shared, integral part of the syndrome itself. Several investigators have shown that memory alone cannot fully account for savant abilities, particularly calendar calculating and musical skills. Formal testing for eidetic imagery shows that phenomenon to be present in some, but certainly not all, savants and when present it may exist more as a marker of brain damage than being central to savant abilities [1].

The most common are splinter skills, which include obsessive preoccupation with, and memorization of, music and sports trivia, license plate numbers, maps, historical facts or obscure items such as vacuum cleaner motor sounds, for example. Talented savants are those cognitively impaired persons in whom the musical, artistic or other special abilities are more prominent and highly honed, usually within an area of single expertise and are very conspicuous when viewed in contrast to overall disability. Prodigious savant is a term reserved for those extraordinarily rare individuals for whom the special skill is so outstanding that it would be spectacular even if it were to occur in a non-impaired person [1]. Savants can be creative, rather than just duplicative, and the skills increase over time on a continuum from duplication, to improvisation to creation, rather than diminishing or suddenly disappearing [15].

The Autistic Savant

Savant syndrome is preferable to ‘autistic savant’, as approximately 50 percent of persons with savant syndrome have an autistic disorder and the other 50 percent have other forms of developmental disability, mental retardation or other CNS injury or disease. Thus, not all autistic persons have savant syndrome and not all persons with savant syndrome have autistic disorder [1]. The underlying disability in congenital savants was autistic spectrum disorder in 75% of cases with various other CNS disorders in 25% of cases, in congenital savants
[4]. Just like in savant syndrome, males have a greater chance of developing the autistic savant condition with the male to female ratio being 4:1[3]. It does not seem to be correlated with any demographic features, such as economic, class, racial, ethnic, etc. [3].

The two halves of the brain specialize in different tasks; in general, the right side is home to creativity and the left is the centre of logic and language. “It tends to be the dominant brain region,” says Dr. Berit Brogaard, “It tends to suppress very marginal types of thinking - highly original, highly creative thinking, because it’s beneficial for our decision-making abilities and our ability to function in normal life.”. The theory goes that as the patients’ left hemispheres became progressively more damaged, while their right hemispheres were free to flourish. One theory suggests that autism arises from abnormally low levels of serotonin in the left hemisphere in childhood, which prevents the region from developing normally. Just as with sudden savant syndrome, this allows the right hemisphere to become more active. Interestingly, many people with sudden savant syndrome also develop symptoms of autism, including social problems, OCD and all-consuming interests [19]. One famous example of autistic savant syndrome is Stephen Wiltshire, who after taking a 20-minute trip on a helicopter of New York City, complete, building-by-building rendition of that aerial view, correct in every detail, was sprawled across the paper [16].

The final sensory link between autism and savant syndrome is the presence of synesthesia, where stimuli such as letters, numbers, and sounds invoke automatic and additional sensory experiences such as colors. Synesthesia occurs at higher levels among autistic individuals with savant skills and not in those without savant skills [18].

**Diagnosis and Treatment**

Savant syndrome is diagnosed when a child’s ability in one area is exceptionally higher than would be expected given his or her IQ or general level of functioning [19]. Based on the identification and definition of the characteristics of those affected, both possible developmental delays and exceptional abilities, it can be identified at the infantile stage through a clinical and psychological approach [9].

Savant syndrome is not a disease or a disorder, but a condition, so it does not have to be treated itself. The underlying disorders that usually accompany savant syndrome need to be treated, such as autism or Asperger’s disorder, and it is believed that making use of the special talent of the child with savant syndrome may help treat the child’s underlying developmental disorders [19]. Treatment for savant syndrome is the same treatment as that directed toward the more basic CNS disorder. Or, in the case of persons with some other form of CNS injury, for example, it would be those treatment and rehabilitation efforts as directed toward overcoming the residual symptoms from such injury. These may include tranquilizers, antiparkinsonian drugs [20].

