Psychopharmacology and Mental Health

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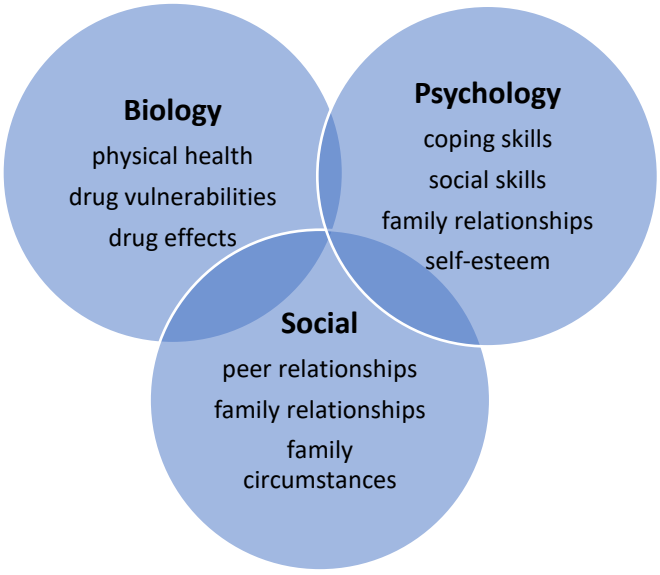
Mental health wellness and innovative comprehensive approaches to treating brain health appear to be on a positive trajectory. So, why does there continue to be a rise in mental health issues, especially among adolescents and young adults? According to a study published in 2019 by the American Psychological Association (APA), mood disorders, including anxiety and depression, and suicide-related outcomes have increased over the last decade (Twenge, 2019). Moreover, the recent COVID-19 pandemic has caused an unprecedented psychosocial disturbance, triggering these numbers to rise even higher. One could describe these times as a global psychological crisis! These unfortunate findings suggest that cultural trends in the last 10 years may have had a larger effect on mood disorders and suicide-related outcomes among younger people compared with older people (Twenge, 2019), according to the researchers.

The psychological consequences are scary, to say the least, and researchers explained "the increase in adolescent major depressive episodes began after 2011, concurrent with the increased ownership of smartphones and a concomitant increase in digital media time in the age group" (Twenge, 2019). These findings suggest the wide-spread usage of smart phones and digital media has played a major role in the rise of mental health issues. So, in conjunction with this cultural trend of digital media usage, complicated by living through a health-related pandemic, psychologists are voicing serious concerns for the mental health of people, especially for our children and adolescents. Keeping these frightening trends in mind, this article will describe the interaction of a Mental Health Model, offer a discussion regarding psychosis and psychotropic drug use, review several brain assessments, discuss both genetic and environmental components that affect mental health, take an in-depth look at psychosis and various brain regions affected, and review medications used to treat psychosis as well as their side effects.

Brain health plays a major role in how we function in society and is directly related to our physical health. In fact, since science and technology are advancing exponentially, health professionals can now offer advanced comprehensive strategies to treat psychiatric health issues. Unfortunately, the vast majority of patients say they have never heard about integrative strategies to treat mental health. This may be because individuals who are experiencing mental health issues are simply not seeking the help they need due to negative stigma. Another reason may be family practitioners are simply not educating and/or referring their patients to mental health professionals that offer comprehensive strategies. Either way, the consequence of not addressing mental health issues as a child or adolescent can extend their issues into adulthood, limiting opportunities to lead fulfilling and productive lives as adults. Current models for understanding the importance of the interaction of our biology, psychological health, and social relationships help us understand the need for balance, and make clear how these factors play a major role throughout an individual's lifespan:

Mental Health Model:



When one is healthy, the delicate interaction between one's biology, social relationships and one's psychological well-being produces a mind/body equilibrium, a biopsychosocial

balance, and as a result we feel healthy, happy, and secure. So, if any of these sections in the mental health model become disconnected, one will experience stress which could lead to serious mental health issues, including psychosis.

