Selective Serotonin Reuptake Inhibitors and Suicide:
A Review of Efficacy, Side Effects, and Alternative Treatments

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ABSTRACT

Objective: This review provides a summary of literature of the use of selective serotonin reuptake inhibitors, reporting bias, prevalence, efficacy, and side effects of antidepressant drugs. In addition, alternative treatment options are reviewed.

Data Collection: Articles were generated using a PubMed search, and articles were relevant to antidepressants, side effects, efficacy, prevalance, and alternative treatments. Among the hundreds of articles identified, 40 articles were selected for inclusion in the current review. Also, a review of the standard diagnostic book used for depressive disorders is referenced.

Data Synthesis: Depressive disorders include major depressive disorder, dysthymic disorder, and bipolar disorder. Depression affects a large number of the population and is a debilitating condition the people suffering from it. Selective serotonin reuptake inhibitors, second generation antidepressant drugs, are the preferred medical treatment option for depressive disorders.

Conclusions: A consensus of the articles reviewed showed no difference in the efficacy of antidepressant drugs when compared to placebo in treating depressive disorders. These drugs have become significantly controversial due to the question of cost-benefit analysis of potential side effects and efficacy. The most devastating side effect is suicide, and is largely associated with the use of antidepressants in children. A review of the side effects showed the majority of patients experience adverse events associated with taking antidepressant drugs. Further, the review showed that alternative treatments such as exercise and nutritional supplementation, like the use of essential omega-3 fatty acids, have proven efficacious to the treatment of depression.

Key Words: antidepressants, suicide, DSM-IV, selective serotonin reuptake inhibitors, efficacy, depression, major depressive disorders, prevalance, side effects, alternative treatments

INTRODUCTION

Mental health disorders plague the people of the United States year after year, and recent statistics along with changes in diagnostic criteria are proving an increase in the number of people affected. One in four Americans, or 26.2 percent of adults ages eighteen or older, is diagnosed with a mental health problem.(1) In 2000, the economic impact of mental health problems was estimated at $83.1 million.(2,3) These mental health disorders are grouped by categories, one of which is mood disorders that include major depressive disorder, dysthymic disorder, and bipolar disorder.(4) Major depressive disorder is the leading cause of disability in the United States for people between the ages of fifteen and forty-four.(1) Suicide is commonly associated with mental health disorders and is becoming more prevalent each year. In the past sixty years, the rate of suicide has quadrupled for males aged 15 to 24, and has doubled for females of the same age group. Suicide rates have increased over 50% between 1981 and 2007 for children aged 10 to 14. In 2007, suicide was the third leading cause of death for people between the ages of 10 and 24. Every two hours and seven minutes a person under the age of 25 completes suicide. It is estimated that for every suicide that is completed, another 100 to 200 attempts at suicide were made. In a typical high school classroom, three students have attempted suicide within the last year. One in every twelve college students has a suicide plan.(5)

Mental disorders are all diagnosed with a book of diseases called The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. It is better known as the DSM IV. It is important to understand the history behind the DSM IV and the way in which it was created before understanding how it is used. The classification of mental disorders started in 1840 with idiocy and insanity, and quickly expanded to a seven category classification system in 1880. By

1917, the Committee on Statistics of the American Psychiatric Association was collection information on statistics in all mental hospitals. This lead to the designation of nomenclature that was to be incorporated in the first edition of the American Medical Association's Standard Classified Nomenclature of Disease. In 1952, a variant of the ICD-6 was developed and became the first edition of the Diagnostic and Statistical Manual: Mental Disorders.(4)

Over 50 years and four editions have proven the DSM to be the standard in diagnosis of mental disorders. The DSM is used by mental healthcare professions of different orientations and in a variety of settings in the mental healthcare world such as inpatient, outpatient, partial hospital, consultation-liaison, clinic, private practice, and primary care. The information provided in the DSM IV is the product of thirteen Work Groups, each consisting of five mental health care providers considered to be experts in his/her respective genre. The Work Groups used statistical information and their opinions to formulate each section of the manual. Each Work Group reported to the Task Force of DSM IV in an attempt to minimize opinion based bias. The Task Force was a group of twenty seven people, many of which were also the chairperson for his/her respective Work Group. The Task Force and Work Groups reviewed all information rendered before arriving at the final decisions of the material added to the 4th Edition of the Diagnostic and Statistical Manual for Mental Disorders.(4)

