Drug Treatment Of Child And Adolescent Obesity

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The Need For Drug Treatment Of Child And Adolescent Obesity

While child and adolescent obesity prevalence are worsening in many countries around the world or tend to stabilize at high levels, therapeutic approach in Europe remains limited to either classical multidisciplinary cares or to bariatric surgery. Classical multidisciplinary approach has to be applied first as soon as overweight or obesity is detected. European Medicine Agency (EMEA) and Food and Drugs Administration (FDA) of the USA both recommend this incremental approach. Bariatric surgery is the last step in the range of existing treatments *(figure 1)*. The goal to reach is a lasting weight loss that will in turn result in a long term improvement of well being and health. The reduction of the risk of short and long term complications of overweight and obesity should overcome the risks level of the intervention and of weight loss. The European Association for the Study of Obesity (EASO) published in 2015 a position statement urging the European ad hoc authorities and member states to work together to ensure that new obesity treatment option can be more readily available while the unmet medical needs are huge[1]. Decisions have to include children and adolescents with severe obesity.
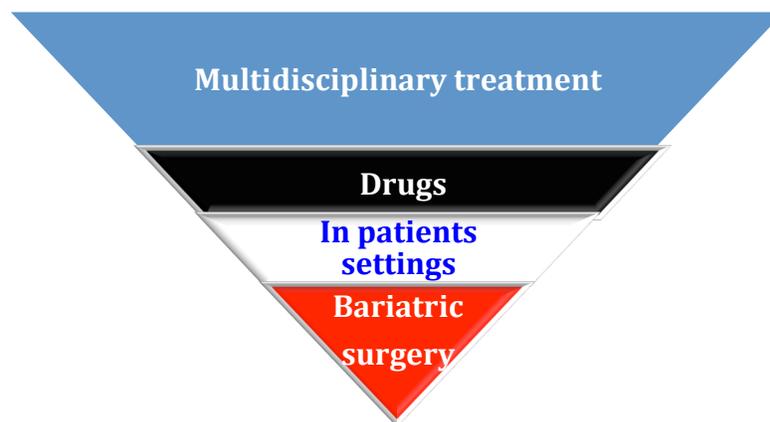
Figure 1: Proposed theoretical hierarchy of the treatments of child and adolescent obesity. Bariatric surgery should not be used before the end of puberty. In patient clinical settings may also be useful for complex multidisciplinary treatments, preparation and follow up of bariatric surgery.

An intermediary step between these two strategies is obviously needed for which drugs are good candidates. The physiopathology of obesity is much better understood although major gaps persist between scientific knowledge and assessment of the mechanisms of an individual's disease. Drug treatment efficiency should not be over rated since:

- Obesity is a syndrome the causes of which vary among individuals. Drug efficiency should not be expected, as it used to be, in the whole population but according the individual's genetic and physiopathological background. This notion which already applies to most diseases such as diabetes, cancer or epilepsies is not yet fully acknowledged in obesity.

- An efficient drug will have side effects to be weighed against the benefits

- Not all patients will be able to benefit a drug treatment.

The broad range of sources of motivation that may lead the obese adolescent to seek/accept a pharmacological treatment of obesity has to be taken into account: passive acceptance of medication, enthusiasm and relief at the prospect of a pharmacological treatment, medication as a last resort, health related fear as a motivating factor, anti-obesity drug as a way out of obesity and perceived uniqueness of a complex form of obesity. In this prospective study, in which only two drugs, orlistat and metformin were assessed among only 15 participants aged 13-18 years, the use of the medication was maintained when perceived benefits were superior to side effects[2].

 Some anti-obesity drugs may not be as effective as behavioral interventions in reducing BMI: a meta-analysis of behavioral interventions in obese adolescents reported an effect of 3.04 kg/m^2 (95% CI 3.14 to2.94) at 6 months, which was maintained at 12 months follow-up.[3] However, behavioral interventions require a great investment from both the medical staff and the family which may not be practical in daily life.