In addition to the cultural trend of digital media usage, the COVID-19 crisis has clearly affected society's social dynamics and how we are able to relate to and interact with others, causing social isolation, loneliness, and feelings of fear/anxiety. This is a paradox because the very thing (digital media) that has contributed to a rise in serious mental health issues in the past, is now something we *need* to keep us connected and improve our mental health! We now need to find a digital media balance combined with strategic treatment models for mental health practitioners to treat patients so these staggering statistics can improve. The concerns about the virus and its effects have caused feelings of uncertainty, which has developed in many parts of the world, into a cycle of panic and fear. Consider the fact that when one is stressed, old psychological patterns can emerge, creating discord with family and/or friends. This compounds our psychological stress, and invariably leads to other major health issues.

Given these considerations, the first step of treatment should consist of an improved understanding and approach to a combination of therapy strategies that include psychotherapy, behavior therapy, and psychopharmacology. Now that mental health is a widespread issue, this combined approach is getting more attention as the field of neuroscience continues to uncover new ways to treat a variety of mental disorders. In combination with psychotherapy, promising breakthroughs and advancements in psychotropic medications may result in refining drug treatments for mental disorders by offering safer and more effective selections with less negative side effects. In this article, the neurochemical effects of psychotropic drugs will be discussed, with an emphasis on the drug Seroquel, as well as both positive and negative side effects that may occur as a result of taking psychotropic medication(s).

Psychosis and Psychotropic Drugs

Let's face it. Many individuals want to avoid taking psychotropic drugs because of the adverse side effects that may ensue. Nevertheless, there are individuals with severe mental health issues that need medications to help them function in everyday life. There are many clinical syndromes that fall into serious mental illness categories, so this paper will focus on severe syndromes such as bipolar disorder, schizophrenia, or dementia, that can develop into psychosis. Only a small portion of the population with genetic, epigenetic, and developmental risk factors, along with exposure to social and environmental factors, may be prone to developing persistent psychotic symptoms (Arciniegas, 2015), but psychologists suspect this number might be on the rise since the novel COVID-19 pandemic attacked our population. Developing a psychotic disorder, such as Schizophrenia, is persistently found to be around one percent of the population in any given culture and environment. However, since the COVID-19 crisis, our population as a whole has been exposed to considerable risk factors, along with social and environmental factors, so a larger portion may be affected, including individuals who are now suffering with PTSD.

The definition of psychosis is multifaceted. It is important, therefore, to define the condition and list how it is classified as a mental disorder so one can better understand how medication can help. Psychosis is defined by abnormalities in one or more of the following domains: positive symptoms (delusions, and hallucinations), disorganized thinking (speech), grossly disorganized or abnormal motor behavior (including catatonia), and negative symptoms (decreased ability to experience pleasure (anhedonia), diminished speech output (alogia), decreased social association (asociality), and diminished emotional expression) (Arciniegas, 2015, and Kupfer, 2013). All of these symptoms cause distress to the patient, along with major impairment in personal function, and extreme distress to the patient's family and friends.

Psychotropic drugs are prescribed to a patient after diagnosis to help diminish the positive and negative symptoms and hopefully improve their quality of life. To further complicate the condition, psychosis is typically comorbid with schizophrenia spectrum disorders, mood and substance use disorders, and many developmental, acquired, and

degenerative neurologic and medical conditions (Arciniegas, 2015). Before describing the different sections of the brain that are dysregulated in patients who are afflicted with psychosis, common neurobiological factors in this spectrum of patients will be addressed in order to better understand how antipsychotic drugs can affect an individual's unique neurobiology. Finally, common neurotransmitters, which are found in deficit or excess, will be examined along with the systems they affect.

Assessment

Psychosis, along with various other serious mental health issues, is usually diagnosed by using both informal and structured clinical assessments for the presence of positive and/or negative symptoms that are clearly defined common features of psychosis (Arciniegas, 2015). There are many observable behaviors and neurobiological factors clinicians must consider before properly diagnosing and treating someone with a mental health problem. An example of a clinical assessment used to diagnose someone with psychosis is the use of biomarkers (Venigalla, 2017). This is a fairly new approach in diagnosing mental disorders and can help physicians prescribe psychotropic medication(s) that better match the individual's unique chemical imbalances.

