Exercise-Induced Analgesia
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Outline
- Exercise is Medicine
- Basic Pain Review
- Quantitative Sensory Testing
- Exercise-Induced Hypoalgesia
  - Humans
  - Clinical Populations
- Exercise-Induced Hyperalgesia
- Adherence
- Cost Effectiveness
- Mechanisms
- Prevention

Physical Activity (WHO)
- Physical Activity= any bodily movement produced by skeletal muscles that requires energy expenditure
- Exercise= a subcategory of physical activity that is planned, structured, repetitive, and purposeful in the sense that the improvement or maintenance of physical fitness is the objective

Physical Activity vs. Inactivity
- Meet exercise guidelines but still have sedentary lifestyle
- "Prolonged sedentary time was independently associated with deleterious health outcomes regardless of physical activity" (Biswas et al., Sedentary Time and Its Association with Risk for Disease Incidence, Mortality, and Hospitalization in Adults: A Systematic Review and Meta-analysis, Ann Intern Med, 2015)
- Half an hour of TV viewing may shorten life to a similar degree as smoking a cigarette ~11 min (Veerman et al., Television Viewing Time and Reduced Life Expectancy: A Life Table Analysis, Br J Sports Med, 2011)
- In adolescents, pain relief following exercise was negatively associated with sedentary behavior (Stolzman et al., submitted)

Physical Activity Initiatives

Use of Pedometers in MSK diseases
- Aim: to investigate evidence for effectiveness of pedometer-driven walking programs to promote physical activity among patients with musculoskeletal disorders (Mansi et al., 2014)
- 7 studies (484 participants)
- Avg. increase 1950 steps/day compared with baseline
- 4 studies: improved pain and/or physical function
- Conclusion: strong evidence in effectiveness of pedometer walking interventions
- Clinical Application:
  - Incorporate into practice
  - Physical activity vs. Exercise

House Bill Would Provide Tax Incentive for Physical Activity Expenses
Rep. Charles Boustany, R-La., introduced the Personal Health Investment Today (PHIT) Act (H.R.1218), a bill that would expand the definition of a medical expense to include qualified physical activities, such as membership in a fitness facility or equipment purchased for use in a physical activity program. The bill would allow individuals to place up to $2,000 a year in existing pre-tax medical accounts for reimbursement of physical activity expenses.

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Physical Activity Initiatives
Physical inactivity is the 4th leading cause of death globally
- 3.3 million attributable deaths/year
- More than half of U.S. adults do not meet the physical activity guidelines
- 40% of U.S. primary care physicians do not meet the guidelines
- Active 80 year olds have lower risk of death than inactive 60 year olds

Exercise is Medicine—ACSM Initiative (www.ExerciseIsMedicine.org)

Institute of Medicine Report, 2011
- The 2010 Patient Protection and Affordable Care Act required the Department of Health and Human Services to enlist the Institute of Medicine (IOM) in examining pain as a public health problem. Purpose was to assess the state of the science regarding pain research, care, and education.
- Chronic pain affects about 100 million American adults—more than the total affected by heart disease, cancer, and diabetes combined.
- Pain costs the nation up to $635 billion each year in medical treatment and lost productivity.

Pain (IASP)
- An unpleasant sensory and emotional experience associated with actual or potential tissue damage
- Subjective
- International Association for the Study of Pain
  - www.iasp-pain.org
  - Taxonomy
  - Global Year Against Pain
    - 2015: neuropathic pain
    - 2016: pain in the joints
    - 2017: surgical pain

Pain Review

Institute of Medicine Report, 2011
- Effective pain management is a moral imperative
  - A professional responsibility
  - The duty of people in the healing professions
- Need for interdisciplinary approaches
  - Produces the best results for people with the most severe and persistent pain

Acute Pain
- Pain associated with tissue damage
- Protective—prevents further tissue damage
  - Develop healing behaviors
### Acute Pain
- Cutaneous pain
  - easy to localize
  - sharp
  - rarely refers
- Muscle pain
  - difficult to localize
  - dull/aching/cramp-like
  - frequently refers to superficial structures
- Neuropathic
  - burning
  - shooting
  - tingling
- Visceral
  - diffuse
  - dull
  - stabbing
  - cramping
  - refers

