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Weight Management: Lifestyle Versus Pharmacotherapy

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Amidst the escalating obesity crisis affecting a substantial portion of the population, exploring tailored weight management strategies is increasingly imperative. What role do pharmacotherapy and lifestyle interventions play in weight management? This article looks at prioritizing lifestyle interventions before pharmacology and the evidence showing that physical activity improves cardiovascular health and reduces mortality in overweight and obese individuals.

Obesity/Overweight: A Global Crisis

Obesity, a condition characterized by a body mass index (BMI) of 30.0 or higher [1], has become an alarming health crisis in the United States and worldwide. In the U.S., approximately 41.9% of adults and 19.7% of children are now classified as obese [1-2], with an additional 33% of adults and 17% of children and adolescents falling into the category of overweight [3] (BMI between 25.0 and 30)[4]. The rapid rise in obesity rates, from 30.5% to 41.9% between 1999–2000 and 2017–March 2020[1], is a cause for concern, especially considering the parallel increase in severe obesity (BMI of 40 or higher), [5] which nearly doubled in the same period [1].

The global scope of the problem is equally troubling, with obesity rates nearly tripling in the last fifty years. [6] Recognized by the National Institutes of Health (NIH) as a chronic disease, [3] obesity is linked to various complications, including type 2 diabetes, heart disease, stroke, fatty liver disease, kidney disease, and cancer. [3]

For cardiovascular healthcare professionals, it is important to recognize that the impact of obesity is not uniform across populations. Certain groups, such as non-Hispanic Black and Hispanic adults, bear a disproportionate burden, with the highest age-adjusted obesity rates. Age, too, plays a significant role, with individuals aged 40 to 59 years being the most affected group.

Given the prevalence of obesity and its associated cardiovascular risks, there is an urgent need to identify safe, effective, and sustainable weight loss strategies tailored to individual backgrounds. It is worth noting that a modest 5-10% reduction in weight achieved through lifestyle changes can substantially reduce CVD risk for overweight or obese adults [7]. The question remains: are lifestyle interventions sufficient to manage the ongoing health problem of obesity?
Prioritizing Effective Weight Management: Lifestyle Before Pharmacotherapy

In the recently published *Clinical Practice Guideline on Pharmacological Interventions for Adults with Obesity*, the American Gastroenterological Association (AGA) recommendations for maintaining a healthy weight include pharmacotherapy in addition to lifestyle interventions in adults who are overweight and obese.[9] They qualify for pharmacotherapy treatment as indicated after an inadequate response to lifestyle interventions [9]. Lifestyle—a healthy diet and exercise for maintenance of a healthy weight—surpasses pharmacotherapy as a first-line treatment for weight management [9].

Further, exercise, not pharmacotherapy, is essential for cardiovascular health. Previous findings from a meta-analysis performed by Gasser and Angadi [10] substantiated the significance of physical activity and exercise for cardiovascular disease (CVD) morbidity and mortality. They examined the relationships between fitness, weight, heart health, and longevity in hundreds of studies that analyzed weight loss and workouts in tens of thousands of primarily obese men and women [10]. The findings indicated physical activity and exercise superseded weight loss pharmacotherapy for improving cardiovascular morbidity and mortality, especially in obese and overweight individuals [11]. Moreover, the cardiovascular benefits gained from fitness far outweighed any benefits observed from losing weight, according to the researchers [11], and had profound implications when determining effective strategies for weight loss treatment.
Benefits of Exercise and Physical Activity

From a cardiovascular perspective, the American College of Cardiology’s recent recommendations, [12] in agreement with the European Society of Cardiology’s state-of-the-art review, [13] highlight nine key benefits from exercise engagement in cardiovascular diseases (CVD) in the context of primary and secondary prevention.

- **Primary Prevention** – Physical inactivity is a significant risk factor for CVD and mortality. In contrast, self-reported leisure-time moderate and vigorous physical activity are independently and inversely associated with CVD and all-cause mortality.

