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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Use of exenatide and liraglutide in Denmark: a drug utilization study

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Abstract
Purpose The purpose of this study was to characterise the utilization of the glucagon-like peptide-1 (GLP-1) analogues exenatide and liraglutide in Denmark.
Methods From the Danish National Prescription Registry, we extracted all prescriptions for either liraglutide or exenatide twice-daily in the period 1 April 2007 to 31 December 2012. Using descriptive statistics, we calculated incidence rates, prevalence proportions, daily consumption, and concomitant drug use. For a subset of users we included data from other registries and characterised the baseline characteristics of incident users of GLP-1 analogues.
Results We identified 21,561 and 2,354 users of liraglutide and exenatide respectively. From market entry in 2009 liraglutide showed an increasing prevalence reaching 2.4 per thousand inhabitants in 2012. Exenatide ranged between 0.01 and 0.25 per thousand inhabitants from 2007 to 2012. Treatment intensity showed geographical variation ranging from 1.84per thousand inhabitants to 3.22 per thousand inhabitants for liraglutide. Average doses were 1.34 mg/day (liraglutide) and 16.4 μg/day (exenatide). Treatment initiation was most often performed by a hospital physician and was not associated with any changes in concomitant treatment with antihypertensives, cholesterol-lowering drugs or anticoagulants. Of liraglutide and exenatide users, 38 % and 43 % also used insulin. Low kidney function (eGFR<30 ml/min) was found in 10.1 % and 9.0 % of users of liraglutide and exenatide respectively.
Conclusions The preferred GLP-1 analogue in Denmark is liraglutide. Certain aspects of the utilization of GLP-1 analogues, such as large regional differences and concomitant use of GLP-1 analogues and insulin, warrant further investigation.

Keywords GLP-1 · Diabetes mellitus · Denmark · Prescribing · Drug utilization

Introduction

More than 200,000 Danes are estimated to suffer from type 2 diabetes [1–3]. The disease and related complications such as ischaemic heart disease, peripheral neuropathy and related micro- and macrovascular complications constitute a worldwide increasing threat to public health and a massive economic burden to society [1, 4]. Metformin in combination with lifestyle changes is the first drug of choice to achieve glycaemic control [5, 6]. This is based on evidence of clinically relevant effects on glucose levels, micro- and macrovascular outcome measures, and mortality [7–10]. However, sufficient glycaemic control is often not maintained using metformin combined with lifestyle changes alone, and additional antidiabetic drugs are needed to achieve glycaemic goals. Current treatment guidelines suggest the use of dipeptidyl peptidase 4 (DPP-4) inhibitors, sulphonylureas, thiazolidinediones, basal insulins or glucagon-like peptide 1 (GLP-1) analogues as second-line add-on treatment. Of these,

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GLP-1 analogues have gained increased interest owing to glucose-lowering properties comparable to sulphonylureas and superior to DPP-4 inhibitors and thiazolidinedione as add-ons to metformin, a low risk of hypoglycaemia, and their body weight-reducing effect [11–14]. GLP-1 analogues stimulate insulin secretion and inhibit glucagon secretion in a glucose-dependent manner [15]. Furthermore, GLP-1 analogues reduce gastric emptying, appetite and food intake, and, consequently, give rise to weight loss [15]. Thus, GLP-1 analogues are considered particularly relevant when weight reduction is central to treatment. Thereby, GLP-1 analogues can be considered in a substantial proportion of overweight patients with insufficient glycaemic control on metformin treatment [16].

At present, three GLP-1 analogues are available: exenatide in a formulation administered twice-daily (Byetta™), liraglutide (Victoza™) administered once-daily, exenatide in a formulation designed for once-weekly administration (Bydureon™), and the most recent lixisenatide (Lyxumia™), administered once-daily. They were introduced in Europe in 2007, 2009, 2011 and 2013 respectively. As current treatment guidelines recommend the use of these drugs in different dosages and in a variety of combinations with other antidiabetic drugs, while also advocating individualised, patient-centred treatment regimens, there is a strong need to have post-marketing knowledge of the use patterns, actual concordance with treatment guidelines and characteristics of the GLP-1 analogue drug users. Unfortunately, data on the utilization of GLP-1 analogues in Denmark are sparse. The nationwide prescription registry available in Denmark offers a unique tool for pharmacoepidemiological research [17, 18]. Accordingly, the aim of the present study was to characterise the utilization of GLP-1 analogues in Denmark from a national perspective, using population-based pharmacy dispensing data. We also compared the characteristics of actual GLP-1 analogue users with characteristics of patients enrolled in the core clinical trials of GLP-1 analogues.

