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Neurochemical Function in Schizophrenia: A Case Study

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Abstract

This research project addresses the topic of schizophrenia. Because of the vast amount of information available regarding schizophrenia, this paper will only focus on a few aspects of the disease. In particular the symptoms, brain abnormalities, hypotheses, and treatment strategies associated with brain abnormalities in schizophrenia will be presented. These emphases were chosen because they are of particular interest to the researcher. The intent of this paper is to discover what brain abnormalities, both physiological and chemical, are associated with schizophrenia. The intent is also to discuss treatment strategies and assess how this information may apply to a case study.

Neurochemical Function in Schizophrenia: A Case Study

Schizophrenia is a multi-faceted disease. It would be an immense task to attempt to capture all the intricacies of the disorder in one research project. Therefore, this document is biased in a way, because only certain topics relating to schizophrenia will be addressed. The purpose of this paper is discover what brain abnormalities, both physiological and chemical, are associated with schizophrenia. Also, this paper intends to discuss various treatment options, relative to their impact on brain neurophysiology. The information gathered will be applied to a case study. While this study is not an exhaustive treatment on the topic of schizophrenia, hopefully it will prove useful in allowing the reader to catch a glimpse of the complexity of schizophrenia.

History and Background

It was Emil Kraepelin who led the way in placing schizophrenia in a distinct category separate from related disorders such as Alzheimer's and manic depression. In his early writings, Kraepelin dubbed schizophrenia 'dementia praecox' and stressed the chronic nature of the disease. Bleuler disagreed with Kraepelin's emphasis on the persistence of the disorder, and shortly after the turn of the twentieth century he renamed it to the commonly recognized name it bears today: schizophrenia. In renaming the disorder, Bleuler sought to underscore the disintegration of thinking and personality that typifies schizophrenia (Andreasen, 1995).

Schizophrenia is an unforgiving disorder, leaving most sufferers unable to completely return to pre-diagnosis functional levels. As yet, there is no cure for the disease, and a great majority of patients must receive ongoing therapy, usually psychopharmaceuticals, for the rest of their lives. Even if all preventative measures are taken after the diagnosis is confirmed, the

person may suffer a relapse and require treatment more intense than maintenance treatment, or even hospitalization.

Approximately 62 million people worldwide suffer from schizophrenia. In US hospitals, schizophrenics are occupying about 25% of all beds and comprise 40% of long-term care days (Pickar, 1995). According to 1980 estimates, schizophrenia costs about \$11.1 billion in terms of medical care and maintenance. Sadly enough, schizophrenia usually arises in the late adolescent to early adulthood stages of life, when opportunities seem boundless, and life is yet to be fully experienced. The victim struggles with loss of identity, independence, and mental functioning abilities. In light of this, it is no wonder that 10% of schizophrenics terminate their existence by committing suicide (Andreasen, 1995).

Symptoms

A wide array of symptoms characterize schizophrenia. Hallucinations, delusions, avolition, affective blunting serve as a few examples of the symptoms displayed in this disorder. A sampling of symptoms is present in all patients, but no single symptom is present in all. Schizophrenia is termed a polythetic disorder because it lacks a unifying characteristic. Because of this complexity, symptoms have been classified into two distinct categories, positive and negative symptoms, in order to simplify the diagnosis of the type of schizophrenia prevalent in the patient (Andreasen, 1995).

Positive

Positive symptoms usually designate the presence of a trait that would normally be absent. According to Mattson, Berk, and Lucas (1997) “positive symptoms include delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness, and hostility”(p. 490). Those who predominately express positive symptoms have an increased

success rate in responding to treatment (Andreasen, 1995). While complete restoration to a pre-diagnosis state may not be possible, typically treatment offers more hope than if negative symptoms were predominately present.

Negative

Negative symptoms tend to indicate the lack of a certain feature that should be present under normal functioning. Typically, negative symptoms are less responsive to treatment than positive symptoms, and disable patients from returning to daily activities such as work or school (Andreasen, 1995). Negative symptoms include “poverty of thought and speech, blunted affect, decreased motor activity, apathy and avolition, and diminished interpersonal interactions. Other symptoms such as poor rapport, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking have been included” (Mattson et al., 1997, p. 490). Findings indicate that many manifestations of negative symptoms may be due to depression (Beck & Rector, 2000).

Brain Abnormalities

While the symptoms offer themselves to classification, the causes of schizophrenia do not. There are a variety of factors that may work together to induce psychosis. Below is a closer look at the brain abnormalities that are associated with schizophrenia.

Over 15 years of computed tomography indicate that people diagnosed with schizophrenia have brain abnormalities. These include an “upward shift in the distribution of ventricular size and dilation of the cortical sulci” (Waddington, 1993, p. 533). MRI studies point to an increase in ventricular volume with some increases in cortical sulcal volume and loss of gray matter. The 3-D MRI brain images indicate a reduced amount of gray matter in the anterior

hippocampus, parahippocampal gyrus, and the superior temporal gyrus in the left hemisphere (Waddington, 1993).

