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Research Based Findings of Anti-depressant Therapy and Suicidality

by

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University of North Dakota

An Independent Study

Submitted to the Graduate Faculty

of the

University of North Dakota

in partial fulfillment of the requirements

for the degree of

Master of Science

PERMISSION

Title Research Based Findings of Anti-depressant Therapy and Suicidality
Department Nursing
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Abstract

Anti-depressant therapy is one of the most common treatments for depression. However, the increasing criticism regarding anti-depressant therapy and increased suicidality has caused both health care providers and the public to question their widespread use (Lader, 2007). In October 2004, the Food and Drug Administration (FDA) mandated that a black box warning be added to anti-depressant medications in order to alert patients of increased risk of suicidal thoughts in the pediatric and adolescent population. This black box warning was expanded further to include patients between 18 to 24 years-of-age at the direction of the FDA in May of 2007 (Friedman & Leon, 2007). It has been noted that a common reason patients do not report their symptoms of depression is due to fear that the physician will recommend an anti-depressant (Bell et al., 2011). Every year in the United States (U.S.), 30,000 people die of suicide and an additional 650,000 people are treated in emergency departments after attempting suicide (Schreiber, Culpepper, & Fife, 2012), making it imperative to investigate the link between anti-depressants and suicidality. Studies which focused on the correlation between anti-depressant therapy and suicidality as well as studies that looked at additional factors (i.e. genetics, toxicological findings) that could have a strong impact on suicidality were reviewed. The findings of this project indicate that, in studies examining whether there is a correlation between anti-depressant therapy and suicidality, there are too many unknown factors to determine whether anti-depressant therapy is the lone factor responsible for the development of suicidality in patients. Additionally, there is a great need for research, particularly in the areas of genetics and toxicology, in order to determine whether these factors play a role in the development of suicidality.

Research Based Findings of Anti-depressant Therapy and Suicidality

The Centers for Disease Control and Prevention (CDC) define depression as an affective disorder characterized by at least five of the following symptoms for a period of two or more weeks: depressed or sad mood, diminished interest in activities which used to be pleasurable, weight gain or loss, psychomotor agitation or retardation, fatigue, inappropriate guilt, difficulties concentrating, or recurrent thoughts of death. Depression not only affects the way an individual feels, but can also have profound effects on an individual's relationships as well as work and/or school performance (CDC, 2011). In fact, depression is currently the number one cause of disability and missed work in the U.S. (Cancro, 2011) and is also one of the most common reasons for suicide (Reeves & Ladner, 2010). It is estimated that approximately 20 percent of women and 12 percent of men in the United States (U.S.) will experience depression during their lifetime (Porth & Matfin, 2009). Of those who encounter one episode of depression, about 50 percent will experience subsequent episodes of depression (CDC, 2011).

With mental health drawing more attention in both the medical world and the public eye, much emphasis has been placed on finding the best methods to treat depression. While many studies have found anti-depressant therapy to be efficacious, the possibility of suicide as an unfortunate outcome resulting from antidepressant therapy leaves many feeling apprehensive about their use. Determining whether anti-depressant medications increase the risk of suicidality has proven both controversial and contradictory. Meanwhile, the emphasis on anti-depressant associated suicidality may have overshadowed the decrease in the rates of suicide attempts and completions that have also been associated with anti-depressant therapy. Furthermore, other factors, such as a history of suicidal ideation or behavior prior to beginning an anti-depressant, co-morbid psychiatric disorders, and/or substance abuse issues may increase the likelihood of

suicidal ideation while taking anti-depressant medications, but may not be at all related to the anti-depressant therapy. The objective of this project was to review literature related to anti-depressant therapy and suicidality (including suicidal ideation, suicidal attempts, and suicide completions) to investigate whether or not treating patients with anti-depressants is linked to increased or decreased rates of suicidal ideation and/or suicidal behavior. These studies were also reviewed to determine whether or not other confounding factors that may contribute to suicidality were considered in the study results. Studies that may support a need for additional research in regards to anti-depressants and suicidality (i.e. toxicological levels and genetic factors) were also reviewed.

Purpose

Suicide is a tragic and unfortunate outcome for patients struggling with psychiatric illness...it is "the ultimate endpoint" (Dolgin, 2012, p. 190). The psychiatric illnesses associated with the highest risk of suicide are: depression, anxiety disorders (including panic disorder and post-traumatic stress disorder), alcoholism, substance abuse, bipolar disorder, schizophrenia, personality disorders, and delirium (Schreiber, Culpepper, & Fife, 2012). Additionally, a prior history of self-harm and/or psychiatric hospitalization significantly increases the risk for suicide (Lader, 2007). In fact, prior history of suicide attempts have been identified as the strongest single predictor of future suicide attempts (Olmer, Iancu, & Strous, 2009).

In addition to personality characteristics or co-morbid mental illnesses associated with suicidality, there are also measureable demographic factors that increase the risk of suicide. Men are four times as likely as women to die of suicide. Suicide rates in those aged 65 years and older occurred at a rate of 14.3 per 100,000 people, versus the 11.3 suicides per 100,000 people of all ages. Suicide rates of non-Hispanic white men aged 85 years and older occurred at a rate

of 47 per 100,000 people (NIMN, 2012). From this data, one could surmise that in order for research studies to properly analyze the link between suicide and anti-depressant therapy with that of the general population, the study should include four times as many men as women, and should also include men over the age of 65 years and 85 years-of-age. The methods that studies use to depict the ages of the participant population (which are often as a mean with a standard deviation) make it difficult to determine the exact demographics of the study population.

Studies have shown that the initiation of anti-depressants reduced suicidal thoughts or behavior in patients who were previously experiencing suicidal thoughts (Simon, 2012). However, warnings that there may be a direct correlation between anti-depressant use and suicidality have left some medical professionals and patients skeptical about their safety (Lader, 2007). This skepticism can lead to the under-diagnosis and under-treatment of psychiatric illness, which is adverse to positive patient care and outcomes.

The facts regarding untreated psychiatric illness and suicide seem to be obscured as the controversy over the correlation between anti-depressant use and suicidality continues to swirl. For example, one observational study performed over a 38 year period found that 14 percent of the participants committed suicide. This suicide rate is an astounding 27 times greater than that of the general population (Simon, 2012). In order to provide for the best interests of the patient, it is important to determine whether or not studies that have focused on this correlation have considered confounding factors, such as those factors listed as high risk for suicide previously in the paper. This project will analyze the outcomes of research studies that focus on the correlation between anti-depressant therapy and suicidality to determine if there could be other factors which contribute to suicidality in participants who reported experiencing suicidality after initiating anti-depressant therapy.

Significance

Anti-depressants are largely considered an efficacious treatment of depression, anxiety, and other mental health disorders. However, the FDA warnings issued in 2004 and 2007 regarding anti-depressant use and increased suicidality in the pediatric, adolescent, and young adult population seems to have decreased the rates of both diagnosing depression and treating patients with anti-depressants (Simon, 2012). This is unfortunate because the meta-analysis which led to the FDA warning included no completed suicides, infrequent suicide attempts, and only found clinical significance related to the correlation between anti-depressants and suicidality when suicidal ideation and possible suicidal ideation were added as endpoints in the study (Valuck, Orton, & Libby, 2009). The reluctance among some prescribers when considering whether or not to use anti-depressants as a treatment is a huge concern (Lader, 2007), especially since studies have found anti-depressant treatment to be associated with significantly lower rates of suicidal mortality when compared to untreated depressed patients (Simon, 2012).

Suicide is the tenth leading cause of death worldwide (Schreiber, Culpepper, & Fife, 2012) and the third leading cause of death in people under 45 years-of-age in the U.S. (Dolgin, 2012). Of those who complete suicide, more than 95 percent have at least one psychiatric diagnosis (Schreiber, Culpepper, & Fife, 2012). In order to diagnose and treat patients appropriately, it is imperative to clarify the risks involved where anti-depressants and suicidality are concerned. However, despite the unknowns related to suicide and anti-depressants, in 2011, the National Institutes of Health (NIH) spent only about 0.6 percent of their total budget on suicide prevention, and a little more than twice that on suicide research in comparison to the 10% of the agency's budget that was utilized to research HIV/AIDS (Dolgin, 2012).

