REVIEW

TYPE 2 DIABETES MELLITUS PREVENTION

• *prescriptions off-label* •

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Abstract

The prescribing a drug without the indications for which the drug was originally approved by regulators is internationally known as prescribing "*off-label*". **Objective**: To describe the *off-label* prescriptions in type 2 diabetes (DM2) prevention, reported international scientific literature, through an integrative bibliographical review. **Method**: An integrative review was made by searching the Medline international database for review of manuscripts. Selection of these databases was based on the wide range of journals covered by each of them and our goal was to provide an overview of the scientific production devoted to the topic over the timeframe under analysis. The following inclusion criteria were considered during the review: articles published between January 1985 and June 2013; use of the keywords "*off-label* use" OR "*off-label*" OR "*off-label* prescribing" OR "diabetes prevention" OR "prevention" MeSH "diabetes mellitus" entered into the search form, and availability of an abstract in English. **Results**: A total 852 scientific productions were identified, and 30 studies were selected by contain information about the *off-label* prescriptions in DM2. **Conclusion**: The practice of *off-label* prescribing itself has notable benefits. In some situations, an *off-label* prescription is the only treatment available to a patient, either because a more targeted drug is does not exist, or because other methods of treatment are ineffective or unavailable due to patient intolerance. In these situations, *off-label* uses of drugs provide the only chance of restored health.

Keywords: Prevention. Drug therapy. Off-label use. Unlicensed use. Diabetes mellitus.

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INTRODUCTION

Many drugs are prescribed outside the terms of the marketing authorization ("*off-label*") from that approved by the health agency. *Off-label* use of drugs is relatively common in medical practice, even if it's often not supported by strong scientific evidence. *Off-label* therapy is defined as the use of medications for indications that is not mentioned in the approved labeling of the drug; using a drug outside of the recommended dosage range or duration of use; using a drug in certain unapproved patient populations, such as those defined by age, sex, or particular clinical parameters, or intentionally using a medication in a patient who has a known contraindication. It is legal, but there are implications for prescribers, outlined by regulatory bodies of health. Several studies have shown that this is a common practice in various healthcare settings, and studies in the United States have shown that *off-label* use may account for approximately 20% of prescriptions, or 150 million prescriptions per year.[1,2]

The spectrum of *off-label* use includes guideline-recommended practice, last-resort therapy, and first-line therapy. It permits innovation in clinical practice, particularly when approved treatments have failed and allows physicians to adopt new practices based on emerging evidence. The drug industry, however, has facilitated *off-label* use by exploiting areas of ambiguity where policy is permissive, undefined, or not enforced. Three broad categories of appropriate *off-label* use are identified: *off-label* use justified by high-quality evidence; use within the context of a formal research proposal; and exceptional use, justified by individual clinical circumstances.[3]

The *off-label* medications use occurs in every specialty of medicine, but it may be more common in areas of medicine in which the patient population is less likely to be included in clinical trials (for example, pediatric, pregnant, or psychiatric patients).[4] In diabetes, the use of *off-label* medications must be considered appropriate based on their known clinical pharmacology, evidence from clinical studies, and sometimes from the personal experience of the prescriber.

Many drugs are prescribed to be given in ways and for conditions not approved in the marketing authorization. However, before recommending or prescribing any therapeutic agent *off-label*, should review the complete prescribing information, including indications, contraindications, warnings, precautions, and adverse events. In this article we report the studies available in literature documenting the extent of current administration *off-label* medications in type 2 diabetes mellitus (DM2) prevention.

METHODS

SAMPLE DELIMITATION

An integrative review was made by searching the Medline international database for review of manuscripts. The Medline is taken to be one of the largest medical literature databases in the world. The MeSH (Medical Subject Heading) was the descriptor for Medline. These keywords produced results specific to documents using the terms which are described below.

Selection of these databases was based on the wide range of medical journals covered by each of them and our goal was to provide an overview of the scientific production devoted to the topic over the timeframe under analysis. The following inclusion criteria were considered during the review: articles published between January 1985 and January 2013; use of the keywords "*off-label* use" OR "*off-label*" OR "*off-label* prescribing" OR "diabetes prevention" OR "prevention" MeSH "diabetes mellitus" entered into the search form, and availability of an abstract in English.

RESULTS

A total 852 scientific productions were identified, and 30 studies were selected by contain information about the *off-label* prescriptions in DM2 prevention.

We describe below the *off-label* drugs used for DM2 prevention.

DIABETIC PREVENTION

Identification of individuals with pre-diabetes provides an opportunity to identify those who are at high risk for developing overt DM2 and at increased risk for cardiovascular disease. Approximately 25% of individuals with prediabetes will develop DM2 in three to five years. Four prospective randomised long-term studies, Diabetes Prevention Study, Diabetes Prevention Program, STOP-NIDDM trial, and XENDOS Study, clearly demonstrate the possibility to delay and/or prevent the onset of DM2 in at high-risk subjects with impaired glucose tolerance, through changes in lifestyle or drug treatment.[5]

Currently, there are no pharmacologic therapies approved by the U.S. Food and Drug Administration (FDA) for the prevention of diabetes. It is difficult to know how often a drug is prescribed *off-label* for diabetes prevention. Thus, any decision to implement pharmacologic therapy for prediabetes *off-label* requires careful judgment regarding the risks and benefits of each specific agent. Several drugs used to treat DM2 and for obesity are also *off-label* used to prevent the development of diabetes in high risk persons. Thus, therapeutic interventions in patients with prediabetes are important in primary prevention of DM2 and its chronic complications.

