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DEPRESSION

ABSTRACT & COMMENTARY

Active Children: Do Higher Levels of Activity Help Prevent Depression?

By Ellen Feldman, MD

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Dr. Feldman reports no financial relationships relevant to this field of study.

SYNOPSIS: This prospective study found moderate to vigorous physical activity in early childhood correlated with a decreased number of depressive symptoms in later years.

SOURCE: Zahl T, Steinsbekk S, Wichstrom L. Physical activity, sedentary behavior, and symptoms of major depression in middle childhood. *Pediatrics* 2017;139(2). pii: e20161711. doi: 10.1542/peds.2016-1711. Epub 2017 Jan 9.

"Lack of activity destroys the good condition of every human being, while movement and methodical physical exercise save it and preserve it."
— Plato

Today, with more automation and less need for physical action or intervention, Plato's words take on greater significance. The essential role exercise plays in maintaining and improving health is unquestionable and validated by numerous well-designed and constructed studies.[1] However, few researchers have studied the role of exercise and movement in the physical and emotional well-being of young children. Recognizing this as a gap in the field, Zahl et al set out to study a community sample of children to answer several relevant questions regarding this age group and mental health.

Specifically, this group was interested in a prospective study looking at a community-based sample of young children and exploring a relationship between

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Summary Points

- Norwegian researchers followed more than 700 participants between 6 to 10 years of age to investigate the reciprocal relationship between physical activity, sedentary periods, and subsequent onset of symptoms of depression.
- Electronic monitors tracked physical exertion; structured interviews measuring depression assessed number of depressive symptoms.
- Higher levels of moderate to vigorous physical activity (MVPA) at 6 years of age correlated with less depressive symptoms at 8 years of age. Likewise, higher levels of MVPA at 8 years of age correlated with less depressive symptoms at 10 years of age.
- Sedentary periods did not correlate with higher levels of depressive symptoms, and depressive symptoms did not correlate with changes in physical activity in subsequent years.

physical activity and symptoms of depression. Specifically, the intention was to characterize the relationship in a bidirectional manner to see if there was a correlation between depressive symptoms and time spent engaging in physical activity and/or if there was a correlation between physical activity and onset of depressive symptoms. Recognizing psychomotor retardation as a symptom of depression, an additional goal was to isolate any effect from sedentary activity on depression.

Older children and adolescents have been the subjects in similar studies regarding physical activity and depressive symptoms. A large investigation in 2012, and another more recent study in 2017, found evidence of a reciprocal link between these two factors (depressive symptoms and physical activity) in this older age group.[2,3] There have been conflicting results regarding the intensity of effort or degree of physical activity that is correlated with decreased depressive symptoms.

The Trondheim Early Secure Study is a prospective, longitudinal investigation beginning with a cohort group of children born in 2003 and 2004.[4] The subgroup of children for this study received invitation letters prior to routine 4-year old well-child visits. Permission to participate was obtained at the visits followed by data collection at age 6 years, age 8 years, and age 10 years (2009-2015.) In total, 799 children submitted usable data.

To identify degree of physical activity, children wore waistband accelerometers that recorded activity for seven consecutive days. Standardized measures permitted identification of sedentary activity level and moderate-vigorous activity level, both represented as hours per day for study purposes. Sleep hours were not included in the study.

Structured, age-appropriate interviews of the children and a corresponding parent interview noted the presence of any symptoms of major depressive disorder. Reported for data analysis were the number of symptoms of depression present, rather than a firm diagnosis. Comorbidity from other psychiatric disorders and body mass index (BMI) were considered as potential confounders. To control for comorbidity, assessments for symptoms of several other psychiatric disorders were collected. BMI was calculated for each participant and controlled for in final statistical analysis.

Hours per day of sedentary activity at each age level and of moderate-vigorous physical activity (MVPA) as well as number of depressive symptoms were the main variables studied. Both states of physical activity — MVPA and sedentary — were defined numerically on the accelerometers; these standardized measures were used for the investigation. To convey this level of activity in words, Zahl et al subjectively described MVPA as "… being active, getting sweaty, and even breathless …."

Table 1: Accelerometer and Interview Results for Each Age Group

Age in years	Mean number symptoms of depression (SD)	MVPA (hours/day)	Sedentary (hours/day)
Age 6	0.52 (0.73)	1.19	8.58
Age 8	0.46 (0.79)	1.18	9.22
Age 10	0.52 (0.90)	1.09	9.94

MVPA = moderate-vigorous physical activity

Out of nine possible symptoms of depression, the mean number of symptoms noted ranged from 0.46 to 0.52. (*See Table 1.*)

A flexible statistical modeling program (M plus)[5] enabled analysis of multiple variables and examination of bidirectional relationships between these variables. For example, using this program, a correlation between MVPA and symptoms of depression was examined, looking at time spent in MVPA and mean number of depressive symptoms between the ages of 6 years to 8 years, and then looking backward between the ages of 8 years to 6 years. In this same manner, bidirectional analysis of sedentary behavior and depressive symptoms proceeded.

