Trends in prescribing of antidiabetic medicines in primary care: a systematic review of the period 2000-2018

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Abstract

Clinicians makes informed treatment choices based on available evidence and treatment guidelines. The aim of this review is to examine changes in the use of diabetes medicines prescribed to treat type 2 diabetes mellitus (T2DM) in the primary care setting. The use of antidiabetic medicines has evolved between 2000 and 2018. The number of drug classes available for treatment has increased steadily over these years, impacting on prescribing patterns. It was not possible to determine how clinicians make choices about the medicines they prescribe for T2DM, or what influences those choices.

1.0 Background

In 2017 globally, 425 million adults were estimated to suffer from type 2 diabetes mellitus (T2DM) and this number was expected to increase by 48 % over the following 25 years[1]. Type 2 diabetes mellitus is the most common type of diabetes among adults. The prevalence of T2DM is associated with obesity and unhealthy lifestyles[2].

An increased patient-centred approach to treatment is key and an increasingly important goal for a health care system. Given the nature of the disease, it is required that both patients and healthcare professionals collaborate closely to avoid both short-term and long-term life-threatening complications related to diabetes [3, 4]. An effective management strategy for T2DM is suggested to include adherence to medication regimens (oral tablets and insulin injections) as well as a change in lifestyle. This includes increased physical activity, dietary changes, smoking cessation and the close monitoring of blood glucose levels[5]. Furthermore, it is important to acknowledge the benefits of shared decision-making when behaviour changes to the patient's current lifestyle are required[6-9]. Treatment guidelines are developed to support health care professionals choosing appropriate treatment for patients with T2DM. Most countries have their own national prescribing guidelines for the treatment of diabetes e.g. *The National Institute of Excellence* (NICE) [10] in The United Kingdom (UK) and *Indsatser for Rationel Farmakoterapi* (IRF) in Denmark [11]. The American Diabetes Association (ADA), form part of the ADA and the European for the study of Diabetes (EASD) Association consensus approach aiming to offer joint recommendations on the management of hyperglycaemia [12]. Despite constantly evolving treatment guidelines, many patients with T2DM are still inadequately controlled.

In recent years, several new drug therapies have been introduced in the market. The major hypoglycaemic agents approved for treatment for the management of T2DM are biguanides (also referred to as metformin in this paper, which is the only approved drug in this drug class), thiazolidinediones (TZD), dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1RAs), sulfonylureas (SU), sodium-glucose co-transport inhibitors (SGLT2-I) and insulin. **Table 1**, gives a historical overview of the introduction of hypoglycaemic agents [13]. Each drug class

has its own mechanism of action. The use of a variety of glucose-lowering drugs is consistent with the heterogenous and progressive pathophysiology of the condition. The choice of drug is guided by drug- and patient-specific characteristics such as safety profile, tolerability, patient co-morbidities, cost and patient preferences [14]. Glycemic efficacy is often used as a marker of the metabolic effectiveness of the prescribed treatment.

<Table 1 Overview of introduction of treatment options for Type 2 Diabetes Mellitus>

Previous reviews have looked at cost of medicines, effectiveness and safety of monotherapy, treatment shared decision-making and outcomes, strategies to prevent T2DM [15-17].

Prescription data indicates that both old and new antidiabetics are being widely prescribed, but the evolution over time regarding the use of antidiabetic medicines remains poorly understood. The current review aims to fill this gap and includes original research articles published after 2000 on the use of antidiabetics to evaluate prescription trends. The aim was to conduct a systematic review to examine changes in the use of diabetes medicines prescribed to treat T2DM in the primary care setting.

2.0 Methods

2.1. Scope of review: Inclusion and exclusion criteria

This systematic review was conducted in accordance with the Cochrane Handbook for Systematic Reviews [18] and is reported by using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19]. The 27-item PRISMA check-list is available as supplementary materials. The review questions and methods were predefined and were not changed during the review process.

Inclusion and exclusion criteria for the review are described in **Table 2**. The search strategy for this systematic review was designed to retrieve population-based studies from primary care with a focus on prescription trends over the past two decades. Empirical studies considered for this review met the following inclusion criteria: a) included both males and females; b) adults (aged ≥ 18 years); c) primarily focused on antidiabetic medicine use; d) patients diagnosed with T2DM; e) published between January 1, 2000 and December 2018) published in English. As there is no set rule for limiting publications to publication by date, a 10-year timeframe is generally considered to be inclusive of recent studies[20]. In this review, the studies from the past two decades were included.

