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Anti-Obesity Medication in the Management of Children and Adolescents With Obesity: Recent Developments and Research Gaps

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ABSTRACT

Background: Paediatric obesity is a global public health concern. While in most countries the incidence keeps rising, the need for effective and long-term management for children and adolescents living with this chronic, relapsing disease is pressing. Health behaviour and lifestyle treatment (HBLT) is recommended as first-line treatment.

Methods: Narrative review.

Results: A new generation of recently approved anti-obesity medications (AOM) now has the potential to fill the gap between limited effects on body mass index (BMI) by HBLT alone and large effects by metabolic and bariatric surgery in adolescents with obesity aged 12 years and older. While, for semaglutide and phentermine/topiramate, effectiveness is substantial with relevant, but mostly mild to moderate adverse events, there is a gap in evidence regarding long-term effects and safety, effects on outcomes beyond BMI reduction and data for certain groups of patients, such as children < 12 years and minority groups. When integrating AOM treatment into national healthcare systems it should be offered as part of a comprehensive patient-centred approach.

Conclusion: This article summarizes recent AOM developments, integration into paediatric obesity management, and identifies research gaps.

1 | Introduction

Obesity is a common chronic disease and health threat that has increased in children, adolescents, and adults in most countries globally [1, 2]. Based on different epidemiological datasets, different definitions of obesity and its severity exist [3]. The chronic relapsing nature of obesity is evident, with less than 15% of youth with obesity managing to lose their excess adiposity in adulthood [4]. Obesity also predisposes to the development of various cardiometabolic, orthopaedic and psychosocial disorders, which places a large burden on healthcare systems [5–12]. The aetiology of obesity is in the majority of cases multifactorial and includes a complex interaction between biological predisposition and a complex

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obesogenic environment, such as media influences, marketing and availability of food, stress, weight stigma and bullying [9, 13, 14]. Monogenic causes are prevalent in 5%–10% of cases with obesity [13]. Understanding the underlying pathophysiology of obesity involves recognition of dysregulation in hunger and satiety, appetite and hedonic reward pathways, which is the basis for recent pharmaceutical breakthroughs, and a future era of emerging medical therapies ('anti-obesity medication' [AOM]) [15–17]. This is true for AOM in both syndromic/monogenic and non-syndromic/common/polygenic obesity.

2 | Anti-Obesity Medication in the Spectrum of Treatment Options for Children and Adolescents With Syndromic/Monogenic and Common Obesity

Due to the chronic nature of the disease, sustainable, long-term and patient-centred care is necessary, irrespective of treatment strategy [11, 18, 19]. In January 2023, the American Academy of Paediatrics (AAP) released its first clinical practice guideline for the evaluation and treatment of children and adolescents with obesity [11]. The guideline recommends baseline and longitudinal assessment of individual, structural and contextual risk factors to offer individualized and tailored treatment of the child/adolescent with overweight/obesity, with consideration for multiple domains including the child, family, community and society [11]. Further, in line with other earlier recommendations, the importance of initiating treatment immediately after the diagnosis of obesity, and, delivering therapy as intensively as possible is highlighted [11, 15, 20]. Rather than viewing treatment as a stepwise process, the guideline emphasizes utilizing the full spectrum of treatment options as appropriate, including motivational interviewing, psychological support where required, 'health behaviour and lifestyle treatment' (HBLT), pharmacotherapy and metabolic and bariatric surgery (MBS) [11]. HBLT is recommended as first-line and basic treatment, showing a good safety profile but limited effects on BMI-reduction ($-1.18\,kg/m^2$ (95% confidence interval, CI: −1.67 to −0.69], from baseline to longest point of follow-up) [21] MBS, especially results from non-randomized controlled trials (RCTs) and observational studies, is known to be highly effective regarding BMI(z)-reduction (e.g., $-13.09\,kg/m^2$ [95% CI: −11.75 to −14.43] for sleeve gastrectomy), while evidence from RCTs is limited [22–24]. Nevertheless, long-term safety aspects after MBS need to be carefully considered before admitting adolescents to such interventions in this crucial phase of life [25, 26]. Despite these limitations, the AAP guideline recommends that adolescents aged 13 years or older with severe obesity should be offered referral for MBS [11]. New-generation AOM, recently approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for non-syndromic and common obesity, might fill this gap between HBLT and MBS [27–29].

