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Supplement Article: Function-Promoting Therapies

Optimizing the Design of Clinical Trials to Evaluate the Efficacy of Function-Promoting Therapies

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Abstract

Background: Several candidate molecules that may have application in treating physical limitations associated with aging and chronic diseases are in development. Challenges in the framing of indications, eligibility criteria, and endpoints and the lack of regulatory guidance have hindered the development of function-promoting therapies.

Methods: Experts from academia, pharmaceutical industry, National Institutes of Health (NIH), and Food and Drug Administration (FDA) discussed optimization of trial design including the framing of indications, eligibility criteria, and endpoints.

Results: Mobility disability associated with aging and chronic diseases is an attractive indication because it is recognized by geriatricians as a common condition associated with adverse outcomes, and it can be ascertained reliably. Other conditions associated with functional limitation in older adults include hospitalization for acute illnesses, cancer cachexia, and fall injuries. Efforts are underway to harmonize definitions of sarcopenia and frailty. Eligibility criteria should reconcile the goals of selecting participants with the condition and ensuring generalizability and ease of recruitment. An accurate measure of muscle mass (eg, D3 creatine dilution) could be a good biomarker in early-phase trials. Performance-based and patient-reported measures of physical function are needed to demonstrate whether treatment improves how a person lives, functions, or feels. Multicomponent functional training that integrates training in balance, stability, strength, and functional tasks with cognitive and behavioral strategies may be needed to translate drug-induced muscle mass gains into functional improvements.

Conclusions: Collaborations among academic investigators, NIH, FDA, pharmaceutical industry, patients, and professional societies are needed to conduct well-designed trials of function-promoting pharmacological agents with and without multicomponent functional training.

Keywords: Clinical trial design, Functional decline with aging, Function-promoting drugs, Sarcopenia, Skeletal muscle dysfunction

Randomized clinical trials constitute the highest level of evidence and are the benchmark for demonstrating the efficacy of an intervention in terms of "superiority," "noninferiority," or "equivalence" relative to placebo or a standard treatment. Because no pharmacologic function-promoting therapy has been approved to date for older adults with 1 or more functional limitations, despite the unmet medical need, the initial randomized trials of function-promoting therapies will necessarily be placebo-controlled superiority trials. Although many aspects of clinical trial design and implementation are important in evaluation of the efficacy, the framing of indications, selection of patient populations, and the selection of primary and secondary endpoints have been widely recognized as the major barriers that have hindered the development and approval of function-promoting therapies. Therefore, this narrative review focuses on considerations in the framing of the indications, the selection of the study populations using carefully crafted eligibility criteria, and the choice of primary and secondary endpoints in the randomized trials of function-promoting therapies.

Potential Indications

An indication is a condition, manifestation, or a symptom of a disease that has a recognizable adverse impact on human health and life, is recognized by clinicians (21 Code of Federal Regulations 201.80(c)(1)(i)), and can be ascertained reliably by a valid, self-reported or a performance-based measure (eg, Short Physical Performance Battery [SPPB] or 6-minute walking distance) and for which an International Classification of Diseases (ICD) code may exist. Some geriatric syndromes do not fit neatly into the U.S. Food and Drug Administration (FDA) guidelines for a medical indication, which requires that a disease, condition, or syndrome be "recognized" before an indication can be approved. "Recognized" may include recognition by 1 or more professional organizations, published guidelines, and current procedural terminology codes. Sarcopenia, for example, has an ICD 10th Revision (ICD-10) code, but efforts to standardize the methods for its diagnosis in the clinical settings are still nascent. Currently, most health care providers, including geriatricians, do not use a standardized assessment of functional status for their older patients. Reimbursement by the Centers for Medicare and Medicaid Services for functional assessments such as the SPPB could support reimbursement and widen their implementation in the clinical settings.

While an indication can be developed for the "treatment of a condition" or for the "prevention of a condition," the prevention trials typically require a larger sample size, longer intervention durations to accumulate sufficient numbers of outcome events, and a higher benefit to risk ratio than treatment trials. Therefore, initially, treatment indications are likely to be received more favorably than prevention indications. Short-term indications for treating grievous conditions are likely to be received more favorably than chronic indications. Examples of grievous conditions that are associated with high burden of physical disability and poor health outcomes include older individuals hospitalized for an acute illness who have mobility disability or activities of daily living (ADL) disability during recovery from an illness; persons with burns or massive trauma, who have functional limitations during recovery; and cachexia associated with some types of cancer that may be accompanied by mobility limitation and/ or ADL disability.