Material and methods

In this study, we described the use of the GLP-1 analogues liraglutide and exenatide (twice-daily) in Denmark, using descriptive statistics. The analysis was divided into five questions, four of which were answered using national data and one was answered using data from the geographical region of Southern Denmark.

Data were extracted from the Danish National Prescription Registry. For the comparison of real-life users and trial enrolees, we also extracted data from the following regional databases: The Odense University Pharmacoepidemiological Database, the Funen County Patient Administrative System and the laboratory database of Odense University Hospital. Exenatide twice-daily and once-weekly were marketed in Denmark in April 2007 and October 2011 respectively, and liraglutide in July 2009. We thus obtained data regarding these drugs from 1 April 2007 to 31 December 2012.

Databases

The Danish National Prescription Registry (DNPR) [19] contains data on all prescription drugs redeemed by Danish citizens (population 5.5 million) since 1995. Prescription data include the type of drug, date of dispensing, and quantity. Dosing information and indication for each prescription are available in the DNPR, but data are incomplete and are therefore not used in the present study. Drugs are categorized according to the Anatomic Therapeutic Chemical (ATC) classification; a hierarchical classification system developed by the World Health Organisation (WHO) for the purposes of drug use statistics [20], and the quantity dispensed for each prescription is expressed by the defined daily dose (DDD) measure, also developed by the WHO [20].

Odense University Pharmacoepidemiological Database (OPED) is a regional prescription database covering Funen County (population 480,000) since 1990, extended to the region of Southern Denmark (1.2 million) in 2007 [21]. The structure of the database is roughly similar to that of the national database. However, contrary to the national database, prescription drugs that are not reimbursed (i.e. oral contraceptives, hypnotics, sedatives, dieting products and certain antibiotics) are not covered.

Funen County Patient Administrative System (FPAS) holds data on all hospital contacts and discharge diagnoses for the population of Funen since 1977 for inpatients and since 1989 for outpatients. The diagnoses have been encoded according to the International Classification of Diseases 10th revision (ICD-10) since January 1994.

The laboratory database of Odense University Hospital (NetLab) is a clinical laboratory system, which holds information on all blood samples analysed at various hospital laboratories in the Funen area since November 1999. The coverage includes both primary and secondary health providers as well as inpatients and outpatients.

Linkage was performed using a unique personal identifier, the Danish Central Person Registry Code, which is assigned to all Danish citizens since 1968 [22].

Study drugs

We included all prescriptions for exenatide twice-daily and liraglutide. Exenatide twice-daily has the ATC code A10BX04 and a DDD of 15 μg. Liraglutide has the ATC code A10BX07 and a DDD of 1.2 mg.

We excluded prescriptions for exenatide in its once-weekly formulation, as it was introduced late in the study period and

was rarely used (234 unique subjects within the study period). Lixisenatide was not included at it was marketed in Denmark after the study period had ended (15 April 2013).

In Denmark, there is no upper limit to the amount of drug that can be prescribed at a time. However, patients most frequently fill their prescription at approximately 3-month intervals.

Analysis

To structure the description of the analysis and the presentation of the results, we divided the analysis into five questions that collectively describe the use of GLP-1 analogues in Denmark.

What is the incidence rate of treatment with GLP-1 analogues?

The incidence rate was calculated per quarter by dividing the number of incident users in each quarter of our data by the estimated person-time at risk, using the size of the Danish population by 1 January in the same year, for each GLP-1 analogue separately. The incidence rate is expressed per 1,000 person-years. We furthermore calculated the percentage of users who by 6 months after their first prescription had redeemed a second prescription, only considering users incident prior to 1 June 2012 to ensure sufficient follow-up.

What is the prevalence proportion of treatment with GLP-1 analogues?

For the first day in each quarter, the number of persons currently treated (point prevalence) was estimated by finding the number of unique persons that had redeemed a prescription that covered this day. As the prescribed daily dose is not recorded in our data, we defined the duration of the single prescription as the redeemed quantity divided by the minimum recommended daily dose (1.2 mg for liraglutide and 10 μg for exenatide) and adding 20 % to account for non-compliance and irregular prescription renewal. The prevalence proportion was calculated per quarter among all Danish citizens on 1 January the same year, for each GLP-1 analogue separately.

Furthermore, we calculated age-specific prevalence proportions in 10-year bands and region-specific prevalence proportions for the five Danish regions. These two analyses were done taking the average over the four quarters in the last year of our data (2012).