The special skills and abilities the savant demonstrates, however, can be used as a tool in overall treatment and rehabilitation efforts directed toward overcoming or lessening the handicaps from the more basic developmental disorder, injury or disease. In many cases, those extraordinary
abilities can be used as a way of engaging the handicapped person in improved communication capacity, improved social interaction and improved mastery of even daily living skills—towards greater independence overall. In that manner, the savant skills can serve as a “conduit toward normalization.” By “training the talent,” not only does the special ability improve, but there also is an increase in language skills, socialization skills, and daily living skills. Each of those leads then to greater independence overall [20]. Important aspects like neurodevelopmental sequencing, vocational exploration and habilitation are also taken into consideration [9].

References


Parkinson’s Disease – Current Advancements & Medical Reality

Shambhavi Chaturvedi

Abstract

The most chronic, progressive neurodegenerative disease that has an impact on mobility and muscle control on the body of patients is Parkinson’s disease. It was discovered by Dr. James Parkinson in 1817 as ‘Shaking Palsy’. The disease is characterized by both motor and non-motor features. Also, there are no standard diagnostic criteria developed to define advanced Parkinson’s in clinical practice. Considering the treatment of the disease, there is no known cure to date, but several symptomatic treatment measures are being taken up by scientists and doctors to reduce the symptoms of the disease. The drug therapy approaches aim towards augmenting the central dopaminergic function or reduction of central cholinergic activity. The other methods are deep brain stimulation, cell replacements using stem cell technologies, gene therapy along with oral medication approach. This article summarizes the current speculations and novel strategies employed to slow down the progression of the medical ailment.

Introduction

Parkinson’s Disease (PD), formerly known as ‘paralysis agitans’ is one of the widely known chronic progressive neurodegenerative disorders of the Central Nervous System (CNS) caused as a result of damage to the basal ganglia cells of the human brain. Parkinsonism is a term used to characterize the symptom complex from either the normal course of the disease or from the result of drug administration like reserpine, procaine, phenothiazines, methyl dopa, and tetrabenazine. It is characterized by important features like akinesia, muscular rigidity, and tremor. It is also described by depigmentation and progressive loss of dopaminergic neurons in the substantia nigra pars compacta. These neurons build an efferent connection system with the neostriatal neurons[2].

Neostriatal neurons are broadly classified into two types, those bearing excitatory D1 receptors and those bearing inhibitory D2 receptors. The former relay impulses via direct (excitatory) pathway while the latter relay impulses via an indirect (inhibitory) pathway. In a healthy individual, the flow of impulses over the direct pathway predominates, thus, dopamine released in the neostriatum enhances the activity of the concerned neurons. A patient suffers from Parkinson’s
due to the degeneration of the dopaminergic neurons and this leads to the predominance of the indirect pathway of neostriatal neurons, which accounts for the observed signs and symptoms[8].

As of now, no specific tests exist to diagnose and detect this medical complication. It is often diagnosed based on medical history, observed signs and symptoms, and physical & neurological examinations. Currently, there is no known cure for this neurological disorder but sundry approaches like symptomatic treatments, deep brain stimulation, cellular replacements or gene therapies, drug therapies including carbidopa-levodopa infusions, and in some cases of advanced parkinsonism, surgeries may also be advised by doctors.

**Signs and Symptoms**

Parkinsonism is characterized on the basis of cardinal manifestations like akinesia (bradykinesia), rigidity and tremor. In addition, the patient may also suffer from drooling, shuffling gait, muscle weakness, impaired speech, sleep disturbances and autonomic hyperactivity like seborrhea. Liver damage may also be present in some patients. Dementia is also seen as one of the prominent symptoms when a patient reaches advanced stages of PD. As the disease progresses, common physiological functions like eating, walking, and writing become increasingly difficult. PD affects both sexes, usually over 50 years of age[8].

