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Pediatric Obesity Pharmacotherapy: Current State of the Field, Review of the Literature, and Clinical Trial Considerations

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Abstract

Despite the increasing number of medications recently approved to treat obesity among adults, few agents have been formally evaluated in children or adolescents for this indication. Moreover, there is a paucity of guidance in the literature addressing best practices in regard to pediatric obesity pharmacotherapy clinical trial design, and only general recommendations have been offered by regulatory agencies on this topic. The purposes of this article are to: 1) offer a background of the current state of the field of pediatric obesity medicine; 2) provide a brief review of the literature summarizing pediatric obesity pharmacotherapy clinical trials; and 3) highlight and discuss some of the unique aspects that should be considered when designing and conducting high-quality clinical trials evaluating the safety and efficacy of obesity medications in children and adolescents. Suggestions are offered in the areas of target population and eligibility criteria, clinical trial endpoint selection, trial duration, implementation of lifestyle modification therapy, and recruitment and retention of participants. Efforts should be made to design and conduct trials appropriately to ensure that high-quality evidence is generated on the safety and efficacy of various medications used to treat pediatric obesity.

Keywords

Pediatric Obesity; Pharmacotherapy; Clinical Trials

Pediatric Obesity Medicine: Commentary on the State of the Field – Why We Need More and Higher-Quality Pharmacotherapy Clinical Trials

The prevalence of pediatric obesity remains excessively high. In the United States (U.S.), approximately 32% and 17% of children ages 2-19 years old are afflicted with overweight

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and obesity, respectively.[1] Perhaps more concerning is the rapid rise in prevalence of severe obesity, defined as having a body mass index (BMI) 20% above the 95th BMI percentile or BMI ≥35 kg/m^2.[2] Severe obesity, which affects nearly 6% of children and adolescents in the U.S.,[1] is associated with serious medical and psychosocial comorbidities including, but not limited to, hypertension, dyslipidemia, arterial stiffness, endothelial dysfunction/activation, myocardial dysfunction, elevated levels of inflammation and oxidative stress, insulin resistance, impaired glucose tolerance, obstructive sleep apnea, musculoskeletal problems, non-alcoholic fatty liver disease, and psychosocial problems such as depression and anxiety.[2;3] Although evidence suggests that lifestyle modification therapy may be modestly-effective in addressing severe obesity in younger children, outcomes among adolescents have been generally poor.[4-7] In fact, one large study reported that only 2% of teens with severe obesity were able to achieve and maintain clinically-meaningful weight loss with lifestyle modification therapy alone.[4] This highlights the need for a more-intensive approach, likely involving adjunctive treatments, to improve the management of this chronic and refractory disease in those for whom lifestyle modification therapy is insufficient as a single strategy.

Severe obesity notwithstanding, the field of pediatric obesity management (within the context of research and clinical care) has focused almost exclusively on interventions targeting how the individual with obesity engages with the *external* environment (i.e., lifestyle modification/behavioral therapy). When disappointing results are observed, many draw the conclusion that these individuals with obesity are not adhering to behavioral recommendations closely enough and need to “try harder.” Conceptually, this assumption is overly-simplistic because it ignores the biological underpinnings of obesity (i.e., the *internal* physiological environment) and is counter to the mounting evidence demonstrating that obesity is a complex and multifactorial disease, which demands a multifaceted treatment approach.[8] Energy balance is dictated by physiological homeostatic and non-homeostatic mechanisms, both of which can be dysregulated in the context of obesity. Homeostatic mechanisms promote increased food intake and decreased energy expenditure when energy reserves are depleted and are heavily influenced by gut hormones and neurotransmitters. Non-homeostatic mechanisms, the biology of which is less well-elucidated, involve reward, cognition, and emotional factors related to eating. Effectively targeting these internal physiological pathways with biologically-based treatments in affected individuals with obesity may enhance weight loss and maintenance.

Furthermore, although short term weight reduction may be achievable, long term weight loss maintenance is more elusive for many individuals owing to numerous biological adaptations occurring in the post-weight loss setting. These include neuroendocrine changes involving appetite and satiety, and reduction of energy expenditure.[9-11] Specifically, following a loss in body weight, peripheral and central mechanisms respond in a way similar to starvation by conveying a sense that energy reserves have dwindled, activating a strong counter-response to increase caloric intake.[10] Moreover, metabolic rate decreases, further compounding the propensity for weight rebound.[9] These counter-regulatory adaptations persist for at least 12 months following initial weight loss and may be permanent.[11] In short, many individuals with obesity face an unrelenting uphill battle against biological forces that favor weight gain/regain.

Based upon this line of evidence, it is reasonable to conclude that changing how an individual with obesity engages with the *external* environment in a sustainable fashion is extremely difficult without also directly changing the *internal* environment. Therefore, effective and durable treatment approaches for many individuals with obesity will necessarily involve the combination of lifestyle modification therapy, which is primarily focused on training the individual on how to engage with the external environment, with medication(s), device therapy, and/or bariatric surgery, which are primarily focused on altering the internal physiological environment. Any of these treatments (lifestyle modification therapy, pharmacotherapy, device therapy, bariatric surgery) deployed in isolation is likely to fail in most individuals, at least over the long-term. Pharmacotherapy, the focus of this report, is one example of a biologically-based treatment that can be used as an adjuvant to lifestyle modification therapy to target the homeostatic and non-homeostatic mechanisms of obesity and potentially improve long-term weight loss outcomes.

Despite the potentially important role of pharmacotherapy in the treatment of obesity and the increasing number of obesity medications recently approved for use among adults, few agents have been evaluated in children or adolescents for this indication. Before pharmacotherapy can be routinely recommended for the treatment of pediatric obesity, high-quality clinical trials assessing the safety and effectiveness of various agents must be conducted. The next section provides a brief review of the literature summarizing the relatively small body of work performed to date in the area of pediatric obesity pharmacotherapy. Then, in an effort to address the paucity of guidance in the literature and limited scope of recommendations offered by regulatory agencies regarding pediatric obesity clinical trials,[12] the final section of this article discusses unique issues and offers suggestions regarding the design and conduct of trials of obesity medications in children and adolescents (note that broad topics applicable to all types of clinical trials are not discussed here). It is hoped that this document may spur the development of future guidelines and stimulate higher-quality research in the area of pediatric obesity pharmacotherapy by clinical investigators and industry.

