



Poly-pills: Are we ready for them today? Tomorrow? Beyond?

American Diabetes Association 2006 Scientific Sessions (June 9-13)

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Executive Summary / Table of Contents

	Slide #
Can a poly-pill solve the diabetes problem? ADA President, Medicine and Science, Dr. Rizza, believes one answer to the diabetes epidemic is the creation of a “poly-pill” to treat diabetes, dyslipidemia, hypertension, and CVD.	4
Could we cure diabetes by treating obesity? We know that even modest weight reduction improves or resolves existing type 2 diabetes and can prevent diabetes in many pre-diabetics. Bariatric surgery is proving to be one way to “treat” diabetes and obesity.	7
Could a needle be the answer, rather than the knife? GLP-1 analogues lower blood glucose and HbA1c levels and also are surprisingly good at promoting weight loss, but currently they require a BID injection. Newer compounds are in development that either reduce the injection frequency or are oral – BUT the oral drugs have no weight-loss effect.	14



Executive Summary / Table of Contents

Slide #

Dual PPARs – Are they dead or alive?

Late-stage setbacks in the development of two of the dual PPARs have left everyone wondering whether we will ever see this class of compounds reach the market. A closer look reveals that they may be down, but they are not out.

21

Poly-Pills: For today? Tomorrow? Beyond?

Regardless of whether we call it Syndrome X, metabolic syndrome, or the cardiometabolic syndrome, we all know that diabetes tends to cluster with other comorbid conditions. Is a single poly-pill the answer to successfully treating this constellation of diseases? Market acceptance has been lackluster in the past – will that trend continue, or are we on the verge of a new paradigm shift?

24



Cure, Optimal Care, and Total Commitment – What if they happened tomorrow?

- ✦ Dr. Robert Rizza, President, Medicine and Science, ADA, presented his vision for diabetes care. In the best of all worlds, a cure for diabetes would reduce the number of serious complications by 42 million over 30 years. Obviously, we are not there yet.
- ✦ If instead our healthcare system could deliver what Dr. Rizza termed “optimal care” – treating 100% of diabetics with the optimal therapy to achieve all of the ADA’s currently recommended treatment goals – there would be a reduction in serious complications of about one-third (18 million over 30 years). Even this goal seems out of our reach at this time.



Committed Care – We can do it, but will we?

- ✦ An even more stepped-down goal of “committed care” in which at least 80% of diabetic patients were able to achieve the ADA recommended goals for lipids, hypertension, and HbA1c would reduce serious complications by almost 25% (11 million over 30 years).
- ✦ He suggests that we could reach this level of committed care with the development of a “**poly-pill**” consisting of 1000 mg **metformin**, 75 mg **aspirin**, 40 mg of a generic **statin**, and 10 mg of an **ACE inhibitor**. He estimates this pill would cost less than \$100 per year.



Committed Care – Yes, but not with a poly-pill

- ✦ In this “somewhat less-than-perfect” world, maybe a poly-pill is part of the answer, but let’s also consider the following:
 - While combinations of drugs to treat single conditions are extremely popular, practicing physicians have not yet embraced the idea of a combo product that treats multiple conditions.
 - Epidemiological studies show that only about 60% to 70% of all Americans with diabetes are even diagnosed, much less treated to achieve the ADA goals.
 - A single poly-pill would not be enough to achieve ADA treatment goals in most diabetics; additional drugs would be needed.
- ✦ While an inexpensive and effective poly-pill could be developed today, it would not replace the need for new and improved agents for diabetes, hypertension, hypercoagulable states, and hypercholesterolemia, especially new drugs with novel and complementary mechanisms to existing products.



Cure – A different approach?

- ✦ The link between obesity and type 2 diabetes is well-known.
- ✦ The three steps of obesity treatment have been 1) lifestyle; 2) pharmacotherapy; and as a last resort 3) surgery.
- ✦ There were several symposia concerning the issue of obesity; the following slides summarize some of the main points and their implications to the pharma industry.