For the management of chronic diseases, adherence is critical to the success of any intervention [30]. Engagement of the individual patient and family, and ongoing support play a central role [31]. An evidence-based, patient-centred approach is crucial to ensure adherence to treatment. Key aspects include the abovementioned content, which are also recommended in the AAP clinical practice guideline, such as shared decision-making, motivational communication strategies, reducing stigma and weight bias (including self-stigma and internal bias), setting realistic expectations and openly addressing root causes and barriers to treatment [30, 32, 33]. A structural guidance, the 5As framework, for the management of patients with obesity in primary care was published for adults and was subsequently adapted for children and adolescents. It consists of the 5As ask, assess, advise, agree and assist and is a helpful approach to support primary care physicians, paediatricians and other health-care providers in the steps of obesity diagnosis and management. The importance and positive effects of such guidance were outlined in several studies [34, 35].

3 | Efficacy and Safety of Anti-Obesity Medication in Paediatrics

3.1 | Current Treatment of Monogenetic Forms of Obesity With Setmelanotide and Metreleptin

A personalized treatment approach targets monogenetic forms of obesity. RCTs in monogenic forms of obesity are scarce, due to its low prevalence [36]. In two phase 3 clinical trials, treatment with setmelanotide, a highly selective MC4 receptor agonist, reduced hunger and weight in subjects with syndromic obesity due to pro-opiomelanocortin (POMC) deficiency, proprotein convertase subtilisin/kexin type 1 (PCSK1), or LEPR deficiency [37]. Thereby, 80% of the individuals in the POMC trial, and 45% in the LEPR trial achieved at least a 10% weight loss at approximately 1 year [37].

In another RCT assessing setmelanotide in Bardet–Biedl and Alström syndromes, the primary outcome of ≥ 10% reduction in body weight after 52 weeks was achieved in 32.3% (95% CI, 16.7%, 51·4%; $p < 0.01$) of patients ≥ 12 years, all of whom had Bardet–Biedl syndrome [38]. A clinically significant change in BMI *z*-score was achieved by 71% of patients with Bardet–Biedl syndrome [38]. Adverse events of setmelanotide treatment included headache and gastrointestinal side effects; the most common was skin hyperpigmentation in 60%–100% of patients [37, 38]. Consequently, the FDA approved setmelanotide in 2020 as a subcutaneous injectable agent for patients aged 6 or more years with genetically confirmed POMC-associated obesity, PCSK1, LEPR deficiency and shortly afterwards also for patients with Bardet–Biedl Syndrome [39]; in 2021 setmelanotide was also authorized for use in the EU [40]. In addition, setmelanotide was granted PRIority MEdicines (PRIME) designation for treating syndromic obesity associated with the MC4 receptor pathway, which is presumed as lifelong treatment as weight will regain once the treatment was discontinued [41].

The recombinant human leptin analogue, metreleptin, has been approved in patients with lipodystrophy since 2014 [42] and has been applied in patients with congenital leptin deficiency since several years [43]. It may also be used to treat patients with congenital dysfunctional or biologically inactive leptin variants due to changes in the LEP gene, which causes impaired binding to the leptin receptor

[44–46]. Metreleptin was shown to be effective and safe in multiple paediatric studies, although antibodies against metreleptin may develop that lead to reduced therapeutic efficacy [43–45, 47]. The long-term safety of metreleptin in patients with lipodystrophy is currently evaluated through registry data [48]. To ensure tailored treatment for leptin deficiency, it is advised to categorize leptin variants based on molecular and functional characteristics [46].