Review of the Literature

In 2013, Sherafat-Kazemzadeh et al.[13] published a comprehensive and detailed systematic review of clinical trials evaluating pediatric obesity pharmacotherapy (we also direct interested readers to other reviews and meta-analyses, which describe outcomes of pediatric clinical trials of obesity pharmacotherapy[14-17]). Here, we provide an update of that review by briefly highlighting the pediatric studies reported in the interim and discuss obesity medications recently approved for adults that will soon be evaluated in pediatric clinical trials. In addition, we provide a table summarizing the features and outcomes of some of the key pediatric trials of the most widely-studied and commonly-used agents to treat obesity (Table 1).

Metformin

Since publication of the Sherafat-Kazemzadeh et al. review,[13] two additional pediatric metformin trials have been reported. The first included 66 children and adolescents (ages

7-18 years old) with obesity who were randomized in an open-label fashion to treatment with lifestyle modification alone or lifestyle modification plus metformin (1,000 mg per day for those <12 years old; 2,000 mg per day for those ≥12 years old) for six months.[18] Compared to the control condition, metformin significantly reduced BMI (-1.3 kg/m^2 control-subtracted difference) and waist circumference. However, metformin did not reduce markers of inflammation or thrombosis compared to the control group. The second trial included 151 children and adolescents (ages 8-18 years old) with obesity who were randomized to either metformin (1,500 mg per day) or placebo for six months.[19] Compared to placebo, metformin significantly reduced BMI (-1.07 kg/m^2 placebo-subtracted difference) and BMI standard deviation score (-0.1 SDS units placebo-subtracted difference). There were no statistically significant differences between groups at six months for any of the cardiometabolic risk factors measured in the trial (glucose, insulin, blood pressure, lipids, liver enzymes, and adipokines).

Exenatide

Recently, our group conducted a pilot clinical trial evaluating the weight loss effectiveness of the glucagon-like peptide-1 receptor agonist (GLP-1RA) exenatide in youth with severe obesity.[20] During the three-month randomized, placebo-controlled phase of the trial, exenatide elicited a greater reduction in percent change in BMI (-2.70% [95% CI, -5.02% to -0.37%] placebo-subtracted difference; P=0.03) and absolute BMI (-1.13 kg/m^2 placebo-subtracted difference) compared with placebo. BMI was further reduced (cumulative reduction of -4%) during the ensuing three-month open-label extension. The most common adverse events were gastrointestinal related, all mild-moderate and transient, with no participants withdrawn owing to symptomatology.

Pediatric Pipeline

Since 2012, four new obesity medications have been approved by the FDA for use among adults: lorcaserin (selective serotonin receptor agonist), the combination of phentermine (norepinephrine reuptake inhibitor) and topiramate (unknown mechanism(s)), the combination of naltrexone (opioid receptor blocker) and bupropion (dopamine reuptake inhibitor), and high dose (3 mg) liraglutide (GLP-1RA). Placebo-subtracted weight loss at one year with these agents ranges from approximately 3-10% (for details about the safety and efficacy of these medications in adults, readers are referred to Yanovski and Yanovski).[21] Manufacturers of these medications plan to perform pediatric trials, which are slated to begin within the next few years. Although the obesity medicine pipeline appears to be strong and growing, the pace of pediatric evaluation is slow. Indeed, since the publication of the Sherafat-Kazemzadeh review in 2013,[13] few pediatric obesity trials have been reported. Research in this arena could be bolstered through additional funding from the National Institutes of Health (and other funders) and a commitment from the manufacturers to accelerate the pace of pediatric development and evaluation of their products.

Clinical Trial Considerations

Target Population and Eligibility (see suggestions in Table 2)

In determining the target population for pediatric obesity pharmacotherapy clinical trials, one must balance the risks of medication use (chronically and potentially life-long) against the liabilities of persistent obesity. As such, factors to consider include age, severity of obesity, pubertal maturation, and the presence or absence of co-morbid conditions. Concurrent use of weight altering medications also should be considered. While not covered in this document, it should be noted that children with rare genetic causes of obesity (e.g., Prader-Willi, Bardet-Biedl syndromes) or with endocrinologic disorders (e.g., Cushing's syndrome or hypothyroidism) should be studied in separately-designed clinical trials, which is in line with recommendations from the European Medicines Agency (E.M.A.)[22]

Age and Pubertal Maturation—The E.M.A suggests that medication could be considered for children with *severe* obesity as young as six years of age.[22] Evidence supporting this view is mixed. Lifestyle modification therapy (without pharmacotherapy) can elicit clinically-meaningful weight loss in the short- to medium-term in young children (<10-12 years old); however, long-term weight loss maintenance is difficult to achieve.[23-25] Of particular concern are adolescents older than 12 years of age, who tend to respond less-favorably to lifestyle modification therapy (vs. younger children) and are more likely to have co-morbidities.[2;4-7] From this standpoint, 12 years of age might be a reasonable threshold for inclusion in pharmacotherapy clinical trials (at least for initial studies) because this population is often at the highest level of risk and most likely to benefit from weight reduction medication owing to limitations of lifestyle modification as a singular treatment. Furthermore, it should be recognized that separate trials of older and younger children should be performed owing to the unique cognitive and developmental features of children vs. adolescents and different lifestyle modification therapy strategies that might be utilized (e.g., a greater degree of parental involvement for younger children). The upper age limit for inclusion in pediatric obesity clinical trials is often set at 18 years old but has varied widely, and the U.S. Food and Drug Administration (F.D.A.) has offered different definitions of pediatric eligibility in numerous guidance documents (not specifically pertaining to pediatric obesity). Using a cutoff of 18 years old is logical considering adult obesity pharmacotherapy clinical trial protocols typically state that individuals ≥18 years old are eligible to enroll. Improved clarity on this issue from the regulatory agencies would be beneficial.