Next generation trials should be built in a way that allows reaching targets instead of assessing in terms of overall rejection /acceptation, a cause of a considerable waste of information and capability to treat[4]. Little good quality data following classical randomized controlled trials (RCTs) are available. Ten studies only, performed in adolescents having a mean age at or above 12 years, were taken into account in 2009 by the Cochrane Collaboration Study[3].

Another concern is the use of anti diabetic drugs in order to reduce insulin resistance and its consequences. The role and place of metformin and liraglutide in adolescents will be briefly discussed.

Drugs Marketed For The Treatment Of Obesity In Adults And Adolescents: The Pediatrician's Concern

We will focus here on relevant points to the understanding of indications and current limits to prescription in children and adolescents. For further detailed information, the reader will refer to extensive reviews performed in children and adolescents [5-9] and to reviews focusing on the treatment of adults' obesity[10-12]. EMEA's (www.**ema**.**europa**.eu) and FDA's (www.**fda**.gov) recommendations and warnings are available and updated on their respective websites and should serve as references in addition to national guidelines. The drugs that are actually allowed or were recently discussed by both agencies are shown in table 1. All but one, orlistat, which is allowed in adolescents, are restricted to adults treatment.

Name	Active substance	EMEA	FDA
Acomplia **Zimulti**	rimonabant	withdrawn	never allowed for obesity
Xenical **Alli**	orlistat	adults	Adolescents starting from 12 years of age
Mysimba **Contrave**	bupropion /naltrexone	adults	adults
Phentermine	Phentermine hydrochloride	refused	Adolescents starting from 16 years of age and adults
Qsiva **Qsymia**	Phentermine hydrochloride/topiramate extended release	refused	adults
Saxenda	liraglutide	adults	adults

Table 1: comparison of the drugs authorized for the treatment of obesity by the EMEA and FDA of the USA in June 2015

Rimonabant is a cannabinoid (CB) receptor 1 antagonist that blocks the CB1 receptor which are expressed in many different neuronal populations of the brain. This drug has been quickly withdrawn in Europe and was never authorized by the FDA because of an increased risk of depression anxiety and suicidal ideation. The mechanisms behind these potential side effects were only recently understood in mice. CB1 receptors blockade induces acute hypophagia. mediated by the β adrenergic receptors of the

peripheral organs including the gastro intestinal tract. The β adrenergic signaling mediates in turn the effect on anxiety-like behaviors. In other words, CB1 receptors modulate bidirectional circuitry between the periphery and the brain to regulate feeding and other behaviors that will have to be taken into account for further drug assesments[13]. Active research is still conducted on this class of molecules.