Which drugs relevant to the treatment of type 2 diabetes are used by users of GLP-1 analogues?

To describe concomitant drug use both prior to and after initiation of treatment with a GLP-1 analogue, we first identified the date of the first prescription for either exenatide or liraglutide (index date) for each subject. We then calculated the user prevalence of certain pre-specified drug classes within 6 months prior to the index date and 6 months after the index date respectively. As we required 6 months of follow-up, we only included users who had an index date prior to 30 June 2012, and furthermore excluded users who died or who did not redeem a second prescription for a GLP-1 analogue during the follow-up period. We included the following drugs in the analysis:

1. Antihypertensives, subdivided into beta-blockers (ATC, C07), calcium-channel blockers (C08), thiazides (C03A, C09BA and C09DA), angiotensin-converting enzyme (ACE) inhibitors (C09A and C09B) or angiotensin II receptor (ATII) antagonists (C09C and C09D)
2. Cholesterol-lowering drugs, subdivided into statins (C10AA) and other (C10A, excluding C10AA)
3. Anticoagulant drugs, subdivided into low-dose aspirin (B01AC06), clopidogrel (B01AC04), vitamin K antagonists (B01AA) and other (remaining ATC codes within B01A)
4. Antidiabetics, subdivided into metformin (A10BA02), sulphonylureas (A10BB), insulins (A10A), DPP-4 inhibitors (A10BH) or other (remaining ATC codes within A10).

Which dose of GLP-1 analogue do patients use per day?

This analysis was only done for subjects who redeemed a prescription within the last year of our data (2012). As the DNPR does not contain dosage information, we estimated the daily doses for GLP-1 analogues using renewal patterns, i.e. the amount of drug picked up at each collection and the time between collections. The "current dose used" was calculated for each user as follows.

The amount of drug used per day in a period between two dispensings was calculated as the amount of active drug substance redeemed at the first prescription divided by the number of days between the two prescriptions. The '"current dose used" was then calculated as a moving average of the drug used per day in the last three periods, weighed by the length of each period. For a patient redeeming 20, 40 and 20 mg each with a 30-day interval, the "current dose used" would then be 0.67 mg at the time of the second prescription and 1.00 mg at the time of the third prescription.

Only periods starting within 365 days before the given prescription were included in the moving average. If only

one or two periods were defined in this interval, i.e. because only two or three prescriptions were redeemed, then the moving average was calculated using only one or two periods. For the same reason, no dose used was calculated if a prescription was the first prescription in a year. Using the above method, we calculated the distribution of "current doses used", using the value for each user at the time of the last prescription within 2012, for users of liraglutide and exenatide respectively.

What are the baseline characteristics of incident users?

We first calculated the incidence rate specified by age (in 5-year intervals), gender and type of drug, over the entire study period. To further describe these subjects we identified the subgroup of incident users who were included in the NetLAB, FPAS and OPED databases (only updated until 31 June 2012).

Via NetLAB, we identified the last measured value before the index date for HbA_{1C}, low-density lipoprotein (LDL) cholesterol, estimated glomerular filtration rate (eGFR), fasting plasma glucose and fasting C-peptide (only including measurements <12 months from the index date). Via OPED we identified the number of years since the first prescription for any antidiabetic drug (ATC, A10) as a proxy for the duration of diabetes and the type of prescriber (hospital doctor, general practitioner or unknown) who issued the incident prescription. Lastly, we used FPAS to identify the proportion of incident users that at any time prior to the index date had been admitted with a discharge code indicating ischaemic heart disease (ICD10, I20–25), heart failure (I50), hepatic failure (B18, K70, K72–4), inflammatory bowel disease (K50–51), proliferative retinopathy or maculopathy (H352, H360) or hypertension (composite measure of diagnoses (I10, I15) or any drug used to treat hypertension (ATC, C03A,C07–C09)). As the early initiators, i.e. those who initiated treatment shortly after the drug was marketed, might differ from those initiating treatment later on, we performed a sensitivity analysis, this time classifying the users into early and late initiators, separated by the median index date.

Results

Over the study period (1 April 2007 to 31 December 2012), we identified 299,871 prescriptions for liraglutide issued to 21,561 subjects and 28,706 prescriptions for exenatide twice-daily issued to 2,234 subjects. For these subjects we furthermore recovered 3,481,306 prescriptions for other medications.

