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Non-pharmacologic, Pharmacologic, and Combination Treatments for Depression:

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Non-pharmacologic, Pharmacologic, and Combination Treatments for Depression: A Case Report and Literature Review

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PERMISSION

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Department Nursing

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Abstract

Depression affects an estimated 350 million people worldwide and is reported to be the leading cause of disability (World Health Organization, 2012). This disease, at its worst, can be fatal by resulting in suicide. Fewer than half of those with a diagnosis of depression receive treatment for the disease. A possible consequence of this may be the one million deaths that suicide is responsible for every year (WHO, 2012). These statistics cause concern for providers and raise questions regarding which treatment options will result in the best outcomes for those suffering from depression. This report will present a case in which a patient is diagnosed with depression and declines pharmacological treatment. This case report leads into a literature review that focuses on the efficacy of non-pharmacological treatment methods, pharmacological treatment methods, and combination therapy.

Keywords: depression, non-pharmacological treatment, pharmacological treatment

Background

Regular screening for depression has become a more routine part of providing primary health care, allowing providers to identify patients who are candidates for treatment and follow up care. In America, one person dies from suicide every 12.8 minutes (Centers for Disease Control and Prevention, 2014). This devastating statistic motivates providers to contemplate which treatment method will be the most efficacious for patients with depression. According to the National Institute for Health and Clinical Excellence (2009), "approximately 20% of people with depression will respond with no treatment at all, 30% will respond to placebo and 50% will respond to an antidepressant" (p. 304). While this statistic may be thought-provoking, it does not address how non-pharmacologic approaches used alone or in conjunction with pharmacologic treatment affect outcomes in those with depression.

The case report that follows is one in which a 55-year-old male is diagnosed with depression in a primary care setting. The provider discussed the implementation of a selective serotonin reuptake inhibitor (SSRI) in combination with cognitive behavior therapy to achieve a marked decrease in symptoms of depression at his follow up appointment in four to six weeks. The patient refuted the idea of starting a medication and requested to be treated with non-pharmacological treatment only.

This leads one to think about whether using solely non-pharmacological methods can be enough to treat depression in certain patients. This literature review will focus on outcomes of depression in those who have used a variety of treatments. It will center in on any differences in outcomes of depression for those who choose to only use non-pharmacological treatments in comparison with those who use pharmacological treatments. This review will also discuss outcomes of patients who participate in combination therapy, which is defined as abiding by

prescribed antidepressants while concurrently participating in cognitive behavioral therapy or other alternative treatments.

Case Report

The patient, "M," is a 55-year-old male with a history of constipation that presented to health center with reports of increasing fatigue over the last month that has worsened this past week. He reports that the fatigue persists all day, is unrelieved by sleep, and is accompanied with a loss of appetite. He has not tried any treatments to help him sleep. He has one cup of coffee in the morning, but no other caffeine products throughout the day. He is able to fall asleep with ease and he stays asleep throughout the night without awakening. His wife sleeps with him and has not reported any snoring. His fatigue is accompanied by a generalized feeling of sadness and lack of motivation to perform his normal daily activities. "M" denies headaches, dizziness, lightheadedness, nausea, vomiting, diarrhea, hematochezia, melena, fevers, chills, night sweats, dysuria, urinary urgency, urinary frequency, numbness, tingling, vertigo, and changes in vision or hearing. "M" does not have any open wounds or sores on his skin. The patient's daily medications include a multivitamin and Metamucil for his constipation, but no other medications. He does not have any significant surgical or family history. The patient is a non-smoker who drinks one to two craft beers per week and is sexually active with his wife only. He received his influenza vaccination in October 2014 and has no known allergies.

The patient's vital signs were as follows: temperature of 98.3, respiratory rate of 20, pulse of 68 and blood pressure of 134/74. His physical exam was unremarkable. Head was normocephalic, sclera without injections, pupils equal and reactive to light, and nasal mucosa was without inflammation or rhinorrhea. Mucus membranes were pink and moist. No lymphadenopathy or thyroid nodules palpated. Cardiovascular assessment revealed regular rate

and rhythm, S1S2 auscultated, and was without murmur. No visible jugular venous distention or edema was noted. Lung sounds were clear to auscultation. Abdomen was soft, non-tender, non-distended, and bowel sounds were active in all quadrants. His abdominal exam was without palpable masses, and was without hepatosplenomegaly. "M" had a negative Murphy's and Rovsing's sign and was without CVA tenderness. Neurological assessment revealed no nystagmus and equal strength in all extremities. Active range of motion of all extremities was intact.