Orlistat is a gastrointestinal lipase inhibitor. Oral caplets contain either 120 mg (Xenical ™) or 60 mg (Alli™) of orlistat. This drug is not allowed by the EMEA below 18 years of age whereas it is approved in adolescents 12 years of age and older by the FDA for the obesity management and to reduce the risk of regaining weight after prior weight loss. This original molecule binds the active sites of the gastrointestinal lipases and irreversibly blocks the enzymes activity. Triglycerides cannot be hydrolyzed into free fatty acids and monoglycerol. This inhibition can prevent up to one third of all dietary fat absorption and thus help losing weight or maintaining weight reduction. The RCTs analyzed in the Cochrane meta-analysis were performed with doses of 120 mg daily in addition to multivitamin supplements. Pooled results in a meta analysis of the data of 576 patients found an additional effect over placebo at 6 months follow up when given in combination with a life style intervention. (-0,76 kg/m², 95% CI: -1.07 to -0.44, Z=4.70, p<0.0001). Although these results are statistically highly significant, the impact on BMI is only marginal. Short term results only are available since the duration of the 3 studies ranged from 6 to 15 months. Adverse effects were higher in the treatment group, mainly affecting the gastro-intestinal tract (oily stools and cramps). Severe hepatotoxicity including liver failure, is reported. Concern is raised about the impact on growth and fat soluble vitamin status. In a systematic review, no one of the two RCTs included reported changes in vitamin A, D and E. However samples cases were low (352 and 20 subjects respectively) and follow-up lasted 6 months and 54 weeks respectively[5]. A previous study focusing on fat soluble vitamins status in 17 adolescents over 3 to 6 months could show that acute absorption of retinol was not altered but that absorption of α-tocopherol was significantly reduced compared to baseline levels. Serum levels of vitamin A and D did not change. Vitamin K decreased non significantly. Vitamin D (cholecalciferol) decreased on average by 2.8 ± 3.4 ng/ml 1 month after the start of the treatment and were no longer significant by the 3-months time point. All adolescents were tacking an oral daily supplementation (Vitamin A 5000 UI (80 % as retinol, 20 % as carotene), vitamin D 400 UI as ergocalciferol, Vitamin E 30 UI as DL-tocopherol acetate, vitamin K 25 µg as phytonadione). Two subjects of African American origin with very low vitamin D serum concentrations (< 9 ng/ml) required prescription of an additional amount of 50 000 UI cholecalciferol. African Americans adolescents had lower serum vitamin D. Recent study show that this biological feature may reveal either a genetic background or an excess storage rather than a mere nutritional deficiency (see chapter on *Nutritional deficiencies of the obese child and adolescent*)[14]. No short term effect was found on calcium and other

minerals balance (Ph, Ca, Mg, Fe, Cu)[15].

Recent reports of severe hepatotoxicity in adults and of case of hepatic failure resolving within one month after withdrawal of orlistat should lead to investigate liver function before starting the treatment and to cautious follow-up in case of fatty liver, an increasing condition found in up to 30 % of the obese children, even without transaminases increase (*see chapter on "Non alcoholic fatty liver disease"*). The use of orlistat in children and adolescents should never be a self medication despite the existence of now freely available caps. To the opposite, it should be carefully prescribed and monitored.

Generic orlistat may not be as efficient as the original product, with all of 9 products identified on the market failing in four or more tests performed according to the company's criteria. The authors also conclude that the high level of impurities in the generic preparation is a major safety and tolerability concern[16].

Naltrexone and bupropion: Naltrexone is a pure opioid antagonist. Bupropion is a weak inhibitor of neuronal reuptake of norepinephrine (noradrenaline) and dopamine that stimulate pro-opiomelanocortine (POMC) neurons in the hypothalamus. POMC is a precursor of α-melanocyte stimulating hormone (MSH) and β endorphin. α-MSH acts on melanocortine 4 receptors (MC4R) to decrease food intakes. Meanwhile β endorphin sends negative feedback signals that weaken this effect. Naltrexone suppresses this negative feedback. Bupropion alone is approved to treat depression and naltrexone to treat alcohol and oipioid dependence.

The first phase III clinical studies in adults reported a significant effect on weight with not major side effect. The drug is authorized since 2014 to treat overweight and obesity in adults both by the FDA and the EMEA. The data reported show a high attrition rate of 42 to 50 %, a significant effect on weight reduction, an increased risk of high blood pressure. The authors propose that the treatment should be stopped if weight loss does not reach at least 5 % after 12 weeks at the full dose. Potential psychopathological side effects should be carefully detected. Whether this drug will be allowed to treat pediatric obesity is still uncertain[17, 18].

Sibutramine: We mention this drug in order to warn against its use since this dual monoamine(noradrenalin and serotonine) reuptake inhibitor, has been withdrawn from marketing by both the EMEA and the FDA in 2010 because of severe cardiovascular side effects. In children, 4 out of 5 trials had met the quality criteria set by the authors of the review. At the time it was allowed, all four

studies performed reported significant changes in BMI at 6 months. Pooled results showed an absolute decrease of 1.66 Kg/m² of sibutramine over placebo (-1.66 kg/m², 95% CI: -1.89 to -1.43, Z=14.23, p<0.0001). Only one study reported significant results at 1 year. Cardiovascular events and modifications of the mood were mostly reported in theses pediatric trials, leading to withdrawals from the study.