A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes or biological responses to a therapeutic intervention (Venigalla, 2017). In other words, a biomarker can be a gene or a group of genes, proteins or other biomolecules (Venigalla, 2017). It is important to note that the development of psychosis is the result from both gene and environment interaction. For example, Schizophrenia is a neurodevelopmental disorder that results from the abnormal development of the prefrontal cortex and hippocampus (Meyer, 2019). The first line of treatment for schizophrenia is usually to reactivate the homeostatic nature of the patient's dopamine system (Meyer, 2019). Unfortunately, the persistent disconnection between the anatomical and pharmacological aspects of the disorder is still unknown.

Observing biomarkers is a new type of diagnostic procedure that can be a very useful tool for healthcare practitioners. As noted above, biomarkers are very complex—since there is not just one abnormality that contributes to severe mental illness, but a combination of various abnormalities. Interestingly, certain electrophysiological biomarkers can show the failure of connectivity among neurons and abnormal neuronal processing (Nenadic, 2015), and are found by using a quantitative electroencephalography (qEEG), or a brain map, which is a precise tool in locating brain dysregulation. Biomarkers commonly found in schizophrenics are characterized by frontal lobe deficits, or hyperfrontality. A qEEG processes recorded EEG activity from a multi-electrode recording using a computer with specialized software. Finally, many types of brain imaging techniques can be used to view these abnormalities in brain activity. These can be detected using a functional magnetic resonance imaging (fMRI) (Nenadic, 2015). An fMRI uses a fast chain of MRI images to monitor blood flow in the brain detecting areas of activity.

Another brain imaging technique is called Single Photon Emission Computed Tomography (SPECT imaging), and is a procedure widely used to study brain issues. It uses a radioactive substance and a special camera to look at 3D images of the brain and measure cerebral blood flow. A common functional abnormality found in a patient who exhibits signs of psychosis is less of an increase in blood flow to the prefrontal cortex (PFC) while performing cognitive tasks that require executive functioning (Nenadic, 2015). Functional imaging data of schizophrenics suggests that there is decreased activation in the PFC when trying to preform cognitive tasks. Another biomarker for individuals who have been diagnosed with schizophrenia is abnormal eye movements. This abnormality is known as smooth-pursuit eye movements and is known as a biomarker of hypofrontality (Meyer, 2019). In individuals with schizophrenia, their eyes tend to dart and then attempt to readjust when tracking an object. This shows that there are obvious deficits in controlling eye movements. Furthermore, this finding suggests that there must be some dysregulation in the frontal eye fields (FEFs), which are located in the PFC (Meyer, 2019).

Genetics

Genetics play a role in many serious mental health disorders, and one mental health disorder that has a strong heritability rate is schizophrenia. Presumably, individuals who share greater proportions of their DNA with a schizophrenic will have increased risk of developing the disorder. Heritability of this neurodevelopmental disorder is estimated to be approximately seventy-six percent (Hiker, 2018). Although these studies indicate a strong genetic component in schizophrenia, scientists do not know what genes are directly involved. This is a very complicated process because the disorder is both polygenic and pleiotropic (Zheutlin, 2019). Therefore, the common genetic loci for individuals with schizophrenia have been grouped into three broad categories.

One category are genes that code for synaptic proteins involved in neuronal excitability and plasticity. This category would be genes that code for NMDA receptors, cytoskeletal proteins, or long lasting (L type) calcium channels (Iasevoli, 2014). Another category is cell to cell recognition molecules that play a role in synapse formation and stabilization. Synapse formation and stabilization involves genes such as the DISC-1 gene, and Neuregulin 1 (NRG-1) and its receptor erbB-3 (Selemon, 2015). The last category includes other types of structural proteins. These include the peptide FMRP and other related proteins (Iasevoli, 2014). Although we do not know exactly what causes the deficits in schizophrenia, they seem to be related to establishing neuronal synapses, keeping those synapses working, and maintaining all of the molecules at the synapse in their proper location so that the synapse can function typically. Thus, one may conclude that genetic vulnerability that alters neurodevelopment might include developmental deficits in cell differentiation, migration, or synaptogenesis.