3.2 | Anti-Obesity Medication for Common Obesity in Adolescents

A Cochrane review, published in 2016, summarized the safety and efficacy of AOM [49]. The AOM investigated in 21 RCTs, were metformin ($n = 11$ RCTs), sibutramine ($n = 6$ RCTs) and orlistat ($n = 4$ RCTs), which demonstrated a mean BMI-reduction of 1.3 kg/m^2 (95% CI: −1.9 to −0.8, low certainty evidence, i.e., that the confidence in the effect estimate is limited). While metformin is not approved by regulatory agencies for the treatment of obesity in children and adolescents, sibutramine was withdrawn, leaving orlistat as the only approved AOM for chronic paediatric weight management at that time. However, with results of other AOM from RCTs in adults with obesity [50] being investigated in paediatric populations, an update of the evidence from the 2016 Cochrane review was required, and recently published [51]. This systematic review reported the effects of additional 14 RCTs that investigated metformin ($n = 7$ RCTs), topiramate ($n = 2$ RCTs), phentermine/topiramate ($n = 1$ RCTs), exenatide ($n = 2$ RCTs), liraglutide ($n = 1$ RCT), semaglutide ($n = 1$ RCT) and included a total of 35 RCTs with $N = 4331$ participants (mean age: 8.8–16.3 years; mean BMI: 26.2–41.7 kg/m^2). Follow-up ranged from 6 to 24 months, and trials were undertaken in a variety of countries. Pooled meta-analysis demonstrated that AOM plus behaviour-changing interventions reduced BMI by 1.71 kg/m^2 (95% CI: −2.27 to −1.14, moderate certainty evidence) for up to 2 years in adolescents when compared to behaviour-changing intervention with or without placebo. Reduction in BMI ranged from −0.8 to −5.9 units between individual drugs, with the largest BMI-reduction shown for semaglutide [52]. Furthermore, 45% of participants taking semaglutide transitioned to a BMI under the obesity cut point [53]. For another weight-based measurement, BMI percent of the 95th percentile for BMI, a reduction of 11.9 percentage points was shown, based on low-certainty evidence. Post-hoc analyzes identified that effects on BMI were more pronounced (reduction of 2.66 kg/m^2), when only drug agency-approved drugs, namely orlistat, liraglutide, semaglutide and phentermine-topiramate, were considered. The systematic review further showed that recently approved AOM in particular, improved health-related quality of life (QoL), although these effects were mainly driven by semaglutide for the physical comfort component of the QoL scale. While the systematic review did not address effects on blood biochemistry or other health surrogate parameters, such as glucose, HbA1c or blood pressure, it did demonstrate an absence of data for type 2 diabetes mellitus, social functioning and self-esteem and a significant gap for younger children, minoritized ethnic groups and weight loss maintenance.

The risk for experiencing a serious adverse event was low (relative risk [RR] 1.22 [95% CI: 0.70–2.10], which equates to approximately 1 in 100 adolescents). No increased risk for discontinuation of the trial due to adverse events was shown, while an increased risk for dosage adjustment due to adverse events was shown (RR 3.74 [95% CI: 1.51–9.26]) and was even higher when considering approved AOM only (RR 8.41 [95% CI: 2.80–25.23]). Gastrointestinal adverse effects were the most predominantly reported adverse event by the study participants. These findings, therefore, show promise for the treatment of obesity in adolescents, however, potential adverse effects need to be considered and monitored when prescribing AOM—especially as there are currently only relatively short-term data available. Nevertheless, the systematic review also highlighted a notable evidence gap for potential long-term or rare adverse events in children and adolescents treated by AOM. Observational data from adults treated by AOM supported short-term evidence from RCTs in adolescents that, due to the mode of action of GLP1-RA, adverse events are especially related to the gastrointestinal system. A higher risk of bowel obstruction, gastroparesis and pancreatitis was shown for adults with obesity, who received GLP-1RA, that is, liraglutide and semaglutide compared to those receiving bupropion-naltrexone from first prescription to the first incidence of the respective adverse outcome [54]. Furthermore, a 10-fold increase in thyroid neoplasm and hyperplasia was shown for adults with diabetes receiving GLP-1RA compared to those receiving sodium-glucose cotransporter (SGLT)-2 inhibitors [55]. There is a strong need for observational data in children and adolescents to investigate, whether these observations in adults might also be relevant for children and adolescents. Thus, documentation of real-life AOM data in registers for children and adolescents with obesity at national and international levels is pivotal [56].

