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Creatine and Resistance Training for Older Adults

By Dónal P. O'Mathúna

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CREATINE REMAINS ONE OF THE MOST POPULAR SUPPLEMENTS for athletes, especially those lifting weights.[1] Much evidence supports claims that creatine enhances power output during short maximal bursts of exercise, such as power lifting or sprinting.[2] The benefit is noted particularly when the bursts are repeated intermittently in what is called interval training.

Building muscle strength and endurance is important in other arenas. Aging is associated with reduced muscle mass and strength, which can lead to functional impairment and reduced quality of life. Sarcopenia refers to the condition when fat-free mass is more than 2 standard deviations below normal.[3] Numerous studies have demonstrated that resistance exercise counteracts sarcopenia, leading to investigation of complementary strategies to supplement those gains.

Because of encouraging results in athletes who were supplementing with creatine while resistance training, suggestions have been made that non-athletes might benefit similarly. Creatine supplementation could be beneficial if it hastened strength gains or reduced the number of repetitions necessary to get desired improvements after injuries.[4] Resistance training is also suggested for age- and disease-related loss of muscle mass, strength, and function.[5] Such exercise, along with supplementation, might be preferable to exercise alone, or other invasive or pharmacological alternatives. This article will review the evidence available to date regarding creatine supplementation for those who are recommended resistance training for age or disease reasons, as opposed to athletic reasons.

Background

Creatine is made from three amino acids common to protein. On average, people require about 2 g of creatine daily, obtained equally from exogenous and endogenous sources.[6] Humans store 95% of their creatine in skeletal muscle, with more found in fast twitch muscle fibers than slow twitch ones.[7]

About 60% of the creatine in skeletal muscle exists as creatine phosphate (CP). Adenosine triphosphate (ATP) supplies energy for muscle contraction when it is converted into adenosine diphosphate (ADP). Muscles normally store enough ATP for only a few seconds of exertion, after which CP replenishes ATP. Muscle CP can provide fuel for an additional 4-6 seconds of intense exercise, and its rate of replenishment depends on free creatine concentrations.[8] Creatine is, thus, essential for short, intense, anaerobic exercise like power-lifting, sprinting, and jumping. Thirty seconds of rest will half-replenish CP levels, though complete recovery may take up to 3-4 minutes.[9]

Mechanism of Action

The mechanism of action by which creatine supplementation could increase muscle strength and exercise performance is only partly understood. However, a number of physiological mechanisms have been proposed and are being investigated.[2] Studies have provided evidence that up to 40% of the ergogenic effect could be due to a direct consequence of making more creatine and CP available for muscle energy production. Increased free plasma creatine could allow faster replenishment of CP stores and, thus, shorten the recovery periods needed during repeated bouts of intense exercise. In addition to these direct effects on exercise performance, creatine has been proposed to contribute to muscle protein growth both directly and via gene activation. Evidence here is lacking.[10] Body mass does increase with creatine, but this is more likely due to increased accumulation of body water.[10]

These different mechanisms could contribute to increased muscle mass and strength. Variation in their influence could account for one of the ongoing controversies regarding creatine supplementation; namely, the great variability found in individual responses to supplementation.

Clinical Studies

The first double-blind study to examine creatine use with resistance training in elderly sedentary adults was published in 1998.[11] Thirty-two men and women (67-80 years old) were randomized into four groups: creatine with resistance training, placebo with training, creatine without training, and placebo without training. None of the participants did weight-lifting before the study and were sedentary to moderately active. Creatine dose was 20 g/day for 5 days, followed by 3 g/day for a total of 8 weeks. Resistance training was carried out 3 times a week. No significant changes in body mass or body fat were found in any group. Training groups had significantly increased strength and endurance compared to those not training ($P < 0.02$). Creatine supplementation did not provide any additional benefit.

A double-blind, randomized trial assigned 30 men (mean age 70 years) to receive either creatine (0.3 g/kg for 5 days followed by 0.07 g/kg daily) or placebo.[12] Both groups engaged in three sessions of resistance training per week for 12 weeks. Both groups had significantly increased fat-free mass (FFM), with the increase being significantly greater in the creatine group ($P < 0.05$). Fat mass did not differ between the two groups. With two of the three muscle groups trained, the creatine group had significantly greater improvements in strength and endurance. The training volumes were 31 percent higher in the creatine group ($P = 0.05$).