<Table 2: Study inclusion and exclusion criteria>

2.2. Search strategy

A systematic search in the literature was conducted in the following electronic databases: PubMed, Medline, Springer Link, Scopus and Science Direct. The search was conducted using the following terms for title and abstract: (“type 2 diabetes”), (“diabetes”), ("antidiabetic"), (“glucose lowering drugs”), (“prescription pattern”), (“prescription patterns”),("prescription rate"), ("antidiabetic prescribing trends"), (“patterns”), (“trends”), ("prescription rate"), ("antidiabetic prescribing trends"), (“prescription”) , (“medication”) , (“medicine”) , (“drugs”). The mentioned key terms were used alone and in combination using the Boolean terms “AND” and “OR”. Furthermore, filters for full-text articles, English language and years 2000-2018 were chosen. These filters were used to ensure only peer-reviewed articles were included. References cited in the reference list of each identified original research were scanned for any additional articles that would be relevant to this review; these were subsequently also scanned for reviews and studies which may have been relevant, and which were subject to the same eligibility evaluation.

Data extraction and synthesis

After possible studies were identified, all retrieved titles were screened by the primary investigator (SR) to determine their potential relevance. The assessed abstracts were independently assessed by another investigator (ZUB) against inclusion criteria. Full papers from potential studies were independently assessed by the investigators (SR and ZUB).

All studies selected for this systematic review were screened by two reviewers independently to validate the results (SR and ZUB). The data from all the retrieved studies were subsequently collected and tabulated using a form developed by the lead author. The extracted information included study

design, study participants and settings, eligibility criteria, sample size, described trends, outcomes measure, , statistical methods.

2.3. Quality assessment

The lead author independently assessed the risk of bias of each of the included studies and discussed their assessments with other two authors to achieve consensus. The Newcastle-Ottawa Scale (NOS) cohort version [21] was used to assess the methodological quality of the included cross-sectional studies on changes in prescribing trends over the study period. The modified Newcastle-Ottawa Scale was selected because it was easier to use and considered reliable to measure biasness in cross-sectional studies Methodological quality was not used as a criterion for inclusion or exclusion [21].

3.0 Results

3.1 Selection of articles for review

Figure 1 summarises the identified, screened and included articles for review. Initially 12,431 peer-reviewed articles were identified, and an additional 36articles were identified through hand-screening of articles. After removing duplicates, 5,578 articles remained for title and abstract screening. Articles which did not meet the inclusion and exclusion criteria described in table 2 were not carried forward for screening. Ninety three full-texts were screened for eligibility of which 12 articles met all the inclusion criteria.

<Figure 1: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis)) flow diagram>

3.2 Assessment of study validity

All eligible studies were associated with changes in the prescribing of antidiabetic medicines. Table 3 provides quality scores for the included studies, assessing the risk of bias. The main reasons for loss of score was response rate not being included.

<Table 3: Quality assessment of the included cohort studies on the changes in prescribing trends over the studies period>

3.3 Study characteristics

The included studies (n=12) were conducted over a number of countries including: France (n=2), England and Wales (n=1), Germany (n=2), UK (n=5), Spain (n=3), Netherlands (n=1), Italy (n=1) and United States of America (n=1). Overbeek [22], was the only study collecting data from more than one country. The population included in the studies all had [ICD]-code diagnosis for T2DM. The main study characteristics are summarised in table 4. All included studies examined the overall use of antidiabetic medicines as well as changes in the use of these medicines. Data in the included articles were presented in a variety of ways, so this information was consolidated and presented as text only in this article to contrast and comparison. In accordance with the exclusion criteria (table 2) findings on switching medicines and discontinuation of medicine were excluded.

<Table 4: Study characteristics>

3.4 Trends in the use of antidiabetic medicines

Sulfonylureas

The described prescribing trends in France [23] showed that a sulfonylurea was the most commonly prescribed drug, however the use of sulfonylureas has decreased from 35 % to 29% between 2001 and 2003. The European countries surveyed by Overbeek [22] reported sulfonylureas to be the second most commonly prescribed drug class across all countries however this study also reported a decrease in the use of sulfonylureas in the Europe (2008-2012). In Spain (2009) [24] and Germany (2004 to 2010) [25] sulfonylureas were reported to be prescribed for about 17% and 12% of patients, respectively. Filion et al. [26] reported a decrease in the number of patients receiving sulfonylurea

prescriptions in the period 2000 to 2006. Mata-Cases [27] reported, a decrease in the rate of sulfonylurea prescriptions in the period 2007 to 2013 (34% to 26%).