Due to the abovementioned safety and efficacy data and summarized by Torbahn et al. [51], also leading to withdrawal or approval of AOM, AOM for chronic weight management in children and adolescents might be grouped into AOM from the first generation (metformin, lorcaserin, sibutramine, orlistat, topiramate, exenatide), transition era (liraglutide) and new era (phentermine/topiramate, semaglutide) (Figure 1) [51].

For the prescription of AOM, regulatory agencies, such as the FDA or EMA, provide indications for AOM. For other regions outside the United States and also between European countries, approvals differ. The FDA has approved four AOM for chronic weight management in the paediatric population 12 years and older: Orlistat (Xenical), Liraglutide (Saxenda), Semaglutide (Wegovy) and Phentermine/Topiramate (Qsymia) [51, 58]. Phentermine is approved by the FDA in adolescents older than 16 years only for short-term treatment (often interpreted as 3 months) [11]. On the other hand, the EMA has only approved Liraglutide and Semaglutide for obesity treatment in children 12 years and older (Figure 1) [51]. In addition to indications several requirements are given, such a certain age or a specific BMI cut-off, for example, ≥ 95th BMI-percentile [36]. However, there has been increasing criticism of defining obesity solely by BMI [59], arguing that AOM treatment should not only target a reduction of BMI beyond the obesity threshold, but address changes is body composition and patient-relevant outcomes as well as reductions of co-morbidities and positive effects on

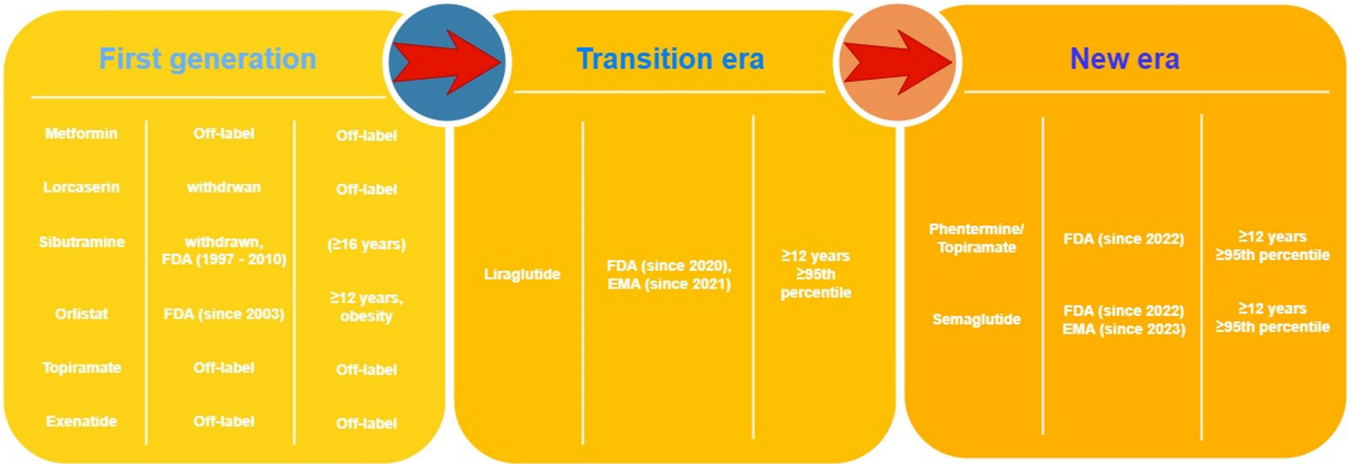

FIGURE 1 | Eras of Anti-obesity medications available for chronic weight management in children and adolescents (from Torbahn et al. [57]).

health and wellbeing [60]. It is currently unclear, what magnitude of weight loss clearly differentiates between treatment success and suboptimal response within the normal distribution of weight loss response to AOM. According to an evidence report and systematic evidence review for the US Preventive Services Task Force recommendation statement, a BMI *z*-score reduction in the range of 0.20–0.25 appears to be a suitable threshold for clinically important change as it is associated with improvements in cardiovascular and metabolic risk factors [61, 62]. In keeping with this, a German expert panel reported that a BMI *z*-score reduction of 0.20 is clinically significant and is comparable to a weight loss of approximately 5% [63].