### Chronic Pain
- Impairment is greater than would be expected from the physical findings
- Not dependent on tissue damage
  - Little to no tissue damage
- Non-protective
  - Serves no adaptive purpose
- Less than 50% of patients report pain relief with treatment

### Patient Perspective
*There is no visible blood test or X-ray to show a trauma, do not look sick.*
- A person with chronic pain

### Terminology (IASP)
[www.iasp-pain.org/Taxonomy#Analgesia](http://www.iasp-pain.org/Taxonomy#Analgesia)
- Hyperalgesia: Increased pain from a stimulus that normally provokes pain
  - Primary - peripheral sensitization
  - Secondary - central sensitization
- Hypoalgesia: diminished pain response to normally painful stimulus
  - Increase in pain threshold
  - Increase in pain tolerance
  - Decrease in pain ratings
- Analgesia (IASP): absence of pain in response to stimulation which would normally be painful

### Biomedical Model: old
- Biopsychosocial Model: new

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**Figure 1. The Biopsychosocial Model of Pain**

- Biological Factors
  - Disease activity
  - Overall physical condition
  - Vascular input
- Psychological Factors
  - Pain behavior
  - Pain coping
  - Self-efficacy
  - Indicators
  - Cognitive distortion
  - Personality characteristics
- Social Factors
  - Social support
  - Marital adjustment/individual responses
  - Children/parental responses
  - Cultural practices

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**Psychosocial Assessments**

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*** Applicable to EIH mechanisms and the prescription of exercise
Psychosocial

• Pain Catastrophizing: negative mental state during actual or anticipated pain experience
  ✓ Related to overall poor treatment outcomes (Edwards et al., 2006)
  ✓ Predicts poor outcomes following exercise-based rehabilitation in people with chronic neck pain (Cecchi et al., 2011)
  ✓ Mediates relation between strenuous exercise participation and pain reports in healthy adults (Goodin et al., 2009)

• Fear Avoidance Behaviors
  ✓ People with high levels of activity-avoidance beliefs are less fit and report more severe pain (de Bruijn et al., 2011)
  ✓ For people with chronic musculoskeletal disorders, fear of movement was related to reports of pain during physical activity (Damsgard et al., 2010)

Abnormal endogenous pain modulation is a shared characteristic of many chronic pain condition. Staud Review, 2012

• Chronic pain-interaction between peripheral input and CNS pain mechanisms.
  • CNS includes both pain facilitation and inhibition (measure with quantitative sensory testing)
    ✓ Increased pain facilitation (temporal summation) and ineffective pain inhibition (conditioned pain modulation)
    ✓ Fibromyalgia, temporomandibular joint disorder, irritable bowel syndrome, headache, and chronic fatigue syndrome
    ✓ Ineffective pain inhibition in OA patients normalized after joint replacement (Reversible)

Brainstorm

• Would you modify your exercise prescription for a patient with a history of chronic pain?
• You are implementing an exercise program for someone with a total knee replacement with a history of Fibromyalgia

Quantitative Sensory Testing

• Measures pain response to various stimuli providing information related to peripheral and central nociceptive functioning
  • Pain thresholds (primary and secondary hyperalgesia), allodynia, pain ratings, temporal summation, conditioned pain modulation
  • Frequently used to characterize pain conditions
• Noxious Stimulus
  ✓ Pressure/mechanical
  ✓ Electrical
  ✓ Thermal: hot or cold
Pain Thresholds and Ratings

- 2 sessions: 1) 30 min cycling at 75% VO2 and 2) quiet rest
- Pressure pain device placed on finger for 2 min pre/post exercise

Pain Facilitation: Temporal Summation

- Increase in pain perception to a repetitive or constant noxious stimulus
- Self-reported total and vigorous physical activity predicts temporal summation (Naugle and Riley, 2014)
  - Did not predict pain threshold or suprathreshold pain ratings

Pain Inhibition: Conditioned Pain Modulation

- Pain Inhibits Pain
- Counterirritant
- Inhibition of pain in response to a noxious stimuli outside the site of injury
- Tests the integrity of central inhibitory pathways
- Reduced in patients with chronic pain