Thirty-nine community dwelling, healthy adults (aged 65-85 years) were randomized to receive either

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creatine (5 g/day) with conjugated linoleic acid (CLA, 6 g/day) or placebo for 6 months.[3] No participants had participated in an exercise program during the previous 2 years, and all participated in supervised resistance training twice a week for the duration of the study. All measures of strength increased for both groups. Isokinetic (resistance at a constant speed) strength increased significantly more in the supplement group ($P < 0.05$), but isometric (performed at static position) strength gains did not differ between the groups. The supplement group had significantly better increases in FFM and decreases in total fat mass ($P < 0.05$). These changes were suggested to arise from creatine because CLA is not known to enhance FFM.

Parkinson's disease (PD) is accompanied by loss of muscle mass, strength, and endurance, along with loss of function in the lower extremities. Twenty patients, aged 62 years, with mild-to-moderate PD were randomized to receive either creatine (20 g/day for 5 days followed by 5 g/day) or placebo.[5] Participants had not been involved in regular exercise, and both groups participated in twice weekly progressive resistance training for 12 weeks. At the end of the study, participants in both groups had significantly increased muscle strength, with the creatine group showing significantly greater improvements than placebo for two of three muscle groups ($P < 0.05$). Both groups had increased muscle endurance and FFM, with no differences between the groups. Functional performance was measured by timing participants rising from a chair three times without using their arms. The creatine group showed a significant 11% reduction in total time, while the placebo group had a non-significant change.

Adverse Effects

Creatine frequently leads to weight-gain of 1-3 kg, probable due to intramuscular water retention resulting from an osmotic effect.[13] Numerous anecdotal reports from athletes claim creatine supplementation causes gastrointestinal problems, muscle cramping, and renal problems. One study with older men found significantly more reports of loose stools during creatine loading than with placebo.[12] Also, after 3-5 weeks, muscle cramping and strains were more frequent with creatine than placebo. Whether creatine adversely effects renal function remains controversial and unclear, suggesting that those at high risk for renal disease should be monitored medically.[14] Patients with McArdle disease experience exercise intolerance, premature muscle fatigue, and exercise-induced muscle pain. Beneficial effects of creatine supplementation alone were demonstrated at 60 mg/kg, but at 150 mg/kg, muscle pain severity and intensity were significantly higher ($P < 0.05$).[15]

Drug Interactions

No drug interactions are known, although concerns about the potential for renal toxicity raise issues about drugs metabolized through the kidneys.

Formulation

Creatine is readily available from meat and fish (containing roughly 4-5 g/kg) and, therefore, is classified as a dietary supplement, not a drug. It is most commonly available as the monohydrate in powder, candy, gum, and liquid. Numerous products combine it with vitamins, nutrients, and supplements, with no evidence of added benefits. Athletes usually "load" with 20 g creatine per day for 4-6 days (usually 5 g qid), followed by one 2 g daily dose. This approach has been adopted in some studies with older people.

Conclusion

Oral creatine supplementation has been studied extensively in athletes. Beneficial effects occur with high-intensity exertion lasting short periods of time. Much less research has been conducted in older people. Where resistance training has shown itself to be beneficial, there is some evidence to support the use of creatine supplements. However, the early stage of this research must be noted, especially given the potential for complications, in the elderly, especially those with co-morbidities.

Recommendation

Creatine supplementation may enhance the effects of resistance training in older adults. However, the functional benefits of this have, for the most part, not been examined in studies. If creatine allows people to gain in strength or endurance with fewer repetitions, their willingness to train may increase. However, such an approach could lead to the neglect of cardiovascular or social dimensions of training. For those interested in taking creatine, it may augment resistance training, and appears to be well tolerated, but given the small number of studies available at this point, creatine supplementation cannot be confidently promoted for older adults. ❖

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Mind/Body Approaches to Managing ADHD

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Apart from dietary interventions, mind/body approaches are one of the most popular groups of non-pharmacological approaches for the treatment of attention-deficit/hyperactivity disorder (ADHD). Many types have been tried, and practitioners need to be aware of the evidence concerning the many programs that are offered to parents of children with ADHD and to adults with the disorder. We are going to focus on four methods that have garnered the most research: biofeedback, meditation, yoga, and t'ai chi ch'uan.