Obesity – The 10,000-step (a day) approach

✦ Lifestyle modification includes the following:

- Reducing caloric intake by 500 to 1,000 calories per day (women – 1,200 to 1,500 calories per day; men – 1,500 to 1,800 calories per day)
 - Ideally, protein is 12%-15% of caloric intake; fat < 30%; carbohydrates > 55%
 - Low-fat or low-carb diets are both effective, although with low-carb diets it may prove difficult to maintain weight loss over the long term.
- Increasing activity – 180 minutes per week
 - Exercise appears to be more important in maintaining weight loss rather than promoting significant weight loss.
- Keeping a food log for 16 to 24 weeks

Patients should not be discouraged if the weight lost is regained – in the DPP trials there was a 58% reduction in the development of type 2 diabetes even though patients regained the weight they lost.



Obesity – Combination therapy will be the Holy Grail

- ✦ Combining either **sibutramine** or **orlistat** with lifestyle modification can double the amount of weight loss seen versus pharmacotherapy alone.
 - Drugs alone – approximately 5% weight loss
 - Drug and lifestyle changes – approximately 11% weight loss
- ✦ Losing weight is difficult because there are a number of compensatory mechanisms. So far, drugs have been able to target only a few of those mechanisms.
- ✦ Analogous to the treatment of hypertension, treatments for weight loss will need to be used in combination, targeting different compensatory mechanisms in the feedback system.
- ✦ Drugs currently used off-label for weight loss, such as **topiramate** and **zonisamide**, are limited by side effects.
 - Perhaps their use at lower doses can be synergized by combining them with agents targeting other areas of the feedback system.



Obesity – There are several promising future drugs in clinical trials today

✦ Future drugs that may hold promise include:

- **Pramlintide** (Amylin, Phase II for obesity)
- **Leptin** (Amgen, Phase II for obesity)
- **Rimonabant** (Sanofi-Aventis, approved for obesity)
- **AOD-9604** – a growth hormone fragment that increases metabolic rate (Metabolic Pharmaceuticals, Phase II for obesity)
- Fixed-dose drug combinations
 - Naltrexone and bupropion
 - Topiramate and phentermine
- Drugs targeting the endocannabinoid system are particularly promising.
 - Sanofi-Aventis has three products in clinical development for obesity: rimonabant, which has been approved in the EU and has an approvable letter from the FDA; AVE-1625, in Phase II development in France; and SR-147778, also Phase II in France.
 - Pfizer has CP-945598, in Phase II in the U.S.
 - Solvay and BMS are co-developing SLV-319, in Phase I in the U.S. and Belgium.



Obesity – Surgery: Last resort or road to the cure?