Conditioned Pain Modulation

- Self-reported physical activity predicts CPM in adolescents and adults across lifespan (Naugle and Riley, 2014; Semley et al., submitted)
- Lean mass (not fat mass) predicts CPM in overweight/obese and normal weight adolescents (Stolzman et al., submitted)
- Higher CPM in triathletes than non-athletes (Geva and Defrin, 2014)

Exercise-Induced Hypoalgesia: Healthy Adults Across the Lifespan


- Examined isometric, dynamic, and aerobic exercise
- All three types of exercise reduce experimental pain in healthy adults (moderate to large mean effect sizes)
- In chronic pain populations, effect sizes were highly variable
  - Optimal dosage could not be determined with available data
Pain relief is associated with aerobic exercise of higher intensity (60-75% VO2 max) and longer duration (>10 minutes)

Smaller effects with lower intensities and durations (Koltyn, 2000, 2002; Naugle et al, 2012)

Adolescents
- 62 adolescents (15.1±1.8 years, 29 males)
- Across weight status
  - normal weight (n=33) or overweight/obese (n=29)
- Physical Fitness Levels
- Inflammatory Markers
- Conditioned Pain Modulation

Isometric (Static) Exercise
- Most common form of muscle contraction
- Easy to prescribe and individualize
- Applicable to majority of individuals (limited mobility)
- Importance of intensity and duration not clear
- Four separate sessions
  - 3 Maximal Voluntary Contractions (MVC)
  - 25% MVC X 2 min
  - 25% MVC x task failure
  - 80% MVC x task failure
- Measured pain threshold and pain ratings before and after the static contractions

Acute Hormonal Fluctuations
- 25% MVC held to task failure (n= 20)
  - Midfollicular (5-8 days post menses)
  - Midluteal (6-8 days post ovulation; per ovulation kit)
- Pain threshold and pain ratings pre/post isometric contraction
Acute Hormonal Fluctuations

Hoeger Bement et al, 2009

Older Healthy Adults
n= 24, 72 yrs

Pain relief was similar across all 3 tasks

Lemley et al., 2014

QST: Temporal Summation

• Naugle et al., 2014
• Healthy young men and women
• 3 min isometric handgrip at 25% MVC
  ✓ Pressure pain thresholds increased
  ✓ Temporal summation decreased
  • Greater catastrophizing associated with smaller decreases in TS
  ✓ Suprathreshold heat pain ratings decreased for women

QST: Temporal Summation

• Isometric Exercise
  ✓ Exhaustive and non-exhaustive decreased temporal summation (Koltyn et al., 2012; Hoeger Bement et al., 2008; Lemley et al., 2013; Vaegter et al., 2014)
• Aerobic Exercise
  ✓ Decreased temporal summation (Vierck et al., 2001; Naugle et al., 2014; Hoffman et al., 2004)
  ✓ No change in temporal summation (Ruble et al., 2005)

QST: Conditioned Pain Modulation

Stolzman et al., submitted

Relation Between CPM and EIH

Adolescents

Adults

Stolzman et al., submitted

Lemley et al., 2015
EIH: Healthy Populations

- Aerobic Exercise: moderate/high intensity of longer duration
  - Adolescents experience EIH at same dose
  - Older adults?
- Isometric Exercise: both high and low intensity decrease pain in young adults
  - Low intensity contractions must be held for longer duration
  - Greatest decrease in pain occurred following the low-intensity isometric contraction held for a longer duration (i.e. to exhaustion)
  - Response may be more pronounced in women compared with men
- Not influenced by phase of the menstrual cycle
- Older Adults: not task specific
- Quantitative Sensory Testing
  - Decreases pain facilitation (temporal summation)
  - Associated with pain inhibition (conditioned pain modulation)

