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Weight Management with Orlistat in Type 2 Diabetes – An Electronic Healthcare Records Study

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Keywords

Type 2 Diabetes, prediabetes, obesity, weight loss, body mass index

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Abstract

Background: Orlistat is recommended as an adjunct to diet and exercise for weight loss in type 2 diabetes mellitus (T2DM).

Aims: The aims were to explore (i) associations between patient characteristics and orlistat prescribing and to determine (ii) associations of orlistat with weight loss in T2DM/prediabetes.

Design & Setting: This cohort study used anonymised records of T2DM/prediabetes (2016-2017) patients ≥18 years, from the UK Clinical Practice Research Datalink (CPRD) database.

Methods: Multivariable logistic regression models determined associations with starting orlistat and stopping it early (<12 weeks of prescriptions) and orlistat's associations with weight loss in those not prescribed 2nd line anti-diabetic medications.

Results: Out of 100,552 patients with incident T2DM/prediabetes, 655 (0.8%) T2DM and 128 (0.7%) prediabetes patients were prescribed orlistat. Younger people, females, those in more deprived regions, current smokers, co-prescribed metformin and recorded with hypertension were significantly more likely to be prescribed orlistat while higher baseline HbA1c levels were associated with early stopping. Those who continued orlistat for >12 weeks were more likely to lose ≥5% weight (adjusted OR: 1.69; 95% CI: 1.07, 2.67) than those not on orlistat, but those who stopped orlistat early were less likely (adjusted OR: 0.56; 95% CI: 0.29, 1.09).

Conclusion: Orlistat was significantly associated with weight loss in T2DM/prediabetes when taken for at least 12 weeks. However, orlistat is infrequently prescribed and often taken for <12 weeks. Orlistat may be a useful adjunct to lifestyle modifications in T2DM/prediabetes however barriers to continuing orlistat means it may not be effective for everyone in managing weight loss.

Accepted Manuscript – BJGP – BJGP.2023.0684

How this fits in

What was previously known on this topic

- Previously randomised controlled trials have shown the effectiveness of orlistat for weight loss in T2DM/prediabetes patients as an adjunct to lifestyle/behavioural factors.
- Orlistat can be prescribed for weight loss in T2DM/prediabetes patients however, the extent of its use and association with weight loss in T2DM and prediabetes in real world settings were lacking.

What this research study adds

- Orlistat used for more than 3 months is associated with ≥5% weight loss in T2DM and prediabetes however, is infrequently used in T2DM and often stopped early.
- There appear to be barriers to continuing orlistat long term in T2DM/prediabetes and may not be effective for everyone.

Accepted Manuscript–BJGP–BJGP.2023.0624

Introduction

Type 2 diabetes mellitus (T2DM) is a major public health burden and remains a health challenge globally [1]. In the United Kingdom (UK), diabetes diagnoses have more than doubled in the past twenty years, with over 4.9 million people having a diabetes diagnosis [2]. Prediabetes prevalence has more than tripled, with 35.3% adults or 1 in 3 having prediabetes [3]. Diabetes-related complications such as blindness, cardiovascular disease (CVD), nerve damage or kidney disease are a major cause of disability, reduced quality of life (QoL) or even death [4]. Obesity increases the risk of T2DM [5, 6] and its complications [7, 8]. In the UK, 90% of those with T2DM have obesity/are overweight however obesity is modifiable [9]. Weight loss is an important therapeutic strategy in those overweight/with obesity in T2DM/prediabetes [9, 10]. Although lifestyle modifications are recommended [10], weight loss and management can be challenging for many [11]. Therefore, additional interventions such as pharmacotherapy may be necessary.

Orlistat (tetrahydrolipstatin) is a National Institute for Health and Care Excellence (NICE) approved oral treatment for obesity in the UK, with a licence to be prescribed as an adjunct to diet and exercise, for a BMI of ≥30kg/m^2 or a BMI of ≥28kg/m^2 with risk factors such as T2DM [12, 13, 14]. Orlistat (as are liraglutide and semaglutide) is available through the National Health Service (NHS), UK [14, 15] for obesity treatment [12, 13, 14]. Liraglutide and semaglutide are injectable and can be expensive, whereas orlistat is an oral medication with evidence of cost-effectiveness [16]. Orlistat is known to cause side effects such as flatulence, diarrhoea, gastro-intestinal disorders, abdominal pain, fatty stools or faecal incontinence [15,17] and can be stopped early due to this or if ≤5% weight is lost within 12 weeks [17]. Whilst randomised controlled trials (RCTs) indicate orlistat is effective in T2DM [18,19,20], real world evidence on the extent it is prescribed and continued for more than 12 weeks, and its impact in overweight/obese T2DM and prediabetes patients is limited.