The use of each of these has been given extra impetus by recent findings that meditation may produce sustained improvement in attention, together with structural and functional alterations in regions of the brain that are involved in attentional mechanisms.[1-3]

It may seem surprising that hyperkinetic children and adults with attentional problems should be able to slow down and focus enough to try yoga, meditation, or biofeedback. Yet there is good evidence that they can and they do, and that all three modalities can be helpful.

Biofeedback

This is a patient-guided method that teaches an individual to control muscle tension, body temperature, electroencephalographic (EEG) activity, and other processes through relaxation, visualization, and other forms of cognitive control. Biofeedback that is aimed at developing skills to help people self-regulate the activity of their brains is usually referred to as neurofeedback. Clinicians may also see it referred to as "EEG biofeedback, "neurotherapy," and "neurobiofeedback." This technique involves recording a relatively simple form of continuous EEG in real time using scalp electrodes. Subjects are given immediate feedback and positive reinforcement, usually using a visual display.

In "frequency" training, people are asked to increase or decrease the activity of different EEG frequency bands. A second system of training is aimed to help people to regulate their level of cortical excitability. They are trained to generate and regulate slow cortical potentials (SCPs), which are slow event-related direct-current shifts of the EEG.

Most children and adults can learn the basic techniques within one or two sessions, although effective treatment usually requires twenty or more sessions. Many young people with ADHD look at it like a game and, therefore, quickly become engaged with it.

Studies of neurofeedback have shown some specific effects on attention and memory processes,[4] and the effect size compares favorably to that seen with stimulant medications.[5] The key point is that the improvements in performance are maintained once the person is engaged in real-life activities. The techniques can be used to help healthy people perform better, as well as helping people with problems.

Several studies have shown that children with ADHD had improvements in behavioral and cognitive variables after both frequency (e.g., theta/beta), training,[6] and SCP training.[7,8] Some of these improvements were sustained for as long as six months. It has also been possible to show improvements in some neurophysiological measurements. One confounding factor in the studies has been that most children were either kept on medications or were given other types of exercises, to reinforce what they were learning.

Results from well designed research utilizing brain imaging[9,10] shows that neurofeedback in children with ADHD normalizes the functioning of the anterior cingulate cortex, a key neural circuit involved in selective attention.

Some experts remain unconvinced[11] about the data concerning neurofeedback, but support the call for further research in the field.

There is also another type of feedback training. There is evidence that the level of activity in a classroom containing hyperactive boys can be reduced using feedback about the level of activity together with positive reinforcement. Some recent research[12] has produced preliminary data in which investigators used a device that combines a beeper and actigraphy technology for measuring, monitoring, and modifying motor excess in children. The feedback reduced the activity level of seven out of nine hyperactive boys.

There remain some unanswered questions about biofeedback in the treatment of ADHD. John Gruzelier and Tobias Egner from London have recently pointed out that use of neurofeedback has grown and been widely adopted with little supportive research.[13] However, their own work has shown that the technique can help improve cognition, and they provided the first evidence of conscious control over the ratio of alpha and theta waves in the brain.[14]

The evidence supporting use of biofeedback is growing, and since it is non-invasive and may be associated with other improvements in mood and cognition, it will likely be an important option for some people with ADHD. Unfortunately, there are many commercially available bio- and neuro-feedback machines for which there is little evidence of efficacy.

Yoga

There are hundreds of different types of yoga, but the one that has been examined the most is hatha yoga. Many experts and yoga teachers consistently report that they have students with ADHD who have improved markedly when they follow a regular yoga regimen; however, the research base remains thin. Some studies have been published in India, and there have also been small studies that included children with ADHD. The first specific ADHD study was a small (N=19) six-week open trial of twice weekly hatha yoga lessons for both parents of, and children with, ADHD. The participants were also encouraged to practice at home. At the end of the six weeks, there were subjective improvements in behavior, and in those who practiced at home, there was an improvement in emotional lability.[15]

Another pilot study, this one from Heidelberg in Germany, suggested that yoga can be an effective complementary or concomitant treatment for ADHD.[16] That was also the conclusion from a recent review article:[17] yoga, like most of the other complementary methods of treatment, may be a good adjunct, but we do not have enough evidence to use it in place of existing treatments.