Systematic Reviews on Pain Relieving Benefits of Exercise in Patient Populations

Patient Populations

- Chronic Musculoskeletal Pain
  - Walking exercise (O’Connor et al., 2015)
- Bone and Muscle Health
  - Exercise beneficial for most MSK conditions (Hagen et al., 2012)
- Fibromyalgia
  - Aerobic (Nuesch et al., 2013)
  - Gold evidence - supervised aerobic exercise (Busch et al., 2007)
- Hip OA
  - Land based or water based with slight to moderate intensity 2-3/wk for at least 4 weeks (Hauser et al., 2010)
  - Aquatic low/moderate evidence (Bidonde et al., 2014)
- Strengthening (Busch et al., 2013)
  - Moderate/high intensity resistance training (low evidence)
  - 8 wks aerobic exercise superior to moderate intensity resistance training to improve pain (low evidence)
- Lower Extremity Osteoarthritis
  - Low Back Pain
    - Low Back Pain
      - LBP
        - Acute LBP and sciatica (Dahm et al., 2010)
          - Acute LBP: small benefits in pain relief for advice to stay active compared to rest in bed
          - Sciatica: little/no difference between two approaches
        - Strongest evidence for chronic LBP (Hayden et al, 2005)
        - Walking (low/moderate evidence) (Hendrick et al., 2010)
        - Motor control exercise similar to manual therapy or other forms of exercise (Macedo et al., 2015)
        - Exercise and spinal manipulation offer similar benefits (low evidence) (Standaert et al., 2011)

Arthritis

- Hand OA
  - No effect on hand pain (Ye et al., 2011)
  - Limited evidence (Kjeken et al., 2011)
- Juvenile Idiopathic Arthritis
  - No evidence that exercise improves function, quality of life, aerobic capacity, or pain (Takken et al., 2008)
- Rheumatoid Arthritis
  - Aerobic exercise (Scarpelli et al., 2011)
  - Aerobic exercise with muscle strength training recommended (Hurkmans et al., 2009)
Low Back Pain

- Post-treatment exercise can prevent recurrences of back pain (Choi et al., 2010)
- LBP in Children and Adolescents (Michaleff et al., 2014)
  ✓ “Exercise interventions appear to be promising”
- Pelvic and Back Pain in Pregnancy
  ✓ Several types of exercise training beneficial (pelvic floor, muscle strength, aerobic, and aquatic) (moderate evidence) (van Benten et al., 2014)
  ✓ Exercise tailored to stage of pregnancy (low evidence) (Pennick and Liddle, 2013)
  ✓ 16-20 week training program was no more successful than usual care at preventing pelvic and LBP (Pennick and Liddle, 2013)

Neck

- Mechanical Neck Disorders
  ✓ Strengthening: inclusion of stretching and aerobic exercise enhances benefits (O’Riordan et al., 2014)
  ✓ Cervical and scapular stretching and strengthening exercises for chronic neck pain and cervicogenic headaches (low/moderate evidence) (Key et al., 2012)
- Chronic Nonspecific Neck Pain
  ✓ Therapeutic exercise (Bertossi et al., 2013)
- Nonspecific Neck Pain in Office Workers
  ✓ Muscle strengthening and/or endurance exercise recommended (Shawong et al., 2011)
- Cervicobrachial Pain (Salt et al., 2011)
  ✓ Inconclusive: potential benefits with exercise
  ✓ Future studies needed to identify subgroups

Spine

- Degenerative Lumbar Conditions (Gilmore et al., 2014)
  ✓ Pre/post-operative exercise in addition to standard PT (very-low evidence)
- Spondyloarthitis (O’Dwyer et al., 2014)
  ✓ Exercise—not clear on most effective type (low-level)
- Ankylosing Spondylitis (Dogfriudn ln la., 2008)
  ✓ Exercise better than no intervention
  ✓ Supervised better than home exercises
- Lumbar Spinal Stenosis
  ✓ Decompressive surgery more effective than land based exercise (Jarrett et al., 2012)
  ✓ Short-term benefit for leg pain (Ammendolia et al., 2013)
  ✓ Low evidence: unable to make recs for clinical practice (Ammendolia et al., 2013; Macedo ln la., 2013)
- Lumbar Disc Herniation with Radiculopathy
  ✓ Stabilization exercises (moderate evidence) (Hahn et al., 2010)

Shoulder

- Painful Shoulder Conditions (Marinko et al, 2011)
- Adhesive Capsulitis (Frozen Shoulder)
  ✓ Combination of manual therapy and exercise may not be as effective as glucocorticoid injection in the short-term (Page et al., 2014)
- Rotator Cuff Tendinopathy (Littlewood et al., 2012)
- Shoulder Impingement (Kuhn, 2009)
  ✓ HEP similar to supervised exercise
  ✓ Exercise effects augmented with manual therapy
- Upper Limb Fracture (Bruder et al., 2011)