Using positron emission tomography (PET) to estimate regional cerebral blood flow has provided important information on the sites of abnormal neuronal activity and metabolism in the brain. Typically, schizophrenic patients demonstrate frontal hypometabolism. MR spectroscopy findings also indicate frontal lobe dysfunction (Waddington, 1993).

Currently there are two views being used to link the clinical view of schizophrenia with its underlying brain mechanisms. One view states that specific symptoms or closely related symptoms are concentrated in a specific brain region. This view tends to look at schizophrenia as a disease like multiple sclerosis, which has lesions at various sites in the brain. The second view emphasizes a problem at the level of the wiring in the brain and states that symptoms are a result of this incorrect wiring. The focus of this view is that one single misconnection can trigger a variety of symptoms because of the complex feedback mechanisms that function in the brain (Andreasen, 1995).

The first view is related with positive symptoms at the temporal and limbic regions of the brain. Magnetic resonance (MR) studies show that a decrease in size of the superior temporal gyrus is associated with auditory hallucinations. MR has also indicated that a smaller planum temporale is linked with thought disorder. Both of these findings support the first view. PET scans have also provided support for this view by revealing that abnormalities in these brain regions are related to psychotic manifestations. Both PET and MR have provided evidence of frontal lobe dysfunction associated with negative symptoms. The main problem faced with this view is that the brain must be dissected and then pieced together one region at a time (Andreasen, 1995).

Applying the second view is still in the beginning stages. Several circuits have been proposed, most of which deal with pathways that link the prefrontal cortex and the subcortical regions such as the basal ganglia and thalamus.

One model that is achieving increasing acceptance locates deficits in the circuitry that gates or filters the information perceived by the brain and forwards the relevant or socially and biologically important information to heteromodal cortex for further prioritization and decisions about action or behavior (Andreasen, 1995).

If this circuit were defective, the individual would be besieged with information, therefore causing hallucinations, delusions, strange behavior, and a variety of negative symptoms. Studies that indicate a lack of information processing in schizophrenia provide support for this model. Neuropathological studies demonstrating abnormalities in the thalamus also supply evidence for this model (Andreasen, 1995).

Development of Dopamine Theory

In order to take a closer look at the role the brain plays in schizophrenia, it is necessary to look at the neurochemistry involved.

It was not until the almost half way into the twentieth century that experimental evidence linked mental disorders with neurochemical abnormalities in the brain. Studies indicated that the endogenous monoamines such as dopamine, noradrenaline, and serotonin were involved with schizophrenia pathology. Later, numerous studies revealed that antipsychotic drugs block the transmission of monoamines (Sedvall & Farde, 1995).

New technology emerged during the 1970s allowing for a closer examination of neurotransmitter activity at the level of neuroreceptors. Isotopically labeled drugs demonstrated that these drugs were indeed binding the dopamine receptors, the use of positron emission

tomography (PET) allowed for the visualization and measuring of this binding (Sedvall & Farde, 1995).

Dopamine Hypothesis

For the last 30 years, the dopamine hypothesis has enjoyed the position of center stage as the main neurochemical theory explaining schizophrenia. The basis of this theory lies in two significant observations: the only unifying trait shared by all antipsychotic drugs is the blockade of dopamine D₂ receptors, and drugs that increase dopamine levels tend to enhance psychosis (Harrison, 2000). In essence, the dopamine hypothesis states that the neurochemical abnormality associated with schizophrenia involves an excessive amount of dopamine due to over active neurotransmission or the presence of extra D₂ receptors. Recent research conducted at Columbia University has indeed revealed elevated synaptic concentrations of dopamine and superfluous amounts of D₂ receptors in schizophrenic patients as compared to control subjects, thus further adding to the credibility of the dopamine hypothesis (Butcher, 2000).

In this study, single-photon emission computed tomography (SPECT) was used to measure “striatal D₂ receptors with a D₂ receptor antagonist S-3-[[123]I]iodo-2-hydroxy-6-methoxy-N-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide ([[123]I]IBZM)” (Harrison, 2000, p. 958). Interesting findings surfaced after subjects were depleted of dopamine using α -methylparatyrosine (α -MPT) and re-scanned using SPECT. Results indicated an increase in ([[123]I]IBZM) binding after α -MPT was administered, presumably because of the reduced competition from dopamine. Therefore, in those suffering from schizophrenia, the D₂ receptors are more occupied and perhaps even more stimulated by dopamine (Harrison, 2000).

Dopamine Receptors

Five dopamine receptor subtypes have been successfully cloned. These are D₁-D₅ receptor subtypes. The receptors are composed of protein that in turn is composed of approximately 400 amino acids. The receptors have both extracellular and intracellular domains and seven regions spanning the nerve-cell membrane. The receptors are grouped into two families: the D₁ family, which includes the D₁, D₂, and D₅ subtypes, and the D₂ family, which includes the D₂-D₄ subtypes (Sedvall & Farde, 1995).