Accepted Manuscript- BJGP_BJGP.2023.0684

The objectives of this study were to determine:

1) Patient characteristics associated with orlistat prescribing and with stopping orlistat early in T2DM in UK primary care.

2) Orlistat's association with weight loss and change in other key diabetes markers in patients with T2DM or prediabetes.

Methods

Study design & Setting

The study was set within the UK CPRD Aurum database [21, 22], with linked neighbourhood-level Index of Multiple Deprivation (IMD) (2019) [23] used as a measure of socioeconomic status. CPRD Aurum contains routinely collected anonymised data from primary care general practices in the UK (currently about 13 million patients registered, covering 20% of the UK population) and predominantly represents the broader English population [24]. The study was approved by the CPRD Research Data Governance (RDG) process in November 2021 (CPRD eRAP Protocol Number: 21_000740).

Study population

The study population was patients aged ≥18 years with a first diagnosis of T2DM/prediabetes in 2016 or 2017. Index date was date of first T2DM/prediabetes diagnosis. Patients also had to have at least 2 years of records in CPRD prior to diagnosis and at least 2 years of follow-up data. Read codes were used in UK primary care prior to 2018 to record diagnoses, and code lists for T2DM and prediabetes were finalised in consensus with the other researchers (Read codes in Supplementary Table 1). For objective 2, analysing orlistat's associations with weight loss/glycaemic parameters/blood pressure (BP), we included only those with baseline BMI of ≥28kg/m^2 and excluded those with records of 2nd line antidiabetic medications/insulin, as these may also result in weight change [25, 26] (Supplementary Figure 1 for derivation of study population).

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Exposure

The exposure for objective 2 was orlistat prescription at time of diagnosis (within 12 weeks before or 12 weeks after diagnosis). We compared 3 groups (i) prescribed orlistat within ±12 weeks of diagnosis and stopped early (group 1) versus (ii) prescribed orlistat within ±12 weeks of diagnosis date and continued past 12 weeks (group 2) versus (iii) no orlistat within ±12 weeks of diagnosis (group 3). Continued use was defined as having at least 1 orlistat prescription more than 12 weeks after initial prescription, with less than a 6 month gap since previous prescription.

Outcomes

The outcome for objective 1 was an orlistat prescription from 12 weeks before to 2 years after diagnosis. The 12 weeks before diagnosis was included in case general practitioners (GPs) prescribed orlistat during the diagnosis window for diabetes. "Stopping orlistat early" was defined as no recorded orlistat prescription after 12 weeks of the initial prescription [13].

The primary outcome for objective 2 was weight loss of ≥5% from baseline to last recorded weight (i) prior to 12 months after diagnosis and (ii) prior to 24 months after diagnosis. Those without weight recordings at baseline or follow up were excluded. For secondary outcomes, association of orlistat with actual change in weight, and changes in HbA1c and systolic BP were assessed using last recorded measurement within 12 and 24 months of diagnosis.

Covariates

The covariates at baseline were selected by consensus of the research team as being potentially associated with prescribing of orlistat. These were age (at T2DM/prediabetes diagnosis), gender, hypertension, HbA1c levels, metformin prescription, geographical region, deprivation, smoking status and baseline BMI recordings (i.e., the last measurement at baseline). Baseline BMI, HbA1c, hypertension and smoking status were defined based on last recordings/status in the 2 years prior to

Accepted Manuscript - BJGP - BJGP.2023.0684

or on diagnosis. Metformin prescription was based on a record of 12 weeks either side of diagnosis. Patients without recorded baseline BMI were included alongside those with a baseline BMI of ≤25kg/m^2. Neighbourhood deprivation was categorised by quintile scores. Geographical regions were combined and categorised into North (North East, North West, Yorkshire and the Humber), Midlands and East (East and West Midlands and East of England), and South and London (South East, South West and London).

Patient and public involvement

A patient and public involvement and engagement (PPIE) session involving people with T2DM/carers was conducted to inform and interpret our findings, to ensure that patient and public perspective were taken into consideration.

Sensitivity analysis

To assess the impact of missing data, patients with no recorded values (e.g., weight/BMI) during follow-up were included by coding them as missing categories. A number of sensitivity analyses were also undertaken to assess associations with orlistat prescribing, where those with a BMI ≤25kg/m^2 were excluded.

Statistical Methods

Objective 1

Associations of covariates with orlistat prescription in T2DM were determined using logistic regression and quantified by adjusted ORs (adjusting for all covariates) with 95% CIs. Analysis was repeated for prescribing at time of diagnosis (±12 weeks of diagnosis date). Within those with an orlistat prescription, associations with stopping orlistat early (within 12 weeks) were also determined using logistic regression. The analysis was repeated excluding those with BMI ≤25kg/m^2.