Many mental health disorders are said to be caused by depression or depressive episodes. The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, defines depression as a major depressive episode. A major depressive episode is defined as a period of at least two weeks during which there is either a depressed mood or the loss of interest or pleasure in nearly all activities. The mood may manifest as irritableness instead of sadness in younger patients. The individual must also experience at least four of the following: changes in appetite, sleep,

weight, psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating, or making decisions; or recurrent thoughts of death or suicidal ideation, plans, or attempts. The symptoms must persist for most of the day, almost every day, for at least two consecutive weeks. To count toward a Major Depressive Episode, the symptoms must be new or significantly worsened since the pre-episode baseline. The episode must be accompanied by clinically significant distress or impairment in social, occupational, or other important areas of functioning.(4)

The pathology of depression is not well understood, and there are many theories as to what the true causes of depressive disorders are. The original hypothesis was that the pathology of depression came from a deficiency of monoamines such as serotonin, norepinephrine, and dopamine. Another theoretical pathology for depression is the hypothalamic-pituitary-adrenal, or HPA, axis theory. This hypothesis was based upon the disruption of the corticosteroid-receptor signaling in the parts of the brain that are associated with depressive symptoms. The interruption of the normal signaling process, along with chronically increased stress hormones, was thought to cause permanent damage to the area of the brain that controls all feelings a person experiences. The neurotrophic theory has developed through the last decade and is based upon reduced levels of chemicals in the limbic structures of the brain causing or worsening depressive disorders. The fourth theory of pathology is the adult hippocampal neurogenesis and cellular plasticity theory. In this particular hypothesis, the pathology stems from a reduction in the volume of neuronal projections present in the brain due to a failure of neurogenesis in the granule cell layer of the dentate gyrus. A fifth pathological theory is the macrophage theory. This theory considers the role of the immune system on keeping a person healthy, and decreasing the number of and amount of time he/she feels “sick”.(3) The final theory of the pathogenesis of

depressive disorders is a disturbance in the circadian rhythm of the patient suffering from depression.(6,7)

The standard of care for treatment of Major Depressive Disorder for last several decades has been the prescription of antidepressant pharmacologies. There are two major families that the pharmacologies are grouped: first generation and second generation antidepressant drugs. The first generation drugs were primarily used before the late 1980's and include two classes. The first class was tricyclic antidepressants, and the second was monoamine oxidase inhibitors. The tricyclic antidepressant drugs were associated with many anticholinergic side effects such as dry mouth, dry eyes, urinary hesitancy and retention, and constipation. Meanwhile, the monoamine oxidase inhibitors had the ability to cause a hypertensive crisis in the patient if taken in accordance with certain foods or dietary supplements. Because of these adverse side effects, the first generation pharmacotherapies are no longer utilized. Drugs referred to as the second generation antidepressants are the treatment of choice today. The majority of drugs used to treat depression come from a class of drugs called selective serotonin reuptake inhibitors, or SSRIs. There is another class of the second generation drugs known as serotonin and norepinephrine reuptake inhibitors. The first SSRI was introduced in 1985, and five other SSRI's have been developed since then. Commonly prescribed SSRIs include Prozac, Luvox, Paxil, Zoloft, Lexapro, and Celexa. Since their introduction, selective serotonin reuptake inhibitors have been a major dynamic in the pharmaceutical industry and have proven to be one of the largest contributors to the pharmaceutical company's profit each year. Out of all of the drug classes, antidepressant drugs ranked third in pharmaceutical sales and accounted for almost $11 billion in the United States alone and over fifty percent of the market share. The mechanism of action for the second generation antidepressant drugs is only poorly understood. The lack of understanding

of how the second generation drugs work supports the fact that all of these drugs have all proved to be controversial in their respective lifetimes.(2)

Other, less controversial and less recognized, treatments exist for depressive disorders. These treatments include exercise (8,9), mindset, and the use of specific dietary supplements such as vitamin D (10), St. John's Wort (10), S-adenosyl methionine (10), and fish oils.(10,11) With the growing correlation between the use of SSRIs, especially when taken by children, and suicide, these alternative treatments are becoming more popular and well-recognized. Other alternative methods include vagus nerve stimulation, transcranial magnetic stimulation, and deep brain stimulation.(3) The controversy between safety and efficacy of the available treatments for depressive disorders, along with the correlation between pharmacotherapies and suicide, serves as the basis for this review.

