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Characteristics of Psychotic Depression in Juveniles and Analyzing 4 Antipsychotics

Deepak Vaidyula[1], Rajagopal Appavu[#] and Jothsna Kethar[#]

[1]Frisco High School, Frisco, TX, USA
[#]Advisor

ABSTRACT

This research paper attempts to answer how psychotic depression differs in children and adults and focuses on the properties of the following four antipsychotics: Mellaril, Clozaril, Zyprexa, and Abilify to analyze which antipsychotic was most effective. This research paper analyzed differences in how children and adults react to psychotic depression by analyzing a recent study. To compare the different drugs, one or more studies were analyzed for each drug, and each drug's properties were analyzed. After evaluating the different effects of psychotic depression, it was found that hallucinations were much more common in teenagers and children. More specifically, it was found that the most common type of hallucination was auditory. It was also found that the number of minors suffering from psychotic depression may be grossly underestimated. Clozaril was found to be very effective for patients that didn't respond to other antipsychotics but dangerous because of its side effects. Mellaril seemed to be effective at treating schizophrenia, but had many side effects. Zyprexa seemed to be useful for weight gain for Anorexia Nervosa (AN), and Abilify seemed to be good for treating schizophrenia over a long period of time. It was concluded that children were more at risk for psychotic depression as they would not tell their guardians because of fear of backlash. It was also found that a few children believed hallucinations to be make-believe and not a disorder. Clozaril was found to be the most effective antipsychotic, while Zyprexa was the least.

Introduction to Psychotic Depression

Psychotic depression is a form of depression characterized by short but severe mood swings, but it can also be characterized by hallucinations and delusions. Treatments for psychotic depression include antipsychotic drugs, electroconvulsive therapy, or antidepressants. The definition of psychotic depression has been debated throughout the years. The DSM II (Diagnostic and Statistical Manual of Mental Disorders Version 2) stated that psychosis was a state of being in which the patient could not adapt to the "ordinary demands of life" because of their mental impairment. However, the next version, the DSM III, modified the definition to state that a patient only had psychotic depression if they had "delusions, hallucinations, or depressive stupor". This definition has subsequently evolved in later versions of DSM. Psychotic depression itself is an elusive disease, but currently it is thought that certain areas of the brain, such as the amygdala (which is hyperactive in people with depression), the hippocampus (which shrinks in people with depression), and the dorsomedial thalamus (greater number of nerve cells) are affected. Note that these parts of the brain are affected by normal depression, and there is currently not much data on which parts of the body psychotic depression specifically affects. Regardless of which parts of the body it affects or its definition, psychotic depression is a very taxing mental illness, and affects people of different age groups differently, with varying degrees of severity. However, there exists various treatments on the market, such as psychotherapy, and antipsychotics. This research paper is focused on evaluating differences in how psychotic depression is expressed in juveniles compared to adults, and finding the most effective antipsychotic out of the 4 studied (Mellaril, Abilify, Zyprexa, Clozaril). Before starting the

study, based on prior knowledge, hallucinations could overall be more common in juveniles with psychotic depression, and either of the two newer antipsychotics (Clozaril, Zyprexa) could be the most effective out of the 4 antipsychotics.