Response to AOM in terms of percent weight loss or BMI reduction has been shown to be highly heterogeneous [64, 65]. A discrepant degree of individual variation in response to either HBLT, pharmacotherapy, or MBS among adolescents with severe obesity from three centres across the United States reported a change in BMI following intervention ranging from −50.2% to +12.9%, with each intervention (lifestyle [range: −25.4% to 5.0%], pharmacotherapy [range: −10.8% to 12.9%], MBS [range: −50.2% to −13.3%]) exhibiting wide individual variation in response. Changes in cardiometabolic risk factors demonstrated similarly high variability [66]. The mechanisms behind this spectrum of response remains largely elusive. A post hoc analysis of the double-blind, parallel-group, placebo-controlled STEP TEENS trial, assessing once-weekly subcutaneous semaglutide or placebo, plus lifestyle intervention for 68 weeks in adolescents aged 12 to below 18 years of age, found that although not powered to determine sex differences, responder analyzes suggested a trend in the effect of semaglutide on changes in BMI and improvement in BMI category across baseline characteristics subgroups, with improved treatment responses seen in females and with younger age and lower BMI [53]. Of interest, Dawed et al. observed that a common variant of the GLP1R gene rs6923761 (Gly168Ser) and low-frequency variants in ARRB1 were associated with a reduction in HbA1c after treatment with GLP1R agonists [67]. Thus, a correlation between genetic variability and individual response supporting a potential role of pharmacogenetics may also apply to anthropometric measures and other obesity-related outcomes. More research is needed to further elucidate the biology of treatment response and might include (secondary) analyzes of genomic, metabolomics and microbiome data of previous and future trials.

However, beyond weight loss, any treatment plan must take in account preferences, goals and barriers of patient-centred care. Misalignments between patients, care takers and healthcare providers should be investigated and addressed [68], for example, by using motivational interviewing to enhance acceptability for the proposed treatment strategy [69].

In addition to indications, further issues might be taken into account, when it comes to the potential prescription of AOM. As of today, some pharmaceutical companies are struggling to meet demand for AOM, especially GLP1-RAs [70]. Under the condition of limited access and availability, healthcare providers might be forced to prioritize patients with higher risk of obesity-related conditions over those without. Future studies should investigate whether, for example, individual weight trajectories or high-risk genetic profile might be used as the trigger for commencement of treatment.

4 | Anti-Obesity Medications in the Long-Term Management of Paediatric Obesity

Current evidence supports a need for long-term obesity treatment due to its chronic, relapsing nature. Hence, use of AOM as an adjunct to HBLT may conceptually be seen as an indefinite treatment strategy [15], although no clear guidance is currently given [11]. Evidence also shows mean weight regain upon withdrawal of AOM with GLP-1RAs in all age groups [18, 71, 72]. Similarly, this has been shown for setmelanotide [37].

In general, treatment response to AOM usually follows a similar pattern: in the first phase, BMI is reduced rapidly; after about 6–12 months the effect gradually levels off and reaches a plateau-phase with no additional improvements thereafter [15, 18, 71], although the underlying mechanisms are incompletely understood. Growing evidence suggests that reduction of adiposity triggers neuroendocrine adaptions, that is, decreased satiety, increased hunger and cravings [73–75]. Under these

circumstances, AOM should be continued, and patients counselled about possible BMI trajectories. In addition, evidence from an RCT on the effects of liraglutide in adolescents with obesity showed that after the end of intervention, patients regained weight, which was also shown in the shorter follow-up period in the RCT on semaglutide by Weghuber et al. [52, 71]. This finding is in line with evidence from an RCT in adults with obesity assessing tirzepatide, a novel dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonist. The authors reported substantial weight regain in the control group, in which tirzepatide was withdrawn after the 36-week lead-in period compared to the intervention group, which received continued treatment for 88 weeks by tirzepatide and experienced a further reduction in body weight [72].