Mobility disability associated with aging and chronic diseases, such as that associated with chronic obstructive pulmonary disease, heart failure, chronic kidney disease, and many types of therapy, is a highly prevalent condition among older adults and an attractive indication for function-promoting therapies for many reasons. First, mobility difficulty is a common, inclusive, validated marker of disablement that is associated with increased risk of hospitalization, instrumental activities of daily living (IADL) disability, and death (1,2). In humans and in species as far removed from humans as *Caenorhabditis elegans*, reduced mobility is associated with adverse outcomes and reduced life span. Second, mobility disability is widely recognized by geriatricians as a "condition" for which ICD-10 codes exist to enable reimbursement. Third, it can be recognized by self-report using standardized questions as well as by performance-based measures. Among the various types of limitations associated with mobility disability, difficulty walking 1/4 mile (34%), difficulty climbing stairs (23%), and difficulty rising from a chair are the most prevalent in community-dwelling older adults (3).

Operationalizing the Definition of Sarcopenia in Clinical Trials

Although several consensus definitions of sarcopenia have been published, these definitions share many similarities among them. Importantly, nearly all the definitions acknowledge that sarcopenia is a multicomponent syndrome related to age-related changes in the skeletal muscle. The specific tests for each component of this multicomponent condition and the associated cut points for defining sarcopenia have tended to differ among various definitions. The challenges in establishing a consensus definition of sarcopenia are not dissimilar from those faced in defining cut points for other common medical conditions, including hypertension, diabetes, hyperlipidemia, and osteoporosis. Sarcopenia is a complex geriatric syndrome which is also the case with dementia, incontinence, and falls.

The Sarcopenia Definitions and Outcomes Consortium (SDOC) was funded by the National Institute on Aging to refine diagnostic cut points for sarcopenia; test the associations of these cut points with a number of different outcomes (ie, disability, mortality, falls, hip fractures, hospitalizations); apply these cut points in other clinical populations to evaluate the prevalence of sarcopenia; and conduct a public review of these analyses (4). The SDOC analyzed data from 8 prospective observational studies by conducting classification and regression tree (CART) analysis to identify cut points in grip strength that best discriminated those who were slow from those who were not. Researchers then evaluated the association of slowness and weakness with incident health outcomes (5,6). For slowness, researchers used a definition of objective walking speed that was less than 0.8 m/s for both men and women and used sex-specific cut points for low grip strength as identified in the CART analyses (4–6). Low grip strength predicted falls, self-reported mobility limitation, hip fractures, and mortality in community-dwelling older adults (4,5,7). In contrast, the SDOC analysis did not find a robust association of dual-energy x-ray absorptiometry (DXA)-derived lean body mass or appendicular lean tissue mass with health outcomes such as mobility disability, mortality, falls, hip fractures, and hospitalizations (4–6).

A panel of experts evaluated SDOC statements at a public Position Development Conference (4). There was strong agreement that grip strength and gait speed are good measures of weakness and slowness, respectively, and that both should be included in the definition of sarcopenia. There was a high degree of uncertainty about the utility of DXA-derived lean mass in the definition of sarcopenia. Based on the results of its comprehensive analyses of epidemiological

data and the SDOC Position Statement Conference, the SDOC operationally defined sarcopenia as the occurrence of low grip strength (<35.5 kg men, <20 kg women) and slowness (walking speed <0.8 m/s) (4).

This operational definition of sarcopenia could facilitate the identification of study participants in clinical trials of function-promoting therapies, depending on the mechanism of drug action and the primary outcome of the study. It is unclear whether this operational definition may be useful as an efficacy outcome in clinical trials.

A particular limitation of DXA-derived lean body mass is that it does not adequately distinguish among diverse nonfat, nonbone soft tissues; consequently, DXA-derived lean mass has not been found to be associated with mobility disability, falls, or fractures (4,5). In contrast, D3 creatine dilution method offers a more accurate measurement of skeletal muscle mass than DXA (8). The method requires the participant to ingest a standardized dose of deuterium-labeled creatine and collection of a fasting urine sample several days later (8). This measure has been implemented in a large prospective, multicenter, observational study of 1 400 older community-dwelling men (9). Those with low muscle mass measured using the D3 creatine dilution method in the study were much more likely to have an incident fall, an incident fracture, die earlier, have incident disability, and have lower strength and physical performance (10,11). The measurement of lean body mass by DXA was unrelated to these outcomes. Data on women are being gathered now, along with observations of how this measure changes over time and with intervention.