Accepted Manuscript – BJGP – BJGP.2023.0684

Objective 2

Associations between orlistat prescribing and change in weight were modelled using (i) logistic regression for weight loss ≥5% versus <5% (ii) linear regression for actual change in weight, adjusting for all covariates and time between baseline and follow-up BMI measurement. Analyses were performed separately for 1 and 2 years after diagnosis. Patients with no recorded outcome values (e.g. weight/BMI) during follow-up were excluded (complete case analysis). In model 1, orlistat (unadjusted) was used as the explanatory variable on its own with weight change as the outcome. For model 2, baseline BMI was added. Model 3 was adjusted for all covariates. For model 4, interaction of orlistat with metformin (multiplicative) was added to see if metformin moderated orlistat's association with outcomes. We repeated analysis for secondary outcomes of change in HbA1c and systolic blood pressure.

Results

Objective 1

There were 100,552 patients included (82,696 with T2DM and 17,856 with prediabetes). Patient characteristics are shown in Table 1. There were a total of 783 (0.8%) T2DM and prediabetes patients prescribed orlistat [655 (0.8%) T2DM patients and 128 (0.7%) prediabetes patients], out of whom 42% of T2DM and prediabetes patients prescribed orlistat received only a single orlistat prescription. T2DM patients received a total of 2,264 orlistat prescriptions at a rate of 173 per 100 person-years (PY) during the study period and prediabetes patients received a total of 429 orlistat prescriptions, at a rate of 168 per 100 person-years (PY) (about 1-2 orlistat prescriptions per person per year in those with at least one prescription).

Within T2DM patients, those with BMI ≥30kg/m^2 were more likely to be prescribed orlistat, as were females (adjusted OR: 2.02, 95% CI: 1.71, 2.39) and younger patients (adjusted ORs: 18-39 years

Accepted Manuscript–BJGP–BJGP.2023.0684

versus 40-64 years: 2.51, 95% CI: 2.01, 3.12; ≥65 years versus 40-64 years: 0.26, CI: 0.20, 0.34) (Table 2). Those from the North of England were more likely to be prescribed orlistat than those from the South/London (OR: 1.25, 95% CI: 1.03, 1.51). Orlistat was also associated with metformin prescriptions, current smoking, and hypertension. Those from more affluent areas were less likely to be prescribed orlistat. Higher baseline HbA1c values decreased the probability of orlistat prescribing. Associations with prescriptions within ±12 weeks of diagnosis (Table 2), and after excluding those with BMI≤25kg/m^2 (Supplementary Table 2), were similar.

Out of 655 T2DM patients with orlistat prescriptions, 292 (44.6%) had stopped early (within 12 weeks). Higher baseline HbA1c values were significantly associated with early stopping (adjusted OR: 1.01/unit increase, CI: 1.00, 1.02). After adjustment, no other statistically significant associations with early stopping of orlistat were found (Table 3).

Objective 2

There were 28,526 patients with T2DM and prediabetes for the outcomes of weight loss after 1st year and 33,873 patients with T2DM and prediabetes after the 2nd year, included (Supplementary Figure 1). At 1 year and at 2 years, all orlistat groups (stopped orlistat early, continued orlistat ≥12 weeks, and no orlistat within 12 weeks of diagnosis) had lost some weight. Those who had continued orlistat for ≥12 weeks had lost the most weight [mean 4.17kg (SD 6.09)] at 2 years whereas the orlistat group that had stopped early had lost the least [1.89kg (SD 9.12)] (Supplementary Table 3). At 1 year, 8,798 (30.8%) had ≥5% weight loss [(mean baseline weight: 97.73kg (SD 19.36) versus 1 year: 88.23kg (SD 17.83)] (continued orlistat: 42.5%, stopped orlistat early: 19.7%, no orlistat: 30.8%). After 2 years, 11,080 (32.7%) patients had lost ≥5% weight [(mean baseline weight: 97.31kg (SD 19.55) versus 2 years: 87.33kg (SD 17.87)] (continued orlistat: 44.6%, stopped orlistat early: 24.6%, no orlistat: 32.7%).

Accepted Manuscript- BJGP_BJGP.2023.0684

In unadjusted analyses, those who continued orlistat were more likely to lose ≥5% weight in 1 year (OR versus no orlistat: 1.66, 95% CI: 1.06, 2.59) whereas those who stopped early were less likely although not statistically significant (OR: 0.55, 95% CI: 0.29, 1.03) (Table 4). A 5% weight loss was equivalent to losing about 5kg on average in this population. After adjustment for all covariates, these strength of associations were maintained (continued versus no orlistat: OR: 1.69, 95% CI: 1.07, 2.67; stopped early versus no orlistat OR: 0.56, 95% CI: 0.29, 1.09). Similar associations were found after two years (continued versus no orlistat: adjusted OR: 1.55, 95% CI 0.99, 2.43; stopped early versus no orlistat OR: 0.68, 95% CI: 0.39, 1.18). There was no significant interaction of metformin and orlistat with weight loss in 1 or 2 years.

