Title:

Rise in anti-obesity drug prescribing for children and adolescents in the UK: a population-based study

Running head: Anti-obesity drugs in children and adolescents

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What this paper adds

What is already known about this subject

- The anti-obesity drugs sibutramine and orlistat and not licensed for use in children and adolescents in the UK or USA.
- Clinical trials suggest anti-obesity drugs are effective and well-tolerated in obese adolescents

What this study adds

- Prescribing of unlicensed anti-obesity drugs in children and adolescents has increased significantly in the past 8 years.
- Most prescribed anti-obesity drugs in children and adolescents are rapidly discontinued before patients can see clinical benefit, suggesting they are poorly tolerated or poorly efficacious.
Summary

Aims: The international childhood obesity epidemic has driven increased use of unlicensed anti-obesity drugs, whose efficacy and safety are poorly studied in children and adolescents. We investigated the use of unlicensed anti-obesity drugs (orlistat, sibutramine and rimonabant) in children and adolescents (0-18 years) in the UK.


Results: A total of 452 subjects received 1334 prescriptions during the study period. The annual prevalence of anti-obesity drug prescriptions rose significantly from 0.006 per 1,000 (95% CI 0.0007 to 0.0113) in 1999 to 0.091 per 1,000 (95% CI 0.07 to 0.11) in 2006, a 15-fold increase, with similar increases seen in both genders. The majority of prescriptions were made to those ≥14 years, although 25 prescriptions were made for children <12 years. Orlistat accounted for 78.4% of all prescriptions; only one patient was prescribed rimonabant. However, approximately 45% of the patients ceased orlistat and 25% ceased sibutramine after only one month. The estimated mean treatment durations for orlistat and sibutramine were 3 months and 4 months respectively.

Conclusions: Prescribing of unlicensed anti-obesity drugs in children and adolescents has dramatically increased in the past 8 years. The majority are rapidly discontinued before patients can see weight benefit, suggesting they are poorly tolerated or poorly efficacious when used in the general population. Further research into the effectiveness and safety of anti-obesity drugs in clinical populations of children and adolescents is needed.
Background

The epidemic of child and adolescent obesity in the UK and internationally is well described, with prevalence of childhood obesity in the UK more than tripling since the 1980s.[1] Strong evidence of the tracking of both obesity and its cardiovascular co-morbidities into adulthood[2;3] have focused attention on intervention in childhood. While attention has appropriately focused upon primary and secondary prevention strategies,[1;4] the management of those children and young people already obese have been relatively neglected.

Those who are already obese currently make up 7-10% of the child and adolescent population (<20 years) using the conservative International Obesity Taskforce definition, proportions predicted by the Foresight modelling project to rise to approximately 14% by 2025.[5] The proportion of this population that require or should receive treatment, whether reduction in overweight or treatment of obesity co-morbidities, remains unclear. However, approximately 2-3% of older children and adolescents in urban areas such as inner London have a BMI ≥ 3.5 standard deviations above the mean,[6] equivalent to the WHO category of morbid obesity (BMI ≥40kg/m2). Furthermore, approximately one-third of obese adolescents have significant obesity-related morbidity.[7;8]

The National Institute for Health and Clinical Excellent (NICE) published guidance on managing obesity in childhood and adolescence in 2006,[9] identifying lifestyle modification as the initial management strategy, but also identifying anti-obesity drug therapy and bariatric surgery as appropriate for the management of older children and adolescents in certain circumstances.
To date, there are three medications approved for obesity treatment in adults in the UK: the gastric and pancreatic lipase inhibitor orlistat (licensed for adults in 1998), the serotonin and noradrenergic reuptake inhibitor sibutramine (licensed for adults in 2001), and the selective cannabinoid CB1 receptor antagonist rimonabant (licensed in 2006). Estimates suggested that in 2005, the drug supply costs of orlistat and sibutramine in England were £38.2 million.[10] In the USA, the FDA (Food and Drug Administration) has approved sibutramine for use in patients aged \( \geq 16 \) years and orlistat for patients aged \( \geq 12 \) years.[11] However, in the UK they are still not licensed for children. Based upon a very small number of clinical trials in children and adolescents, the recent NICE guidelines suggest that orlistat and sibutramine should be considered as useful adjuncts to lifestyle modification in adolescents \( \geq 12 \) years with physical comorbidities, and that use \(< 12 \) years be reserved for those with life-threatening comorbidities.[9]