While AOM address the roots of biological and physiological causes, it is of utmost importance to also address the (individual) roots of health and psychosocial behaviour causes to ensure sustainable therapeutic success [15].

5 | The Future of Anti-Obesity Medication Use in Paediatrics—Ongoing Trials and Outlook From Anti-Obesity Medications for Adults

With currently four drugs approved by regulatory agencies for adolescents ≥ 12 years for chronic weight management: orlistat, liraglutide, semaglutide and phentermine-topiramate, ongoing RCTs are investigating efficacy and safety for liraglutide, and semaglutide in children 6–12 years old [76, 77]. Recently registered and ongoing RCTs will also add more evidence for effects of tirzepatide in children 6–11 years of age and adolescents aged 12–17 years [15, 78, 79]. Tirzepatide (10 and 15 mg q.d.) administered in adults with obesity, showed higher weight-loss compared to other GLP1-RA, such as semaglutide, with a similar safety profile [80]. Another AOM being investigated in a phase-2 RCT, retatrutide, glucose-dependent insulinotropic polypeptide, GLP-1 and glucagon RA, showed, dose-dependent, substantial reductions of body weight; with almost 25% for the highest initial dose (12 mg s.c. given weekly) administered for 48 weeks in adults [81]. Given the efficacy and safety profiles of liraglutide and semaglutide were similar to those for adults [80, 82–84], the recent developments in adult AOM research, are starting to raise expectations for use in adolescents and younger age groups, who are not responsive to HBLT.

6 | Integration of Anti-Obesity Medication Into National Healthcare Systems and Cost-Effectiveness

A lack of equity in modern obesity therapy has been acknowledged internationally [85]. Specifically, the newer AOM are costly with prices, for example, for a 30-day course of semaglutide, ranging between 804 and 95 USD in different countries, which appears above the estimated minimum price of 40 USD [86]. However, only 1%–2% of adults with obesity received AOM in the United States, in sharp contrast to the 8.4% of adults diagnosed with diabetes of whom 86% receive pharmacotherapy [85]. In keeping with this, most US private health insurers refuse to cover anti-obesity therapies, requiring patients to pay out of pocket. A change in health policy by including coverage of AOM by healthcare insurers would improve access to treatment on an individual level.

Regarding cost-effectiveness, data on AOM in adolescents is scarce. A simulation model for phentermine/topiramate treatment in adolescents indicated that treatment by this AOM might be cost-effective after 5 years [87]. This finding was supported by another analysis, in which AOM were compared and pharmacological treatment by phentermine/topiramate was superior in cost-effectiveness to other AOM, such as orlistat, liraglutide and semaglutide [88].

It is currently recommended that AOM should be prescribed as an adjunct to HBLT [11]. AOM should not be prescribed without adequate diagnosis, assessment and further support for behaviour change [89, 90]. As mentioned above, frameworks, such as the 5As are available, to support health-care professionals in primary care. It might be necessary to initiate AOM treatment under the supervision of an experienced healthcare professional, even if comprehensive HBLT is not available or adherence to it is only hardly possible, provided the patient is carefully monitored. There is consequently a need for primary care provider education on obesity and use of AOMs in different care and management settings, while also reducing barriers of primary care physicians to prescribe AOM, such as the reimbursement of medical services [91]. This is particularly important as it is well-known that structures for obesity care are insufficient [92, 93]. Therefore, there is a need for adequate integration in health systems, which still needs to be clarified.