Cancer

- Cancer (Mishra et al, 2012)
  ✓ Improves quality of life
  ✓ Influence of exercise mode, cancer type, and cancer treatment not known
- Advanced-Stage Cancer (Albrecht and Taylor, 2012)
  ✓ Exercise (resistance, aerobic, or combined) performed 2-3/week improved quality of life (strong evidence)
  ✓ Group better than home based (both are beneficial)
- Upper-Limb Impairments After Breast Cancer Treatment (De Groef et al., 2015)
  ✓ Multifactorial PT (manual stretching and active exercises) and active exercise improves postoperative pain
- Shoulder Dysfunction in Head and Neck Cancer
  ✓ Progressive resistance training (limited evidence) (Carvalho et al., 2012)

Patient Populations

- Patellofemoral Pain Syndrome
  ✓ Low quality but consistent evidence for exercise therapy: not clear on specific mode (van der Heijden et al., 2015)
  ✓ Systematic review on therapist-guided quadriceps-strengthening exercises (Kooiker et al., 2014)
  ✓ Beneficial with or without other interventions (strong evidence)
- Midportion Achilles Tendinopathy ( Rowe et al., 2012)
  ✓ Eccentric loading exercises (strong evidence)
  ✓ Concentric exercises (moderate evidence but inferior to eccentric exercises)
- Lateral Epicondylitis/Epicondylodylosis
  ✓ Support inclusion of eccentric exercise as part of multimodal therapy (Cullinan et al., 2014)
  ✓ Resistance exercise beneficial- optimal dose not defined (Raman et al., 2012)
Patient Populations

• Osteoporotic/Osteopenic Postmenopausal Women
  ✓ Greater pain improvements with long-duration exercise programs (>12 wks) and combined exercise (stretch, strengthening, posture) vs. strength alone (Li et al., 2009)

• Osteoporotic Vertebral Fractures
  ✓ Inconsistent results—low evidence (Giangregorio et al., 2013)

• Intermittent Claudication—pain free walking (Lane et al., 2014)
  ✓ Supervised walking therapy better than instructions on walking advice and HEP (Fokkenrood et al., 2013; Gommans et al., 2009; Fakhry et al., 2012)
  ✓ Alternative exercise modes (cycling, strength training, and upper extremity ergometry) may be beneficial when supervised walking exercise not an option (Lauret et al., 2014)

• Postpolio Syndrome
  ✓ Muscle strengthening (inconclusive) (Koopman et al., 2011)

• Headache
  ✓ Incorporating aerobic exercise into behavioral treatments appears promising: individual contribution of exercise is unclear (Bailie et al., 2013)
  ✓ Exercise is beneficial for tension type headaches and temporomandibular disorder muscle pain (small effect) (Fricton et al., 2009)
  ✓ Stretching and postural relaxation—no studies on aerobic exercise

• Spinal Cord Injury Chronic Pain (Boldt et al., 2014)
  ✓ Insufficient evidence

• Exercise-Related Groin Pain (Almeida et al., 2013)
  ✓ Hip and abdominal strengthening (low quality)

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Limitations

• Quality issue
  ✓ Poor description of dosage
  ✓ Lack of comparisons

• Adherence
  ✓ Exercise programs of relative short duration
  ✓ Progression
  ✓ Long-term effectiveness
  ✓ Few mechanistic studies

QST: Temporal Summation

• Rheumatoid Arthritis: submaximal bicycling test decreased temporal summation (Meeus et al., 2014)
• Fibromyalgia: Max treadmill test (modified Bruce protocol) increased temporal summation; temporal summation decreased in healthy controls (Vierck et al., 2001)
  ✓ Referenced frequently as indication that “exercise” makes central sensitization worse
• Knee OA: 12 week supervised exercise program decreased temporal summation (Henriksen et al., 2014)
• LBP: 5 min stationary cycling or lumbar extension exercises (3 set of 15 reps) did not change temporal summation (Bialosky et al., 2009)

QST: Conditioned Pain Modulation

• Rheumatoid Arthritis and CFS/FMS: CPM responses to a submaximal cycling test were inconclusive but seem to worsen (Meeus et al., 2015)
  ✓ Temporal summation decreased in patients with RA

Exercise-Induced Hyperalgesia

“I don’t prescribe exercise to my patients. It makes their pain worse.”
Exercise-Induced Hyperalgesia

