REVIEW ARTICLE

Rehabilitative and habilitative perspectives of exercise in treating major depressive disorder

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Abstract

Background: Major depressive disorder (MDD) is a most frequently occurred neuropsychiatric condition. About 25% of the female and 12% of the male in the population suffer from MDD at least one time in their lifetime. The treatment with currently available antidepressants are mostly effectively. Among other benefits to the health, exercise has been found to have therapeutic effect on improving MDD, and preventing from a new-onset MDD. But those benefits are often overlooked by psychiatrists, non-psychiatrist physicians, physical therapists, speech therapists, and occupational therapists.

Methods: Besides my lifetime experiences of living my life, receiving training, teaching, and practicing psychiatry, I also collected information from published papers pertinent to beneficial issue related to exercise for patients with MDD in this review.

Results: In this review, I have highlighted some important information that exercise helps in improving patients with MDD, and in preventing a new onset episode of MDD.

Discussion: To keep the readership for rehabilitation therapists to be in mind, the author discusses the issue of exercise in the rehabilitative and habilitative perspectives in MDD treatment and prevention of future occurrence of MDD. Therefore, I also recommend that all patients with MDD are encouraged to start with a lifestyle of more physical activities and routine exercise.

Key words: *brain-derived neurotrophic factors, antidepressants, physical activity, change of lifestyles*

INTRODUCTION

In a 2016 comprehensive review "antidepressant therapy" (Shen, 2016) published in *Aino Journal* (Osaka), the author of that article covered the topic with sections —— diagnosis of major depressive disorder, history of antidepressant development, monoamine hypothesis of depression, functional classification of antidepressants, remission as a goal in antidepressant therapy, maximalization in antidepresasant therapy, potentiations in antidepressant therapy, antidepressants as versatile drugs, and drug lag for antidepressants in Japan. Under the section "potentiations in antidepressant therapy," I gave three headings —— regular and adequate exercise, add-on treatment (augmentation therapy), and management of treatment-refractory depression.

In the heading "regular and adequate exercise," I used only 227 words to describe the importance of exercise. The text of the heading ends with "In my opinion, a psychiatrist is liable for malpractice if he/she just prescribes antidepressants to the depressed patients without instructing them to do regular exercise. The depressed patients should continue the habit of regular exercise to help reduce the chance of relapse or recurrence of depression even after antidepressant therapy is discontinued."

With those powerful messages in mind, I am writing the current review which is intended to amplify the main theme of "antidepressant therapy." For this inauguration issue of *Cognition and Rehabilitation*, I am adding some extra text to update important messages to carry the issues of under-diagnosis and under-treatment in previous antidepressant therapy. Then, the rest of the article is more descriptions of exercise in the context of treatment and prevention of major depressive disorder (MDD). To better amplify my ideas, I am using the format with a "case vignette" to demonstrate my message.

MAJOR DEPRESSIVE DISORDER IS A COMMONLY SEEN NEUROPSYCHIATRIC CONDITION

Major depressive disorder is often under -diagnosed

As listed in the 2016 article (Shen, 2016), Soseki Natsume (1867-1916), a writer at Meiji Era; Kanoko Okamoto (1889-1939), writer and poet; Akira Kurosawa (1910-1990), a film director; Jiro Tamiya (1935-1978), an actor; Akiko Koyama (1935-), a film actress; Nana Kinomi (1946-), an actress and singer; as well as Anna Ogino (1956-), a writer and novelist were or are those well-known Japanese celebrities who had or have depression. At this final stage of writing this manuscript, we just heard a suspected suicidal tragedy of Yuko Takeuchi who was a Japanese award-winning actress and best known for *Miss Sherlock* and *Ring*, died of age 40 years (www.ew.com/movies/yuko-takeuchi-miss-sherlock-actress-dies/).

In spite of their outstanding performance in their lives, those celebrities with MDD are not easily detected by themselves or by the family in Eastern Asia even nowadays. As stated in my previous article (Shen, 2016), the lifetime prevalence of MDD in the communities in Taiwan was 1.14% in 1980s (Hwu, 1996), and 1.20% in 2000s (Liao, 2012) based on questionnaire of *the Diagnostic and Statistical Systems* (American Psychiatric Association (APA), 1980; APA, 1987).