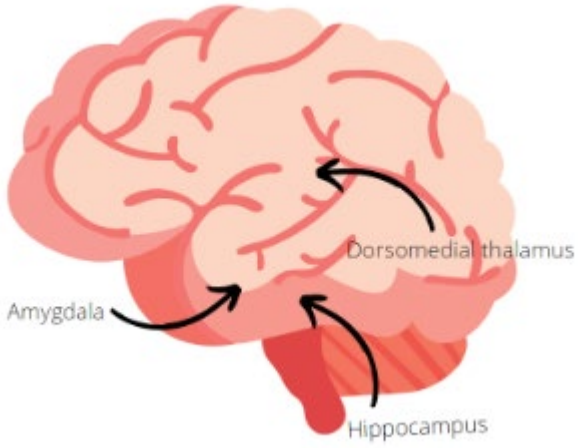

Figure 1. Parts of the Brain Thought to Be Affected by Depression

Juvenile Psychotic Depression

Based on community samples, around 5-11% of adolescents and 9-35% of children showed signs of hallucinations, but it can be difficult to diagnose this type of depression in children because of their inability to differentiate fantasy and reality. This is why around 75-90% of these "hallucinations" tend to be transient. Childhood psychotic experiences also seemed to play a major role in the development of depression, as these childhood experiences tripled or quadrupled the odds of a mood or psychotic disorder in children. In a study of 20,000 patients older than 14 years, around 18.5% of patients who exhibited symptoms of MDE had psychotic features, and 60% of children admitted to the hospital for depression had some type of psychotic feature. Because adolescents are reluctant to tell their parents about psychotic symptoms, however, the number of children and teens suffering from this mental disorder is most likely underestimated. Hallucinations have historically been more common in teenagers and children than adults. In fact, around 80% of these groups have hallucinations, while around 22% have delusions. Auditory hallucinations are usually the most common type, but olfactory, visual, and/or haptic hallucinations often accompany auditory hallucinations. Delusions are less common in adolescents, but the most common types of delusions in children are delusions of reference, mind reading, and thought broadcasting. Psychotic symptoms in younger children can increase the chance of bipolar syndrome. Brief psychotic experiences occur in about 7-10% of the general population, but more specifically, about 17% of children aged 9-12 and 7.5% of teenagers suffer from psychotic depression. However most commonly, the symptoms are much different than clinically proven psychotic depression, and the most likely symptoms include paranormal beliefs and magical thinking without impairment. These symptoms are more likely to be exhibited in a person that is not ill, instead of paranoia, bizarre experiences, and hallucinations. However, there are multiple ways to treat psychotic depression.

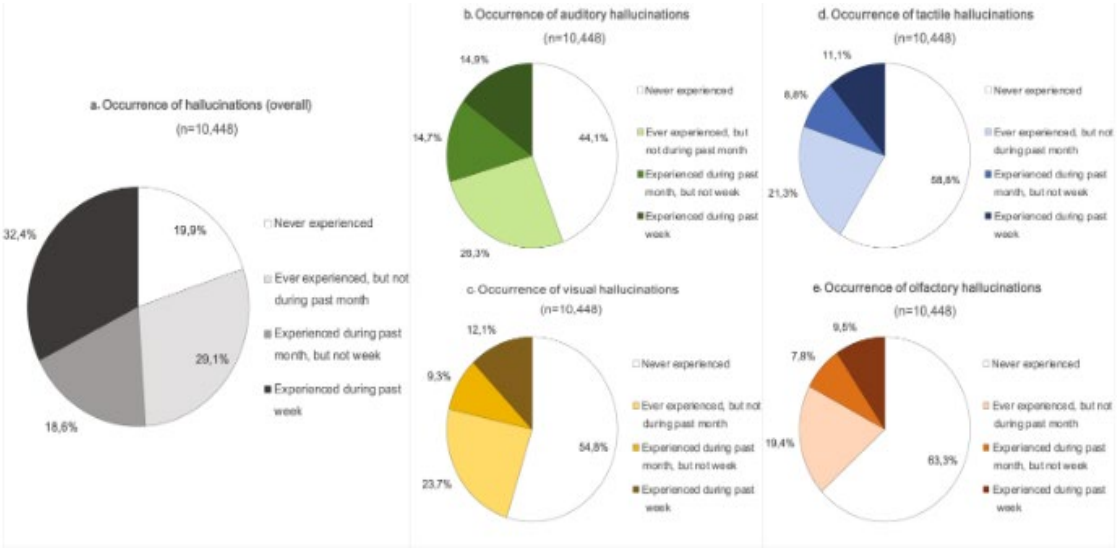

Figure 2. Occurrence and phenomenology of hallucinations in the general population: A large online survey by Mascha M. J. Linszen, Janna N. de Boer, Maya J. L. Schutte, Marieke J.H. Begemann, Jacqueline de Vries, Sanne Koops, Renske E. Blom, Marc M. Bohlken,Sophie M. Heringa, Jan Dirk Blom & Iris E. C. Sommer

Methods

Treatment

When deciding which form of treatment to use for psychotic depression, it is very important for the doctor to consider whether the psychosis in the patient could be considered a more severe form of depression or a separate disease entirely. The former is usually much easier to treat as in most cases, only a strong antidepressant is required. However, with the latter, there would need to be two separate treatments: one for psychosis, and one for depression. There exist many available drugs on the market for psychosis, which are referred to as antipsychotics. All of these drugs come with various side effects, and have very different active and inactive ingredients.

Mellaril®

Mellaril is an older antipsychotic that is currently not available for purchase in the market. Its active ingredient is thioridazine hydrochloride and its inactive ingredients include colloidal silicon dioxide, croscarmellose sodium, FD&C Yellow No. 6 Aluminum Lake, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium lauryl sulfate, and titanium dioxide.