D₁ Receptor Family

The receptor most commonly found in the brain is the D₁ subtype. Large quantities of this receptor may be found in the basal ganglia and in neocortical and limbic regions. D₁ found in neocortical, prefrontal regions has been linked to intermittent functions such as memory, emotion, and cognition, which are known to be irregular in schizophrenia (Sedvall & Farde, 1995).

Participants that had not received pharmacological treatment for schizophrenia were used in a study involving PET and [11C]SCH 23390. It was discovered that D₁ binding was lower in the basal ganglia of schizophrenic patients as compared to the control group. This decreased binding may be due to less D₁ subtypes in that particular section of the brain. Another study was done with PET using SCH 39166, a D₁-dopamine antagonist. When tested on animals, the dopamine antagonist functioned as an antipsychotic. However, when put to the test in human participants, there was no evidence of similar results. On the contrary, SCH 39166 appeared to make psychosis even more pronounced. These results would only occur if reduced D₁ binding and psychosis are both linked to reduced D₁ function in schizophrenia (Sedvall & Farde, 1995).

Typical neuroleptics act only to produce and release dopamine, having little effect on D₁. Therefore, releasing dopamine will balance the reduced amount of D₁ as compared to D₂ that occurs in schizophrenia. Based on studies conducted on monkeys, it appears that typical and atypical neuroleptics stimulate D₁ regulated pathways and increase the D₁ to D₂ balance in the brain. This dual effect is an important consideration when looking at antipsychotic effects of medication (Sedvall & Farde, 1995).

Much less information is available regarding D₅, the other receptor in this family. It is known to occur in a few areas of the brain, including the striatum although at much lower concentrations than D₁. Currently its function has not been discovered, and no medication specific to the D₅ receptor is available (Sedvall & Farde, 1995).

D₂ Receptor Family

The second most abundant receptor is the D₂ subtype. It is mainly found in the basal ganglia. Because extrastriatal regions of the brain have low concentrations of D₂ receptors, these brain areas attract much research attention (Sedvall & Farde, 1995).

Using PET, the occupancy of D₂ receptors can be measured in the basal ganglia of patients treated with medications. When dealing with typical neuroleptics, occupancy reflects blockade, so that high occupancy means profuse blocking of the D₂ receptor. The occupancy at the D₂ receptor was found to be 70-90% for patients receiving typical neuroleptics. It was discovered that those exhibiting extrapyramidal symptoms (EPS) had a larger occupancy than those lacking EPS. These results denote that EPS are due to blockade of the D₂ receptor in the basal ganglia. Much of the research involving antipsychotic drugs therefore centers around its effect on the D₂ receptor (Sedvall & Farde, 1995).

The D₃ receptor is mostly located in the limbic region. The focus of research involving this receptor subtype involves developing a drug that can selectively act on D₃ without the involvement of D₂. D₄ receptor is present in concentrations 10-100 times smaller than either D₁ or D₂ in the striatum (Sedvall & Farde, 1995). More research is required to better understand the role that D₃ and D₄ receptors play in schizophrenia.

Antipsychotic Function at the D₂ receptor

The ability to estimate binding at the D₂ receptor has proved extremely useful in discovering the mechanism of D₂ receptor blockade induced by neuroleptic drugs. When treated with typical antipsychotics, that is drugs that cause EPS, the binding seen at the D₂ receptor is approximately 80% or higher. Evidence suggests the possibility that such a high binding rate at the D₂ receptor is associated with onset of EPS (Pickar, 1995).

Serotonin Hypothesis

While the dopamine hypothesis is traditionally used in explaining the neurochemistry of schizophrenia, other theories do exist. One that closely ties in with schizophrenia involves serotonin.

The discovery that LSD-25 interacts with the serotonin system has prompted further inquiry into this area of research in relation to schizophrenia. Several research findings have proven that there are advantages to administering serotonin 5-HT₅ antagonists to patients diagnosed with schizophrenia (Sedvall & Farde, 1995). For example, some studies suggest that 5-HT_{2C}/5-HT_{2A} receptor antagonists may prove helpful in treating schizophrenia. Preliminary results have revealed that 5-HT_{2A} antagonists lessen neuroleptic-induced EPS (Kunovac & Stahl, 1995).

Treatment

After looking at the symptoms and neurochemistry associated with schizophrenia, it is also important to consider the various treatment options that are available to the patient.

When making decisions regarding the course of treatment, clinicians assess the presence of both negative and positive symptoms in order to choose the most effective treatment option (Andreasen, 1995). Because of the heterogeneity of schizophrenia, it is often difficult to choose precisely the right combination of treatment alternatives. The more current approaches involve an integration of both medication and therapy. An added dimension of treatment is the importance of family and community support. Even with all these characteristics present, it may be possible to succumb to 'revolving door' patterns of treatment (Kane & McGlashan, 1995).