In similar Japanese epidemiologic studies of community study, the prevalence of depression according to *DSM-IV* criteria (APA, 1994) was 3% - 7% for lifetime in Japan (Kawakami 2007). In a nationwide, cross-sectional on-line survey on 500 Japanese patients with rheumatoid arthritis, Sruamsiri et al. with the Patient Health Questionnaire (PHQ-9) intended to measure the presence and severity of depressive symptoms (Sruamsiri, 2017). The investigators found that 35% of the patients with rheumatoid arthritis suffer from depression, but that only 5% of the study population have been officially diagnosed with depression. But the reference number for the lifetime prevalence for MDD in the United States of America was 17.1% in National Comorbidity Survey (Blazer, 1994) in the USA. One explanation of the under-reporting of depression might be related to Asian cultural factors (Sruamsiri, 2017). People in Asian societies are reluctant to speak openly about depression due to the stigma attached to it and the need to maintain perceived strength of character (Margaretten, 2009).

With *the DSM* diagnostic system, we need to take cultural factors carefully into considerations (APA, 2013). For example, “How are you?” and “How do you do” are used in greetings in the US and United Kingdom, respectively. Contrariwise, Taiwanese greet the friends, “Have had your meal?” The feeling of a person has been inhibited in Japanese culture too as Soseki Natsume used “The moon is beautiful tonight” as a substitute for “I love you” in translating an English novel into the Japanese (Fukada, 2018; Lee, 2018).

Furthermore, “diminished ability to think or concentrate, or indeciveness, nearly every day, (either by subjective account or as observed by others),” the eighth symptom in MDD diagnostic criteria of *the DSM-5* (APA, 2013) is often exaggerated in the elder adults in Taiwan. See case vignette 1 for illustration. This patient might have been a case of “pseudodementia” (Kiloh, 1961; APA, 2010; Shen, 2011).

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Case vignette 1

An 84 year-old Taiwanese pro-bono volunteer *enka* teacher is a retired civil engineer who teaches a singing class 8: 30 - 9: 30 a.m. Saturdays under a roofed pavilion inside Taan Forest Park, in Taipei. This *enka* class has been going go without interruption Saturdays in the past 14 years.

One day in January 2020, a 94 year-old Taiwanese lady and her 66-year son came together sitting in the empty seats of the pavilion for the *enka* class. The mother started to learn an updated new *enka* by reading the printed handout for the class. The teacher was surprised with her ability to read Japanese *kana*, and started to lead the class to sing “*Momotaro San No Uta*” and “*Ginza Kankan Musume*” (by Hideko Takamine in 1949). The mother participated in singing actively and loudly.

At the end of the class, the son explained that her mother just had had spent one year at a local nursing home as a case of dementic resident. He just checked her out of the institution to let her adjust her life for the society. I commented “you mother does not have obvious symptoms of dementia, she needs to see a psychiatrist for a possible antidepressant treatment.

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Major depressive disorder is often under-treated

In a recent survey on 51, 547 respondents, Thornicroft et al. in 2017 reported that only 4.6% met 12-month criteria for *DSM-IV* MDD (APA, 1994) and of those 56.7% reported needing treatment, and that among those who recognized their need for treatment, most (71.1%) made at least one visit to

a service provider. Furthermore, among those who received treatment, only 41.0% received treatment that met a minimal standard, and only 16.5% of all individuals with 12-month MDD receiving minimally adequate treatment. The investigators further concluded that only a minority of participants with MDD received minimally adequate treatment: 1 in 5 people in high-income and 1 in 27 in low- or lower-middle-income countries (Thornicofy, 2017).