Positive findings: At 6 and 8 years of age, higher levels of MVPA predicted lower levels of depressive symptoms two years later. The effect was statistically significant but not large; a 0.20 decrease in number of symptoms of depression correlated with one hour more spent in MVPA. However, with a mean number of depressive symptoms for all age groups close to 0.50, a decrease by even this small amount could prove meaningful in prevention of progression to full-blown depressive disorders. Table 2 shows the statistical results.

Negative findings: There was no identified correlation between sedentary activity and symptoms of depression. Symptoms of depression at any age did not correlate with changes in levels of MVPA in later years. In other words, although higher levels of MVPA were associated with a decrease in depressive symptoms in subsequent years, higher levels of depressive symptoms did not correlate with any specific change in MVPA in future years.

■ COMMENTARY

Can young children develop depression? The existence of depression in the first decade of life and the validity of diagnosis at such a young age was once a question in the field. Backed by empirical studies documenting confirmed diagnosis of depression in children as young as 3 years of age, it is a question no longer.[6]

Table 2: MVPA and Number of Depression Symptoms

	Beta coefficient*	95% confidence interval	*P* value
Ages 6-8	-0.58	-0.95 to -0.21	0.001
Ages 8-10	-0.58	-1.03 to -0.03	0.002

Results from bidirectional analysis
MVPA = moderate-vigorous physical activity
* negative value indicates reciprocal relationship

However, treatment is another matter. Unfortunately, there are only a few small, randomized, clinical trials looking at treatment interventions. Current best practice recommendations for intervention involve specific, age-adjusted psychotherapy and parental/guardian intervention. Although studies are limited in scope and numbers, the implications of untreated depression are significant; specific findings about the effect of depression on growth and development in young children has propelled the standard away from "watchful waiting" and toward active treatment and prevention.[7]

Until recently, preventive efforts in the field primarily have revolved around psychosocial interventions. Future studies looking at active intervention, such as inducing higher levels of activity in children to prevent development of future depressive symptoms (and potentially of depressive disorders), will be useful in further understanding if this study is looking at strictly correlation or if causation is significant.

The study results looking at natural higher levels of MVPA in young children and the effect on later development of depressive symptoms are not particularly robust at first glance, but they hold significant potential. Zahl et al identified only a limited number of depressive symptoms in young children, consistent with a known rate of depression among this age group — 1% of preschoolers and 2% of school-aged children.[7] Given that the baseline numbers are tiny, a decline in this area (representing number of depressive symptoms) could be difficult to detect. That there exists a reciprocal correlation between MVPA and symptoms of depression at a young age may be the most significant finding, as opposed to the quantification of this relationship.

Zahl et al speculated that the relationship between MVPA and depression may be explained on several levels, including that a significant portion of the MVPA in children stemmed from engagement in sports. They wondered if increased self-esteem and socialization from sports activities is a potential guard against later

development of depression. Other explanations considered include the possibility of a genetic link between an innate temperament geared toward movement and mood stability (an explanation proposed in a comment connected to the original study).[8]

Interestingly, Zahl et al did not find a correlation between longer periods of sedentary activity and depressive symptoms. However, there is no information regarding low levels of physical activity and depressive symptoms; thus, it is difficult to form any conclusions regarding intensity of physical activity. It is also important to note that limiting the physical activity measurements to just one week every two years may have limited the power of the study. There is no evidence that an accurate reflection of a child's level of activity can be extrapolated from measures taken over this relatively brief period. Expanded activity measurements may help develop a more nuanced understanding of the relationship between all levels of activity and development of depressive symptoms.

Limits of this study include a lack of geographical diversity among subjects — certainly larger, multiethnic/geographic studies are necessary to formulate conclusions. Additionally, it is important to note that having symptoms of depression (measured by clinical interview in this study) is different from a firm diagnosis of depression. Future studies looking at these and other factors — including an extended time of investigation to determine the effect of early MVPA during adolescent years, for example — will be useful in developing a better understanding of the relationship between MVPA and development of depression.

We know from previous studies that depressive symptoms are a risk factor for a later diagnosis of major depressive disorder. We know that untreated depression tends to run a waxing and waning course throughout a lifetime and is associated with considerable disability and functional impairment. We also know that current treatment of depression in childhood has limited efficacy, and that there is little evidence for use of conventional antidepressants in this age group.[6,7]

The integrative provider aligns with patients to develop a comprehensive health and wellness plan. Informing parents of young children that early engagement in MVPA may help delay or prevent the development of depressive symptoms in offspring may add a new dimension to such a plan.