Analysing actual weight loss, those who stopped early lost significantly less weight (adjusted β versus no orlistat: -1.79kg, 95% CI: -3.35, -0.24) and those who continued lost more weight but this was not statistically significant (adjusted β versus no orlistat: 0.64kg, 95% CI: -0.71, 2.00) over 1 year (Table 4). Findings were similar after 2 years. Those who stopped orlistat early had significantly less reductions in HbA1c in 1 year (adjusted β versus no orlistat: -5.08mmol/mol, 95% CI: -8.45, -1.72) and after 2 years [adjusted β versus no orlistat: -4.40mmol/mol, 95% CI: -7.21, -1.59) (Table 5). There was no difference in change in HbA1c between those who continued orlistat and those not prescribed it. Those who continued orlistat had significantly greater reductions in systolic BP after 1 year (adjusted β versus no orlistat: 3.98; 95% CI: 0.44, 7.52) (Table 5).

Discussion

Summary

This study assessed the association of patient characteristics with orlistat prescribing and orlistat's associations with weight loss in T2DM and prediabetes patients using a large nationally representative UK primary care database. Our study showed that the incidence of orlistat was low, with less than 1% patients having received orlistat and 42% received only a single prescription, with

Accepted Manuscript – BJGP.2023.0684

no further prescriptions beyond 12 weeks. This indicated patients had received little treatment. These low numbers can imply difficulty with generalisation and less significant impact on health care. However, our findings indicate that UK NICE guidelines for orlistat prescribing were being followed, i.e., to adults with T2DM and BMI ≥28kg/m^2, consistent with a previous UK study' findings [26].

Prescribing of orlistat appeared higher in younger patients females, and those with higher HbA1c, co-prescribed metformin, with hypertension and current smokers. Orlistat was prescribed more in the most deprived areas than in the most affluent areas. This may reflect higher levels of severe obesity [27, 28]. Our study showed associations of continuing orlistat with ≥5% weight loss. Continuing orlistat had less impact on HbA1c although stopping early was associated with less reduction in HbA1c. Systolic BP was reduced more in those continuing orlistat. Smokers and those with hypertension were more likely to be prescribed orlistat [29,30,31] possibly for CVD risk reduction in T2DM. Those with lower HbA1c values were more likely to be prescribed orlistat whilst higher HbA1c values were positively associated with stopping early. Orlistat may not prescribed for long in those with higher HbA1c values if proving ineffective in reducing weight/HbA1c, as reducing high blood glucose levels is a key priority in T2DM.

However, less than 1% of patients received orlistat in our study. Moreover, 42% of those prescribed orlistat received a single prescription, indicating they had received little treatment. This study cannot elucidate the reasons for the low prescribing but it may be orlistat's prescribing recommendations are not being followed [32]. This may be because individuals are prioritising lifestyle and dietary changes. However, the low use of orlistat and early stopping could also be because GPs consider it ineffective or that its side effects are intolerable, or patients are declining it even if it is offered.

Accepted Manuscript - BJGP - BJGP.2023.0684

There is also a possibility that orlistat may have adverse effects, that may influence GPs decisions. Orlistat is contraindicated in cholestasis/chronic malabsorption syndrome and it is advised that caution should be observed in those with chronic kidney disease (CKD) [14, 17]. However, the European Medicines Agency (EMA) reviewed orlistat's safety concerns in 2012 and concluded that its benefits outweigh the risks [32].

There has also been a surge in 2nd line antidiabetic medication prescribing for example, glucagon-like peptide-1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter-2 inhibitors (SGLT-2i) in recent times [25, 34]. These may have reduced the need for simultaneous orlistat prescribing alongside metformin in T2DM due to their associations with greater weight loss [34].

Comparison with existing literature

In our study, continuing orlistat after 12 weeks was associated with losing at least 5% of weight. By contrast, stopping orlistat reduced the likelihood of losing ≥5% of weight. Those continuing orlistat lost on average 1.33kg more weight than those not prescribed it and 2.65kg more than those who stopped orlistat early. This weight loss was maintained over 2 years and 45% of patients who continued for ≥12 weeks had still lost ≥5% weight after 2 years. This level of weight loss matches findings from RCTs in T2DM [35, 36] and a meta-analysis in which those on orlistat in the general population lost a mean of 2.7kg (95% CI: 2.3, 3.1) more than placebo in 1 year [37]. Similar to our findings, weight changes in a UK general population cohort using CPRD data showed an average of 2.2kg reduction with orlistat in 3 years [26]. A weight reduction of ≥5% has been considered 'clinically meaningful' [38]. Glycaemic parameters and systolic BP can improve with just ≥2.5% weight loss [39]. Furthermore, even 1-2kg of weight loss can be beneficial, for example, one study suggested that for each 1kg of weight loss, T2DM risk decreases by 16% [40]. However, weight loss

Accepted Manuscript- BJGP–BJGP.2023.0684

rates may be slower in T2DM, so less strict goals may be considered [13]. Weight loss benefits may last for ≥5 years, and even if regained, improvements to blood glucose levels remain [41].