In a recent case report in *the Jinmeikai Journal of Psychiatry* (Kobe), Aoki et al. in 2020 described vividly that their 67 year-old Japanese male inpatient with MDD and/or GAD wasted about 40 days (from day 1 to day 40) under the treatment of up to 40 mg/day of paroxetine (a selective serotonin reuptake inhibitor, SSRI) without any observable improvement (Aoki, 2020; Shen, 2020). But their patient showed remarkable improvement in eight days (from day 41 to day 49) under 75 mg/day of venlafaxine (a serotonin and norepinephrine reuptake inhibitor, SNRI) and later achieved significant improvement with ability of being discharged under the final dosage of 150 mg/day of venlafaxine (from day 55 to day 85). Based on the findings of this case report and information published in the literature (Lopez-Ibor, 1998; Thase, 2001, 2007, 2010; Kennedy, 2016; Cipriani, 2018; Shen, 2020), I would like to suggest that Japanese clinicians simply just prescribe only "dual action antidepressants" (Figure 1) to for every next MDD and/or GAD patient (Shen, 2020). In this kind of practice, I believe that the next patient can have better chances of achieving remission from MDD and /or GAD.

Beside the right diagnoses and drugs, the adequate dosages of antidepressants are always required (Shen, 2016). In prescribing SNRIs, we need to remember the minimal defined daily doses — 100 mg (two pills of a 50-mg pill) per day for milnacipran, 60 mg (two capsules of a 30-mg capsule) per day for duloxetine, and 150 mg (two capsules of a 75-mg capsule) for venlafaxine. For prescribing mirtazapine, we need to prescribe it at least 30 mg (1 table) per day as the final treatment dose. Do not worry about the possible side effect of constipation caused by a dual antidepressant. The managements of constipation include (Shen, 2011) adequate water intake (2,000 mL per day), walking (at least 20 minutes per day), as well as vegetables and fruits, especially plum or prune (*ume, toramu, or sanzashi*) .

In case a patient cannot achieve a minimal defined daily dose of either an SNRI or mirtazapine, the clinician should not hesitate to shift the medication to alternative kind in other kind of medication class. For example, clinicians should not hesitate to give up mirtazapine therapy if the patient cannot move up the dose of mirtazapine to 30 mg/day in one month or by the third clinic visit which comes sooner. Vice versa, an SNRI should be given up without any hesitation if the patient cannot move up the dose of two capsules or tables per day of any of

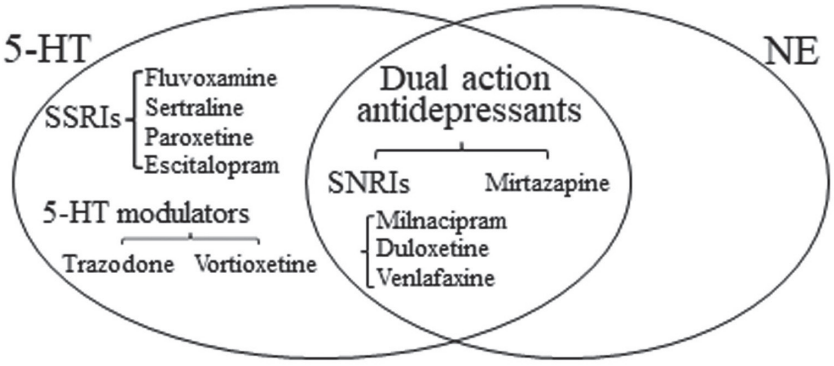

Figure 1. Currently available post-tricyclic antidepressants in Japan.
5-HT, 5-hydroxyl-trptaphant, serotonin
NE, norepinephrine
SSRIs, selective serotonin reuptake inhibitors
SNRIs, serotonin and norepinephrine reuptake inhibitors
Modified from a figure published in *Aino Journal* (Shen, 2016) and a table in *Jinmeikai Journal of Psychiatry* (Shen, 2020)
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those three SNRIs in one month or by the third clinic visit which comes sooner.