ALPHA-GLUCOSIDASE INHIBITORS

The alpha-glucosidase inhibitors acarbose, miglitol, and voglibose delay the absorption of carbohydrates from the small intestine, therefore, reducing postprandial blood glucose and insulin levels. Furthermore, alpha-glucosidase inhibitors showed to augment incretin secretion, and modifies gut microbiota flora this could explain in part their beneficial effects on glucose homeostasis and on glucose tolerance.[6,7] The alpha-glucosidase inhibitors acarbose and miglitol they are FDA approved for the treatment of DM2 as monotherapy or in combination with other antidiabetic medications.[8]

The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus trial reported that acarbose treatment was associated with a 25% reduction in the incidence of diabetes in a large, cohort of high-risk individuals with impaired glucose tolerance.[9] Another study showed the decrease of platelet-derived microparticles and selectin levels during acarbose therapy in patients with DM2, suggest that acarbose may be beneficial for primary prevention of atherothrombosis.[10]

Voglibose has also been found to be useful in the prevention progression of impaired glucose tolerance to DM2. In clinical trial the patients treated with voglibose had a significantly lower risk of progression to DM2 compared to the placebo group. A significantly higher number of subjects in the voglibose group achieved normoglycemia than those in the placebo group.[11]

Thus, the *off-Label* use of alpha-glucosidase inhibitors may have some effects on lowering cholesterol levels in the blood, and prevention of DM2.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme (ACE) is a zinc-dependent glycoprotein (dipeptidyl carboxypeptidase) that cleaves a C-terminal dipeptide from angiotensin I to create the vasoconstrictor peptide, angiotensin II. Because of this, ACE and its peptide substrates and products affect many physiologic processes, including blood pressure control, hematopoiesis, reproduction, renal development, renal function, and the immune response.[12]

Angiotensin II has been implicated in a number of pathophysiologic processes with the potential to indirectly or directly influence the pathogenesis of insulin resistance and DM2. The potential mechanisms of angiotensin II-mediated insulin resistance and DM2 may include impaired blood flow and sympathetic activity, increased oxidative stress, alterations in insulin signaling, and effects on adipose tissue.[13]

ACE inhibitors are medicines that block the conversion of the chemical angiotensin I to a substance that increases salt and water retention in the body. ACE inhibitors are widely used to treat hypertension and cardiovascular diseases, and have also been used

off-label to help prevent the onset of DM2. Secondary analyses of large-scale clinical trials are revealing the potential benefits of ACE inhibitors in diabetes prevention and demonstrated that ACE inhibitors may preserve pancreatic function and prevent new-onset diabetes, especially for patients who are hypertensive with impaired glucose tolerance.[14] These trials have demonstrated an approximately 15-30% reduction in the new onset of diabetes in those receiving ACE inhibitors when compared with placebo or other active therapy.[15]

METFORMIN

Metformin is an oral antihyperglycemic drug used in the management of type 2 diabetes. Metformin (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Therefore, metformin has been used there many years being well tolerated and relatively safe, thus becoming the leading candidate for preventive treatment of DM2.[16]

Metformin reduces the risk of developing diabetes in individuals at high risk for the disease and has been considered as a reasonable *off-label* approach in selected individuals for diabetes prevention.[17] *Off-label* use of metformin has been shown to decrease advancement to diabetes. Given its efficacy, potential for cost savings, and excellent safety profile, metformin offers another approach to diabetes prevention, particularly in people less than 60 years of age and in women with a history of gestational diabetes.[18]

Trials demonstrated that diabetes risk was reduced by 31% in those who received metformin.[19] Metformin is one of the most studied drugs for DM2 prevention. It is an insulin-sensitizing agent that acts by reducing hepatic gluconeogenesis. By inhibiting free fatty acid production and oxidation, reduces free fatty acid-induced insulin resistance and promotes peripheral glucose uptake. It may also exert protective effects on pancreatic islet cells and it is not related to body weight gain.[20] Consideration of metformin use in overweight adolescents not meeting criteria for DM2 is *off-label* and based on limited published data.