Although previous pediatric obesity pharmacotherapy clinical trials have used Tanner stage as an eligibility criterion, it may not be particularly relevant considering inclusion should be based on potential risk/benefit ratio of the pharmacotherapy. Unless reasonable evidence suggests a potential developmental risk is associated with a specific medication, Tanner stage should probably not be used as an eligibility criterion; rather, it should be evaluated throughout the trial as a safety endpoint (see below). It may be useful to stratify randomization by Tanner stage and sex (and potentially evaluate outcomes by these factors) to avoid large imbalances between groups in linear growth velocity and other factors associated with pubertal maturation that may impact changes in BMI.

Co-Morbid Conditions—The F.D.A. recommends that initial obesity pharmacotherapy trials include participants with BMI ≥95th percentile and ≥1 weight-related co-morbid condition; and, once a satisfactory risk/benefit profile has been established in that group, studies of lower-risk individuals can be considered (http://www.fda.gov/downloads/Drugs/Guidances/ucm071612.pdf). In contrast, the E.M.A. recommends that trials include participants with obesity (defined by BMI z-score) regardless of the presence of co-morbid conditions.[22] Owing to the lack of consensus regarding what constitutes a co-morbid condition in childhood and often insufficient evidence from which to determine the risk/benefit balance, both positions seem reasonable. One argument for broader inclusion is that, as a disease, obesity is serious enough to warrant treatment with pharmacotherapy even when co-morbidities are not present. Moreover, effective treatment of obesity early in life may offer the opportunity for prevention of co-morbidities.[26] And, it is conceivable that some healthcare providers might utilize pharmacotherapy to treat youth with obesity in the absence of co-morbidities. Therefore, it seems prudent to include these participants in clinical trials (and potentially stratify randomization on select co-morbidities) since they represent a patient population that might receive these therapies in the clinical setting. Finally, decisions of whether to include this "lower-risk" population without co-morbidities in a given clinical trial could also be influenced by the specific agent(s) under investigation (e.g., degree of safety concern based on adult trials and/or juvenile animal toxicology studies).

Upper BMI Threshold—Some obesity pharmacotherapy clinical trials in youth have excluded potential participants with very high BMIs (e.g., BMI >44 kg/m^2 in the large trials of orlistat and sibutramine).[27;28] Indeed, there is a growing prevalence of youth with very high BMI[1] and it is possible that, in general, these individuals may respond differently to a given intervention compared to those with less severe forms of obesity. However, rather than excluding potentially-eligible participants based upon an arbitrary upper BMI threshold, an alternative option is to conduct pre-specified sub-analyses within baseline BMI strata, perhaps likely combined with stratified randomization on such groups. This approach would make enrollment easier (by widening the recruitment pool) and increase the generalizability and clinical relevance of the findings while allowing for differential effects between BMI categories to be identified.

History of Bariatric Surgery and Concurrent Use of Obesity Pharmacotherapy or other Weight Altering Medications—For most obesity pharmacotherapy trials, individuals who have undergone bariatric surgery should be excluded (separate studies could be performed for individuals who have regained weight after surgery). Similarly, concurrent use of obesity pharmacotherapy should be an exclusion criterion for most trials (a washout phase could be utilized but the time period needs to be well-justified) owing to uncertainties regarding the weight loss trajectory of the concurrent medication and unknown interactions of the agents when used in combination including overlapping, additive, or synergistic effects. However, it is not uncommon for many potentially-eligible participants to be using other medications, which may have modest weight altering effects, for treatment of co-morbidities or other conditions. Examples of these medications include selective serotonin reuptake inhibitors, atypical antipsychotic medications, stimulants, insulin, metformin, and

hormonal contraception. Researchers should strive to strike a balance between a "clean" evaluation of obesity pharmacotherapy and the need for generalizability. One strategy is to include participants who have been on a stable dose of a weight altering medication for a minimum period of time and demonstrate relative weight neutrality prior to enrollment.

History of Weight Loss Attempts—The F.D.A. and E.M.A. recommend that potentially-eligible participants should have a documented history of a failed weight loss attempt via lifestyle modification therapy before enrolling in an obesity pharmacotherapy clinical trial. In fact, the E.M.A. guidelines require a 3 to 6-month run-in period consisting of only lifestyle modification therapy to ensure that the risks associated with medical management are justified.[22] However, utilizing such a design can influence the subsequent efficacy assessment in the randomized, placebo-controlled phase of the trial since even modest weight loss (an amount less than the designated threshold defined as being "successful") and/or risk factor improvements achieved during the run-in period could mask the benefits of the medication under study. Given the challenges of defining what constitutes a failed attempt (unclear in the F.D.A. guidance) and considering the relatively modest amount of weight loss associated with lifestyle modification therapy as a single treatment modality in many youth,[23;24] particularly among adolescents with severe obesity,[2;4-7] this recommendation appears to lack empirical support and should be reevaluated. Similarly, a placebo run-in period, typically used as an assessment of medication adherence and compliance to the trial protocol, is not recommended because of the selection bias it introduces (i.e., selecting individuals most likely to comply with the treatment regimen), thereby limiting generalizability, and the difficulty in comparing results with trials that do not include this design feature.

Clinical Trial Endpoint Selection (see suggestions in Table 3)

Primary Endpoint Selection—The choice of primary outcome should be influenced by the following considerations (in order of importance): 1) clinical relevance (interpretability); 2) an endpoint the treatment is expected to affect, and 3) statistical precision. When evaluating the efficacy of weight loss medications for potential approval among adults, the F.D.A. has outlined two standard benchmarks. The first is a mean placebo-subtracted weight loss of at least 5% and the second is ≥35% of participants in the active medication group experiencing 5% or greater weight loss, which should be at least double that of the placebo group.[29] No clear guidance exists regarding appropriate pediatric benchmarks. In 2007 the F.D.A. offered some insight by recommending that primary efficacy endpoints for pediatric trials should include the mean percent change in BMI and the proportion of participants achieving ≥5% BMI reduction from baseline (http://www.fda.gov/downloads/Drugs/Guidances/ucm071612.pdf).