Meditation

Eugene Arnold's review[18] of unorthodox treatments for ADHD cites two studies from the 1980s that showed significant improvements in the behavior of children who were taught to practice meditation. (Kratter J. The

use of meditation in the treatment of attention deficit disorder with hyperactivity. *Dissertation Abstracts International*. 1983;44:1965 and Moretti-Altuna G. The effects of meditation versus medication in the treatment of attention deficit disorder with hyperactivity. *Dissertation Abstracts International*. 1987;47:4658.) Neither of the reports is easily available, and the studies were not published in peer-reviewed journals. A small six-week pilot study using Sahaja Yoga meditation for children with ADHD and their families reported a small but useful benefit.[19]

As mentioned in the introduction, there are some good theoretical reasons for thinking that meditation should help attention, and this continues to be a fertile area for further research.

T'ai Chi Ch'uan

There are a large number of anecdotal reports of people with ADHD improving if they practice t'ai chi or qigong. However, the research base is quite small.

First, there is an interesting and well-designed study involving 13 adolescents with an average age of 14.5 years.[20] They were taught basic t'ai chi moves for 30 minutes twice a week for five weeks. The sessions consisted of breathing exercises, accompanied by slow raising and lowering of the arms, twisting and turning of the arms and legs, shifting body weight, and rotating and changing direction.

The researchers used the 28-item Connors' Teacher Rating Scale to evaluate the students' behavior prior to the t'ai chi classes, during the classes, and two weeks after the classes ended. The adolescents' teachers perceived them as less anxious, emotional, and hyperactive. These improved scores remained consistent throughout the two-week follow-up period.

The anecdotal reports and empirical research into the benefits of t'ai chi ch'uan and qigong with respect to attention, concentration, depression, and anxiety[21] imply that they would be good candidates for further research in ADHD.

Recommendations

Recent research has indicated that attention can be trained, but the evidence for attentional training in ADHD is, so far, only suggestive.

There is growing evidence that neurofeedback may be helpful for children with ADHD.

There are many commercially available neurofeedback machines, but most have little data to support them, relying instead on statement about neurofeedback in general. Thus, practitioners should insist on seeing data obtained with a specific model.

Yoga, meditation, and t'ai chi ch'uan may all help children, and also perhaps adults with ADHD, though the research base is small, and at the moment, each should be considered an adjunctive treatment.

There are no recognized adverse effects associated with any of the mind/body therapies that we have discussed, apart from the potential problems of eschewing established treatments in favor of ones with less scientific validity. ❖

[Editor's Note: Dr. Petty is the author of Healing, Meaning and Purpose, *and has lectured to more than a quarter of a million people in 45 countries. His newsletter, reports, blogs, and podcasts on health, personal growth, and integration are available at www.richardgpettymd.com or call (770) 554-8812.]*

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43. Creatine is believed to increase muscle strength and endurance by:

a. directly stimulating growth of new muscle mass.
b. increasing the availability of biochemical energy for muscle function.
c. preventing muscle injuries.
d. hastening the repair of muscle.

44. The adverse effects from creatine supplementation are:

a. relatively minor, in most instances, typically gastrointestinal and muscle cramping.
b. very serious, with renal toxicity commonly reported.
c. non-existent.
d. All of the above

45. Beneficial effects of creatine supplementation with resistance training in older adults is supported by:

a. numerous large, randomized, controlled trials.
b. anecdotal reports.
c. a small number of controlled trials.
d. large numbers of epidemiological studies.

Answers: 43. (b); 44. (a); 45. (c)

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PS Form **3526**, September 1999 *(Reverse)*

With Comments from Russell H. Greenfield, MD

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Pills in Peds: Supplement Use in Children

Source: Picciano MF, et al: Dietary supplement use among infants, children, and adolescents in the United States, 1999-2002. *Arch Pediatr Adolesc Med*. 2007;161:978-985.

Goal: To describe the extent of dietary supplement (DS) use in a nationally representative sample of US children.

Study Design: Analysis of data from the 1999-2002 National Health and Nutrition Examination Survey (NHANES, an annual cross-sectional, population-based examination survey), representing the latest estimates of DS use available.

Subjects: Children from birth to 18 years who participated in NHANES (n = 10,136).

Methods: Parents of children younger than age 16 years, or participants aged 16-18 years, were asked about their use of DS in the 30 days prior by trained interviewers. If DS use was confirmed, additional questions regarding duration, dosage, and frequency of use were asked and specific supplement data (including name and manufacturer) recorded. Data from the 1999-2000 and 2001-2002 NHANES data releases were combined, and children were categorized by age into one of 5 groups (< 1 year, 1-3 years, 4-8 years, 9-13 years, and 14-18 years).