Environment, Pregnancy, and Fetal Development

The environmental stressors that seem to affect the development of neurodevelopmental disorders tend to revolve around prenatal complications in the early stages of development. Some common complications that can cause the development of

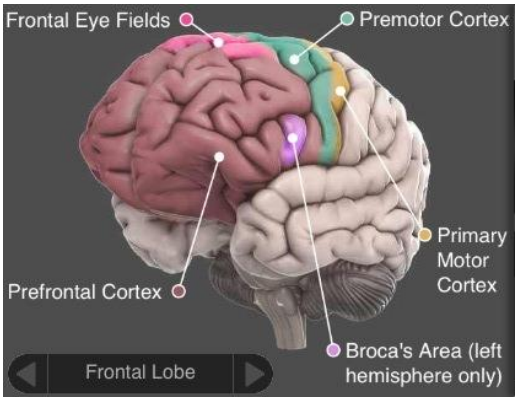
neurodevelopmental disorders include maternal illness, poor maternal nutrition, and low birth weight or premature birth (Selemon, 2015). It is believed that the immune response presented by a mother who is sick with either influenza or rubella can change the developmental trajectory of a genetically as risk fetus (Selemon, 2015). It has been theorized that cortical development in the first trimester must be derailed by some environmental factors in early gestation (Selemon, 2015). For example, schizophrenics are known to have decreased neuronal volume, most likely initiated by reducing neuronal proliferation in early gestation (Selemon 2015). An environmental factor that might disrupt the development of the fetus's cortex is the inflammatory immune response of the mother (Selemon, 2015). The interaction between genes and environment leads to the development of symptoms that usually emerge in late adolescence to early adulthood (Selemon, 2015). These interactions change developmental trajectories, leading to anatomical and functional deficits.

Psychosis – Brain Regions Affected

Numerous regions of the brain are affected by the presence of psychosis. Areas of cortical deficits include, right dorsolateral prefrontal, bilateral medial prefrontal, bilateral ventrolateral prefrontal and insular cortical areas, left medial temporal, as well as thalamus (bilateral), left superior temporal cortex, and minor right cerebellar and right temporal pole areas (Nenadic, 2015). It is understood that individuals suffering from schizophrenia have gross anatomical changes. Particularly in males that display negative symptoms, there are enlarged ventricles (Johnstone, 1976). In fact, there is an overall decrease in brain volume, seen in total brain size (Meyer, 2019). This includes areas like the prefrontal cortex and hippocampus, along with a widening of brain sulci (Meyer, 2019). The brain volume loss in schizophrenics is not a whole scale neurodegeneration like we see in Parkinson's and Huntington's disease. Instead, the area of synaptic contacts is largely what is lost (Meyer, 2019). There is no loss of cells bodies, but loss of all the synaptic contacts due to abnormal or excessive pruning of synapses (Meyer, 2019). Additionally, there is disorganized brain anatomy seen in the prefrontal cortex and

hippocampus. The disorganized anatomy seen in schizophrenia leads to functional deficits (Meyer, 2019). It is believed that the negative and cognitive symptoms of schizophrenia are the result of inefficient PFC function (Meyer, 2019).

Given this glimpse into the brain, one can conclude that symptoms of psychosis, including some types of dementia and schizophrenia, are mainly related to deficits in the prefrontal cortex (PFC). Hypofrontality, which is a state of decreased cerebral blood flow, causes impaired executive functioning of the prefrontal cortex (Meyer, 2019) and is present in individuals afflicted with severe mental illnesses such as schizophrenia, bipolar disorder, and major depressive disorder (MDD). The PFC is responsible for decision making, planning, personality expression, motor control, working memory, inhibition of inappropriate behaviors, and attention (Meyer, 2019). Cognitive deficits commonly seen in patients suffering from psychosis affect working memory, language and executive function, episodic memory, speed processing, attention inhibition, and sensory processing (Brisch, 2014). With damage to the PFC, there are deficits in working memory, social and cognitive impairments, poverty of speech, flat affect, and a lack of motivation (Meyer, 2019). These resemble the negative symptoms seen in individuals with schizophrenia, for example. Thus, in individuals with severe mental disorders that include psychosis we see that the PFC is unable to execute top-down control over subcortical systems resulting in the social and emotional deficits.