Phentermine is an amphetamine analog which was first approved for short-term use by the US FDA in 1959. Increased tolerance and dependency were evidenced in long term trials. It acts as a sympathomimetic agent and increases catecholamines (dopamine and norepinephrine/noradrenaline) and serotonin activity in the central nervous system. This results into appetite suppression. Side effects include increased blood pressure and heart rate. This drug is contraindicated in patients with cardio respiratory diseases. FDA recommendation is a short term prescription only in adults.

Phentermine and topiramate: these two drugs are combined in order to reach a better efficiency at lower doses of each than when administered separately. Topiramate is administered as extended release capsules. Two major studies CONQUER and SEQUEL have led the EMEA and FDA to opposite conclusions. In Europe psychological and cardiovascular side effects have been estimated to overcome the benefit on weight and cardiovascular risk factors reduction leading to its prohibition while in the US authorization was delivered.

Topiramate is an antiepileptic drugs authorized since nearly 20 years in children. Topiramate is a γ aminobutyric acid (GABA) agonist and a weak inhibitor of carbonic anhydrase. It is also used as an anti migraine drug in adults and was tested in this case in children[19]. About 25 % of treated subjects, at all ages, develop a marked anorexia followed by significant weight loss[20].

Several phase III studies were performed in adults. The first ones used the recommended antiepileptic doses range, the last ones, much lower doses in association to phentermine. All strategies led to significant weight reduction[21-26]. Large studies using lower doses of extended release form (23-92 mg/d) in association to phentermine (3.75-15 mg/d) have lead to its approbation to treat obesity in 2012 by the FDA in adults, as an adjunct to diet and physical activity in individuals with BMI ≥30kg/m² or 27 kg/m² and comorbidities. Topiramate seems to reduce binge eating, a difficult to manage feature of some obese patients[27, 28] and to reduce hyperphagia and neuroleptic induced weight gain[23]. Significant and common side effects restrain its use. Neurological side effects are commonly rep: paresthesia, taste impairment, difficulties with concentration and sedation. Suicidal ideation was very rarely reported in adults. Topiramate may also induce calcium nephrolithiasis when hydration is insufficient.

Topiramate has several interesting characteristics: a lasting efficiency, significant weight loss at or beyond 5 % of initial body weight, previous use in children and adolescents on long term basis. Trials results are expected to show whether a subgroup of obese children and adolescents face significant weight loss without side effects. Long term follow-up would be ideal. It is is currently under investigation among "healthy" obese children and adolescents and among those suffering a Prader Willi syndrome.

Lorcaserin is highly selective $5-HT_{2C}$ receptor agonists, approved as an anti obesity drug in adults only by the FDA in 2012[29] but not the EMEA. The main reason to this discrepancy are observed and potential side effects: sibutramine which was a non specific agonist of 5-HT2 receptors (i.e. 5-HT2 b and eventually 5-HT2 a) was withdrawn because of valvulopathy. The specificity of lorcaserin should avoid such a dramatic side effect. FDA before giving its approval required a complementary cardiologic survey. Careful follow-up and treatment disruption when weight loss does not reach 5 % within 12 weeks of use is recommended by the FDA[30].

Liraglutide is a glucagon like peptide 1 (GLP1) agonist approved by both EMEA and FDA for the treatment of overweight and obesity in adults. It is secreted by the intestine in response to a meal, enhances endogenous secretion of insulin induced by meal consumption and decreases glucagon secretion. Weight loss induced by sub cutaneous injection of liraglutide is dose –dependent up to 3,0 mg once daily. Its action seems to be mediated by a reduction in appetite and energy intake rather than by an increase in energy expenditure[31].