However, there are no published data on the use of anti-obesity drugs in children and adolescents in the UK, with no data concerning acceptability, effectiveness and duration of treatment in clinical practice. National primary care databases provide useful sources of paediatric prescribing data in the UK.[12;13] While NICE guidance recommends that anti-obesity drugs for children and adolescents be initiated from secondary care in the UK,[9] routine practice is for general practitioners to prescribe after recommendation from paediatricians. We therefore used the General Practice Research Database (GPRD) to undertake an investigation of the prevalence of anti-obesity drug prescribing and treatment duration amongst children and adolescents aged 0-18 years between 1999 and 2006.
Methods

The GPRD contains anonymised patient records from general practices in the UK, covering approximately 5% of the UK population.[14] The database is broadly representative of the UK population[15] and comprises anonymised records from approximately 8 million people from 1987 onwards, totalling about 30 million person-years of observation. Data held include subject demographic and clinical details including data on drug prescriptions and co-morbid conditions. The quality of the GPRD data has been validated in a number of studies, the completeness of medical recording is reported to be high,[14] and the GPRD has been used to investigate paediatric prescribing issues.[12;13]

Our study population was defined as all children and adolescents aged 0-18 years inclusive at the time of data collection, registered with a general practitioner (GP) who contributed data to the GPRD. From these we identified all subjects who had received at least one prescription for an anti-obesity drug (orlistat, sibutramine or rimonabant) in the study period between 1 January 1999 and 31 December 2006. We calculated age and sex specific annual prevalence of overall and each anti-obesity drug use. Prevalence was defined as the number of subjects with at least one anti-obesity drug prescription during the year of investigation divided by the total number of patient-years in the same year stratified by age, and was calculated using the Poisson distribution with a 95% confidence interval. The $\chi^2$ test (Cochran-Armitage test for trend) was used to examine yearly trends. We also obtained data on obesity-related comorbid diagnoses available in the database on subjects prescribed anti-obesity drugs; given the range of conditions
potentially co-morbid with obesity, we a priori restricted our search to common diagnoses such as hypertension, dyslipidaemia, insulin resistance syndrome (metabolic syndrome), non-alcoholic fatty liver disease and depression.

The duration of anti-obesity drug treatment was analysed by using the Kaplan-Meier estimator. Treatment was considered as stopped if there were no further prescriptions issued within 90 consecutive days (3 months) after the date of the last prescription. Subjects were censored either if the end of the study period was within less than 90 consecutive days after their last prescription or if they left the practice without stopping treatment. Log-rank test was applied to compare duration of treatment between orlistat and sibutramine. The analyses were conducted using Stata version 9.1 (Statistical Software: Release 9.1. College Station, TX).

Ethics Approval: The study protocol was approved by the GPRD Independent Scientific Advisory Committee.
Results

A total of 452 children and adolescents received 1334 prescriptions for anti-obesity drugs during the study period. As there was only one prescription for rimonabant (in a patient aged 18 years in 2006), further analyses refer only to orlistat and sibutramine. Orlistat made up 78.4% (n=1045) of all prescriptions.

The great majority of prescriptions were issued to females (82.3%; n=372). The mean age for first prescription was 17.0 years (SD 1.33; range 10-18 years; for females, mean 17.1 years (SD 1.27); for males mean 16.7 years (SD 1.53). The median number of anti-obesity drug prescriptions per subject was 2.0 (interquartile range 3.0), however, 40.5% (n=183) received only one prescription. Figure 1 shows numbers of prescriptions by calendar year. The use of both orlistat and sibutramine increased rapidly after each drug was introduced into the UK. From 1999 to 2006, orlistat prescriptions rose from 10 to 282, a 28-fold increase; sibutramine prescriptions rose 16-fold from 8 to 128 between 2001 and 2006.

Figure 2 shows the prevalence of total anti-obesity drug prescriptions by calendar year for each gender. Overall use increased 15-fold from 0.006 per 1,000 person-year (95% CI 0.0007 to 0.0113) in 1999 to 0.091 (0.07 to 0.11) in 2006 (p<0.0001). Similar increases were seen in both genders over the study period, increasing in girls from 0.009 (0.0001 to 0.019) to 0.156 (0.126 to 0.186) (p<0.0001), and in boys from 0.002 (0.0019 to 0.004) to 0.027 (0.012 to 0.04) (p=0.02).
Figure 3 shows trends by age. No anti-obesity drugs were prescribed to children <10 years, although 25 prescriptions were issued to those <12 years old. Prescribing dramatically increased from age 14 years onwards.