7 | Research Gaps

7.1 | Pairing HBLT and AOM

As recommended in the AAP guideline, AOM should be prescribed as an adjunct therapy to HBLT [11]. As mentioned above, HBLT is regarded as first-line and basic treatment and emphasizes the importance of multidisciplinary healthcare professionals in obesity care. Of interest, a recent systematic review found four RCTs on AOM in adolescents with obesity that did not report any concomitant behaviour change intervention [57]. It remains unclear, whether other co-interventions were part of the intervention and have not been reported, or if they were no part of the intervention. Methodological studies showed that reporting of intervention characteristics is often poor [94]. Future research should therefore implement stricter reporting of intervention characteristics (e.g., TIDieR checklist [95]), to understand the influence of HBLT in AOM studies on reported outcomes. This will help to inform guideline developers and their users to implement the needed interventions.

As AOM reduce energy intake by markedly enhancing satiation and decreasing hunger, they seem to reduce the need for some traditional dietary-focused behaviour change strategies

(e.g., monitoring food intake, develop strategies to reduced portion size) to achieve calorie restriction. However, there is a lack of knowledge about whether patients, adults and youth, who lose weight with these AOM develop healthier diet and physical activity levels [96]. Thus, when pairing with the new AOM, the focus of HLBT will possibly shift from inducing weight loss (through calorie restriction) to facilitating patients' adoption of healthy dietary choices and increased activity levels that will promote optimal changes in body composition and overall health [96]. Again, for HBLT in addition to AOM some evidence and guidance are available for adults, but completely lacking for adolescents. Almandoz et al. recently published nutritional recommendations for health-care providers to support adults with obesity receiving AOM [97]. According to their publication, identification of pre-existing nutritional risk factors is recommended to prevent adverse outcomes, such as malnutrition or eating disorders. This also includes screening for both malnutrition and eating disorders, as well as the assessment of other diseases for which nutritional deficiencies are known, for example, malabsorptive disorders before AOM treatment. Based on the results of screening and assessment, persons with obesity should be counselled on recommended intakes of certain nutrients and foods, such as protein, dietary fibre, micronutrients and fluids. During treatment with AOM, patients should be monitored to compensate for insufficient intake of fluids or nutrients or to better manage adverse events. For example, it has been recommended to avoid foods with a high-fat content, for example, fried food, to decrease gastrointestinal adverse events [98].

In addition to a patient-centred and evidence-based approach (e.g., by use of the 5As), health-care practitioners should also recommend physical activity. While the recommendations by Almandoz et al. do not list specific recommendations on the type, duration and dose of physical activity, an RCT in adults with obesity investigated, which of four weight maintenance strategies (i.e., exercise plus placebo, liraglutide plus usual activity, exercise plus liraglutide, or placebo plus usual activity) is superior to the others [99]. While after 1 year posttreatment, the most effective strategy was the combination of liraglutide and resistance exercise, notably, the resistance exercise-only group showed less weight regain when compared to liraglutide or placebo plus usual activity) [100]. So far, no specific recommendations for physical activity as component of HBLT is available. In a perspective, Jakicic et al. are in favour that, also for physical activity, health-care professionals experienced and trained in exercise for people with obesity are involved in the multiprofessional management team and physicians not merely give recommendations for health-promoting physical activity and limiting sedentary behaviour [101].

The chronic and—if treated insufficiently—relapsing nature of obesity demands ongoing treatment. Nevertheless, cessation of AOM may have multiple reasons (e.g., tolerability, monetary reasons, or changes in the management strategy). Pairing AOM with specifically tailored HBLT may be important to support patients during AOM treatment but may also be advantageous following cessation of therapy by enhancing self-management skills and strategies. It is currently unclear, whether weaning from AOM treatment or on-off-strategies might be feasible within a (life-)long treatment strategy.

Evidence-based recommendations on how to adapt HBLT to different phases of AOM treatment along the obesity treatment chain are warranted [9, 11, 15, 60]. However, evidence as to which content is specifically relevant for HBLT as basic therapy in addition to AOM is scarce—especially for children and adolescents. More research is necessary to inform the design of HBLT paired with AOM in an evidence-based manner.