The European Medicines Agency (EMA) is considering sarcopenia and frailty as indications and exploring tools for evaluating these syndromes. EMA recommended the evaluation of frailty using the SPPB or gait speed and has published summary cutoff scores, which define the risk of disability and mortality (12). Other specific geriatric syndromes may meet regulatory criteria for novel pharmacological therapy to treat poor functional capacity. The FDA has reviewed the SDOC definition favorably and has emphasized the use of appropriately validated patient-reported outcomes (PROs) in the population of interest to demonstrate that the intervention is improving how the study participants "functions or feels."

Metabolic Disorders as Indications

Skeletal muscle by virtue of its sheer mass is a major consumer of energy and an important regulator of adipose tissue mass and distribution, and metabolism. Therefore, anabolic function-promoting therapies that increase skeletal muscle mass, in addition to their hypothesized beneficial effects on muscle performance and physical function, would be expected to improve cardiometabolic outcomes. In preclinical models, anabolic interventions that increase muscle mass have been shown to reduce adiposity and improve insulin sensitivity. Transgenic mice that overexpress myostatin selectively in the skeletal muscle have lower muscle mass and higher fat mass than wild-type controls (13). Male mice with genetic disruption of the myostatin gene have increased muscle mass and are resistant to fat accumulation in response to feeding of a high-fat diet, development of hepatic steatosis, insulin resistance, proatherogenic dyslipidemia, and progression of aortic atherogenesis (14). Similarly, transgenic mice that constitutively hyperexpress Akt1, a protein kinase that regulates muscle growth, demonstrate muscle hypertrophy, a reduction in white adipose tissue, and improvements in insulin sensitivity and hepatic steatosis (15). In a randomized trial in adults with type 2 diabetes, body mass index between 28 and 40, and hemoglobin A1c levels between 6.5% and 10.0%, treatment for 48 weeks with bimagrumab, a monoclonal antibody that blocks the activin type II receptor signaling was associated with significantly greater loss of body weight and fat mass, and a greater reduction in hemoglobin A1c than placebo treatment (16). In the Testosterone for Diabetes Mellitus Trial (17), a randomized, placebo-controlled trial in men, aged 50–74 years, at increased risk for type 2 diabetes or with newly diagnosed type 2 diabetes were randomized to a lifestyle program plus placebo injections or lifestyle program with testosterone injections for 2 years. Testosterone treatment plus lifestyle program was associated with a significantly lower proportion of participants with type 2 diabetes at 2 years than placebo plus lifestyle program (10). Taken together, these data suggest that anabolic drugs that increase skeletal muscle mass could induce loss of body weight and fat mass and improve metabolic outcomes; and that markers of metabolic improvements such as changes in hemoglobin A1c or prevention of diabetes should be considered for inclusion as secondary outcomes in trials of function-promoting anabolic agents. Older adults with sarcopenic obesity and functional limitations may be excellent candidates for such trials.

Selecting the Inclusion and Exclusion Criteria for Clinical Trials of Function-Promoting Therapies

Careful selection of eligibility criteria is necessary to reconcile the dual goals of selecting a diverse, representative population of participants with the condition of interest with high level of objectivity as well as ensuring generalizability and ease of recruitment. Clearly defined inclusion criteria are needed for recruiting study participants with the condition (the indication) for which the study medication is being tested and establish objectivity and precision in subject selection. Exclusion criteria are designed to exclude people who are unlikely to respond to the study medication, who might respond substantially differently from the general population, or are at increased risk of being harmed by the study medication than the general population. Ideally, eligibility criteria may include self-reported measures and objective performance-based measure/s to ensure that the participant has the condition and that it is patient-important.