- **‘Excessive’ Exercise/Physical Activity** – Although data suggest that long-term exposure to strenuous endurance exercise might be associated with coronary artery calcification (CAC), atrial fibrillation, and myocardial fibrosis, exposure to very high levels of leisure-time moderate or vigorous physical activity does not appear to increase the risk of CVD or related clinical events.

- **Secondary Prevention** – An active lifestyle is a cornerstone for secondary CVD prevention. In general, exercise should include 150-300 minutes/week of moderate-intensity exercise or 75-150 minutes/week of vigorous-intensity aerobic exercise, or a combination of the two. It should also include moderate-intensity muscle-strengthening activities involving all major muscle groups at least twice weekly and limited sedentary time. Exercise training may be contraindicated in some circumstances.

- **Metabolism, Inflammation, and Cellular Integrity** – Exercise training is associated with:
  - Improved blood lipid profiles, with aerobic exercise followed by resistance training, the most effective interventions to improve high-density lipoprotein (HDL) cholesterol
  - Improved insulin sensitivity
  - Attenuation of systemic chronic inflammation
  - Promotion of cellular maintenance and repair

- **Vascular Health**
  - Endothelial cell integrity
  - Endothelial function. Aerobic exercise and resistance training improve endothelial function in a dose-response relationship among people with or without CVD.
  - Anti-atherogenic adaptions
  - Structural adaptations. Exercise training increases luminal diameter and vasodilation capacity and decreases wall thickness and vascular stiffness.

- **Myocardial Regeneration** – Exercise before myocardial infarction (MI) might reduce infarct size and improve cardiac function after MI. Exercise training after MI can induce favorable left ventricular remodeling with decreased diastolic volume.

- **Exerkines** – A wide variety of signaling molecules such as hormones, metabolites (including lactate), proteins and peptides (mainly cytokines, such as interleukin-6), nucleic acids, and free radicals (including NO) released during exercise have cardiovascular health benefits distinct from modification of traditional CHD risk factors. The cardiovascular effects induced by exerkines include the enhancement of vascularization and angiogenesis, a decrease in blood pressure, and an improvement in endothelial function.
Protection Against Malignant Arrhythmia – Regular exercise helps protect against life-threatening arrhythmias.

Cardiac Preconditioning – Regular exercise also can help prevent fatal arrhythmias by inducing cardiac preconditioning [12-13].

Exercise produces greater impacts on cardiovascular health for prevention and disease management and should be emphasized for patients in every clinical practice. Providing support such as educational materials, links to effective online apps, and program referrals can contribute to patient engagement in healthy exercise regimens. Recognizing and suggesting modification options for those with physical or environmental limitations provides opportunities for all individuals to garner the benefits of exercise and reduce barriers to participation.

Pharmacotherapy for Weight Loss

In those individuals who require pharmacotherapy for long-term weight management, the recent AGA Clinical Practice Guideline recommends six medications in adults who are overweight or obese [9]. These include semaglutide, liraglutide, phentermine-topiramate ER, naltrexone-bupropion ER (based on moderate-certainty evidence), and phentermine and diethylpropion (based on low-certainty evidence). The guideline panel suggested against the use of orlistat. Besides the recently approved semaglutide, most pharmacotherapeutics demonstrate a safe cardiovascular risk profile, but long-term follow-up is lacking [8].

Additional information on the five pharmacotherapies below may be found in associated guidelines, referenced resources, and manufacturer websites. Be sure to check updated guidelines before use.

1. **Semaglutide** [17]. Required in conjunction with lifestyle interventions and supervision by a healthcare provider. A summary of semaglutide includes:
   - **Indication**: Approved for chronic weight management in adults with obesity or overweight (BMI of 27 kg/m\(^2\) or greater with at least one weight-related ailment, or a BMI of 30 kg/m\(^2\) or greater with at least one weight-related condition such as high blood pressure, type 2 diabetes, or high cholesterol)
   - **Administration**: 2.4 mg injection
   - **Mechanism of Action**: GLP-1 agonist to regulate appetite and intake to slow gut motility, increase satiety, and decrease absorption
   - **Side effects**: Pancreatitis, nausea, diarrhea, vomiting, abdominal pain, headache, fatigue, GI complications and hypoglycemia
   - **Black Box Warning**: Potential risk of thyroid C-cell tumors. Multiple Endocrine Neoplasia syndrome type 2, pancreatitis, gallstones, hypoglycemia, acute kidney injury, diabetic retinopathy, increased heart rate, and suicidal ideations. [More information](#).