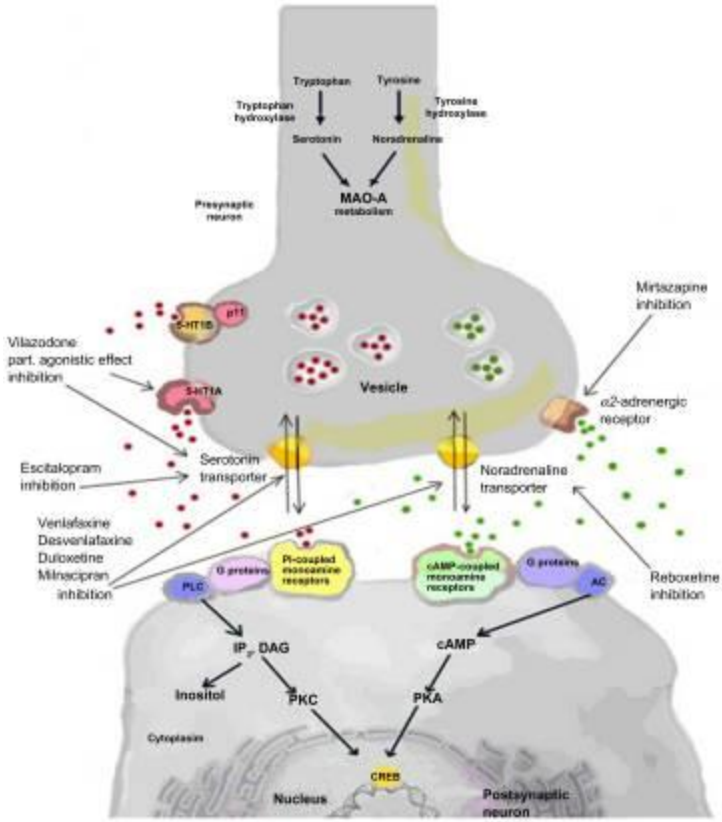
DISCUSSION

PATHOPHYSIOLOGY OF DEPRESSION

Monoamine Deficiency

The vague understanding of the pathophysiology of depressive disorders makes the successful treatment of depression very difficult. There are several theories as to the cause of depression. The first and original theory was that the depressed patient had a deficiency of monoamines. Three important neurotransmitters in the brain are serotonin, norepinephrine, and dopamine, all of which are monoamines. These neurons are located in the nuclei of the midbrain and brainstem and are thought to have the ability to project to large areas of the brain. Thus, serotonin, norepinephrine, and dopamine can be suggested at having an impact on mood, attention, sleep, appetite, reward processing, and cognition. Observations show that an increase in the concentration of these neurotransmitters in the synaptic cleft has an antidepressant affect.

The monoamine theory is based upon the assumption that the pathology of depression stems from a depletion of serotonin, norepinephrine, and dopamine in the central nervous system. (Fig 1, 12)



Perovic, 12

Effects of Hormones on Hypothalamus

The second theory of depression's pathology is in relation to the release of certain stress hormones and the effect they have on the hypothalamus. Cortisol is a well-known stress hormone and according to this theory, an increase in the body's system will cause a stress response and lead to depressive disorders.(3) The mechanism behind this stress response starts with the brain's perception of a stressful event. The cortical parts of the brain will perceive a psychological stress and trigger the release of corticotrophin-releasing hormone, CRH, from the hypothalamus. An increase in CRH triggers the release of pituitary corticotropin that will, in

turn, force the adrenal gland to secrete cortisol. Further studies have shown that CRH will produce similar physiological responses in the body to depressive disorders. Symptoms include decreased appetite, disrupted sleep, decreased libido, and psychomotor changes.(6) Because of the similarity of symptoms, this theory is no longer accepted.(3)