Identifying and recruiting functionally limited older persons who reflect the sex, race, and functional capacities of the population that might benefit from interventions and implementing efficient ways to screen people in randomized trials of function-promoting therapies are particularly challenging. Operational considerations in the selection of inclusion and exclusion criteria for function-promoting therapies are summarized in Table 1. Older people with multiple comorbid conditions may be at increased risk of adverse events that may be related to their underlying medical condition; they may also respond differently from those without comorbid conditions. However, because of the high prevalence of comorbid conditions in older adults with functional limitations, excluding older people with 1 or more comorbid conditions may limit the generalizability of the findings and may hinder enrollment. Individuals with no or only minimal physical disability may be less likely to show improvement; at the other end of the spectrum of physical disability, individuals with very severe disability may experience limited impact of the intervention on their lives—a case of too little, too late—or may have high burden of comorbid conditions and increased risk of adverse events. Other participant-level factors that may influence adherence to the intervention, and treatment effect and sample size

Table 1. General Considerations in Framing the Inclusion and Exclusion Criteria for Efficacy Trials of Function-Promoting Therapies

Inclusion criteria
The inclusion criteria are designed to:
1. Enable the selection of people with the condition (the indication) for which the study medication is being tested
2. Establish objectivity and precision in participant selection
3. Preferably include both self-reported measures and some objective performance-based measures to ensure that the participant has the condition and that it is patient-important
4. To minimize heterogeneity of the study participants while ensuring that the study participants are representative of the general population
Exclusion criteria
The exclusion criteria are designed to exclude people:
1. Who are unlikely to respond to the study medication
2. Who might respond substantially differently from the general population
3. Who are at higher risk of being harmed by the study medication than the general population
4. Have conditions or are using medications that would alter the bioavailability or metabolism of the study medication

include nutritional intake, baseline level of exercise and physical activity, cognitive function and behaviors (18,19). A number of rapid screening tools are available to assess nutritional status at baseline although these tools cannot reliably identify specific nutrient deficiencies. Older adults with unstable medical conditions such as recent major adverse cardiovascular events, recent hospitalization or major surgery, or end-stage renal disease requiring renal replacement therapy may not be suitable candidates or may require re-evaluation for eligibility after resolution of these conditions. People with major organ dysfunction, those using medications that affect the metabolism of study drug through drug–drug interaction, and those harboring genetic variations that may affect the metabolism of the study drug, also may not be suitable candidates. The oldest old have often been excluded from randomized trials; their inclusion is particularly important because they are the most in need of safe and efficacious function-promoting therapies.

Selection of Endpoints in Clinical Trials of Function-Promoting Therapies

An endpoint is a precisely measured event or outcome of interest that can be statistically analyzed to determine whether the intervention being studied is beneficial (20,21). The definition of the endpoint should specify precisely the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other essential details. The primary endpoint helps determine whether an intervention improves how a person lives, functions, or feels (21). The careful selection of endpoints is critical to establishing proof of efficacy and securing treatment approval.

The endpoints are categorized as primary, secondary, or tertiary. The primary endpoint is usually a measure of the intervention's effects on how a study participant survives, functions, or feels and addresses the primary hypothesis (21). Secondary endpoints may support the claim of efficacy by demonstrating additional benefits or by providing evidence of causal mechanisms (21). Tertiary endpoints may be included to capture additional outcomes that may be useful for exploring novel hypotheses or mechanisms or less frequent outcomes for which there is insufficient statistical power (21).

The endpoint/s must meet some minimal measurement properties of reliability and validity. Test–retest reliability can be measured as an intraclass correlation coefficient, internal consistency as Cronbach's alpha, and interinterviewer reliability for PROs as an interclass correlation coefficient. The endpoint must also have content as well as construct validity, be responsive to the intervention such that the change can be detected over time and between individuals. The measures of muscle performance and physical function should have adequate precision and accuracy in the range of functional ability of the population being studied. Ideally, the measure of performance should be related proportionally to a person's ability over a wide range of ability observed in the population being studied. Ceiling and floor effects should be considered. It is particularly important to ensure that the endpoint is appropriate in the context of use in the target population, well-aligned with the attributes of the disease or condition that the intervention intends to treat, the mechanism of drug action, the phase of the trial, and is comprehensible to clinicians.

Both PROs and performance-based measures have some inherent assets and limitations (22). Only patients can tell us how they "function and feel," but self-reported assessments of function are susceptible to mood, pain, sleep, and placebo effects. Performance-based measures can provide objective assessment of muscle performance and physical function under standardized conditions but measurements in the laboratory setting have some artificiality and may not always be aligned with symptoms or the types of limitations in functional activities that the participants experience in their daily lives. Inclusion of both types of measures can provide a more comprehensive assessment of efficacy than either type of measure alone.

