Addressing Unmet Type 2 Diabetes Needs

Novel Drugs Needed to Prevent Loss of Beta-cell Function and Weight Gain

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Type 2 diabetes (T2D) has reached epidemic proportions throughout the world. The worldwide number of diabetics was 30 million in 1985 and is projected to increase to at least 366 million by 2030. The vast majority of this increase is due to T2D. In 2005, diabetes was the sixth leading cause of death in the U.S. Increased rates of obesity coupled with an aging population are the major drivers of the T2D epidemic, especially in the U.S. and in emerging industrial countries such as India and China.

Most of the mortality and morbidity as well as the economic costs of diabetes are due to diabetic complications. Antidiabetic drugs, which account for only 13% of the total costs of diabetes in the U.S., are the mainstay of efforts by physicians and patients to prevent diabetic complications.

Necessity of New Antidiabetics

Despite the epidemic of T2D, leading medical authorities have recently questioned the need for new drugs to treat the disease. In 2006, the ADA and the European Association for the Study of Diabetes (EASD) published a consensus statement on optimal ways to treat T2D using current oral antidiabetics and insulin. These recommendations emphasized using the older, more inexpensive drugs: insulin, metformin, and sulfonyureas (of which the latter two are available as generics), as well as the more expensive, branded thaizolidinediones (TZDs), pioglitazone (**Lilly's** Actos), and rosiglitazone (**GlaxoSmithKline's** Avandia).

The consensus statement de-emphasized the use of the more recently approved agents: exenatide (**Amylin/**Lilly's Byetta) and pramlintide (Amylin/Lilly's Symlin). The latter two drugs were rejected because of their expense, their lesser efficacy in lowering plasma glycosylated hemoglobin (HbA1c, a measure of long-term glycemic control) than the older drugs, and the lack of experience in using the newer drugs in the medical community.

In early 2007, the head of the panel that developed the consensus statement, David M. Nathan, M.D., at Massachusetts General Hospital and Harvard Medical School, published a Perspective in the *New England Journal of Medicine* that questioned whether the novel drugs launched in the last two years including exenatide and pramlintide as well as sitagliptin (**Merck's** Januvia), which the FDA approved after the publication of the ADA/EASD consensus statement, are necessary to treat type 2 diabetes or even whether at least some of them should have been approved at all.

As in the ADA/EASD consensus statement, the reason for this conclusion was that the efficacy of the newer drugs in lowering HbA1c is less than that of established drugs, there is little experience in using them in humans (especially in the case of Januvia, which was approved after a few clinical trials), they may have new side effects that may emerge during the postmarketing period, and they are expensive.

Since the publication of Dr. Nathan's Perspective, the safety of the TZD Avandia has been questioned. This is the result of the publication of a meta-analysis by cardiologist Steven Nissen, M.D., that concluded that Avandia increased the risk of myocardial infarction (MI) in diabetics by approximately 40%.

A later meta-analysis by Dr. Nissen concluded that the other marketed TZD, Actos, in contrast to Avandia, reduced the risk of MI in diabetics. The results of these meta-analyses are controversial. However, both TZDs are known to increase the risk of heart failure in diabetics. In August 2007, the FDA mandated a new black box label warning on the risk of heart failure for both TZDs.

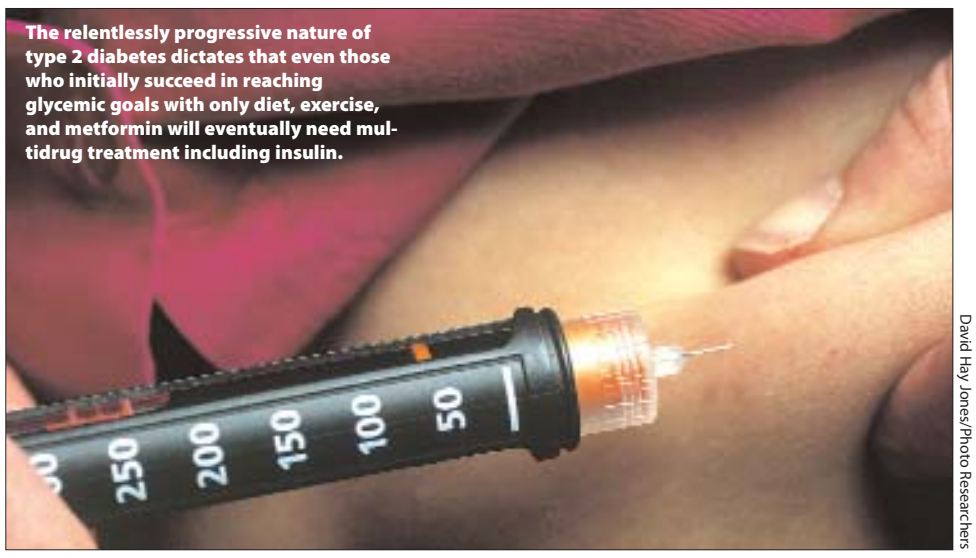
In his Perspective, Dr. Nathan stated that, in his opinion, type 2 diabetes is already treatable with fairly safe and effective established drugs and that the biggest issue is to implement currently available therapeutic regimens aggressively, not to develop and market new classes of drugs.