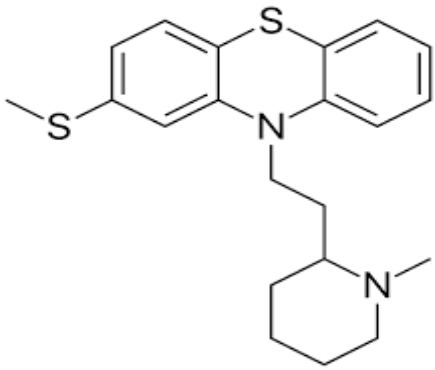

Figure 3. Thioridazine chemical structure from Wikipedia entry

However, it has many side effects including drowsiness, blurred vision, dry mouth, nausea, vomiting, diarrhea, constipation, changes in appetite, weight gain, stuffy nose, pale skin, darkening of the skin or eyes, swelling of the arms, hands, feet, ankles, or lower legs, blank facial expression, shuffling walk, unusual, slowed, or uncontrollable movements of any part in the body, restlessness, unusual dreams, breast milk production, breast enlargement, missed menstrual periods, decreased sexual ability in men, difficulty urinating, fever, muscle stiffness, confusion, sweating, neck cramps, tightness in the throat, difficulty breathing or swallowing, tongue that sticks out of the mouth, fine, worm-like tongue movements, uncontrollable, rhythmic face, mouth, or jaw movements, and vision loss, especially at night. This drug is unique in a few certain ways. First of all, unlike other antipsychotics, its internal structure resembles mephazine. However, unlike mephazine, the piperidine ring is linked to a phenothiazine nucleus through an ethyl group, whereas in mephazine, it is linked through a methyl group. Another important difference is that unlike mephazine, which is unsubstituted, the phenothiazine ring in Mellaril is substituted at the 2nd position with a thiomethyl group. In a recent study, 14 patients were treated in a double-blind study with successive month-long courses of either a placebo or 50 mg of the drug. Only the physician knew whether the drug the patient took was the placebo or Mellaril. 9 people who had taken the drug were significantly better, while only one person who took the placebo got better. These results showed that Mellaril had some positive effect on patients, even though the sample was very small in scale.

Another study involves the use of Mellaril along with other phenothiazines. 24 patients were involved in this study. Only 9 of these patients improved decidedly and/or moderately. Along with this, 15 of the patients had either a very slight improvement or were unchanged/worse. Moreover, 3 of the 5 patients that reported being unchanged or worse were worse. Therefore, this shows how Mellaril doesn't work well in combination with other drugs.