Strengths and Limitations

This is the largest study to our knowledge that examined the real world associations of orlistat with patient characteristics and weight loss in T2DM/prediabetes, and used a large, nationally representative primary care database in the UK. This real world study confirmed the weight loss results of RCTs that underpinned the use of orlistat in T2DM and prediabetes.

The current study has some limitations. Most importantly, the number of patients prescribed orlistat was limited which can imply difficulty with generalisation. The small number of patients prescribed orlistat who were not on 2nd line medications and had recorded weight over time reduced the power of our study and larger studies are needed. Patient characteristics associated with orlistat prescribing were examined only within T2DM, as numbers with prediabetes were very low. However, we combined the groups for our 2nd objective, as orlistat was likely to have a similar effect in T2DM and prediabetes. Some patients may have started orlistat as an over-the-counter (OTC) medication, which are unrecorded in primary care EHR, underestimating orlistat's incidence. Orlistat can be bought OTC at a lower 60mg dose in the UK however, even if offered by GPs, patients may have refused it. Some confounding factors e.g., diet/exercise, are not captured in CPRD, which can give rise to residual confounding.

The reasons for stopping orlistat early are recorded as free text (unavailable for research) and diet, exercise or severity of T2DM, are not well-recorded in EHR. We also excluded patients on 2nd line antidiabetic medications/insulin to explore only orlistat's association with weight loss, as these may also lead to weight loss. Metformin was only included as it is the first line in the UK and most frequently prescribed antidiabetic medication [42]. Weight data was only available for a subset of

Accepted Manuscript – BJGP – BJGP.2023.0684

patients which could cause bias if reasons for recording weight varied between orlistat users and non-users. Unexplained or unintentional weight loss can also be a symptom of new-onset diabetes, caused due to osmotic diuresis under high blood glucose conditions [43], and this may partially explain some of the weight loss observed for some patients in all groups.

Implications

Continued use of orlistat was associated with targeted reductions in weight. Reductions in systolic BP may have important clinical implications in reducing major cardiovascular risks. Whilst other approaches e.g., diet and exercise, need to be considered first, lifestyle modification and weight loss/management, especially in T2DM/prediabetes, can be challenging for many. Whilst it needs to be seen if weight loss with orlistat is maintained over longer follow-up periods, orlistat could have an important role in T2DM/prediabetes to get people started off with losing some weight, if lifestyle factors are difficult to adhere with. Patient comorbidities need to be considered, as well as orlistat's potential side effects, which may prove a barrier to the continued use of orlistat needed for it to be effective.

Conclusion

Weight loss appeared to be sustainable in patients who continued treatment with orlistat however there appear to be barriers to continuing orlistat and may not be effective for everyone. Ideally, orlistat should be prescribed only after diet changes and exercise have been advised for weight loss and evaluated but future studies need to examine the impact of orlistat alongside these lifestyle interventions as well as its longer-term impact on weight loss.

Accepted Manuscript–BJGP–BJGP.2023.0684

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Conflict of interest statement

None of the authors have any conflicts of interest to declare.

Data availability

Data may be obtained from a third party and are not publicly available. The data were obtained from the CPRD. CPRD data governance does not allow us to distribute patient data to other parties. Researchers may apply for data access at http://www.CPRD.com/

Ethics statement

The study was approved by the CPRD's Research Data Governance (RDG) process for using CPRD Aurum and the linked IMD datasets (CPRD eRAP Protocol Number: 21_000740). The approved protocol was made available to reviewers.

