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Antidepressants as a Standalone Treatment Modality Compared to Antidepressants with Conjunctive Therapies for Treatment of Major Depressive Disorder

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Abstract

Major Depression Disorder is a wide spread epidemic in our country. Antidepressants are commonly prescribed by general medical practitioners as well as mental health practitioners with a low success rate (de Jonghe, 2008). The purpose of this Independent Study was to conduct a literature review to determine if antidepressants are effective as a standalone therapy in the treatment of Major Depressive Disorder or if they have a higher success rate when used with conjunctive therapies such as cognitive therapy, exercise, and electroconvulsive therapy (ECT). An evidence based review of the literature was conducted to determine the current knowledge base regarding the effectiveness of standalone antidepressants compared to antidepressants with other therapies. It was found that antidepressants as a standalone therapy was can be as effective as it is combined with other therapies provided certain measures are being followed. The antidepressant should be indicated, and before administration, a review of the case needs to be conducted. Upon completion of the Independent Study, the information was presented to the clinical staff at South Central Human Service Centre located at Jamestown, North Dakota (see appendix A).

Antidepressants as a Standalone Treatment Modality Compared to Antidepressants with Conjunctive Therapies for Treatment of Major Depressive Disorder

According to Mayo clinic (2011), major depression is a mood disorder characterized by the development of a feeling of sadness, unhappiness, misery, anger or frustration, along with the development of various physical problems. The individual's routine daily functioning is seriously affected leading to suicidal thoughts. The condition usually needs long-term treatment.

The exact cause of depression is not clearly understood, but researchers consider it to be associated with certain chemical changes in the Central Nervous system (CNS). The chemicals known as 'neurotransmitters' play an important role in mood functions, and any changes in these chemicals can result in the development of depression (Mayo, 2011). Several hormones are present in the body, and when a balance of these hormones has been lost in the body, it could result in depression. For example, thyroid hormone changes or menopause could result in the development of depression (Zieve, 2011). Biological differences in people could also make people more prone to develop depression, while others may become more resistant to developing depression. For this reason, inherited factors contribute to people being more prone to develop depression. Life-events, childhood trauma and medications can increase the risk of developing major depression as well. These events can trigger changes to occur in the brain thus increasing the chances of developing depression (Mayo Clinic).

Some of the common risk factors that are associated with depression include having a close relative with the disorder, traumatic childhood experiences, child abuse, traumatic life-events, relatives with a history of alcohol abuse, history of suicide in the family, loss of a loved one, just after birth, serious illness (i.e. cancer, HIV/AIDS and heart disease), substance abuse,

and consumption of certain drugs (Mayo Clinic, 2011). The condition can occur in almost any age group but occurs more often after the age of 25 years. It is more often reported in women than men, but in children it is equal in both boys and girls (Boland, 2005). However, women are more likely to seek treatment for depression in comparison to men (Mayo Clinic).

According to Boland (2005), major depressive disorder includes the presence of one or more depressive episodes in the patient's lifetime and each episode can last for a few months to a few years. The disorder is considered to be periodic in nature, characterized by the presence of periods or cycles involving remissions and exacerbations. In some instances, the disorder may be chronic in nature with the presence of a persisting episode of depression throughout the patient's lifetime. About 5% of the adult population is affected with major depressive disorder, but at any given point of time, about 2 to 5 % may actually be affected with the disorder.

The condition usually appears in a gradual and insidious manner with certain prodromal symptoms such as anxiety, fatigue and moodiness (Boland, 2005). The core symptoms of depressive illness include depressed mood, loss of energy, poor concentration, short-term memory loss, inability to make decisions, loss of interest in life or events that were previously pleasurable, sleeplessness or excessive sleep, anorexia or excessive eating, weight loss or weight gain, psychomotor agitation or retardation, suicidal ideation, pessimistic attitude, etc (Mayo Clinic, 2011). The individual may experience a diurnal variation of symptoms. The symptoms tend to be worse in the morning, and the individual may have some relief later during the day (Boland). Some patients may also experience severe mental symptoms such as hallucinations and delusions (Boland).

According to Boland (2005), the overall treatment of depression is divided into 3 phases. The first phase is the acute phase and includes treating the current episode of depression. The

second phase is the continuation phase and includes preventing relapse of depression. The last phase is the prophylactic phase and includes preventing further episodes of depression. There are several treatment modalities for depression including routine supportive psychotherapy, antidepressant medication therapy and specific psychotherapy. In severe cases, admission to the psychiatric inpatient facility may be required. There are several schools of thought regarding the manner in which treatment of major depression is viewed. Some practitioners believe that antidepressant therapy is alone sufficient to help the patient to get rid of the symptoms. Whereas others feel that antidepressant therapy may be required with other forms of treatment including routine and specific psychotherapy. This project is being undertaken to look into the literature regarding the current state of knowledge surrounding major depression treatment modalities to determine the effectiveness of antidepressant therapy compared to that of antidepressant and conjunctive treatment modalities combined for the treatment of major depressive illness.

Purpose

One of the important modalities used in the treatment of major depression is pharmacotherapy in the form of antidepressants. It is a well-known fact that antidepressants can be used effectively and safely in various populations. In practice, antidepressants are often combined with psychotherapy in treating depression. Ideally, the antidepressant dosage is started at a low dose and then slowly titrated up to the lowest required dosage for alleviation of symptoms. Today new antidepressants that are, more effective and safer for patients are being introduced into the market. Most of the antidepressants act on serotonin, nor-epinephrine, dopamine or a combination of pathways helping to reduce the symptoms of depression. However, their precise mechanism of action is not known as often there is a lag between the onset of neurotransmitter action and the clinical activity. There is also a concern

about the consequences when administering the medications to patients that have co-morbidities such as brain tumors or epilepsy, although this is not usually viewed as a serious contraindication. A greater concern, however, is when other medications are administered to patients taking antidepressants and there becomes a risk of drug-to-drug interactions occurring. At times there may be a need to lower the dosage of the antidepressant medications when a patient is taking other medications.