Mechanism: neurobiological basis of major depressive disorder and antidepressant treatment

Through a guanine nucleotide-binding proteins receptor (Shen, 2011; Drazinic, 2017), an antidepressant with serotonin (5-HT) action interacts with postsynaptic 5-HT receptor (first messenger protein). Due to the coupling effect with stimulating G-protein, adenylate cyclase (the second messenger protein) activates cyclic adenosine monophosphate, resulting in producing increased protein kinase A (the third messenger). Finally, cAMP-regulating element binding (CREB, the fourth messenger protein) inside the nucleus activates brain-derived neurotophic factors (BDNF, the fifth messenger protein). (To note, BDNF has been a hot topic in various laboratories, including the one of Masatoshi Takeda at Osaka University (e. g., Yamamori, 2013; Hashimoto, 2015).

On the other hand, an antidepressant with norepinephrine (NE) action (Shen, 2011; Drazinic 2017) interacts with post synaptic NE receptor (first messenger protein). Due to the coupling effecting with inhibitory G-protein, adenylate cyclase (the second messenger protein) becomes less inhibited. Therefore, more Ca^{++} -dependent kinase (the third messenger) is produced. Inside the nucleus, CREB is increased (the fourth messenger protein) to activate BDNF (the expression of the fifth messenger protein).

Due to the differences in the second messenger proteins between stimulating and inhibitory G protein in 5-HT and NE receptors, respectively, the decreased 5-HT and increased NE levels of the brain before the antidepressant treatment can be corrected into similar final result of increased BDNF levels inside the nuclei of the neurons after the neurotransmission through in the G protein receptors of the brain (Shen, 2011; Drazinic 2017). Consequently, those newly produced BDNFs can nourish their own neurons, the surrounding neurons, and possibly surrounding glia cells (Cotman, 2002).

In a laboratory rat study, only chronic use of antidepressant or electroconvulsive seizure (ECS) treatment can increase the levels of trkB mRNA or BDNF mRNA expression in the hippocampus and the frontal lobe, respectively (Nibuya, 1995). But the findings have not been found when the animals received chronic use of non-antidepressant drugs such as morphine, cocaine, haloperidol, or normal saline. In addition, chronic use of antidepressants or ECS showed that the down-regulation of BDNF mRNA in the hippocampus is completely blocked in response to stress due to restraint. Based on the study results, the investigators concluded that increased induction and prolonged expression of BDNF in response to chronic use antidepressant and ECS treatment can improve neuronal survival, and protect neurons from the damage of stress (Nibuya, 1995).

The increased BDNF mRNA expression of the brain especially in hippocampus, is involved in the growth, survival, differentiation, and repair of neurons (Lewin, 1996), and is found to be associated with improvement of depression (Thompson, 2011) and anxiety symptoms (Allgulander, 2001; Shen, 2016) through the process of improved neurogenesis and improved neuronal plasticity (Cotman, 2002; Duman, 2005).

EXERCISE HAS TREATMENT BENEFIT FOR MAJOR DEPRESSIVE DISORDER

Clinical evidence of improved MDD through exercise

In a 2009 literature review, Deslandes et al. listed four published papers showing that exercise improves patients with MDD symptoms (Singh, 1997, 2001, 2005; Mather, 2002) as compared to controls without exercise. They also listed four papers showing that in sertraline-medicated MDD patients, exercise improves more MDD symptoms (Blumenthal, 1999, 2007; Babyak, 2000; Herman 2002) as compared to those medicated controls without exercise.

In a 2014 mini-review for the *JAMA* clinical evidence synopsis, Cooney et al. reviewed 39 trials that fulfilled inclusion criteria, 37 trials provided data for meta-analysis; 35 trials (1,356 study participants) compared exercise with no treatment. The investigators concluded with a bottom line statement that exercise is linked to greater decrease in patients with depressive symptoms compared to those with no treatment, placebo, or active control treatments (such as relaxation, mediation), but that analysis of high quality studies alone suggests only small difference of benefit (Cooney, 2014).

In a 2016 updated review in 2016 with a meta-anal-

ysis, Kvam et al. included 23 full text articles with 977 study participants, and 7 of them had follow-up data. The investigators found:

1) that physical exercise has a moderate to large significant effect on depression compared to control conditions (g = -0.68), but the effect is small and not significant at follow-up (g = -0.22);
2) that exercise compared to no treatment yields a large and significant effect size (g = -1.24), and that exercise has a moderate and significant effect compared to usual care (g = -0.48);
3) that the difference is small and not significant (g = -0.22 and g = -0.08) when compared to psychotherapy or antidepressant; and
4) that exercise as an adjunct to antidepressant medication yields a moderate effect (g = -0.50) that trends toward significance (Kvam, 2016).