Accepted Manuscript–BJGP–BJGP.2023.0684

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Accepted Manuscript–BJGP–BJGP.2023.0684

Table 1: Study population (T2DM & Prediabetes) - Baseline characteristics

Baseline Characteristics of Registered Patients, *n* (%)	**T2DM/Prediabetes *n*=100,552**	**T2DM *n*=82,696**	**Prediabetes *n*=17,856**
Age (years), mean (SD)	62.5 (13.9)	62.1 (13.8)	64.0 (13.9)
Gender (Males), *n* (%)	55,028 (54.7)	46,468 (56.2)	8,560 (47.9)
Gender (Females), *n* (%)	45,524 (45.3)	36,228 (43.8)	9,296 (52.1)
Body Mass Index (BMI)			
Baseline measurement, *n* (%)	72,894 (72.5)	61,519 (74.4)	11,375 (63.7)
<18.5kg/m^2 (Underweight), *n* (%)	470 (0.7)	305 (0.5)	165 (1.5)
18.5-24.9kg/m^2 (Normal), *n* (%)	9,443 (13.0)	7,300 (11.9)	2,143 (18.8)
25-29.9kg/m^2 (Overweight), *n* (%)	24,111 (33.1)	19,756 (32.1)	4,355 (38.3)
≥30kg/m^2 (Obese), *n* (%)	38,870 (53.3)	34,158 (55.5)	4,712 (41.4)
Mean (kg/m^2) (SD)	31.3 (6.5)	31.6 (6.6)	29.6 (5.8)
Index of Multiple Deprivation (IMD)			
1 (Least deprived), *n* (%)	18,762 (18.9)	15,140 (18.5)	3,622 (20.6)
2, *n* (%)	18,311 (18.5)	15,084 (18.5)	3,227 (18.3)
3, *n* (%)	18,901 (19.0)	15,448 (18.9)	3,453 (19.6)
4, *n* (%)	21,883 (22.0)	18,025 (22.1)	3,858 (21.9)
5 (Most deprived), *n* (%)	21,412 (21.6)	17,956 (22.0)	3,456 (19.6)
Geographical Region			
Region 1: North England, *n* (%)	22,043 (21.9)	18,292 (22.1)	3,751 (21.0)
Region 2: Midlands/East, *n* (%)	27,632 (27.5)	22,974 (27.8)	4,658 (26.1)
Region 3: South/London, *n* (%)	49,465 (49.2)	40,442 (48.9)	9,023 (50.5)
Baseline smoking status, *n* (%)	77,151 (76.7)	64,318 (77.8)	12,833 (71.9)
Ex-Smoker, *n* (%)	19,015 (24.6)	15,928 (24.8)	3,087 (24.0)
Current Smoker, *n* (%)	21,842 (28.3)	18,366 (28.5)	3,476 (27.1)
Non-Smoker, *n* (%)	36,294 (47.0)	30,024 (46.7)	6,270 (48.8)
Prescribed Orlistat, *n* (%)	783 (0.8)	655 (0.8)	128 (0.7)

Abbreviations: n=Number of participants; T2DM: Type 2 Diabetes mellitus; SD: Standard deviation; BMI: Body mass index; IMD: Index of Multiple Deprivation; Region 1: North of England; Region 2: Midlands & East of England; Region 3: South of England & London.

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Table 2: Associations of Baseline characteristics with Orlistat prescriptions in T2DM patients (n=82,696)

Independent Variables		Orlistat prescription at any time			Prescription within ±12 weeks of diagnosis		
Independent Variables	**Total *n***	**Orlistat *n***	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**Orlistat *n***	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Age (18-39.9 years)	4,709	117	2.34 (1.90, 2.87)	2.51 (2.01, 3.12)	40	2.19 (1.55, 3.10)	2.30 (1.60, 3.31)
Age (≥65 years)	35,828	83	0.21 (0.17, 0.27)	0.26 (0.20, 0.34)	34	0.24 (0.17, 0.35)	0.32 (0.22, 0.47)
Age (40-64.9 years)	42,159	455	1	1	164	1	1
Gender (Females)	36,228	391	1.91 (1.63, 2.23)	2.02 (1.71, 2.39)	139	1.80 (1.39, 2.34)	1.82 (1.39, 2.39)
Gender (Males)	46,468	264	1	1	99	1	1
BMI: 18.5-24.9kg/m^2/Not recorded	28,782	108	0.25 (0.20, 0.30)	0.27 (0.21, 0.33)	29	0.17 (0.12, 0.26)	0.18 (0.12, 0.27)
BMI: 25-29.9kg/m^2	19,756	30	0.10 (0.07, 0.14)	0.14 (0.09, 0.20)	11	0.10 (0.05, 0.18)	0.12 (0.06, 0.23)
BMI: ≥30kg/m^2	34,158	517	1	1	198	1	1
Region 1: North England	18,292	185	1.30 (1.08, 1.56)	1.25 (1.03, 1.51)	68	1.29 (0.95, 1.74)	1.24 (0.90, 1.70)
Region 2: Midlands/East	22,974	148	0.82 (0.68, 1.00)	0.96 (0.78, 1.17)	51	0.77 (0.55, 1.07)	0.87 (0.62, 1.22)
Region 3: South/London	40,442	316	1	1	117	1	1
IMD (1): least deprived	15,140	63	0.37 (0.28, 0.49)	0.68 (0.50, 0.91)	20	0.35 (0.21, 0.58)	0.67 (0.40, 1.11)
IMD (2)	15,084	107	0.63 (0.50, 0.80)	0.93 (0.73, 1.20)	43	0.76 (0.52, 1.12)	1.13 (0.75, 1.70)
IMD (3)	15,448	104	0.60 (0.47, 0.76)	0.82 (0.64, 1.05)	42	0.73 (0.50, 1.07)	1.05 (0.70, 1.56)
IMD (4)	18,025	170	0.84 (0.68, 1.03)	1.02 (0.82, 1.26)	62	0.92 (0.65, 1.30)	1.12 (0.78, 1.61)
IMD (5): most deprived	17,956	202	1	1	67	1	1