Despite virtually universal agreement about the need to use BMI-based vs. body weight-based metrics in pediatric obesity studies owing to growth and development, there is no consensus on which BMI-based metric is most appropriate. There are many from which to choose, including, but not limited to: absolute BMI, percent change in BMI from baseline, BMI percentile, BMI z-score (or standard deviation score), BMI percent above the 95th percentile, BMI sympercent (the percentage difference from the 50th BMI percentile based

on the natural log scale), and percent over BMI (percentage above the 50th BMI percentile). Historically, some of the large pediatric obesity clinical trials (e.g., sibutramine[27] and orlistat[28]) used absolute change in BMI from baseline as the primary endpoint. However, one drawback of using change in absolute BMI is the difficulty in interpreting results when there is a large range of baseline BMI values. BMI percentile can be problematic because of the ceiling effect at the 99th percentile, that is, many eligible subjects spanning a range of BMI would all have nearly identical BMI percentiles. Although recommended as the primary endpoint of choice by the E.M.A.,[22] the BMI z-score is difficult to interpret in the clinical setting, suffers from a similar ceiling effect as BMI percentile, and is not ideal because the data set on which the scores were developed had few data points at the extremes. Therefore, relatively large absolute weight reductions in youth with severe obesity correspond to small changes in the BMI z-score.[30] BMI percent above the 95th percentile[2;31] provides a flexible means by which to track changes in BMI status over time among youth with severe obesity.[32] However, changes are not as easy to interpret as other endpoints, which may diminish its clinical usefulness. Neither the BMI sympercent[33;34] nor percent over BMI[35] appear to have a clear advantage over the use of BMI percent above the 95th percentile at least in terms of interpretability.

Endpoints based on percentiles or z-scores are also sex- and age-specific. As such, the same change in BMI is not counted the same for two individuals differing by sex and/or age. While a similar argument can be made about absolute change from baseline versus percent change for individuals differing in baseline BMI, the differential treatment of change in BMI is viewed more favorably as it only depends on the baseline BMI and not also on sex and age. If change in BMI should be larger for those with higher BMI at baseline, then percentage from baseline will incorporate that and be preferred while absolute change will not. It is unclear whether the change in BMI associated with meaningful clinical impact would be best represented through a measurement that is differential across sex and age rather than baseline BMI alone.

Other potential primary endpoints include body fat and anthropometric measures such as waist circumference and waist-to-hip ratio. The primary argument against the use of body fat as a primary endpoint for clinical trials is that many of the methods are expensive, uncomfortable for the participant, unreliable, and are not often used in the clinical setting. Therefore, results of trials using body fat as the primary endpoint would have limited application in the clinical setting in terms of measurement and tracking. Waist circumference and waist-to-hip ratio are not ideal primary endpoints owing to the high amount of measurement variability and error, particularly in youth with severe obesity.[2] Measurement and reporting of body fat and anthropometric variables within the context of clinical trials should be encouraged (e.g., as secondary endpoints – see below); however, it seems sensible to use a BMI-based metric as the primary endpoint in clinical trials because it is easy to obtain, interpretable, and has clinical utility.[36]

Consistency and uniformity in the use and reporting of standard endpoints is crucial to the advancement of the field of pediatric obesity medicine. Primary and secondary endpoints should be clearly delineated and pre-specified. Considering all of the above, it seems advisable to use percent change in BMI from baseline as the primary endpoint in pediatric

obesity clinical trials. Until consensus is reached regarding which endpoint(s) should be utilized, erring on the side of reporting more vs. fewer endpoints is suggested, including absolute change in BMI, change in BMI z-score, and the proportion with ≥5% and ≥10% BMI reduction from baseline (although separate, dedicated studies should investigate whether this degree of weight loss is associated with clinically-meaningful improvements in risk factors and co-morbidities as has been established in adults - in terms of body weight reduction). Most of these endpoints are intuitive, easy to interpret, and translatable to the clinical environment. Consistent reporting of these endpoints in all pediatric obesity clinical trials (including studies of lifestyle modification and bariatric surgery) would facilitate direct comparison of results across studies.

Selection of Secondary Endpoints: Co-Morbidities, Risk Factors, and More— To improve consistency across studies, Bryant and colleagues proposed the Childhood obesity Outcomes Review (CoOR) framework,[36] which identified measures (based on instrument development, reporting, and evaluation) in the following domains: diet, eating behaviors, physical activity, sedentary time, fitness, physiology, health-related quality of life, psychological well-being, and environment. Bryant et al.[36] recommended that researchers select the domains that may demonstrate change or are believed to mediate such change given the intervention being evaluated.

Pediatric obesity pharmacotherapy clinical trials should ideally include, at a minimum, measures in the domains of physiology and quality of life. The physiological measures (i.e. cardiometabolic risk factors) that should also be included are: fasting glucose, fasting lipid panel, and blood pressure. Others to consider include measures of insulin sensitivity and/or glucose tolerance, vascular structure and function (e.g., heart rate variability, brachial artery flow-mediated dilation, pulse wave velocity, carotid artery compliance and distensibility, and carotid artery intima-media thickness), adipokines, inflammatory markers, and body fat and/or anthropometric measures (see discussion in *Primary Endpoints* section). Aspects of psychological functioning (e.g., depression), eating behaviors, and/or diet could also be included as these may provide clues to predictors of response.

Safety Endpoints—In addition to standard monitoring for adverse events, pediatric obesity pharmacotherapy clinical trials warrant extra attention to safety. Childhood is characterized by physiological and psychological development, and medications that affect weight have the potential to disrupt these processes. Tanner stage and height should be serially-measured in all trials to monitor for disruptions in pubertal development and linear growth, respectively. One could consider also measuring bone age, bone mineral density, and pubertal hormones. In addition, monitoring of eating disorders should be performed and the incidence reported. Other safety endpoints should be considered depending on the mechanism(s) of action of the medication under investigation. For instance, many obesity medications are centrally-acting (affecting appetite and satiety centers in the brain). As such, neuropsychiatric function, including cognition and mood, should be monitored during these trials. It should be noted that appropriate neuropsychiatric measures and cognitive assessments may differ depending upon the age-range of participants, further highlighting the need for separate trials performed in children vs. adolescents.

