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Exercise in the Treatment of Depression and/or Depressive Symptoms

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PERMISSION

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Abstract

Depression is a significant issue in the United States (U.S.) that accounts for millions of outpatient visits each year (Centers for Disease Control and Prevention [CDC], 2016; National Institute of Mental Health [NIMH], 2014). Exercise as a treatment for depression and/or depressive symptoms has the potential for significant cost savings for the patient and health care system, in addition to being a low-risk intervention that also improves overall physical health. This article features a case study of an adult with depressive symptoms consistent with mild depression. A literature review that investigates the efficacy of exercise in the treatment of depression and/or depressive symptoms follows the case study. Eligibility criteria for the literature review included articles concerning aerobic exercise, resistive exercise, or physical activity in the treatment of depression or depressive symptoms in adults, whereas studies with a focus on exercise as prevention of depression were excluded.

After a review of 10 articles, including 3 meta-analyses, 4 randomized clinical trials, and 2 non-randomized controlled trials, it was found overall that exercise has a positive effect on depression and/or depressive symptoms. However, there is variance among studies regarding a recommended exercise regimen. Preferences and individual factors should be taken into consideration when prescribing exercise as an adjunct for depression or depressive symptoms. Additionally, more research is needed before conclusions can be drawn regarding exercise as a monotherapy.

Background

Depression is a significant issue in the U.S. It is estimated that in 2014 there were 15.7 million adults with an episode of depression, which is nearly 7% of the U.S. adult population (NIMH, 2014). Major depressive disorder is characterized by either depressed mood or loss of interest or pleasure, in addition to four or more other depressive symptoms for greater than two weeks (Dunphy, 2015). It accounted for an average of eight million outpatient visits between 2009 and 2010 (CDC, 2016; NIMH, 2014).

Currently, initial treatment of depression may include psychotherapy, pharmacotherapy, or a combination of the two (Sudak, 2016). The decision for the appropriate treatment modality is based on the severity of depression, the patient's preference, and the clinical picture as a whole (Sudak, 2016). Stigma, cost, and side effect profiles have all been proposed as barriers to the current treatments. Exercise, electroconvulsive therapy, St. John's Wort, and vagus nerve stimulation are additional treatment options that have been studied with lesser support (Sudak, 2016). Low-to-no cost, low-risk, improvement of quality of life, as well as improvement of overall physical health make exercise a particularly attractive treatment to explore further.

The following case report presents an adult male with depressive symptoms consistent with mild depression. After presenting options for treatment, the patient declined psychotherapy and pharmacotherapy and instead opted for exercise as his primary initial treatment modality. The case study will be followed by a literature review, which will present the latest evidence regarding exercise in the treatment of depression and/or depressive symptoms.

Case Report

History of Present Illness: A 25 year-old African-American male presents to the clinic with a chief complaint of feeling unmotivated and fatigued for the last month, which has been worsening in the last week. He reports no sleep disturbances and on average sleeps from 10:00 p.m. to 8:00 a.m. He reports he naps occasionally with minimal relief. Average caffeine intake is one cup of coffee in the morning and one cup of coffee in the afternoon, with minimal relief of fatigue. He denies fever, chills, weakness, or recent illness. He denies personal or family history of depression.

Past Medical History: The patient reports a history of hypertension, for which he was never medicated. Current medications include a multivitamin by mouth daily and Metamucil by mouth daily for constipation. He has no known allergies.

Health Maintenance: He denies a regular exercise routine. He reports 10 hours of sleep per night and feels unrested when he wakes. He reports diet is generally well balanced, but has been eating more "junk food" recently.

Family History: He denies mental health conditions, thyroid disease, or diabetes in either side of family. He reports his father has hypertension and cardiovascular disease.

Psychosocial: He lives at home with his wife and three dogs, and has no children. He reports feeling well supported by his wife. Currently, he works as a full-time mechanic. He reports one to two beers per night during the week, and no more than four drinks at a time on the weekend. He denies history of tobacco use.

Review of Systems: He reports fatigue, and feeling unrested after waking. He denies chest pain or palpitations. He reports constipation, but denies melena. He denies dysuria or hematuria. He

denies weakness or muscle aches. Denies feeling down, depressed, or hopeless to this provider in initial history.