Based on that study data, antidepressant medications and exercise have similar efficacy in antidepressant effect.

Clinical evidence of preventing new onset MDD through exercise

Recent literature has shown that higher physical activity levels and exercise can protect incident depression, and that exercise has shown efficacy in reducing symptoms for people with depression (Schuch, 2019). The investigators suggested that some people may benefit more from exercise, and identifying these potential predictors of response is necessary to deal with patients' and professionals' expectations, and that dropout from exercise interventions is comparable to dropout from other treatments for depression and is similar to dropout from exercise in other clinical populations.

Based on a healthy cohort of 33,908 adults, chosen on the basis of having no mental and physical health conditions, Harvey et al. in 2018 in Norway did a prospective cohort study with a 11-year follow-up, and collected validated measures of exercise, depression, anxiety, and a range of potential confounding and mediating factors before and after this 11-year study. The investigators found that taking regular leisure-time exercise is associated with reduced incidence of future onset of depression but not anxiety, and that one identified protective factor is low-level exercise regardless of exercise intensity. After adjusting for confounders, the investigators found that 12% of future new cases of depression would have been prevented if all participants had engaged in at least a one-hour physical activity per week. They concluded that regular leisure-time exercise of any intensity provides protection against future depression but not anxiety, and that relatively modest changes in population levels of exercise may have important public mental health benefits in preventing a substantial number of new cases of depression. The investigators suggested that physical exercise has potential to be an effective treatment for depression, and that exercise can be a reliable adjunct treatment in combination with antidepressants (Harvey, 2018).

Japanese celebrities —— Hiroshi Itsuki, an *enka* singer and Yuki Amaumi, an actress —— have well-known reputation for their consistent habit of exercise. I would like to ask an oncological question: What would happen to Yuko Takeuchi's mortality outcome if she had the lifestyle of regular exercise?

Exercise can increase the level of brain-derived neurotrophic factor in existing antidepressant treatment

In a 2002 review in *Trends in Neurosciences*, Cotman and Berchtold have outlined four things —— antipressants, exercise, hormone adjustment (decreased cortisone and/or increased estrogen), and insulin-like growth factor (IGF) 1 —— to improve depressive symptoms. The investigators reported that voluntary exercise can increase levels of BDNF and other growth factors, stimulate neurogenesis, increase resistance to brain insult, as well as improve learning and mental performance (Cotman, 2002).

In another 2007 review in the same journal, Cotman et al. have advanced a key mechanism mediating those broad benefits of exercise on the brain through inducing central and peripheral growth factors and growth factor cascades, resulting in causing downstream structural and functional changes. The investigators described that exercise reduces peripheral risk factors such as diabetes, hypertension and cardiovascular disease, converging to cause brain dysfunction and neurodegeneration. They have also proposed the hypothesis of "inflammation mechanism" (Kiecolt-Glaser, 2015) to explains the central and peripheral effects of exercise, indicating that inflammation can impair growth factor signaling both systemically and in the brain, and that exercise ensures successful brain function through regulating growth factors and reducing peripheral and central risk factors, (Cotman, 2007).

As depicted in two figures printed in the article written by Cotman et al. (2017), exercise can:

1) counteract "inflammation";
2) improve metabolic syndrome, hypertension, insulin resistance, age-related cognitive decline, neurodegeneration, and neurotrophin resistance;
3) facilitate growth factor induction and signaling cascades through improving the passage through the blood brain barrier.

After the permeability of the blood-brain barrier is improved, IGF-1 and vascular endothelia growth factor (VEGF) can easily enter the brain, producing cell proliferation, neuronal differentiation, endothelial cell proliferation, and increased vessel size/branching. Finally, the expressed levels of BDNP and other growth factors are increased, promoting brain health to improve depression, cognition, plasticity, neurogenesis, and vascular function (Cotman, 2007).