In the systematic review updating the Cochrane review of AOM, two RCTs investigated the impact of AOM as an adjunct therapy following an initial weight loss intervention achieved by meal replacement [57, 102, 103]. Both studies, exenatide for 52 weeks (injection 2 mg once weekly) and topiramate for 24 weeks (75 mg g.d.), showed higher BMI reductions compared to control, with greater effects for exenatide. These findings demonstrate the utility of AOM as an adjunct therapy to support further weight loss following more traditional dietary restriction approaches [30]. In terms of a comprehensive approach to health, incorporating assessment of underlying psycho-social contributors to obesity in the process is crucial [11]. Support of family and children in this respect must be offered irrespective of AOM and may even enhance sustainability of AOM treatment [104, 105]. Possible benefits of AOM on emotional eating and stress-induced compulsive overeating are topic of future studies [105].

7.2 | Long-Term Effects of AOM, Rare Adverse Events and Potential Phenotypes

While new-generation AOM shows promising positive effects, little is known regarding long-term effects. Starting treatment of AOM in this crucial phase of life might have differential effects on healthy growth, such as brain development and potential future health risks, such as psychological disorders or cancer [15]. Furthermore, the investigation of rare adverse effects is often not covered by the available evidence up to this time, as it almost exclusively consists of that published by RCTs, which have strong limitations due to too-small sample size and short follow-up time to show sufficient data on long-term safety. Therefore, evidence from observational data is needed in the future, which might add further knowledge.

Moreover, predictors of treatment response are often not detectible due to too small sample sizes and follow-up periods, which are often not long enough. Knowledge of predictors of AOM treatment response in adolescents is scarce. A recent publication identified that a higher score in food responsiveness and elevated alanine aminotransferase were associated with a smaller reduction in percentage of the 95th BMI-percentile at three and 6 months in adolescents with obesity treated by phentermine plus HBLT [106]. More evidence for obesity management by AOM is available for adults. For example, a publication reports on a combined investigation, in which first, a cohort of adults with obesity receiving AOM treatment was investigated for potential treatment predictors and another cohort was subsequently and prospectively enroled into an pragmatic clinical trial, in which participants were allocated to either receive AOM treatment guided by former identified phenotypes or non-phenotype-guided AOM treatment [107].

Results show that those, who received the phenotype-guided AOM treatment showed a 1.75-fold greater weight reduction after 12 months [107]. Further research, for example, also explored by observational data, is important to derive implications for the design of clinical trials and other types of evidence to derive potential phenotypes. This can lead to evidence-based AOM treatment algorithms that support a patient-centred treatment approach. Unfortunately, the algorithms proposed to date lack verifiable evidence [108, 109]. Finally, a number of unique challenges in terms of designing and conducting clinical trials investigating the safety and efficacy of AOM need to be overcome. This will help remove barriers that can delay AOM development and evaluation, reduce the cost of performing trials, improve the interpretation of results and generalizability of the findings and address ethical challenges.

8 | Conclusions

Any treatment option for patients with obesity, including AOM, must be part of patient-centred care that addresses roadblocks to treatment. AOM show promising effects regarding BMI reduction in adolescents, making effective obesity management possible outside of MBS. Nevertheless, adverse events and long-term effects need to be considered, which is critical given the lack of current long-term data. Any drug therapy introduction to real-world settings must consider the impact of wider environmental factors, adherence and safety must be carefully monitored. Furthermore, there exist several research gaps that need to be further evaluated for existing approved AOM, to address the lack of data for children aged less than 12 years of age, from minoritized ethnic groups, and for children with other co-morbidities; and data on long-term cost and clinical effectiveness. In addition, more research trials conducted in children from diverse sociodemographic groups are needed to understand the financial, cultural and environmental considerations that face families from different backgrounds, and therefore make the evidence base and resulting guidance more equitable and generalizable. Further AOM are under development and investigation, which will inform the future clinical guidance. When integrating AOM treatment into national healthcare systems, a comprehensive, compassionate and non-stigmatizing patient-centred approach is needed.

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