While being clear that this is preliminary information, recommending that parents look toward a more active lifestyle for their children has potential benefits, not only for the prevention of depression, but also for wellness and health in general. A side benefit: Some parents will engage in MVPA along with children, leading to a more active and potentially healthy lifestyle for the entire family. ■

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EXERCISE

ABSTRACT & COMMENTARY

High-intensity Interval Training in Older and Younger Adults

By Mercy Kagoda, MD, MPH

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Dr. Kagoda reports no financial relationships relevant to this field of study.

SYNOPSIS: High-intensity interval training performed over 12 weeks reversed age-related differences of mitochondrial proteins in adults 65 to 80 years of age, as well as increased insulin sensitivity and VO_2 peak, and decreased fat free mass in adults 18 to 30 years of age and 65 to 80 years of age.

SOURCE: Robinson MM, Dasari S, Konopka AR, et al. Enhanced protein translation underlies improved metabolic and physical adaptations to different exercise training modes in young and old humans. *Cell Metabolism* 2017;25:581-592.

The clinical benefits of exercise are well-accepted for improving various diseases.[1,2] However, the changes occurring at the molecular level are not completely understood. Robinson et al contrasted the changes at the physical level with changes at the molecular level.[3]

A total of 399 participants initially were recruited and sorted into two age groups: 18 to 30 years or 65 to 80 years. Participants were tested over 12 weeks after randomization into three groups: high-intensity interval training (HIIT), resistance training (RT), or combined training (CT). Exclusion criteria included performing structured physical activity of > 20 minutes twice a week, body mass index (BMI) > 32 kg/m^2, cardiovascular disease, diabetes, untreated thyroid disease, renal disease, type 2 diabetes or fasting glucose > 110 mg/dL, pregnancy, smoking, implanted medical devices, and numerous classes of medications (insulin sensitizers, insulin, corticosteroids, beta-blockers, peroxisome proliferators activated receptor gamma agonists, tricyclic antidepressants, etc.). Of the 399 initially assessed, 72 (18%) were eligible for the study.

HIIT was undertaken five days per week: three days/week of cycling at > 90% peak oxygen consumption 4 x 4 minutes with three minutes pedaling at no load, and two days/week of treadmill walking for 45 minutes at 70% peak oxygen consumption.

RT was done twice weekly with both upper and lower body exercises (four sets of eight to 12 repetitions).

The CT group first completed a 12-week sedentary period wearing accelerometers to track any structured activity, after which they began activity that included five days/week of cycling at 70% peak oxygen consumption for 30 minutes, and four days of weight lifting but with fewer repetitions than the RT group.

Baseline characteristics of both age groups (18 to 30 years and 65 to 80 years) included BMI, body fat, fasting insulin, and fasting glucose. As expected, the older age group had statistically significantly higher BMI (26.6 ± 3.8 kg/m^2 vs. 25.6 ± 3.3 kg/m^2), body fat (37.9 ± 6.1% vs. 31.9 ± 4.7%), and fasting glucose (105 ± 8 mg/dL vs. 96 ± 7 mg/dL). However, the fasting insulin concentration between the two groups was similar: 5.5 ± 2.6 ulU/mL for 18 to 30 years, and 4.3 ± 1.8 ulU/mL for 65 to 80 years. Within the two age groups, baseline characteristics of the three exercise groups were similar.

Summary Point

- Twelve weeks of high-intensity interval training reversed age-related differences of mitochondrial proteins in participants age 65 to 80 years, and was associated with the greatest increase in gene transcripts for both participants 18 to 30 years of age and 65 to 80 years of age.

VO_2 peak or VO_2 max is the maximum volume of oxygen that a body can use during intense exercise. It depends on cardiac output and arteriovenous oxygen difference, and is a measure of cardiorespiratory function. VO_2 peak changes at different age groups. VO_2 peak can be used to approximate the metabolic equivalent (MET), which is a unit of sitting resting oxygen uptake. Elite endurance athletes have METs of 18, while moderately active young men have a VO_2 max that is approximately 12 METs.[4] In this paper, VO_2 peak was measured indirectly using expired and inspired volumes of carbon dioxide and oxygen on an electronically braked cycle ergometer and not on a graded intensity treadmill walking test. VO_2 max indicative of good health and good cardiorespiratory capacity is ≥ 42 mL/kg(-1) min(-1) in men, and ≥ 35 mL/kg(-1) min(-1) in women.[5] The authors used a cycle ergometer to measure VO_2 peak. Of note, other studies have found that VO_2 peak measured using a treadmill tends to be higher (~7%) than cycle values, presumably due to greater muscle mass activation in treadmill testing.[5]

Body composition was measured with a dual-energy X-ray absorptiometry after an overnight fast.