Pharmacological

Drug therapy is considered a phenomenon of modern times, with chlorpromazine (thorazine) as the pioneering medication. The patient of the 90s and beyond can benefit from many advances that have been made since drug treatments began about 50 years ago. The improvements can be seen in the "validity and reliability of the diagnostic process, establishment of optimum dosing practices, the development of strategies for preventing relapse, and the introduction of medications that can be effective when other[s] have failed" (Kane & McGlashan, 1995, p. 821).

Conventional antipsychotics offer hope of treatment for schizophrenia, but they do have limitations. Approximately one quarter to one third of patients do not respond to typical antipsychotics. Also, these drugs offer little in treating negative symptoms and induce EPS. The newer atypical antipsychotics are supposed to answer to the limitations of conventional medications. The atypical drugs improve EPS. However, a drawback is that they tend to be more

expensive than typical neuroleptics. (Campbell, Young, Bateman, Smith, and Thomas, 1998).

Below is a review of the more popular atypical antipsychotic medications prescribed.

Clozapine. The subcategory of atypical antipsychotic neuroleptics arose from the notion that typical neuroleptics cause EPS, while atypical neuroleptics do not. Clozapine is the prototype atypical antipsychotic medication (Pickar, 1995).

When originally introduced in the 1970s, clozapine's popularity soared yet faded almost as quickly when it was discovered that it caused agranulocytosis. Clozapine was later reintroduced in the 1980s. Because of the risk of agranulocytosis, clozapine is not recommended as the first choice of treatment; rather it is used as a last alternative when other treatment options have failed to give adequate results (Kane & McGlashan, 1995).

When clozapine is administered to patients, strict guidelines are followed. The medication is given weekly only after establishing that the patient has a sufficiently high white blood cell count. Currently, the drug is withheld if leukocyte counts fall below $3 \times 10^9/L$ or if granulocyte counts fall below $1.5 \times 10^9/L$ (Pickar, 1995).

Compared with typical neuroleptics, clozapine usage has demonstrated a 15-25% reduction of symptoms, with even greater reduction in some individual cases. A few have experienced a near total remission after taking clozapine for years (Pickar, 1995). Clozapine may also lower the occurrence of hostile and aggressive behavior and reduce the incidence of suicide attempts (Kane & McGlashan, 1995).

Those that respond best to clozapine treatment have severe EPS caused by typical neuroleptics. Clozapine usage is also recommended for those individuals who have tardive dyskinesia (TD). Preliminary evidence indicates the possibility that clozapine helps to alleviate

EPS caused by typical drug treatments. Clozapine reduces TD symptoms more slowly (Pickar, 1995).

Clozapine has comparable affinity for both D₁ and D₂ receptors, while typical neuroleptics demonstrate a greater affinity for D₂ receptors. Additionally, clozapine also has high affinity for D₄ receptors. Clozapine's advantage in treatment over typical drugs may revolve around its combination of a high D₄ affinity with a low D₂ affinity (Pickar, 1995). "The notion that (relatively weak) D₂ antagonism, coupled with potent serotonergic effects . . . is critical to atypicality . . . is the single most important influence in current antipsychotic drug development" (Pickar, 1995, p. 558). Clozapine has a strong affinity for 5-HT₆ and 5-HT₇ receptors which points to a connection between serotonergic function and the antipsychotic properties of clozapine (Pickar, 1995).

Using PET and [[11]C]NMSP, serotonin 5-HT₂ receptor occupancy was determined in the neocortex area of the brain. Results indicate that typical antipsychotics induce low 5-HT₂ binding, meanwhile clozapine induced a high 5-HT₂ occupancy of over 80%. This supports the observation that part of clozapine's atypicality may be linked with its 5-HT₂ antagonism (Sedvall & Farde, 1995).

Another characteristic in clozapine's antipsychotic mechanism of action is its affinity for alpha₂ receptors. Clozapine acts in a way that increases plasma concentrations of adrenaline and noradrenaline turnover, these effects are in part associated with blocking presynaptic alpha₂ autoreceptors. When an alpha₂ antagonist was added to the treatment protocol of patients using typical neuroleptics, a reduction in symptoms occurred. This supports the probability that alpha₂ antagonism is part of the explanation for clozapine's effects (Pickar, 1995).

Risperdal. Another atypical antipsychotic drug is risperdal. It is an S₂ and D₂ antagonist. It was developed as a result of the observation that S₂ antagonists caused improvement of negative symptoms, depression, and reduced anxiety. Risperdal's unique quality does not lie in the fact that it combines both S₂ and D₂ antagonism, but rather because of a greater affinity for S₂ receptors (Livingston, 1994).