In Germany, 10% of patients were reported to be initiated on sulfonylurea monotherapy (2003 to 2009) [28] . In England and Wales this number was 16 % (200- to 2012) [29]. Maguire et al. [30] reports that the use of sulfonylureas as first-line treatment decreased from 10% to 6% in the period from 2006 to 2010 in the UK. A third UK study [31] reported the use of the sulfonylurea group as first-line treatment to peak in 2000 (51.1 %) and then declined again by 2013 (6.3 %). Lastly, Wilkinson [32] reported sulfonylurea to be used for 15% of patients in the studied period (2000 to 2017).

Metformin

An increase (17% to 21%) in the use of metformin was reported during the studied period in France (2001 to 2003) [23]. A similar trend was described in Germany (2004 to 2010) [25] where 20 % of patients were prescribed metformin. Mata-cases (2014) [24] reported that 41% of the patients in Spain were prescribed metformin. Metformin was also reported to reach its peak as a first-line treatment in the UK in 2013 (91.0 %) [31] and another study [30] conducted over the same time-period showed similar results (90.7%). Filion et al. [26] reported that from 2000 to 2006 there was an increase in the rate of metformin prescriptions. Likewise, Mata-Cases [27] reported an increase in the prescription rate of metformin prescriptions in the period 2007 to 2013 (49% to 68%).

Datta-Nemdharry and colleagues (2000 to 2012) [29] reported 80% of the patients to be initiated on metformin. Likewise, other studies reported an increase in the use of metformin as treatment initiation; 63% to 80% (2003 to 2009) [28], 84 % to 91 % (2006 to 2010) [30] and 45% to 91% (2000 to 2013) [31]. Overbeek et al. (2008 to 2012) [22] reported metformin monotherapy to be the most common initial treatment ranging from 65% to 88% across the surveyed countries (Netherland, Spain, UK, Italy and France). In the studied period in the UK, Wilkinson [32], observed that the 73% of patients were reported to be initiated on metformin.

Insulin

An increase in the use of insulin as monotherapy (1.71 % to 2.27%) was reported in France (2001-2003) [23]. In Spain, Mata-cases (2014) [24], reported that 8 % of the patients were treated with insulin. This number was 11% among German patients (2004 to 2010) [25]. On the contrary, a stable number of prescriptions for insulin (20% to 24%) was reported in the UK (2000-2013) [31]. Fillion [26] reported that a 10 % increase in the rate of insulin prescriptions was observed (2000 to 2006).

Twelve percent of the patients were reported to receive insulin as first-line treatment (2000 to 2012) [29]. Maguire et al. (2006 to 2010) [30] reported a decrease (10% to 2%) in the use of insulin as first-line treatment. In the UK in 2013, the reported figures were as low as 1.7 % [31]. Datta-Nemdharry and colleagues (2017) reported that when insulin was used early in treatment it was used to achieve rapid glycaemic control. Wilkinson reported 2% of patients were reported to be initiated on insulin (2000 to 2017) [32].

Thiazolidinediones

Prescriptions of thiazolidinediones were reported to have had a rapid increase as soon as these agents became available on the market. Sharma et al. [31] reported, thiazolidinediones to gradually increase since they were launched and reached their peak in 2007 (16 %). Filion and colleagues (2000 to 2006) [26] reported that thiazolidinediones were launched early in the study and hence a rapid increase was observed in the overall prescription rate. A decrease in the use of thiazolidinediones was reported in The Netherlands, Spain and France [22]. Moreover, the use of thiazolidinediones as monotherapy was withdrawn in France [22]. In Germany (2004 to 2010) [25] the use of thiazolidinediones was reported to be less than 1% while it was reported to be about 8% in the UK (2000 to 2013) [31].

DDP-4

There are reports that DDP-4 inhibitors were frequently prescribed soon after they became available around 2006. Overbeek et al. (2008 to 2012) reported on an increased in the use of DDP-4 inhibitors in France (0% to 27%), UK (<1% to 9%) and Spain (0% to 9%) [22]. The use of DDP-4 inhibitors was reported to remain low in The Netherlands (4%) and in Italy (2%) [22]. Another study conducted in Spain [33] reported a uptake of 13 % in the period 2007 to 2013.

GLP

Overbeek and colleagues [22] reported an increase in the use of GLP-1RAs in France and UK while the use was reported to be decreased in The Netherlands, Italy and Spain. Mata-Cases [27] reported the use of GLP-1RA to increase from 0% to 1% in the period 2007 to 2013.