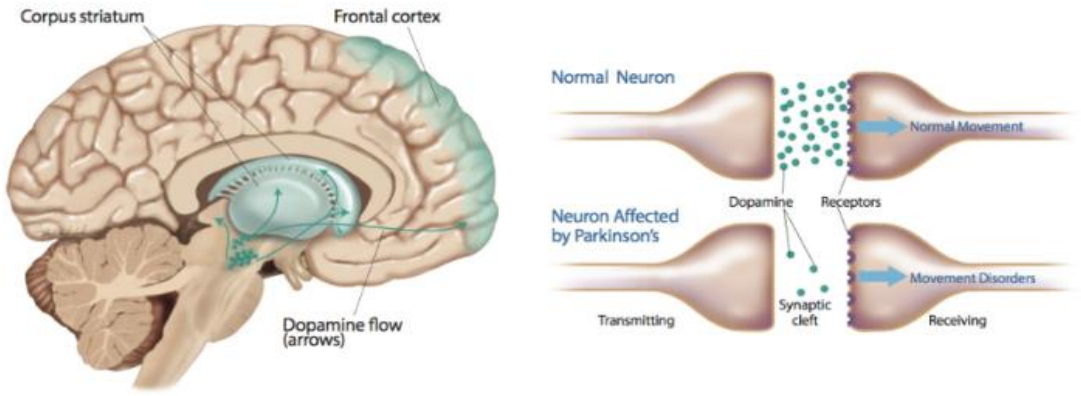


Working memory discrepancies of patients suffering from psychosis has been extensively studied by neuroscientists by examining the PFC and cognitive function. However, there are additional challenges among patients afflicted with psychosis. Auditory processing involving memory procedures is impaired as well in working memory (Brisch, 2014). In a clinical test setting, patients demonstrated significant limited capacity of their working memory, as shown by an increased rate of false positives and errors (Nenadic, 2015).

Episodic memory discrepancies seen in patients suffering from psychosis involve deficits in the medial temporal cortex, particularly the hippocampus, and in the PFC, particularly the ventral and dorsolateral regions (Brisch, 2014). Furthermore, increases in both phasic and tonic activity in the PFC, commonly seen in patients suffering from psychosis, leads to an increase in inhibitory post-synaptic currents, which would ultimately cause inhibition in the thalamus (Avery, 2017).

Neurochemical Abnormalities of Psychosis

Regarding the more direct neurochemical abnormalities of psychosis, pathophysiological models assume that psychosis is caused by hyperactive dopamine



(DA) transmission in the mesolimbic pathways and PFC (Brisch, 2014). This is known as the DA hypothesis, and it has been around ever since clinicians have attempted to explain the pathophysiology of psychosis. Parkinson's disease research has majorly contributed in supporting the DA hypothesis. As shown in the above image, Parkinson's disease is characterized by a significant DA deficiency in the basal ganglia, located in the center of the brain (Brisch, 2014). It is important to note the dopamine theory of schizophrenia has been challenged. Although medications produce their pharmacological effects rapidly, their clinical effects take weeks or months to kick in. This is known as a therapeutic lag. Furthermore, other receptors in other systems are involved along with the dopamine system. Finally, there is a need to reconcile the anatomical/developmental abnormalities.

In fact, through the use of certain drugs such as neuroleptics, drugs that helps to reduce nervous tension by depressing nerve functions, and the DA precursor L-Dopa, clinicians have developed a better understanding of the biology of psychosis (Brisch, 2014). Neuroleptics are DA receptor antagonists and, when prescribed, can cause parkinsonian symptoms (Brisch, 2014). These are known as extra pyramidal system (EPS) side effects. These side effects are caused by increased dopamine in the nigrostriatal pathway. The DA precursor L-Dopa is a DA receptor agonist and, when prescribed, can actually *cause* symptoms of psychosis (Meyer, 2019). This is also true for stimulants such as cocaine and amphetamine, which increase dopamine levels and have to potential to induce psychosis. Neuroleptics (typical antipsychotics) medications are high affinity D_2 receptor antagonists (Meyer, 2019). These findings further conclude the DA receptor hypothesis for psychosis.

Due to the promising findings of the DA hypothesis, researchers have sought to find the direct cause of psychosis by looking at DA subtypes. DA receptors are G-protein-coupled receptors and can be divided into D_1, D_2, D_3, and D_4 receptors respectively (Brisch, 2014). Brain imaging studies show that individuals who suffer from narcolepsy, a sleep disorder, selectively inhibit D_2 receptors in the striatum, and serotonin (5-HT) 2A receptors in the PFC, which results in increased dopamine activity (Brisch, 2014). It was also found that the D_2 receptor is required to be at least eighty percent occupied in order to effectively treat the positive effects of psychosis (Brisch, 2014). Based on this finding, we now know that not all positive and negative symptoms of psychosis are caused by this receptor alone. This challenged the DA hypothesis and called for a new theory of causation.