Another reason why the dosage of antidepressant medications may have to be reduced is to the lower the side-effects that may be associated with administration of any antidepressant medication. Some of the common side effects of antidepressants include sedation, dry mouth, constipation, deliriums, urinary retention, nausea, vomiting, sleep problems, sexual dysfunctions, hyponatremia, anxiety, headache, hypertension, orthostatic hypotension, confusions, hepatotoxicity, cardiotoxicity, interaction with food, etc. Most of these side effects may be reduced if the lowest possible effective dose is prescribed (Walsh, 2008). There is also a very serious risk of increased suicidal ideation associated with certain antidepressants when consumed by children, adolescents and young adults (below 24 years). There is a risk of suicidal ideation and suicidal risks especially during the first few weeks of initiating pharmacotherapy. There is also a risk when taking antidepressants during pregnancy, as the drug can negatively affect the growth and development of the fetus (Mayo Clinic, 2011).

There are also risks associated with other treatment modalities for depression. People receiving Electroconvulsive therapy (ECT) treatments or psychotherapy usually have to make several and frequent visits to a healthcare facility and ECT has to be administered under anesthesia. Some of the side-effects of ECT include headaches, muscle aches, temporary loss of memory, confusion, permanent loss of memory in some cases, personality changes, etc (Royal

College of Psychiatrists, 2011). Psychotherapy may not work during the initial stages of depression. It may be very difficult to make appointments with the therapists and often the individual needs to put forth a lot of efforts during the treatment. If the symptoms of depression are stressful, it may be difficult of follow the advice placed during psychotherapy (Zieve, 2011).

Keeping the above issues in mind, it is imperative to investigate if antidepressants monotherapy is as effective as combination therapies involving antidepressants and other treatment modalities such as psychotherapy and ECT. A literature review needs to be conducted looking into the current state of knowledge regarding antidepressant therapy alone versus antidepressant therapy in combination with other treatment modalities such as CBT, ECT and Interpersonal therapy.

Significance

There is a need to find the most effective means of treating depression and ensuring patient safety using the faster means of treating the condition. More than 50% of the elderly patients suffering from major depressive illness are able to achieve remission through antidepressant therapy. However in the remaining 50% of the patients, the symptoms tend to remain leading to functional impairment (Wilkins, 2010). According to Charney (2003), there may be certain reasons for the symptoms to remain including co-existing anxiety, other medical problems, severity of the depression, and chronicity of the condition, cognitive problems, and presence of suicidal ideation. When the symptoms tend to remain, depression can become chronic and relapsing in nature, and if the patient is undergoing treatment for a coexisting medical condition, then the adherence to that particular treatment would be poor. Cognitive impairment and functional activity could worsen, if the patient has suicidal tendency, the same could aggravate.

Today more and more pharmaceutical companies are bringing out antidepressant drugs that are more effective, can be used in a wider range of situations in the treatment of depression and have fewer side-effects. However, it is still being perceived that cognitive behavior therapy is effective for the treatment of depression and has the greatest chances of preventing depression (Jarrett, 2010). In many patients, cognitive treatment is just conducted to prevent depression from relapsing, although there may not be the need for the same from empirical data. However, in many instances of using cognitive behavior therapy, there may be a recurrence and relapse rate of over 50%. Jarrett found certain factors that could increase the risk of relapse and recurrence after 2 years which included manner in which the patient's symptoms remitted during the final weeks of cognitive therapy. If the age of onset was high and if the remission was stable after 12 weeks of therapy, then the risk of relapse and recurrence was low (Jarrett).

Olfson (2009) conducted a study to determine the national patterns of usage of antidepressants in the US. According to Olfson, antidepressant usage has become very common. He tried to compare the clinical and socioeconomic patterns of antidepressant usage in the US between 1996 and 2005. Several surveys were conducted across various households in the US. The participants of the study included people above the age of 6 years and who received at least one antidepressant drug. Between 1996 and 2005, the antidepressant usage jumped from 5% to 100%. A neutral trend being noticed is that there seems to be greater reduction in the usage of psychotherapy from 31% in 1996 to 20% in 2005. Amongst various racial groups, the usage of antidepressants has not been on a rise between 1996 and 2005. However, the use of adjunct drugs in the other symptoms in depressed patients was on the rise (Olfson). Between 1996 an 2005, there has been a marked rise in the antidepressant usage in the US, but the use of the same has been low amongst African-American (Olfson).

Brent (2009), Weisz (2006), and NICE (2008) studies have reported that though SSRI antidepressant medication, psychotherapy or both can be used in the treatment of depression, the most ideal and the most often studied therapy would be psychotherapy. Even with combination treatment modes, about 40% of the adolescents were not able to demonstrate an adequate clinical response and only in about 30% complete clinical remission of the symptoms had been noticed. However, when a switch from one antidepressant to another was made, there was some improvement, irrespective of the use of psychotherapy (Brent).

Hence, in the above mentioned group of studies it can be found that comparing antidepressant monotherapy against antidepressant plus other modalities would be worthwhile, although several current literature demonstrate that multitherapy would be more effective and safe for the patient. Nursing professionals would particularly benefit from the same, as nursing professionals play a vital role in administering treatment to individuals with major depression including antidepressants and psychotherapy.