Trial Duration

Considering that weight loss maintenance is so challenging and the fact that chronic pharmacotherapy will probably be required for most individuals (perhaps life-long), it is critically important that confirmatory pediatric clinical trials be of sufficient duration to evaluate at least mid-term safety and efficacy. Guidance provided by the F.D.A. and E.M.A. (both in 2007) stated that pediatric obesity clinical trials should be at least one year in duration. Ideally, trials would last longer than one year; however, obstacles such as participant attrition (notoriously high in obesity clinical trials) and funding/resource limitations often make this impractical. Nevertheless, full-scale confirmatory trials should be designed to include a minimum of one year of double-blind placebo-controlled treatment. Interestingly, for trials designed for pediatric approval of weight loss medications in Europe, the E.M.A. requires a six-month follow-up period (after cessation of drug treatment) to assess relapse and weight rebound.[22] Considering the strong biological propensity for weight regain, the rationale for, and relevance of, such a requirement is unclear (i.e., weight gain is an expected outcome). Obesity is a chronic disease; therefore, life-long treatment with pharmacotherapy will likely be required for most individuals. One would expect weight rebound upon withdrawal of obesity pharmacotherapy in the same way that one would expect increases in blood pressure and blood glucose upon withdrawal of anti-hypertensive and anti-diabetic pharmacotherapies, respectively, even with concomitant lifestyle modification.

Design and Implementation of Lifestyle Modification Therapy

Lifestyle modification counseling should be included in all pediatric obesity clinical trials and should be delivered to all participants regardless of assignment to active medication or placebo. Indeed, the intent of pharmacotherapy is to modify the internal physiological environment by targeting the biological pathways associated with body weight regulation in an effort to help the individual with obesity more successfully implement and maintain lifestyle changes over the long-term. No clear guidance exists regarding the appropriate breadth or intensity of the lifestyle modification component in the context of pharmacotherapy clinical trials as evidenced by the wide array of approaches utilized in previous studies. On the one hand, it seems advisable to implement the most intensive lifestyle counseling protocol possible considering the fact that clinically-meaningful weight loss is the ideal outcome. On the other hand, trials ought to be designed to maximize generalizability, and intensive lifestyle modification therapy approaches are not always available to youth seeking medical weight management. The ideal frequency of contact is unknown; however, evidence suggests that at least 26 to 75 hours of contact over six to 12 months is necessary to derive meaningful outcomes.[24] This degree of contact frequency may not be practical within the context of all clinical trials nor is it representative of what is offered in the clinical setting. With these issues in mind, it seems advisable that all pediatric obesity clinical trials include lifestyle modification counseling that addresses diet, physical activity and behavioral domains (trials including younger children should include a parental component) and that contact with participants (at least by phone) be as frequent as possible with a goal of at least monthly sessions throughout the course of the trial. Furthermore, details of the curriculum content and frequency of contact should be reported to aid in data/results interpretation.

Recruitment and Retention of Participants

Recruitment and retention of participants are two of the most arduous challenges researchers encounter when conducting pediatric obesity clinical trials. Some of the challenges of recruitment can be minimized with careful selection of inclusion/exclusion criteria (as discussed earlier). Although attractive from a scientific perspective, developing overly-strict exclusion criteria can make recruitment difficult and also can limit the generalizability of the results. Designing studies to have an active treatment component, such as lifestyle modification counseling, a meal replacement induction period, and/or an open-label extension (during which all are offered the experimental medication), may increase recruitment and retention. It should be recognized, however, that an open-label extension may not add meaningful scientific benefit except for continued safety monitoring due to the un-blinded nature of that period and could be costly.

Missing data in clinical trials jeopardizes the integrity and validity of results through potential bias of unknown magnitude and direction. Because all methods for handling missing data have some level of untestable assumptions, the issue is quite serious and best avoided if possible.[37] That said, despite best efforts, some missing data cannot be avoided. For these situations, careful attention to the assumptions about the nature of missing data underlying the estimates of treatment effects needs to be exercised. The planned approach to handling missing data should be specified in the study protocol.

Strong communication skills are essential in building a trusting relationship between study personnel and the participants and their families. Creating a culture of customer service in all interactions is important. Further, the availability of a language interpreter can increase the number of potentially-eligible participants and cultural awareness can facilitate positive relationships and establish trust between study personnel and the participants and their families. Providing flexibility in scheduling study visits by offering weekend or evening appointments can potentially minimize attrition. Finally, appropriate reimbursement (including time, travel, parking, and meals) is another key factor. Level of reimbursement will vary by study; however, participants and families often lead busy lives and participation in clinical trials can be time-consuming and expensive.

Conclusions

The number of medications approved to treat obesity in adults has increased recently, yet the options available for the pediatric population remain scant. Given the burgeoning rate of pediatric severe obesity, a pressing need exists to properly evaluate these agents in children and adolescents by generating pediatric safety and efficacy data from well-designed clinical trials. The field of obesity medicine is primed and ready for studies aimed at understanding and characterizing phenotypic features of eating behavior to inform a tailored treatment approach. Early identification of individuals most likely to respond favorably to a specific agent(s) will maximize positive outcomes and minimize unwanted side effects. Because of the unique aspects associated with pediatric obesity, pharmacotherapy clinical trials need to be carefully designed. Ideally, as guidelines for best practices are developed and refined, there would be consensus among regulatory agencies, such as the F.D.A. and E.M.A., in an effort to provide unified principles regarding the design of pediatric obesity

pharmacotherapy clinical trials. It is hoped that this document may be useful as a starting point for the development of future guidelines and that it will stimulate higher-quality research in the area of pediatric obesity pharmacotherapy by clinical investigators and industry.