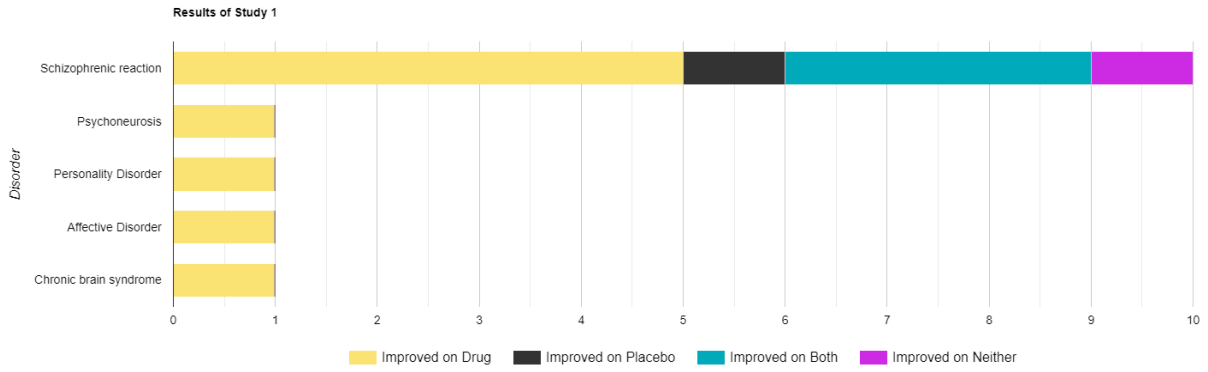

Figure 4. Results of Study 1

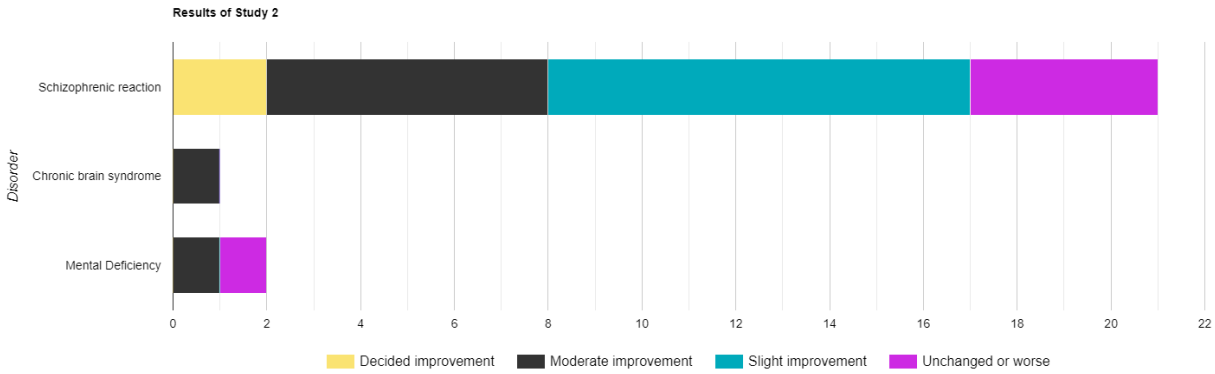

Figure 5. Results of 2nd Study

Abilify

Abilify is also another drug that is not available for purchase on the market. Its active ingredient is Aripiprazole. Its inactive ingredients are cornstarch, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and microcrystalline cellulose.

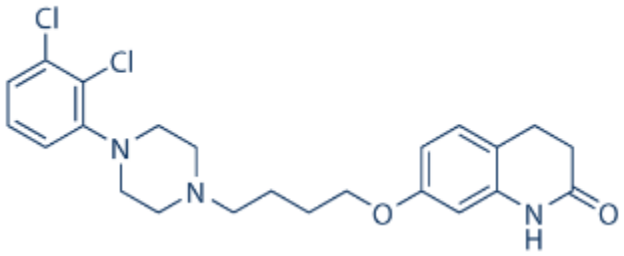

Figure 4. Aripiprazole chemical structure from Selleckchem

In a recent study called QUALIFY(QUAlity of LIfe with AbiliFY Maintena), a national, 28 week study comparing 400mg of Abilify and 50-234 mg of paliperidone palmitate, it was established that Abilify led to greater improvements in the quality of life, disease severity, and was more effective overall, especially in patients 35 or younger. However, because of the relatively small sample, another study was conducted in Canada. This study was 24 months long and focused on patients treated with Abilify for schizophrenia. Study assessments took place during the patient's regular assessments, and additional visits were recommended during every 3rd month. The results were then supposed to be assessed at the end of 2 years. However, the study was terminated one year into the study, so the researchers were only able to collect data from 1 year. 108 patients were classified as having early-stage psychosis, while 59 were classified as having late stage psychosis. On the CGI-S, patients began at a 4, which meant moderately ill. At month 12, patients dropped to a 3, which meant mildly ill. On the BPRS, patients were also "moderately ill". By the 12th month, they were "mildly ill". However, there were also many side effects. Of the patients, 137 experienced a total of 366 adverse effects. 45 were considered not related to Abilify, 53 were possibly related, and 134 were probably related. This shows that while Abilify might help with schizophrenia, it takes a relatively long amount of time, and patients are more likely to get adverse effects than not.

Clozaril

Clozaril is a newer antipsychotic that is theoretically proven to be effective in schizophrenic patients that don't respond to other antipsychotics. Its active ingredient is clozapine. Its inactive ingredients are colloidal silicon dioxide, lactose, magnesium stearate, povidone, starch (corn), and talc.

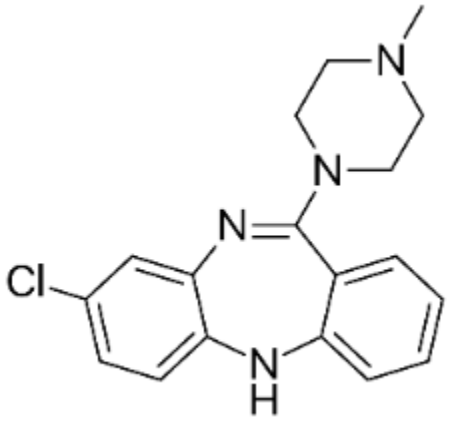

Figure 5. Chemical Structure of Clozapine from "Clozapine-A Novel Antipsychotic" by Ross J. Baldessarini, M.D., and Frances R. Frankenburg, M.D.