Figure 4 shows Kaplan-Meier survival curves for treatment duration for orlistat and sibutramine. The mean duration of orlistat use was significantly shorter (3.0 months; 95% CI: 2.72 to 3.47) compared with sibutramine (4.2 months; 95% CI 3.4 to 5.0), (p=0.003), respectively. Note that 45% of orlistat prescriptions were discontinued within the 1st month, with approximately 10% remaining on the drug after 6 months. For sibutramine, approximately 25% of prescriptions were discontinued within the first month, with less than 20% remaining on the drug at 6 months.

There were 39 subjects who were prescribed both orlistat and sibutramine in our study; 34 subjects initially used orlistat and subsequently switched to sibutramine, and 5 subjects initially received sibutramine then switched to orlistat. Data on reasons for changing between drugs were not available.

Table 1 shows obesity-related comorbid diagnoses in those prescribed anti-obesity drugs. Note that all patients with a diagnosis of diabetes were also receiving anti-diabetic drug treatment (either insulin or oral hypoglycaemic drugs).
Discussion

Prescribing of anti-obesity drugs in children and adolescents, while off-licence, has increased dramatically over the last 8 years. Our 2006 data suggest that approximately 0.1 per 1000 of those aged ≤ 18 years are currently prescribed anti-obesity drugs. Generalised across the UK population of 13,928,000 persons aged ≤ 18 years, this would suggest that approximately 1300 young people are prescribed off-licence anti-obesity drugs annually. However, persistence with these drugs past the first month is strikingly poor, and only 25% of those prescribed orlistat and 35% of those prescribed sibutramine remained on the drug for longer than the 3 months generally regarded as an adequate time to ascertain whether significant weight loss has occurred.

These data suggest anti-obesity drug prescribing is an emerging paediatric pharmacological risk issue. We document a rapid increase in prescribing for children and adolescents of unlicensed drugs which are in most cases rapidly discontinued before patients can reasonably expect to see clinical benefit. Furthermore this pattern of drug use is likely to be significantly wasteful of resources, as anti-obesity medications are relatively expensive.[10] While orlistat and sibutramine have shown significant but limited benefits for weight reduction and have reported good tolerability in a small number of randomised placebo-controlled trials, evidence for their effectiveness in large populations of young people is largely lacking.[16] NICE and FDA guidelines on the use of sibutramine and orlistat have been based upon very limited effectiveness data. Further research into effective and safe use of anti-obesity drugs in children and adolescents outside of efficacy trials is needed. Investigation of the reasons for discontinuation of
anti-obesity drugs may allow the development of support strategies that minimise side-effects and maximise drug continuation when used in the general population.

**Strengths and Limitations**

We believe this is the first published population-based study of anti-obesity drug prescribing in children and adolescents. The NHS in the UK provides universal coverage. The GPRD contains robust data on prescriptions in primary care, and given the universal nature of the National Health Service in the UK, our estimates of population prescribing prevalences are highly likely to be sound and generalisable in the UK primary care.

However, several limitations need to be highlighted. Firstly, the GPRD records prescriptions issued in primary care only, excluding drugs dispensed from hospitals. However, the vast majority of anti-obesity drugs are prescribed from primary care in the UK in both adults and children,[10] although often under the advice of hospital specialists. In children and young people, NICE guidance suggests that anti-obesity drugs should be initiated from specialist paediatric services but that prescribing is appropriate in primary care (see Table 1). It is thus possible that our data do not include a very small number of initial hospital prescriptions; unfortunately, there is not existing data to investigate the extent of hospital prescribing. Secondly, the GPRD does not contain data on socioeconomic status and ethnicity, thus precluding analysis of their impact on prescribing patterns. Thirdly, we had no access to data on reasons for discontinuation of anti-obesity drug treatment. However, given that the commonest causes of drug discontinuation are lack of efficacy and adverse effects, we believe it is reasonable to
speculate that discontinuation represents either of these events. A further limitation is the lack of data on BMI. While weight was recorded frequently in the database, there were relatively few recordings of height for most patients. Because of this we were unable to calculate accurate BMI data in relation to prescription dates and thus could not assess either the mean BMI of those prescribed anti-obesity drugs, nor the change in BMI in those prescribed.