Differentials for this patient case included depression, hypothyroidism, anemia, and diabetes mellitus. The patient filled out a PHQ-9 while a TSH, Hgb, HgbA1C were drawn. A complete CBC and BMP were considered, but the patient did not display any signs or symptoms of infection or dehydration, so they were ruled out at this time. His total PHQ-9 score was 12, which is significant for moderate depression. The remaining labs were in normal range, which indicated a primary diagnosis of depression.

Next, the provider assessed whether the patient was safe. "M" denied suicidal ideations, nor has he ever thought of hurting himself or anyone else. The provider then explained to the patient that the best treatment option is to start a medication known as a selective serotonin reuptake inhibitor, or a SSRI, and begin psychotherapy. It was recommended that he begin a medication called escitolopram, or Lexapro, at 10 milligrams per day and to follow up with primary care provider in one month. Education regarding common side effects of SSRI's including nausea, diarrhea, and dizziness were explained, as well as the importance of not skipping doses was discussed.

"M" stated that he was not willing to try drug therapy at this time. He felt that he was just "blue" because of the winter and did "not want to take any pills." He stated he was willing to try

psychotherapy. The provider then discussed the possibility of seasonal affective disorder and that he could also try light therapy in conjunction with psychotherapy; however, he still needs to follow up in one month to see if these therapies are effective. "M" was advised that if these non-pharmacological treatments used alone are not improving his depressive symptoms upon follow up, then the addition of drug therapy would be advised. "M" agreed with this plan of care and agreed to follow up with primary care provider in one month.

Literature Review

This patient case leads into the literature review regarding which existing treatment for depression yields the most promising outcome. The outcome can be measured by a decrease in symptoms of depression as reported by the patient or a lower score on a depression scale, such as the PHQ-9 in the case report. Can a patient with depression report a decrease in their depressive symptoms after using solely non-pharmacological treatment methods? Would pharmacologic treatment of depression yield better outcomes in patients with depression than non-pharmacologic methods? Or, would a combination of both non-pharmacological and pharmacological treatments be the most efficacious?

A literature review was completed using CINAHL, Cochrane Library, and PubMed database using the search terms "depression and non-pharmacological treatment," "depression treatment," "pharmacological treatment in depression," and "depression combination therapy." Limitations of this search were set for January 2005-January 2015 and for English language only. The research includes hospitalized patients, those in long-term care, and those who live at home independently. Ages of the populations range from adolescents to the elderly. Studies that focused on non-pharmacological treatment outcomes were limited to those that only utilized non-pharmacological therapy in the population without any coexisting medication administration.

There are many non-pharmacological treatment methods for depression. Apostolo, Cardosa, Rosa, and Paul (2014) completed a randomized controlled trial on elders with depression in a long term care setting. The specific non-pharmacological method studied was cognitive stimulation therapy performed on 56 residents over seven weeks. This cognitive stimulation therapy, also known as "Making a Difference," focused on using new ideas to form associations, orientation, opinions, reminiscence, recall, and stimulating language and executive functioning. The idea behind this therapy is that a patient may be able to enhance his or her cognitive functioning, and in turn the increase in cognitive functioning will provide more joy and decrease depressive symptoms. The symptoms of depression were measured at baseline and post intervention using the geriatric depression scale. Although cognitive stimulation therapy increased the resident's cognitive functioning, there was no reported change in depressive symptoms (Apostolo et al., 2014).

One study that addressed non-pharmacological treatment of depression was a randomized controlled trial that reviewed the outcomes of patients who exclusively used one of the following: acupuncture, electro acupuncture (EA), or fluoxetine (Sun et al., 2013). Electro acupuncture is the application of a pulsating electrical current to acupuncture needles as a means of stimulating the acupoints (Dharmananda, 2002). This study used a total of 61 patients with depression. Twenty of these patients were treated with acupuncture for six weeks, while 16 of these patients were treated with EA in the same time frame. These participants received acupuncture five times a week. The other 25 patients were treated with fluoxetine 20 milligrams per day for six weeks. All subjects were evaluated by the Hamilton Depression Rating Scale at baseline, two, four, and six weeks after treatment. The participants also had serum glial cell line-derived neurotrophic factor (GDNF) measured at baseline and six weeks after the beginning of

treatment. This lab value has been shown to play a role in the pathogenesis of depressive disorder and may be a biomarker for damage to nerve cells (Sun et al., 2013). The results of this study concluded that EA and fluoxetine had similar curative effects on depressive disorder in patients. Electro acupuncture's onset was quicker, had a better response rate, and better improvement rate than fluoxetine. Fluoxetine and EA were equally effective in restoring the serum concentration of GDNF. This particular study concluded that EA treatment for depression "is as effective as a recommended dose of fluoxetine" (Sun et al., 2013, p. 733).