Some professionals have suggested that the FDA consider utilizing epidemiologic data as a way to determine whether or not medications have the outcomes sought in the general population. For example, one psychiatrist petitioned to have the FDA consider 31 observational studies showing that lithium “can reduce the risk of suicidal behaviors in individuals with bipolar disorder or other major mood disorders by as much as 80 percent” (Dolgin, 2012, p. 192). The FDA stated that, in order to consider epidemiologic data, there would need to be “an overwhelming amount of observational data” showing that lithium did reduce suicide (Dolgin, p. 192). What the FDA recommended was performing randomized trials that consisted of 5,000 participants exposed over a time period of two years or more.

The medical field (and the general public) needs accurate information on whether anti-depressant therapy, in itself, causes suicidality, or whether other confounding factors cause suicidality in patients who are being treated with anti-depressants. Finding answers to the question of suicidality related to anti-depressants may be difficult, however, due to the rarity of suicidal behaviors in clinical trial participants, an inadequate amount of information related to people who attempt suicide in the real-world population, and “ethical issues involved in studying this severe outcome with randomized, placebo controlled trials,” (Valuck, Orton, & Libby, 2009, p. 1069). In fact, drug trials involving psychiatric medications exclude patients experiencing suicidal thoughts from their studies due to ethical concerns (Dolgin, 2012). However, despite the controversy regarding the correlation between anti-depressants and suicidality and the ethical issues that limit research parameters in this area, providers and patients alike have a right to know the risk factors associated with anti-depressants and what other factors may contribute to suicidality so, together, they can make an informed decision about the treatment plan.

Theoretical Framework

There are many factors that play a part in an individual's suicidality. While some of these factors are easy to determine by reviewing a patient's medical record (i.e. comorbid medical and mental illness, prior history of suicide attempts or psychiatric hospitalizations, or comorbid substance abuse), some factors (such as brain derived neurotrophic factor levels or genetics) are more difficult to detect. The biopsychosocial theory fits the purpose of this project because there are many components that can play a role in the development of suicidality during anti-depressant treatment, and all factors must be considered while assessing what role, if any, anti-depressants play in suicidality.

This project includes several studies which emphasize different factors that can play a role in the development of suicidality among patients. This is necessary in order to establish an understanding that the development of suicidality is multi-factoral. It is not something that can be accurately measured by a study which analyzes one specific factor (i.e. genetic factors involved in suicidality or a correlation between anti-depressant use and suicidality). Therefore, determining whether or not anti-depressant therapy increases the risk for suicidality is difficult because there are numerous factors that play a role in this.

By using the biopsychosocial theory to guide this project, the author reviewed studies that analyzed the correlation between anti-depressant therapy and suicidality. However, studies that analyzed other factors, such as genetics, that may play a role in suicidality were also reviewed. Three studies in which serum toxicology levels were tested in individuals who committed suicide were reviewed to determine what percentage of these individuals had anti-depressants in their system. The only competent way to look at suicidality is to look at the information from a multi-faceted view. It is difficult to get a broad view of how anti-depressant therapy correlates with

suicidality when many studies do not take the other multiple possible reasons for suicidality into account.

Definitions

There are several key terms pertinent to this project. These terms are defined below. It is important for readers to understand the differences between these terms in order to better understand how each has been used for the purpose of this project.

- **Depression:** An affective disorder characterized by at least five of the following symptoms for a period of two or more weeks: depressed or sad mood, diminished interest in activities which used to be pleasurable, weight gain or loss, psychomotor agitation or retardation, fatigue, inappropriate guilt, difficulties concentrating, or recurrent thoughts of death (CDC, 2011).
- **Suicidality:** A term inclusive of suicidal thoughts, preparatory acts, suicide attempts and suicide completions
- **Suicide attempt:** An act that is carried out with the intention of resulting in one's own death
- **Suicide completion:** An act that is committed with the intention of, and has resulted in, one's own death
- **Suicidal ideation:** Thoughts of killing oneself
- **Non Suicidal Self Injury:** Self-injurious bodily injury performed to damage the body surface, but not done as a way to commit suicide. Examples include cutting, burning, or hitting oneself (APA, 2012).

Review of the Literature

Several research studies have attempted to provide answers to the question of whether or not there is a correlation between anti-depressant use and suicide and/or suicidal thoughts/behaviors. However, study results have proven controversial. Some studies have found that anti-depressants do cause suicidal thoughts/behaviors while other studies have found just the opposite. Outcomes of other studies have referenced an increase in suicidal thoughts, but a decreased rate of both suicidal behavior and mortality due to suicide where anti-depressant treatment is utilized.

Observational studies attempting to link antidepressants to suicidality may be skewed solely by confounds of indication due to the increased risk in suicide in the population being studied (Isacsson, Holmgren, & Ahlner, 2005; Isacsson, Holmgren, & Ahlner, 2009; Cougnard et al., 2009), while randomized controlled trials often exclude potential participants experiencing suicidal ideation. Furthermore, the short period of follow-up and stringent inclusion and exclusion criteria of randomized controlled trials make it difficult to test theories on a population of participants similar to the population of patients treated with antidepressants in real world conditions. Furthermore, it is often difficult to draw a conclusive theory in regards to the outcome of randomized controlled trials, due to the short treatment duration and small number of participants in the studies (Cougnard et al., 2009).

In addition to the mental health diagnoses listed previously in the paper as increasing the risk for suicidality, studies have also identified an association between genetic factors and suicidality. Perroud et al. (2009) found that a genetic polymorphism in the brain derived neurotrophic factor (BDNF) gene could also be a strong genetic factor contributing to increased suicidality. The authors further noted that several studies have found, "a decreased level of

BDNF in the hippocampus and prefrontal cortex (PFC) of suicide victims and in the cerebrospinal fluid (CSF) and plasma of suicide attempters (Perroud et al. 2009, p. 2523).” In addition, Olmer, Iancu, and Strous, (2012) found that, with separate interventions of psychotherapy and antidepressant therapy, and a combination of the two interventions, the incidence of suicide is highest in the month prior to initiation of treatment and the risk declines steadily over the next six months.

Rucci et al. (2011) studied whether 318 participants who were randomly assigned into treatment with either the serotonin reuptake inhibitor (SSRI) escitalopram or psychotherapy (IPT) would experience emergent suicidal ideation (ESI) during the course of a 20 week period in which they were followed. The participants were selected from two University Outpatient Clinics (University of Pittsburg and the outpatient clinic of the Ospedale Santa Chiara of the University of Pisa) between April 2003 and April 2008. Of the 318 participants, 210 were female and 108 were male. All participants were between 18 and 66 years of age and had a diagnosis of a non-psychotic major depressive episode. Ninety participants were experiencing their first episode of depressive illness, while 201 reported having two or more episodes of depression. Additionally, suicidal thoughts were present in 59 of the participants at the time of pretreatment interview, while one participant noted having a suicide plan. The strengths of this study are as follows: participants were referred from outpatient clinics (and not based from the general population) who were randomized assigned to treatment groups; the outcomes of two commonly used interventions for the treatment of major depressive episodes were compared; participants experiencing suicidal thoughts at the baseline interview were included in the study. The limitations of the study were: a small participant pool (N=318); the participant pool consisted of 72 percent females; the mean age was relatively young (38.3 years); the study did

not include patient over 64 years old or those under age 19; the study only utilized one medication as a therapeutic intervention which limits the results of the study from use in other drug populations; patients with psychotic depression, active suicidal ideation with a plan, current alcohol or drug abuse, current eating disorders, and newly diagnosed and unstable physical illness were excluded from the study.

The findings of this study were interesting because of the 21 participants who had a history of previous suicide attempts, none developed ESI during treatment. Of the 231 participants who were free of any suicidal thoughts at baseline, 32 exhibited ESI at some point during the follow-up period. Twenty-two of the participants who developed ESI had been assigned to the IPT group, while ten had been assigned to the escitalopram group. Time from initiation of treatment to development of ESI was as follows: less than four weeks (N=13); between five and eight weeks (N=9); and after eight weeks (N=10). The study also found that time to suicidal ideation was significantly longer for those in the SSRI group versus the IPT group. Patients who developed ESI during the study were able to be managed successfully by the study protocol, and referral to a higher level of care was only required in two cases (Rucci et al., 2011).

Mulder, Joyce, & Frampton, (2008) scrutinized whether treating patients, who were either currently experiencing suicidal ideation or had a history of suicide attempts with antidepressants, reduced those thoughts/behaviors over time. The study focused on 195 patients who were referred by psychiatric emergency services, community mental health centers, and general practitioners from 1993 to 2001. The inclusion criteria were: at least 18 years of age, primary current diagnosis of major depression; willing and able to give informed consent; treatment with antidepressants was deemed to be appropriate management. Patients who were breastfeeding,

pregnant, likely to become pregnant, had a major medical disorder that could complicate assessment or treatment, severe drug or alcohol dependence; and a history of mania, schizoaffective disorder, or schizophrenia were all exclusionary criteria.