Accepted Manuscript – BJGP.2023.0

Baseline HbA1c	77,109	631	1.00 (1.00, 1.01)	0.990 (0.99, 1.00)	231	0.99 (0.99, 1.00)	0.98 (0.97, 0.99)
Metformin	35,963	246	2.17 (1.86, 2.55)	1.87 (1.56, 2.24)	143	1.96 (1.51, 2.54)	1.83 (1.37, 2.46)
No Metformin	46,733	409	1	1	95	1	1
Not recorded Smoking status	18,378	144	1.09 (0.88, 1.34)	1.41 (1.12, 1.78)	56	1.17 (0.83, 1.66)	1.83 (1.27, 2.63)
Ex-Smoker	15,928	112	0.97 (0.77, 1.22)	1.26 (0.99, 1.61)	34	0.82 (0.55, 1.23)	1.01 (0.65, 1.55)
Current Smoker	18,366	182	1.38 (1.13, 1.68)	1.29 (1.05, 1.59)	70	1.47 (1.06, 2.03)	1.47 (1.05, 2.06)
Non Smoker	30,024	217	1	1	78	1	1
Recorded Hypertension	27,947	240	1.13 (0.97, 1.33)	1.27 (1.07, 1.51)	81	1.01 (0.77, 1.32)	1.09 (0.82, 1.44)
No Hypertension	54,749	415	1	1	157	1	1

Abbreviations: n=Number of participants; T2DM: Type 2 Diabetes mellitus; OR: Odds ratio; CI: Confidence interval; 1: Reference category; BMI: Body Mass Index; IMD: Index of Multiple Deprivation; Region 1: North of England; Region 2: Midlands & East of England; Region 3: South of England & London.

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Table 3: Associations of Baseline characteristics with stopping Orlistat prescription early in T2DM patients (n=655)

Independent Variables	T2DM patients (*n*)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age (18-39.9 years)	117	0.66 (0.44, 0.99)	0.70 (0.45, 1.10)
Age (≥65 years)	83	0.97 (0.61, 1.56)	1.06 (0.64, 1.75)
Age (40-64.9 years)	455	1	1
Gender (Females)	264	1.19 (0.87, 1.63)	1.09 (0.77, 1.53)
Gender (Males)	391	1	1
BMI: Normal/Not recorded	108	0.85 (0.56, 1.29)	0.79 (0.49, 1.28)
BMI: 25-29.9kg/m^2	30	1.18 (0.56, 2.51)	1.40 (0.63, 3.14)
BMI: ≥30kg/m^2	517	1	1
Region 1: North England	185	1.47 (1.020, 2.13)	1.37 (0.91, 2.05)
Region 2: Midlands/East	148	1.20 (0.81, 1.78)	1.18 (0.78, 1.79)
Region 3: South/London	316	1	1
IMD (1): least deprived	63	0.62 (0.35, 1.09)	0.68 (0.38, 1.24)
IMD (2)	107	1.08 (0.67, 1.74)	1.14 (0.68, 1.90)
IMD (3)	104	1.12 (0.69, 1.81)	1.18 (0.70, 1.98)
IMD (4)	170	0.73 (0.48, 1.10)	0.80 (0.52, 1.24)
IMD (5): most deprived	202	1	1
Baseline HbA1c	631	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)
Metformin	246	0.87 (0.63, 1.19)	0.92 (0.63, 1.33)
No Metformin	409	1	1
Not recorded Smoking status	144	0.82 (0.54, 1.26)	0.87 (0.54, 1.39)
Ex-Smoker	112	0.91 (0.58, 1.45)	0.77 (0.47, 1.28)
Current Smoker	182	0.90 (0.60, 1.34)	0.91 (0.60, 1.40)
Non Smoker	217	1	1
Recorded Hypertension	240	1.38 (1.00, 1.90)	1.36 (0.95, 1.93)
No Hypertension	415	1	1

Abbreviations: n=Number of participants; T2DM: Type 2 Diabetes mellitus; OR: Odds ratio; CI: Confidence interval; 1: Reference category; BMI: Body Mass Index; IMD: Index of multiple deprivation; Region 1: North of England; Region 2: Midlands & East of England; Region 3: South of England & London.