The next randomized controlled trial was performed on a total of 170 patients with breast cancer that had depression. This study focused on using music therapy and muscle relaxation training twice a day within 48 hours after radical mastectomy surgery. The results showed that the intervention group had significant improvement of depression and anxiety symptoms. Subsequently, they also had a shorter length of hospital stay than the control group. This study was only performed during the post-operative hospital stay, so it may have been too short of a time frame to apply the results to depression in the outpatient setting (Zhou et al., 2015).

While the previous studies of cognitive stimulation therapy, electro acupuncture, and music therapy may provide insight to adjunct therapy for depression, there were not many studies found regarding these particular interventions. A more commonly used and studied non-pharmacologic intervention for depression is cognitive behavioral therapy, or psychotherapy. This intervention has been shown in a variety of studies to be effective at relieving depressive symptoms (Howard, 2009; Melynk, 2014; Wang, 2007).

Wang, Tsai, Chou, and Chen (2007) completed a randomized controlled trial that evaluated the efficacy of cognitive behavioral therapy (CBT) on depressive symptoms and its impact on glycemic control in patients with diabetes mellitus. Cognitive behavioral therapy was

performed once a week for 60 minutes for a total of 10 weeks on 42 patients with diabetes mellitus and coexisting depression. Outcomes were measured using Beck Depression Inventory (BDI) six months following the subject's last treatment session. A BDI score equal to or less than nine was regarded as remission from depression, or a reduction of BDI score of 50% or greater was regarded as a significant improvement in depressive symptoms. This study found a statistically significant increase in depression remission rate and decrease in depressive symptoms following 10 weeks of CBT.

Similarly, Melynk, Kelly, and Lusk (2014) utilized cognitive behavioral therapy on a group of adolescents with depression. The study was only performed on 16 adolescents, but leaves room for further research in a program that may be beneficial in depression therapy. This study used a cognitive behavioral therapy approach called COPE, which stands for Creating Opportunities for Personal Empowerment. COPE is a cognitive-behavioral skills building group that was conducted by a family nurse practitioner and a psychologist in seven sessions on select high school students with depression. COPE emphasizes a triangle comprised of thinking, feeling, and behaving. This triangle explicates that how a person thinks directly correlates with how they feel and how they behave. Sessions focused on positive thinking, coping with stress, problem solving, goal setting, and dealing with emotions. Each student was given homework after each session to provide reflection on his or her emotions. The adolescents were given the Beck Youth Inventory after the intervention for evaluation which indicated that the group COPE intervention reduced depressive and anxiety symptoms while enhancing the adolescent's beliefs about their ability to cope and manage stress.

Howard, Dupont, Haselden, Lynch, and Wills (2009) addressed a cognitive behavioral approach to treating patients with depression and COPD. This intervention, known as a cognitive

behavioral breathlessness intervention, is a non-exercise based program that focuses on education regarding the understanding of COPD, associated medications, anxiety, panic, depression, activity pacing, relaxation, breathing restraining and goal settings. Data was collected on 48 patients six months before and six months after the four week intervention. The results showed significant improvements in depression following the cognitive behavioral therapy without any usage of antidepressants.

The research studies summarized above have provided insight into the efficacy of non-pharmacological treatment in depression. Some of these studies are limited by sample size or time, while others may only apply to specific age groups or persons with a specific comorbidity. Each study used various non-pharmacological methods, so while one method may decrease depressive symptoms, a different method may not be effective. Only one of the aforementioned studies reported no change in depressive symptoms following intervention, which was cognitive stimulation therapy. These studies seemingly agree that non-pharmacological treatments for depression have a positive effect on depressive symptoms, which leads into a literature review focused on pharmacological treatments and depression outcomes.