2. **Liraglutide** [18]
   - **Indication**: Similar indication as semaglutide. Pediatric ages 12 years and older, body weight > 60 kg, initial BMI of 30 kg/m\(^2\) for adults by international cut-offs.
   - **Administration**: 3.0 mg injection
Mechanism of action: GLP-1 agonist
- Side effects: Headache, constipation, heartburn, sneezing, cough, tiredness, pain, burning, difficulty with urination, injection site rash, skin redness. Increased heart rate [24]
- **Black Box Warning**: Medullary thyroid carcinoma, thyroid C-cell tumors. Caution in multiple endocrine neoplasia type 2 or history of medullary thyroid carcinoma.

3. **Phentermine-topiramate ER** [19] – The long-term CV morbidity and mortality are not yet established, although resting heart rate should be monitored [20, Chao].
   - **Indication**: Short-term (a few weeks) adjuncts with lifestyle weight reduction behaviors; otherwise, a similar indication as semaglutide.
   - **Administration**: PO medication
   - **Mechanism of action**: Anticonvulsant, GABA agonist
   - **Side effects**: Dizziness, drowsiness, dry mouth, difficulty sleeping, tiredness, tingling of the hands/feet, constipation, and metallic taste may occur
   - **Black Box Warning**: increased suicidal ideation

4. **Naltrexone/bupropion** [8, 21-22]
   - Heart rate and blood pressure monitoring; contraindicated in uncontrolled hypertension, caution in existing cardiac or cerebrovascular disease [20]
   - **Indication**: Similar to semaglutide
   - **Administration**: PO medication
   - **Mechanism of Action**: Bupropion is a weak dopamine and norepinephrine reuptake inhibitor. Naltrexone is an opioid antagonist. The combination produces melanocyte-stimulating hormone (alpha-MSH) and beta-endorphin, an endogenous opioid.
   - **Side Effects**: N/V, diarrhea, constipation, dry mouth, taste change, HA, dizziness
   - **Black Box Warning**: Suicidal ideations, especially in young adults and adolescents

   - **Indication**: Short-term adjunctive to lifestyle interventions in obese patients previously unable to lose weight.
   - **Administration**: PO. 25 mg three times daily (immediate-release tablets) or 75 mg (controlled-release tablets) in adults 17 years and older. Not recommended for children 16 years or younger.
   - **Mechanism of Action**: Sympathomimetic amine and anorectic agent used for short-term therapy of obesity
   - **Side Effects**: Dry mouth, unpleasant taste, restlessness, anxiety, dizziness, depression, tremors, upset stomach

**Clinical Takeaways**
- For weight management, the magnitude of overweight and obesity in adults and existing comorbidities should be considered [7].
- Cardiovascular health is feasible at any weight if accompanied by adequate physical activity and exercise [10].
• Since a healthy diet, physical activity, and exercise trump pharmacotherapy as a first-line treatment for weight management [9], CVD nurses and APRNs should first and foremost consider an individualized approach.
• For those who are overweight or obese and for whom lifestyle interventions are inadequate, long-term pharmacological therapy and effective and safe treatment options are indicated for weight management [10].

Related Resources

• Obesity Patient Tool – Fact Sheet: What is Obesity?
• Heart Healthy Toolbox: Lifestyle and Behavior Change Tools
• CE Courses
  o Exercise and Lifestyle Interventions: What’s their Role in Cardiovascular Disease (CVD) Prevention and Treatment?
  o Behavior Change Principles in Action: Helping Patients Set Goals and Follow a Heart-Healthy Eating Plan
  o Behavior Change Mini-Certificate
  o Obesity’s Impact on Mental Health
• Social Determinants of Health and Obesity
• Talking About Obesity

References


