



Indiana Medicaid Drug Utilization Review Board Newsletter

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Indiana Medicaid DUR Board

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Inside this Issue

- Exercise To Reduce Depression
- Cost comparison table for brand and generic medications
- Plavix update
- Program Assistance and PDL Listing Information
- Top 20 Drugs for 1Q2008

Exercise To Reduce Depression

A

relationship between physical activity and mental health has long been recognized with much of the attention focused on activity levels and depression.¹ This relationship was recently confirmed when data from the National Comorbidity Survey indicated that individuals who exercise regularly were less likely to report being depressed or having an anxiety disorder.² In this data, the relationship between regular physical activity and decreased rates of depression (odds ratio 0.75) was fairly specific. Dysthymia rates appeared to be minimally affected and there was no effect seen on bipolar disorder or other psychotic disorders. Only selected anxiety disorders, such as panic attacks and phobias, had a relationship similar to depression. Beneficial effects of exercise in minimizing the risk of depression was also shown in a recent study that followed a cohort of 424 adults for 10 years.³ Subjects in this study were diagnosed with major depression at baseline and then re-assessed at four time points over 10 years. A higher level of physical activity was associated with less concurrent depression, even after controlling for gender, age, medical problems, and negative life events. In other recent publications the use of exercise as a potential treatment for depression has been investigated. This newsletter will briefly review the historical data related to using exercise as a treatment for depression and present the findings from some of the recent studies.

Historical Perspective:

Exercise is generally broken down into three basic types: aerobic exercise (e.g. walking or jogging), anaerobic exercise (e.g. weightlifting), or flexibility exercise (e.g. yoga). Most exercise intervention studies involving depression have investigated the effects of aerobic-type exercise, sometimes supervised and sometimes self-reported. A 2002 article reviewed 12 studies published between 1979 and 1997 that investigated exercise as a treatment for depressed adults.⁴ Most of these studies compared exercise to

psychosocial interventions or a "wait list" (no treatment) condition. Only two used a medication in the comparison group, one in a controlled manner and the other compared routine psychiatric care to such care delivered along with prescribed aerobic exercise. Some studied younger adults while others included subjects in their seventies. All 12 of these studies found exercise to be just as effective – and in some cases, more effective – as other types of interventions. Of course, the medications most commonly employed in the management of depression have changed substantially over the years, and even the diagnostic criteria have been modified during the time frame covered by this review. So, what does the more recent literature tell us about the use of exercise as a management strategy to combat depression?

Recent Studies:

Controlled Trial vs. Medication

In a study published in 2007, Blumenthal and Associates investigated whether patients participating in aerobic exercise achieved reductions in depression greater than placebo and comparable to a standard antidepressant medication.⁵ They studied a total of 202 adults (age ≥ 40 years, 153 women and 49 men) who were diagnosed with major depressive disorder (MDD) using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria.⁶ Subjects were assigned randomly to home-based aerobic exercise ($n = 53$), supervised aerobic exercise ($n = 51$), sertraline ($n = 49$), or placebo ($n = 49$). Participants in the supervised aerobic exercise program attended three supervised group exercise sessions per week for 16 weeks with assigned training ranges equivalent to 70% to 85% maximum heart rate reserve. Participants in the home-based exercise program received the same exercise prescription but exercised at home on their own. Participants in the medication groups who were given sertraline could have the

Continued from page 1

Depression and Exercise (cont'd)

dose increased in 50 mg increments to 200 mg per day contingent on therapeutic response and presence of side effects. The mean dose of medication prescribed over the course of the study was similar for the sertraline and placebo groups (mean = 2.3 tablets per day for both groups).