Theoretical Framework

The biopsychosocial model of theory was the framework chosen to provide a framework for this project. Currently there are several newer medications and psychotherapeutic methods that are available for the treatment of depression in adults, adolescents and children. However, though there are these new forms of treatment, the quality and standards of treatment for the population has not improved and is currently poor. Today more than 140 million prescriptions are delivered across the US for antidepressants, and expenditure for the same are in the tune of $450 per month. (Mayo, 2011) With greater introduction of newer and safer antidepressants, there seems to be changes with patient outcomes. Along with newer and safer antidepressants, there are also advanced forms of psychotherapy that aim and improving the relief in patients

suffering from mental illness. One reason for major failures in treatment of depression patients with either psychotherapy or antidepressants is that the treatment provided to them may be inappropriate, and in some patients the treatment actually provided to them are not consistent with the quality standards. The quality of care for depression has not improved over a period of time that is usually seen with other conditions, even though there have been drastic improvements with the quality of medications and psychotherapy techniques that have been developed (Crogan, 2006).

The theoretical framework used to give structure to this article review is based on George Engel's biopsychosocial model of theory. In his article, Dr. Engel states, "By evaluating all the factors contributing to both illness and patienthood, rather than giving primacy to biological factors alone, a biopsychosocial model would make it possible to explain why some individuals experience as "illness" conditions which others regard merely as 'problems of living', be they emotional reactions to life circumstances or somatic symptoms" (Engel, 1977).

Engel developed a model that included the biological component, psychological/behavioral component, and a social component. The model states mind, body, and environment interact in causing disease (AIPPG, 2012).

In reviewing the symptoms of Major Depressive Disorder, many of them could be considered "problems of living" rather than a mental illness. Some symptoms are characterized by the development of a feeling of sadness, unhappiness, misery, anger or frustration (Mayo, 2011).

The review of articles and their conclusions is the target of this research study. If in accordance with Dr. Engel's biospychosocial with consideration of the patient's medication management, their environment, and their social support will work in combination for the best

possible outcome. An application example: Social isolation and joblessness -------> depression/self-incrimination/sedentary lifestyle ------> hypercholestrolemia/myocardial infarction/diabetes. (AIPPG, 2012)

The research has shown that in Major Depressive Disorder, an antidepressant medication management is as effective as an antidepressant with a conjunctive therapy. If Dr. Engel's model was clearly effective, the research should have shown that the antidepressant with conjunctive therapy was more effective.

Process

A Search was conducted across 6 databases including Pubmed, Cochrane, Google Scholar, BMJ, NEJM, MD Consult for searching the search string "major depression comparison antidepressants AND psychotherapy versus antidepressants" and "major depression comparison medications versus multiple therapy". The Support terms used were comparison, AND Versus. THz research study was conducted only on humans, and included both males and females in the study. Only article that were published in the last 10 years were reviewed. Beside, the articles sought were English language as well as foreign language article, belonging to all the journal groups. The Type of articles that were selected was Clinical editorial, letter, Meta-analysis, Practice Guidelines, RCT, and Review. The relevant search results that were obtained included: 84 Articles in Pubmed; 150 articles in Google Scholar; 5 Articles in NEJM; 6 Articles in Cochrane; 7 Articles in BMJ; 47 on MD Consult. As the articles were repetitive in the various search engines, the grand total of all the articles could not be obtained.

From these studies that have been obtained, 15 articles would be selected and would be critically analyzed. The research question being analyzed is "Are antidepressants as standalone

therapy as effective as antidepressants with conjunctive therapies for Major Depressive Disorder". Data from the studies would be utilized to test the hypothesis to determine if the same is true and valid. Once the review of literature is conducted, the findings of the study would be used to develop inference points that could be utilized in nursing practice in the management of psychiatric patients. The target audience for this study is the nursing population who would be responsible to implement the findings of this study. The patients on whom this study would be implemented are patient suffering from major depression.

Review of the Literature

Reynolds et al. (2010) conducted a study that was focused on elderly patients, aged 60 and above and their response to treatment with first-line antidepressants. It was found that more than 50% of the elderly patients with major depression respond only partially to treatment with a first-line antidepressant drug. Hence, the hypothesis of the study was to test out if depression-specific psychotherapy such as Interpersonal therapy (IPT) when used in combination with a first-line antidepressant 'escitalopram' would reduce the rate of recurrences and ensure that the symptoms get better faster. Currently, most of the elderly patients are left with significant symptoms remaining and often this tends to affect normal functional activities. Besides, there is also the risk of relapses and in case the patient is suffering from a co-existing condition, the chances of those symptoms worsening are high. In this study, several age age-relatectors were taken into consideration such as presence of a co-existing condition that may worsen the symptoms of depression, need for longer treatment duration, slower resolution of the symptoms, and hesitation of the patient to consume higher doses of the drug. IPT was chosen as it specifically meant to handle some of the problems related to the elderly age group such as bereavement, retirement, social isolation and disputes. This was a 16-week RCT that was

conducted in two groups, one with IPT and antidepressants, and the other group with antidepressant and depression care management (DCM) which is a supportive treatment modality for depression. There were 124 OP patients who were included in this study. Hamilton Rating Scale of Depression consisting of 17-items was used. It was found that the rates of remission in the IPT group and the DCM group was similar in the inattention-to-treat (IPT: DCM – 58%: 45%) and in the complete analysis IPT: DCM – 58%: 43%). In both groups, the symptom reduced at the same rate. There was no added advantage of IPT. Hence DCM could be used in more than 50% of the elderly patient to achieve remission. However, DCM was not a pure pharmacotherapy as it employed supportive means as may be deemed necessary.