**Comparison with the literature**

We are aware of no published population-based data on prescriptions of and/or use of orlistat and sibutramine in children and adolescents. The only comparable data on prescription prevalence come from a report of total national prescription counts in England from 1998-2005, which were not broken down by age but are almost certain to be almost entirely for adults in whom anti-obesity drug use is licensed. This study reported a 25-fold increase in orlistat prescriptions (from 1998) and a 4-fold increase in sibutramine prescriptions (from 2001).[10] We identified a similar increase in orlistat prescriptions in children and adolescents (28-fold increase from 1999) but a much larger increase (16-fold increase from 2001) in sibutramine prescriptions. We found that orlistat prescriptions outweighed those for sibutramine by approximately four to one over our study period, however this was likely to be an artefact of the later introduction of sibutramine. In 2006, there were only approximately twice as many prescriptions for orlistat as sibutramine, similar to the ratio described for adults. [10]
The only comparable data on tolerability and persistence with orlistat and sibutramine in children and young people come from a small number of efficacy studies. For orlistat, published reports conclude repeatedly that it is “well tolerated.”[17-19] However published trial data show that while persistence with orlistat for ≥3 months in clinical trials was markedly longer than in our data, gastrointestinal side-effects were reported in over 50%. The largest study of orlistat in adolescents, a randomised placebo-controlled study of 539 subjects over 12 months, reported that 65% of those randomised to orlistat completed 12 months of treatment, and that only 2% (2/357) in the orlistat arm dropped out due to adverse reactions. However, gastrointestinal adverse events were reported by 50% of those taking orlistat.[18] A detailed study of the tolerability of taking orlistat together with a comprehensive behavioural and dietetic programme in 20 adolescents over 3 months, found that 85% completed 3 months on orlistat, but that 50-60% reported a combination of unpleasant gastrointestinal side-effects.[17] In an early small open-label randomised controlled trial, gastrointestinal side-effects were reported in all 22 adolescents receiving orlistat, of whom 7 (32%) dropped out of the trial during the first month of the trial due to side-effects attributable to orlistat.[20]

Similarly for sibutramine, published studies report that this drug is generally well tolerated in adolescents.[21-23] The largest trial, a randomised placebo-controlled trial in 498 obese adolescents over 12 months, reported that 76% of those in the sibutramine arm continued the drug for the full 12 month trial period, with only 6% of subjects withdrawing because of adverse events.[22] In a smaller randomised controlled trial of 60 obese adolescents over 6 months, 93% completed the 6 month trial and no subjects
withdrew due to sibutramine side-effects.[23] In a further small randomised trial of 46 obese adolescents, 81% in the sibutramine arm completed the 6 month trial, but none withdrew because of adverse events.[24]

Our findings do not support the above reports on tolerability of and persistence with orlistat and sibutramine. In contrast, we found that in general use, one-third or less of prescriptions were continued past 3 months. While we do not have data on reasons for discontinuation, we believe that this is likely to reflect either poor therapeutic efficacy of the drug in the general population, or poor patient education and preparation before prescription. This poor preparation is likely to be both in terms of high levels of side-effects due to excessive intake of dietary fat[16] or, alternatively, unrealistic expectations of rapid major weight loss, leading to discontinuation when this is not achieved. Whilst we do not have data on reasons for discontinuation in our study, our data suggest that both orlistat and sibutramine are more poorly tolerated and more rapidly discontinued in use in the general population than in highly selected, motivated and supported clinical trial populations. These differences may reflect the routine weight management support programmes that were integral parts of many of the clinical trials of orlistat and sibutramine.[17;18;22;23]

A further reason for early discontinuation in this sample may have been the relatively high proportion (approximately 29%) with a co-morbid diagnosis of depression, as feelings of hopelessness and negativity may contribute to early discontinuation of the drug. While we have no further information about the validity of recorded diagnoses of
depression, this figure is higher than the 13% reported from population-based estimates of psychological distress in obese UK adolescents.[25] This suggests that in clinical practice, obese adolescents with significant psychological distress may be over-represented in those prescribed anti-obesity drugs.