The primary end point was MDD remission, defined as no longer meeting the diagnostic criteria for major depression and achieving a Hamilton Rating Scale for Depression (HAM-D) score of <8. The results indicated home-based exercise, supervised exercise, and active medication tended to achieve higher remission rates compared with placebo ($p = 0.057$). There were no statistically significant differences between the exercise groups and active medication or between home-based and supervised exercise. The unadjusted remission rates were: supervised exercise = 45%; home-based exercise = 40%; medication = 47%; and placebo = 31%. Because there was no placebo run-in, the data was also analyzed after excluding early responders. Patients with depression who exhibit significant improvement rapidly (<1 week) have been shown in other studies to be placebo responders. In this study, 14 subjects (7%) exhibited more than 50% reduction in depression scores after the first week of treatment: five (9%) patients in home exercise; one (2%) patient in supervised exercise; four (8%) patients on medication; and four (8%) patients receiving placebo. When the analysis was limited to the patients who did not show an early response, all three active treatment groups had significantly higher remission rates compared with placebo ($p = 0.022$). Again, the differences between the exercise groups and medication ($p = 0.879$), and the difference between the two exercise groups compared to each other ($p = 0.519$), were not statistically significant.

The finding that exercise interventions, as employed in this study, were comparable to an SSRI in producing remission is impressive and consistent with results from older studies. This study

was not powered to determine if exercise was equivalent to the antidepressant, but was adequate to demonstrate non-inferiority. The demonstration of substantial benefit should promote recommending exercise to depressed individuals.

Exercise as Augmentation to Medication

A pilot study published in 2006 indicated that exercise can be effectively employed to augment the response to antidepressant medication.⁷ In this pilot study, 17 adults – diagnosed with MDD (using the DSM-IV criteria⁹) who had incomplete remission of depressive symptoms following adequate treatment with an antidepressant – participated in a 12-week exercise program while continuing to take their antidepressant medication at the same dosage level. The exercise consisted of a combination of supervised and home-based sessions and was designed to be consistent with current public health guidelines recommendations (moderate aerobic exercise 30 minutes per day at least 5 days a week OR intense aerobic exercise 20 minutes per day at least 3 days a week). The medication used in this study was an SSRI. Intent to treat analysis of all subjects indicated significant decreases in HAM-D scores (5.8 points, $p < 0.008$). An analysis of those who completed all 12 weeks of the study ($n = 8$) found that their HAM-D score decreased by an averaged 10.4 points. These positive results were so encouraging that the investigators have undertaken a more comprehensive, NIMH-funded study to assess the efficacy of exercise as an augmentation strategy.⁸

Amount of Exercise

With the growing evidence that exercise can be an effective intervention for the management of depression, attention needs to be paid to what is the optimal amount of exercise to recommend. A study published in 2005 indicates that the amount of exercise may be an important determinant of how much benefit a depressed individual might receive.⁹ In this

study, 80 individuals who were diagnosed with MDD using the DSM-IV criteria⁶ were randomly assigned to supervised exercise or exercise placebo (stretching). The exercise groups were divided into high-dose (17.5 kcal/kg/week energy expenditure) or low-dose (7kcal/kg/week energy expenditure). The high-dose was designed to correlate with the amount of physical activity recommended in public health recommendations. The exercise was supervised and occurred over a 12 week time period. The primary outcome measure was the change in HAM-D rating scores from baseline to 12 weeks. Response and remission were secondary outcomes. The results showed the high-dose condition was significantly more effective than the low-dose or control conditions in reducing weekly HAM-D scores ($p = 0.04$ and $p = 0.03$, respectively). The low-dose condition was not significantly different from the control condition ($p = 0.88$).

At the last observation, 24 of the 80 randomized participants had responded to treatment and 20 of the 80 had achieved remission (mean HAM-D score=5.0). The response rate was highest in the high-dose group. While this study did not include an active medication group, again exercise was shown to be effective in treating depression to remission. A more recent article indicates that even less strenuous exercise may be beneficial in helping to stave off depression.¹⁰ This study surveyed almost 20,000 people to examine the relationship between mental health and physical activity. They found that any form of daily physical activity was associated with a lower risk of psychological distress. A dose-response relationship was apparent with only moderate reductions with less frequent activity and the strongest effects observed for sports (OR = 0.59, 95% CI = 0.54 - 0.66, $p < 0.001$). Therefore, it appears that greater levels of exercise work better but any activity is better than none.