Since the introduction of liraglutide in 2009, the incidence rate of exenatide has fallen from approximately 0.05 per 1,000 person-years to 0.00 (n <5). The incidence rate for liraglutide quickly rose to approximately 0.3 per 1,000 person-years and has been stable between 0.2 and 0.4 since (Fig. 1). By

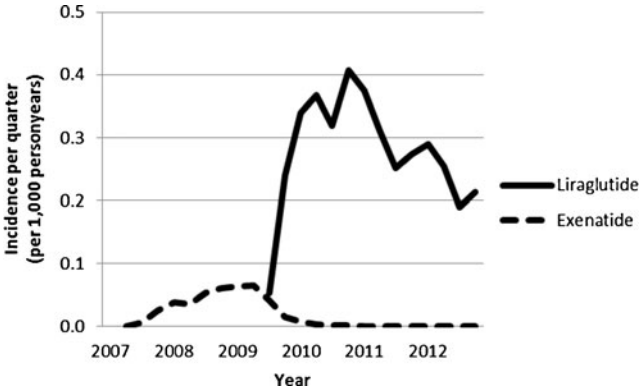

Fig. 1 The incidence rate of liraglutide and exenatide respectively over the entire study period (1 April 2007 to 31 December 2012)

6 months after their first prescription, 93 % and 87 % had redeemed a second prescription for liraglutide and exenatide respectively.

These incidence patterns led to a steeply and steadily increasing prevalence proportion for liraglutide, reaching 2.4 per 1,000 inhabitants in the last year of our data (Fig. 2). The age-specific prevalence proportions for the last year of our data can be seen in Table 1. The region-specific prevalence showed quite different utilization patterns with almost twice the proportion of users in the region with the highest intensity of treatment (Region Sealand, 3.22 per 1,000 inhabitants) compared with the region with the lowest intensity of treatment (Region South, 1.84 per 1,000 inhabitants; Table 2).

The introduction of a GLP-1 analogue was not associated with any changes in concomitant treatment with antihypertensives, cholesterol-lowering drugs or anticoagulants (Table 3). Furthermore, users of exenatide and liraglutide were found to be comparable with regard to co-medication. Metformin was used in the before-period by 78 % and 81 % of the users of liraglutide and exenatide respectively, and 83 % and 84 % in the after-period (Table 3). Twelve percent (n =2,223) of liraglutide users did not use metformin or sulphonylurea drugs in the after-period. The corresponding

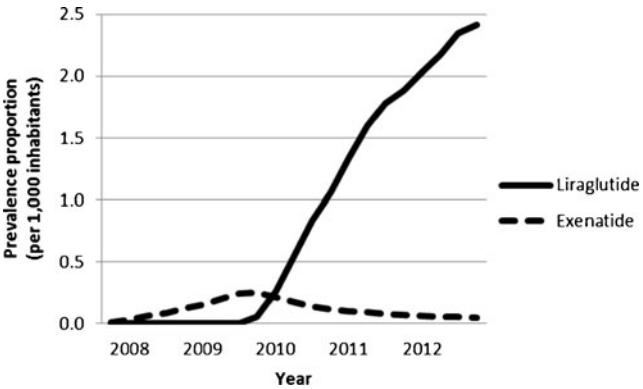

Fig. 2 The prevalence of liraglutide and exenatide over the entire study period (1 April 2007 to 31 December 2012)

Table 1 Age-specific prevalence proportions (per 1,000 inhabitants) on average during 2012

Age group	Liraglutide	Exenatide
20–29	0.13	0.00
30–39	0.62	0.01
40–49	2.06	0.06
50–59	4.93	0.12
60–69	6.96	0.17
70–79	4.53	0.09
80–89	0.86	0.02
90+	0.08	0.00

figure for exenatide was 10 % (n = 204). Overall, 38.5 % (n = 6,877) of liraglutide users and 43.2 % (n = 878) of exenatide users used insulin concomitantly with their GLP-1 analogue (Table 3). 7.2 % (n = 1,286) of liraglutide users and 7.3 % (n = 148) of exenatide users only used insulin in addition to their GLP-1 analogue.

The average daily dose used was calculated for users in the last year of our data (2012). For liraglutide (n = 16,906), the average dose was 1.34 mg/day with 48 % of users using 0.96–1.44 mg/day, 30 % using 1.44–2.16 mg/day and 22 % using other doses. For exenatide (n = 329), the average dose was 16.4 μg/day with 14 % of users using 8–12 μg/day, 57 % using 16–24 mg/day and 28 % using other doses. These dosage bands correspond to recommended doses for both drugs ±20 %. The full distributions for the average daily dose can be seen in Fig. 3.