In a study conducted by Segal et al. (2010), the relapse rates of depression patients treated with antidepressants pharmacotherapy and comparing mindfulness-based cognitive therapy (MBCT) versus maintenance antidepressant pharmacotherapy. The current standard of care was maintenance antidepressant therapy. The study included 160 patients between the ages of 18 to 65 years and had been undergoing treatment for major depressive disorder with antidepressant medications. 84 patients were able to achieve remission with antidepressant therapy within 6 months and were placed randomly into 3 groups, one receiving MBCT, one receiving a maintenance antidepressant drug and the third a place. This study was conducted in outpatient settings in Ontario Canada. After remission, the antidepressant drug was stopped and they were switched to their respective maintenance therapy. If the symptoms returned and stayed on for two weeks, and the symptoms could be classified as major depression under DSM-IV-TR, it was considered as a remission. For the unstable remitters, the decrease in hazards was about 73% in the MBCT and the maintenance antidepressant group. However, in the stable remitters, there were no differences between all the three groups. Thus it can be concluded that

in unstable remission, when there is a need for greater maintenance therapy, the effectiveness of antidepressant therapy and MBCT (psychotherapy was similar).

To improve the effectiveness of treatment of depression, drug therapy would be sufficient, but there is a need to improve adherence by having a policy system to provide antidepressant drugs to the patients. In a study conducted by Sanglier et al. (2011), the antidepressant treatment patterns were compared in elderly patient (above 65 years) and young patients (25 to 64 years) and to determine the factors that may be associated with 180-day non-persistence. This study was conducted in a US managed care setting, where the data of the cohort was retrospectively matched before and after January 1st 2006, following which Part D of Medicare was implemented. Medicare Part D would ensure free prescription outpatient drugs. As the drugs were provided free of cost under Part D, the chance they would adhere to treatment was higher, and the chances of consuming the required doses was better. The adherence to treatment was better after Jan 2006, when elders could afford the drug. As the dose of antidepressant during treatment was low, the chances of non-persistence increased. In fact, the higher rate of non-persistence in elders before 2006 had reversed after 2006, when non-persistence began to increase in youngest. Following greater adherence to treatment, people seldom discontinued antidepressant drugs and very rarely were psychotherapy required.

There may be only certain instances in which antidepressants may be required with other forms of treatment such as psychotherapy. For example, in elderly patients where the rate of remission is slower or those with comorbid conditions, psychosocial interventions are required in combination of antidepressants for increased efficacy. Wilkins (2010) found that psychotherapy and other non-pharmacological interventions are not able to reduce any cognitive impairment and the disability that may able present (Wilkins).

There may not be a need to have cognitive behavior therapy in combination with the antidepressant, especially SSRI, during the initial treatment. A switch to another antidepressant belonging to the same or a different group was sufficient in being effective and reducing the side-effects (Brent, 2008). In this study conducted by Brent et al., treatment of SSRI-Resistant Depression in adolescents, the effectiveness in switching to another SSRI, Venlafaxine, with or without using CBT was being examined. It has been found that 60% of the adolescents demonstrate a positive response to SSRI's and 40% require additional modalities of treatment. This study was a Randomized controlled trial of 334 patients between the ages of 12 to 18 years who were suffering from major depressive disorder that had not responded positively for 2-months therapy with SSRI's. Hence, the patients were divided into four groups. The first group received a different SSRI (i.e. citalopram or paroxetine), and the second group received a different SSRI and CBT. The third group received venlafaxine whereas the fourth group received venlafaxime along with CBT. When the patient was given CBT another SSRI, it was equally effective as venlafaxine and the side-effect that developed were much lesser.

Several antidepressants can promote neurogenesis in the hippocampus and the olfactory bulb of the central nervous system, which can promote the formation of neurons. Perera et al. (2008) conducted a study to support the hypothesis that in depression, neurogenesis is impaired and in order to overcome depression, generation of new neurons is needed. The study examined three areas, neuronal maturation, functions of the new neurons, and the factors that affect neurogenesis. To detect changes in the environment and coupling the emotions to the external relevancy, the neurons in the hippocampus is needed. If the neurogenesis is seriously affected, there are chances the emotions would get uncoupled from the external environment leading to a negative mood. If the negative mood tend to get exacerbated to a period beyond that of the

initial traumatic stressor, the condition is likely to be depression. Neurogenesis, that has been induced by the antidepressants and in the same way can be attached with coupling.

Klerman et al. (2004) conducted a study to determine the effect of psychotherapy and TCA antidepressants, alone and in combination in the prevention of relapse of cases of depression. Patients receiving TCA's had a 12% relapse rate compared to 16% in those who had received psychotherapy alone. Besides the rate of relapse was similar to those who received TCA antidepressants or antidepressants in combination with psychotherapy. Psychotherapy may be beneficial only in some instances such as when the patient is significantly affected.

Nierenberg et al. (2011) conducted a study to determine the safety and efficacy of antidepressants and their ability to treat mild to moderate depression. Currently the data that is available for the efficacy of antidepressants is costly. The committee formed in this study demonstrated that patient suffering from mild-to-moderate depression is likely to benefit from psychotherapy. In order to improve the efficacy, accuracy and safety of other cases of depression, if there is implementation of a measurement-based pharmacotherapy it would help reduce the rates of remission and relapse.

Leelahanai (2010) conducted a study to investigate the role of an adjunctive drug aripiprazole (atypical antipsychotic) for the treatment of major depressive disorder. This was for a group of patients who showed an incomplete response to 8 weeks of treatment with antidepressant drugs. Here an economy model was chosen rather than an effective model for the major depressive disorder treatment to measure the economic and the clinical outcomes in a Thailand population. The primary outcome chosen for the study was remission of the symptoms and the secondary outcome was quality-adjusted life-year. Aripiprazole was more cost-effective than a placebo when utilized in antidepressant therapy that is unable to respond completely to

antidepressants alone. To ensure the cost-effectiveness of the drug, unit costing of the drug and remission need to be lower.