A systematic review by Leucht, Huhn, and Leucht (2012) studied the efficacy of amitriptyline versus a placebo. This review utilized randomized controlled trials comparing amitriptyline with a placebo or no treatment in patients diagnosed with major depressive disorder. There were 39 trials included with a total of 3509 participants, while length of studies fell between three and 12 weeks. Some participants who were given the placebo or no treatment withdrew from the study due to lack of symptom improvement; however, even more participants withdrew from the studies due to anticholinergic side effects of amitriptyline. The results of the outcome "were rather homogeneous, reflecting comparability of the trials" (Leucht et al., 2012,

p. 5). A majority of the studies concluded that amitriptyline is "an efficacious antidepressant drug," but also included that, "it is, however, also associated with a number of side effects" (Leucht et al., 2012, p. 5).

A systematic review completed by Yohannes and Alexpoulous (2014) examined antidepressant treatments in patients with depression and coexisting COPD. A retrospective study over a period of two years documented that patients with depression had a higher rate of COPD exacerbations, thus making this study relevant. This review gathered data from six randomized controlled trials of SSRI treatment and four randomized double-blind studies of tricyclic antidepressant (TCA) therapy. The first set of studies were designed to test the efficacy of fluoxetine. The first of these studies was an eight week randomized double-blind study using fluoxetine or a placebo on 42 elderly inpatients with coexisting depression and COPD. There was a 50% reduction in the Hamilton Depression Rating Scale when compared with baseline of those who took fluoxetine versus a 37% reduction in the placebo group. However, there was no improvement in lung function tests. The second study with fluoxetine was a single-blind which examined fluoxetine efficacy over six months in 14 patients with depression and COPD. Only seven patients ended up completing the study due to drop out from unwanted side effects. Of these patients, four displayed a 50% reduction on the Geriatric Mental State Scale. However, there were not any changes in lung function scores (Yohannes & Alexpoulous, 2014).

The next set of studies in the systematic review evaluated the effectiveness of paroxetine. The first study was a double-blind, randomized controlled trial that examined paroxetine therapy in 15 patients with COPD and depression over a 12-week span. Eight of these patients received paroxetine therapy and showed statistically significant decrease in depressive symptoms, while the placebo group did not show improvement. The next study gave 20 mg of paroxetine daily to

28 patients with depression and COPD over a period of six weeks. Although there were no differences in lung function tests, there was a statistically significant improvement in depression scores three months after the study began (Yohannes & Alexpoulous, 2014).

The final SSRI studies reported in this systematic review evaluated sertraline. In a pilot study, sertraline was only studied in six patients and did not statistically show any improvement in depressive symptoms after six weeks of treatment; however, patients did report improvement in dyspnea after treatment. The last study was a retrospective study of those with depression and COPD who were treated with sertraline. It was performed on a total of seven patients and showed significant improvement in depressive symptoms and dyspnea (Yohannes & Alexpoulous, 2014).

The next article is a review of two studies that evaluated the efficacy of two antidepressants used in patients with multiple sclerosis (MS). The first medication was the TCA desipramine which was used in 14 patients in compared to a placebo in 14 patients for five weeks. There was a trend toward a decrease in depressive symptoms; however, there were a significant number of patients that did not follow up, so the confidence intervals were wide. This did not yield statistically significant results. The other trial used paroxetine and had similar results. There were 22 participants using paroxetine versus 22 using a placebo over a 12 week period. Once again, there were a significant number of patients who did not follow up, so no statistically significant decrease in depressive symptoms was found. However, the results that were gathered did show a decrease in depressive symptoms. The paroxetine was also associated with greater adverse effects, specifically nausea and headache (Koch, Glazenborg, Uyttenboogaart, Mostert, & De Keyser, 2011).

The final article that discusses pharmacological therapy in depression is a non-blinded, randomized controlled trial using 137 participants who were given fluoxetine over a period of 36 weeks. These participants were "HIV-positive homeless and marginally housed adults, a vulnerable population with multiple barriers to adherence" (Tsai et al., 2013, p.1). Fluoxetine therapy showed a statistically significant improvement in depression symptom severity and remission. There were no statistically significant differences in secondary HIV outcomes (Tsai et al., 2013).