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References

1. Skinner AC, Skelton JA. Prevalence and trends in obesity and severe obesity among children in the United States, 1999-2012. JAMA Pediatr. 2014 Jun; 168(6):561–6. [PubMed: 24710576]
2. Kelly AS, Barlow SE, Rao G, Inge TH, Hayman LL, Steinberger J, et al. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. Circulation. 2013 Oct 8; 128(15):1689–712. [PubMed: 24016455]
3. Skinner AC, Perrin EM, Moss LA, Skelton JA. Cardiometabolic Risks and Severity of Obesity in Children and Young Adults. N Engl J Med. 2015 Oct; 373(14):1307–17. [PubMed: 26422721]
4. Danielsson P, Kowalski J, Ekblom O, Marcus C. Response of severely obese children and adolescents to behavioral treatment. Arch Pediatr Adolesc Med. 2012 Dec; 166(12):1103–8. [PubMed: 23108856]
5. Knop C, Singer V, Uysal Y, Schaefer A, Wolters B, Reinehr T. Extremely obese children respond better than extremely obese adolescents to lifestyle interventions. Pediatr Obes. 2015 Feb; 10(1):7–14. [PubMed: 24347523]
6. Johnston CA, Tyler C, Palcic JL, Stansberry SA, Gallagher MR, Foreyt JP. Smaller weight changes in standardized body mass index in response to treatment as weight classification increases. J Pediatr. 2011 Apr; 158(4):624–7. [PubMed: 21035822]
7. Kalarchian MA, Levine MD, Arslanian SA, Ewing LJ, Houck PR, Cheng Y, et al. Family-based treatment of severe pediatric obesity: randomized, controlled trial. Pediatrics. 2009 Oct; 124(4): 1060–8. [PubMed: 19786444]
8. Ochner CN, Tsai AG, Kushner RF, Wadden TA. Treating obesity seriously: when recommendations for lifestyle change confront biological adaptations. Lancet Diabetes Endocrinol. 2015 Apr; 3(4): 232–4. [PubMed: 25682354]
9. Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. N Engl J Med. 1995 Mar 9; 332(10):621–8. [PubMed: 7632212]
10. MacLean PS, Bergouignan A, Cornier MA, Jackman MR. Biology's response to dieting: the impetus for weight regain. Am J Physiol Regul Integr Comp Physiol. 2011 Sep; 301(3):R581–R600. [PubMed: 21677272]
11. Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A, et al. Long-term persistence of hormonal adaptations to weight loss. N Engl J Med. 2011 Oct 27; 365(17):1597–604. [PubMed: 22029981]
12. Schwimmer JB. Clinical trials for adolescent obesity: cooking up an alphabet stew of what to do. JAMA Pediatr. 2013 Apr; 167(4):391–3. [PubMed: 23381196]
13. Sherafat-Kazemzadeh R, Yanovski SZ, Yanovski JA. Pharmacotherapy for childhood obesity: present and future prospects. Int J Obes (Lond). 2013 Jan; 37(1):1–15. [PubMed: 22929210]

14. Freemark M. Pharmacotherapy of childhood obesity: an evidence-based, conceptual approach. Diabetes Care. 2007 Feb; 30(2):395–402. [PubMed: 17259519]
15. McDonagh MS, Selph S, Ozpinar A, Foley C. Systematic review of the benefits and risks of metformin in treating obesity in children aged 18 years and younger. JAMA Pediatr. 2014 Feb; 168(2):178–84. [PubMed: 24343296]
16. Park MH, Kinra S, Ward KJ, White B, Viner RM. Metformin for obesity in children and adolescents: a systematic review. Diabetes Care. 2009 Sep; 32(9):1743–5. [PubMed: 19502540]
17. Rogovik AL, Chanoine JP, Goldman RD. Pharmacotherapy and weight-loss supplements for treatment of paediatric obesity. Drugs. 2010 Feb 12; 70(3):335–46. [PubMed: 20166770]
18. Mauras N, DelGiorno C, Hossain J, Bird K, Killen K, Merinbaum D, et al. Metformin use in children with obesity and normal glucose tolerance--effects on cardiovascular markers and intrahepatic fat. J Pediatr Endocrinol Metab. 2012; 25(1-2):33–40. [PubMed: 22570948]
19. Kendall D, Vail A, Amin R, Barrett T, Dimitri P, Ivison F, et al. Metformin in Obese Children and Adolescents: The MOCA Trial. J Clin Endocrinol Metab. 2013 Jan; 98(1):322–9. [PubMed: 23175691]
20. Kelly AS, Rudser KD, Nathan BM, Fox CK, Metzig AM, Coombes BJ, et al. The effect of glucagon-like Peptide-1 receptor agonist therapy on body mass index in adolescents with severe obesity: a randomized, placebo-controlled, clinical trial. JAMA Pediatr. 2013 Apr 1; 167(4):355–60. [PubMed: 23380890]
21. Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. JAMA. 2014 Jan 1; 311(1):74–86. [PubMed: 24231879]
22. Karres J, Tomasi P, Saint RA. The development of pharmacological treatment of obesity in children. A European regulatory perspective. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2011 May; 54(5):570–6. [PubMed: 21547648]
23. Oude LH, Baur L, Jansen H, Shrewsbury VA, O'Malley C, Stolk RP, et al. Interventions for treating obesity in children. Cochrane Database Syst Rev. 2009; (1):CD001872. [PubMed: 19160202]
24. Whitlock EP, O'Connor EA, Williams SB, Beil TL, Lutz KW. Effectiveness of Weight Management Interventions in Children: A Targeted Systematic Review for the USPSTF. Pediatrics. 2010 Feb; 125(2):e396–e418. [PubMed: 20083531]
25. Wilfley DE, Stein RI, Saelens BE, Mockus DS, Matt GE, Hayden-Wade HA, et al. Efficacy of maintenance treatment approaches for childhood overweight: a randomized controlled trial. JAMA. 2007 Oct 10; 298(14):1661–73. [PubMed: 17925518]
26. Juonala M, Magnussen CG, Berenson GS, Venn A, Burns TL, Sabin MA, et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. N Engl J Med. 2011 Nov 17; 365(20): 1876–85. [PubMed: 22087679]
27. Berkowitz RI, Fujioka K, Daniels SR, Hoppin AG, Owen S, Perry AC, et al. Effects of sibutramine treatment in obese adolescents: a randomized trial. Ann Intern Med. 2006 Jul 18; 145(2):81–90. [PubMed: 16847290]
28. Chanoine JP, Hampl S, Jensen C, Boldrin M, Hauptman J. Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. JAMA. 2005 Jun 15; 293(23): 2873–83. [PubMed: 15956632]
29. Colman E. Food and Drug Administration's Obesity Drug Guidance Document: a short history. Circulation. 2012 May 1; 125(17):2156–64. [PubMed: 22547756]
30. Woo JG. Using body mass index Z-score among severely obese adolescents: a cautionary note. Int J Pediatr Obes. 2009; 4(4):405–10. [PubMed: 19922058]
31. Flegal KM, Wei R, Ogden CL, Freedman DS, Johnson CL, Curtin LR. Characterizing extreme values of body mass index-for-age by using the 2000 Centers for Disease Control and Prevention growth charts. Am J Clin Nutr. 2009 Nov; 90(5):1314–20. [PubMed: 19776142]
32. Gulati AK, Kaplan DW, Daniels SR. Clinical tracking of severely obese children: a new growth chart. Pediatrics. 2012 Dec; 130(6):1136–40. [PubMed: 23129082]
33. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ. 2000 May 6; 320(7244):1240–3. [PubMed: 10797032]