Trivedi et al. (2008) conducted a study to evaluate the efficacy of adjunctive aripiprazole to standard antidepressant therapy. This was mainly for patients having anxiety and other atypical symptoms along with major depressive disorder. Although this was not another form of therapy, the presence of atypical features along with depression meant that additional or adjunctive drugs were needed. This study involved pooling the data from 2 similar studies of 14-week duration – the 1st study was an 8-week ADT treatment phase, and the second study was a – week double blind randomized phase. In these studies aripriprazole was combined with the 2 sub-groups and its efficacy and safety was being evaluated. The MADRS score evaluated the primary efficacy end of randomized treatment, the Hamilton Rating Scale for Depression was used for anxious depression and the Inventory of Depressive Symptomatology-Self-Report was used to score out atypical depression. In both the studies the patients were enrolled between the periods of 2004 to 2006 and the total randomized population was 472, the anxious and non-anxious population was 740 and the atypical and typical population was 737. There was an improvement in the group that aripiprazole with improvement in the MADRS scores. The remission rates were better with aripiprazole than with the placebo. Hence, the use of adjunctive aripiprazole has been recommended for treatment of major depression especially when symptoms of anxiety or atypical symptoms are present.

Wijkstra et al. (2009) conducted a study for the pharmacological treatment of psychotic depression rather than major depressive disorder. He was not certain of the effects of antidepressants alone compared to a combination of antipsychotics and antidepressant. This was a literature review study to compare the effectiveness for patients suffering from psychotic

depression and was given the following treatment modalities: - antidepressant monotherapy, antipsychotic monotherapy, combination therapy, and placebo. Various databases were searched with appropriate search strings and limits. More than 3333 abstracts were obtained, but finally only 10 RCT's containing 548 patients could be utilized. There was no conclusive evidence that combination of antidepressant and antipsychotic was effective than the antidepressant. However, a combination of antipsychotic and antidepressant was more effective than the antipsychotic. The author mentions that it would not be a good option to treat the patient alone with an antipsychotic agent. The patient can be started off on treatment with an antidepressant, and only if the does not respond to the treatment properly, can an antidepressant be added. This is for psychotic depression where the patient is at risk of psychosis and would require the administration of antipsychotic agent. However, the author claims that the data available in this regard currently is rather short. The standard option to start off for all patients with psychotic depression would be an antidepressant drug.

In a study conducted by Blier et al. (2010), combination therapy may have demonstrated that the remission rates were higher. When fluoxetine was used alone the remission rate was 25% and when used in combination the remission rate is about 52%. If one of the agents was discontinued in a double blind fashion then the relapse rate could be as high as 40%. Here the authors studied multitherapy involving fluoxetine and mirtazapine and mirtazapine and bupropion or venlafaxine. The author advices the use of combination therapy of antidepressant drugs sufficient as the chances of remission is doubled compared to monotherapy. Once remiss has been enabled the chances of relapse of depression would be reduced. The author finds that from day 1 multiple antidepressant drugs should be administered. However, the authors noticed that the time of response initially for monotherapy and for multiple therapies was the same. On

the other hand, when the drug fluoxetine was administered as a single drug, the dosage had to be fixed at 20 mg per day and could not be adjusted towards a higher value. The authors are also considering the situations in which multiple antidepressants should actually be utilized. Some are considering to be utilized for the first episode of major depressive disorder, whereas others are considering that it should be administered following various experiences with monotherapy. However, the author suggests that it would be ideal to have 2 drugs administered at one time, and the best way to do the same would be to have a combination pill.

Trivedi et al. (2008) found that a combination of 2 or more drugs may not be more effective in treating major depression (for the chronically ill) compared to a single drug. In many instances, the doctors may pick a second antidepressant drug and may include it with the monotherapy, in case the patient's situation does not improve within a few weeks. This is because certain antidepressants may actually work in certain individuals and others may actually not work. Due to this, the odds of remission may be increased. As per the treatment guidelines, it would not be wise to add one antidepressant to another unless there is clear evidence that the first antidepressant has failed. In Trivedi et al. at the Texas South Western university, 665 patients from various parts of the US who were suffering from major depression were actually assigned to one of the groups:- Escitalopram plus placebo, Bupropion sustained release plus Escitalopram or Venlafaxine plus mirtazapine. The patients were actually blind to the treatment they were receiving and the physicians could adjust the doses in order to manage the symptoms and side-effects. The Quick Inventory of Depressive Symptoms was used as a tool to measure the primary outcomes. Following 3 months of therapy, the remission rate, similar in three groups was about 38% and after 7 months, the remission rate again similar was about 45%. However, in the Venlafaxine plus mirtazapine group, side-effects and adverse reactions were high. This study

goes on to demonstrate that monotherapy would have the same effect as that of multiple drug therapy, as in the first group, there was just one antidepressant and a placebo agent. The lower remission rate in this study may be attributed to the chronic nature of depression that was observed. Another factor that played an important role in outcomes was the dosages of various drugs. However, the authors wanted to review if biological markers played a vital role in the responses to drug treatment, and in this way treatment could be personalized to improve the rates of remission in the population.

In the final review, Perahia et al. (2008) examined or compared the effectiveness of an antidepressant (duloxetine) alone against the same antidepressant along with a standard telephonic adherence support intervention. It may be considered that the telephonic intervention would increase the adherence and improve the outcomes compared to the antidepressant alone therapy. Patients were either assigned to the Antidepressant (AD) group or the antidepressant + telephonic intervention (AD+TI) group and were placed in same for about 12 weeks. One of the major aims of the study was to achieve remission within the 12 week duration. TI was provided at 1, 4, & 9 Weeks. There were about 480 individuals in each of the two groups. The remission rates at the end of 12 weeks stood at about 43% for both of the groups and the response rates stood at 56%. The adherence to the drugs in both the groups was high and similar to each other at 90%. Hence, it can be said that the telephonic intervention may not actually be of significant help compared to the antidepressant, and would not provide drug adherence. However, the chances of reporting adverse events were much higher in the AD+TI group compared to the AD group.