The primary outcome in the efficacy trials of function-promoting therapies could be a performance-based and/or a self-reported measure of physical function. The performance-based measure and self-reported measures of physical function could serve as coprimary endpoints; alternately if either of the 2 (a performance-based or the self-reported measure) is used as the primary endpoint, the other could serve as a key secondary endpoint. The FDA has emphasized the importance of demonstrating that improvements in physical performance are associated with a downstream beneficial effect on how a person functions or feels. The measures of mobility, such as walking speed in standardized setting (6-minute walking distance and speed, 4-m walking speed, SPPB, or 400-m walking speed) and stair climbing power and speed can be useful as endpoints in studies of older people with mobility limitation and chronic diseases such as chronic obstructive pulmonary disease, heart failure, or end-stage renal disease. Mobility can be ascertained reliably by self-report or by performance-based measures like 6-minute walking distance, short-distance walking speed, SPPB, and stair climbing speed and power. Walking speed is an excellent integrated measure of physical function and mobility that is predictive of impactful health outcomes such as incident disability, mortality, hospitalization, and ability to live independently (1,2). Walking speed can be measured with precision and reproducibility and has been shown to be

responsive to some types of anabolic interventions. The ranges of changes in walking speed perceived by several different populations have been reported (23–25). Loaded and unloaded stair climbing power has high test–retest reliability, is associated more robustly with leg press strength, is more sensitive than walking speed to anabolic interventions that increase leg press strength (26) and may be a more responsive outcome than gait speed to evaluate the efficacy of some function-promoting therapies (10). Standardization of the performance-based measures of physical function and rigorous staff training in these procedures across trial sites is crucial for obtaining reliable data.

The endpoints should be aligned with the mechanism of drug action. Some examples of potential mechanistic pathways by which various function-promoting therapies might act include increased skeletal muscle mass (testosterone, other androgens, selective androgen receptor modulators [SARMs], growth hormone [GH] and GH secretagogues, myostatin/activin blockers); improved muscle contractile response to neural input thereby increasing force production (eg, fast skeletal muscle troponin activator); and improved bioenergetics (eg, nicotinamide adenine dinucleotide boosters).

The selection of endpoints also varies with the phase of drug development. For example, measures of skeletal muscle mass or biomarkers of skeletal muscle mass or protein turnover can be useful in early-phase studies, while in efficacy trials, a performance-based as well as a patient-reported measure of physical function may be needed to demonstrate functional improvements.

The PROs are important in demonstrating whether the treatment improved how a person lives, functions, or feels. PROs have been underutilized and underemphasized in prior trials of function-promoting therapies. High level of rigor is required in the validation and psychometric evaluation of PROs being used in clinical trials to support drug approval.

Accurate estimates of whether the observed changes in the outcomes are patient-important are required for interpreting the clinical relevance of the observed treatment effects in randomized trials. The estimates of patient-important change may vary in the context of use and in different patient populations, so these estimates ideally should be derived in the same population for which the indication is being sought.

The FDA's Perspective on Clinical Outcome Assessments

Clinical outcome assessments (COAs) come in many different types, including clinician-reported outcomes, PROs, observer-reported outcomes, and performance-based outcomes (27,28). When used in clinical trials, COAs should measure the way a patient functions, feels, or survives. A best practice for developing outcome measures in clinical trials is to start by gathering patient-focused data from qualitative interview research, patient surveys, and publications.

When interpreting whether the treatment effect observed in an efficacy trial is clinically meaningful to patients, statistical significance alone is not sufficient. The FDA considers 2 questions to establish clinical benefit—does the assessment measure something of significance to patients and do changes in the assessment at the individual level correspond to important changes considered impactful by patients?

It is important to define the within-patient change that would be considered clinically meaningful. The FDA's 2009 Patient-Reported Outcome Guidance offers some direction, such as the fact that the clinically meaningful threshold (or range) may not be comparable for all patient populations. Anchor-based methods are emphasized and empiric evidence for any responder definition should be derived using anchor-based methods. Triangulation of evidence is a good way to ensure that a number of different lines of evidence point to a range of thresholds that would define what is clinically meaningful.

The FDA is developing a series of methodological patient-focused drug development guidance publications that include: (1) Collecting Comprehensive and Representative Input; and Guidance; (2) Methods to Identify What is Important to Patients while one, Guidance; (3) Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments, is in a draft form; and, (4) Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision Making. The FDA can also be engaged for review and advice on COAs in several ways. A number of questions are important to consider when evaluating COAs. Examples include: (i) Was the instrument developed in the studied population? Does the COA measure the concept of interest in the patient population and is the threshold for clinical meaningfulness appropriate for that study population? (ii) Is the instrument reliable? Is it sensitive to detecting change over time? (iii) Did response to 1 item in the COA disproportionately influence the overall score?