Neurotrophic Theory

Neurotrophic theory of depression is another suspected etiology for this debilitating condition and is closely related to another theory called the hippocampal neurogenesis theory.(3) The neurotrophic theory is concerned with neurotrophic factors, which differs from the hippocampal neurogenesis theory. Neurotrophic factors are associated with the activity dependent area of the body's neuronal network. The neurotrophic factor of primary concern in this theory is brain-derived neurotrophic factor, otherwise known as BDNF, and is regulated by neuronal activities such as learning and memory. It is thought that depression comes from a decrease of BDNF levels in the brain resulting from chronic exposure to stress hormones. Antidepressant treatments are thought to alleviate the symptoms of depression by increasing the availability of BDNF through decreasing the stress hormone levels in the brain. A decreased BDNF level is associated with decreased neuroplastic functions of the brain such as neurogenesis, synaptogenesis, and neuronal maturation.(13) However, animal studies did not support the fact that a decreased BDNF level causes depressed mood or behavior.(3)

Hippocampal Neurogenesis

One of the theories that was widely accepted was the adult hippocampal neurogenesis hypothesis and is associated with neural plasticity.(3) Plasticity refers to the brain and central nervous system's ability to adapt. Adaptation happens in response to specific environmental, psychosocial, or physical stressors to central nervous system.(13) The first depressive episode

that a person encounters is typically in response to one of these stressors, especially a psychosocial factor. As the depressive order progresses, the episodes are increasingly brought on my spontaneous factors.(3) With each episode the brain is adapting to each of the stressors that initiated the attack, and it is the thought that this plasticity causes a loss in the volume of the hippocampus and other portions of the brain.(13) Since there are no imaging tools to assess neural plasticity, there is no sound evidence of this theory.(3)

Macrophage Theory

Macrophage theory is thought to be the most promising and considers the role of the immune system in depressive disorders.(3) A large factor in this theory is the similar symptoms seen in depression and "sickness behavior". Symptoms common to both sickness behavior and depression include fatigue, anhedonia, psychomotor retardation, and cognitive impairment. Anhedonia is the lack of pleasure of the capacity to experience it. Sickness behavior describes the physically ill patient whose immune system is chronically activated by the diseases and infections from which he or she suffers. The chronic activation of the immune system leads to a pro-inflammatory state of the body that is controlled by immune response mediators known as cytokines. Some of these cytokines include interleukin-1α, tumor necrosis factor-α, interleukin-1β, and interleukin-6. The inflammatory mediators are produced at the site of injury and are the body's way to promote the local inflammation that is vital to the healing process. However, when the body is thrown into a pro-inflammatory state, the cytokines become excessive and the inflammation that was designed to deal with local injuries becomes systemic in the body.(6) Systemic inflammation puts the body into a constant state of being stressed and ultimately causes a continuous "fight-or-flight" response from the body. These cytokines have an effect on the central serotonin system that is closely associated with depressive disorders. Animal studies

have shown that by blocking the pro-inflammatory state the cytokines force the body in to, there are anti-depressive benefits. In other words, promoting an anti-inflammatory state for the body can have a major effect on reducing the symptoms of depression.(3)

Circadian Rhythm Cycle

There is also a theory that associates disturbances in the circadian rhythm cycle with the pathological cause of depressive disorders.(6) The circadian rhythm cycle is also known as the sleep-wake cycle. A person's circadian rhythm cycle is the biological adaptation to the 24 hour lightness and darkness cycle that is experience each day. A person is supposed to get "sleepy" when the sun has set and it is dark outside. Vice versa, a person is supposed to wake up when the sun rises and lightness first reaches the individual again. The sleep-wake cycle is essential to promoting health. This theory suggests that there is a disturbed sleep-wake cycle in patients suffering from depressive disorders. In a study of healthy young adults, even minimum changes to the subject's circadian rhythm cycle had significant effects on his or her mood, causing it to be depressed. Symptoms of the depressed mood are thought to be caused by alterations to psychomotor activities and the accessibility of the memories of good experiences versus the bad.(7)