Discussion

The literature review examined more than 15 studies that were concerning the effectiveness and safety of Antidepressant therapy versus combination therapy to be used in the treatment of major depressive disorder. In recent years there has been a trend of administering antidepressants in cases of severe depression and using psychotherapy techniques in mild and moderate depression (Brown, 2005). The most often used approach of psychotherapy is cognitive therapy and interpersonal therapy, and sometimes a combination of both (Zieve, 2011). In patients with severe major depression or with symptoms of co-morbidities such as psychotic symptoms (hallucinations, delusions, etc), there may be a need to use antidepressants. Some of the antidepressants that are used often include SSRIs (citalopram), tricyclics antidepressants (nortriptyline), the MAOIs (phenelzine) and other groups (i.e. venlafaxine, mirtazapine, bupropion, nefazodone and trazodone) (Mayo, 2011).

When using a particular antidepressant for a depression, the drug selected should be indicated for that particular condition. Besides, if there are comorbid conditions, the antidepressant selected may not be effective for that particular condition. Hence, they may be a need to couple other treatment modalities (Zieve, 2011). For example, in case the patient is suffering from psychotic symptoms, an antipsychotic drug should be administered for treating the condition. Besides, to ensure effectiveness of the antidepressants several factors should be taken into consideration including the overall effectiveness of the drug. Secondly, the individual should not have a personal history of ineffectiveness or adverse events following the administration of that particular antidepressant. The individual should be tolerable to that particular antidepressant and no family history should exist for negative events regarding that particular antidepressant. Fourthly, the risk of side-effects should be properly addressed along

with ensuring that all the drug-drug interactions are avoided. Lastly, the dosage of the drug should be appropriately managed (Brown, 2005).

With regards to effectiveness, there is strong evidence that newer antidepressants such as venlafaxine are better over other agents. Family history may not be a major role in determining ineffectiveness of a particular antidepressant, but it should also be given importance before a decision is made on prescribing the drug. Whenever, the antidepressant is chosen it is utmost importance to take into consideration the general situation of the patient. Some of these include history of cardiac disorders, history of seizures, food consumed, history of bulimia, and any drugs consumed by the patient. For example, TCA's have a risk of cardiac arrhythmias, whereas, SSRI's have a reduced risk of the same. SSRI's and MAOI's are the most problematic with several food groups being consumed. There may be a need to avoid several foods in case SSRI's or MAOI's are being consumed. MAOI's and TCA's are difficult as far as dosing of the drug is being considered. Before the antidepressant therapy course can be initiated it is important to take the possibility of having a drug trial before implementing the full course. In elders, reduced doses are always safer. Some drugs such as nortiptyline has a greater therapeutic window allowing for better testing of dosage of the drug (Brown, 2005).

During the first few weeks of drug therapy, major changes with relation to symptom reduction should not be expected. However, in today's practice, if a drug fails during the first two weeks or does not provide effective results, then the drug may be considered to have failed and a different drug may be selected or combined with psychotherapy. The other option left to manage the symptoms during the first few weeks through other treatment modalities. If by the third or fourth week symptom changes do not occur, then the drug is more likely not to be effective. In some cases, it may take about three months to demonstrate the full effect of the

antidepressant. The exact reason as to why antidepressants do not provide immediate effect although it has been understood that they act by affecting the neurotransmitters in the CNS, is not clearly known. However, if the patient is unable to demonstrate effects within 3 weeks, the TSH and the T3/T4 levels can be checked. In case the TSH levels are elevated, there are chances that the effect of the antidepressant would be neutralized, the treatment considered ineffective. In case the TSH, T3/T4 levels are normal and the side-effects are manageable, then there are better chances that an increase of the dosage of the drug within permissible limits can improve the effectiveness. Most of the dosage curves of antidepressants are linear, which means that with an increase in the doses, the effect of the drug would be enhanced. In case the patient still does not respond positively to that particular antidepressant, then a switch can be made to another antidepressant, or another antidepressant can be utilized in combination. If still no positive effect is noticed then, it would be ideal to use combination therapy with psychotherapy, or ECT as indicated. Before using two antidepressants it would be ideal to evaluate the possible drug-drug interactions or the chances of one drug inhibiting the effects of another. This study finds that two antidepressants administered together could be effectively used in treating depression and may have similar effects as combination therapy (Brown, 2005).

Following the administration of the acute phase of treatment, there would be a need to administer antidepressants for the continuation treatment. Continuation or maintenance therapy is the phase during which depression symptoms would continue (as antidepressants do not affect the course of depression but merely manages the symptoms), but the intensity of the problems would be reduced. Hence, there would be a need to reduce the dosage of the antidepressants or in case more than one antidepressant is being administered, the one of lesser importance can be tapered off. In most situations, patient would like to continue antidepressants during

maintenance phase, although they have an option of using other forms of therapy such as psychotherapy or ECT (Brown, 2005). Usually, the length of the depressive episode can be estimated from the patient history but in case there is no history of depression, then it would be ideal to find if the patient has a reached a symptom-free phase. Only when the condition undergoes natural remission should the antidepressant drug be stopped. Once the remission of the condition occurs, the treatment could be stopped. It would also be ideal to check for signs of relapse, as a small number of cases are known for relapse of the symptoms of depression (Zieve, 2011).

Some patients may also require preventive treatment with antidepressants if it is known that there would be an interval between two episodes of depression. If the patient declines for preventive treatment, then it would be recommended to keep a watch for the prodromal symptoms of depression (Mayo, 2011).