34. Cole TJ, Faith MS, Pietrobelli A, Heo M. What is the best measure of adiposity change in growing children: BMI, BMI %, BMI z-score or BMI centile? Eur J Clin Nutr. 2005 Mar; 59(3):419–25. [PubMed: 15674315]
35. Paluch RA, Epstein LH, Roemmich JN. Comparison of methods to evaluate changes in relative body mass index in pediatric weight control. Am J Hum Biol. 2007 Jul; 19(4):487–94. [PubMed: 17546615]
36. Bryant M, Ashton L, Nixon J, Jebb S, Wright J, Roberts K, et al. Framework of outcome measures recommended for use in the evaluation of childhood obesity treatment interventions: the CoOR framework. Pediatr Obes. 2014 Dec; 9(6):e116–31. [PubMed: 24729517]
37. Little RJ, D'Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med. 2012 Oct 4; 367(14):1355–60. [PubMed: 23034025]
38. Evia-Viscarra ML, Rodea-Montero ER, Apolinar-Jimenez E, Munoz-Noriega N, Garcia-Morales LM, Leanos-Perez C, et al. The effects of metformin on inflammatory mediators in obese adolescents with insulin resistance: controlled randomized clinical trial. J Pediatr Endocrinol Metab. 2012; 25(1-2):41–9. [PubMed: 22570949]
39. Rezvanian H, Hashemipour M, Kelishadi R, Tavakoli N, Poursafa P. A randomized, triple masked, placebo-controlled clinical trial for controlling childhood obesity. World J Pediatr. 2010 Nov; 6(4): 317–22. [PubMed: 21080144]
40. Burgert TS, Duran EJ, Goldberg-Gell R, Dziura J, Yeckel CW, Katz S, et al. Short-term metabolic and cardiovascular effects of metformin in markedly obese adolescents with normal glucose tolerance. Pediatr Diabetes. 2008 Dec; 9(6):567–76. [PubMed: 18761646]
41. Freemark M, Bursey D. The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. Pediatrics. 2001 Apr.107(4):E55. [PubMed: 11335776]
42. Love-Osborne K, Sheeder J, Zeitler P. Addition of metformin to a lifestyle modification program in adolescents with insulin resistance. J Pediatr. 2008 Jun; 152(6):817–22. [PubMed: 18492523]
43. Srinivasan S, Ambler GR, Baur LA, Garnett SP, Tepsa M, Yap F, et al. Randomized, controlled trial of metformin for obesity and insulin resistance in children and adolescents: improvement in body composition and fasting insulin. J Clin Endocrinol Metab. 2006 Jun; 91(6):2074–80. [PubMed: 16595599]
44. Wiegand S, l'Allemand D, Hubel H, Krude H, Burmann M, Martus P, et al. Metformin and placebo therapy both improve weight management and fasting insulin in obese insulin-resistant adolescents: a prospective, placebo-controlled, randomized study. Eur J Endocrinol. 2010 Oct; 163(4):585–92. [PubMed: 20639355]
45. Yanovski JA, Krakoff J, Salaita CG, McDuffie JR, Kozlosky M, Sebring NG, et al. Effects of metformin on body weight and body composition in obese insulin-resistant children: a randomized clinical trial. Diabetes. 2011 Feb; 60(2):477–85. [PubMed: 21228310]
46. Lavine JE, Schwimmer JB, Van Natta ML, Molleston JP, Murray KF, Rosenthal P, et al. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. JAMA. 2011 Apr 25 27; 305(16):1659–68. [PubMed: 21521847]
47. Metformin Extended Release Treatment of Adolescent Obesity: A 48-Week Randomized, Double-Blind, Placebo-Controlled Trial With 48-Week Follow-up. Arch Pediatr Adolesc Med. 2010 Feb; 164(2):116–23. [PubMed: 20124139]
48. Maahs D, de Serna DG, Kolotkin RL, Ralston S, Sandate J, Qualls C, et al. Randomized, double-blind, placebo-controlled trial of orlistat for weight loss in adolescents. Endocr Pract. 2006 Jan; 12(1):18–28. [PubMed: 16524859]
49. Kelly AS, Metzig AM, Rudser KD, Fitch AK, Fox CK, Nathan BM, et al. Exenatide as a weight-loss therapy in extreme pediatric obesity: a randomized, controlled pilot study. Obesity (Silver Spring). 2012 Feb; 20(2):364–70. [PubMed: 22076596]

Table 1

Randomized controlled trials of the most widely-studied and commonly-used obesity medications in youth

