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Persistence Patterns with Oral Antidiabetes Drug Treatment in Newly Treated Patients—A Population-Based Study

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ABSTRACT

Objective: We assessed persistence patterns with oral antidiabetes drug (OAD) in patients newly dispensed with different OAD classes.
Methods: We conducted a population-based cohort study using Quebec Health Insurance Board data. Patients aged 18 years or more newly dispensed an OAD between January 1, 1998 and December 31, 2003 were included in the study (n = 98,940). Persistence was defined as consistently refilling a prescription for the initial OAD within three times the days' supply of the preceding claim. For nonpersistent patients, a second course of therapy was defined as treatment initiation with any OAD after a first discontinuation. Patients were followed from treatment initiation up to December 31, 2004, ineligibility for the drug plan or death, whichever came first, and treatment discontinuation or second course of treatment. Cox regression models were used to compute adjusted hazards ratios (AHR) of persistence and initiation of second courses of therapy.
Results: The probability of persisting with the initial OAD over a 12-month period was 65% and 56% for patients initiated on metformin and sylfonylurea, respectively. Compared to metformin, the likelihood of discontinuing the initial OAD over the study period was significantly higher for patients on sulphonylureas (AHR: 1.32; 95% CI 1.29–1.34). Patients started on sulphonylureas were also less likely to start a second course of therapy after a first treatment discontinuation (AHR: 0.91; 95% CI 0.89–0.93).
Conclusions: Compared to diabetic patients initiated on metformin, those initiated on sulphonylureas displayed poorer persistence patterns.
Keywords: diabetes, discontinuation patterns, oral antidiabetes drugs, persistence.

Introduction

Diabetes is a common chronic disease. According to the World Health Organization [1], around 177 million people were suffering from diabetes in 2000, and this number should total at least 300 million by 2025. Diabetes is responsible for 9% of the total worldwide mortality. Type 2 diabetes accounts for more than 90% of diabetes cases.

When diet and exercise have failed to achieve glycemic control, then starting to take an antidiabetes medication is recommended [2]. First-line classes of medications include biguanides (metformin), insulin secretagogues sulfonylureas (gliclazide, glimepiride, glyburide) and nonsulfonylureas (nateglinide, repaglinide), thiazolinediones (TZDs) (pioglitazone, rosiglitazone), and the alpha-glucosidase inhibitor, acarbose.

Medication persistence refers to the act of conforming to a recommendation of continuing treatment for the prescribed length of time [3]. Persistence with drug treatment is an important factor in determining the success of long-term therapy. This is of particular relevance in the treatment of diabetes given that this condition is chronic and typically requires long-term commitment to pharmacotherapeutic regimens to gain and maintain glycemic control and, as a consequence, prevent complications [4].

Although many studies [5–12] have examined persistence with oral antidiabetes drug (OAD) regimens, they generally suffer from some limitations. For example, in most studies [8–10,12], the duration of follow-up was no more than 1 year and none has actually described returns to any antidiabetes therapy after a first discontinuation. Moreover, persistence with metformin has been compared to persistence with sulfonylureas in only two of these studies [6,7]. As perceived side effects are known to be associated with discontinuation of drug treatment [13] and as metformin and sulfonylureas are associated with different side effects, there is a need to compare these two classes of drugs in terms of persistence. Also, initial therapy may have been dictated by contraindications which also modulate the risk of side effects.

Our study was designed to examine and characterize persistence and discontinuation patterns in actual clinical practice in a Canadian population-based setting, using patients who were prescribed antihyperglycemic pharmacotherapy with metformin or a sulfonylurea for the first time.

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Methods

Study Design and Data Sources

A retrospective population-based inception cohort study was undertaken, utilizing the databases of the Quebec Health Insurance Board (RAMQ) and the Quebec Registry of Hospitalizations. These databases include information on patient demographics, and hospital and physician services pertaining to all permanent residents of the province of Quebec (population approximately 7 million). The RAMQ drug plan database contains also information on prescription drugs for Quebec residents who are not eligible to a private drug insurance plan, welfare recipients, and people aged 65 years and over (3.2 million in 2003). The drug plan database is known to be accurate for prescription claims [14].

Eligible for cohort entry were new users of antihyperglycemic pharmacotherapy aged 18 years or over; newly dispensed OAD between January 1, 1998 and December 31, 2003 (no OAD or

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insulin prescription claimed in the 12 months leading up to the first dispensing date) and initiating antihyperglycemic treatment with one of the five major drug classes (ATC class code A10B), i.e., metformin, insulin secretagogues sulfonylureas, insulin secretagogues nonsulfonylureas, TZDs, and alpha-glucosidase inhibitor. Patients who were not eligible to the Quebec's drug plan for the entire 365-day period before the OAD treatment initiation date were excluded. Those who received more than one OAD at treatment initiation were also excluded. We later excluded patients initiated on insulin secretagogues nonsulfonylureas, TZDs, and on the alpha-glucosidase inhibitor, acarbose, because few patients were initiated on these drugs and they likely had different characteristics from those initiated on metformin or on a sulfonylurea. Indeed in Quebec, reimbursement of insulin secretagogues nonsulfonylureas and TZDs, as first-line agents is restricted to those patients with a contraindication to the use of both metformin and a sulfonylurea, or to individuals with renal failure, whereas acarbose is mostly used in combination with other OADs.