Conclusion

From the study the hypothesis that Standalone Antidepressant therapy is as effective as combination therapy for the treatment of major depression can be provided. Antidepressants are able to change the levels of various chemical in the brain and promote neurogenesis of the hippocampus which undergoes changes with depression. Although the effect of antidepressants may take a few weeks to get noticed, the treatment would be as effective as other forms of combination treatment with antidepressants. Besides, in some instances a combination of antidepressants could be used effectively to treat depression compared to coupling antidepressant and psychotherapy. However, the patient should be sufficiently managed for comorbid conditions such as psychosis by using antipsychotic drugs. In certain cases, cognitive and functional impairments cannot be managed effectively through psychotherapy, and

antidepressant therapy is more effective in treating the same. In the studies reviewed in the paper, some of the TCA antidepressants may be more effective than combination therapy. However, to ensure effectiveness, proper evaluation of each case, ensuring that the antidepressant is indicated for that particular condition and preventing any risks of side-effects, drug-to-drug reactions and adverse events, along with studying the past/family history of the patient is needed. Lastly, the systemic condition of the patient should be monitored during antidepressant therapy and drugs that can affect the condition of the patient should not be administered. (Figure 1-conclusion list)

However, there is a need for further studies that can compare treatment between antidepressants and combination therapy. In each case there may be issues that are may act as hindrances to provide effectiveness of the antidepressant therapy alone. The newer antidepressants are safer and are more effective. There can be used in combination with a number of other antidepressants, and during the maintenance phase, minimal doses of drugs would be required. Besides, it is also important to note that immediate effects with antidepressants is difficult to obtain and often the patient has to be managed for a few weeks using supportive therapy.

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Figure 1. Conclusion List

- Supportive treatment along with antidepressants may be required especailly in elders affected with depression.
- During maintenance, the remittance should be identified as stable to ensure effectiveness of antidepressant therapy.
- Major cause for failure with antidepressants is adherence to treatment. If it can be addressed, the effectiveness of antidepressants is similar to combination therapy.
- Cognitive impairments and disability cannot be addressed through psychotherapy or non-pharmacological means. Using two antidepressants may be as effective as combination therapy.
- Antidepressants can promote neurogenesis of the nerve cells in the hippocampus, thus reversing the effect of depression.
- TCA antidepressants is as effective as combination of 2 antidepresants or combination of antidepressants and other therapies.
- Antidepressants should be used after proper evaluation of the cases and only in patients whom it is indicated without a history of adverse events or serious side-effects.
- In patients with comorbid conditions such as psychosis and anxiety, there is a need to administer antipsychotics (such as Aripiprazole) as antidepressants is not effective against the same.
- Antidepressants can be effective to treat psychotic depression.
- In chronically-ill, combination of 2 or more drugs may not be significantly effective than a single drug.
- Antidepressants plus telephonic intervention as effective as antidepressant only.

Appendix A

Is Antidepressants Better alone or with Conjunctive Therapies for Treatment for MDD?

Power point presentation.

Is Antidepressants Better alone or with Conjunctive Therapies for Treatment for MDD?

Patricia Moos, RN, CNS-Student UND

Major Depressive Disorder

- Is a mood disorder.
- Characterized by the development of a feeling of sadness, unhappiness, misery, anger or frustration, along with the development of various physical problems.
- The individual's routine daily functioning is seriously affected leading to suicidal thoughts.
- The condition usually needs long-term treatment. (Mayo, 2011)

Depression

- Exact cause is not clearly understood.
- It is thought that neurotransmitters play an important role in mood functions.
- Thyroid hormone changes or menopause could result in depression.
- Inherited factors contribute to people being more prone to develop depression.
- Life-events, childhood trauma, and medications can increase the risk of developing depression. (Mayo, 2011)

Common Risk Factors

- Having a close relative with the disorder.
- Traumatic childhood experiences.
- Child abuse.
- Traumatic life-events
- Relatives with a history of alcohol abuse
- History of suicide in the family
- Loss of a loved one,
- Postpartum depression.
- Serious illness (like cancer, HIV/AIDS and heart disease),
- Substance abuse. (Mayo Clinic, 2011).
- Can occur in almost any age group but occurs more often after the age of 25 years.
- It is more often reported in women than men, but in children it is equal in both boys and girls (Boland, 2005).

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- Can occur in almost any age group but occurs more often after the age of 25 years.
- It is more often reported in women than men, but in children it is equal in both boys and girls (Boland, 2005).

Major Depressive Disorder

- The presence of one or more depressive episodes in the patient's lifetime and each episode can last for a few months to a few years.
- The disorder is considered to be periodic in nature, characterized by the presence of periods or cycles involving remissions and exacerbations.
- In some instances, the disorder may be chronic in nature with the presence of a persisting episode of depression throughout the patient's lifetime.
- About 5% of the adult population is affected with major depressive disorder.
(Boland, 2005)

Signs/Symptoms

- Depressed mood
- Loss of energy
- Poor concentration
- Short-term memory loss
- Inability to make decisions
- Loss of interest in life or events that were previously pleasurable
- Sleeplessness or excessive sleep
- Anorexia or excessive eating
- Weight loss or weight gain
- Psychomotor agitation or retardation
- Suicidal ideation (Mayo Clinic, 2011).

Treatment Phases of MDD

- The first phase is the acute phase and includes treating the current episode of depression.
- The second phase is the continuation phase and includes preventing relapse of depression.
- The last phase is the prophylactic phase and includes preventing further episodes of depression. (Mayo, 2011)

Treatment Modalities

- Routine supportive psychotherapy, antidepressant medication therapy and specific psychotherapy.
- In severe cases, admission to the psychiatric inpatient facility may be required.
- There are several schools of thought regarding the manner in which treatment of major depression is viewed.
- Some practitioners believe that antidepressant therapy is alone sufficient to help the patient to get rid of the symptoms. Whereas others feel that antidepressant therapy may be required with other forms of treatment including routine and specific psychotherapy.