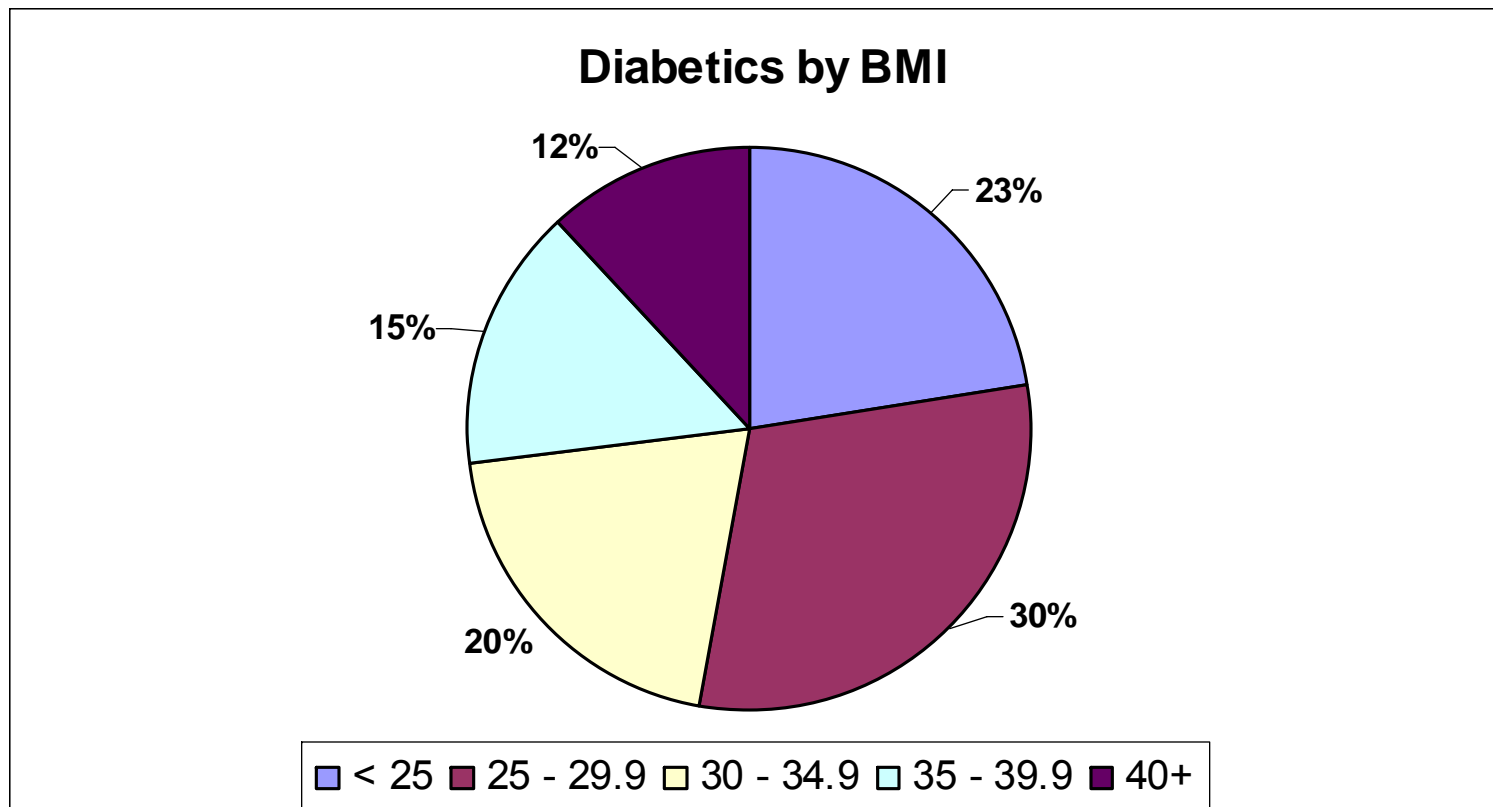
- ✦ Currently, surgery is indicated only for those with a body mass index (BMI) greater than or equal to 40 or a BMI of 35 with other risk factors.
 - Even with these restrictions, about 140,000 bariatric procedures were performed last year.
- ✦ Surgery can achieve weight loss on the order of 40-50 kg – an order of magnitude higher than that achieved with pharmacotherapy alone.
- ✦ There are three commonly used procedures. Lap-band surgery is the least invasive and is reversible but tends to show a slower rate of weight loss in the first year than the other two surgical procedures. By the fourth year, weight loss is similar in all three procedures. Roux-en-Y surgery and duodenal switch surgery are more commonly performed in the U.S., although lap-band is gaining in popularity
- ✦ Surgery is cost-effective at less than \$50,000 per QALY (quality-adjusted life year).

Interestingly, it isn't the weight loss that causes improvement in diabetic symptoms – in many patients, their diabetes improves in days to weeks after the surgery, long before there is a large weight loss. This begs the question of whether diabetics with BMIs less than 35 should be surgical candidates. Some physicians believe the surgery should be done in patients with a much lower BMI of 33, but this is controversial.



Almost half of all diabetics are obese (BMI > 30)

The chart below depicts diagnosed diabetics by BMI category (NHANES 1999-2000).






Bariatric surgery could “whittle away” the diabetes market

- ✦ Only 12% of diabetics have a BMI of 40 or greater and would thus be eligible for surgery today (which has the potential to resolve their type 2 diabetes).
- ✦ If less invasive, reversible lap-band surgery becomes more accepted and the criteria for eligibility for gastric bypass changes to diabetics with a BMI of 35 or higher, we are now looking at over a quarter of the diagnosed type 2 diabetic patient population that could potentially “cure” their diabetes via surgery.
- ✦ If the standard were lowered to diabetics with a BMI of 30, the prevalence of diabetes could potentially shrink to almost half of its size today.

Obviously, not everyone with diabetes who is obese will have surgery, and surgery does not restore normal blood glucose in everyone, particularly if diabetes is long-standing and significant beta cell mass has been lost, but surgery could represent a threat to the pharmacotherapeutic diabetes market that bears watching.