The participants of the above study were 57.4% were female and the mean age was 32.2 (SD 11.4) years. Most of the patients denied any suicidal ideation, however, 34.6% of participants reported at least moderate suicidal ideation. Additionally, 23.3% (39 patients) had reported a suicide attempt within six months prior to treatment, while 12 participants reported more than one suicide attempt in the previous six months. Participants met DSM-III-R criteria for at least one of the following disorders: bipolar II disorder (9%); melancholia (44%); atypical depression (8%); recurrent depression (52%); chronic depression (64%) (Mulder, Joyce, & Frampton, 2008).

The participants were then randomly assigned to receive a treatment of either fluoxetine or nortriptyline. They were interviewed and asked about whether they had experienced suicidal ideation in the past 14 days. Their answers were rated as none, occasional, moderate, and regular. At weeks 3, 6, 9, 13, 20, and 26, participants were asked about any suicide attempts since the previous visit. After six weeks of treatment, participants continued on their current medications if they had responded to it. Those who did not respond to the initial medication were switched to the other medication group. If participants did not respond to the second medication, the two medications were combined, and subsequently, the clinician was free to use whatever medication he/she felt was clinically indicated. The patients were divided into three groups based on their treatment outcome; patients who recovered and remained well until the six-month assessment; patients who either achieved remission or recovered but subsequently relapsed; patients with persistent depression (Mulder, Joyce, & Frampton, 2008).

Of the 195 participants initiated into the study, 176 remained at the time of the six month follow up. Ten participants dropped out...nine left the area, and one withdrew without treatment and later committed suicide. Sixty-six percent of the patients had continued to take fluoxetine or nortriptyline, while 24 patients had either elected to stop the medications or had found it intolerable (however they did remain in the study). Throughout the six month course of treatment, 29 patients attempted suicide. This is in comparison to the 51 patients who reported attempting suicide at least once in the six months prior to the study. The study further found that that antidepressant treatment reduced suicidal ideation by 33% in the first three weeks of treatment and 38% over the course of six months, and that the number of suicide attempts dropped by 50 % in comparison to the six month period prior to treatment. None of the patients without suicidal ideation or suicide attempts in the six months prior to treatment who developed ESI during the study (N=5) attempted suicide (Mulder, Joyce, & Frampton, 2008).

Similarly, Seemuller et al. (2009) performed a prospective naturalistic study that included 1,014 participants who were recruited from seven German psychiatric university hospitals. The participants were between 18 and 65 years of age, were willing and able to sign informed consent, and had a diagnosis meeting criteria for any major depressive episode confirmed using the Structured Clinical Interview for DSM-IV. This study analyzed 18 predictors: "HAMD total score; gender; age (also dichotomized >45 or over <_45); years since first diagnosis; suicide attempt immediately before hospitalization; suicide in first and second-degree relatives; alcohol abuse or dependency; any substance abuse or dependency; any comorbid personality disorder; diagnosis of any bipolar disorder; number of hospitalizations; akathisia; presence of childhood trauma; treatment resistance; family status; children; native language German" (Seemuller et al. p. 183). The HAMD score in most of these patients indicated they were either moderately or

severely depressed upon admission. Of the 1,014 study participants, 137 had attempted suicide immediately prior to being admitted to the hospital. During treatment, 10 participants attempted suicide and two participants completed suicide. The study found that 14.4% of participants experienced worsening of suicidal ideation, compared to 90 percent of participants who reported improvement in suicidal ideation. The study additionally identified that patients under age 45 years are more likely to experience ESI. When compared to that general population, suicide rates among study participants were much higher; however, these rates were only slightly elevated in comparison to those commonly found in RCTs. Furthermore, 22 potential risk factors for extended emergence suicidal ideation were determined, but two independent statistical methods identified age, treatment resistance, number of hospitalizations, presence of akathisia, and comorbid personality disorder.

Olmer, Iancu, and Strous (2012) performed a retrospective study in which they reviewed adult patients admitted to the Beer Yaakov Mental Health Center from 2000 to 2007 with a diagnosis of major depressive disorder (MDD). The aim of the study was to analyze whether antidepressants have a significant relationship in suicide attempts. Upon review of the charts from patients hospitalized following a suicide attempt, 103 patients met all of the inclusion criteria, which were: no diagnosis of bipolar spectrum disorder; diagnosis of major depressive disorder; and a recorded suicide attempt within four weeks prior to hospitalization. The study population consisted of 69 women and 34 men with a mean age of 49.21 years (SD 14.56 years). The study found no significant correlation between antidepressants and suicide attempts. However, the researchers also suggested that SSRIs may be less effective in treating suicidal depressed patients who are hospitalized in comparison to antidepressants that have effects on multiple neurotransmitters.

Cougnard et al. (2008) examined whether antidepressants decrease suicide. The participants were broken into three age groups (children and adolescents 10 to 19 years of age, adults 20 to 64 years old, and elderly patients 65 years of age or older) diagnosed with major depression. Data was extracted from both published studies and databases of the French general population. The number of suicides induced or avoided by antidepressant therapy and no antidepressant therapy was then estimated. The researchers estimated that antidepressant therapy would prevent 31.9% of suicides in depressed subjects over one year in comparison to no antidepressant therapy in the 10 to 19 year age group, 32.2% of suicides in adult depressed subjects, and 32.3% of suicides in elderly depressed patients. The finding that antidepressants act as a protective factor against suicide can also be carried into the general population. While this study did include a large population of subjects, the simplified model constructed for the purpose of this study is a weakness.

When it comes to the link between antidepressant use and suicidality, there are many unknown factors. Many studies rely solely on the report of the patient when determining whether or not they are taking antidepressants. However, some toxicology studies have found that only a small number of suicide victims have traces of antidepressants in their system. Isacson, Holmgren, and Ahlner (2005) tested this theory. They believed that if SSRIs posed an increased risk of suicide, the medication should be found more often in toxicology reports. This study analyzed the toxicology reports of 14,857 suicide cases in Sweden between the years 1992 and 2000. The study also looked at 4,301 deaths by uncertain causes to ensure that deaths by overdose were not overlooked. Seventy-one percent of the cases studied were men and the median age was 49 years. The study group was then compared to a control group consisting of 26,422 cases determined to be death by accident or natural causes. The control group consisted

of 73% men and a median age of 55 years. The study also analyzed 52 suicides in children under 15 years-of-age and 326 cases of suicide in adolescents between the age of 15 and 19.

The study by Isacsson, Holmgren, and Ahlner (2005) found that only 7 of the 52 cases of suicide in children under age 15 were positive for any kind of anti-depressant, and no cases were positive for SSRIs, compared to 5 cases of the 998 total persons in the control group under 15 years of age. In the age group of 15 to 19, 13 of 326 suicide cases were positive for antidepressants. Only six of these cases were positive for SSRIs. This is compared to antidepressant detection in five cases (three of which were SSRIs) of the 577 total cases in the 15-19 control group. Antidepressants were detected in only 13% of children, 4% of adolescents, and 23% of suicide cases among all age groups. As a result of this study, the researchers reported that SSRIs were detected at lower rates than other anti-depressants in suicide victims, and suggested that under-treatment with antidepressants is still an issue.

Isacsson, Holmgren, and Ahlner (2009) repeated a similar study in Sweden to include suicides (N=16,937), natural deaths (N=12,181) occurring between 1995 and 2005. The mean age of the suicide group and control group combined was 50.6 years, with 70.8% being male. During the period from 1995 to 2005, the number of suicides exposed to antidepressants increased by 46% while the suicides decreased by 18.6%. Among the control group, the use of anti-depressants increased by 109%. The authors suggested that antidepressants reduced the risk of suicide by 43%.

A smaller study of 253 persons conducted by Cortes et al., (2011) found similar results. This retrospective study was conducted on suicide victims aged 24 years-of-age or younger in Miami-Dade County Florida from 1990 to 2007. The researchers then reviewed demographic data, psychosocial factors, suicide characteristics, and toxicology reports. The study found that

approximately 90% (N=228) had no trace of antidepressants on review of the serum toxicology report. Six percent of these antidepressants were found to be SSRIs. Interestingly, the researchers also noted several other substances in these patients upon review of the toxicology report, including: 31.6% (N=80) showed a presence of alcohol, while 17.8% (N=45), opioids 6.7% (N=17), hallucinogens 1.2% (N=3), benzodiazepines 12.3% (N=31); other types 13% (N=33); and unknown 5.9% (N=15). Ninety seven patients (38.3%) had no substances shown on the toxicology report. The suicide victims studied were 85% male and 53.4% were Hispanic. Women were more frequently found to have positive results for antidepressants on the toxicology reports than men.