Physical Examination: Well-groomed male with flat affect. Alert and oriented. Normocephalic. PERRLA. Oral mucosa pink and moist. Uvula midline. No cervical lymphadenopathy or thyromegaly. Regular heart rate and rhythm without murmur or rub. Clear, vesicular breath sounds bilaterally without increase in effort. Abdomen soft, nontender with tattoo noted to RUQ, bowel sounds normoactive. Gait steady.

VS: Blood pressure 134/74, Heart rate 68, Respiratory rate 20, Temperature 98.3 F

Laboratory: CBC, TSH, and BMP within normal limits, except fasting glucose 100. PHQ-9 score of 8.

Assessment: 1.) Major depressive disorder, single episode, mild (F32.0); 2.) Abnormal blood glucose (R73.09); 3.) Elevated blood pressure reading, without diagnosis of hypertension (R03.0)

Plan: The provider and patient discussed his PHQ-9 score, which is indicative of mild depression. The provider presented options for one-on-one counseling, group counseling, and/or medication, in addition to more conservative options such as exercise. The patient states he wishes to try exercise, in addition to communicating with his wife further about his mood. He states he will consider other options in the future if there is no change. The provider encouraged 30 minutes of exercise five times per week, and made recommendations for how to attain that goal. Patient was educated on his mildly abnormal blood glucose results. The benefits of exercise and dietary improvements for glycemic control were discussed. The provider advised patient to take his blood pressure once per week for the next six weeks. Follow up is planned in six weeks to discuss depression and blood pressure. The patient was agreeable to plan.

Literature Review

Current Guidelines

The purpose of this literature review is to review the evidence regarding exercise in the treatment of depression and/or depressive symptoms. As the case report demonstrated, the patient had symptoms consistent with mild depression. The patient preferred not to begin psychotherapy or anti-depressants, and instead opted for increasing exercise to combat his depressive symptoms. Current recommendations vary with regard to exercise as a primary treatment option.

First, it is essential to review the current guidelines regarding the use of exercise in the treatment of depression. The current National Guideline Clearinghouse recommendations for treatment of depression, which are based off of the American Psychiatric Association recommendations, do not include exercise as a primary treatment option (American Psychiatric Association [APA], 2010). Instead, the guideline only mentions exercise as part of overall health promotion or to treat associated weight gain (APA, 2010).

On the other hand, the Institute for Clinical Systems Improvement (ICSI, 2013) states that exercise may be a viable option for monotherapy or adjuvant therapy for moderate depression, and offers considerations when prescribing exercise as a form of treatment. The ICSI (2013) specifically recommends "a goal of 30 minutes of moderate-intensity aerobic exercise, three to five days a week… for otherwise healthy adults" (p. 42).

Additionally, authors of the current UpToDate recommendations suggest exercise only as an adjunct in the treatment of most major depression, though they state it may be reasonable as a monotherapy in mild depression with proper monitoring (Simon & Ciechanowski, 2015).

Specifically, Simon and Ciechanowski (2015), recommend three to five 45 to 60 minute long aerobic or resistance training sessions per week for at least 10 weeks.

It is evident that there is no current standard agreed upon at this time with regards to exercise in the treatment of depression. A review of the literature is necessary because of the many potential benefits of exercise in the treatment of depression and/or depressive symptoms. The following PICO question was used to guide the literature review: "What is the efficacy of exercise in the treatment of adults with depression and/or depressive symptoms?"

Search strategies

A literature search was conducted using the Harley E. French Library of Health Sciences website through the University of North Dakota as the starting point of the search. The following databases were used to conduct the search: Cumulative Index of Nursing and Allied Health Literature (CINAHL), PubMed, and Cochrane Library.

CINAHL was the initial database used. *Depression* with the subheading of *therapy* as well as *exercise* were chosen as major concepts using the CINAHL Headings smart search. The results were limited to articles pertaining to adults published in the last five years in English. Eight results were retrieved, however, none were applicable to the current review.