Guidance on appropriate prescribing of orlistat and sibutramine in children and adolescents in the UK were published by NICE in 2006 (see Table 2).[9] We were unable to assess prescribing in our study against each element of NICE guidance. However, we note that there were a number of children <12 years prescribed anti-obesity drugs, in contravention of the guidance, and that very few of our subjects continued their anti-obesity drug for the 6-12 month trial suggested by NICE.

We found that use of anti-obesity drugs was higher in girls than in boys. This sex ratio is similar to that seen in a population-based study of anti-obesity drug use in Taiwanese adults,[26] and reflects well-described higher proportions of body-weight concerns in adolescent girls[6]

Conclusion

Prescribing of unlicensed anti-obesity drugs in children and adolescents has dramatically increased in the past 8 years. The majority are rapidly discontinued before patients can see clinical benefit, suggesting they are poorly tolerated or poorly efficacious when used in the general population, in contrast to findings from clinical trials. The role of depressive symptoms in early discontinuation is unclear. Further research into the
effectiveness and safety of anti-obesity drugs in children and adolescents in clinical populations is needed.
• Contributions and Conflict of interest

Russell Viner: I declare that I conceiving the idea for the study, and participated in analyses and writing of the paper, and that I have seen and approved the final version. I have the following conflicts of interest: Nil.

Yingfen Hsia: I declare that I participated in obtaining the data, analyses and writing of the paper, and that I have seen and approved the final version. I have the following conflicts of interest: Nil.

Antje Neubert: I declare that I participated in obtaining data and writing of the paper, and that I have seen and approved the final version. I have the following conflicts of interest: Nil.

Ian C K Wong: I declare that participated in obtaining the data, analyses and writing of the paper, and that I have seen and approved the final version. I have the following conflicts of interest: Nil.

Guarantor: Ian Wong had full access to the data in the study, final responsibility for submission for publication, and guarantees the paper.
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Publication

This paper has not been and will not be published in whole or in part in any other journal.

All the authors have agreed to the contents of the manuscript in its submitted form.
Table 1. Obesity related comorbidity within population treated with anti-obesity drugs

<table>
<thead>
<tr>
<th>Co-morbidity diagnosis</th>
<th>% (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>4.9 (22)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.2 (10)</td>
</tr>
<tr>
<td>Depression</td>
<td>28.5 (129)</td>
</tr>
<tr>
<td>Polycystic ovarian syndrome</td>
<td>7.5 (28/372 females)</td>
</tr>
</tbody>
</table>
Table 2. NICE criteria for use of orlistat and sibutramine in children and adolescents[9]

- Drug treatment is not generally recommended for children younger than 12 years.
- In children younger than 12 years, drug treatment may be used only in exceptional circumstances, if severe life-threatening comorbidities (such as sleep apnoea or raised intracranial pressure) are present. Prescribing should be started and monitored only in specialist paediatric settings.
- In children aged 12 years and older, treatment with orlistat or sibutramine is recommended only if physical comorbidities (such as orthopaedic problems or sleep apnoea) or severe psychological comorbidities are present. Treatment should be started in a specialist paediatric setting, by multidisciplinary teams with experience of prescribing in this age group.
- Orlistat or sibutramine should be prescribed for obesity in children only by a multidisciplinary team with expertise in:
  - drug monitoring
  - psychological support
  - behavioural interventions
  - interventions to increase physical activity
  - interventions to improve diet.
- Orlistat and sibutramine should be prescribed for young people only if the prescriber is willing to submit data to the proposed national registry on the use of these drugs in young people.
• After drug treatment has been started in specialist care, it may be continued in primary care if local circumstances and/or licensing allow.

• If orlistat or sibutramine is prescribed for children, a 6–12-month trial is recommended, with regular review to assess effectiveness, adverse effects and adherence.
Figure 1 Distribution of anti-obesity prescriptions in the UK general practice, 1999-2006

- Orlistat licensed in 1998
- Sibutramine licensed in 2001
Figure 2. Sex-specific prevalence of anti-obesity drug prescribing, 1999-2006
Figure 3. Age-specific prevalence of anti-obesity medication prescribing, 1999-2006
Figure 4. Kaplan-Meier curves for children and adolescents who received anti-obesity drug treatment.
Reference List


Orlistat licensed in 1998
Sibutramine licensed in 2001