Leon, et al., (2004) conducted a small toxicological study on 66 suicide victims less than 18 years-of-age between 1993 and 1998 evaluated whether or not serum blood samples revealed the presence of anti-depressants. Because the longest acting anti-depressant, fluoxetine, has a half-life of 21 hours, 12 victims (who lived for 3 days or more following their suicidal act) were excluded from the study, leaving 54 persons available for toxicological testing. The age range of the deceased ranged from 10 to 17 years-of-age with seven being younger than 13 years of age. The ethnicities of the deceased were evenly split between Hispanics, African Americans, and Caucasians. Additionally, 75 percent of the deceased were males. The toxicological results found that paroxetine was not present in any of the suicide victims, two screened positive for the presence of imipramine, and two screened positive for fluoxetine. While the study is small, it does confirm, as do the other toxicological reports discussed above, that the large majority of suicide victims are not taking anti-depressants at the time of their death.

In addition to serum toxicology levels, genetic predisposition is another factor that is not commonly analyzed in studies questioning the link between antidepressants and suicidality. A

study by Perroud, et al., (2009) examined whether emergent suicidal ideation during antidepressant treatment could be driven by genetic factors. The researchers selected nine genes involved in neurotrophic, serotonergic, and noradrenergic pathways. The participants (N=796) were then treated with antidepressants and were studied for emergence of suicidal ideation and genetic variances over a 12 week time frame. Participants were included in this study if they met criteria for an episode of major depression that was of at least moderate severity. Patients were randomly assigned to either escitalopram or nortriptyline treatment groups. However, patients that had a contraindication to taking one of the medications were assigned to the other antidepressant group. Participants were 18 to 72 years of age. Participants with a primary substance misuse or primary organic disease, pregnancy or lactation, current treatment with an antipsychotic or mood stabilizer, history of hypomanic or manic episode, mood incongruent psychotic symptoms, or a first degree relative with a bipolar disorder diagnosis or schizophrenia, were excluded from the study.

In their study, Perroud et al. (2009) found that a larger number of males experienced suicidal ideation when taking nortriptyline if they had the A allele compared to the C allele. The study also found that “variants in the genes encoding BDNF and its receptor (NTRK2) were associated with an increase in suicidal ideation during antidepressant treatment in subjects suffering from major depressive disorder” (Perroud et al., p. 2524). The researchers, “found an even stronger effect for an interaction between the known functional BDNF-LCPR GT (n) polymorphism and SNPs in the 3’ region of NTRK2” (Perroud et al., p. 2524). The small sample size of participants is a weakness of this study. In addition, the limited number of participants under 25 and over 65 years-of-age made it impossible to make any assumptions on how genetic polymorphisms may affect these age groups.

Ecological studies have analyzed the number of anti-depressant prescriptions provided to a population against changes in suicide rates. Studies conducted since 2005 have consistently shown an inverse correlation between the number of anti-depressants prescribed and the number of completed suicides (Castelpietra, et al., 2008; Henriksson, et al., 2006; Korkeila, et al., 2007). One study conducted in Finland, a country where two-thirds of the population suffer from a depressive disorder, analyzed the number of anti-depressants prescribed and the number of suicides between 1994 and 2001. There were a total number of 1,387 completed suicides in 1994 compared to 1,204 completed suicides in 2001. During that same time period, the number individuals prescribed anti-depressants increased from 140,438 in 1994 to 272,370 in 2001. The study found that an increase in the number of anti-depressants prescribed was significantly associated with a decrease in suicide rates (16 percent in men and 14 percent in women) after gender, age, and region were taken into account (Korkeila et al., 2007).

A similar study done among individuals living in the Friuli Venezia Giulia region of Italy (which is the region of Italy found to have the highest rate of suicide in the country) between the years of 1997 and 2006 found that the use of anti-depressants increased from 11.9 individuals users per 1,000 inhabitants in 1997 to 56.7 individual users per inhabitants in 2006. During that time frame, suicides rates decreased from 13.8 per 100,000 in 1997 to 9.1 per 100,000 in 2001. This equates to a relative suicide risk reduction of 35 percent in women and 34 percent in men (Castelpietra, et al., 2008). Another ecological study in done in Jamtland county, Sweden from 1995-2002 focused on educating general practitioners as a way to improve treatment in patients struggling with depression in Jamtland county, Sweden, but also analyzed whether the program had an impact on the number of anti-depressants prescribed and suicide rates. The study found that sales of anti-depressants increased 161% in Jamtland County between 1995 and 2002. With

regard to anti-depressant use and suicide rates, the study found that the increased use of anti-depressants were associated with a decreased rate of suicide of 30 percent and 47 percent in men and women of Jamtland County, respectively (Henriksson, & Isacson, 2006).

All three of the ecological studies discussed above found that the antidepressants prescribed were primarily from the SSRI class (Castelpietra, et al., 2008; Korkelia et al., 2007; Henriksson & Isacson, 2006). Two of the three studies noted that more women than men were prescribed anti-depressants (Henriksson, & Isacson, 2006) and all three studies found that more men committed suicide than women (Castelpietra, et al., 2008; Korkelia et al., 2007; Henriksson & Isacson, 2006). One main weakness of all three studies is that none examined serum blood levels of those who had committed suicide for the presence of anti-depressants.

A cohort study performed in Finland included 100 percent of people hospitalized for suicide attempts between 1997 and 2003. The study population was 15,390 patients, including 7,466 males and 7,924 females. The researchers calculated the relative risk of suicide attempts, suicide completions, and overall mortality of patients being treated with anti-depressants versus no treatment with anti-depressants. The anti-depressants included were TCA (amitriptyline or doxepin), SSRI (fluoxetine, citalopram, paroxetine, sertraline, or fluvoxamine), and SNA (mianserin, mirtazapine, or venlafaxine). The results of the study found that, while there was an increased risk of suicide attempts in patients taking anti-depressants versus no treatment with antidepressants, there was no increased risk of suicide completions. Additionally, the study found a decreased mortality rate, particularly in the rate of cardiovascular-related deaths (Tiihonen, et al., 2006).

Furthermore, the American College of Neuropsychopharmacology (ACNP) formed a task force that reviewed several studies, including the meta-analysis which was conducted by the

FDA and later resulted in the black box warning for anti-depressants, epidemiologic studies, RCTs and post-mortem toxicological studies. The ACNP found that, while the FDAs meta-analysis does show a small increase in suicide attempts or suicidal thinking in youths, the effect varies across the RCTs reviewed in the meta-analysis. The ACNP further determined that, while the variance could be due to a difference between medications, it is also possible that the variance could be due to an error in measurement. The epidemiologic and post-mortem studies as well as cohort surveys reviewed by the ACNP did not support an increase in suicidal acts or suicide, and instead found a possible beneficial effect between anti-depressants and suicidality. The ACNP also surmised that, based on the post-mortem toxicological youth studies, only a small number of youth who commit suicide are taking anti-depressants at the time of suicide (Mann, et al., 2006).

Methods

A systematic literature search was conducted to identify randomized controlled trials and epidemiologic studies indexed between 2005 and 2012. Cochrane Library, CINAHL (Headings), PubMed (MeSH), and PsychInfo (Thesaurus) were utilized to conduct the search. The search terms utilized for the purpose of this project were “antidepressive agents” and “suicide” or “suicidal ideation.” Two separate searches were performed in CINAHL (Headings), PubMed (MeSH), and PsychInfo (Thesaurus). The initial search included the search terms previously listed, but limited the search to only randomized control trials. The second search included the initial search terms, but limited the search to epidemiologic studies.

Cochrane Library was first searched for studies using these terms. This search returned 26 results, 21 of which were published after 2004. Of those results, three were found to be of particular interest for the purposes of this project.

CINAHL (Headings) was searched next using the same terms. The search limited to randomized controlled trials returned 323 results. Limiting the results to PDF full text only returned 50 results. Excluding studies published prior to 2005 further confined results to 40 studies. Including only peer reviewed articles limited the results to 34. Further review of these results determined that four of the studies were pertinent to the topic of this paper. A second search was then performed in CINAHL (Headings) to include prospective studies. This search returned 607 results. Further limiting this search to PDF full text only returned 99 results. Including only studies published between 2005 and 2012 further confined the number of results to 72 articles. Including only those studies that had been peer reviewed and available in the English language limited the results to 65. Review of the resulting prospective studies revealed that six were appropriate for further review for this paper.