Continued on Page 3

Continued from Page 2

Mechanism of Action

If exercise works to treat depression, the legitimate question that arises is, How? Speculation has ranged from improved socialization due to exercise in a group setting to exercise having an effect on central monoamine (norepinephrine and serotonin) functioning.⁴ In addition to monoamines, depression is associated with hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and studies have shown that exercise training leads to an attenuation HPA axis response to stress.¹¹ A more recent hypothesis has centered on the potential for exercise to promote the synthesis of new neurons in the brain.¹² It was recently discovered that antidepressant medications appear to increase the synthesis of new neurons and animal studies have demonstrated a 2-3 fold increase in hippocampal neurogenesis associated with regular exercise compared to control animals. While the mechanism may be of scientific interest, from a clinical perspective it is more important to recognize that regular exercise has a beneficial effect on the symptoms of depression than to understand how that might happen.

Conclusion

Available evidence strongly supports an association between increased levels of physical activity and decreased signs and symptoms of depression in the general population. Accumulating evidence supports the potential for regular exercise to serve as a treatment strategy for individuals suffering from major depression. Considering that exercise is a low-risk intervention with potential multiple benefits, it seems to be time to do more to encourage depressed individuals to push themselves to increase their level of physical activity.

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Preferred Drug List Update:

Recently FDA approved a new 300-mg strength of Plavix[®] and is approved as a one-time loading dose with aspirin for the indication of acute coronary syndrome followed by a daily 75-mg dose of Plavix[®] and aspirin.

For Indiana preferred drug list, both strengths (75-mg and 300-mg) of Plavix[®] are preferred. In order to avoid confusion and mishaps at the pharmacies, the T-Committee and the DUR Board recommended to add quantity limit of 1 tablet per prescription for Plavix[®] 300-mg. By adding the quantity limit, it would also increase the patient drug safety as taking Plavix[®] 300-mg daily can increase the risk of bleeding and other severe consequences.

Table 1. Cost Comparison of Generic vs. Brand Name Agents for Indiana Medicaid Fee-for-Service Program

Generic Name	Generic Cost for Quantity Specified <small>(Allowable ingredient amount that could be paid to the dispensing pharmacy as of 06/13/2008, does not include dispensing fee)</small>	Brand Name	Brand Cost for Quantity Specified <small>(Allowable ingredient amount that could be paid to the dispensing pharmacy as of 06/13/2008, does not include dispensing fee)</small>
Antidepressants (SSRIs / SNRIs)			
Citalopram 20mg	\$3.43 (60 tabs)	Celexa 20mg	\$180.78 (60 tabs)
Duloxetine	Generic unavailable	Cymbalta 20mg	\$105.18 (30 caps)
Escitalopram	Generic unavailable	Lexapro 10mg	\$80.20 (30 tabs)
Escitalopram	Generic unavailable	Lexapro 20mg	\$83.69 (30 tabs)
Fluoxetine 20mg	\$0.74 (30 caps)	Prozac 20mg	\$151.78 (30 caps)
Paroxetine 20mg	\$6.65 (30 tabs)	Paxil 20mg	\$97.04 (30 tabs)
Sertraline 50mg	\$2.87 (30 tabs)	Zoloft 50mg	\$93.95 (30 tabs)
Venlafaxine 75mg	\$55.25 (30 tabs)	Effexor 75mg	\$58.02 (30 tabs)
Psychotropic Agents			
Aripiprazole 20mg	Generic unavailable	Abilify 20mg	\$519.83 (30 tabs)
Clozapine 100mg	\$201.62 (180 tabs)	Clozaril 100mg	\$969.10 (180 tabs)
Haloperidol 10mg	\$104.18 (90 tabs)	Haldol 10mg	Brand unavailable
Haloperidol 20mg	\$209.75 (90 tabs)	Haldol 20mg	Brand unavailable
Olanzapine 10mg	Generic unavailable	Zyprexa 10mg	\$343.60 (30 tabs)
Olanzapine 20mg	Generic unavailable	Zyprexa 20mg	\$686.70 (30 tabs)
Paliperidone 6mg	Generic unavailable	Invega 6mg	\$328.65 (30 tabs)
Perphenazine 4mg	\$20.84 (90 tabs)	Trilafon 4mg	Brand unavailable
Perphenazine 8mg	\$71.98 (90 tabs)	Trilafon 8mg	Brand unavailable
Quetiapine 300mg	Generic unavailable	Seroquel 300mg	\$275.88 (30 tabs)
Quetiapine XR 300mg	Generic unavailable	Seroquel XR 300mg	\$275.88 (30 tabs)
Quetiapine 400mg	Generic unavailable	Seroquel 400mg	\$324.23 (30 tabs)
Risperidone 2mg	Generic unavailable	Risperdal 2mg	\$212.97 (30 tabs)
Risperidone 4mg	Generic unavailable	Risperdal 4mg	\$335.99 (30 tabs)
Ziprasidone 60mg	Generic unavailable	Geodon 60mg	\$200.97 (30 caps)
Ziprasidone 80mg	Generic unavailable	Geodon 80mg	\$200.97 (30 caps)
Sleep Agents			
Eszopiclone 2mg	Generic unavailable	Lunesta 2mg	\$132.93 (30 tabs)
Ramelteon 8mg	Generic unavailable	Rozerem 8mg	\$92.97 (30 tabs)
Zaleplon 10mg	Generic unavailable	Sonata 10mg	\$106.06 (30 caps)
Zolpidem Tartrate 10mg	\$1.18 (30 tabs)	Ambien 10mg	\$129.51 (30 tabs)
Zolpidem Tartrate ER	Generic unavailable	Ambien CR 12.5mg	\$122.39 (30 tabs)
Temazepam 15mg	\$2.10 (30 caps)	Restoril 15mg	\$187.43 (30 caps)
Temazepam 30mg	\$2.73 (30 caps)	Restoril 30mg	\$187.43 (30 caps)