Many of the pharmacologic research studies indicate that antidepressant therapy causes a statistically significant decrease in depressive symptoms, but the side effects of the medications may outweigh the benefit the drug has on outcomes. In the patient case reported above, it was suggested that "M" start on escitalopram, the pure S-enantiomer of the racemic SSRI citalopram. A systematic review of randomized controlled trials completed by Cipriani et al. (2009) compared escitalopram against other antidepressants. Fourteen trials differentiated escitalopram with another SSRI, while eight studies compared escitalopram with newer antidepressant agents such as venlafaxine, bupropion, and duloxetine. The review showed there were statistically significant differences in the efficacy of escitalopram over other antidepressants, specifically other SSRI's such as citalopram and fluoxetine, as well as the serotonin-norepinephrine reuptake inhibitor duloxetine in the acute phase of treatment for depression. Escitalopram specifically performed better than citalopram in reducing depressive symptoms faster and with less side effects in six studies of nearly 2,000 patients. However, according to Cipriani et al. (2009), "there is insufficient evidence to detect a difference between escitalopram and other antidepressant classes in early response to treatment" (Cipriani et al., 2009, p. 3). Although there is insufficient evidence to prove the efficacy of escitalopram over other antidepressant classes,

one can use this information to conclude that escitalopram may yield better patient response when compared to other SSRI's (Cipriani et al., 2009).

A study by Hollon et al. (2014) reviewed antidepressant and psychotherapy used in combination therapy to treat depression. The study used 452 adult outpatients with "chronic or recurrent major depressive disorder." One group of patients was assigned antidepressant therapy alone, while the other group was assigned antidepressant treatment with cognitive behavioral therapy over varying period of time depending on when a patient met criteria for remission. Remission was defined by Hamilton Rating Scale for Depression (HRSD) scores of eight or less weekly for four consecutive weeks without relapse. HRSD scores of 16 or more indicate relapse of depression. The study also "allowed for a maximum of 19 months for remission and 42 months for recovery" (Hollon et al., 2014, p. 1159). Recovery was defined as 26 consecutive weeks after remission without relapse. There were not stipulations on the medication the patients were prescribed; however, Hollon et al. (2014) states they were prescribed "mainly venlafaxine at the outset of the study and then duloxetine as the medication began to emerge in practice" (p. 1160). Results showed that 22.6% of people dropped out, most within the acute phase. Those in combination therapy were less likely to drop out. Remission rates were high at 63.6% for those using combination therapy and were 60.3% for the antidepressant-only therapy. Fewer relapses occurred in the combination therapy group, but the result was not statistically significant. Recovery rates were higher in the combination therapy group.

Learning Points

This literature review covered several articles and studies that assessed the efficacy of non-pharmacologic, pharmacologic, and combined therapies for those suffering with depression. From that, the following learning pearls were gathered:

- Non-pharmacological interventions alone may have potential to decrease depressive symptoms without the aid of a medication. Multiple studies found that cognitive behavioral therapy helped decrease depressive symptoms and remission rates of depression. There are promising studies that suggest electro acupuncture and music therapy may help depressive symptoms without pharmacologic intervention.
- More research is needed to be done on each specific non-pharmacologic intervention. Sample sizes and length of time of studies were smaller in the non-pharmacologic treatment reviews, thus making them less reliable.
- Many pharmacologic treatments provided significant improvement for those with depression without the aid of non-pharmacologic interventions; however, these medications often caused adverse side effects. Some studies showed the adverse effects increased non-compliance with the medication.
- A systematic review of escitalopram demonstrates that escitalopram is a promising medication that performed better than other SSRI's in reducing depressive symptoms faster and with less side effects in six studies of nearly 2,000 patients.
- Patients achieved remission faster when receiving combination therapy for their depression.

Conclusion

Depression is a debilitating disease that can exist on its own or combination with other comorbidities. Many patients are resistant to treatment, with nearly 50% of those diagnosed not receiving treatment (WHO, 2012). This literature review is useful to providers who have patients who are resistant to pharmacological treatment, such as in the case report involving Mark. The above research has indicated that certain non-pharmacological methods used alone may decrease

depressive symptoms. The key to managing depression in those resistant to treatment is education and follow up. In the patient case, Mark was willing to try non-pharmacologic methods for a month and take another PHQ-9 at his follow up visit. If the non-pharmacologic methods are unsuccessful, it will be highly encouraged to add the escitalopram to his treatment regimen. It is important to note that if a patient is resistant to treatment, they may not be adherent if a medication is prescribed; therefore, non-pharmacologic methods are better than no treatment at all.

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