Much like clozapine, risperdal effects both dopaminergic and serotonergic systems. It blocks both D₂ and 5-HT₂ receptors. Unlike, clozapine it is a relatively weak D₂ antagonist. Additionally, risperdal has some affinity for the alpha₂ receptor (Pickar, 1995). Another difference between the two drugs is that risperdal causes EPS when the dosage is over 6mg/day while clozapine does not. However, according to a 1997 study (Brown & Radford), risperdal appears to cause less EPS than clozapine or conventional drugs used in the treatment of schizophrenia. There appears to be some debate regarding this issue.

The drug's role in ameliorating negative symptoms is not well defined. Some studies indicate an improvement in negative symptoms, while others do not. To add complexity, it is difficult to accurately quantify and measure negative symptoms (Livingston, 1994).

Researchers are interested in whether risperdal functions in helping those patients previously unresponsive to treatment. A study conducted in Belgium indicated an improvement in both positive and negative symptoms after taking risperdal. Patients who are expressing negative symptoms or EPS-like symptoms are targeted for this medication. Even though it is not clear that risperdal helps those resistant to treatment, it may be a better alternative to start with this medication than turning first to clozapine which is the more toxic option (Livingston, 1994).

Sertindole. The last atypical antipsychotic considered here is sertindole. Research has shown that sertindole blocks D₂, 5-HT_{2A}, 5-HT_{2C}, and Alpha₁ receptors. After sertindole was

administered to subjects, tests for dopamine antagonism were negative, while the drug's effect on the 5-HT_{2C} receptor was strong and enduring (Blin, 1999). Sertindole may be safer and more tolerable than typical antipsychotic medications and clozapine. It has proven to be at least as effective as traditional treatments for positive symptoms and even more effective than traditional treatments at alleviating negative symptoms (Brown & Radford, 1997).

In a study conducted on 205 patients, sertindole given at doses of 8mg and 12mg for 40 days was not more effective than placebo. When the dosage was increased to 20mg, sertindole caused noticeable improvements (Campbell et al., 1998).

However, proving all of this to the Food and Drug Administration (FDA) is certainly a task. In 1998, sertindole was expected to premier on the drug market, but progress was halted because patients given the drug showed alterations in their cardiac rhythms. The FDA wanted further studies before approving the drug (Sertindole [Serlect], 1998).

The Committee for Proprietary Medicinal Products (CPMP) met earlier this year in October and decided to lift the ban on H. Lundbeck's Serdolect(R) (sertindole). The Lundbeck company as agreed to continue conducting research on this drug. It is expected that sertindole will not available until 2003, pending FDA approval (H. Lundbeck A/S, 2001).

Sertindole vs. Haloperidol. All of the above mentioned drugs are atypical antipsychotics. Below is a comparison of sertindole, an atypical antipsychotic, with haloperidol, a traditional antipsychotic.

Studies indicate that sertindole is effective in treating both positive and negative symptoms of schizophrenia without EPS. One particular research project was undertaken to compare the relative efficacy of three doses of sertindole and haloperidol, a typical antipsychotic. Patients were given 12, 20, or 24 mg of sertindole/day or 4, 8, or 16 mg of haloperidol/day.

Some patients were also given placebos. Treatment continued for eight weeks after which patients were given the Positive and Negative Symptoms Scale (PANSS) in conjunction with tests that measure EPS. Results showed that the most effective treatment of negative symptoms was offered by sertindole at a dosage of 20mg/day during weeks four through eight. A haloperidol dosage of 8mg/day was seen to be more effective than the placebo only after week five of the treatment. When EPS were measured, it was impossible to differentiate sertindole from placebo. Haloperidol at all dose levels caused more EPS than either placebo or sertindole (Sertindole, Haloperidol Compared for Schizophrenia, 1997).

Cognitive therapy

In addition to drug therapy, cognitive therapy is also an option to help schizophrenic patients recuperate. Cognitive therapy has proven to help those who were not totally helped by taking medications. Mounting evidence indicates marked improvement of residual symptoms. The cognitive approach looks at the patient as a whole with many problems, but with the ability of improvement (Beck & Rector, 2000).

Recent experiments have revealed biases that serve to sustain incorrect beliefs and perceptions. For example, paranoid schizophrenics have a “selective perceptual bias for threat-related stimuli” (Beck & Rector, 2000, p. 292). Knowing this type of detail enables the clinician to better understand the patient’s point of view, thus allowing for more effective treatment.

The approach to cognitive therapy is based on the idea that while the patient may currently be acting in psychotic ways, deep inside there exists a zone that is free of psychosis. The therapist attempts to tap into that place and bring it into recognition thereby helping the patient make sense of hallucinations and delusions. Even thinking disorders characterized by highly symbolic patterns may be alleviated. In this situation the therapist identifies the common

theme manifested in the symbols and presents it to the patient. Thus, the patient is forced to enter a higher level of cognition. In order for any of these procedures to work effectively, it is imperative that a strong, trusting relationship develops between the patient and clinician (Beck & Rector, 2000).

