

Review: Mixed signals from trials concerning pharmacologic prevention of type 2 diabetes mellitus

Padwal R, Majumdar SR, Johnson JA, Varney J, McAlister FA. A systematic review of drug therapy to delay or prevent type 2 diabetes. *Diabetes Care*. 2005;28:736-44.

Clinical impact ratings: GIM/FP/GP ★★★★★☆ Endocrinology ★★★★★☆☆

QUESTION

What is the evidence that pharmacologic therapies can prevent type 2 diabetes mellitus?

METHODS

Data sources: MEDLINE (1966 to June 2004), EMBASE/Excerpta Medica (1980 to 2004), the Cochrane Controlled Trials Register (2004), and reference lists of articles. **Study selection and assessment:** Randomized controlled trials (RCTs) and cohort studies that provided sufficient data to calculate the incidence of type 2 diabetes using an intention-to-treat analysis, included patients > 18 years of age with a minimum sample size of 50 patients, and compared oral hypoglycemic agents (including biguanides, acarbose, sulfonylureas, and thiazolidinediones), antiobesity agents, antihypertensive drugs, statins, fibrates, or estrogen with placebo. Studies were excluded if they tested an intervention in patients with preexisting diabetes, were duplicates, or were in abstract form. 2 reviewers independently assessed studies for inclusion.

Outcomes: Diabetes incidence and adverse effects.

MAIN RESULTS

25 studies met the inclusion criteria (18 RCTs and 7 cohort studies). 9 RCTs (n = 8251) prespecified diabetes incidence as

the primary outcome. Meta-analysis was not done because studies were heterogeneous. **Oral hypoglycemic agents:** 1 RCT showed that metformin reduced diabetes more than placebo, and 1 RCT found no difference between groups (Table). In 1 RCT, acarbose reduced diabetes more than placebo (Table), but 25% of patients discontinued therapy because of gastrointestinal (GI) toxicity. 2 RCTs that investigated sulfonylureas showed no difference between tolbutamide and placebo for reducing diabetes (Table). 1 RCT showed that troglitazone reduced diabetes more than placebo (Table). **Antiobesity agents:** 1 RCT showed that orlistat reduced diabetes more than placebo (Table), but caused GI side effects in 91% of patients, and patient

follow-up was only 43%. In RCTs that investigated other pharmacologic agents, analysis of the diabetes incidence was done post hoc.

CONCLUSION

In patients with type 2 diabetes mellitus, some oral hypoglycemic agents and antiobesity drugs reduce the incidence of diabetes, but the findings are inconsistent and many studies have low patient follow-up or show high drug-related gastrointestinal adverse effects.

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Pharmacologic agents vs placebo for preventing type 2 diabetes mellitus at 1 to 10 years*

Drug class	Number of trials (n)	Patient follow-up (%)	Comparisons with placebo	Event rates	RR (95% CI)	HR (CI)
Oral hypoglycemic agents	1 (2155)	93	Metformin	5% vs 8%	0.69 (0.57 to 0.83)	—
	1 (90)	94	Metformin	7% vs 14%	0.51 (0.14 to 1.9)†	—
	1 (1429)	96	Acarbose	32% vs 42%	0.75 (0.63 to 0.90)	—
	1 (97)	100	Tolbutamide	10% vs 12.5%	0.82 (0.27 to 2.5)†	—
	1 (248)	Not stated	Tolbutamide	11% vs 9%	1.20 (0.56 to 2.6)†	—
	1 (266)	67	Troglitazone	20% vs 45%	0.45 (0.25 to 0.83)	—
Antiobesity agents	1 (3305)	43	Orlistat	6% vs 9%	—	0.63 (0.46 to 0.86)

*RR = relative risk; HR = hazard ratio. CI defined in Glossary. †Not significant.

COMMENTARY

Padwal and colleagues concluded that no single agent is a clear choice for preventing diabetes in patients with impaired glucose tolerance (IGT). They noted that the main results from the Diabetes Prevention Program trial (which used metformin) and the STOP-NIDDM trial (which used acarbose) were based on oral glucose tolerance tests (OGTTs) that were done while patients were still taking their medication. In addition, the rate of diabetes increased in these patients after washout periods. The XENDOS trial, which used orlistat in patients with a body mass index (BMI) ≥ 30, reported a similar analysis.

Analyses of OGTTs in diabetes prevention trials while participants are still on, or only recently stopped, the intervention cannot distinguish prevention of diabetes from good diabetes control in those who developed diabetes during the trial. Thus, any claim of prevention cannot be addressed by studies with short or absent drug washout periods. Nevertheless, we see 3 conclusions for clinicians. First, we suggest that lifestyle changes are the basis for prevention, delay, and management of diabetes (number needed to treat [NNT] = 62 [1]). Second, increased fasting and increased postload glucose levels could be used as continuous variables, with treatment decisions based on absolute risk reduction,

tailored to the individual's baseline risk for diabetes-related complications. This is currently done for treating elevated blood pressure and dyslipidemia (2). Third, if drugs are used to treat prediabetes, it might be most logical to use metformin for patients with a raised fasting glucose level, age < 60 years, or BMI > 35 (NNT 92); acarbose for patients with a raised postload glucose level (NNT 33); and orlistat for patients with IGT and BMI > 30 (NNT 133) (NNTs are based on studies in the current review and another study [1], and adjusted for a 1-year period).

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