Program Assistance

All prior authorization requests or questions regarding the PDL should be directed to the ACS Clinical Call Center at 1-866-879-0106.

Preferred Drug List (PDL)

The fee-for-service PDL may be found at the following Web site:

<http://www.indianapbm.com/>

Top 20 Drugs for 1Q 2008

Top 20 Drugs 1 st Quarter 2008 Ranked by Total Amount Paid		
Drug	Total Paid	Total Claims
Risperidone	\$3,888,540.15	14,525
Aripiprazole	\$3,366,192.77	9,058
Quetiapine Fumarate	\$3,332,856.21	13,041
Olanzapine	\$3,140,979.08	6,771
Antihemoph.FVIII Plas/ Alb Free	\$2,119,444.05	76
Divalproex Sodium	\$1,837,930.96	11,276
Antihemophilic Factor, Hum Rec	\$1,707,039.51	64
Lamotrigine	\$1,595,614.92	7,043
Topiramate	\$1,567,802.27	6,361
Insulin	\$1,328,700.88	9,619
Ziprasidone HCL	\$1,266,183.53	4,235
Oxycodone HCL	\$1,260,755.38	5,281
Fentanyl	\$1,183,674.87	3,758
Levetiracetam	\$1,108,544.28	4,310
Factor VIIA, Recomb (BHK Cells)	\$985,902.00	7
Atorvastatin Calcium	\$977,740.24	8,895
Fluticasone/Salmeterol	\$967,635.08	5,154
Duloxetine HCL	\$895,282.68	7,183
Methylphenidate HCL	\$815,302.13	8,740
Clopidogrel Bisulfate	\$795,180.07	5,865

Top 20 Drugs 1 st Quarter 2008 Ranked by Total Claims Paid		
Drug	Total Claims	Total Paid
Hydrocodone/APAP	45,165	\$383,992.95
Aspirin	40,012	\$32,165.92
Docusate Sodium	37,824	\$77,468.07
Alprazolam	33,590	\$216,510.59
Acetaminophen	32,535	\$82,730.52
Calcium Carb/Vit D	31,482	\$64,222.59
Multivitamins	26,665	\$37,444.86
Loratadine	25,010	\$233,175.75
Clonazepam	23,127	\$112,016.66
Lorazepam	21,539	\$128,096.03
Albuterol	18,844	\$426,213.75
Omeprazole	17,968	\$514,122.34
Multivitamins with Minerals	16,468	\$48,194.65
Risperidone	14,525	\$3,888,540.15
Levothyroxine	13,205	\$92,488.19
Lisinopril	13,111	\$54,920.73
Quetiapine Fumarate	13,041	\$3,332,856.21
Amoxicillin Trihydrate	12,287	\$91,025.20
Diazepam	12,263	\$284,679.31
Ferrous Sulfate	11,933	\$11,136.91