A systematic review and meta-analyses on effects of glucagon-like peptide-1 receptor agonists on weight loss, taking in account two molecules, liraglutide and exenatide, found a significant but modest effect on obese diabetic and non diabetic subjects. No hypoglycemia was reported. Blood pressure and plasma lipid concentrations were improved but not liver enzymes[32]. A recent review showed that liraglutide can increase weight loss among overweight and obese adults in a dose-dependent manner with once-daily doses of 1.2 to 3.0 mg. A higher proportion of patients experienced 5% and 10% weight loss from baseline as compared to placebo and orlistat[33]. These results were confirmed by a double blind trial involving 3731 non diabetic obese adults [34].

Large scale clinical trials are still needed to evaluate the safety and efficacy of liraglutide in the pediatric population with type 1 diabetes. To the best of our knowledge, no trial is yet aiming at validating its use in obesity in children.

Metreleptin: The discovery of leptine deficiency in children and its historical successful treatment by a recombinant analog of human leptine (metreleptin) injection opened wide perspective in the treatment of severe early obesity. Metreleptin is composed by the 146 amino acids of mature leptin with an additional methionyl residue at the N-terminal end of the recombinant protein. Although only a few children carrying mutations were concerned, these genetic findings highlighted how urgent it was to analyze childhood obesity in a scientific rationale way[35]. In children leptin deficiency were unevenly associated with several neuroendocrine defects including hypogonadotropic hypogonadism, central hypothyroidism that had to be specifically treated[36].

The first children treated with metreleptin, carried a frame shift mutation of the gene encoding for leptin (LEP) that led to the lack of circulating leptin. A second type of mutation, abnormal circulating leptin cannot bind to its receptor[37]. In both situations treatment with metreleptin was successful. However current authorizations are given for the rare lipodystrophy diseases by both the EMEA (in 2012) and FDA (in 2014). This rare obesity cases should be considered as new orphan diseases.

No significant weight reduction was obtained when metreleptin was administered alone to adults suffering common obesity[36]. In adults suffering diet induced obesity, leptin sensitivity was restored by the association to an amylin analog, pramlintide. Amylin is a pancreatic peptide hormone cosecreted with insulin from pancreatic β cells which binds specific receptor in the hindbrain area postrema[38].

Atomoxetine and methylphenidate: Recently successful treatment of subjects suffering morbid obesity due to MC4R homozygote mutation, a condition present in about 2% of the obese young, associated to hyperactivity attention disorder was reported. The drugs used were in one case methylphenidate and the other atomoxetine, two drugs inhibiting selectively serotonine reuptake[39, 40]. Neither of these drugs is indicated in the treatment of pediatric obesity. However, such report confirm that a detailed evaluation of the mechanism underlying obesity is necessary in each patient and may lead to drug treatment by a specialized team. Many studies focusing on the MC4R are at the preclinical phase I or II of developement[41].

Metformin: This antihyperglycemic agent from the biguanide family is approved for use in adults and children age 10 years and above for treatment of type 2 diabetes. Metformin controls hyperglycemia in patients with diabetes by decreasing hepatic glucose output, increasing intestinal glucose utilization, and by improving insulin-mediated glucose disposal in peripheral tissues. Metformin induces the activation of AMP-activated protein kinase (AMPK) which is viewed as as a fuel gauge monitoring systemic and

cellular energy status and which plays a key role in protecting cellular function under energy restricted conditions. AMPK activation results into the following switches: glucose, lipid and protein synthesis as well as cell growth are inhibited whereas fatty acid oxidation and glucose uptake are stimulated. This activation of AMPK in the liver and probably in other tissues is the direct consequence of a transient energy deficit induced by the mild and specific inhibition of the respiratory chain complex. Metformin action in polycystic ovary syndrome and cancer, two conditions enhanced by T2D is currently evaluated[42].