Clozaril is a newer antipsychotic that is theoretically proven to be effective in schizophrenic patients that don't respond to other antipsychotics. Its active ingredient is clozapine. Its inactive ingredients are colloidal silicon dioxide, lactose, magnesium stearate, povidone, starch (corn), and talc. However, clozapine is not as widely used because of its many side effects (ex: seizures), and these limitations give clozapine a very specific use. In a trial in Finland, 16 people developed agranulocytosis, and about half of those people died due to serious infection. Because of this, production of clozapine drastically slowed down. However, the publication of Kane et al. drastically changed perception of clozapine. It showed that clozapine was substantially more effective than chlorpromazine according to the Positive and Negative Symptoms Scale, with minimum extrapyramidal side effects. Along with that, frequent blood monitoring during the use of clozapine allowed it to be used more safely. There are many studies involving the use of clozapine. For example, in 1988, Kane and his colleagues evaluated the efficacy of clozapine in patients with treatment resistant schizophrenia. In this trial, patients with a history of poor responses to other antipsychotics were given the antipsychotic haloperidol for 6 weeks, and of those that didn't show substantial improvement with their condition, half were given clozapine, and half were given chlorpromazine treatment for 6 more weeks. The patients that took clozapine had significantly greater improvements in Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impressions (CGI) compared to patients who took chlorpromazine. These findings have been further supported by a follow up double-blind study comparing haloperidol and clozapine in treatment resistant patients. In this study, the patients who were administered clozapine had less psychotic symptoms as measured by the Positive and Negative Symptoms Scale. Another meta-analysis has also confirmed that clozapine is very efficient at treating treatment-resistant schizophrenia. Moreover, two major studies (Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE], and Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study [CUtLASS]) have showed clozapine is one the most effective antipsychotics for treatment-resistant schizophrenia right now.

Table 3. History of studies with Clozapine from "Clozapine-A Novel Antipsychotic" by Ross J. Baldessarini, M.D., and Frances R. Frankenburg, M.D.

Study	Year	No. of subjects	Dose of clozapine	Dose of other drug	Percent improvement

Van Praag	1976	28	300	Perphenazine(21)	Data not available
Guirguis	1977	50	260	Chlorpromazine(525)	With clozapine-51.1 With other drug-50.8
Gelenberg and Doller	1979	15	280	Chlorpromazine(600)	With clozapine-40 With other drug-17
Kane	1988	267	460	Chlorpromazine(850)	With clozapine-26.2 With other drug-8.2

Zyprexa

Zyprexa is a newer drug that is specialized in treating Anorexia Nervosa (AN), an eating disorder characterized by low body weight and distortion of body image that can be a side effect of psychotic depression.

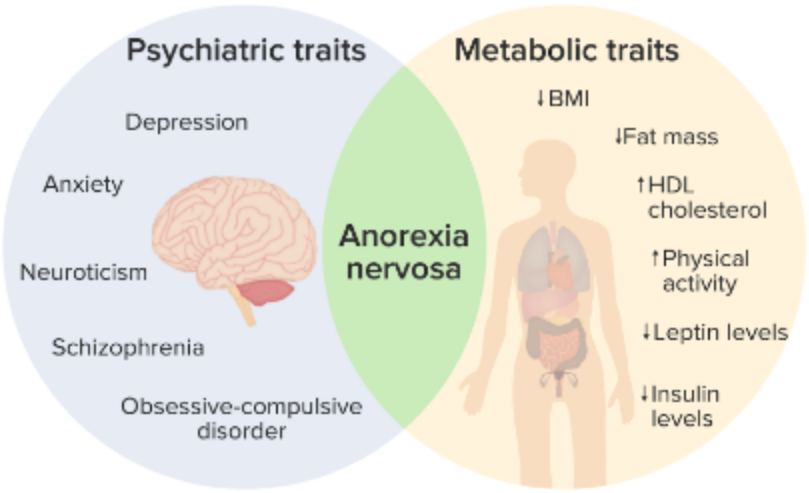

Figure 6. Diagram of Anorexia Nervosa symptoms from The Lecturio Medical Concept Library

The active ingredient of Zyprexa is Olanzapine, while the inactive ingredients include gelatin, mannitol, aspartame, sodium methyl paraben and sodium propyl paraben.