The result of the new safety concerns with TZDs, as well as their expense, would seem to mandate focusing on treatment with the three older classes of antidiabetic drugs following the logic of the ADA/EASD consensus statement and Dr. Nathan's Perspective. To the extent that this approach is valid, it would put a damper not only on the use of the newer classes of marketed drugs but also on the development of agents now in corporate pipelines and on further diabetes R&D.

Unmet Needs

There are still, however, major unmet needs that are not addressed by older antidiabetic agents. One major unmet need is the relentlessly progressive nature of type 2 diabetes. As noted in the ADA/EASD consensus guidelines, because of this progression, even patients who initially succeed in reaching glycemic goals with only diet/exercise and metformin will eventually need multidrug treatment, including insulin.

Moreover, the results of the U.K.'s Prospective Diabetes study showed that even when intensive monotherapy with metformin, insulin, or a sulfonylurea is successful in lowering fasting blood glucose and HbA1c over the short term, these measurements steadily increase with time due to disease progression.



The relentlessly progressive nature of type 2 diabetes dictates that even those who initially succeed in reaching glycemic goals with only diet, exercise, and metformin will eventually need multidrug treatment including insulin.

David Hay Jones/Photo Researchers

Table 1. Current and Late-stage Antidiabetics

Class	Drug	Comments
Amylin analogues	Pramlintide (Amylin's Symlin, approved in 2005)	Peptide drug delivered via subcutaneous injection. It is approved for diabetics on insulin therapy who have failed to achieve desired glycemic levels. It promotes satiety and can prevent weight gain.
Incretin mimetics (glucagon-like protein-1 analogues)	Exenatide (Amylin/Lilly's Byetta, approved in 2005); Exenatide LAR: (Amylin/ Lilly/Alkermes, Phase III); Liraglutide (Novo Nordisk's NN2211, Phase III)	Peptide drugs delivered via subcutaneous injection. Exenatide is approved for type 2 diabetics taking standard oral agents. It promotes modest progressive weight loss. Animal studies suggest that it may preserve beta-cell function.
Dipeptidyl peptidase-IV (DPP-IV) inhibitors	Sitagliptin (Merck's MK-0431/ Januvia, approved in 2006); Vildagliptin (Novartis' Galvus/ LAF-237, received approvable letter from FDA in 2007); Saxagliptin (Bristol-Myers Squibb/AstraZeneca, Phase III)	Oral small molecule drugs that inhibit DPP-IV, an enzyme that cleaves GLP-1 and another incretin, gastric inhibitory peptide (GIP). Drugs appear to be weight neutral. Animal studies suggest that they may preserve beta-cell function.
Cannabinoid-1 receptor (CB1) antagonists	Rimonabant (sanofi aventis' Accomplia, approved in Europe for obesity, Phase III for T2D); Taranabant (Merck, Phase III)	Selective antagonist of the cannabinoid-1 receptor. Originally developed for obesity, in late-stage development for type 2 diabetes. They have both antiobesity and antidiabetic effects.