Scientists then sought to look for the causes of the negative symptoms of psychosis. Through research, the cognitive deficits of psychosis were found to correlate with a decline in DA receptors in the PFC, predominantly at D_1 receptors (Brisch, 2014). It is believed that the negative symptoms of schizophrenia, for example, are caused by excessive pruning, or loss of brain volume in the PFC (Meyer, 2019). The positive symptoms are caused by the loss of top down (prefrontal) control of VTA (brainstem)

dopamine neurons (Meyer, 2019). Since antipsychotics target the dopamine system, they are effectively treating the positive symptoms and are equally ineffective in treating the negative symptoms. This opened up the theory that not only were D_2 receptors responsible for psychosis, but it is primarily due to an imbalance of D_1 and D_2 receptors in the PFC (Brisch, 2014). Furthermore, the D_2 receptor, in disinhibition, was recognized to be main reason of promoting positive symptoms of psychosis while the D_1 receptor, in disinhibition, was recognized to be the main reason of promoting negative symptoms (Brisch, 2014). In summary, the extreme chaotic release of DA in the brain of a patient suffering from psychosis, with emphasis on the PFC, was found to be a potential mediator in the development of psychotic symptoms.

There is more than one neurotransmitter involved with psychosis. As mentioned above, neuroleptic drugs work with D_2 receptors, along with 5-HT_{2A}. The hallucinogenic drug, LSD, exerts its effects by activating the 5-HT_{2A} receptors as an agonist (Meyer, 2019). Due to this, atypical antipsychotics were developed to have a lower affinity for the D_2 receptor and a higher affinity for the 5-HT_{2A} receptor (Meyer, 2019). The blocking of 5-HT_{2A} receptors by atypical antipsychotics was found to be just as useful as the neuroleptics, just with less severe side effects (Meyer, 2019). The specific D_2 receptor occupancy of neuroleptics in the striatum interacts with the antagonistic effects of 5-HT_{2A} receptors (Brisch, 2014).

In studies of psychosis, an increase in D_2 receptor density can be found in high-affinity in specific neurotransmitter pathways such as those of glutamate, gamma-aminobutyric Acid (GABA), and acetylcholine (ACh) (Brisch, 2014). The presence of D_1 receptors can be found in GABA interneurons as well, therefore if a drug affects GABA receptors, it subsequently affects DA receptors (Brisch, 2014). Similarly, certain D_1 and D_2 receptors cooperate with the major glutamate subtype receptor NMDA as a receptor mosaic (Brisch, 2014). GABA and glutamate are both known for regulating DA activity in the brain (Brisch, 2014). Furthermore, D_2 receptor antagonists that can act as D_1 receptor agonists, improve NMDA synaptic transmission (Brisch, 2014). In summary, to have an

effective antipsychotic drug, DA must properly interact with other neurotransmitter pathways to get the desired effect.

In schizophrenia there is hippocampal dysregulation of dopamine system function. Part of the deficit that arises from the changes in hippocampal structure in development is the loss of GABAergic inhibition in the hippocampus (Meyer, 2019). This results in a strong excitatory drive of glutamate from the hippocampus to the Nucleus Accumbens (NAcc) (Meyer, 2019). Therefore, there is far too much disinhibition of the ventral pallidum by the NAcc, which results in increased activation of dopamine neurons in the ventral tegmental area (VTA) to the NAcc (Meyer, 2019). This is known as the hypoglutamate hypothesis of Schizophrenia (Meyer, 2019). The VTA is comprised of two major kinds of cells: spontaneously active cells; and cells under tonic inhibition by the ventral pallidum (population neurons) (Meyer, 2019).