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Table 4: Associations of Orlistat prescription with weight loss of ≥5% & with actual Weight loss in T2DM & Prediabetes

Logistic Regression Models 1-3					
Groups 1-3	***n***	**Lost ≥5% weight *n* (%)**	**Model 1: (Unadjusted)**	**Model 2: (Adjusted for Baseline BMI)**	**Model 3: (Adjusted for all covariates)**
			OR (95% CI)	OR (95% CI)	OR (95% CI)
One year (n=28,526)					
Group 1 (Stopped early)	61	19.7%	0.55 (0.29, 1.03)	0.50 (0.27, 0.95)	0.56 (0.29, 1.09)
Group 2 (Continued)	80	42.5%	1.66 (1.06, 2.59)	1.53 (0.98, 2.39)	1.69 (1.07, 2.67)
Group 3 (No orlistat group)	28,385	30.8%	1	1	1
Two years (n=33,873)					
Group 1 (Stopped early)	69	24.6%	0.67 (0.39, 1.16)	0.60 (0.4, 1.04)	0.68 (0.39, 1.18)
Group 2 (Continued)	83	44.6%	1.66 (1.07, 2.55)	1.49 (0.97, 2.30)	1.55 (0.99, 2.43)
Group 3 (No orlistat group)	33,721	32.7%	1	1	1
Linear Regression Models 1-3					
			Model 1: (Unadjusted)	**Model 2: (Adjusted for Baseline BMI)**	**Model 3: (Adjusted for all covariates)**
Groups 1-3	***n***		β (95% CI)	β (95% CI)	β (95% CI)
One year (n=28,526)					
Group 1 (Stopped early)	61		-1.32 (-2.88, 0.24)	-2.29 (-3.84, -0.74)	-1.79 (-3.35, -0.24)
Group 2 (Continued)	80		1.34 (-0.03, 2.70)	0.41 (-0.95, 1.76)	0.64 (-0.71, 1.10)

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Group 3 (No orlistat group)	28,385		1	1	1
Two years (n=33,873)					
Group 1 (Stopped early)	69		-1.19 (-2.84, 0.47)	-2.42 (-4.06, -0.78)	-2.03 (-3.68, -0.38)
Group 2 (Continued)	83		1.10 (-0.41, 2.62)	-0.09 (-1.58, 1.41)	0.11 (-1.40, 1.62)
Group 3 (No orlistat group)	33,721		1	1	1

Abbreviations: n=Number of participants; T2DM: Type 2 Diabetes mellitus; OR: Odds ratio; β: Beta estimate; CI: Confidence interval; BMI: Body Mass Index; 1: Reference category.
Covariates included: Age 18-39.9 years; Age 40-64.9 years; Age ≥65 years; Gender (Males); Gender (Females); Baseline BMI; Region 1: North of England; Region 2: Midlands & East of England; Region 3: South of England & London; Index of Multiple Deprivation (IMD): 1-5; Baseline HbA1c; Metformin; No Metformin; Not recorded Smoking status; Ex-Smoker; Current Smoker; Non-Smoker; Recorded Hypertension; No Hypertension.

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Table 5: Associations of Orlistat with changes in HbA1c & BP in T2DM & Prediabetes (fully adjusted)

Groups 1-3	HbA1c	Systolic BP
	Adjusted β (95% CI)	Adjusted β (95% CI)
One year		
n	**27,995**	**31,140**
Group 1 (Stopped early)	-5.08 (-8.45, -1.72)	2.71 (-1.34, 6.76)
Group 2 (Continued)	1.55 (-1.38, 4.48)	3.98 (0.44, 7.52)
Group 3 (No orlistat group)	1	1
Two year		
n	**36,921**	**38,657**
Group 1 (Stopped early)	-4.40 (-7.21, -1.59)	-0.77 (-4.27, 2.72)
Group 2 (Continued)	-0.51 (-3.20, 2.19)	2.61 (-0.72, 5.93)
Group 3 (No orlistat group)	1	1

Abbreviations: n=Number of participants; T2DM: Type 2 Diabetes mellitus; β: Beta estimate; CI: Confidence interval; 1: Reference category; BP: Blood Pressure.
Covariates included: Age: 18-39.9 years, Age: 40-64.9 years; Age: ≥65 years; Gender (Females); Gender (Males); Baseline BMI (Body Mass Index); Region 1: North of England; Region 2: Midlands & East of England; Region 3: South of England & London; Index of Multiple Deprivation (IMD): 1-5; Baseline HbA1c; Metformin; No Metformin; Not recorded Smoking status; Ex-Smoker; Current Smoker; Non-Smoker; Recorded Hypertension; No Hypertension.

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