Pre- and post-intervention measurements of insulin sensitivity and muscle biopsies were performed after 72 hours of specific weight maintenance meals consisting of 30% fat, 20% protein, and 50% carbohydrates. The muscle biopsies of the vastus lateralis, one of the quadriceps muscles, were used for analysis of RNA, protein, methylation, and total genes that changed (either up-regulated or down-regulated).

WEB-based Gene Se T Analysis Toolkit (WebGestalt) is a free "functional enrichment analysis web tool."[5] Functional enrichment analysis, also known as gene set enrichment analysis, is a tool used to interpret gene lists or sets. In an analysis of genome scale data, lists of

up-regulated or down-regulated genes or proteins are created.[6,7] WebGestalt helps "translate the identified gene sets into a better understanding of the underlying biological themes."[8]

The statistical analysis test included paired t-test for the before and after (sedimentary followed by combined training), and analysis of variance (ANOVA) to compare the different means from the three groups: HIIT, RT, and CT. Tukey's procedure was used in conjunction with ANOVA to decrease the number of false positives.

Within the age groups, baseline characteristics were similar. Of the 72 subjects who met the strict inclusion criteria (45 in the younger category and 27 in the older category), 29 of the younger category completed both baseline screening and the training protocol, and 23 of the older category completed both baseline screening and the training protocol. In the younger category, five subjects discontinued training because of moving, medical issues unrelated to the study, lack of time, and incomplete baseline screening. Of the older category, three subjects discontinued training because of medical issues unrelated to the study and loss to follow-up.

1. VO_2 peak, skeletal muscle mass, and insulin sensitivity improved with training.
VO_2 peak increased in both age groups, with maximal and statistically significant increase in the HIIT groups (~28% vs. ~17% in younger and older, respectively) and CT groups (17% vs. 21% in younger and older, respectively). There was no significant change following RT in both younger and older groups. Fat free mass increased in all age groups, with the greatest increase in RT in the younger group, as expected. Insulin sensitivity, measured as the glucose rate of disappearance, increased in most of the training groups with the exception of older CT. At baseline, there was no difference in insulin sensitivity between the two age groups despite lower mitochondrial respiration in older adults. Fasting insulin and glucose did not change over 12 weeks in any training group.

2. Exercise training in the 65 to 80 years group led to up-regulation of mitochondrial proteins, and an improvement in mitochondrial function.
Mitochondrial function was assessed from mitochondria obtained by muscle biopsy pre- and post-intervention. As expected, at baseline, mitochondrial respiration was lower in older adults. HIIT statistically significantly increased mitochondrial respiration in both age groups +49% vs. +69% in younger and older, respectively. CT statistically significantly increased mitochondrial respiration in only the younger group at +38%. RT did not increase mitochondrial respiration in either group.

3. There was an increase in skeletal muscle gene expression in both age groups.
As expected, at baseline, there were differences in messenger ribonucleic acid (mRNA) in older vs. younger groups, with 267 gene transcripts lower and 166 higher in the older group. Mitochondrial, muscle growth, and insulin signaling genes were down-regulated in the older group. However, HIIT increased insulin signaling, mitochondrial, and muscle growth genes in older adults, and overall HIIT increased the expression of genes in both age groups. Proteins involved with mitochondrial biogenesis and mitochondrial envelope also increased with HIIT. Despite an increase in protein abundance, mRNA was inversely related to mitochondrial and ribosomal protein abundance.

Genes primarily involved in angiogenesis were the most commonly up-regulated across both age groups and all training groups. These genes were 55 in number, and upstream analysis identified them to include angiotensinogen, vascular endothelial growth factor, interleukin-10 receptor subunit, and fibroblast growth factor. Interestingly, skeletal muscle methylation was not affected significantly by 12 weeks of training.

■ COMMENTARY

The findings in this study showed that HIIT increased VO_2 peak, mitochondrial respiration, fat free mass, muscle strength, and insulin sensitivity in both younger and older age groups. CT had lower improvements in VO_2 peak and fat free mass than both HIIT and CT. RT did not increase VO_2 peak or mitochondrial function, and fasting insulin and glucose did not change over 12 weeks in any training group. Perhaps with either a longer duration of exercise sessions or increased frequency of sessions in a week, we could expect changes in fasting insulin and glucose.

One of the main strengths of this prospective study is that it spanned both clinical research and basic science research, shedding light on the molecular changes occurring with physiologic changes. For example, angiogenesis was a common factor among the three training groups, and was one of the main 55 gene sets that overlapped in all training groups and ages. Also, since this paper straddled two usually distinct publishing fields, it easily could have been two or even three papers. When presenting results, there is a discussion of prior studies that may be helpful.