Acute Treatment

The acute phase of treatment involves managing relapses. Usually relapses involve a variety of positive symptoms such as hallucinations, delusions, and abnormal behavior in conjunction with negative symptoms such as social withdrawal and apathy. If negative symptoms predominate, the individual may require hospitalization. At times relapses may occur if the patient discontinues drug treatment (Kane & McGlashan, 1995).

Most clinicians turn to antipsychotic medication first in acute phase treatment, which means the introduction or reintroduction of medication in order to lessen psychotic symptoms. All schizophrenic patients are advised to use pharmacologic treatment for all acute psychotic episodes, unless there is a specific reason preventing the usage of medication (Kane, 1997).

Studies indicate that typical antipsychotics should be prescribed at a dosage of 5-20 mg/day. Doses higher than that offer no advantages and actually increase the probability of developing EPS (Kane & McGlashan, 1995). About half of the improvement in psychotic symptoms will be seen after four weeks of treatment. However, a maximum amount of change may not be evident until weeks or months later (Kane, 1997). An insignificant amount of change after 6-8 weeks of treatment indicates that improvement with that drug is not likely (Kane & McGlashan, 1995).

The important variables to consider in acute treatment are the specific drugs chosen, the dosage, the timeline for increasing the dosage, and the possibility of prescribing more than one medication (Kane, 1997).

Maintenance Treatment

After a relapse has been properly handled, the patient will require maintenance treatment. Various double-blind studies have established the importance of maintenance treatment. Schizophrenic patients who have been in remission for over a year, yet discontinued the use of antipsychotic medication experienced a relapse after about a year and a half. Despite these poor statistics, the majority of schizophrenic patients do not receive adequate maintenance treatment (Kane, 1997).

The focus of recent research has been on finding the best way to achieve maximum results with minimal risks or side effects. Currently tardive dyskinesia, and EPS, continues to be a side effect associated with long-term treatment. Although lower doses are generally linked with less unwanted effects, this relationship is not clear with respect to tardive dyskinesia (Kane, 1997). For many patients, a low-dose drug treatment is possible, but the advantages have to be considered in light of the increased risk of relapse (Kane & McGlashan, 1995).

After one or two years of successful treatment, meaning that that the patient is in remission, those who have experienced only one acute psychotic episode may be suitable candidates for complete withdrawal of drug treatment. Those patients who have at least two acute episodes should continue treatment for about five years. A periodic psychiatric review is recommended for those patients who are receiving a reduced drug treatment (McGrath & Emmerson, 1999).

Psychosocial Treatment

Another form of treatment that may help a schizophrenic patient is psychosocial treatment. A wide range of psychosocial treatments is readily available, but a common feature unifies all of them: a strong community support program (Kane, 1997). It was actually because of thiorazine that effective community treatment became possible. It caused the practice of institutionalization to become less popular. The psychosocial model has been in use for over forty years now, with the main addition to the treatment strategy being a more aggressive outreach for those who require a more structured living environment (Kane & McGlashan, 1995). Treatments are provided along with the use of medication and not as a mere substitute for it (Kane, 1997).

The model psychosocial program is community-oriented. The leader may be a doctor, psychologist, social worker, or nurse. It is the responsibility of the leader to give the patient individual attention. The tasks of psychosocial treatment are varied and include assessment, treating psychosis, preventing relapse, and giving patients and families support and information. These are not the only methods of practicing psychosocial treatment, but they are the ones most commonly used (Kane & McGlashan, 1995).

Family Burden

Often the types of treatments available are not sufficient and the patient's family is faced with a tremendous amount of strain. Unfortunately, all families do not readily adjust to the new demands. The patient may even feel estranged from their family; this situation does not promote a prompt recovery.

In the U.S. alone, 65% of hospitalized psychiatric patients are released to their families to receive care. In this context, family may mean immediate family such as a spouse or parents or

even extended family such as aunts, uncles, and cousins. The continuing trend towards deinstitutionalization forces people to return to their families. Relatives give much of their time and support for the individual with schizophrenia (Rhoades, 2000).

There are a variety of areas in which families may feel burdened because a family member has schizophrenia. For example, there may be financial problems, an interruption of household activities, or the psychological state of the relative's own health may be compromised (Fadden, 1998).

Both the family and the schizophrenic individual face a disruption in their lives. A young person who receives the diagnosis may never marry or have a family of their own. In this situation, the parents assume the role of caregivers. Often times, parents in their 50s and 60s find themselves taking care of a middle-aged child. Those married to schizophrenics may feel angry because of the changes brought to the marriage due to the disorder. In addition, the patient may display behavior that is violent, self-destructive, or socially unacceptable, which adds to the emotional stress placed on the family. Another source of stress is the social labeling that may result because of a schizophrenic family member (Rhoades, 2000).

Caregivers may feel like they have no one supporting them, not even professionals. It may become very expensive to pay for necessary treatments because insurance companies only cover a certain amount and also have high co-payments or deductibles (Rhoades, 2000).