Population	Dose	Study Length and Design	Weight Loss [a]	Attrition	Side Effects	Cost / Month [b]	Reference
Metformin							
9 - 18 yr old; Obese; IR n = 12 (drug) ; n = 14 (placebo)	500 mg (2× / day)	3 months; RCT; DBPC	Δ BMI = -0.01 kg/m^2	16.2%	None different than placebo	$42.23	(38)
10 - 16 yr old; Obese n = 41 (drug) ; n = 42 (placebo)	500 mg (3× / day)	12 weeks; RCT; DBPC	Δ BMI = -0.60 kg/m^2 Δ waist circumference = -1.7 cm	8.9%	Gastrointestinal discomfort and loose stool	$63.34	(39)
13 - 18 yr old; Obese; NGT n = 15 (drug); n = 12 (placebo)	500 mg (3× / day)	4 months; RCT; DBPC	Δ BMI = -2.0 kg/m^2 Δ body weight = -3.9 kg	18.0%	Gastrointestinal and stomach discomfort	$63.34	(40)
12 - 19 yr old; Obese n = 14 (drug) ; n = 17 (placebo)	500 mg (2× / day)	6 months; RCT; DBPC	Δ BMI = -0.73 kg/m^2	10.4%	Mild abdominal discomfort and diarrhea	$42.23	(41)
12 - 19 yr old; Obese; IR n = 60 (drug) ; n = 25 (placebo)	850 mg (2× / day) [c]	6 months; RCT; DBPC	Δ BMI = -0.79 kg/m^2	24.0%	Gastrointestinal discomfort	$72.00	(42)
9 - 18 yr old; Obese n = 28 (randomized)	1000 mg (2× / day)	6 months; RCT; DBPC; Crossover	Δ BMI = -1.26 kg/m^2 Δ BMI Z-score = -0.12	21.5%	None different than placebo	$86.41	(43)
10 - 17 yr old; Obese n = 36 (drug) ; n = 34 (placebo)	500 mg (2× / day)	6 months; RCT; DBPC	Δ BMI = +0.38 kg/m^2	10.0%	None different than placebo	$42.23	(44)
6 - 12 yr old; Severe Obesity; IR n = 53 (drug); n = 47 (placebo)	1000 mg (2× / day)	6 months; RCT; DBPC	Δ BMI = -1.09 kg/m^2 Δ BMI Z-score = -0.07	15.0%	Gastrointestinal discomfort	$86.41	(45)
8 - 17 yr old; Obese; NAFLD n = 57 (drug); n = 58 (placebo)	500 mg (2× / day)	96 weeks; RCT; DBPC	Δ BMI = -0.60 kg/m^2 Δ BMI Z-score = -0.06	13.1%	None different than placebo	$42.23	(46)
13 - 18 yr old; Obese n = 39 (drug); n = 38 (placebo)	XR 2000 mg (1× / day)	52 weeks; RCT; DBPC	Δ BMI = -1.10 kg/m^2 Δ BMI Z-score = -0.08	26.0%	None different than placebo	$89.40	(47)
8 - 18 yr old; Obese; IFG or IGT n = 74 (drug); n = 77 (placebo)	500 / 1000 mg (2× / day) [d]	6 months; RCT; DBPC	Δ BMI = -1.07 kg/m^2 Δ BMI Z-score = -0.1	27.0%	Gastrointestinal discomfort	$64.33	(19)
7 - 18 yr old; Obese; NGT n = 35 (drug + lifestyle); n = 31 (lifestyle)	Up to 1000 mg (2× / day) [e]	6 months; RCT; Open Label	Δ BMI = -1.30 kg/m^2 Δ body weight = -3.2 kg	36.0%	None different than placebo	$86.41	(18)
Orlistat							
14 - 18 yr old; Overweight n = 20 (drug); n = 20 (placebo)	120 mg (3× / day)	6 months; RCT; DBPC	Δ BMI = -0.50 kg/m^2	15.0%	Soft stools, oily spotting, oily evacuation, liquid stools	$614.53	(48)
12 - 16 yr old; Obesity n = 357 (drug); n = 182 (placebo)	120 mg (3× / day)	6 months; RCT; DBPC	Δ BMI = -0.86 kg/m^2 Δ waist circumference = -1.45 cm	3.6%	Gastrointestinal discomfort, oily spotting, oily evacuation	$614.53	(28)

Population	Dose	Study Length and Design	Weight Loss [a]	Attrition	Side Effects	Cost / Month [b]	Reference
			Exenatide				
12 - 19 year old; Severe Obesity n = 12 (drug); n = 10 (placebo)	10 μg (2× / day) [f]	3 months; RCT; DBPC	% change in BMI = - 2.70% Δ body weight = -3.26 kg	15.0%	Mild: Nausea, abdominal pain, diarrhea, headache, vomiting.	$619.93	(20)
8 - 19 year old; Severe Obesity n = 12 (randomized)	10 μg (2× / day) [f]	6 months; Randomized, Crossover Open Label	% change in BMI = - 4.92% Δ body weight = -3.90 kg	8.3%	Mild: nausea, vomiting, headache, and abdominal pain	$619.93	(49)

Abbreviations (order of appearance): IR = insulin resistance; RCT = randomized controlled trial; DBPC = double-blind, placebo-controlled; BMI = body mass index; NGT = normal glucose tolerance; NAFLD = non-alcoholic fatty liver disease; XR = extended release; IFG = impaired fasting glucose; IGT = impaired glucose tolerance

A: Weight-loss is placebo/control-subtracted unless otherwise noted.

B: Cost / Month is reflective of average wholesale price (AWP) plus dispensing fees.

C: Started at 500 mg once daily. At 1 month, the dose increased to 500 mg twice daily, followed by an increase to 850 mg twice daily at 2 months.

D: 1000 mg taken 1× / day in the morning, 500 mg taken 1× / day in the evening.

E: Initiated at a dose of 250mg (2× / day), then increased to 500 mg (2× / day) and if older than 12 increased to 1000 mg (2×/day) if tolerated.

F: Initiated at a dose of 5 μg, subcutaneously, twice per day. After 1 month, exenatide was uptitrated to 10 μg twice per day for the remaining 2 months.

Table 2
Suggestions regarding target population and eligibility

- Age: 12-17 years old (once safety/efficacy is established in this age-group, trials of younger children can be initiated)
- BMI ≥95th percentile (depending upon the risk/benefit of the agent(s) under investigation, requirement of ≥1 co-morbid condition may be appropriate)
- Tanner stage: no lower limit unless evidence suggests developmental risk of specific agent
- No upper BMI threshold (can consider sub-analyses by BMI categories)
- Include participants taking potentially weight altering medication(s) with stable dose for ≥6 months
- Observed or documented history of failed weight loss attempts unnecessary

Table 3

Suggestions regarding endpoint selection

- Primary efficacy endpoint: percent change in BMI from baseline
- Additional endpoints to report: absolute change in BMI, change in BMI z-score, and the proportion with ≥5% and ≥10% BMI reduction from baseline
- Secondary endpoints: include measures in the physiological (cardiometabolic risk factors) and quality of life domains; measures of psychological functioning, eating behaviors, and/or diet should also be considered
- Safety endpoints: include serial assessment of Tanner stage and height; measures of neuropsychiatric function should also be considered; additional safety endpoints may be necessary based on the mechanism(s) of action of the drug(s) under investigation