TREATMENT OF DEPRESSIVE DISORDERS

Second Generation Antidepressant Medication

Second generation antidepressant drugs, more specifically selective serotonin reuptake inhibitors, are the most commonly used form of treatment for depressive disorders.(14) The efficacy of these drugs compared to the established side effects has created a foundation of controversy surrounding the excessive prescription of SSRIs. Some of the most commonly prescribed second generation antidepressant drugs include fluvoxetine, sertraline, fluvoxamine,

paroxetine, escitalopram, venlafaxine, and citalopram.(12) The common industry names for these drugs are Prozac, Zoloft, Luvox, Paxil, Effexor, and Lexapro, respectively. Selective serotonin reuptake inhibitors work under one main mechanism of action; as their name suggests, they block the reuptake of serotonin (14), also known as 5-hydroxytryptamine, 5-HT, at the presynaptic neuronal membrane.(2) Serotonin is a neurotransmitter responsible for sending messages from the brain to other tissues via the presynaptic neuronal membrane. At this junction, receptors react to the serotonin and pass it along to the next receptor until it gets disseminated to the rest of the body. If the presynaptic terminal does not recognize or interact with the serotonin it is sent back to receptor of origin and is taken up again, causing a result of lowered serotonin in the rest of the body. This decrease in what is known as the mood neurotransmitter is associated with depressive disorders.(15)

Efficacy

With the emergence of adverse side effects of second generation antidepressants, more specifically selective serotonin reuptake inhibitors, numerous reviews of the drugs studies have been completed. Two of these reviews were done by Kirsch and another by Gartlehner, et. al. Kirsch reports that "Convention meta-analyses are often limited to published data, and in the case of antidepressant medications, this limitation has lead to significant reporting bias." The reporting bias is characterized by multiple publications, selective publication, and selective reporting in studies funded and/or sponsored by pharmaceutical companies.(16) Other sources for bias are the difficulty in assessing the percentage of imputed measurements, or financial interest of the pharmaceutical companies and loss to follow-up numbers. Most of the studies completed on the efficacy of antidepressants received only a fair rating for internal validity of scientific evidence. Seven criteria are used to assess internal validity: populations in primary

care, less stringent eligibility requirements, health outcomes, length of study duration, assessment of adverse events, sample size, and intention to treat.(17) Most studies measured the efficacy of the antidepressant drug by changes to the primary endpoints from baseline rates on investigator-rated diagnostic depression scales. Changes in the rating of the scale are typically viewed as intermediate outcomes as opposed to general health outcomes. Intermediate outcomes are not always reliably related to general health outcomes. Quality of life and functional capacity were seldom assessed, but if assessed were considered only secondary outcomes. Sixty-five percent of the trials were only of short duration, six to eight weeks, and trial reporting was found to be incomplete often. Also, most articles did not report the method of randomization or allocation concealment.(2)

One of the meta-analyses done by Kirsch to evaluate the efficacy of second generation antidepressant medications compared to placebo. The analysis utilized the Freedom of Information Act to request the publicly releasable information on the clinical trials of the six most commonly prescribed SSRI: fluoxetine, venlafaxine, nefazodone, paroxetine, sertraline, and citalopram. All sponsors are required to submit information on all trials, but the FDA did not allow public access to some of the trials that were deemed adequate and well controlled, but failed to achieve clinical significant benefit of drug over placebo. Forty-seven trials were reviewed and studied in the meta-analysis. In order to avoid biased results of the information, only those medications for efficacy was available on all trials were used in the analysis. It was found that the overall effect of second generation antidepressant medications is below the recommended criteria for clinical significance. Also, it was found that efficacy reached clinical significance in only the upper end of the most severely depressed patients, and this was shown to be due to a decrease in response of the patient to the placebo rather than an increase in the

patient's response to the medication. Prior reports have suggested an association between the benefit of the antidepressant medication and severity of the depressive disorder. However, this study was unable to reproduce those results after analyzing published and unpublished trial data. No linear relation was found between severity and response to medication. Further, the differences between the placebo and antidepressant drug being tested were not shown to be clinically significant in clinical trials involving moderately to severely depressed patients. The placebo showed response duplicated more than eighty percent of the improvement observed in the drug groups. The meta-analysis states, "Given these data, there seems little evidence to support the prescription of antidepressant medication to any but the most severely depressed patients." (16)