PubMed was searched next using the Medical Subject Headings (MeSH) with the terms *exercise* and *depressive disorder,* with the subheading *therapy.* As done in the CINAHL search, results were limited to articles pertaining to adults published in the last five years in English. Forty-eight articles were retrieved from the PubMed database. From the results, seven articles were deemed appropriate based on the title and/or abstracts available.

Cochrane Library was then searched using the Quick Search option. *Depression, therapy* and *exercise* were the search terms used in the Title, Abstract, and Keywords search. The results

were again limited to articles pertaining to adults published in the last five years in English. The search yielded 48 results, only one of which was applicable to the current literature review.

Lastly, the author reviewed the reference list from chosen articles for strong evidence, such as meta-analyses. Two additional articles were chosen in this manner. Although they were outside of the five-year limit that was set for the previous searches, they were used because of their high level of evidence.

Articles were chosen if they fit the following criteria: aerobic exercise, resistive exercise, or physical activity in the treatment of depression or depressive symptoms. Studies looking at the benefits of stretching and yoga were not included. Additionally, studies examining the possibility of exercise as prevention of depression were not included. Also, studies examining effects on Treatment-Resistant Depression were not included due to the low generalizability of that subgroup. In total, 10 articles were reviewed for the purpose of this literature search. Of the 10 articles, three were meta-analyses, four were randomized clinical trials (RCT), and two were non-randomized controlled trials.

Summary of Findings

The American Association of Critical Care Nurses (AACN) evidence-leveling system was used in the evaluation of articles due to its ease of use and clearly defined terms. Level A is considered the highest level of evidence, which includes meta-analyses and systematic reviews of controlled trials (Peterson et al., 2014). Level B is assigned to controlled studies that are consistent and well designed; they may or may not be randomized (Peterson et al., 2014). Qualitative and descriptive studies, systematic reviews composed of qualitative or descriptive studies, and "RCTs with inconsistent results" all fall into the level C evidence category (Peterson

et al. 2014, p. 60). Level D, E, and M are lower levels of evidence used to evaluate recommendations; they will not be used for the purposes of this literature review.

There were three level A articles reviewed. Cooney et al. (2013) conducted a meta-analysis that found a small to moderate effect on depression from exercise versus the control (controls varied by study). Of particular interest, their research implied that "exercise may be as effective as psychological or pharmacological treatments," however, there were not enough trials to make a strong conclusion (Cooney et al., 2013, p. 35). This suggests that exercise may be effective enough to be used as a monotherapy, although more studies are needed. Cooney et al. (2013) were unable to determine an optimal duration and/or type of exercise, and did not make any specific recommendations.

Rethorst, Wipfli, and Landers (2009) also conducted a meta-analysis, which included evidence from RCTs only. Rethorst, Wipfli, and Landers (2009) suggested exercise could have great potential in the treatment of depression. They found significantly lower depression scores in the exercise groups as compared to the control groups. Aerobic and resistance exercise were found to be equally effective interventions (Rethorst, Wipfli, and Landers, 2009). Also, it was noted that the optimal duration of exercise in people with depression was 45 to 49 minute bouts versus 20 to 29 minutes in non-depressed patients (Rethorst, Wipfli, & Landers, 2009). Like Cooney et al. (2013), Rethorst, Wipfli, and Landers (2009) found an insufficient number of studies that compared exercise as a monotherapy to psychotherapy or pharmacotherapy.

The third meta-analysis by Conn (2010) examined the effects of supervised and unsupervised exercise on depressive symptoms in healthy adults without clinical depression. Depressive symptoms were assessed using the Profile of Mood States, the Beck Depression Inventory (BDI), and the Center for Epidemiologic Studies Depression Scale. The average

duration of supervised exercise was 45 to 60 minutes compared to 30 to 60 minutes of unsupervised exercise; both groups exercised three times a week (Conn, 2010). It was found that exercise, both supervised and unsupervised, significantly decreased depressive symptoms among participants (Conn, 2010). This may be beneficial because of the potential cost savings associated with unsupervised exercise (Conn, 2010). It is possible, however, that the same results might not have occurred in patients with clinical depression.