Weight loss, even if small, was observed in patients with type 2 diabetes treated with metformin and in adults with prediabetes. Starting from these observations, the potential use of metformin in non diabetic but hyperinsulinemic obese subjects has been assessed. The efficacy of metformin in child and adolescent obesity was shown in several studies. A meta analysis published in 2012, included 9 studies and 498 participants. Significant reductions were reported: BMI -1.42 kg/m² (95% CI -2.18 to -0.66), fasting insulin -9.9µU/ml (-3.32 to -6.06), HOMA -1.78 (-3.32 to -0.23)[43]. Similar results at 6 months were more recently reported in a meta analysis relying on 14 studies. Gastro intestinal side effects were observed in 26 % of the treated group vs 13 % in the placebo one. No serious side effect was reported[44]. A 6 months RCT followed by a 6 months open labeled metformin treatment was then designed. In this study, the baseline dose, set at 500 mg twice daily, was increased according to tolerability up to a maximum of 1000 mg[45]. The mechanism behind this effect was then tested: metformin decreased perceived hunger in a group of obese hyperinsulinemic non diabetic children and adolescents aged 6 to 12 years. This effect resulted in diminished food intakes (-104 ± 84 Kcal vs + 144 ± 97 Kcal, p= 0.03) and contributed to a mild weight reduction of -3.38 kg (95% CI -5.2 to -1.57, p = 0.001) i.e. -1.09 kg/m² (95% CI -1.87to -0.31, p=0.006) fasting plasma glucose and Insulin resistance index were also improved. Gastro-intestinal side effects limited the maximal dose in 17 % of these patients[46].

Metformin is not a drug designed to reduce obesity. It may rather help obese young patients at high risk of type 2 diabetes to reduce insulin resistance and facilitate weight reduction. Metformin may also not be as effective as behavioral interventions in reducing BMI as shown by a meta-analysis which reported a decrease of 3.04 kg/m² (95% CI 3.14 to 2.94) at 6 months, maintained at 12 months follow-up[3].

In the absence of contraindications, metformin is usually prescribed at doses ranging from 500 mg up to 1000 mg twice daily based on tolerability. Adverse effects of this drug are primarily related to gastrointestinal intolerance leading to use lower doses than desirable or even causing discontinuation of the medication.

Oligofructose, an inulin-type fructan with prebiotic properties was recently assessed by a RCT during 12 weeks in a group of 97 children and adolescents aged 7 to 18 years. The placebo used was maltodextrin. The oligofructan doses were 8 g/d in children aged 7-11 years and 15 g/d beyond that age. No effect on bodyweight was observed[47].

Perspectives And Conclusion

Assessment and management of child and adolescent obesity is a complex task that requires medical training, cooperation between medical doctors, psychologists, physical activity specialists and dieteticians[48]. Age, growth and intellectual maturation are distinct features between children, adolescents and adults that need to be taken into account. The best possible clinical, psychosociological and biological evaluation, including the detection of complications, has to be initially performed and in order to implement the ad hoc components of individually appropriated cares. Parts of the therapeutic failures are the mere consequences of an inappropriate evaluation of the psychological background or of the physical fitness. The lack of distinction between a trouble of satiation and a binge eating disorder is in our experience frequent. Both troubles sometimes combine in a single adolescent, lead to obesity but require quite distinct therapeutic approaches in which distinct drugs may be used[49]. Physical fitness improvement may require an adapted training programme which is more complex than a simple increase in spontaneous physical activity *(see corresponding chapters)*.

Drugs should not be prescribed instead of other treatments but should be, in most cases, a step to discuss before performing bariatric surgery. New techniques such as electronic interventions or support may increase success rate of existing methods but still need to be evaluated.

Improving the understanding and classification of the different kinds of obesity is the only way to avoid massive failure of drug treatment trials. Treatment with metreleptin demonstrates how efficient this approach can be. Recent publications show that this way to proceed is just beginning and will rely on exploring new drugs as well as rescreening and reevaluating existing ones[12, 39, 50]. MC4R agonists, new GLP1 agonists, Ghrelin and PYY derived molecules are among the most investigated, if not promising, drugs.

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