3.5 Mono- versus combination therapy

While metformin has been reported as the cornerstone of T2DM treatment a variety of drugs has been reported as second- and third-line treatment. In the following we will describe the trends reported in the reviewed studies. Overall, there was an increase in the number of patients on metformin and insulin while treatment with sulfonylureas had declined.

Boyc and colleagues [23] reported a number of patients to be treated with two oral antidiabetics (55.79% to 54.65%), and similarly for patients on one oral antidiabetic plus insulin (5.01% to 54.65%). Furthermore, it was reported that the number of patients receiving oral triple therapy remained stable (6.69% to 5.95%) and two oral antidiabetics plus insulin (1.71% to 1.35%). In Germany [25] it was reported that 43 %, 11% and 4% were prescribed monotherapy, oral combination therapy and oral antidiabetic medicine plus insulin, respectively.

Geier et al. [28] reported combination therapy to be uncommon at treatment initiation. A combination therapy of sulfonylurea and metformin was reported to be used for 2 % of patients[29]. 0.12% of patients received insulin plus another drug class as their first treatment [29]. [30] reported 0.2% of patients to be prescribed combination therapy and of these, 85% received a combination of metformin and sulfonylurea.

4.0 Discussion

4.1 Overall use of antidiabetic medicines

This systematic review set out to understand the evolving patterns of global drug class use for T2DM and found that the overall use of glucose-lowering drugs has increased [26, 34, 35]. This review suggests that the use of glucose-lowering drugs has changed significantly, reflecting the introduction of newer glucose-lowering classes such as thiazolidines, GLP-1RA , DDP-4 inhibitors and SGLT-2 inhibitors as well as a change in recommendations for first-line treatment of T2DM. This trend is ascribed to several factors such as the increased prevalence of T2DM among younger people, obesity and risk factors as well as more aggressive treatment strategies [2, 36]. The historical evolution suggests medicines use has peaked across the drug classes at various times in different countries, dependent on their availability in the global marketplace. As expected, this review has found that men are affected by T2DM more frequently than women [37-39], and this trend is more prevalent with increasing age of the patient. Further, there is a gap in the literature where studies have not been initiated to assess the impact of life-style changes in this context.

4.2 Trends in the use of individual antidiabetic drug classes as monotherapy

Metformin and sulfonylurea use

The small variance in the number of patients reported to be treated with metformin in the surveyed studies and the decline in the of sulfonylurea is not surprising in relation to the national and international diabetes prescribing guidelines [10, 11, 40, 41]. The results from the UK Prospective Diabetes Study (UKPDS) in 1998 [42] has been said to play a major role in this development. After the study was published an increasing number of national and international guidelines were updated to recommend metformin as first-line treatment [12, 43]. The UKPDS [42] showed, that obese patients treated with metformin gained less weight and presented with a lower number of hypoglycaemic events compared with a sulfonylurea and insulin. We further suggest this shift to be due to external factors such as the launch of metformin as a new entity in the USA in the late 1990s [44] and presentation of 10-year data UKPDS data at the EASD Conference in Barcelona [45]. Another reason could be that there are several second generation sulfonylureas available and this contributes to a higher overall prescribing rate for sulfonylureas, as opposed to only metformin being prescribed in its drug class[46].

Insulin

One reason for the increased use of insulin in studies conducted after 2005 is the introduction of long-acting insulins [23, 35]. This was considered a step forward in diabetes care which fulfilled the need for the use of insulin analogues in clinical setting [47].

Numerous longer trials in both T1D [48, 49] and T2DM [42, 50] reported that intensive control of glucose levels in patients with diabetes helps to prevent chronic implications. Likewise, ADA and EASD guidelines advocate for more intensive control of blood glucose [12, 26] with the effect of tight glycaemic control early in the stage of disease having a lasting effect[51]. Older people were found more likely to achieve glycaemic control with HbA1c values ≤ 7%, than younger patients. This pattern was observed in all subgroups regardless of duration of treatment for T2DM and prior cardiovascular disease [52]. One recent trial differs to these findings. The Action to Control Cardiovascular Risk in

Diabetes (ACCORD) study[53], found a small increase in mortality among patients on long-term intensive glucose lowering drugs with HbA1c values ≤ 6%.
Insulin is normally added into treatment of T2DM as a last resort to combat disease progression rather than as initial or early intervention, which reflects where it sits in the hierarchy of treatments recommended by ADA, EASD and NICE. We suggest that the increase in use of insulin reflects the increased in prevalence of T2DM. Further, the condition is presenting earlier in patients, and hence there is an increased need for insulin administration in the population.