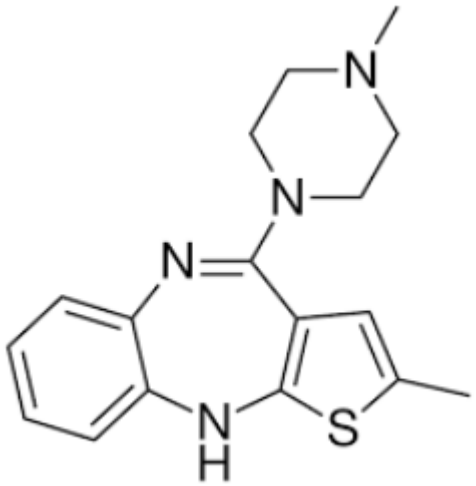

Figure 7. Olanzapine Chemical Structure from Wikipedia article

A randomized, 16-week olanzapine vs. placebo trial was done to see how olanzapine helped in patients with AN. In order to apply to the study, patients had to be diagnosed with AN according to DSM-IV (be between the ages of 18 and 65, and have a BMI greater than or equal to 14 kg but less than 18.5, along with no known extra problems, and no anti-psychotics to gain weight in the previous 4 weeks). In the study itself, 152 patients met with a psychiatrist weekly for a total of 16 weeks. For two weeks, patients were given 2.5 mg per day. Then for the next two weeks, it was increased to 5 mg per day. At week 4 and beyond, the dosage was increased to 10 mg. The dosage was halted or decreased if the patient experienced adverse effects in subsequent weeks. The outcome was measured by the height and weight at the baseline, and weight (which was the main physical outcome measured) was recorded weekly. The primary psychological outcome measured was obsessionality in patients. At the end of the study, it was concluded that olanzapine led to moderate weight gain, as patients who took doses of olanzapine gained approximately 0.165 kg more per month than patients who took the placebo, which is around 1 pound per month for a woman of average height. Patients that took olanzapine were more likely to be rated as a little improvement or a lot of improvement. However, it didn't seem to affect obsessionality. Therefore, this drug is effective for gaining weight when suffering from AN, but other symptoms may need to be managed through different means.

Discussion

Based on the data collected about differences in how juveniles react to psychotic depression, it was found that hallucinations were much more common, and the diagram showed how auditory hallucinations seemed to be the most common type. Of the 4 drugs compared, based on the first study corresponding to Table 1, 9, people improved with the use of Mellaril, but in the 2nd study corresponding with Table 2, only 2 people improved when Mellaril was used with other medication. For Abilify, during the Canadian study, there was only a transition from moderately ill to mildly ill, but the improvement took over a year. For Clozaril, multiple studies showed how Clozaril was effective as an antipsychotic, with one of the most notable being the study conducted by Kane and colleagues. The table showed a history of different studies involving clozapine, the active ingredient in Clozaril. Lastly, for Zyprexa, the study showed how patients only moderately gained weight when treated for AN, but there was no notable psychological improvement.

Conclusion

Psychotic depression is a very dangerous disease because of how little research has been done on it. Scientists are still unsure about what parts of the brain psychotic depression affects, but currently they believe the parts affected are the amygdala, hippocampus, and dorsomedial thalamus. These are the parts of the brain affected by regular depression, and it is not currently known if psychotic depression is a more severe form of depression or a different disease altogether. Psychotic depression is also known to affect children and adults differently. For example, in children and teenagers, hallucinations are much more common than in adults.Of the 4 drugs compared, Mellaril seems to be fairly effective for treating schizophrenic reactions, but because of the many side effects, it doesn't seem safe to use. Abilify seems to be good for schizophrenia over a long period of time, but leads to a higher chance of adverse effects. Clozaril has proven to be useful in patients that don't respond to other medications, under careful monitoring because of how dangerous the side effects are. Lastly, Zyprexa is seen to be helpful for slight weight gain in order to manage AN, but not as helpful for the psychological impacts of AN. Therefore, it seems that Clozaril is the most effective antipsychotic while Zyprexa was the least.

Antipsychotics	Summary
Mellaril	Fairly effective for schizophrenia reactions, but many side effects, and less useful is combination with other antipsychotics
Abilify	Good for schizophrenia over a long period of time, but only improves symptoms mildly
Clozaril	Good for patients who don't respond to other medications, but needs to be monitored because of potentially lethal side effects
Zyprexa	Helpful for moderate weight gain in patients with Anorexia Nervosa, but not as effective for the psychological effects of Anorexia Nervosa

Limitations

The main limitation in this research paper was the lack of tools to conduct studies. These resources are all secondary, but there has been an attempt to examine the existing studies in this research paper.

Acknowledgments

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