Those with schizophrenia must have highly structured lives. They need to become involved in activities that are meaningful to them. Often it is up to the family to be the source of these activities. A schizophrenic may have a poor diet and take no interest in personal hygiene; therefore, the family must also closely monitor this area of the schizophrenic relative's life

(Rhoades, 2000). Having to take care of a person with schizophrenia is definitely not an easy task.

Research Method

In order to better understand the concepts learned through the review of research, it is important that the knowledge of neurochemistry and treatment options be applied. In this paper the case study research method will be used to further understand the possible brain malfunctions and treatments available for a schizophrenic patient.

Case Study

The patient in this case study is a male named Sam. He is currently in his late-thirties. Sam was initially diagnosed with schizophrenia when he was 22 years old.

Initial Behavior. Before receiving the diagnosis, Sam was a very sociable and friendly person. Seemingly, he was always surrounded by friends. Sam enjoyed working and had a desire to work. He then experienced the first schizophrenic episode. He did not leave his bed. It was as if a deep depression had engulfed him. Sam had no desire to do anything. Life no longer offered any meaningful or relevant experiences. Family members had to constantly encourage Sam to take care of his own personal hygiene. He lost all desire to work or leave the house.

Schizophrenic Episodes and Symptoms. Sam has had two episodes. After initially receiving the diagnosis of schizophrenia, he had to be hospitalized. This marked the beginning of treatment for acute schizophrenia. Most patients in this phase are given pharmacologic treatment (Kane, 1997). Sam was no exception to this rule. Throughout a period of 3 months he was shuffled between 3 hospitals and took numerous medications before finally being released. Neither he nor family members know what these medications were. His family indicated that after his return home, he almost literally slept the year away. He only left bed to take care of

essential necessities such as eating. At times, he did not even leave bed to eat. His mother frequently brought him breakfast in bed. Sam was in remission for 3 years before he relapsed again into another schizophrenic episode. When Sam was at his worst functioning level he had visual and auditory hallucinations. He does not like to address this topic; as a result it remains unclear as to when he experienced these positive symptoms. During the first schizophrenic episode he also experienced a short-lived negative symptom in the form of loss of speech. This persisted for only one week.

During the second episode, he was hospitalized for 2 months, this time visiting 4 different hospitals. This relapse marked a return to the acute phase of treatment. His family believes that the relapse was brought on because Sam was working too many hours at his job. They feel that he was trying to go beyond his capabilities. He was also engaged to be married, and perhaps the emotion of the upcoming wedding was too overwhelming for him. A new positive symptom manifested during this time was a delusion of grandiosity. For a short time he believed that he was a very important person.

Sam has not relapsed since 1991 and thus has been in the maintenance phase of treatment for over ten years now. Although by standard conventions he qualifies to discontinue treatment (Kane & McGlashan, 1995), Sam has never been taken off his medication. To him, this is not a plausible treatment option.

Discussion and Analysis

Brain Abnormalities and Medications

After the first episode, Sam was prescribed loxapine, a typical antipsychotic medication. A key feature of this medicine is that it behaves like an atypical antipsychotic agent when given in low doses. This also implies a lower risk for developing EPS (Nazareth, 2000). Because of

the receptors this drug targets, it appears that Sam has a malfunction of the D₂ and D₃ receptors. Loxapine is a D₂/D₃ receptor antagonist, with a higher affinity for the D₃ receptor (Fenton, Murphy, Wood, Bagnall, Chue, & Leitner, 1999). From the binding tendencies, it can be seen that loxapine does not act like a typical neuroleptic because it has a higher affinity for the D₃ rather than the D₂ receptor.

Interestingly, Sam was not given clozapine, the prototype atypical antipsychotic (Pickar, 1995). A reason for this may stem from the perceived receptor malfunction in Sam. Clozapine has high D₄ affinity with a low D₂ affinity (Pickar, 1995). As noted above, the key feature for loxapine is high D₃ affinity. Clozapine does not appear to offer the correct combination of receptor effects for Sam's case.

Sam took loxapine until 1996. Unfortunately, this medication did not prove to be the best choice for him because he developed EPS. This might have been caused by a dosage that was too high, meaning that the drug did not behave like an atypical antipsychotic medication so the risk for EPS would not be lowered. Another possibility suggested by a doctor is that perhaps taking the medication for eight years was too long. It is possible that Sam should have switched to an actual atypical antipsychotic instead of using a medication that merely acts like one at the correct dosage.

A major change in medication occurred in 1996. Loxapine was replaced by risperdal. The chemical activity of risperdal slightly varies from that of loxapine. Risperdal is an S₂ and D₂ antagonist, blocking both D₂ and 5-HT₂ receptors with a greater affinity for the 5-HT₂ receptors (Livingston, 1994). S₂ antagonists have been shown to improve negative symptoms, depression, and anxiety. It is interesting to note that Sam returned to work in the same year that he began taking risperdal. This medication appears to work better for Sam than loxapine. It appears that it

is a closer match for the brain abnormalities he manifested. This may mean that the target area of malfunction in Sam's brain is more closely related to serotonin rather than dopamine abnormalities. Sam is still on risperdal.