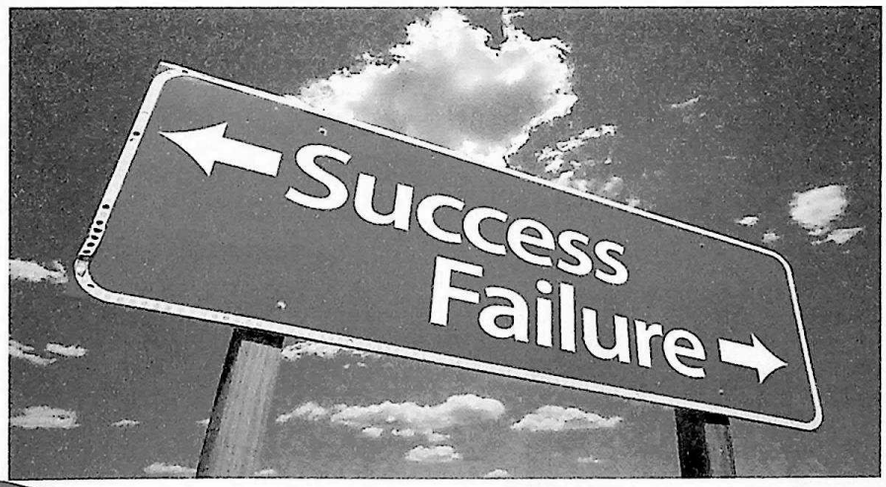
Which Treatment Modality is Most Effective?

- A literature review was conducted to evaluate the most effective treatment modality.
- Antidepressants alone.
- Antidepressants with CBT, ECT, and/or Interpersonal therapy.

Significance

- There is a need to find the most effective means of treating depression and ensuring patient safety using the faster means of treating the condition.
- More than 50% of the elderly patients suffering from major depressive illness are able to achieve remission through antidepressant therapy. However in the remaining 50% of the patients, the symptoms tend to remain leading to functional impairment (Wilkins, 2010).
- According to Charney (2003), there may be certain reasons for the symptoms to remain including co-existing anxiety, other medical problems, severity of the depression, and chronicity of the condition, cognitive problems, and presence of suicidal ideation.
- Cognitive impairment and functional activity could worsen, if the patient has suicidal tendency, the same could aggravate.

Choosing the right path??



Types of Treatment

- Exploring the use of antidepressants alone.
- With CBT, ECT, or Interpersonal therapy based on the Biopsychosocial Model.

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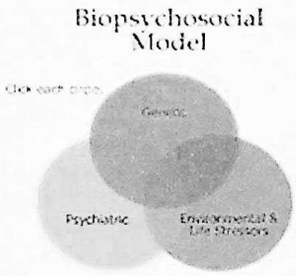
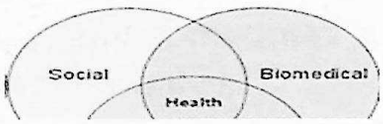


Biopsychosocial Theory

- In 1977, Dr. George Engel proposed this model of treatment.
- Engel developed a model that included the biological component, psychological/behavioral component, and a social component.

Biopsychosocial Model

- The model states mind, body, and environment interact in causing disease.
- An application example: Social isolation and joblessness-> depression/self-incrimination/sedentary lifestyle -> hypercholestrolemia/myocardial infarction/diabetes. (AIPPG, 2012)



Review of Literature

- A Search was conducted across 6 databases including Pubmed, Cochrane, Google Scholar, BMJ, NEJM, MD Consult.
- Only articles that were published in the last 10 years were reviewed.
- From these studies that have been obtained, 15 articles would be selected and would be critically analyzed.
- A detailed reference list will be provided upon request.

Discussion

- In recent years there has been a trend of administering antidepressants in cases of severe depression and using psychotherapy techniques in mild and moderate depression (Brown, 2005).
- The most often used approach of psychotherapy is cognitive therapy and interpersonal therapy, and sometimes a combination of both (Zieve, 2011).

Further Discussion

- Each patient and their unique symptoms should be taken into consideration.
- Need of an antidepressant only?
- If they have psychotic features, then possibly an antipsychotic as well as an antidepressant.
- Has a family member had effective treatment on a particular antidepressant?
- Proper dosage of medication.
- Consider general medical conditions and use of a safe mental health medication. (Brown, 2005)

Conclusions

- Through the review of literature, it was found that Standalone Antidepressant therapy is as effective as combination therapy for the treatment of major depression.
- Although the effect of antidepressants may take a few weeks to get noticed, the treatment would be as effective as other forms of combination treatment with antidepressants.

Some Considerations

- The patient should be sufficiently managed for comorbid conditions such as psychosis by using antipsychotic drugs.
- In certain cases, cognitive and functional impairments cannot be managed effectively through psychotherapy, and antidepressant therapy is more effective in treating the same.
- In the studies reviewed in the paper, some of the TCA antidepressants may be more effective than combination therapy.

Effectivesness

- **To ensure effectiveness:**
  - Proper evaluation of each case.
  - Ensuring that the antidepressant is indicated for that particular condition and preventing any risks of side-effects, drug-to-drug reactions and adverse events, along with studying the past/family history of the patient is needed.
  - The systemic condition of the patient should be monitored during antidepressant therapy and drugs that can affect the condition of the patient should not be administered.

Clinical Pearls

- Supportive treatment along with antidepressants may be required especially in elders affected with depression.
- During maintenance, the remittance should be identified as stable to ensure effectiveness of antidepressant therapy.
- Major cause for failure with antidepressants is adherence to treatment. If it can be addressed, the effectiveness of antidepressants is similar to combination.
- Cognitive impairments and disability cannot be addressed through psychotherapy or non-pharmacological means.
- Using two antidepressants may be as effective as combination therapy.
- Antidepressants can promote neurogenesis of the nerve cells in the hippocampus, thus reversing the effect of depression.

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