Among the seven level B articles, five of the studies found support for exercise in the treatment of depression and/or depressive symptoms. Periera et al. (2013) studied the effects of both strength exercise and aerobic exercise in elderly women on depressive symptoms, as measured by the Geriatric Depression Scale (GDS) scores; depression was neither a criterion nor an exclusion to be in the study. Periera et al. (2013) found a statistically significant improvement in GDS scores with both strength and aerobic exercise. Unfortunately their results are less generalizable because their population was restricted to only elderly women.

Mata et al. (2011) examined the effects of exercise on positive affect and negative affect. They compared the effects of exercise in depressed individuals versus non-depressed individuals, and found that both groups reported higher positive affect after exercise (Mata et al., 2011). Interestingly, depressed individuals demonstrated higher levels of positive affect on days they exercised than their non-depressed counterparts, which implies that people who are depressed have a stronger response to the exercise (Mata et al., 2011). Their results also suggested a dose-related effect, meaning the greater the duration and/or intensity of the physical activity, the greater the improvement in positive affect (Mata et al., 2011). This is an important concept because it may help individualize exercise regimens for patients with depression or depressive symptoms.

Schuch et al. (2014) conducted an RCT that evaluated exercise as an adjunct to usual treatment on severely depressed inpatients as measured by the Hamilton Scale for Depression (HAM-D). Additionally, they studied the effects of exercise on quality of life. Their results demonstrated improvement in HAM-D scores and quality of life after two weeks of exercise (Schuch et al., 2014). Unfortunately, while improvement was noted, there were no cases of complete remission (Schuch et al., 2014). This, however, could be due to the short duration of the study, which may have limited the effect (Schuch et al., 2014).

Like Schuch et al. (2014), Kerling et al. (2015) evaluated exercise in the treatment of severely depressed inpatients. While overall exercise appeared to improve depressive symptoms, as measured by the BDI, the study lacked enough power to make an accurate conclusion regarding the efficacy of exercise on depression (Kerling et al., 2015). It should be noted that "the contrast in the study [was] not between exercise and completely sedentary" lifestyle; instead, the comparison was between moderate intensity exercise and structured low intensity group exercise, such as walking and stretching (Kerling et al., 2015, p. 5). This may have made the effect of the intervention weaker by comparison (Kerling et al., 2015).

An RCT by Danielsson, Papoulias, Petersson, Carlsson, and Waern (2014), compared the efficacy of monitored aerobic activity for 10 weeks to a single counseling session that encouraged physical activity in adults with depression. Exercise was an adjunct to antidepressant therapy in this study. Danielsson et al. (2014) found that aerobic exercise reduced depression severity based on the Montgomery Asberg Rating Scale (MADRS). They did not find any significant improvement in the group that received the single counseling session. This suggested that counseling and encouraging a person with depression to exercise is not enough to improve depression (Danielsson et al., 2014). Instead, it may be necessary to include supervised physical

activity, such as with a physical therapist or personal trainer (Danielsson et al., 2014). Their findings are in contrast to Conn's (2010) meta-analysis findings, which found both supervised and unsupervised exercise effective.

De la Cerda, Cervello, Cocca, and Viciana (2011) conducted a study that evaluated exercise as an adjunct to antidepressant therapy in adult women with moderate depression. Their intervention was group exercise such as gymnastics, dance, and walking for three days a week over eight weeks. Depressive symptoms, measured by the BDI, improved significantly in participants in the exercise group (de la Cerda et al., 2011). It was pointed out, however, that the improved symptoms may not be fully attributed to the exercise, but may have been a mixed effect from the increase in social and leisure activity (de la Cerda et al., 2011).

Finally, Krogh, Videbach, Thomsen, Gluud, and Nordentoft (2012) conducted an RCT that compared aerobic exercise to stretching exercise in adults with depression. Using the BDI to measure self-reported depressive symptoms, Krogh et al. (2012) found no effect from either group on reducing depression. There were significant limitations to this study, including early termination due to insufficient enrollment and poor attendance (Krogh et al., 2012). These factors severely limit the strength of their results (Krogh et al., 2012).