In a nutshell, exercise has exactly effect from the antidepressant treatment, to increase the levels of BDNF expression and neurogenesis in various brain regions, which have been best-studied in the hippocampus (Duman, 2005; Cotman, 2007).

REHABITATIVE AND HABITATIVE PERSPECTIVES OF PHYSICAL ACTIVITY AND EXERCISE IN TREATING PATIENTS WITH MAJOR DEPRESSIVE DISORDER

From moving around, increasing physical activity, and exercising

Differing from plants, animals have the ability to move. Human being can move around to effectively interact with the external environment, depending on one's capacity for physical activity. Not just a convenience, movement is a fundamental human evolutionary development which is not less important than the complexities of intellect and emotion (McArdle, 2016).

In studying the benefit of dancing for depression, Akandere and Demir in 2011 enrolled 120 healthy male and female conservatory students with age of 20-24 years, and randomly assigned 60 students to dance training group and the rest of remaining 60 counterparts to the control group. With Beck Depression Inventory (Lu, 2002) score as pre- and post-test measurements, the investigators found that the group with a 12-week dance training improve in BD-I rating score compared to the control group without dance training (Akandere, 2011).

In a cohort study evaluating incident depression in 49 prospective studies with 266,939 subjects with follow-ups in Asia, Europe, North America, and Oceania, Schuch et al. in 2018 found that compared to people with high level physical activity, those with low level of physical activity have higher risk of developing increased incidence of positive screen for depressive symptoms (adjusted odds ratio = 0.84, 95% confidence interval (CI) = 0.79 - 0.89) or major depression diagnosis (adjusted odds ratio = 0.86, 95% CI = 0.75 - 0.98). The study results have been consistent for unadjusted odds ratios and for adjusted and unadjusted relative risks/hazard ratios. The investigators concluded that physical activity can confer protection against the emergence of depression regardless of age and geographical region (Schuch, 2018).

Exercise has been well-recognized to have benefit in people with various physical conditions such as obesity, diabetes mellitus, ageing, cardiovascular diseases, post-stroke recovery, etc. (Stocchi, 2007). The internists and geriatric physicians routinely recommend those patients to increase physical activity and exercise. But physical activity and exercise for improving MDD has not been well-accepted for routine treatment or adjunctive intervention for those MDD patients (Kvam, 2016), although the benefits from exercise for improvement and prevention of cognitive impairment have been suggested (Takeda, 2015).

To motivate a beginner to exercise

To motivate the individuals to start the physical rehabilitation is challenging. In a recent movie (Shinohara, 2019), the grand-mother is depicted to motivate herself to envision her ability to walk and give away grand-daughter in a coming wedding. The physical rehabilitation therapists can be inspired through this movie to encourage their patients to achieve a successful rehabilitation, and even in an exercise program.

"All the beginning is difficult. (Aller Anfang ist schwer.)" says a German proverb. The therapists (including physical therapists, occupational therapists, and speech therapists) need more work to motivate those patients who have never learned to exercise before. In this case, the word "habilitation" (Figure 2) instead of "rehabilitation" is more appro-

priate because the patients have not received any training in the first place before receiving a rehabilitation.

Luckily, endorphin is released from the body after a decent intensity of exercise. As shown in Figure 3 (Shen, 2018), endorphin is an endogenous ligand in a G protein-coupled opioid receptor, which can stimulate μ, κ, or δ opioid receptors after being stimulated by an intake of a dose of opiate or synthesized opioid drugs (e.g. heroine, morphine, oxycordone, etc.). The persons can get the same euphoric feeling after doing an aerobic exercise (Mimasa, 1996) or playing *pachingo* (Shinohara, 1999) without actually taking any opiate at all. Exercise can reward a person to do more exercise; the more a person exercises, the more he/she likes to continue the exercise. As we are aware, most marathon runners keep participating in marathon events from one city to the other city, from one country to the other country.