The activity state of the ventral subiculum is dependent on environmental context (Meyer, 2019). When activated, it disinhibits the ventral pallidum, therefore removing the ventral pallidum's inhibitory influence on the dopamine neurons of the VTA (Meyer, 2019). This increases the firing rates of DA neurons in the VTA (Meyer, 2019). Thus, it sets the gain of the dopamine system that influences our perception and actions for behaviorally relevant stimuli (Meyer, 2019). When a behaviorally relevant stimuli arrives, it results in the excitatory inputs from the pedunculopontine tegmental nucleus (PPT) to send cholinergic and glutaminergic drive to the hippocampus (Meyer, 2019). In fact, the population neurons can become spontaneously active allowing burst firing in the dopamine neurons to go and influence the system (Meyer, 2019). In summary, controlling the number of dopamine neurons firing spontaneously controls the gain of the system that is able to respond when any behaviorally relevant signal arrives.

Drugs that Treat Psychosis

Henri Laborit, a French surgeon during World War II, noticed that antihistamines had a sedative effect (Linda, 2017). He later collaborated with a pharmaceutical company creating a specialized phenothiazine in order to reduce psychosis in patient's post-surgery

(Linda, 2017). The medication he used was called chlorpromazine (CPZ), and he later observed that it caused a state of sedation in the patients, but without narcosis (Linda, 2017). Impressed by this observation, Laborit used this medication to reduce psychosis in patients who experienced severe psychotic symptoms (Linda, 2017). This resulted in a major advancement in the use of this drug to treat various symptoms of psychosis.

The drug CPZs chemical makeup was used to make antipsychotic drugs and lead to the development of other ways to properly sedate people who suffered from psychosis (Linda, 2017). These original antipsychotics, such as CPZ, caused the occurrence of extrapyramidal symptoms (EPS) or movement disorders (Linda, 2017). They worked by blocking DA receptors, therefore increasing DA release, and relieving psychotic symptoms (Linda, 2017). Approaching this problem of EPS from excessive DA blockade, atypical antipsychotics were created, combining both DA and 5-HT blockade to increase free DA in the synapse (Linda, 2017). One atypical antipsychotic drug created was Seroquel.

Seroquel, as well as many other commonly prescribed psychotropic drugs, is an atypical antipsychotic medication used to treat many serious cases of psychosis such as schizophrenia, bipolar disorder, and dementia, and may be used off label for other neurological disorders that have an unstable mood component such as major depression and in some cases anxiety (Dine, 2015). Atypical is defined as a second-generation antipsychotic medication that is FDA approved to treat certain psychiatric conditions (Dine, 2015). While seroquel has less EPS occurrences than other atypical antipsychotics, it is considered a sedative and causes weight gain (Linda, 2017). Because of the drugs sedative effects, it is occasionally prescribed to patients suffering from post-traumatic stress disorder (PTSD) and to help with sleep (Linda, 2017). Seroquel acts on D_2 receptors and 5-HT_{2A} receptors as an antagonist to get the desired effect.

This combination of medications decreases mesolimbic and dopaminergic pathway hyperactivity, therefore acting as a D_1 receptor agonist in the PFC and improving NMDA synaptic transmission (Brisch, 2014, and Linda, 2017). Once a patient continuously

takes Seroquel, it is not an easy process to stop because it can lead to withdrawal effects, and a possible return to the original problem (Hager, 2015). In fact, once the brain accommodates to the everyday dosage of the drug, if abruptly stopped, the new equilibrium that has developed will cease, causing a new imbalance and new series of problems (Hager, 2015). The common withdrawal symptoms include dizziness, insomnia, anxiety, nausea, tremors and muscle twitching (Hager, 2015). Sometimes these withdrawal effects from Seroquel can occur for months to years (Hager, 2015). In conclusion, Seroquel is an atypical antipsychotic that is effective in reducing the symptoms of psychosis, but there can be serious negative consequences.

In the treatment of psychosis through medication, Seroquel is not the only drug that can be prescribed, and not the only drug with side effects and withdrawal symptoms. Some of the other drugs commonly prescribed to patients suffering from psychosis are Clozapine (Clozaril), Iloperidone (Fanapt), Lurasidone (Latuda), and Rexulti (Brexpoprazole) (Linda, 2017). Clozaril is known as one of the most effective antipsychotics due to its higher affinity for the limbic areas of the brain rather than the striatal areas (Linda, 2017). Other than this key characteristic, it works similarly to Seroquel including its side effects. Fanapt is an antipsychotic that is structurally different from the other atypical antipsychotics (Linda, 2017). This drug works as an antagonist for both D_2 and 5-HT_2 receptors with a low affinity for histamine and muscarinic receptors (Linda, 2017). The effects of this drug causes minimal weight gain, but it is associated with orthostatic hypotension (alpha blockade) therefore not making it any more effective than existing atypical antipsychotics (Linda, 2017).