Results: For the time period 1999-2002, 31.8% of children used DS, with no significant gender differences. The highest rate of use was in 4-8-years-olds (48.5%), with a higher rate of use in 14-18-year-olds (25.7%) than in infants (11.9%). DS use was also higher in non-Hispanic white and Mexican American families, among children with lower body mass index, in families with higher levels of income, in smoke-free homes, and where screen time (television, computer, video games) was limited. The most common type of agent used was a multivitamin and mineral supplement (18.3%). Prevalence of DS use increased from low levels during infancy and early childhood to their highest levels at age 5 years, followed by a steady decline to 20% among 15-year-olds, and a bump in prevalence of use among older teens (28%). Use of botanical supplements in this sample of children was but 0.8%, with very few children under age 3 years being exposed to herbal medicine. Iron was used by 19% of children, and fluoride by 3.0%. The majority of children (83.9%) took only one DS.

Conclusion: Nearly one-third of American children take dietary supplements on a regular basis.

Study strengths: Multivariate analysis data taken directly from participants in their homes and from supplement labels.
Study weaknesses: Cross-sectional design.

Of note: The majority of US adults take dietary supplements (57% of women and 47% of men reported using a DS in the past 30 days in the 1999-2000 NHANES); DS use has remained stable or decreased in children (use has declined especially in young children), while it has increased in adults; it is possible that DS use is higher among children with lower BMI because parents feel they are more in need of nutrients.

We knew that: The American Academy of Pediatrics recommends nutritional supplementation for children at risk for deficiency states (to prevent rickets, for example); the prevalence of DS use in adults increases linearly from 19-65 years of age, with highest levels in those > 65.

Comments: Picciano and colleagues of this well done study plead their case that in future evaluations of the nutritional status of children, DS use be taken into serious consideration. Indeed, this can now only be considered a necessity. Over 30% of American children consistently get some of their daily nutrients from DS. It is important, if not ironic, to note that the highest rates of DS use in children can be found among those whose families have the highest incomes, which should translate into exposure to the healthiest diets. Indeed, it is clearly preferable that children get their nutrients from healthy fare, but for many, that is simply not possible. Yet the children who might benefit most from DS, often do not have access to them, another inequity that should be addressed. For those practitioners who care for children, it is important to ask about the use of DS and to review the contents of DS with families in order to optimize potential benefits and minimize potential untoward effects.

What to do with this article: Keep a hard copy in your file cabinet.

Eye C? Dietary Antioxidants and ARMD

Source: Chong, E W-T, et al: Dietary antioxidants and primary prevention of age related macular degeneration: systematic review and meta-analysis. *BMJ*. 2007 doi:10.1136/bmj.39350.500428.47

Goal: To determine whether or not a range of dietary antioxidants are effective for the primary prevention of age-related macular degeneration (ARMD).

Study Design: Systematic review and meta-analysis.

Source material: Seven databases without limits on language or year of publication, and references from reviews and articles. Only randomized clinical trials (RCTs) and prospective cohort studies (PCS) were considered for inclusion in the analysis.

Methods: Two reviewers independently searched the databases and selected the studies using standardized criteria. Disagreement between the reviewers was resolved through discussion with senior investigators. Out of 4,192 abstracts screened, a total of 12 studies (9 PCS with data on 149,203 people including 1,878 incident cases of ARMD, and 3 RCTs) met selection criteria, and data extraction and study quality evaluation were independently reviewed, also using standardized criteria. Results of meta-analysis were pooled quantitatively.

Results: All trials were performed in the United States or other Western countries. Participants in the cohort studies were generally over age 49 years, but 2 trials included subjects in their early forties, and subjects were followed for a mean of 9 years. Pooled results from PCS showed that dietary intake of vitamins A, C and E, as well as zinc, lutein, zeaxanthin, alpha carotene, beta carotene, beta cryptoxanthin, and lycopene, has little or no benefit with respect to primary prevention of ARMD. Results from the 3 RCTs that followed people for 4-12 years did not support the use of vitamin E or beta carotene for the primary prevention of ARMD.

Conclusion: Sufficient evidence is lacking for a primary preventive effect of dietary antioxidants, including dietary supplements, against ARMD. The only widely accepted modifiable risk factor for the primary prevention of ARMD remains smoking.

Study strengths: Authors of published trials were contacted if salient data were missing; authors are frank regarding shortcomings of results.