**Neurochemical Basis of Parkinsonism**

Parkinsonism is characterized by a combination of symptoms like rigidity, bradykinesia, tremor, and postural instability that can occur for a variety of presumed or hypothetical reasons[1]. PD affects the basal ganglia and its neurochemical origin was discovered in 1960 by Hornykiewicz, who showed that the dopamine content of the substantia nigra and corpus striatum in postmortem...
brains of PD patients was extremely low (usually less than 10\% of normal) and is associated with the loss of dopaminergic neurons in the substantia nigra pars compacta, located in the midbrain\cite{2}. The dopaminergic neurons form the efferent connection with the neostriatum (as shown in figure 1) where they make contact with two types of neurons, those bearing excitatory D1 receptors and those bearing inhibitory D2 receptors. The former relay impulses via direct (excitatory) pathway from the cerebral motor cortex to basal ganglia, stimulating the spinal motor neurons and later relay impulses via an indirect (inhibitory) pathway to decrease the stimulation. The excitatory segments of the relay system are glutamatergic, whereas the inhibitory segments are GABAergic. In a healthy individual, the flow of impulses over the direct pathway predominates, thus, dopamine releases in the neostriatum which enhances the activity of the concerned neurons \cite{8}.

From histopathological studies, it can be concluded that the corpus striatum and the basal ganglia have selectively depleted dopamine content due to the presence of the pathological lesion of PD, causing degeneration of the dopaminergic neurons having their bodies in the substantia nigra in midbrain. The corpus striatum receives dopamine supply from the substantia nigra. In Parkinson's, there is a decrease in the nigrostriatal neurons which decreases the functional amount of dopamine to caudate nucleus and putamen, thereby, disturbing the normal balance of brain regions of dopamine and acetylcholine, causing bradykinesia, one of the key symptoms of the degenerative disease.

On the molecular aspect, this idiopathic disorder is associated with the development of the intracellular protein aggregates, called Lewy bodies which are eosinophilic round inclusions, in various parts of the brain. From recent studies, it is revealed that Lewy bodies consist of a synaptic

![Figure 2: The diagram labels different parts of brain that affect movement. The loss of dopaminergic neurons in substantia nigra cause bradykinesia, a key symptom of Parkinson's disease.](image)
protein, α-synuclein, in large amounts in normal healthy brains. This α-synuclein exists as helical conformation and may act like a prion-like protein and, PD, in fact, maybe a prion-like disease. It has also been revealed that certain gene mutations may also be responsible for the early onset of PD. These genes code for a protein involved in mitochondrial functions, making cells more susceptible to oxidative stress, similar to AD pathogenesis, thus, showing symptoms of dementia [6].

New light was thrown on the possible etiology of PD by a chance event. In 1982, a group of young drug addicts in California suddenly developed an exceptionally severe form of PD (known as the ‘frozen addicts’ syndrome), and the cause was traced to the compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which was a contaminant in illegal preparation of a heroin substitute. MPTP causes irreversible destruction of nigrostriatal dopaminergic neurons in various species and produces a PD like a state in primates [2].

It is seen that upon the administration of dopamine agonists, like bromocriptine and pramipexole in PD patients, the neostriatum helps to correct and provide relief from certain signs and symptoms of Parkinsonism. But this also suggests that certain other undiscovered mechanisms exist which account for the unrelieved signs of PD. There are two candidate neurons or neuron receptors: one is a cholinergic neuron receptor, through which the inter-neurons within the basal ganglia operate, and the other is GABAergic or glutamatergic neuron receptor in the basal ganglia. Thus, the therapy approaches employed on the treatment of PD are based broadly on two angles – either to increase the level of dopamine in the patient’s body by the administration of dopamine like substances or dopaminergic agents i.e. levodopa or by decreasing the acetylcholine actions by using anticholinergic agents.