Besides the above-noted biological motivation from endorphin, some other motives for older adults to participate in exercise (Chodzko-Jajko, 2014) include maintaining or improving fitness and health, enjoying the activity, releasing tension, improving joint mobility, improving appearance, and enjoying the company with new friends or old acquaintants (Kolt, 2004; Whitbourne, 2008). In a 2020 survey on mental health lifestyle choices among Taiwanese, Li et al. published a report in *the Taiwanese Journal of Psychiatry* (Taipei), finding that exercise and contact with the nature are considered moderate difficult mental health lifestyle choices while the most easy ones are relaxation and stress management, and the most difficult one is to do volunteer work. Therefore, we need to mobilize the lay public to have the habit of exercise. Hopefully, the patients with MDD can easily find a reason to do and to stay on exercise.

The actual practice of exercise

In a 2018 case study article published in *the American Journal of Psychiatry*, Noordsy et. al. specifically recommend some guidelines for prescribing exercise to psychiatric patients. I just paraphrase some important points from their suggestions (Noordsy, 2018):

1) to consider current physical capacity and titrate to target and to choose:
   - to have 30-60 minutes of exercise, 3-7 days per week
   - to have up to 180 minutes of exercise per week, the more the better
   - to have a mix of strength training and aerobic exercise
2) to suggest that patients' exercise intensity 60% to 85% of maximum heart rate (220 minus age in years)
   - Moderate intensity may be better for those with anxiety disorder.
   - Higher intensity has greater benefits in other dis-

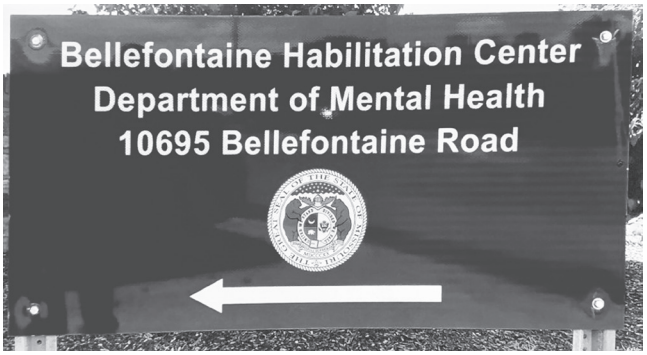

Figure 2. A road sign of Bellefontaine Habilitation Center
Bellefontaine Habilitation Center in Saint Louis is a training facility under Missouri Department of Mental Health for children with the mentally ill. Its original name was Bellefontaine Rehabilitation Center. But the name was challenged by some state representatives who believed that most children did not get the needed trainings in the first place. Therefore, the term "habilitation" has been used under a majority of voting at the Missouri House of Representatives. Photo courtesy of Kevin W. Shen, 2020.

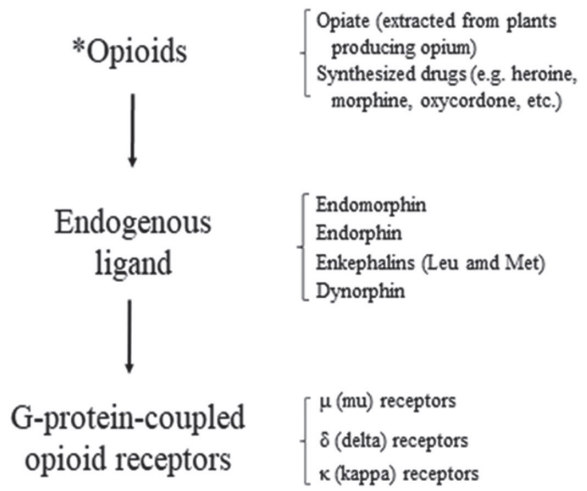

Figure 3. Endorphin is one of the ligands in G-protein-coupled opioid receptor. Endorphin can be produced from exercise to act on opioid receptor of the brain, Reproduction with permission from a review (Shen, 2018) published in *Neuropsychophamacogy Reports.*

orders.
3) to let the patient choose the activity
4) to consider of access, cost, familiarity, enjoyment of the facility
5) to consider preference for variation versus repetition.