Study weaknesses: One of 9 PCS, and one of the 3 RCTs, were published in abstract only; relatively short periods of follow-up, problems inherent in the use of food frequency questionnaires FFQ (for example, in the PCS trials the FFQ was administered but once, at baseline); few RCTs; mainly well-nourished subjects; as the authors state, meta-analyses of observational data offer the potential for even bias than meta-analyses of RCTs; unable to evaluate potential antioxidant synergism.

Of note: The AREDS trial, a secondary prevention study, showed that patients with intermediate forms of ARMD treated with high-dose zinc, beta carotene, vitamin C, and vitamin E had a 28% reduction in risk of disease progression compared with placebo; the only consistently reported risk factors for ARMD include older age, genetic markers, and cigarette smoking; in this review there was significant heterogeneity among the PCS with respect to specific types of antioxidants under investigation (not all studies contributed to the meta-analysis of each antioxidant), but little heterogeneity beyond that; the reviewers specifically excluded studies of people with early ARMD (secondary prevention trials); some of the diet data in the PCS were obtained prior to 1988.

We knew that: ARMD is the leading cause of significant central vision loss in people over age 50 years living in industrialized nations; early ARMD is characterized by changes in retinal pigmentation and the presence of drusen (yellow deposits), while with late ARMD, there can be new vessel formation that results in sub-retinal bleeding ("wet" ARMD) or macular atrophy ("dry" ARMD); treatment is available for a small proportion of people with "wet" ARMD, but no effective treatment yet exists for "dry" ARMD; the retina is highly susceptible to oxidative damage due to constant light exposure and high oxygen concentrations; preventive treatment against ARMD with antioxidants is plausible because they (especially carotenoids) may help reduce photo-oxidative damage from blue light.

Comments: As Chong and colleagues point out, there is a common perception that a diet rich in antioxidants can protect against ARMD. The results of this meta-analysis made its way into the lay media and dampened the hopes of many people; however, a thorough review of the data reminds us that there's more to research than headlines.

Even the best of meta-analyses are plagued with problems that make interpretation, let alone evaluation, of clinical management difficult at best. Chong et al are to be commended for their attempt to clarify a chal-

lenging issue, but perhaps even more so for being forthright about the limitations of their work. Beyond what is printed in the way of limitations, however, there are other problems, not the least of which is duration of follow-up in the studies analyzed. The majority of people enrolled in the trials were over 50, but some had not yet reached age 45. Consider that the average follow-up was 9 years in the PCS and 4-6 years in the RCTs. This is quite problematic, as the average age at which the diagnosis of ARMD is made is over age 65 years. In addition, because ARMD develops and progresses slowly, and may be essentially asymptomatic early on, it is very difficult to identify unless people seek regular ophthalmologic evaluation.

The data supporting antioxidant therapy for established ARMD seem quite strong. Results of this trial, focusing on primary prevention of ARMD, were not positive, but the methodology employed negates the findings for practical purposes. There remains promise that antioxidant therapy may help prevent ARMD, but this study does not contribute significantly to the discourse. Better-designed, prospective trials are needed.

What to do with this article: Remember that you read the abstract.

A Fit Mind: Exercise and Depression

Source: Blumenthal JA, et al: Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosom Med*. 2007;69:587-596.

Goal: To evaluate the effects of home or supervised group aerobic exercise on major depressive disorder (MDD) as compared to use of sertraline (Zoloft) or placebo.

Study Design: Prospective, randomized, parallel group, controlled study performed over 16 weeks.

Subjects: Adults over age 40 years (mean age = 53 years) with MDD (n = 202, 153 women).

Methods: Potential subjects were screened using the Beck Depression Inventory II (BDI). Those who scored 12 or above on the BDI and subsequently met diagnostic criteria for MDD, were recruited through public media. A structured clinical interview for depression was performed by a licensed clinical psychologist, and the Hamilton Depression Rating Scale (HAM-D) employed at baseline and at 16 weeks. Participants were randomly assigned in roughly equal proportion to one of 4 groups: supervised exercise in a group setting (3 supervised sessions per week); home-based exercise (initial home visit to establish training routine, visit from exercise physiologist at end of months 1 and 2, and telephone calls at weeks 1 to 4 and biweekly thereafter); sertraline 50-200 mg daily (starting dose of 50 mg/day with increases contingent upon response and absence of side effects); or placebo pill. The BDI was administered by phone weekly for the first 4 weeks, then biweekly until the end of the trial. Clinic visits occurred at baseline and then at weeks, 2, 4, 8, 12, and 16. Graded treadmill exercise testing was conducted before treatment and again at study's end to document subjects' fitness levels. The primary endpoint of interest was remission of MDD (no diagnosis of MDD and a HAM-D score < 8).