**Treatment Approaches**

It is true that currently there is no known cure for the disease, but with the help of medications, the symptoms can be controlled. Upon diagnosis, the doctors recommend physical therapies, lifestyle changes, and may advise speech-language pathologists to improve the patient’s condition. Some supportive therapies that can make living with Parkinson’s easier include physiotherapy, occupational therapy, and speech-language therapies [4]. Parkinson’s patients have low brain dopamine concentration and so the first approach is based on the drug-based therapies, which tend to increase or substitute the dopamine level. Levodopa is the first-line treatment for PD and is combined with peripherally acting dopa decarboxylase inhibitors such as carbidopa, which reduces the dose needed by 10 fold and diminishes the peripheral side effects. A combination of levodopa and dopa carboxylase inhibitor with catechol-o-methyltransferase (COMT) inhibitor (e.g. Entacapone or tolcapone) to inhibit its degradation is used in patients troubled by ‘end dose’ motor fluctuations [2]. Other drug therapy approaches involve the administration of dopamine agonists like pramipexole (Mirapex), rotigotine (Neupro) ropinirole (Requip) and Apomorphine (Apokyn).

The surgical procedure employed to provide relief to PD patients is Deep Brain Stimulation (DBS). It is one of the prime non-destructive surgical treatment approaches which involve implanting a device in the patient’s brain to stimulate certain targeted regions via electrical impulses.
generated through battery-operated neurostimulator. DBS is used to revert or slow down the motor symptoms observed in PD patients who haven’t found any relief from the disease in the last four years of other medical treatments including the drug therapies. After the device implantation, the symptoms can be monitored, and certain adjustments can be made on the neurotransmitter as per the patient’s need. It has been reported that the electrical signals generated by DBS result in significant motor control by interrupting abnormal signaling patterns. Though the treatment is not the cure of the disease, it is known to reduce symptoms, provide relief to PD patients, and help them to maintain the quality of their life.

The novel treatment approaches of this deadly disease have been brought up by the cell replacement therapies using stem cell technology, which strongly focuses on increasing the level of dopamine by restoring dopaminergic inputs into the body of patients in a localized and physiological manner. This will ultimately provide benefits in terms of effect and longevity when compared with other medications, particularly the oral medications. In this method, the Embryonic Stem Cells (ESC) were generated via IVF procedures, harvested from early blastocyst and embryonic cell lines were developed successfully. Thereafter, using differentiation protocols these cells were directed to become dopaminergic neurons that survived transplantation into animal models and produced a noticeable motor response. Although the transplanted cells secreted dopamine, they failed to express important markers (LMXIA and FOXA2) required for optimum dopaminergic neuronal activity, and being non-native, they required continuous administration of immunosuppressant. Also, to maintain constant dopamine levels, transplantation had to be carried out repeatedly at regular intervals.

In the modern era, where we discuss on the molecular level, genomic level, and the DNA level, treatment considerations can also include dopaminergic gene introduction, gene replacements and substitutions that will ultimately serve as the permanent cure of this disease. It has previously been proved through sundry cases that when different systems of medicines are combined, the patient’s health is drastically improved. The allopathic surgeries and procedures can be combined with the ayurvedic sciences, involving proper selection and utilization of herbs that are known to have certain beneficial effects on the functioning of the brain, like Ephedra, Glycyrrhiza glabra, and Nux vomica can serve as another novel approach to control the progression of this disease.

Conclusion

The second most chronic, progressive neurodegenerative medical complication discovered by Dr. James Parkinson in 1817 as “shaking palsy” is Parkinson’s disease. PD is also referred to as a degenerative disorder and is characterized by both motor and non-motor features. It has been estimated that around 7 to 10 million people worldwide suffer from PD. The disease is known to cause severe disability 10 to 15 years after its onset and this marks the urgent need for its effective cure and treatment. To date, there is no effective cure on record, but several measures have been taken up by scientists and doctors to reduce the symptoms and slow down the progression of the disease but the potential cure is yet to be discovered. Some data from the ayurvedic studies suggests
that there are several drugs that have an effect on cognition and dementia. Elaborated studies of these herbs can give promising results that may alter the dynamics of the disease progression. The article summarizes all the current speculations about Parkinson’s disease, its rapid expansion, an urgent need for cure and the possibilities which may impact different current therapies in Parkinson’s disease treatment over the next two decades.