Although this study further characterizes the molecular processes that go with various physiologic VO_2 peak measurements, the older subjects used are not average 65- to 80-year-old people. The exclusion rate was high, with more than 80% of the initial subjects excluded as described above. It also was not clear if the final participants had any diseases or medical

conditions. In clinical practice, how many 65- to 80-year-old patients do not have cardiovascular disease or diabetes or are not taking any of the extensive list of medications that was provided? For the select small number of 65- to 80-year-old patients without any medical conditions and not on any medications, one could consider recommending HIIT after assessing medical safety of physical activity. Although the findings in the older age group have limited generalizability, the younger age group does not. Most 18- to 30-year-olds are similar to those who were studied.

It is not clear why there was a wait time of 72 hours prior to performing the pre- and post-intervention measurements. Pre- and post-metabolic measurements were done after three days of weight maintenance meals (20% protein, 50% carbohydrates, and 30% fat). The percentage of the major food groups is approximate to the percentage of the general public. Perhaps if the measurements were completed within 24 hours, there would have been greater changes.

Interestingly, at baseline, there was no difference in insulin sensitivity between the two age groups despite lower mitochondrial respiration in older adults. The authors suggested that differences in insulin sensitivity could be better explained by adiposity and changes in exercise capacity rather than the functional capacity of mitochondria. Other studies have shown that insulin resistance is associated with decreased efficiency of the mitochondrial respiratory chain. Overall, this was a very good study that provided further understanding of some of the genetic changes that occur with resistance training and HIIT, and why exercise in general is prescribed for continued health as well as particular medical conditions. ■

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CANCER

ABSTRACT & COMMENTARY

Helping Women at Risk for Breast Cancer to Exercise More and Lose Weight

By David Kiefer, MD, Editor

Dr. Kiefer reports no financial relationships relevant to this field of study.

SYNOPSIS: A web- and phone-based intervention led to significant weight loss and a modest increase in moderate-to-vigorous activity in women at risk of breast cancer.

SOURCE: Cadmus-Bertram L, Nelson SH, Hartman S, et al. Randomized trial of a phone- and web-based weight loss program for women at elevated breast cancer risk: The HELP study. *J Behav Med* 2016;39:551-559.

What classifies as an integrative health intervention? Lifestyle recommendations are surely a part of what every practicing clinician brings to a patient encounter, although perhaps it is emphasized more in some fields than others. A key part of a healthy lifestyle is increasing activity, or exercise, levels as much as possible; the data support this for a variety of diagnoses and conditions. With the rise of technology, many eHealth interventions can serve as useful adjuncts to patients' efforts at behavior change. This clinical trial was an offshoot of pilot work showing that telephone-based coaching, web-based logs, and the use of an accelerometer (in this case the ActiGraph accelerometer, to count steps) to measure physical activity can lead to important changes in physical activity and weight loss.

In this way, Cadmus-Bertram sought a unique solution to modifying two important risk factors for breast cancer: physical inactivity and obesity. They identified

Summary Points

- In this study, 105 women with a history of breast cancer were randomized to exercise and dietary intervention (either administered via phone or internet) or usual care for 12 months.
- Women in the intervention groups exercised more (moderate intensity only) than the usual care group, but weight loss was less only at the six-month mark (by 12 months weight changes were the same in all groups).

women in San Diego at risk for breast cancer: women with a prior history of carcinoma in situ or a Gail model score of 1.7 or higher (or a 1.7% five-year risk of breast cancer, factoring in several variables). Women were excluded if they already exercised 150 minutes (moderate intensity) weekly, did not have access to high-speed internet, or did not speak fluent English.

Study participants were randomized to either phone- and web-based intervention or usual care for 12 months. There were several activity and weight loss goals in the intervention group. (*See Table 1.*)

Over the year, the study participants had 18 phone calls (30 minutes each) with trained lay health coaches. The coach did not change over the course of the study, providing some continuity, and the sessions were spaced over the 12 months with decreasing frequency. Topics ranged from sleep and stress management, to exercise and dietary choices. These were reinforced in a written manual that each participant received. Furthermore, the website Sparkpeople.com was used to log activity levels and food intake, and help study participants with motivation, provide feedback about dietary choices, and share useful ideas relevant to their behavior change.

People in the usual care group were given a copy of the U.S. Dietary Guidelines for Americans, and received four 15-minute phone calls (one every three months). This call was merely to check in, ensure continued participation in the study, and ask whether the participant had reviewed the guidelines and which part(s) they found most useful. No directed coaching was administered.

With respect to measurement, height, weight, and number of steps as per the accelerometer were noted. The outcome variable was the total activity (accelerometer) at 12 months, and the independent variable was the percent weight loss. Of note, the accelerometer was only worn at baseline prior to randomization and

Table 1: Physical Activity and Weight Loss Goals in the Intervention Group

- 150 minutes of moderate-to-vigorous physical activity per week
- Calorie restriction to achieve 1 to 2 pound weight loss weekly (500 kcal per day less ingestion)
- First 3 to 6 months: 10% weight loss
- Remaining 6 to 9 months: maintenance

12 months; at each of these time points, the accelerometer was worn during waking hours for seven consecutive days.