Previously, only aerobic exercise, but not muscle-strength training, has been considered to have beneficial effect on depression and other psychiatric diseases of the brain (Goekint, 2010; Shen, 2016). But now such a distinguishing difference is not more existing, and the only thing counts is the intensity of the exercise regardless in aerobic exercise or muscle-strength training.

To exercise in the gymnasia usually starts with walking or running on the treadmill or elliptical machine, spinning (cycling) for 20 - 30 minutes. Or joining group sessions of exercise is also a good option to start. Then, the individuals can do muscle-strength training for another 30 minutes. Considering for more effectiveness and time-saving, we usually choose the machines for big muscle groups of lower extremities —— such as seated leg press for training Glutei maximi and Quadriceps, etc. We use a leg curl machine in seated or supine lying position to load the muscles in the back or posterior of the uppe leg, primarily for training hamstrings (Semimembranosus, Semitendinosus, and Biceps femoris). With the leg extension machine, we can straighten our leg against resistance and thus works the muscles on the front or anterior of the leg, i.e., Quadriceps.

We can also do chest press machines, focusing on our Pectorals, Deltoid anterior, and Triceps, etc. Strength and power of those muscles in the upper body help us with daily activities such as pushing heavy doors, strollers, etc. The rowing machines use the principles of rowing crew on a boat and apply them in an indoor equipment without water. The rowing movements help train muscles of Deltoid posterior, Latissimus dorsi, Biceps brachii, Trapezius, Rhomboids, etc.

Of course, a skillful athlete can do all kinds of muscle-strength training with free-weights. For older adults, neuromuscular trainings for improving proprioceptive function and balancing are recommended. To get a professional trainer to supervise the exercise is highly recommended to use correct position and movement, avoiding getting injuries from exercise.

We can jog or do fast walking outdoors. Simple machines for muscle-strength training are popularly available in the parks or on school campuses. *Yoga* and *tachi* can also help (Takeda, 2015). Of course, paying proper attention to adequate rest, water and nutrition is also advised.

CONCLUSION

In this review, I have reviewed the benefits of exercise in the treatment and prevention of MDD. The evidence of the benefit is convincing. Therefore, I am urging occupational, physical, or speech therapists to be more aware of identifying patients with MDD, to refer them to psychiatrists for antidepressant therapy. I also suggest that all patients with MDD are encouraged to start with a lifestyle of more physical activities and routine exercise, for the benefit of not only MDD, but also for their lives.

ACKNOWLEDGEMENTS

This article is dedicated to Zoe 11 years, Mila 9 years, and Vesper 7 years of age —— my lovely three grand-daughters. They are always actively participating in gymnastic training, swimming, and ice-skating. Their enthusiasm and endurance in long-hour devotion to sports without any complaints have been inspiring me to write this review.

Professor Masatoshi Takeda gave valuable comments on a previous version of this manuscript. Yukako Nagakami and Nozomu Oya helped with some information about antidepressants in Japan.

The clinician readers are advised to consult package insert, especially for the indications and dosages of antidepressants before prescribing them to the patients. Some prescriptions can be off-label uses according to Pharmaceutical and Medical Devise Agency in Japan. Table 1 lists chemical names and trade names of all antidepressants which are currently available on the market in Japan.

FUNDING

None.

Table 1. Updated new antidepressants with chemical and trade names available in Japan

SSRIs
Fluvoxamine (Luvox®, Depromel®)
Sertraline (J Zoloft®)
Paroxetine (Paxil®)
Escitalopram (Lexapro®)
Serotonin modulators
Vortioxetine (Trintellix®)
Trazodone (Desyrel®, Reslin®)
Dual action antidepressants
SNRIs
Milnacipram (Toledomin®)
Duloxetine (Cymbalta®)
Venlafaxine (Effexor®)
NaSSA
Mirtazapine (Remeron®, Reflex®)

SSRIs, selective serotonin reupatake inhibitors;
SNRIs, serotonin and norepinephrine reuptake inhibitors;
NaSSA, noradrenergic and specific serotonergic antagonist antidepressant.
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