References


The Possibility of Developing Dementia from Long-Term Benzodiazepine Use

Kaitlyn Ramesh

Abstract

Due to their fast-acting and evident effects, benzodiazepines (BZDs, BDZs, BZs) are widely prescribed and taken for treating conditions like anxiety and insomnia. That being said, benzodiazepines are also known for their high risk of dependence, which can lead to cognitive impairment, affecting one’s memory and personality, as well as motor impairment, inducing falls and injuries [1]. Considering these known effects of benzodiazepines, it seems likely that conditions such as dementia may arise from heavy use. This article, however, will discuss how the effects of long-term benzodiazepine use do not correlate with an increase in one’s risk of developing dementia due to interference from multiple confounding factors.

Benzodiazepines

Benzodiazepines refer to a class of psychoactive drugs prescribed for those suffering from anxiety and insomnia. Within benzodiazepines, there are different types varying based on their elimination half-life, or time spent in the bloodstream until its original concentration is halved, and relative potency, which determines the dose prescribed [4]. It is likely for one to have heard about benzodiazepines by their more commonly known brand names. For example, Xanax and Valium are the names that benzodiazepines alprazolam and diazepam are sold under, respectively [2]. Despite there being variation within the benzodiazepines, many share side effects including drowsiness, fatigue, and lethargy [4]. Overdosing on benzodiazepines intensifies these effects to dangerous levels, leading to cognition and motor impairment, as well as increases the risk of dependence.

Figure 1. This diagram depicts a GABA receptor, and its BZD receptors are responsible for the effects of benzodiazepines on the brain [4].
The Pharmacology Behind Benzodiazepines

To produce its sedative and hypnotic effects, benzodiazepines operate through the $\text{GABA}_A$ receptor as a positive allosteric modulator. Out of the three major types of GABA receptors, $\text{GABA}_A$ is the chlorine-selective ion channel; like the rest of the GABA receptors, the inhibitory neurotransmitter GABA primarily binds to it. Once bound, GABA hyperpolarizes the neuron by inciting a conformational change in its receptor that causes an influx of negatively charged chlorine ions to enter the neuron. This will prevent excitation of the neuron and, on a wider scale, will produce a calming effect on the brain [4]. Benzodiazepines, as positive allosteric modulators, bind to its own receptors on $\text{GABA}_A$ receptors, which enhances the ability of the $\text{GABA}_A$ receptor [5]. While calming the brain is a benefit for those who struggle with conditions like insomnia, uncontrolled and increased suppression of brain activity will have more deleterious results.

The Pros and Cons to Benzodiazepines

One study shows that 30.6 million adults in the U.S. use benzodiazepines, with 25.3 million prescribed with the drug and 5.3 million misusing it [6]. The prevalence of benzodiazepines is likely due to their multiple uses as anxiolytics, hypnotics, anticonvulsants, and even muscle relaxants. Furthermore, benzodiazepines are fast-acting without any unfavorable, initial side-effects. Serotonergic antidepressants like SSRIs, which can be taken in place of benzodiazepines, often cause nausea and dizziness at the start of treatment and take time to result in any noticeable change [1]. Therefore, having immediate relief for a wide variety of conditions makes taking benzodiazepines seem much more preferable.

However, the negative effects of benzodiazepines can outweigh such benefits. As mentioned earlier, at high doses benzodiazepines lead to impairment in cognition and motor abilities. Additionally, benzodiazepines are associated with dependence since withdrawal symptoms can occur from usage lasting 3 to 4 weeks [7]. Dependence can then lead to BZD-induced toxicity, which in addition to previous side-effects, will result in delirium, anterograde amnesia, and making one prone to injury and falls. Moreover, disinhibition stemming from benzodiazepine use can compromise driving performance. It should be noted that the prescription quantity of benzodiazepines has increased 50% from 2005 to 2015, putting the public at a higher risk of these consequences [8]. In particular, the elderly community is targeted due to the decline in renal function with age, which would lead to a toxic buildup of benzodiazepines in fatty tissue [4]. Unawareness of the downsides to benzodiazepines can lead to misguided prescriptions that endanger a patient’s cognitive ability and life overall.