Discussion

In general, the evidence that was reviewed illustrates that exercise does have a positive effect on depression and/or depressive symptoms. However, there were a few factors that reduced the ability to define a specific recommendation. First, there was very limited research on exercise as a monotherapy. This issue was also recognized by the meta-analyses conducted by Cooney et al. (2013) and Rethorst, Wipfli, and Landers (2009). The vast majority of the articles studied exercise as an adjunct to current therapy. Further research is needed in order to

confidently recommend exercise as a monotherapy for the treatment of depression and/or depressive symptoms.

Additionally, it is difficult to determine an ideal exercise regimen due to the many variables associated with exercise. For example, the duration, type, and intensity of physical activity varied greatly from study to study. Duration ranged most often from 30 to 60 minutes three times per week in the studies. However, the meta-analysis by Rethorst, Wipfli, and Landers (2009) found that 45 to 49 minutes of exercise was the most beneficial in clinically depressed participants, whereas 20 to 29 minutes was most beneficial for reducing depressive symptoms in non-depressed participants.

The type of exercise also varied greatly among studies; for example, exercise interventions ranged from resistance training to group dance classes to walking on a treadmill. While it seems likely that different exercises might lead to different levels of efficacy, in fact, Periera et al. (2013) found that both resistance training and aerobic activity resulted in lower depressive symptoms, which corresponded with the results of the meta-analysis by Rethorst, Wipfli, and Landers (2009). This allows for more flexibility in prescribing an exercise regimen. Motivating factors and individual preferences should be taken into consideration.

Another factor that was considered when making a recommendation is that exercise interventions can be either supervised or unsupervised. Examples of supervised settings in the studies include physical activity monitored by physical therapists or instructor-led group exercise. While it is reasonable to believe that a person who is being monitored by a physical therapist may work out more intensely than a person who works out independently, the meta-analysis by Conn (2010) actually found that supervised and unsupervised activity were both effective. In considering whether to prescribe supervised or unsupervised activity, it is important

to consider the individual's preference and motivation level, in addition to the cost and availability.

Conclusion

Overall, it was found that exercise as an adjunct to current therapy has a positive effect on depression and/or depressive symptoms. Based on the current review, it is recommended that exercise be utilized as an adjunct in the treatment of depression and/or depressive symptoms. Due to the many variables associated with exercise, a specific regimen for the treatment of depression or depressive symptoms cannot be derived from the current evidence. However, it seems reasonable to recommend at least 30 minutes of moderate aerobic or resistance activity five times per week in otherwise healthy adults, as consistent with the CDC physical activity guidelines (CDC, 2015). Because there was no particular type of exercise that was found to be more effective than others at this time, the type of exercise should be based on the patient's preference. Also, both supervised and unsupervised exercise appear to be effective, therefore, this decision should be individualized to the patient. The current available evidence restricts the recommendation of exercise to adjunctive therapy only; thus, further research is needed before exercise can be recommended as a monotherapy. Exercise for depression and/or depressive symptoms has great potential to improve the well being of millions of people, and it should be utilized to a greater extent.

Learning Points

- Current guidelines vary with regard to exercise as an option for initial therapy in the treatment of depression.
- Exercise is effective at improving depression and depressive symptoms.
- Exercise should be considered in the treatment of depression and/or depressive symptoms as an adjunctive therapy.
- Unfortunately, there is not enough evidence to advise exercise as a monotherapy at this time. Further research is needed.

References

American Psychiatric Association. (2010). Practice guideline for the treatment of patients with major depressive disorder, 3rd ed. Arlington, VA: American Psychiatric Association. Retrieved from https://www.guideline.gov/content.aspx?id=24158

Centers for Disease Control and Prevention. (2016, Feb 3). *National center for health statistics: Depression.* Retrieved from http://www.cdc.gov/nchs/fastats/depression.htm

Centers for Disease Control and Prevention. (2015, June 4). *How much physical activity do adults need?* Retrieved from http://www.cdc.gov/physicalactivity/basics/adults/index.htm

Conn, V. S. (2010). Depressive symptoms outcomes of physical activity interventions: Meta analysis findings. *The Society of Behavioral Medicine, 39,* 128-238. doi: 10.1007/s12160-010-9172-x