Metformin may reduce the risk of developing gestational diabetes in polycystic ovary syndrome patients. Various reports confirmed the efficacy of metformin treatment in polycystic ovary syndrome pregnant women reducing significantly the risks of gestational diabetes.[21] Metformin is also used *off-label*, though controversial, to treat gestational diabetes in women.[22]

ORLISTAT

The synthetic drug orlistat ((S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]-dodecyl ester) is a potent inhibitor of pancreatic and gastric lipases that decreases fat absorption by binding to pancreatic lipase, the principal enzyme that hydrolyses triglyceride. Its mechanism of action results in an inhibition of dietary fat absorption of 30% at the approved dosage, acting locally in the gut lumen with minimal absorption. It is not extensively metabolised, with 83% of excreted orlistat found to be intact drug primarily via the faeces.[23]

The largest placebo-controlled study performed with orlistat was the XENDOS (XENical in the Prevention of Diabetes in Obese Subjects), aimed at assess orlistat efficacy in preventing DM2 in obese patients. It presented a cumulative incidence of diabetes significantly reduced by 37.3%, and in people with impaired glucose tolerance at baseline the decrease in the risk of developing diabetes was 45% at four years, being also associated with sustained improvements of several other cardiovascular risk factors, including blood pressure, waist circumference and lipids.[24] Other studies involving smaller number of patients have also demonstrated several features of amelioration in metabolic profile.[25] Furthermore, multicentre European study, orlistat also generated improvements in serum insulin and glucose levels, when compared to the placebo group.[26]

Therefore, the studies presented so far denote that orlistat treatment has a favorable effect on carbohydrate metabolism and can prevent DM2 onset in obese individuals with impaired glucose tolerance at baseline. However, whether preventive therapy with orlistat, postpone or mask the diagnosis of DM2,

instead of put forth an authentic preventive outcome is an uncertain matter.

THIAZOLIDINEDIONES

The thiazolidinediones are a class of synthetic compounds whose structural characteristic common to all they are a thiazolidinedione ring that is assumed to relate to their antihyperglycaemic action, whereas the substituted moieties seem to modulate pharmacokinetic and pharmacodynamic properties. They are a class of agents that have been developed to treat of DM2, that act as peroxisome proliferator-activated receptor gamma agonists, binding the response elements of specific genes that regulate molecules that effect insulin action and lipid metabolism, and this leads to an increase in glucose uptake in skeletal muscle and adipose tissue, a reduction in hepatic glucose output, and finally, an increase in free fatty acid uptake. These factors combine to lower glucose levels and can decrease HbA1c levels over time.[27]

The single-entity thiazolidinediones may also be used *off-label* in a variety of clinical situations as management of impaired glucose tolerance in cerebrovascular disease, treatment of diabetic nephropathy in DM2, and prophylactic treatment of disorder of cardiovascular system in DM2, and as preventive treatment of diabetes.[28]

The potential of thiazolidinediones in diabetes prevention is being investigated, and studies suggest that early treatment with thiazolidinediones may prevent the progression from insulin resistance to DM2.[29] Intervention studies suggest that thiazolidinediones have the potential to delay, stabilize and possibly even prevent the onset on diabetes in high-risk individuals, because that clinical evidence suggests that thiazolidinediones have effects on the beta-cell, such as improving insulin secretory capacity, preserving beta-cell mass and islet structure and protecting beta-cells from oxidative stress, as well as improving measures of β-cell function, such as insulinogenic index and homeostasis model assessment of beta-cell function.[30]

Four studies using thiazolidinediones provide solid evidence for slowing or arrest of metabolic deterioration. The Diabetes Prevention Program study, observed that the thiazolidinediones have produced relative risk reductions in the range of 55–62% in progression to diabetes.[31] The TRIPOD Study and Pioglitazone in Prevention of Diabetes Study provide proof that falling beta-cell function can be arrested for relatively long periods of time, albeit in only a subset of treated subjects, establishing the potential for true diabetes prevention. In both studies, the mechanism for prevention appeared to be a reduction in insulin secretory demands that resulted from amelioration of chronic insulin resistance.[32,33] The Diabetes REduction Assessment with rosiglitazone and ramapril Medication Study showed a relative risk reduction for diabetes during 4 years of treatment with rosiglitazone was 62% and ramipril had no significant impact on the risk of diabetes.[34]

FINAL THOUGHTS

This study presented an integrative review on *off-label* drugs use in diabetes prevention. When a doctor prescribes a drug for a use, or in a manner, not authorized by the FDA is called *off-label* prescribing. *Off-label* treatment can be experimental, standard, or even state-of-the-art. It has become a part of main stream medical practice, with many *off-label* uses recommended by medical textbooks, research institutes, professional organizations, and standard pharmaceutical reference works. In the meantime, off label prescribing remains acceptable if there is no suitable alternative and physicians are confident that they are using agents in accordance with the body of respected medical opinion, and *off-label* prescribing has been common in most medical specialties.

The current system allows drugs that are safe and effective for one indication could be used for any other indications without adequate safeguards. However, prescription of drugs *off-label* does not should convert into experimental or investigational products, but a number of occasions such *off-label* treatments have proven to be essential to the successful treatment of some very serious illnesses. It is therefore at least

conceivable that if such *off-label* uses are permitted, the drug may in reality be worthless or even dangerous for its alternative use, yet doctors may be freely employing it for that purpose. Thus, *off-label* drug use is just one aspect of the larger question about how to balance benefits, harms, and costs of medical interventions when technological advances are rapid, evidence is imperfect, and resources are finite.

Therefore, the use of *off-label* drugs in diabetes prevention is an alternative, and its use has demonstrated an improvement in signs and symptoms while specific medications yet not have been released for use on-label.

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