- Pain with exercise is barrier to exercise participation
- Healthy Humans Review (Dannecker and Koltyn, 2014)
  - Many different modes, intensities, and duration can increase pain
  - Dose-response effects are mixed

DOMS

- Muscle stiffness, aching pain, and/or muscular tenderness about 24 hours after exercise completion
- Peaks within 72 hours and resolves 5-7 days
- Sensitive to stretch and activity

Pain During Exercise vs. Pain Following Exercise

Pain Response Changes Over Time in Patient Populations

- Andersen et al, 2008
  - Chronic neck pain (trapezius myalgia)
  - Supervised high intensity training 3x/wk for 10 weeks
    - Localized Strengthening
      - 70-80% maximal intensity reps
    - General Fitness (LE bicycling)
      - 50-70% maximal oxygen uptake for 20 min
- Measured acute and prolonged pain response

Subgroups (FMS, n= 15, 52 yrs)
FMS Subgroups: 25% MVC task failure

Exercise Induced Hyperalgesia

- **Education**
  - Initial increase in pain
  - DOMS vs. condition worsening
  - Hurt does not equal harm
- **Expectations**
  - Temporal aspect of pain
  - Evidence
- **Supplemental Pain Management**
  - Ice, TENS
  - Recovery
  - Progression

Exercise Adherence

- Exercise is frequently discontinued despite pain relief
- Adherence issues increase with time and discharge from PT
- PT Adherence (McLean et al., 2010)
  - Up to 70% of patients non-adherent
  - Conflicting evidence that interventions increase short term adherence
  - Strong evidence that strategies are NOT effective for long term adherence with HEP
- Poor treatment adherence (Jack et al., 2010)
  - Low levels of physical activity
  - Low self-efficacy: one's belief in ability to complete goals
  - Depression
  - Anxiety
  - Helplessness
  - Poor social support
  - Increased pain during exercise
  - Barriers: cost, child care, work, transportation
  - Conflicting evidence for age and pain at baseline

Exercise Delivery to Improve Adherence

- Supervision
- Motivational interventions (McGrane et al., 2015)
  - Optimal length and type of motivation not defined
- Individualize
  - Integrate into ADLs
  - Use exercise to meet patient's goals
- Family Involvement
- Education
  - Explain purpose and provide written hand-out (Schneiders et al., 1998)
  - Evidence- give abstracts
  - Expectations (Smets et al., 2008)
  - Greater adherence when patients expect to exercise
  - Treatment expectancy associated with perceived effect
  - Progression
  - Follow-up

General Practioner (Exercise) Beliefs

- "I don’t prescribe physical therapy. I tell my patients to get an activity monitor and walk."
- Health care providers (primary care doctors, PT, and rheumatologists) that have a biomedically (or structure) orientated pain beliefs are more likely to advise patients to restrict activity, including return to work (Houben et al., 2005; Pincus et al., 2007)
General Practitioner Exercise Beliefs

- Systematic review on beliefs of GPs regarding exercise for chronic knee pain (Cottrell et al., 2010)
  - Guidelines recommend exercise as a first line-management strategy for chronic knee pain (UK)
  - Limited evidence
  - Evidence underused
  - ~50% GPs would refer to PT

- Concerns
  - Cause harm
  - Lack of awareness regarding guidelines
  - Co-morbidities
  - Patient age
  - Limited access to services
  - Belief that patients will not exercise

Exercise Referral Schemes

- Small effect for exercise referrals to increase physical activity in sedentary people
  - 17 sedentary adults need to be referred for 1 to become moderately active (Williams et al, 2011, 2012)
- Women more likely to begin exercise but less likely to adhere to exercise program compared with men (Pavey et al, 2011, 2012)
- Older people more likely to begin and adhere to exercise program (Pavey et al, 2011, 2012)

Cost Effectiveness

- "I would never send my patients to physical therapy for exercise. It is too expensive."
- Exercise vs. usual care vs. surgery vs. education
- Roine et al., 2009: systematic review on exercise in treatment of various diseases - not specific to pain or PTs
  - Limited evidence: stringest for cardiac and back pain patients
  - Exercise outcomes highest for rheumatoid - but few studies
- Lin et al., 2011: systematic review for LBP treatments
  - Exercise cost-effective for sub-acute or chronic conditions
- Driessen et al., 2012: systematic review for neck pain treatment
  - No definite conclusions