A total of 105 women were included in the randomization, 71 for the intervention group and 34 for usual care. At the end of 12 months, 59/71 remained for the intervention group, and 29/34 remained for the usual care group. The average age was 60.3 years, the average Gail Model score was 2.6, and the average body mass index (BMI) was 32.1 kg/m^2. Results for weight gain and physical activity are shown in Table 2. The intervention group lost more weight than the usual care group at six months, but by 12 months, the usual care group's weight loss had caught up to the point of being similar to the intervention group's weight loss. For exercise, an increase of 12 minutes daily of moderate-to-vigorous physical activity was seen in the intervention group, but not in usual care. Interestingly, overall physical exercise, which includes light-intensity exercise, decreased in both groups, although less so in the intervention group: 13 minutes/day (intervention) vs. 61 minutes per day (usual care group) (P = 0.03).

The authors stressed the significant weight loss at six months in the intervention group, and they noted the plateau of weight loss in the latter six months as possibly because of the decrease in phone coaching interaction as the study progressed. They also provided a positive spin on the fact that the intervention group had less of a decrease in total exercise time, while modestly increasing moderate intensity exercise. Their conjuncture was that moderate-to-vigorous intensity exercise partially displaced the light intensity exercise, a positive switch to the type of exercise most convincing in the literature for health benefits.

■ COMMENTARY

It's not easy to lose weight. As this trial found, even when weight loss initially occurs (and the intervention group lost a significant amount of weight at the six-month mark), the maintenance phase can be an additional challenge. At least the intervention in this study, a web- and phone-based approach, stabilized the weight loss, showing a non-significant change in weight over the second six months.

Table 2: Six- and 12-month Results			
Results, at 6 and 12 months, for the intervention group vs. usual care compared to baseline			
	Intervention group	**Usual care group**	***P* value**
Weight: 6 months	3.9 kg decrease	0.3 kg gain	< 0.001
Weight: 12 months	2.9 kg decrease	1.2 kg decrease	0.06 (NS)
Physical activity: 12 months	12 minute/day increase	No change	0.04
NS = not significant			

Sometimes, clinicians need to use whatever tools are available to help patients achieve their health goals. With integrative health, that might mean tapping into knowledge that's been refined over thousands of years, such as with traditional Chinese medicine or Ayurvedic medicine. Alternatively, using technology, in this case a web-based, self-monitoring technique for weight loss and activity promotion, might be the "prescription" that someone needs. These technological approaches are permeating the marketplace, and clinical research, with some data, like this study, are promoting their positive effects. The lead researcher of this study since has been involved with numerous other eHealth initiatives in other demographics.[1] Perhaps someday, the medical literature, mixed with clinical experience and patient preference, will be able to pinpoint the best combination of coaching and technology to help patients achieve their health goals.

This study is methodologically sound, with its randomized, prospective design convincing in tracing the outcomes back to the specific intervention studied. The small size of the control group (usual care) may have led to the weight loss findings (1.2 kg at 12 months, on par statistically with the intervention group) that may have disappeared with a larger sample size. Furthermore, hopefully the researchers will tackle the appropriateness and effectiveness of this approach on other demographics, cultural groups, and ethnicities, expanding beyond the "English speakers only" inclusion criteria. In our diverse society, as clinicians we need to know what works for everyone.

There is little reason not to bring this approach to our patients wishing, or needing, to increase their activity and/or achieve weight loss goals. In our clinics, we will want to have access to health coaches, and make sure that we are familiar with the websites and technology available, including costs, to our patients. If we are organized in these respects, our patients should be able to reach the weight loss and exercise targets realized in this study. ■

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DIABETES

ABSTRACT & COMMENTARY

Capsaicin for Painful Diabetic Peripheral Neuropathy

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Dr. Merry reports no financial relationships relevant to this field of study.

SYNOPSIS: An 8% capsaicin patch relieves pain and improves sleep in patients with painful diabetic peripheral neuropathy.

SOURCE: Simpson DM, Robinson-Papp J, Van J, et al. Capsaicin 8% patch in painful diabetic peripheral neuropathy: A randomized, double-blind, placebo-controlled study. *J Pain* 2017;18:42-53.