Another meta-analysis was done to compare the efficacy of second generation antidepressants to each other and also to placebo. Hundreds of studies involving hundreds of thousands of patients were evaluated and reviewed for the meta-analysis.(2) A study involving escitalopram compared to fluoxetine showed that neither drug was more efficacious than placebo.(18) A study with a good, as opposed to fair, rating showed similar results when comparing fluoxetine to placebo. Additionally, no difference in quality of life was noted between the commonly prescribed selective serotonin reuptake inhibitor and placebo.(19) Comparable results were found in studies involving paroxetine, venlafaxine, escitalopram, sertraline, citalopram, and nefazodone. Table 1 summarizes the results of each study along with each study's validity rating and authors.(2)

Table 1. Selective serotonin reuptake inhibitors compared with placebo and alternative treatments (2)

Author, Year	Antidepressant in Question	N	Results	Quality Rating
Devanand et al. 2005 (19)	Fluoxetine compared with placebo	90	No difference in response rate or quality of life	Good
Judd et al. 2004 (20)	Fluoxetine compared with placebo	162	No difference in psychosocial outcomes	Fair
Lam et al. 2006 (21)	Fluoxetine compared with light therapy	96	No difference in the efficacy	Good
Keller et al. 2001 (22)	Paroxetine compared with Imipramine compared with placebo	275	No differences	Fair
Wagner et al. 2006 (23)	Escitalopram compared with placebo	268	No differences	Fair
Emslie et al. 2006 (24)	Paroxetine compared with placebo	206	No differences	Fair
Berard et al. 2006 (25)	Paroxetine compared with placebo	286	No differences	Fair
Martenyi et al. 2007 (26)	Fluoxetine compared with placebo	411	No difference in the efficacy	Fair
Van der Kolk et al. 2007 (27)	Fluoxetine compared with placebo compared with eye movement densensitization	88	No difference in efficacy between fluoxetine and placebo	Fair
Kobak et al. 2002 (28)	Fluoxetine compared with placebo	60	No differences in efficacy	Fair
Van Ameringen et al. 2007 (29)	Nefazodone compared with placebo	105	No significant difference in efficacy	Fair

ADVERSE EVENTS ASSOICATED WITH ANTIDEPRESSANTS

Within the meta-analysis, the attempt to review adverse events was made, and often times these events were associated with causing a subject to drop out of a given trial. Adverse events include suicide, sexual dysfunction, weight changes, seizures, cardiovascular events, hyponatremia, hepatotoxicity, increased drowsiness, and sedation. Table 2 summarizes studies that that assessed the experience of these adverse events by patients who were taking the second generation antidepressant drugs that were in question. It was found that such adverse events, or side effects, associated with antidepressant drugs are reported by physicians and not the patients. With a forty percent nonresponse rate, bias can be present due to measurement bias, selection bias, and potential confounding. Even with the reporting bias, an estimated 57% of the subjects suffered from one of the aforementioned adverse events.(2) A Dutch study, showed that 74.1% of patients reported at least one adverse event when taking a second generation antidepressant drug. A psychiatrist recorded any adverse events experienced by the patients during each visit.(30)

Suicide

It is because of these adverse events that the use of second generation antidepressant medications, more specifically SSRIs, to treat depressive disorders has become so controversial. An association of second generation antidepressants and suicidality is at the forefront of the controversy surrounding these medications. Suicidality is suicide ideation and suicide attempts.(2) A meta-analysis showed that clinical trial data consistently demonstrated an increased risk of suicide in patients taking second generation antidepressants as compared to placebo.(31) Another meta-analysis based on published data of more than 87,000 patients showed that patients taking selective serotonin reuptake inhibitors had a significantly higher risk

of suicide than those patients receiving a placebo drug.(32) An observational study of over one thousand patients demonstrated an average occurrence of 59% of sexual dysfunction after the onset of therapy with second generation antidepressant drugs. All subjects had normal sexual function prior to the trials. Paroxetine was among the drugs with the highest percentage of patients suffering from dysfunction.(33) Another placebo-controlled study was completed to assess the effects of antidepressants on weight change. The study showed that fluoxetine caused a significant amount of weight gain as compared to patients that were given a placebo drug.(34) An increased diastolic blood pressure is another adverse event associated with the use of second generation antidepressants. Table 2 summarizes the studies completed regarding adverse events associated with the use of antidepressant drugs.(2)