Future of PT

- Exercise prescription and delivery
- Prevention initiatives
Psychosocial and EIH

- Review on aerobic exercise and changes in pain perception and mood (Hoffman and Hoffman, 2007)
  - Mood enhancement (3-24 hours)
  - Greater improvement in mood among habitual exercisers compared with non-exercisers

Mechanisms: Local vs. Systemic

- Systemic
  - Central and/or circulating hormones
- Local
  - EIH may be greater at exercise body part than distal body part (Kosek and Lundberg, 2003; Vægter et al., 2014)

Quantitative Sensory Testing

- In healthy adults, majority of research shows exercise to decrease temporal summation
  - Mixed in pain patients
- In healthy adults, EIH and conditioned pain modulation are associated
  - Unknown in pain patients

Mechanisms: Opioid

- Opioid Activation
  - Pituitary- into blood stream (peripheral)
    - Majority of exercise studies assess plasma levels
  - PAG-RVM-SC (central)
    - Animal Research

Mechanisms: Opioids (Healthy Subjects)

- Increasing beta-endorphin levels are associated with decreased pain reports
  - Mixed in pain patients
- EIH
  - Pressure pain thresholds increased
  - Pain ratings decreased
  - Temporal summation decreased
- Did not differ between placebo or opioid antagonist
  - Increase in endocannabinoids

Opioids and Endocannabinoids (Koltyn et al., 2014)

- 3 min of submaximal (25% MVC) isometric exercise with hand dynamometer in healthy young men and women
  - Opioid antagonist or placebo administration
- EIH
  - Pressure pain thresholds increased
  - Pain ratings decreased
  - Temporal summation decreased
- Did not differ between placebo or opioid antagonist
  - Increase in endocannabinoids
Morphine is less effective for the exercisers than non-exercisers (Kanarek et al., 1998). Decrease in morphine sensitivity is correlated with the amount of running (Smith and Lyle, 2006).

Cross-Tolerance Between Endogenous and Exogenous Activation of the Opioid System

- Clinical Translation
  - Exercise progression
  - Patient populations
    - Frequently exercise
    - Take opioid medication
    - Dysfunction of opioid system

Mechanisms: Opioids (Patient Populations)

Optimal dosage is unknown; depends on pain condition

Systematic Review: Effects of Exercise Therapy on Endogenous Pain-Relieving Peptides in Musculoskeletal Pain (Fuentes et al., 2011); one study of low quality considered relevant - inconclusive - need more research!

Animal Research

Low Intensity Exercise and Chronic Pain

- To determine if low intensity exercise decreases chronic muscle pain
- Induced chronic muscle pain model
- Walked on treadmill for 5 consecutive days
- Control group placed in treadmill for same time period as exercise group
- Measured pain response before and after exercise

Opioid Activation and Chronic Muscle Pain

- To determine if a low-intensity exercise protocol activates the opioid system in pain subjects
- Induced chronic muscle pain
- Walked on treadmill for 5 consecutive days
- Intraperitoneal injection of either vehicle (saline) or Naloxone (10 mg/kg dissolved in saline) given 20 min prior to each exercise session
- Measured pain response before and after exercise

Bement and Siuka, 2005
Exercise and Neuropathic Pain: Role of Endogenous Opioids

- Stagg et al., 2011
  - Neuropathic pain model: ligated L5/L6 spinal nerves
  - Two groups: sedentary and exercise (5 weeks on treadmill)
  - Tabled paw withdrawal thresholds 24 h after exercise
  - Opioid receptor antagonists were administered subcutaneous, intrathecal, or intracerebroventricular

Results:
- Exercise reversed neuropathic pain
- Neuropathic pain returned 5 days after discontinuing exercise
- Effects of exercise reversed by using systemically or centrally administered opioid antagonists
- Blockade of peripheral opioid receptors had no effect
- Exercise increased beta-endorphin and met-enkephalin in RVM and mid-brain PAG

Prevention....

Physical Activity Does Not Prevent Acute Inflammatory Pain

Physical Activity Prevents Development of Chronic Pain

Take Home Message

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