Patient-generated health data collected from digital health technologies (DHTs) allow researchers to understand patient behavior in the context of their daily lives rather than in the clinic or a research unit. DHTs may offer many advantages, particularly for function-based outcome assessments by virtue of the extensive, rich body of information on patients' status at home or work that addresses: patient functioning: for example, activity, mobility, ambulation; disease status: for example, gait speed, tremor, oxygenation, glucose, electroencephalogram, skin lesions; drug-related safety events: for example, falls, arrhythmias, hypoglycemia, hypotension; PRO measures: for example, eDiaries and ePROs; adherence to trial procedures; recruitment and retention of a more diverse population by eliminating travel barriers; and the potential to develop novel/highly useful endpoints.

The data collected by DHTs have to be translated into a clinical endpoint, which needs to be formulated clearly and precisely to measure the concept of interest. Researchers can refer to the FDA guidance publication Digital Health Technologies for Remote Data Acquisition in Clinical Investigations (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/digital-health-technologies-remote-data-acquisition-clinical-investigations).

Consideration of Exercise Level and Nutritional Intake in Clinical Trials of Function-Promoting Therapies

Adjunct Multicomponent Functional Training for Achieving Functional Improvements and Reducing Disability

Pharmacologic function-promoting therapies, especially androgens and myostatin antagonists, have shown significant improvements in lean body mass and muscle strength, but the translation of these into improvements in important measures of physical function has been inconsistent.

The purpose of traditional progressive resistance training (PRT) is to enhance the ability of the muscle groups to produce or sustain force, and improve quality. Systematic reviews and meta-analyses of randomized controlled trials of the effects of PRT on various

measures of physical function in older adults concluded that PRT 2–3 times a week improves muscle strength and several measures of physical function (balance, gait speed, time and up go test, chair rise, and climbing stairs) and reduces some types of functional limitations in older people (29,30). PRT has been typically performed with isolated muscles or muscle groups in a limited range of motion and often not integrated with balance or postural control. In contrast, the purpose of functional training is to develop movement patterns with resistance, specific to a targeted activity. Multicomponent functional training integrates whole-body, multiplanar movement; includes training in balance and stability, strength and power; and is specific to a target activity (31). Studies suggest that older adults with poor function have a larger window of adaptation in which to improve. Therefore, well-designed and executed multicomponent functional exercise training, appropriate to ability, followed by progression to larger doses of exercise specific to the target task could lead to better outcomes (Figure 1).

In the design of exercise interventions to improve physical function, it is important to consider the type of exercise (resistance training vs endurance exercise training); exercise dosage; participant's baseline characteristic, ability, and comorbid conditions; delivery of the intervention; and alignment of the type of exercise intervention with the trial's endpoint. Adherence is of particular concern with any type of exercise training; cognitive and behavioral strategies are needed to improve adherence to exercise training and to target the behavioral and psychological components of physical disability. Missing from the research on improving physical function in older adults is the concurrent use of pharmacologic agent and multicomponent functional training to improve physical function and health outcomes. Combined administration of a pharmacologic anabolic agent with well-conceived and executed multicomponent functional training intervention could help translate muscle size and strength gains from anabolic agents to meaningful and more consistent changes in physical function and health outcomes and may even be additive with respect to functional improvement (Figure 1). The choice and intensity of functional exercise training should be guided by the subject's ability and should ideally be standardized and progressive, and aligned with the trial's endpoints.

