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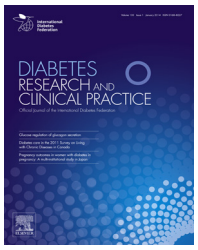

Use of antidepressants and statins and short-term risk of new-onset diabetes among high risk adults

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ABSTRACT

Aims: We evaluated the association of combined use of antidepressants and statins and the risk of new-onset diabetes among high-risk adults.

Methods: We used a retrospective, observational, longitudinal design among adults (age ≥22 years) who were diabetes free at baseline and had reported hypertension or hyperlipidemia or heart disease. We used data were from 2004 to 2009 Medical Expenditure Panel Survey and identified from self-reported diabetes or insulin use. We categorized antidepressants and statins use into four groups: antidepressants only, statins only, combined use of antidepressants and statins (antidepressants–statins), and neither antidepressant nor statins. We conducted chi-square and multivariable logistic regressions to examine the association between use of antidepressants–statins and new-onset diabetes after controlling for demographic and economic characteristics, health-status, access to care, presence of depression, and lifestyle risk factors.

Results: In our study sample, 9.3% used antidepressants only, 10.7% used statins only and 2.4% adults reported use of antidepressants–statins. Nearly 2% of the study sample reported new-onset diabetes. In unadjusted analyses, significantly higher proportion of adults using antidepressants–statins (3.2%) reported new-onset diabetes compared to those using neither antidepressants nor statins (1.1%). However, after controlling for all other variables in multivariable regression we did not observe a statistically significant association between use of antidepressants–statins and new-onset diabetes.

Conclusions: Our study results do not suggest that use of antidepressants–statins may increase the risk of new-onset diabetes. Future research needs to examine this relationship with specific combinations of these drug classes and using longer follow up periods.

1. Introduction

Statins and antidepressants are the most prescribed classes of medications in the United States (US) [1]. The use of statins has been shown to be associated with a decrease in low density cholesterol levels and reduction of mortality and cardiovascular events [2–4]. The use of antidepressants also leads to improvements in health outcomes and quality of life among individuals with depression [5,6]. However, adverse effects such as an

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increase in blood glucose levels and risk of new-onset type 2 diabetes mellitus (hereafter referred to as diabetes) have been reported with antidepressants [7–10] and statins use [11–15].

Findings from a three-arm randomized controlled diabetes prevention trial first revealed that, compared with no use of antidepressants, use of antidepressant was associated with new-onset diabetes among individuals in placebo (hazards ratio (HR): 2.60; 95% confidence interval (CI): 1.37, 4.94) and intensive lifestyle treatment (HR: 3.39; 95% CI: 1.61, 7.13) [16]. Since then, several observational studies [17–21] and meta-analyses [22–24] have suggested a positive association between antidepressant use and new-onset diabetes. Some studies have suggested that the presence of depression and not antidepressant use is associated with new-onset diabetes [25,26].

Large scale randomized clinical trials [13,27] have reported conflicting results regarding diabetes risk with statins. For example, compared to the placebo, the use of rosuvastatin have been shown to increase the risk of developing diabetes (270 with diabetes in rosuvastatin group, vs. 216 in the placebo group; $p = 0.01$) in individuals with low density lipoprotein-c (LDL-c) levels <130 mg/dl and triglycerides <500 mg/dl [13]. The use of pravastatin on the other hand, has been shown to reduce the risk of new-onset diabetes (HR: 0.70:95% CI: 0.50, 0.99; p-value: 0.042) among non-elderly adult males (45–64 years) compared to the placebo [27]. Two different meta-analyses of randomized controlled trials, have also found either a 9% or a 13% increased risk of new-onset diabetes among statin users as compared to the control group (which may include placebos or active controls) [12,28].

The exact biologic pathway through which combined use of both antidepressants and statins (hereafter referred to as antidepressants–statins) may increase the risk of new-onset diabetes is not known. However, there are molecular connections linking the use of these drugs to diabetes-related pathways [29,30]. For example, it has been shown in animal studies that use of antidepressants is associated with increased hyperglycemia [8,31–33]. Antidepressants have high affinity toward 5HT1C, 5-HT2C [34,35] receptors which are known to influence insulin resistance and weight gain [36]. Paroxetine, a selective serotonin reuptake inhibitor have high affinity to muscarinic M3 receptors [37] and thus, by binding with M3 receptors in pancreatic beta cells it can influence insulin secretion [36]. Antidepressants are also known to induce hypercortisolemia and thereby increase insulin resistance [38]. Similarly, experimental studies have suggested that statin use can affect insulin secretion by causing potential loss of islet beta-cell function via mechanisms such as disruption of calcium channel functions in pancreatic beta cells [39] and decrease in expression of glucose transporters (e.g. glucose transporter 4) in adipocyte cells [40,41]. Statins also have adverse influence on mitochondrial function [42,43]; interestingly mitochondrial dysfunction in adipose tissue [44], skeletal muscle [45] and pancreatic beta cell [46] is highly associated with insulin resistance and diabetes. As antidepressants and statins both impact insulin secretion, it is highly plausible that when these two drugs are used in tandem, there may be a very high risk of impaired insulin secretion and insulin resistance, which in turn may lead to new-onset diabetes. One retrospective study using the Food and Drug Administration's Adverse Event Reporting System data reported that combined administration of paroxetine, a selective serotonin reuptake inhibitor and pravastatin, increased blood glucose levels among a cohort of individuals with and without diabetes; the average increase was 19 mg/dl overall, and in those with diabetes it was 48 mg/dl. No such increases in glucose levels were observed when the drugs were administered separately [47].

Clinical trials often focus on establishing the efficacy and safety of single drugs. Unpredictable synergistic effects of drug combinations are observed from results of epidemiological observational studies. Given the high rates of use of antidepressants and statins, high biologic plausibility and reports of independent association of these drug classes with new-onset diabetes, it is important to examine the increased risk of new-onset diabetes, if any, with combined use of these drug classes. Therefore, the primary objective of our study was to evaluate the independent association of antidepressants–statins and new-onset diabetes after adjusting for other known risk factors—demographic and economic characteristics, health status, access to care variables, presence of depression and lifestyle risk factors (lack of physical activity, smoking, overweight and obesity), in a sample of high risk adults with hypertension, hyperlipidemia and heart disease. We selected individuals with hypertension, hyperlipidemia and heart disease as they have higher risk of new-onset diabetes as compared to general population [48,49]. Therefore, it is important to examine the role of additional modifiable risk factors such as use of antidepressants–statins, which may independently contribute to the increased risk of new-onset diabetes in this population.

2. Methods

2.1. Study design

We used a retrospective, observational, longitudinal design using data from multiple years (2004–2009) of a nationally representative household survey, the Medical Expenditure Panel Survey (MEPS). As MEPS collects data spanning over a 2-year period, we used first year as the 'baseline period' and the second year as the 'follow-up period'.

2.2. Data sources

We pooled longitudinal data from multiple years of the MEPS to examine the association between use of antidepressants–statins and the risk of new-onset diabetes. The MEPS is a nationally representative survey of the US civilian non-institutionalized population that collects person and household level information on respondents' demographic and economic characteristics, access to care, diagnosis dates, conditions and related charges and payments and information on prescription medications [50]. The survey has multistage, clustered sample design involving overlapping panels. Extensive health care utilization data including demographics characteristics, health conditions, health status, use of medical care and prescription medications, detailed charges and payment, insurance coverage, income, and employment are captured in the household component (HC) of MEPS.

We used the household full year consolidated, medical conditions, and prescribed medicines files of the MEPS data in