Ironically enough, Sam also began to take a sleep medication named benadryl in 1996. He went from sleeping a year away to needing medication to help him sleep. Benadryl appears to be habit forming because now he cannot fall asleep unless he takes the medicine.

In 1998 Sam was given cogentin, which for him was used to treat the Parkinson-like symptoms caused by the antipsychotics (Benztropine [Cogentin], 2001). The drug helps to improve muscle control thus counteracting the effects of EPS. Unfortunately, it appears that this medication could not make an impact on Sam. After seeing no results, he was taken off the medication. Doctors suggested that he take Tylenol in order to alleviate the pain associated with his EPS. Currently, there is no cure for EPS. Sam had an electroencephalogram (EEG) done to discover if his EPS were related with brain abnormalities, but the results have been negative.

Therapeutic Intervention

Since 1987, Sam has regularly visited a psychiatrist. The purpose of the visit is mainly for drug maintenance. Currently, he goes to see the psychiatrist once every 3 months, which is the least frequent it has ever been. Several years ago, Sam went to see a psychologist for two sessions. Sam did not believe that the therapeutic process could be beneficial for him. He refused to continue seeing the psychologist and has never returned since.

Treatment Recommendations

Pharmacologic

As far as medications are concerned, risperdal seems to work very well for Sam. If the malfunction in his brain does stem from a serotonin problem, it may be useful to try a medication

that has a higher affinity for serotonin receptors. As more research is conducted and more medications are put on the market, one might alleviate Sam's symptoms even more than risperdal. However, it is important to take caution with this decision because no extensive studies on side effects would be available for new drugs. The effect could be worse in the long run.

If Sam relapses again, I would recommend a new serotonin targeting medication, if one was available. If he continues to stay in remission, then there is no reason to change his current medication.

A PET scan may reveal sites of abnormal neuronal activity in Sam's brain. These sites could be further analyzed to pinpoint if there are certain receptor types predominantly found in this area. This could lead to the acceptance or rejection of the theory that serotonin receptors appear to be the predominant malfunction for Sam. PET scan can also reveal sites where drugs are binding, which could also prove beneficial to determine the usefulness of certain drugs. If Sam needs serotonin antagonists, but PET reveals that his current medication is not binding serotonin receptors, a change in medication may be needed.

Therapeutic

Most studies indicate that the main way to alleviate the psychosis associated with schizophrenia is to turn to pharmacologic treatment. This is definitely a first choice option in order to emotionally stabilize the patient. Sam does not appear to be an exception to this rule. Therapeutic interventions such as cognitive therapy are mostly used when the patient clings to irrational beliefs (Beck & Rector, 2000). Sam did not appear to have this type of symptom.

However, my belief is that Sam would have benefited if he had continued to see the psychologist instead of refusing treatment after the second session. Talking about emotions and

coping strategies may have helped Sam to better understand his disorder. After the initial diagnosis it was very difficult for Sam to accept the mandatory changes he would have to make in his life because of schizophrenia. Perhaps talking about how he felt would have helped him go through less psychological pain than what he was already experiencing.

Evaluation

Due to the medication trials it appears that the main chemical abnormality in Sam stems from a problem with serotonin. Perhaps there is too much being made or there are too many serotonin receptors in his brain. This helps explain why the switch to risperdal was a more effective treatment option for him. As with most disorders of the mind, it is difficult to pinpoint the area of malfunction. Because of this, the preferred treatment involves rotating through various prescription medications in order to find the one that is best suited for the individual. Of course, this picking and choosing may lead to unnecessary side effects. In Sam's case, this meant the development of EPS. Since there is no cure for EPS, Sam will have to deal with uncontrolled muscle movement combined with pain for the rest of his life. Sam has accepted the way he must live his life. He realizes that he will most likely be on medication for the rest of his life.

Compared to the typical image of schizophrenia, it appears that Sam has escaped the more debilitating types of the disorder. Even though he manifested both positive and negative symptoms, it appears that his negative symptoms were mild. This is the key to explaining the amount of recovery he has experienced. Treatment is more promising for those with more positive rather than negative symptoms (Andreasen, 1995).

Sam currently works and has regained some of his social characteristics. He carries on his life like most adults his age. It is difficult to discern from a first impression that Sam carries

a diagnosis of schizophrenia. This scenario is not the same for everyone because schizophrenia is a very diverse type of disorder. It is increasingly difficult to understand, especially because a lot of the characteristics of the disorder are very individualistic.

Conclusion

The vast array of symptoms form a unique combination in each individual. The brain mechanisms involved in pathology are complicated. The neurochemical abnormalities can also differ from patient to patient. A lot more research is needed in order to pinpoint the elusive chemical pathways that malfunction and the possible implications. Without new information, schizophrenia will remain a partially understood disorder.

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