The average age for incident users of liraglutide was 58 and 57 years for men and women respectively. The corresponding figures for exenatide were 56 and 55 years. The full age distribution can be seen in Fig. 4.

In the regional databases of NetLAB, FPAS and OPED, we identified 929 and 122 incident users of liraglutide and exenatide respectively. The baseline characteristics for these subjects are shown in Table 4. Median HbA_{1c} was 8.3 % for users of liraglutide and 8.5 % for users of exenatide. Prevalence of missing values was acceptable for HbA1c, LDL cholesterol and renal function (5.7–12.2 %) and very high for fasting plasma glucose and C-peptide (62.3–70.9 %). No significant changes were observed when stratifying by users initiating before and after the median index date (early vs late initiators), except that the proportion of liraglutide users with very low kidney function (eGFR < 30 ml/min) was 14.8 % among early initiators and fell to 5.6 % among late initiators.

Table 2 Region-specific prevalence (per 1,000 inhabitants) on average during 2012

Region	Liraglutide	Exenatide
Capital Region	2.26	0.03
Sealand Region	3.22	0.04
North Region	1.89	0.05
Mid Region	2.11	0.08
South Region	1.84	0.07

Discussion

To our knowledge this is the first study to map the utilisation of the GLP-1 analogues exenatide twice-daily and liraglutide in a real-life clinical setting covering a whole country. Liraglutide essentially displaced exenatide on market entry in 2009, resulting in a steeply increasing prevalence for liraglutide during the study period. This utilisation pattern was accompanied by distinct differences in treatment intensity among the five Danish geographical regions.

Our study has several strengths. First, the use of the DNPR allows us to evaluate the drug use of the entire population of Denmark, thereby ruling out any potential selection bias, from market entry of the two drugs and onward. Second, we can do so with very little lag-time, including data up to and including the fourth quarter of 2012. Last, the DNPR has been found to have a very high data coverage and data validity of the variables used in our study [19]. It is a limitation that the DNPR does not contain complete dosing instructions, which required us to estimate doses used based on sequential assumptions.

While metformin remains the drug-of-choice for first-line pharmacotherapy in the treatment of type 2 diabetes according to both national and international guidelines, the logical second-line treatment alternative seems less obvious [5, 6]. Also, the best alternative to metformin as monotherapy (e.g. when metformin is not tolerated) is also uncertain. The choice is dependent on, for example, individual patient preferences and risk factors, drug properties and treatment price. GLP-1 analogues are only licensed as add-on treatment to metformin, sulphonylureas and/or thiazolidinediones. Exenatide twice-daily is also licensed as adjunctive therapy to basal insulin with or without metformin. Administration of GLP-1 analogues as mono-therapy is therefore considered off-label use. As with sulphonylureas, thiazolidinediones and DDP-4 inhibitors, the GLP-1 analogues have glucose-lowering properties comparable to metformin [5, 23]. Furthermore, GLP-1 analogues are at little risk of inducing hypoglycaemia, exert a modest blood pressure-lowering effect and reduce body weight [11, 24–32]. However, the long-term effect on mortality and cardiovascular risk remains undetermined. In 2011, exenatide and liraglutide together accounted for approximately 7 % of the total DDD consumption in Denmark within non-insulin antidiabetics [33]. Whether this share expresses the correct proportion of patients where GLP-1 analogues can be considered a rational second alternative

Table 3 Drug classes relevant to the treatment of diabetes used by patients on liraglutide and exenatide in the 6-month period before and six month period after they received their first prescription for the GLP-1 analogue

	Liraglutide (n = 17,866)		Exenatide (n = 2,032)	
	Before (%)	After (%)	Before (%)	After (%)
Antidiabetic drugs				
Metformin	78.2	83.4	81.3	84.1
Sulphonamides	32.4	19.3	40.4	34.7
Insulin	39.3	38.5	45.4	43.2
DPP-4 inhibitors	21.4	3.9	15.5	3.4
Other	3.7	1.2	9.3	4.8
Number of antidiabetic drugs[a]				
0	3.8	5.0	2.2	2.3
1	26.8	47.5	21.4	34.3
2	54.9	43.0	57.2	53.7
3	13.6	4.3	17.3	8.8
≥4	1.0	0.3	1.9	0.9
Antihypertensives				
Beta blockers	27	28	27	27
Calcium channel blockers	30	32	28	30
Thiazides	17	17	20	20
ACE inhibitors	43	44	43	46
ATII antagonists	31	33	35	36
Cholesterol-lowering drugs				
Statins	71	74	74	76
Other	4	5	4	4
Anticoagulant drugs				
Low-dose aspirin	43	45	46	49
Clopidogrel	3	3	2	2
Vitamin K antagonists	5	5	5	6
Other	3	3	2	2

ACE angiotensin-converting enzyme, *ATII* angiotensin receptor II, *DPP-4* dipeptidyl peptidase 4

[a] Not counting prescriptions for GLP-1 analogues

remains unknown. As this is the first nation-wide study on GLP-1 analogue utilization, we have no point of reference in terms of comparing the observed consumption, incidence and prevalence numbers with other national or international studies.