The PubMed database was then searched using the same terms (“antidepressive agents” and “suicide” or “suicidal ideation”). The search was further limited to include randomized controlled trials (as a publication type). This search returned 78 results. Delimiting the search further to publications dates between 2005 and 2012 returned a total of 65 articles. Limiting the articles to full text only further limited the number of articles to 63. Further review of these articles determined that six were pertinent to this project. One of the articles found pertinent to the project was a task force review of multiple study types (meta-analysis, RCTs, epidemiologic, and post-mortem toxicology studies) that examined the correlation between anti-depressants and suicidality among children and adolescents (Mann, et al., 2006). A second search in PubMed using the terms returned 35 results when the criteria was further delimited to full text prospective studies published between 2005 and 2012. Of these studies, two were appropriate for the purpose of this paper. A third search (using the same terms) was also conducted in

PubMed (MeSH) to include the term “epidemiologic studies.” The initial search returned 480 results. Further limiting the results to full-text articles published between 2005 and 2012 returned 351 results. Of the studies reviewed, 12 were found pertinent to the topic of this paper.

A search of the PsychInfo (Thesaurus) database was then searched using the terms “antidepressant drugs” and “suicide” or “suicidal ideation” and “clinical trials” returned 32 results. Further limiting the search to articles published between 2005 and 2012 returned 30 results. When the author further delimited results by adding criteria for peer reviewed and full text articles only, seven articles were returned. Further review of these articles revealed that two were appropriate for use in this project. There were no full text results for prospective studies related to the key terms searched in PsychInfo (Thesaurus).

The author also reviewed the reference lists of the articles chosen for inclusion in the paper, and utilized three studies from those lists. One of the studies chosen was published in 2004; however, it provided important post-mortem toxicological evidence of youth suicide and anti-depressant use and thus, was included in the study. All of these articles focused on the presence of serum antidepressant level during post-mortem autopsy. Kim Gregg, RN, CNS, was consulted to review and provide recommendations and guidance of this project. The hopes is that this project will affect a change in clinical practice by revealing whether studies that question the link between anti-depressants and suicidality have taken confounding factors into consideration when reporting their results. If that is not the case, then whether or not antidepressants alone increase the risk for suicide and or suicidality should be open for deliberation.

Results

A copy of both the written paper and the Power Point presentation for this project was provided to Registered Nurses and Psychiatrists who are members of the Integrated Behavioral Health Team at Mayo, Clinical Nurse Specialists who are members of the Psychiatry Department at Mayo, and student colleagues in the Mental Health Nurse Practitioner Program at the University of North Dakota for feedback. Colleagues provided positive feedback regarding the types of studies that were reviewed for the project. The colleagues noted the tremendous impact keeping meticulous medical records (such as those depicted in the studies performed in Finland and Sweden) could have on both medical research and patient outcomes. Most were particularly interested in toxicological and genetic findings from the studies reviewed.

Discussion and Implications for Nursing

According to the National Institute of Mental Health (NIMH), the U.S. suicide rate was 11.3 deaths per 100,000 in the general population in 2007 (NIMH, n.d.). Since more than 95% of people who die of suicide suffer from depression or other mental disorder (Schreiber, Culpepper, & Fife, 2012), it can be deduced that the suicide rate is much higher in the sub-population of those who are struggling with mental illness in comparison to the general population. Controlled studies completed with a goal of showing whether there is a correlation between anti-depressants and suicide or suicidal thoughts and/or behaviors on the sub-population mentioned above often exclude patients who are at higher risk for developing suicide or suicidal ideation/behaviors due to ethical issues (Tiihonen et al., 2007). It would make sense that the exclusion of participants at higher risk for suicide from controlled studies would, in turn, cause controlled studies to have lower rates of suicide or suicidal ideation/behavior in comparison to epidemiologic studies (Howland, 2006). However, several epidemiologic studies have shown

that treatment with anti-depressants decrease the rate of suicide (Tiihonen, et al., 2006; Olfson, Marcus, & Shaffer, 2006; Castelpietra, et al., 2008).

It is crucial to delineate any confounding factors (other than the use of anti-depressants) that may contribute to an increase in suicide and or suicidal thoughts/behaviors in these studies in order to authentically state that anti-depressant therapy is the sole cause of a participant's suicidal thoughts and/or behaviors. Making claims that anti-depressants increase suicide and/or suicidal thoughts/behaviors without fully exploring every other plausible explanation is not only unfounded, but creates a falsity throughout the medical field and in the public eye that can substantially impact patient treatment and outcomes.

There is concern among both health care providers and the lay public with regard to the correlation between anti-depressant therapy and suicidality. While the FDA warning label was based on a meta-analysis that reviewed the correlation between anti-depressant use and suicidality, no completed suicides were reported during this study (Valuck, Orton, & Libby, 2009). There are too many unknowns to determine whether or a direct correlation between antidepressant treatment and suicidality exists. Genetic factors, comorbid medical or psychological disorders, and history of prior self-harm/suicide attempts are just a few of the unknown factors that could be influencing the study outcomes. These factors could play a role in suicidal thoughts or behaviors in both adolescents and adults, and while these thoughts and behaviors may occur in conjunction with anti-depressant treatment, it should not be an indication that the anti-depressants caused the thoughts or behaviors to occur.

One study of suicide attempts and non-suicidal self-injury in adolescents (ages 12 to 18 years-of-age) with treatment resistant depression found that 47.4% reported non-suicidal self-injury at baseline. National surveillance data also indicates that approximately 6.3% of high

school students attempt suicide (Rosenbaum-Asarnow et al., 2011). It is difficult to show that anti-depressants cause increased suicidality in adolescents, where self-harm behavior is common.

Further research is needed to determine whether there is a link correlating antidepressants and suicide levels. The lack of studies that include drawing toxicological serum levels alone can impact the study findings because patient report alone is used to determine whether or not participants are taking their anti-depressants. It is of particular importance to obtain serum antidepressant levels in children, adolescents, and adults who participate in self-harm, attempt suicide, or complete suicide, especially since post-mortem studies have consistently found that over 80 percent of depressed adult suicide victims are not taking anti-depressants at the time of their death (Mann, et al., 2006). Another area for possible research is genetic studies. Testing for factors, such as BDNF, may also prove helpful in decreasing suicidality in patients in the future.

As nurses, there are many things that we can do to promote mental wellness among our patients while promoting health policy in our communities. Continued education both among the public and among the health care community is essential in order to recognize and accurately treat patients with mental illness. Advocating for our patients by helping to increase the diagnosis and treatment of mental illness in the outpatient setting is one step that could have a very positive impact on patient outcome. Another positive step would be creating awareness programs in our middle schools and high schools, where the risk for self-harm behavior and suicide attempts is high. In order to effectively improve patient outcomes where mental illness is concerned, it is essential to evaluate each community on an individual basis. High risk areas in which there is potential for improved outcomes should be identified, and programs tailored to those high risk areas should be developed integrated into health care policy.

Summary/Conclusions

The correlation between mental illness and suicidality is a huge health concern. While many studies have been done to identify whether anti-depressant treatment is directly correlated with an increase in suicidality, these studies do not take into account many of the confounding factors that could increase suicidality independent from anti-depressant use. Ecological studies have consistently found a decrease in suicide rates with a corresponding increase in anti-depressant use. Toxicological studies have also consistently found that the majority of patients who commit suicide do not have anti-depressants present in their system at the time of death. However, few studies include toxicological serum levels to ensure compliance with anti-depressants. Some studies have also correlated a decreased level of BDNF with increased suicidality, yet few studies have considered low BDNF levels as a possible variable for increased suicidality.

The studies reviewed for evidence of whether or not anti-depressants increase suicidality in patients do not account for many of the factors that increase the risk for suicidality independent from anti-depressant use. Because of this, it is not possible to say whether or not there is a correlation between the use of anti-depressants and suicidality. Furthermore, it is important to separate the terms of self-injurious behavior, suicide attempt, and suicide completion instead of using the term suicidality to discuss the effects anti-depressants have on behaviors. There is evidence that the risk of suicidality increases in the initial four weeks following treatment for depression (whether it is psychotherapy or medication based), but then decreases significantly after that time. It is imperative to monitor patients closely for suicidality after initiating treatment for mental illness. However, the fear that antidepressants may cause suicidality in some patients should not overshadow the need to treat them. There is strong

evidence to support that anti-depressant treatment offers long term benefit to patients struggling with mental illness in relation to suicide risk.