Benzodiazepine-Induced Dementia Vs. Memory Loss

One recognized concern surrounding long-term benzodiazepine use is potential memory loss. Anterograde amnesia has been detected as a side-effect, which is evident considering that $\text{GABA}_A$ receptors decrease synaptic plasticity and brain activity. This would then contribute to a
decline in retaining memory. Benzodiazepines undermining memory has also been recorded in mice, where the long-term administration of diazepam caused a decrease in their production of BDNF, a neurotrophic factor that enhances memory processing. Similarly, another test on mice under midazolam shows an increase in the phosphorylation of the tau protein; such a result is a precursor to Alzheimer’s disease [10]. These effects from benzodiazepines suggest that dementia could develop from a more long-term use.

Dementia is a set of symptoms that can arise with brain damage or the diagnosis of various neurological disorders. Having dementia results in cognitive changes such as difficulty with problem-solving, socializing, and memory loss, as well as psychological changes, affecting one’s personality and mental state. Known progressive dementias present in Parkinson’s and Alzheimer’s disease include Alzheimer’s dementia, vascular dementia, and Lewy body dementia. Risk factors for dementia include age, cardiovascular health, psychiatric disorders, as well as diet and exercise. [9]. Acknowledging what is known to lead to the development of dementia is crucial for uncovering whether use of a particular drug like benzodiazepines will have the same effect.

Numerous independent studies researching the connection between benzodiazepines and dementia have made various conclusions with their collected data. Consequently, meta-analysis studies were conducted in the years following to detect trends among these case-controlled and cohort studies. Here, several factors were recognized to have influenced the diagnosis of dementia instead of the use of benzodiazepines. To clarify, if one is treating their insomnia, anxiety, or depression, with benzodiazepines, these mental illnesses are more likely responsible for their dementia, not their benzodiazepine use [3][2]. The side-effects of benzodiazepines may also cause a dementia-like condition, which can be reversible with proper withdrawal of the drug [8]. Figure 2 shows that by excluding these variables, erroneous relationships, as indicated by dashed lines, between benzodiazepine use and dementia are made [4]. With so many influences involved, it is difficult to determine any causal relationship between long-term benzodiazepine use and the development of dementia.

**Conclusion**

Benzodiazepines are still prescribed today, just with greater caution when determining doses and the duration of treatment. A greater awareness of these drugs in the medical field can further research and the development of less addictive alternatives. To elaborate, current research has been using the effects of benzodiazepines to study the brain for treating certain neurological disorders.
For example, specific benzodiazepine receptors that are responsible for a decline in memory, such as the alpha-5 GABA\(_A\) receptor, could be targeted to lessen the effects of dementia \[10\]. Alternatives like SSRIs and SNRIs can be improved to reduce side-effects and increase efficacy, so they can be prescribed for cases that would otherwise require benzodiazepines. On the other hand, benzodiazepines can be experimented with in the future so they provide fast-acting effects without a high risk of dependence.

Studying the mechanisms through which benzodiazepines operate could shed light on how memory is lost and give rise to alternative treatment for those with dementia \[10\]. Furthermore, these investigations on the possible connections between benzodiazepines and dementia ultimately show that there are multiple factors other than drug use that can lead to the development of certain illnesses. Accounting for these influences will allow for more accurate diagnoses and the increased reporting of conditions that need attention.

References


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We could not have made this issue of the IYNA Journal possible without the following people:

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Featured Writers: Francesca Venditti, Shambhavi Chaturvedi
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