Incidence and prevalence

The steeply increasing prevalence proportion for liraglutide during the study period is noteworthy. The introduction of twice-daily exenatide in 2007 appears to only have had a moderate impact on drug sales, compared with the steep sales increase seen for liraglutide since market entry in 2009. These findings cannot be explained by differences in drug properties or treatment prices, as the two drugs are recommended as equal alternatives in both previous and current national and international treatment guidelines. Instead, the drug use pattern seen for liraglutide is suspected to be affected by the fact that the drug originates from a Danish drug manufacturer. This assumption is supported by the distribution of consumption (measured in DDD per 1,000 inhabitants per day) of liraglutide in 2012 in the Nordic countries: 2.8 (Denmark), 1.0 (Finland), 1.2 (Iceland), 0.7 (Sweden) and 0.8 (Norway) [33–37].

Denmark is divided into five distinct geographical regions whose main responsibility is the provision of hospital services. The regions have between 0.6 and 1.6 million inhabitants and differ in size and therefore also in population density. Although there are socio-economic differences across the five regions they are similar in demographic parameters such as gender and age distribution [38]. We observed very large regional differences in prevalence. For the last year of data the regional prevalence for liraglutide given per 1,000 inhabitants varied from 1.84 (South Region) to 3.22 (Sealand Region) (Table 2). Exploratory analyses of regional-specific incidence rates (data not shown), showed that uptake of the GLP-1 analogues happened simultaneously, but stabilized at different levels in each region. As such, the observed differences in the prevalence proportions were not simply a matter of a lag-effect, i.e. differences in the rate with which the

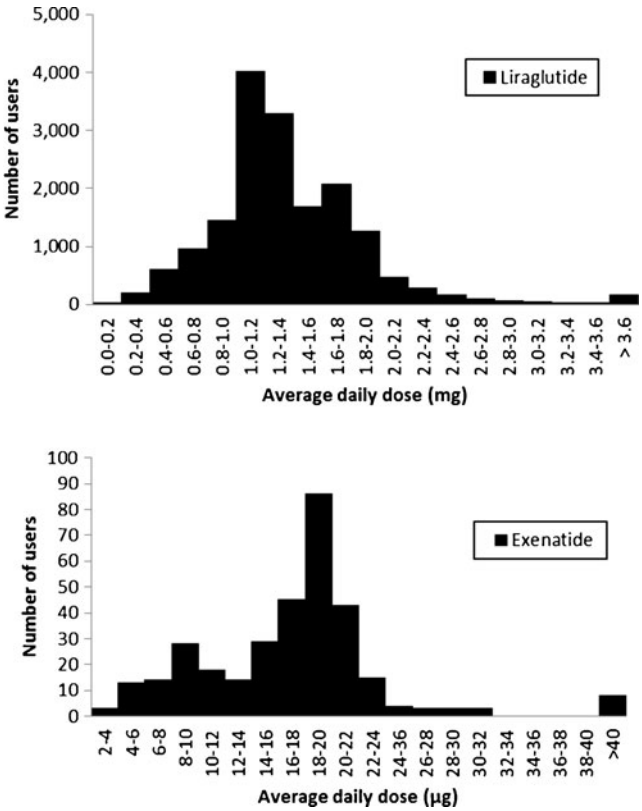

Fig. 3 The average daily dose for users in the last year of our data (2012), taken as the floating average over the last up to four prescriptions

drugs were introduced in each region. No minor demographic variations in the regional gender and age distribution can account for an almost two-fold difference in therapeutic intensity. Accordingly, differences are most likely explained by differences in therapeutic tradition (e.g. prescribing habits and clinical experience of single prescribers), marketing campaigns by drug companies or socio-economic differences. Future research will be able to determine which of these factors in fact is responsible for the observed differences.