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Appendix A

Appendix A

Research Based Findings of Anti-depressant Therapy and Suicidality: Power Point Presentation


Research Based Findings of Anti-Depressant Therapy and Suicidality

Melissa Webster
University of North Dakota


Purpose of the Project

- ▶ Review literature related to anti-depressant therapy and suicidality including:
 - Suicidal ideation
 - Suicide attempts
 - Suicide completions
- ▶ Determine whether or not confounding factors that might contribute to suicidality were considered in the study results
- ▶ Review studies that may provide areas needing additional research (i.e. toxicological levels and genetic factors)

Theoretical Framework

- ▶ Biopsychosocial model was utilized to guide this project
 - ▶ The biopsychosocial model allows for a multi-faceted analysis regarding the reasoning for the development of suicidality in patients
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Methods

- ▶ Systematic literature searches were conducted in Cochrane Library, CINAHL (Headings), PubMed (MeSH), and PsychInfo (Thesaurus)
 - ▶ Search terms utilized were "antidepressive agents" and "suicide" or "suicidal ideation"
 - ▶ Search criteria were delimited to full text articles in the English language with publication dates between 2005 and 2012
 - ▶ Randomized controlled trials and epidemiological studies (i.e. cohort, retrospective, or observational) fitting the criteria above were identified and were further reviewed for pertinence
 - ▶ Review of the reference list of the articles selected for use in the project were reviewed, and three articles from these reference lists were utilized in the project
 - ▶ Kim Gregg, RN, CNS, was consulted for guidance throughout this project
- 

Mental Illness and Suicide

- › Mental illnesses associated with the highest risk of suicide include:
 - Depression
 - Anxiety disorders (including panic disorder and PTSD)
 - Alcoholism
 - Substance abuse
 - Bipolar disorder
 - Schizophrenia
 - Personality Disorder
 - Delirium

(Schreiber, Culpepper, and Fife, 2012)
- › Additional factors that increase suicide risk are:
 - Prior psychiatric hospitalization
 - Prior history of self-harm behavior
 - Prior history of suicide attempts (this is the strongest single predictor of future suicide attempts)

(Lader, 2007)
(Olmer, Iancu, & Strous, 2009)



Depression

- › One of the most common mental health disorders associated with increased suicide risk
- › Defined as an affective disorder characterized by at least five of the following symptoms for at least two weeks:
 - Depressed or sad mood
 - Weight loss/gain
 - Fatigue
 - Inappropriate guilt
 - Psychomotor agitation/retardation
 - Difficulty concentrating
 - Diminished interest in activities which used to be pleasurable
 - Recurrent thoughts of death

(CDC, 2011)



Depression Statistics

- ▶ Depression can also profoundly effects an individual's interpersonal relationships as well as work and school function
- ▶ #1 cause of missed work and disability in U.S
(Cancro, 2011)
- ▶ Estimated 20% of women and 12% of men in U.S. will experience depression during their lifetime
(Porth &Matfin, 2009)
- ▶ Of those who experience one episode of depression, the rate of recurrence is approximately 50%
(CDC, 2011)



Suicide Statistics

- ▶ Suicide is the third leading cause of death in those under age 45 in the U.S.
 - It is the 10th leading cause of death in the world
(Dolgin, 2012)
- ▶ U.S. suicide rate in the general population is 11.3/100,000 people
(NIMH, n.d.)
- ▶ Every year in the U.S. 30,000 people die of suicide
 - An additional 650,000 are treated in emergency rooms annually following suicide attempts
- ▶ Of those who complete suicide, more than 95% have at least one psychiatric diagnosis
(Schreiber, Culpepper, & Fife, 2012)



Suicide Statistics, cont.

- › Men are 4xs more likely than women to die of suicide
 - › Rate of suicide in general public is 11.3 per 100,000 people
 - Rate is increased to 14.3 per 100,000 people in men 65 years and older
 - Rate is 47 per 100,000 people in non-Hispanic white men aged 85 years and older

(NIMH, 2012)
 - › Adolescents ages 12 to 18 years of age have suicide attempt rate of 6.4%
 - Rate of non-suicidal self-injury among adolescents 12-18 is 47.7 %

(Rosenbaum-Asarnow, et al., 2011)
 - › One study found that patients with mental illness had a suicide rate of 27 times greater than that of the general population
- (Simon, 2012)

Importance of determining correlation between anti-depressant use and suicidality

- › Anti-depressants are one of the most common treatments for depression, anxiety, and other mental illnesses.
- › 2004: The (FDA) mandated a black box warning be added to anti-depressant medications in order to alert patients of increased risk of suicidal thoughts in the pediatric and adolescent population (Friedman & Leon, 2007)
- › 2007: FDA mandated that the black box warning be expanded further to include patients between 18 to 24 years-of-age
- › The mandated warning was based on a meta-analysis that included no completed suicides and infrequent suicide attempts
 - Clinical significance was only found when endpoints of when suicidal ideation and possible suicidal ideation were added


(Valuck, Orton, & Libby, 2009)

Impact of FDA Warning

- ▶ A common reason that patients do not report symptoms of depression is the fear an anti-depressant will be recommended (Bell, et al., 2011)
- ▶ Decreased both the rates of diagnosing depression and treating patients with anti-depressants (Simon, 2012)
- ▶ These negative impacts are unfortunate because studies have found that anti-depressant treatment is associated with significantly lower rates of suicidal mortality (Simon, 2012)



Literature Review

- ▶ Rucci et al., 2011
 - Randomly assigned 318 participants to receive SSRI (escitalopram) treatment or psychotherapy (IPT) groups
 - Participants selected from two University Outpatient Clinics between April 2003 and April 2008
 - 210 female participants, 109 male participants
 - 90 participants were experiencing their first episode of depression
 - 201 participants had at least 2 depressive episodes
 - 59 participants had suicidal ideation and 1 had a plan at time of pretreatment interview
 - The goal of the study was to determine whether or not the participants in the groups would experience emergent suicidal ideation (ESI) during treatment
- 

Literature Review

› Rucci et al., 2011, (Cont.)


- Strengths:
 - Participants were referred from clinic setting, not from the general population
 - Two commonly used interventions (SSRI and IPT treatments) were compared
 - Participants experiencing suicidal ideation were included in the study
- Limitations:
 - Participant pool was 72% female
 - Study did not include those under 19 or over 64 years-of-age
 - Results are limited to the use of escitalopram versus other medications
 - Patients with a plan to commit suicide, those with psychotic depression, current alcohol or drug use, or newly diagnosed and unstable physical illness were excluded

Literature Review


› Rucci, et al., 2011

- Findings
 - None of participants (N=21) who had history of previous suicide attempts developed ESI during the study period
 - Of 231 participants who denied suicidal thoughts at baseline, 32 developed ESI at some point during follow-up. Timeline for ESI development is as follows:
 - Less than 4 weeks: N=13
 - 5 to 8 weeks: N=9
 - After 8 weeks: N=10
 - Time to ESI was significantly longer for the SSRI group than in the IPT group

Literature Review

- ▶ Mulder, Joyce, & Frampton (2008)
 - Goal: To determine whether patients who were either currently experiencing s.i. or had a history of suicide attempts with antidepressants reduced those thoughts/behaviors over time
 - 195 participants
 - Referred from psychiatric emergency services, community mental health centers, and general practitioners between 1993 and 2001
 - Inclusion criteria:
 - 18 years-of-age or older
 - primary current diagnosis of major depression
 - treatment w/ antidepressants
 - willing and able to give informed consent
 - Met criteria for bipolar II disorder, melancholia, atypical depression, recurrent depression, or chronic depression
 - Exclusion criteria:
 - Breastfeeding/pregnant/likely to become pregnant
 - Major medical disorder that could complicate treatment
 - Severe drug/alcohol dependence
 - History of mania/schizoaffective disorder/schizophrenia
- 

Literature Review

- ▶ Mulder, Joyce, & Frampton (2008), cont.
 - ▶ Statistics:
 - 57.4% female
 - Mean age 32.2 years (Standard Deviation 11.4)
 - 34.6% reported at least moderate suicidal ideation
 - 39 patients reported a suicide attempt within the 6 months prior to treatment
 - 12 participants reported more than one suicide attempt within the 6 months prior to treatment
- 