Table 2. Adverse events associated with the use of second generation antidepressant drugs (2)

Author, Year	Antidepressant in Question	N	Results	Quality Rating
Aursnes et al. 2005 (35)	Paroxetine compared with placebo	1466	Higher risk of suicides in patients taking paroxetine	Fair
Bridge et al. 2007 (36)	SSRIs	5310	Higher risk of suicides in patients on SSRIs	Good
Fergusson et al. 2005 (32)	SSRIs compared with placebo	87650	Higher risk of suicide attempts for SSRI-treated patients	Good
Hammad et al. 2006 (37)	SSRIs	4582	Higher risk of suicidality for SSRI-treated patients	Good
Jick et al. 1995 (38)	Antidepressants	172598	Significantly higher risk of suicide with fluoxetine as compared with other antidepressants	N/A
Pedersen et al. 2005 (39)	Escitalopram as compared with placebo	4091	Higher rate of self-harm in escitalopram than	Fair

			placebo	
Tiihonen et al. 2006 (40)	Antidepressants	15390	Use of antidepressants was associated with increased risk of attempted suicide	Fair

Antidepressant Medications and Children

Not only are second generation antidepressant medications popular in adults, but the prescription of these drugs to children and adolescents has proven to be largely profitable for the pharmaceutical companies.

> "In September 2004, the Food and Drug Administration completed a review of existing data for the risk of both suicidal ideation and suicide attempts in children taking antidepressant drugs for major depressive disorder. Based on this review, the Food and Drug Administration instructed the manufacturers of all antidepressants included in this review to revise the labeling for their products to include a boxed warning and expanded warning statements that alert health care providers to an increased risk of suicidality in children and adolescents being treated with these agents."

An increased risk of suicidal thoughts and self-harm was consistently seen in clinical trials involving the use of antidepressants in children. It was also shown that the risk for suicide is greater in the first months of treatment. The average risk of suicidal thoughts, behavior, attempts, or completions was twice as high in children, adolescents, and teens taking antidepressants compared to patients not receiving any type of antidepressant medications.(2)

Alternative Treatments

Second generation antidepressant drugs and selective serotonin reuptake inhibitors are controversial not only because of the devastating side effects seen while taking them, but also because of the safer alternatives to the drugs that have proven to be efficacious. Other treatments for depressive disorders include exercise (8,9), mindset, and the use of specific dietary supplements such as vitamin D (10), St. John's Wort (10), S-adenosyl methionine (10), and fish oils (10,11). Other alternative methods include vagus nerve stimulation, transcranial magnetic stimulation, and deep brain stimulation.(3) The alternative treatments are quickly becoming more popular as fewer side effects of using antidepressants are going unnoticed by the public.

Exercise

Exercise is a safe, noninvasive, effective treatment for depression. Several studies have been completed on the effect of exercise on depressive mood disorders, and consistently it is found that exercise has significant mood improving benefits. One study found that by simply walking thirty minutes per day patient's symptoms of depression improved more quickly than patients taking antidepressant drugs.(8) Studies demonstrate that different types of exercise and intensities have varying effects on a person's mood.(9) Several other studies have also shown that aerobic activity is a potent way of altering a depressed mood.(8) Consistently it is found that exercise has a stronger, quicker effect on depression than pharmacotherapies that include second generation antidepressant drugs and selective serotonin reuptake inhibitors. The specific mechanism for which it works is unclear, but it is well known that exercise has an influence on mood-related hormones.(8)