Results: At trial's end, a total of 41% of participants no longer met criteria for MDD and had a HAM-D score < 8. Those who received active treatments had higher remission rates than those in the placebo group: supervised exercise 45%; home-based exercise 40%; medication 47%; and placebo 31% (P = .057). The adjusted odds ratio for remission was 2.6 when comparing active treatment with placebo. All treatment groups had lower HAM-D scores at the end of the study, but scores were not significantly different between placebo and active groups. Aerobic capacity improved more in the group exercise arm than for those exercising at home, with both groups' aerobic capacity improving more than either "pill" group. Dropout rates were as follows: 14% sertraline. 29% placebo group, 6% home exercise, and 20% group exercise. Results suggest that treatment affected subjects in similar fashion regardless of severity of depression.

Conclusion: Exercise is generally as effective as antidepressant medication, and both are more effective than placebo, for the treatment of MDD in middle-aged and older adults.

Study strengths: Comparison of home-based vs group exercise to try to control for effects of non-specific social support; eligibility criteria and close follow-up established to ensure subject safety in the event they received placebo; intention-to-treat analysis; blinding of psychologists to treatment condition.

Study weaknesses: Significant amount of interaction with staff even in home study group; compliance with medication or placebo evaluated by pill count; limited generalizability (subjects were mainly Caucasian women over age 40 years with mild depression, and all were volunteers); attrition rates.

Of note: MDD is the 4th leading cause of disability-adjusted life-years worldwide; findings of prior studies of exercise for people with MDD have largely been compromised due to methodological flaws and confounding factors; Blumenthal and colleagues note that they chose sertraline as standard treatment for MDD for purposes of comparison due to its "widespread usage and proven efficacy, tolerability, and low toxicity"; the fitness prescription was the same for both exercise groups, the only difference being the setting; for inclusion in the study, participants had to have been relatively sedentary prior to randomization; only the research pharmacist was aware of which people were using sertraline vs. placebo; if difficulties with the exercise prescription were being experienced by participants, an additional 2 home visits by staff was permitted; 40% of subjects had a history of recurrent depression; the majority of participants in the trial enrolled with the hope they would receive exercise treatment for treatment of their depression.

We knew that: The lifetime prevalence of MDD is 15-20%; it is estimated that MDD will be second only to cardiovascular disease as a worldwide cause of illness burden by the year 2020; in studies of MDD, the placebo group often experiences marked improvement (response rates of 30-50%), especially during the first week of treatment; no single treatment is effective for everyone with MDD; simple reduction in the symptoms of MDD does not result in as good a prognosis or as improved levels of daily functioning as does remission; HAM-D scores < 8 are associated with low relapse rates; MDD remission rates range from 35-40% in most psychopharmacology trials; exercise might help ameliorate MDD through a wide variety of mechanisms including effects on neurotransmitters and enhanced self-efficacy.

Comments: The results of this trial should give us reason to smile - a prescribed fitness regimen may be as effective as prescription aids for the treatment of MDD. People should be dancing in the streets (literally) when they learn of this…except that methodological shortcomings do muddy the waters a bit.

The researchers tried hard to limit interaction with the home-based exercisers, but there was still quite a bit of contact between subjects and staff that may have non-specifically benefited participants through social support. In addition, the results are not easily generalizable, as the subjects were mainly middle-aged white women, but even more importantly because they were all volunteers (the majority of who were hoping to be randomized to an exercise group).

The study's flaws are not so great that its conclusions can be eschewed. The independent effects of exercise appear to be comparable to those of antidepressant medication, and better than placebo, for the treatment of MDD in select instances. Of additional interest is the finding that exercise was equally effective for the treatment of MDD in both fitness groups, even though the supervised group developed better aerobic conditioning. These are data that can be built upon with further study that hopefully includes a broader swath of patients reflecting a variety of ages and patient circumstances. Until that time, however, fitness activities can, and perhaps should, be recommended as part of a multidisciplinary approach to management of MDD.

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In Future Issues:

Melatonin and Hypertension