Literature Review

- › Mulder, Joyce, & Frampton (2008), cont.
- › Randomly assigned to groups for treatment with either nortriptyline or fluoxetine
 - Participants were followed for 6 months
 - They were asked if they experienced suicidal ideation in the past 14 days.
 - They were evaluated for suicide attempts since the beginning of the study six times in the 6 month period
 - Participants who did not respond to the initial medication at 6 weeks after treatment were switched to the other medication group
 - If the patients didn't respond to the second medication, they were treated with a combination of the two medications
 - If there was no response with combination treatment, the clinician used whatever medication they felt was indicated


Literature Review

- › Mulder, Joyce, & Frampton, (2008) Results:
 - Patients were divided into three groups based on their treatment outcome:
 - Patients who recovered and remained well until the six-month assessment
 - Patients who either achieved remission or recovered but subsequently relapsed
 - Patients with persistent depression
 - 176 of the 195 participants remained at the 6 month follow-up
 - 9 participants left the area, 1 participant withdrew without treatment and later committed suicide
 - 66% of patients remained on either fluoxetine or nortriptyline at 6 month follow-up
 - 24 patients had stopped the medication because they either elected to or found it intolerable
 - 29 patients attempted suicide (compared to the 51 participants who attempted suicide in the 6 months prior to the study)


Literature Review

- ▶ Mulder, Joyce, & Framptom, 2008– Results (cont).
 - Suicidal ideation was reduced by 33% in the first 3 weeks of treatment & 38% over course of 6 months
 - The number of suicides dropped to 50% compared to 6 month period prior to treatment
 - None of the 5 participants who had no suicidal ideation or suicide attempts in the six months prior to treatment but developed ESI during the study attempted suicide
- 


Literature Review

- ▶ Seemuller, et al. (2009)
 - Naturalistic study that included 1,014 participants
 - Participants were recruited from 7 German psychiatric university hospitals
 - Inclusion criteria:
 - 18–65 years of age
 - Willing and able to sign informed consent
 - Diagnosis meeting criteria for any major depressive episode
 - 137 of the participants had attempted suicide immediately prior to hospitalization
 - 10 participants attempted suicide and two participants completed suicide during treatment
- 

Literature Review

- Results: Seemuller, et al. (2009)
 - 14.4% of participants experienced worsening of suicidal ideation
 - Patients under 45 years-of-age were more likely to experience ESI
 - Suicide rates among study participants were much higher than the general population
 - Suicide rates were only slightly elevated compared with that of other RCTs
- 

Literature Review


- Olmer, Iancu, and Strous (2012)
 - Retrospective study
 - Reviewed adult patients admitted to the Beer Yaakov Mental Health Center from 2000–2007 with diagnosis of MDD
 - Goal of study was to analyze whether anti-depressants have a significant relationship in suicide attempts
 - Inclusion criteria:
 - Diagnosis of MDD
 - Recorded suicide attempt within four weeks prior to hospitalization
 - Exclusion criteria:
 - Diagnosis of bipolar spectrum disorder
- 

Literature Review

- Olmer, Iancu, and Strous (2012), cont.
- Study population
 - 103 patients, including 69 women and 34 men
 - Mean age of 49.21 (standard deviation of 14.56 years)
- Results
 - No significant correlation between anti-depressants and suicide attempts
 - Researchers also suggested that SSRIs may be less effective in treating hospitalized suicidal depressed patients than anti-depressants that may have effects on multiple neurotransmitters



Literature Review

- Cougnard, et al. (2008)
 - Aim of the study was to analyze whether anti-depressants decrease suicide
 - Data for the study was extracted from both published studies and databases of the French General population
 - Participants broken into 3 age groups:
 - Children and adolescents ages 10-19 years of age
 - Adults 20-64 years of age
 - Patients 65 years of age or older
 - Number of suicides either induced or avoided by anti-depressants was estimated
- 

Literature Review

- › Cougnard, et al. (2008), cont.
- › Results:
 - In the 10–19 year age group
 - Anti-depressant therapy would prevent an estimated 31.9% of suicides in depressed subjects over one year in compared to no anti-depressant therapy
 - In the 20–64 year age group
 - Anti-depressant therapy would prevent an estimated 32.2% of suicides in depressed subjects over one year in compared to no anti-depressant therapy
 - In the age group over 65 years-of-age
 - Anti-depressant therapy would prevent an estimated 32.3% of suicides in depressed subjects over one year in compared to no anti-depressant therapy

Literature Review

- › Isacson, Holmgren, and Ahlner (2005)
- › Tested the theory that traces of anti-depressants would be found commonly in suicide victims if anti-depressants did increase suicide risk
- › Toxicology reports of 14,857 suicide cases in Sweden from 1992–2000 were analyzed
- › Study also examined a control group of 26,422 who died of natural or accidental causes
- › Median age in suicide group was 49 years old vs. 55 years old in control group
- › 52 suicides in children under 15 and 326 suicides in adolescents aged 15–19 were also analyzed


Literature Review

- › Isacson, Holmgren, and Ahler (2005), cont.
- › Findings
 - Under 15 years of age:
 - 7 of 52 cases were positive for anti-depressants, although none were positive for SSRIs, vs. 4 cases among the 998 controls in this age group
 - Age 15-19
 - 13 of 326 suicide cases were positive for anti-depressants, only 6 of the 13 cases were positive for SSRIs
 - 5 cases among the 577 controls were positive for anti-depressants (3 were positive for SSRIs)
 - Overall outcome
 - Anti-depressants detected in 13% of children, 4% of adolescents, and 23% of suicide victims among all age groups


Literature Review

- › Isacson, Holmgren, and Ahlner (2009)
- › Study similar to 2005 was performed
- › Evaluated the number of anti-depressants prescribed in 1995 and 2005 to the number of suicides that occurred in 1995 and 2005
- › 16,937 suicides in Sweden between 1995-2005 were examined and compared it to a control group of 12,181 natural deaths
- › Findings:
 - Anti-depressant use increased by 46% in the suicide group while suicides decreased by 18.6%
 - In the control group, the use of anti-depressants increased by 109%
 - Anti-depressants reduced suicide risk by 43%


Literature Review

- ▶ Cortes et al. (2011)
 - ▶ Retrospective study of suicide victims 24 years-of-age or younger in Miami Dade County, Florida from 1990-2007
 - ▶ 253 cases were analyzed
 - ▶ Demographic data, suicide characteristics, psychosocial factors, and toxicology reports were reviewed
 - ▶ Demographics
 - 85% men (N=215)
 - Average age 20.3 years (standard deviation of 2.6 with a range of 11-24 years)
 - 53.4% (N=135) Hispanic; 26.9% (N=68) Caucasian; 15.4% (N=39) African American; 4.3% (N=11) of other ethnic origin
 - 87% (N=219) were single, 70% (n=177) were living w/ family
- 


Literature Review

- ▶ Cortes, et al., 2011
 - ▶ Psychiatric history
 - 91% (N=231) had undetermined family history of mental illness
 - 4% (N=9) had documented family history of at least one family member with mental illness
 - Almost 45% (N=112) of cases had a personal history of mental illness
 - 8% (N=21) of cases known to have a history of treatment for mental illness
 - 19% (N=49) had a known legal history
 - 76% (N=192) were known to have had stressors of some type in their lives
- 


Literature Review

- ▶ Cortes, et al., 2011
 - ▶ Toxicology Report
 - 90% (N=228) did not have any kind of anti-depressants present
 - 6% (N=15) were positive for SSRI, SNRI, TCCA, or other type of anti-depressant
 - 31.6% (N=80) positive for alcohol
 - 17.8% (N=45) positive for stimulants
 - 6.7% (N=17) positive for opioids
 - 1.2% (N=3) positive for hallucinogens
 - 12.3% (N=31) positive for benzodiazepines
- 


Literature Review

- ▶ Cortes et al., cont
 - ▶ Findings
 - Women and those at least 19 years of age were found to have been using antidepressants compared to men
 - 13% women were positive for presence of antidepressants compared to 4% of men
 - 90% of the sample did not have any kind of antidepressant in their system
 - No difference in detection of anti-depressants was found between Hispanic and Non-Hispanic cases
 - Alcohol was present in 31.6% of the cases
- 