Cooney, G. M., Dwan, K., Greig, C. A., Lawlor, D. A., Rimer, J., Waugh, F. R., … Mead, G. E. (2013). Exercise for depression. *Cochrane Database of Systematic Reviews, 9*(CD004366). doi:10.1002/14651858.CD004366.pub6

Danielsson, L., Papoulias, I., Petersson, E., Carlsson, J., & Waern, M. (2014). Exercise or basic body awareness therapy as add-on treatment for major depression: A controlled study. *Journal of Affective Disorders, 168,* 98-106. doi:10.1016/j.jad.2014.06.049

de la Cerda, P., Cervello, E., Cocca, A., & Viciana, J. (2011). Effect of an aerobic training program as complementary therapy in patients with moderate depression. *Perceptual and Motor Skills, 112*(3), 761-769. doi: 10.2466/02.15.PMS.112.3.761-769

Dunphy, L. M., Winland-Brown, J. E., Porter, B. O., & Thomas, D. J. (2015). *Primary care: The art and science of advanced practice nursing* (4th ed.). Philadelphia, PA: F. A. Davis Company

Institute for Clinical Systems Improvement. (2013). Health care guideline: Adult depression in primary care guideline. Retrieved from https://www.icsi.org/_asset/fnhdm3/Depr-Interactive0512b.pdf

Kerling, A., Tegtbur, U., Gutzlaff, E., Kuck, M., Borchert, L., Ates, Z., … Kahl, K. G. (2015). Effects of adjunctive exercise on physiological and psychological parameters in depression: A randomized pilot trial. *Journal of Affective Disorders, 177*, 1-6. doi:10.1016/j.jad.2015.01.006

Krogh, J., Videbach, P., Thomsen, C., Gluud, C., & Nordentoft, M. (2012). DEMO-II trial: Aerobic exercise versus stretching exercise in patients with major depression, a randomized clinical trial. *PLoS One, 7*(10), e48316. doi: 10.137/journal/pone.0048316

Mata, J., Thompson, R. J., Jaeggi, S. M., Buschkuehl, M., Jonides, J., & Gotlib, I. H. (2011). Walk on the bright side: Physical activity and affect in Major Depressive Disorder. *Journal of Abnormal Psychology*, *121*(2), 297-308. doi:10.1037/a0023533

National Institute of Mental Health. (2014). Major depression among adults. Retrieved from http://www.nimh.nih.gov/health/statistics/prevalence/major-depression-among-adults.shtml

Pereira, D. S., de Queiroz, B. Z., Miranda, A. S., Rocha, N. P., Felicio, D. C., Mateo, E., … Maximo Pereira, L. S. (2013). Effects of physical exercise on plasma levels of brain derived neurotrophic factor and depressive symptoms in elderly women: A randomized clinical trial. *Archives of Physical Medicine and Rehabilitation, 94*(8), 1443-1450.

Peterson, M. H., Barnason, S., Donnelly, B., Hill, K., Miley, H, Riggs, L, & Whiteman, K. (2014). Choosing the best evidence to guide clinical practice: Application of AACN levels of evidence. *Critical Care Nurse, 34*(2), 58-68. doi:10.4037/ccn2014411

Rethorst, C. D., Wipfli, B. M., & Landers, D. M. (2009). The antidepressive effects of exercise: A meta-analysis of randomized trials. *Sports Medicine, 39*(6), 491-511. doi: 0112-1642/09/0006-0491

Schuch, F. B., Vasconcelos-Moreno, M. P., Borowsky, C., Zimmermann, A. B., Rocha, N. S., & Fleck, M. P. (2014). Exercise and severe major depression: Effect on symptom severity and quality of life at discharge in an inpatient cohort. *Journal of Psychiatric Research, 61*, 25-32 doi: 10.1016/j.jpsychires.2014.11.005

Simon, G., & Ciechanowski, P. (2015). Unipolar major depression in adults: Choosing initial treatment. In Roy-Byrne, P. P. (Ed.), *UpToDate*. Waltham, M.A.: UpToDate. Retrieved from www.uptodate.com

Sudak, D. (2012). *First consult: Depression in adults*. Retrieved from https://www clinicalkey-com.ezproxy.undmedlibrary.org/#!/content/medical_topic/21-s2.0 1011026