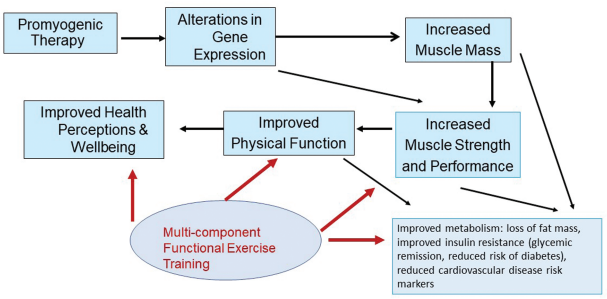

Figure 1. Rationale for combining a multicomponent functional training with a pharmacologic promyogenic anabolic drug. Among the various classes of function-promoting molecules, promyogenic anabolic drugs that are intended to increase muscle mass such as testosterone and other androgens, selective androgen receptor modulators, myostatin and activin antagonists, and growth hormone and growth hormone secretagogues are the farthest along in clinical development and have undergone efficacy trials. It has been hypothesized that these promyogenic anabolic drugs through various mechanisms would increase skeletal muscle mass and that the increase in skeletal muscle mass would translate into improved muscle performance, physical function, and health outcomes. Randomized trials of these promyogenic drugs have shown consistent increases in lean body mass, and androgens and selective androgen receptor modulators have shown improvements in muscle performance measures, but improvements in performance-based measures of physical function such as gait speed have been small and inconsistent across trials. It is hypothesized that multicomponent functional exercise training that integrates whole-body multiplanar movement, includes training in balance and stability, strength and power, and is specific to a target functional activity could facilitate neuromuscular adaptations that are necessary for translating the muscle mass gains into improved physical function and performance of daily tasks. Multicomponent functional exercise training could also confer additional benefits in terms of improved metabolic outcomes, mood, and well-being.

Standardizing Nutritional Intake and Outcomes Assessment Across Trial Sites

Despite the clear connection between nutrition and physical function, nutritional status and intake are often not given appropriate attention when designing clinical trials of function-promoting therapies that do not include nutritional interventions. Many nutritional factors, such as energy intake, protein/amino acids, fat, micronutrients, fluid, and fiber can affect function in older adults (32).

Both extremes of energy intake—malnutrition and obesity—can negatively affect physical and cognitive function. Between 5% and 30% of community-dwelling older adults suffer from malnutrition. Malnutrition is associated with poor functional and health outcomes in older adults, particularly among institutionalized and hospitalized older people (33). Obesity also is associated with a significant increase in measured and reported functional impairment in older individuals (34).

Dietary protein stimulates muscle protein synthesis and provides the essential amino acids necessary for muscle growth. Dietary amino acids are particularly important for muscle growth and homeostasis, immune function, skin integrity, gut function, and synthesis of neurotransmitters (35). Observational studies have reported that a higher protein intake is associated with lower muscle loss with aging (35). A positive association between protein intake and walking speed has also been reported by the PROMISS consortium (36). The role of caloric restriction and alignment of food intake with the circadian clock in aging biology also is being increasingly appreciated (37,38).

Controlled feeding studies of protein supplementation in mobility-limited older adults who are eating less than the recommended dietary allowance (RDA) have not found protein intake above the RDA to improve lean body mass, muscle strength, or physical function compared with the RDA (39). Studies in malnourished or severely ill geriatric patients, however, may yield more promising results. Micronutrients also affect functional outcomes. Higher intake of vitamin B6 is associated with a lower risk of impaired mobility. Recent clinical trials do not support the use of vitamin D supplementation for primary prevention of falls, fractures, and other health outcomes in healthy older adults (40,41).

Many instruments are available for measuring nutritional status and intake with variable level of complexity. The Subjective Global Assessment and the Mini Nutritional Assessment, for example, are qualified assessment tools that combine data on nutritional status with clinical observation and laboratory data.

Rigorous control of nutritional intake and dietary composition is often not feasible in large multicenter trials of pharmacologic function-promoting therapies. However, baseline nutritional assessment can ensure that the person is not malnourished or experiencing involuntary weight loss, and is eating some minimal level of energy and protein.

Intervention Duration

Randomized trials of function-promoting anabolic drugs, such as testosterone, SARMs, and myostatin antagonists, have been typically 3–6 months in duration; these trials have reported improvements in lean body mass and maximal voluntary strength but not walking speed (42–47). Only a few trials of function-promoting anabolic drugs have included intervention durations of longer than 6 months and these trials have shown modest improvements in loaded stair climbing power and mobility (48,49). It is possible that intervention durations of longer than 1 year may be needed to induce neuromuscular adaptations necessary for the translation of muscle mass and strength gains into functional improvements.

Conclusion

The success of the efficacy randomized trials of function-promoting therapies is predicated crucially upon careful framing of the indication, the selection of the study populations using well-crafted eligibility criteria, and the appropriate choice of primary and secondary endpoints. There is a compelling public health need for adequately powered, large randomized trials to determine whether combined administration of a pharmacologic anabolic agent with well-conceived and executed multicomponent functional training intervention could translate muscle size and strength gains from anabolic agents into meaningful improvements in how a person "functions and feels" and other patient-important health outcomes.

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Conflict of Interest

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