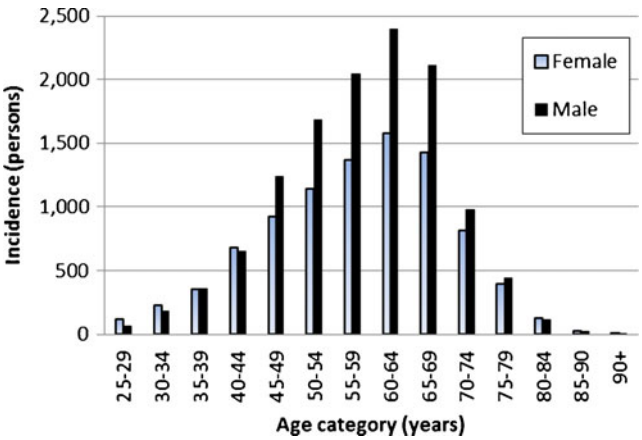

Fig. 4 The age distribution among incident users of liraglutide over the entire study period (1 April 2007 to 31 December 2012). The distribution for exenatide is not shown as it was found to be similar

Which drugs relevant to the treatment of diabetes are used by patients on GLP-1 analogues?

In type 2 diabetes, ACE inhibitors, statins and low-dose aspirin are considered first-line treatment for treating hypertension, dyslipidaemia and risk of thrombosis respectively [6]. Only the observed user proportions for antihypertensives are not largely consistent with guidelines and a prescription for a GLP-1 analogue did not appear to change the use pattern for antihypertensives, cholesterol-lowering drugs or anticoagulant drugs in the 6-month period before and after patients received their first GLP-1 analogue prescription.

As suspected when a logical second-line treatment alternative is absent, no clear use pattern of antidiabetic therapy can be concluded from our analyses. Both GLP-1 analogues are primarily used in combination with metformin as dual therapy or in combination with metformin and sulphonylureas or metformin and insulin as triple therapy. Interestingly, the majority of subjects not using either metformin or sulphonylureas were using GLP-1 analogues with insulin alone as dual therapy. While combinations with metformin and sulphonylureas are consistent with both national and international treatment guidelines, only exenatide has proved to be clinically beneficial in combination with insulin as dual therapy and as such has a licensed indication for this use [39, 40]. However, the evidence is still limited, and current Danish treatment guidelines are therefore reluctant to recommend any GLP-1 analogue/insulin combination [5].

Which dose of GLP-1 analogue do patients use per day?

The average daily doses used for exenatide and liraglutide were 16.4 μg/day and 1.34 mg/day respectively, consistent with the DDDs established by the WHO.

The maintenance dose can be a determinant when selecting between the two GLP-1 analogues. Current Danish treatment guidelines consider the glycaemic effect of exenatide 20 μg/day and liraglutide 1.2 mg/day to be equieffective [23]. Up until now, the treatment price for liraglutide 1.2 mg/day has equalled exenatide 20 μg/day. However, there is a 1.5-fold price increase between liraglutide 1.2 mg/day and 1.8 mg/day leading to a substantial difference in the yearly treatment price. With the majority of patients in our sample using a lower dose of liraglutide, there are no strong economic reasons to prefer one drug over the other.

What are the baseline characteristics among incident users?

In Denmark, the goals for treating hyperglycaemia are individualised according to patient risk factors. Target HbA1c values are as follows: Uncomplicated patients <6.5 %, patients with risk of hypoglycaemia <7 % and complicated patients <7.5 % [5, 6]. Only for the minority of patients where the

Table 4 Baseline characteristics among incident users of liraglutide and exenatide. Only users covered by the regional prescription, hospital and laboratory databases are included