Latuda is a strong antagonist of both D_2 and 5-HT_2 receptors with little interaction with histamine, therefor causing minimal weight gain (Linda, 2017). The sedation, and mood improvement effects of this drug are apparently caused by its antagonistic interactions with 5-HT_7 receptors (Linda, 2017). It is suggested that this drug could potentially improve cognitive functioning by promoting nerve growth due to an upregulation of brain-derived neurotropic factors (BDNF) in the PFC (Linda, 2017). Brexpoprazole is a newer antipsychotic that acts on D_2 and 5-HT_{1A} receptors as a partial

agonist, and 5-HT_{2A} receptors as an antagonist (Linda, 2017). This drug also promotes nerve growth in the PFC like Latuda, and has a risk for weight gain (Linda, 2017).

An interesting finding is that patients who use nicotine and suffer from psychosis, seem to have improved cognitive functioning (Brisch, 2014). Overall, antipsychotic drugs seem to react with both DA and 5-HT receptors in attempt to reduce symptoms of psychosis. Although side effects such as weight gain, sedation, and EPS are negative side effects in all of these drugs, they are producing positive results in reducing psychotic symptoms.

Medication Side Effects and Combined Comprehensive Approaches

Antipsychotics suppress the positive symptoms—but often leave the patients with continuous signs of negative symptoms along with the side effects from the medication (Nieman, 2015). Due to this, a high percentage of patients (40-50%) do not comply with their clinician's instructions to properly take the medication and seventy-four percent discontinue within eighteen months (Nieman, 2015). This high rate of non-compliance calls for a combined approach to treatment of mental illness that includes psychotic symptoms. Health-care practitioners are starting to use the term *brain health*, instead of mental illness, to treat more severe cases and are integrating complex assessments to address severe symptoms as mentioned above.

Cognitive behavioral therapy has been proven to significantly improve psychotic symptoms for those who have chosen not to take antipsychotic medication (Nieman, 2015). There have been studies on cognitive behavioral therapy (CBT), with patients suffering mainly from psychosis symptoms that include persecutory delusions, that have shown favorable results such as a ninety-five percent reduction in both worry and persecutory delusions (Nieman, 2015).

This reduction in both obsessive/worrisome thoughts and persecutory delusions led to a significant overall improvement in the patients' psychiatric symptoms as a whole (Nieman, 2015). Although this brings other questions to surface, overall CBT is a very

promising approach and has an important contribution to the treatment of psychosis. Finally, studies involving EEG brainwave training (neurofeedback) are revealing dramatic improvements and positive long-term outcomes for patients who suffer from severe mental illness such as schizophrenia.

Conclusions

Clearly, we are living in unprecedented times as mental health issues continue to climb. Both medicative and comprehensive therapies can help individuals who suffer from a wide range of mental health conditions, including psychosis, and these modalities continue to be explored and redefined every day. There are many unique, individual neurobiological factors that contribute to the origin of psychosis; therefore, the direct causality is still unfolding. Since many sections of the brain are affected by mental health conditions such as psychosis, there are also various dysregulations in vital brain systems. In addition, the DA hypothesis was a huge step in the right direction as we advance our understanding of the brain - especially with individuals suffering from psychosis.

Antipsychotic medications, along with parkinsonian research, have significantly contributed to our current understanding of psychosis and the role of DA, 5-HT, GABA, and glutamate receptors. The unwanted side effects of antipsychotic medications have caused clinicians to strategize and apply needed changes by implementing an integrative/comprehensive treatment approach due to the high rate of medicative non-compliance. The many promising discoveries currently being made are pointing clinicians in the right direction of better understanding and treating severe mental illness. Hopefully, in the near future, we will have an even better picture of mental illness, a clearer diagnosis of psychosis, improved psychotropic medications, and continued innovative integrative therapies with zero negative side effects.

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