Table 2. Selected Preclinical and Research-stage Agents

Agent	Companies Involved	Comments
Protein tyrosine phosphatase 1B (PTP1B) inhibitors	Small molecules: Incyte, Wyeth, Onset Thera, Alinea, Merck Serono, Ceptyr, TransTech Pharma, various academic groups. Alinea, Ceptyr and TransTech have preclinicals. Antisense agent: Isis Pharmaceuticals (ISIS 113715, Phase II)	Small molecule and antisense inhibitors of PTP1B, a well-validated but undruggable negative regulator of the insulin-signaling pathway. Compounds may be active against diabetes, obesity, and the metabolic syndrome.
Adenosine mono phosphate-activated protein kinase (AMPK) activators	Abbott (A-769962, preclinical), Mercury Therapeutics, TransTech, Onset Thera, Metabasis/Merck, Elixir Pharmaceuticals, CytRx (upstream AMPK pathway modulators)	Small molecule compounds to inhibit the whole-body and intracellular energy sensor and metabolic regulator AMPK. Compounds may be active against diabetes, obesity, and metabolic syndrome.
Sirtuin modulators	Sirtris Pharmaceuticals: (SRT501, Phase Ia) surtuin 1 (SIRT1) activators, Elixir Pharmaceuticals: sirtuin activators and inhibitors	Small molecule compounds to modulate sirtuins. Compounds may be active against diabetes, obesity and metabolic syndrome.
Ghrelin receptor antagonists	Elixir Pharmaceuticals (lead optimization and preclinical studies). Several other companies have been developing ghrelin antagonists as antiobesity therapeutics.	Small molecule antagonists of the receptor for ghrelin. Compounds may be active against diabetes, obesity, and metabolic syndrome.
GRP119 agonists	OSI/Prosidion (preclinical candidates)	Small molecule agonists of GRP119 inhibit food intake and fat deposition in rodent models and also improve glucose tolerance and insulin sensitivity. Thus, these compounds might be active against both diabetes and obesity.

Progression of T2D is mainly due to the loss of pancreatic beta-cell function, which results in increased impairment of patient's ability to produce insulin in response to increased blood glucose.

Reducing weight in obese diabetics undergoing drug treatment is another major unmet need. Of the established drugs for treating type 2 diabetes, insulin, sulfonylureas, and TZDs cause weight gain. Only metformin is weight neutral and is sometimes associated with modest weight loss. Some medical authorities would like to see a greater emphasis on antidiabetic treatments that produce weight loss than what was seen in the recommendations of the ADA/EASD consensus statement.

Even Dr. Nathan, in his Perspective, notes the need to develop new antidiabetic drugs that lower blood glucose while promoting weight loss and/or slow the progression of the disease.

Addressing These Needs

What are drug developers doing to address these unmet needs? *Table 1* lists novel and emerging drug classes that may address these needs including several drugs that have been approved since 2005. *Table 2* lists early stage agents that are designed to address unmet needs in T2D.

Among the drugs listed in *Table 1*, pramlintide, an amylin mimetic that is approved for diabetics who use mealtime insulin, promotes satiety and thus reduces average caloric intake and can prevent weight gain.

The recently approved drug exenatide, an incretin mimetic, has been used together with metformin or a sulfonylurea to both meet glycemic goals (HbA1c less than 7%) and to give significant weight loss. Incretins such as glucagon-like protein-1 are gut-derived hormones that promote insulin secretion by beta cells in response to intake of food.

Another incretin mimetic in development, **Novo Nordisk's** liraglutide, has also been shown to produce significant weight loss in type 2 diabetics in Phase II clinical trials.

Despite its related mechanism to incretin mimetics, the DPP-IV inhibitor sitagliptin is only weight neutral and causes no significant weight loss. Some researchers believe that weight loss may be an advantage of incretin mimetics over DPP-IV inhibitors, however, it is still too early to definitively make this statement. Animal studies indicate that both incretin mimetics and DPP-IV inhibitors may preserve beta-cell function, which addresses the other major unmet need. However, it is not yet known if these drugs mediate beta-cell protection or regeneration in humans.

The Phase III antidiabetic agent, rimonabant, **Sanofi-Aventis'** Acomplia, is a cannabinoid-1 (CB1) receptor antagonist. It is already approved in Europe for inducing weight loss in obese individuals. However, the use of rimonabant for treatment of obesity or T2D is under a cloud, due to the incidence of depression and suicides associated with use of the drug. It is this adverse effect profile that has kept rimonabant from approval in the U.S. Merck has a CB1 reverse agonist in Phase III development, taranabant. The Phase II results in obesity with taranabant are encouraging, but the determination of the efficacy and safety profile of this drug must await the completion of the Phase III trial.

As illustrated by *Table 2*, a major theme of the early-stage drug discovery and development efforts in T2D is developing agents that potentially target both Type 2 diabetes and obesity. They are attempting to address common pathways of both diabetes and obesity, for example, targeting sirtuins and adenosine monophosphate-activated protein kinase, which takes addressing this unmet need one step further than what current agents such as incretin mimetics and DPP-IV inhibitors do.

In addition, at least one type of early-stage program listed in *Table 2*, development of sirtuin modulators, has the potential for resulting in agents that may slow or reverse declines in beta-cell function in type 2 diabetes. Thus there are early-stage programs that are designed to address this major unmet need as well.

There is a need for novel drugs in T2D, provided that they address major unmet needs in the disease, such as halting disease progression and mediating weight loss. Drug developers have already produced several drugs that may address these needs and they are at work to develop other drugs that are designed to do so. GEN