One-quarter of patients with type 2 diabetes mellitus experiences painful diabetic peripheral neuropathy.[1] The current standard of care for painful diabetic peripheral neuropathy focuses on centrally acting agents, such as antidepressants, anticonvulsants, and opioid analgesics.[2] These oral treatments may not

Summary Points

- A 12-week study showed that an 8% capsaicin patch treatment provided modest pain relief and sleep quality improvements compared to a placebo patch in patients with painful diabetic peripheral neuropathy.
- This was a single 30-minute treatment.
- The topical therapy was well-tolerated and did not compromise peripheral sensation.

be well-tolerated and offer modest clinical benefit.[3] Capsaicin is derived from chile peppers (*Capsicum* spp.). An 8% capsaicin patch has been suggested as a second-line agent for management of peripheral diabetic neuropathy pain.[3]

Capsaicin is a vanilloid receptor (subtype one) agonist that provides rapid, sustained pain relief by depolarizing hyperactive nociceptors.[4] Since capsaicin is delivered topically, the risk of drug-drug interactions and systemic side effects are minimized.[5] Studies have shown that the 8% capsaicin patch was beneficial in post-herpetic neuralgia, HIV-associated peripheral polyneuropathy, and painful neuropathic pain in non-diabetic patients.[6,7,8]

Simpson et al assessed the safety and efficacy of the 8% capsaicin patch vs. placebo in patients with painful diabetic peripheral neuropathy. There are several important factors to consider when analyzing the study results.

First, Astellas Pharma Europe funded the study and provided the study drug. The first author of the paper consults for Astellas Pharma, and the senior author was a paid consultant to support the study design. Four other study authors are employees of Astellas Pharmaceutical Company, and only three of the authors disclosed no conflicts of interest. Second, an unspecified amount of the manuscript was outsourced. The article stated that the authors were "fully responsible for the content and editorial decision for the report." Of note, the paper did not follow the standard referencing guidelines and began with reference number 8, followed by reference number 22. Reference 22 in the text relates to consensus guidelines, while the paper listed in the reference section as number 22 is a randomized, controlled trial. Reference 21 in the reference section is a paper on consensus guidelines.

This was a four-week, Phase III, randomized, double-blind, placebo-controlled trial conducted at multiple sites across the United States. Eligible patients were ≥ 18 years of age and had a diagnosis of painful diabetic peripheral neuropathy due to type 1 or type 2 diabetes mellitus for ≥ 1 year; HbA1C ≤ 11 and < 1% difference in the HbA1C level between the screening and prescreening values; stable doses of pain medication for four weeks prior to the screening visit; and an average numeric pain rating scale ≥ 4 (scale 0 to 10).[9]

Exclusion criteria included significant foot deformity, body mass index ≥ 40 kg/m^2, impaired glucose tolerance not meeting the criteria for diabetes, amputation, current or previous foot ulcer, use of topical pain medication within the previous seven days, or history of hypersensitivity to capsaicin.

The primary endpoint of the study was the percentage change in the daily numeric pain rating scale according to question 5 of the Brief Pain Inventory-Diabetic Neuropathy (BPI-DN) from baseline to the mean daily score over the two- to eight-week follow-up period.

There were nine secondary study endpoints, including time to treatment response and change in sleep interference (question 9F of the BPI-DN). Seven safety and tolerability assessments were listed independently of the primary and secondary endpoints.

The researchers screened 761 patients at 29 participating U.S. sites; 369 of the 761 patients fulfilled the inclusion and exclusion criteria and participated in the study. Failure to meet the glycemic control criteria was the main reason for the high number of patients who were screened but not enrolled in the study.

Most participants were Caucasian (71.3%), and baseline demographics were similar between the treatment and control arms.

Use of pain medication was similar among the treatment and placebo arms, with 76.3% of patients in the capsaicin group taking pain medications compared to 71.6% in the placebo group. Patients were randomized 1:1 to receive a single treatment with an 8% capsaicin patch or an identical placebo patch to painful areas on the feet for a period of 30 minutes. The treatment area was mapped at screening and application visits. A local anesthetic cream was applied prior to the application of the treatment/placebo patch. Patients were required to call daily and report their average pain over the previous 24 hours. Patients also visited the clinic at weeks 2, 4, 8, and 12 for review.

Application of a capsaicin patch can cause local pain and erythema. This raised the possibility of functional unblinding in the treatment arm of the study. Extra steps were taken to try to minimize this risk. The staff

assigned to apply patches (capsaicin or placebo) were different from the staff who assessed the safety and efficacy of these patches.

Seventeen screened and enrolled patients did not complete the study. Nine patients discontinued in the capsaicin arm — seven patients withdrew from the study and two patients were lost to follow-up. Eight patients discontinued in the placebo arm — six patients withdrew from the study, one patient was lost to follow-up, and one patient discontinued because of a treatment emergent adverse event. The treatment emergent adverse event was hypertension, which was not thought to be related to the study.

An intention-to-treat analysis showed a reduction in the average daily pain from baseline to weeks 2 to 8 in the capsaicin vs. placebo group (mean [SD] = -27.4% [26.79%] vs. -20.9% [28.92%], respectively; P = 0.025). The authors interpreted this as "modest but within the boundary of statistical significance" for a reduction in average daily pain. The authors recommended that clinicians decide for themselves as to the clinical relevance of these findings.