Essential Fatty Acids

Essential fatty acids have gained major recognition over the last thirty years, mostly in association with cardiovascular disease. However, recent studies have shown a significant correlation between levels of essential fatty acids in the blood and depressive disorders and symptomatology. Omega-3 and omega-6 fatty acids are known as the essential fatty acids because the body cannot produce them and must be ingested. Essential fatty acids and the specific ratio of which they appear in the human body is vital to the optimal health of an individual. The proper ratio of omega-6 to omega-3 fatty acids is one to one. Due to the North American diet, this ratio is largely out of proportion with omega-6s showing up in a twenty to one ratio as compared to omega-3s. In addition, the overall daily intake of essential fatty acids of 130 milligrams is well below the recommended level of 650 milligrams. The deprivation of fatty acids has major effects on the brain, as two-thirds of brain tissue is made up of essential fatty acids. Epidemiological studies have found decreased levels of essential fatty acids in almost all patients suffering from depression. Research studies have found that a deficiency of omega-3 causes alterations in levels of serotonin and norepinephrine, two important neurotransmitters in the brain associated with mood. All clinical and research studies conducted on the effect of omega-3 fatty acids on mood, with the exception of one, have shown a positive outcome.(11)

St. John's Wort

Hypericum is an extract from the St. John's Wort flower that has been used as a natural remedy of depression for centuries. While the mechanism of action is not fully understood, it is known that the extract has an effect on the activity of serotonin receptors in the brain. Studies have proved St. John's Wort to be more effective than placebo, and it is a safe alternative when

taken alone. However, there have been reports of drug-drug interactions between St. John's Wort and patients currently under the use of multiple pharmacotherapies.(10)

Vagus Nerve Stimulation

Vagus nerve stimulation was approved in July 2005 for use in patients suffering from depressive disorders. The approval came after an observation of elevation in mood following vagus nerve stimulation in seizure suffering patients. Positron emission tomography (PET) studies showed that vagus nerve stimulation decreased cingulate activity and changed the blood flow and metabolism in the limbic structures of the brain. A stimulation device is implanted into the chest wall with a stimulating lead with helical node is wrapped around the left cervical vagus nerve and attached to surrounding tissues. The device is then programmed using an external wand and every five minutes thirty seconds of constant current will stimulate the vagus nerve.(3)

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation is a noninvasive way of targeting cortical areas of the brain. A pulsing current is passed over a circular of figure-8 coil that is positioned over the cortical regions of interest. In turn, the current penetrates the cortical tissue and has a stimulating effect on it by creating a magnetic field. Device size is large in nature, as the magnitude of the current generated is proportional to the size of the coil used and size of the area of cortex being stimulated. There are two types of transcranial magnetic stimulation: rapid rate/repetitive using frequencies greater than 1 hertz and low frequency/slow using frequencies less than 1 hertz. Studies have shown that transcranial magnetic stimulation increases blood flood to cortical areas of the brain and to the limbic system.(3)

Deep Brain Stimulation

Deep brain stimulation is a more invasive way of treating depressive disorders and has been in use since 1954. High frequency electrical stimulation is utilized to activate a particular area of the brain through the implantation of a stimulating device in the brain. The technique gained research interest in 1987 when it was used to stimulate one thalamic nucleus in patients suffering from Parkinsonian tremors. A study showed that deep brain stimulation of a dysfunctional brain structure was as effective as surgically removing the same area of the brain. Within the last decade, use of deep brain stimulation as a treatment protocol has become more popular. Treatment efficacy is largely dependent on dose and specificity of location of device placement.(3)

CONCLUSION

The objective of this review was to present information on the harmful side effects of antidepressant medications, more specifically selective serotonin reuptake inhibitors, and especially the use of these drugs in children. Also, alternative treatment options were discussed. Major reporting bias was found in the vast majority of the clinical trials on efficacy of second generation antidepressant medications. Most trials were funded by the pharmaceutical companies that would be receiving large profits for the prescription of these drugs if the trials showed efficacy. Depression is a condition that affects a large number of people in the United States and proves to be over an eighty billion dollar per year industry for the pharmaceutical companies. Devastating side effects of taking antidepressant drugs, like suicide, are often disregarded as coincidental or they are not made publicly known. Knowledge of the potential side effects of these drugs is especially vital information to have when children are being considered for antidepressant prescription. However, seldom do parents ever get all of the

information needed to make an informed decision about allowing their children to be drugged. Exercise and quality nutrition have proven to be more effective at eliminating the symptoms of depression than antidepressant drugs. The question must be asked if the devastating increase in prescription of antidepressants to not only adults but also the children is largely being driven by the profitability of the industry. This serves as the basis for possible future review.

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