	Liraglutide ($n=929$)	Exenatide ($n=122$)
Age, years (IQR)	60 (51–66)	54 (45–62)
Men, *n* (%)	528 (56.8 %)	73 (59.8 %)
Women, *n* (%)	401 (43.2 %)	49 (40.2 %)
Duration of diabetes, years (IQR)	6.3 (3.1–10.7)	6.4 (3.0–10.3)
HbA_{1c} (%), mean (IQR)	8.3 (7.5–9.4)	8.5 (7.6–9.8)
LDL cholesterol (mM), mean (IQR)	2.2 (2–3)	2.4 (2–3)
Fasting plasma glucose (mM), mean (IQR)	10.7 (9–13)	11.2 (9–15)
Fasting C-peptide (nM), mean (IQR)	1,208 (816–1,665)	1,327 (969–2,130)
Kidney function (eGFR)[a]		
<30 ml/min, *n* (%)	94 (10.1 %)	11 (9.0 %)
30–60 ml/min, *n* (%)	91 (9.8 %)	($n<3$)
>60 ml/min, *n* (%)	91 (9.8 %)	14 (11.5 %)
Unknown, *n* (%)	653 (70.3 %)	95 (77.9 %)
Prescriber of first prescription		
General practitioner, *n* (%)	335 (36.1 %)	34 (27.9 %)
Hospital, *n* (%)	518 (55.8 %)	81 (66.4 %)
Unknown, *n* (%)	76 (8.2 %)	7 (5.7 %)
Previous diagnoses		
Ischaemic heart disease, *n* (%)	162 (17.4 %)	22 (18.0 %)
Heart failure, *n* (%)	42 (4.5 %)	6 (4.9 %)
Hepatic failure, *n* (%)	5 (0.5 %)	($n<3$)
Inflammatory bowel disease, *n* (%)	12 (1.3 %)	($n<3$)
Retinopathy or maculopathy, *n* (%)	71 (7.6 %)	7 (5.7 %)
Hypertension, *n* (%)	358 (38.5 %)	49 (40.2 %)

IQR interquartile range, *HbA1c* haemoglobin A1c, *LDL* low-density lipoprotein, *eGFR* estimated glomerular filtration rate

[a] eGFR was estimated using the MDRD equation [42]

target is symptom relief is a HbA1c level between 7.5 and 9.0 % accepted [6]. In our subsample of incident GLP-1 analogue users, the high baseline HbA1c values (8.2–8.6 %) demonstrate that either initiation of or change in current antidiabetic treatment was warranted. Based on these observations GLP-1 analogues can be considered a valid treatment option. A considerable proportion of patients in both groups had mild renal impairment and a previous history of ischaemic heart disease and/or hypertension. The average duration of diabetes before GLP-1 analogue initiation was 3–4 years. In the clinical development programmes for exenatide twice-daily and liraglutide patients had HbA1c levels at screening in the range 7.0–11.0 % [11, 24–32]. Studies of liraglutide excluded patients on insulin therapy and patients with renal or liver dysfunction or with active cardiovascular disease, including history of myocardial infarction within the past 6 months and/or heart failure (New York Heart Association class III and IV) [11, 27, 31]. Studies of exenatide excluded patients with evidence of clinically significant co-morbid conditions [24–26, 28–30, 32]. On average, patients in these trials had a duration of diabetes, which was twice as long as that seen in our sample [11, 24–32]. As thereby shown, there are relevant differences between the patients in the clinical settings and the enrolled patients in the randomized trials. As also observed for other treatment areas, trial patients do not accurately represent the majority of patients in the actual clinical population [41]. However, whether these differences have actual clinical implications for the effectiveness of GLP-1 analogues remains unanswered.

Although the prescriber was unidentifiable in almost one fifth of prescriptions, the prescriber profile for incident users shows that treatment initiation is most often performed by hospital physicians (see Table 4). Unlike type 1 diabetes, the treatment of type 2 diabetes in Denmark is not considered a specialist task, and pharmacological treatment is encouraged to start at the general practitioner. However, some treatment combinations, including the GLP-1 analogues and insulin, are considered to be best handled by specialists and this may explain the high proportion of hospital prescriptions seen in our study.

Conclusion

We have shown that liraglutide is used in Denmark at a disproportionately high level compared with exenatide twice-daily and that large regional differences exist in the use pattern for both drugs. The use of GLP-1 analogues in

combination with insulin and other treatment changes observed coinciding with GLP-1 analogue initiation warrants further investigation. At present, other GLP-1 analogues are ready to be marketed with exenatide and liraglitude. In addition, drug companies are conducting studies to investigate the effect of long-term treatment with GLP-1 analogues on hard end-points such as cardiovascular disease and mortality, and to substantiate the evidence of the weight reduction capabilities of GLP-1 analogues. It will be interesting to see whether new drugs and results from these studies will change the use pattern observed in Denmark.

Conflicts of interest FKK has received lecture fees from AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly and Company, Gilead Sciences, Merck Sharp & Dohme Ltd, Novo Nordisk, Ono Pharmaceuticals, Sanofi and Zealand Pharma, is an advisory board member at Eli Lilly Danmark, Bristol-Myers Squibb/ AstraZeneca, Sanofi and Zealand Pharma, and has consulted for AstraZeneca, Gilead Sciences, Ono Pharmaceuticals and Zealand Pharma. The remaining authors declare no conflicts of interest.

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