Secondary endpoints included time to treatment response and sleep interference. The median time to treatment response was shorter with the 8% capsaicin patch than the placebo patch, with 50% of patients achieving a ≥ 30% reduction in average daily pain after 19 days (95% confidence interval [CI], 12-37) in the 8% capsaicin patch group vs. 72 days (95% CI, 190 to noncalculable) in the placebo group.

A greater mean percent of reduction in the BPI-DN sleep interference score was seen in the 8% capsaicin group vs. the placebo group from baseline to between weeks 2 to 8 (P = 0.030 for weeks 2 to 8; P = 0.020 for weeks 2 to 12). Clinically, this means that people in the treatment arm enjoyed better sleep than those in the placebo arm of the study.

About 46.8% of patients in the capsaicin group reported treatment adverse events as opposed to 33.9% in the placebo group. Most were mild to moderate in severity, with three patients in the capsaicin group reporting severe treatment-associated adverse events, burning sensation (n = 2), and application site pain (n = 1). There were no drug-related treatment adverse events, and no drug-related study discontinuations were necessitated in either group.

The change in sensory perception was measured at the end of the study, showing that most patients had no change in sensation or slightly improved sensation in both capsaicin and placebo groups. Specifically, 52.5% to 83.8% of patients across tests had no change, and 12% to 30% across tests had improved sensation in both groups.

Overall, the study authors concluded that a single 8% capsaicin patch provided modest improvements in pain relief compared with a placebo patch over 12 weeks for patients with painful diabetic peripheral neuropathy. They acknowledged that the treatment delta observed was narrow but stated that it was within the boundary of statistical significance as laid out in the intention-to-treat analysis.

■ COMMENTARY

Painful diabetic peripheral neuropathy can be very debilitating. Consultations can be frustrating for both physician and patient when the diabetes is well-controlled metabolically but the patient is unable to sleep despite trying usual treatments. This study found that the 8% capsaicin patch provided modest pain relief and sleep quality improvements in patients with painful diabetic peripheral neuropathy.

The onset of pain relief in the capsaicin arm occurred (on average) one week later than studies of capsaicin in other groups (e.g., HIV, post-herpetic neuralgia).[10] The authors proposed a number of possible explanations for this, including thickened skin, dehydration, or a reduction in the number of vanilloid receptors.

This study has a number of significant limitations. As noted above, many of the study team members had conflicts of interest. Additionally, the paper referencing was both unconventional and inaccurate. The study excluded patients with foot deformities, such as Charcot's foot, amputation, or foot ulcers. The study results were at best "within the boundary of statistical significance." However, the treatment was well-tolerated. Given the favorable safety profile of the patch, the lack of alternative effective options, and the negative effect of the combination of chronic pain plus lack of sleep on quality of life, this patch is worth considering for patients with painful diabetic peripheral neuropathy who fail to respond to other interventions. ■

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CME INSTRUCTIONS

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CME QUESTIONS

1. **Which of the following is true based on the study of children and physical activity?**
   a. Young children observed to have higher number of sedentary periods on the accelerometer developed more symptoms of depression over time.
   b. Young children with higher levels of moderate to vigorous physical activity (MVPA) had more symptoms of depression over time.
   c. Young children with higher levels of MVPA had lower numbers of symptoms of depression over time; the sedentary periods were not correlated with depressive symptoms.
   d. Young children with higher levels of MVPA and lower levels of sedentary periods had a decreased number of symptoms of depression over time.

2. **Which of the following statements is *false* regarding the study by Robinson et al on exercise training in younger and older adults?**
   a. This study showed that there was no difference in insulin sensitivity between the two age groups at baseline, despite lower mitochondrial respiration in older adults.
   b. This study showed that free fat mass increased in all age groups, with the greatest increase in the resistance training group of subjects 18 to 30 years of age.
   c. Resistance training increased VO_2 peak and mitochondrial function, while combined training had lower improvements than high-intensity interval training in VO_2 peak and fat free mass.
   d. Despite an increase in protein abundance, mRNA was inversely related to mitochondrial and ribosomal protein abundance.
   e. All of the above

3. **In the study about weight loss and exercise in women with a history of breast cancer, which of the following is true about the web- or phone-based intervention groups compared to usual care?**
   a. There was more weight loss at 12 months.
   b. There was less decrease in overall physical exercise at 12 months.
   c. There was less moderate-intensity exercise at 12 months.
   d. There was less weight loss at 6 months.

4. **Painful diabetic peripheral neuropathy:**
   a. affects one quarter of patients with type 2 diabetes.
   b. does not affect sleep quality.
   c. has a range of highly efficacious well-tolerated oral treatment options.
   d. does not have a placebo response.

[IN FUTURE ISSUES]

- Vitamin D and colorectal cancer
- Omega-3 fatty acids for cardiovascular disease
- Essential oils and depression
- Migraine: Prevention and treatment