Literature Review

- ▶ Leon, et al. (2004)
 - Small toxicological study of 66 suicide victims less than 18 years-of-age between 1993-1998
 - Study evaluated whether or not anti-depressants were present in serum blood samples of suicide victims
 - Victims who lived for 3 days or longer after the suicidal act were excluded as anti-depressant levels would be undetectable after that time
 - 12 were excluded as a result, leaving 54 available for serum testing
 - Age range was 10 to 17 years of age (7 were younger than 13)
 - Ethnicity was evenly divided between Hispanic, African American, and Caucasian
 - 75% were males
- 


Literature Review

- ▶ Leon, et al. (2004)
 - ▶ Findings:
 - Paroxetine was not present in any of the cases
 - Imipramine was present in two cases
 - Fluoxetine was present in two cases
 - The large majority of victims were not taking anti-depressants at the time of their death
- 

Literature Review

- ▶ Perroud, 2009
 - ▶ Examined whether emergent suicidal ideation (ESI) during antidepressant treatment could be driven by genetic factors
 - ▶ 9 genes that involved neurotrophic, serotonergic, and noradrenergic pathways were selected
 - ▶ 796 participants were treated with antidepressants and studied for genetic variances and ESI during a 12 week time frame
- 

Literature Review

- ▶ Perroud, et al., (2009), cont.
 - ▶ Inclusion criteria:
 - 18–72 years of age
 - Must have met criteria for an episode of major depression that was of at least moderate severity
 - ▶ Exclusion criteria:
 - First degree relative with a diagnosis of bipolar disorder or schizophrenia
 - Primary substance misuse
 - Primary organic disease
 - Pregnancy or lactation
 - Current treatment with an antipsychotic or mood stabilizer
 - History of hypomanic or manic episode
 - Mood incongruent psychotic symptoms
- 


Literature Review

- Perroud, et al. (2009) cont.
- Method
 - Participants were randomly assigned to either escitalopram or nortriptyline treatment groups
 - Patients that had a contraindication to one of the medications were assigned to the other medication group
- Findings
 - A larger number of males experienced suicidal ideation when taking nortriptyline if they had the A allele compared to the C allele
 - Variants in the genes encoding BDNF and its receptor (NTRK2) were associated with an increase in suicidal ideation during antidepressant treatment in subjects suffering from major depressive disorder
 - The BDNF-LCPR GT (n) polymorphism and SNP in the 3' region of NTRK2 was found to have an even stronger relation to suicidal ideation


Literature Review

- Korkeila et al., 2007
 - Analyzed the number of anti-depressants prescribed and compared it to the number of completed suicides in Finland between 1994 and 2001
 - 1994:
 - individuals prescribed anti-depressants= 140,438
 - Completed suicides=1,387
 - 2001:
 - Individuals prescribed anti-depressants=272,370
 - Completed suicides=1,204
 - Findings:
 - An increase in the number of anti-depressants prescribed was significantly associated with a decrease in suicide rates (16% in men and 14% in women)


Literature Review

- › Castelpetra, et al. (2008)
 - › Study in Italy between 1997 and 2006
 - › Looked at the number of anti-depressants prescribed compared to number of completed suicides
 - › Anti-depressant use increased from 11.9/1,000 individuals in 1997 to 56.7/1,000 individuals in 2006
 - › Suicide rates decreased from 13.8/100,000 in 1997 to 9.1/100,000 in 2006
 - › This represents a suicide risk reduction of 35% in women and 34% in men
- 

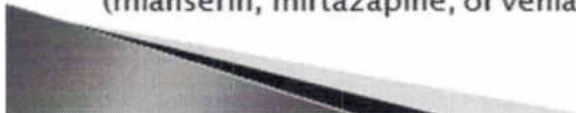
Literature Review

- › Henriksson & Isacson, (2006)
 - › Study done in Jamtland County Sweden between 1995–2002
 - › Focused on educating general practitioners to improve treatment for patients struggling with depression, but also analyzed if the program impacted the number of individuals prescribed antidepressants and how the number of antidepressant prescriptions impacted the suicide rate.
 - › Results:
 - Antidepressants increased 161% between 1995 and 2002
 - The increased use of antidepressants correlated with a decreased rate of suicide (30% in men and 47% in women)
- 


Literature Review

- ▶ Common findings among Castelpietra, et al., (2008), Korkelia et al., (2007) and Henriksson & Isacsson, (2006):
 - The majority of the anti-depressants prescribed were SSRIs
 - All three studies noted more men than women completed suicide
 - Two of the three studies noted that more women than men were taking antidepressants (Castelpietra et al., 2008; Korkelia et al., 2007)
 - Main weakness of all three studies is that they did not perform toxicological testing for presence of antidepressants in suicide victims
- 


Literature Review

- ▶ Tiihonen et al., (2006)
 - ▶ Cohort study done in Finland that included 100% of people hospitalized for suicide attempts from 1997–2003
 - ▶ Goal was to calculate the relative risk of suicide attempts/completions and overall mortality of patients being treated with antidepressants vs. no antidepressant treatment
 - ▶ Study included 15,390 patients (7,466 men and 7,924 females)
 - ▶ Antidepressants included in the study were: TCA (amitriptyline or doxepin), SSRI (fluoxetine, citalopram, paroxetine, sertraline, or fluvoxamine), and SNA (mianserin, mirtazapine, or venlafaxine)
- 


Literature Review

- ▶ Tiihonen et al., (2006)
 - ▶ Results:
 - There is an increased risk of suicide attempts with the use of anti-depressants, however, there was no increased risk of suicide completions
 - Also found that antidepressants increased mortality rate overall, particularly where cardio-vascular related deaths are concerned
- 


Literature Review

- ▶ Mann et al., (2006)
 - American College of Neuropharmacology (ACNP) formed a task force that reviewed several studies, including the meta-analysis that resulted in the FDA black box warning
 - Epidemiologic studies, RCTs, and post-mortem toxicological studies were also reviewed
- 


Literature Review

- › Mann et al., (2006)
 - › Findings
 - The FDA meta-analysis did show a small increase in suicide attempts or suicidal thinking in youths, but added that the findings of the RCTs reviewed for the meta-analysis varied
 - The ACNP noted that the variance between these RCTs could be due to a difference between medications, or it could be due to an error in measurement
 - Postmortem and cohort surveys
 - No evidence to support an increase in suicidal acts or suicide and instead found a possible beneficial effect between anti-depressants and suicidality
 - Postmortem toxicological youth studies found only a small number of youth who commit suicide are taking anti-depressants at the time of suicide
- 


Implications for Nursing

- › What can nurses do to improve patient outcomes?
 - Educate ourselves about mental illness and pass our knowledge on to both the public and other health care providers in order to increase the diagnosis and treatment of mental illness
 - Identify populations at high risk for mental illness in the community
 - Develop programs geared towards the recognition and treatment of mental illness in order to improve patient outcomes
- 

Conclusion

- ▶ Concern regarding a correlation between antidepressant use and suicidality have caused a decrease in the diagnosis and treatment of depression and has also caused some patients to be fearful of trialing antidepressants
 - ▶ The meta-analysis utilized by the FDA to implement the mandatory black box warning included no completed suicides, infrequent suicide attempts, and only found clinical significance related to a correlation between antidepressant use and suicidality when the endpoints of suicidal ideation and possible suicidal ideation were added as endpoints (Valuck, Orton, & Libby, 2009)
- 

Conclusion

- ▶ The term suicidality should be broken into terms including suicidal ideation, suicide attempt, and suicide completions because there is evidence to support that antidepressant therapy is associated with significantly lower rates of suicidal mortality compared to untreated depressed patients (Simon, 2012).
 - ▶ Confounding factors (i.e. prior history of self-harm or suicide attempts, history of psychiatric hospitalization, comorbid personality disorders or substance dependence) may increase the risk for developing suicidality, but these are not commonly accounted for in studies
 - ▶ Few studies include toxicological findings, however, post mortem toxicological studies have consistently found that few suicide victims have antidepressants in their system at the time of their death (Isacsson, Holgren, & Ahler, 2005; Cortes et al., 2011; Leon et al., 2004)
- 

Conclusion

- ▶ Genetic factors, such as decreased levels of BDNF, may also contribute to suicidal ideation in patients
- ▶ There is evidence to support that suicidality is increased in the initial four weeks following treatment, but that the risk decreases significantly after that time.
- ▶ Overall, antidepressants have been found to have a protective effect against suicide
- ▶ There is not enough evidence to definitively say that antidepressants alone cause suicidality
- ▶ Further research is needed to determine if there is any correlation between anti-depressants and suicidality
 - There is a need for further research in the areas of genetics and toxicological studies
 - particular attention should be paid to the end point of suicide completion in all studies performed

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