Other oral antidiabetic medicines

Thiazolidinediones (TZDs) were received favourably when they were first introduced, but as adverse reactions emerged, physicians were eager for agents that were at least as effective, but without the side effect profile of TZDs. The reported decline in the use of thiazolidinedione in the late 2000s is likely due to the publication of adverse event profiles for these agents resulting in the withdrawal of troglitazone in US and UK markets [44, 54]. This can be due to safety alerts about increased cardiovascular risk [55-57] resulting in reduced number of new users. The FDA also outlined in their published recommendations, that patients treated with a combination of rosiglitazone and insulin were observed to be at higher risk of myocardial ischemia [56]. Following the withdrawal, 8.4 % of rosiglitazone users were switched to pioglitazone [54] which has been linked with an increased risk of bladder cancer, but there is insufficient evidence to withdraw it from the market [54, 58, 59].

The safety profile of DDP-4i's along with several clinical studies on optimal glycaemic control prior to DDP-4i's introduction to the market is suggested to be one of the reasons this class was so rapidly adopted. [60]. In contrast, reduced insulin levels play a significant role in the pathophysiology of Japanese T2DM patients [61] hence is not surprising that DDP-4 inhibitors are reported to be used for treatment initiation [60]. Newer antidiabetics are rarely used for treatment initiation and in the UK[62] this is consistent with the NICE 2009 guidelines which recommended DDP-4 inhibitors to be used as second or third line-treatment when prescribed metformin and sulfonylurea are failed to control the disease. It is also recommended as an alternative to thiazolidinediones.

4.3 Overall use of individual antidiabetic drug classes for treatment initiation

It is estimated that about 50%-60% of patients with T2DM will die from a cardiovascular disease [63] hence it crucial to find treatment pathways which reduce this number. Metformin has consistently been used and recommend as first-line treatment in most guidelines has not shown any significant clinical benefits on mortality or improving microvascular complications [64]. Newer cardiovascular trials show that SGLT-2 have lower events of hospitalization for heart failure events and cardiovascular mortalities as compared to other antidiabetic medicines [65, 66]. Likewise, GLP-1RAs have also shown to reduce cardiovascular outcomes and mortality [67]. However, GLP-1RAs are injectables and hence we see it unlikely to be recommended as first-line treatment.

4.5 Limitations of the study

The studies were included which were using the primary care data. Use of primary care data means that data from secondary care was not included. This can be rationalised by the fact that most of the studies consider the patient to be in treatment for T2DM when they have already been receiving glucose-lowering drugs for a defined period of time, and thus are unlikely to have received any

prescriptions from secondary care.. It should be noted that the used databases do not justify the use of lifestyle interventions and other drugs used to treat comorbidities as a part of the treatment of T2DM.

There are different inclusion and exclusion criteria applied across the studies. Most of the studies classified the patients as having T2DM if they had a diagnosis of diabetes 2 as defined by *International Statistical Classification of Diseases and Related Health Problems[68].* Other studies consider a person to be a user of glucose-lowering drugs when having bought the drug at least once in the year. Because of the structure of data, there is limited knowledge regarding how many patients are treated with diet and lifestyle changes. Some studies published 2000 and 2018 present scarce data on the prescribing patterns, hence they are not included in this review.

4.6 Future implications

Despite the significant amount of work in recent years overall use of glucose lowering drugs and glucose lowering drugs used at treatment initiation, we find that significant gaps in our knowledge remains. There is relatively limited knowledge on the factors influencing physician's prescribing. In addition, there remain ambiguity as to how many patients are successfully treated with diet and exercise. Another gap in our knowledge is whether the doses of each glucose lowering medicine has been pushed to maximum before changing to another glucose lowering drug, and if so after how long time? A systematic evaluation of the prescribing process and how clinicians make decisions would allow for policy changes and guideline development.

5.0 Conclusion

The literature suggests that the number of prescribed antidiabetic medicines used to treat T2DM has increased since the year 2000. The emergence of new therapies has resulted in rapid uptake as there is a genuine therapeutic need for newer, more effective and better tolerated agents for the management of T2DM. Over time metformin has become the first-line drug of choice for physicians which is in-line with the expectations of international guidelines. Regardless of the introduction of newer drugs, outcomes don't seem to have shifted and glycaemic control has not improvedFurther investigation is expected to help improve guidance and dissemination thereof for the management of adults with T2DM.

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Conflict of interest

Sara Ramzan, Peter Timmins, Syed Shahzad Hasan and Zaheer-Ud-Din Babar declare that they have no conflict of interest.

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