Study subjects were followed from treatment initiation (index date) until December 31, 2004, ineligibility to the drug plan or death, whichever came first.

Persistence Analysis

Persistence with initial therapy was defined as continuously refilling a prescription for the initial single OAD within thrice the days' supply of the preceding claim, regardless of add-on OAD or insulin. Hospital-days were excluded from the calculation of this "permissible gap" requirement for treatment discontinuation as there is no information available on drug use during hospital stays. Discontinuation date was defined as the date of the last prescription refill plus the number of days' supply. For nonpersistent patients, a new course of therapy was defined as treatment initiation with any OAD after a first treatment discontinuation. For illustrative purposes, Figure 1 displays OAD use in a hypothetical patient considered to have discontinued therapy after 210 days (first 90-day period, i.e., 3 times the days' supply without prescriptions, excluding hospital-days, ends at day 210) and started a new course of therapy after 330 days.

Patients who were dispensed an additional OAD before or at the date of the initial OAD discontinuation were regarded as having been switched to another OAD before discontinuation and therefore were not considered in the calculation for subsequent new courses of therapy.

Length of time to a first treatment discontinuation (days from treatment initiation to discontinuation), and length of time to a new course of therapy after initial treatment discontinuation (days from first discontinuation to new course of therapy with any OAD) were computed and described by subcohorts, as defined by initial OAD. Patients were censored at study termination date if they were persistent with therapy throughout follow-up, or when they became ineligible for the drug plan, or at time of death, if applicable. Persistence was evaluated for up to an 84-month period from the index date.

Statistical Analysis

Initial treatment patterns, patients' characteristics at treatment initiation, as well as discontinuation patterns were described and significance tests were carried out using chi-square tests for proportions and analyses of variance for continuous variables. Persistence data for each OAD subcohort was analyzed longitudinally. Length of time from a first OAD initiation to discontinuation, and length of time from a first OAD discontinuation to a second new course of OAD were described using Kaplan–Meier curves. Statistical significance of the differences between curves was assessed using the log-rank test. Cox regression analyses were conducted to compare the likelihood of treatment discontinuation for the sulfonylureas subcohort to that of the metformin subcohort over the 84-month study period, controlling for age, sex, calendar year of treatment initiation, initial prescriber's specialty, hospitalization for diabetes in the year before treatment initiation, comorbidity score measured as the number of different prescribed medications claimed in the year before treatment initiation [15], obesity (ICD-9 278.0), and mental disorder (ICD-9 290-319, 331.XX). This therefore allowed the proportion of subjects still on initial OAD therapy at different points in time to be compared across the two initial treatment groups. The likelihood of starting a new course of therapy after treatment discontinuation was also compared across initial treatment groups using Cox regression models adjusting for age, sex, calendar year of treatment initiation, hospitalization for diabetes, the number of different prescribed medications claimed in the year before treatment initiation, for obesity and mental disorder. The proportionality assumption for the proportional hazards models was met. To test the sensitivity of the "thrice the days' supply" permissible gap for persistence, we repeated the analysis using "twice the days' supply" as a

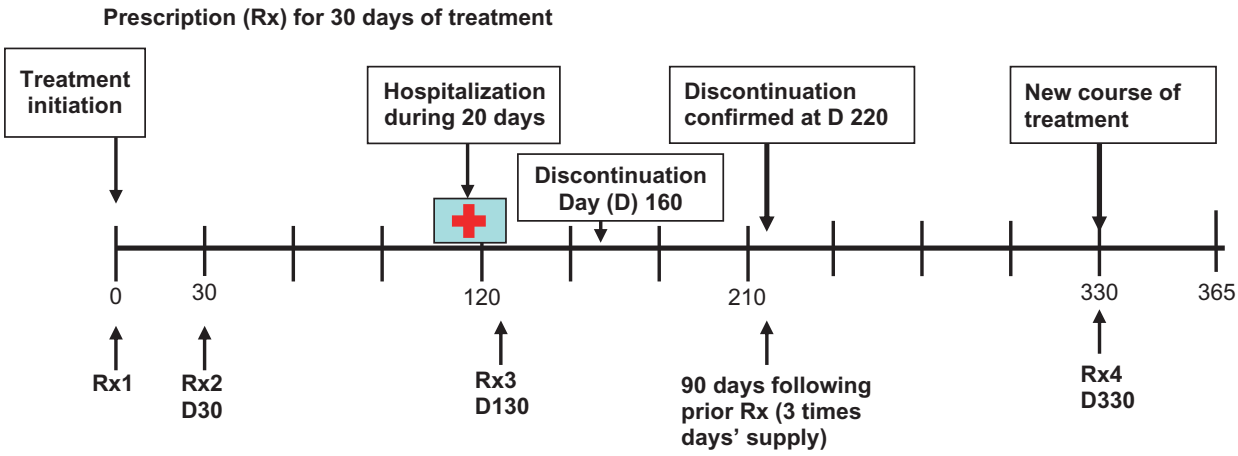

Figure 1 Measurement definition.