Could weight loss be achieved by the needle rather than the knife?

- ✦ Just as bariatric surgery is enjoying a great deal of success, along comes **Byetta**.
- ✦ **Byetta**, Amylin's GLP-1 analogue, **exendin-4** derived from the gila monster (BID subcutaneous injection), not only reduces blood glucose in a glucose-dependent fashion – so there is less chance of developing hypoglycemia – but also shows a pretty significant weight loss effect.
- ✦ The GLP-1 analogues have been given the name “incretin hormones” and were another hot topic at the meeting, as were a variety of other gut hormones that have both systemic and central (CNS) effects on appetite, metabolic regulation, and blood glucose.
- ✦ A handful of injectable GLP-1 analogues are currently in late-stage development, as well as the oral inhibitors of GLP-1 breakdown, the DPP-4 inhibitors.



GLP-1 Analogues– Poly-pills of a different sort? They may not be just for diabetes...

- ✦ After about a year of clinical experience with the GLP-1 analogue **Byetta** (exendin-4, Amylin), the reactions seem to be quite favorable. It is generally well-tolerated at an SQ BID dose of 10 mg. Average weight loss of almost 5 kg has been seen, making Byetta almost as effective as a weight loss agent as orlistat or sibutramine.
- ✦ While that is great news, here is even better – the long-acting form of **Byetta, LAR**, is in Phase II clinical trials. This is a once-weekly injectable formulation using a dose of 2 mg per week that has shown in 15-week clinical trials to lower HbA1c by 1.7% and cause a 4 kg weight loss. Tolerance issues are similar to those of Byetta.
- ✦ **Liraglutide** (Novo Nordisk, Phase III) is another GLP-1 analogue with a half-life of 12 to 14 hours, allowing for once-daily injections. It lowers HbA1c about 1.75%, similar to Byetta and LAR, but may not affect gastric emptying to the same degree as the exendin-4 formulations; thus, there is a more modest 2.4 kg weight loss.



DPP-4 Inhibitors – Pro: oral formulation; Con: no weight loss

- ✦ Several oral DPP-4 inhibitors are close to reaching the market.
 - **Vildagliptin** (Novartis, NDA filed) lowers HbA1c about 1.1% after one year, similar to the effects of metformin. All the DPP-4 inhibitors are termed “weight neutral,” so no weight loss (or gain) is seen with any of the drugs in this class.
 - **Sitagliptin** (Merck, NDA filed) is another drug in this class and is expected to be on the market in the next year. In a 24-week study, it lowered HbA1c by about 0.8%. The starting A1c level is important – if a patient starts sitagliptin therapy with an HbA1c level less than or equal to 8%, the average drop is 0.7%; however, if the patient starts with an HbA1c of 9% or greater the drop is about 2%. For many patients this should get them close to the recommended A1c level of 7.0% or less.



GLP-1 analogues versus DPP-4 inhibitors

Drug Characteristics	GLP Analogues	DPP-4 Inhibitors
Administration	Injection	Oral tablet
Effect on HbA1c	↓ 0.8-1.8%	↓ 0.5-1.1%
Weight Change	↓ 3-5 kg	No effect (neutral)
Beta Cell Mass Effect (in Animals)	Robust increase	Not as robust



Other GI hormone drug targets are being investigated, but they are not ready for “prime time” yet

- ✦ With the success of the incretin modulators (like GLP-1 analogues), more attention is now focused on a variety of other gastrointestinal (GI) hormones for diabetes and obesity. Four such hormones were discussed at one symposium.
- ✦ **Oxyntomodulin** (Thiakis Ltd., Phase I) comes from the cleavage of the preproglucagon peptide. It is secreted in proportion with food intake and is thought to affect satiety. The weight loss potential is greater than for GLP-1, with less nausea. Rimonabant and oxyntomodulin given together appear to have a synergistic effect.
- ✦ **GIP** was another GI hormone that seemed to get a lot of interest at this year’s meeting. It comes from the same peptide family as GLP-1. In animals, it has been shown to cause an increase in insulin secretion, an increase in B-cell proliferation, and a decrease in apoptosis. Some people with type 2 diabetes are resistant to GIP due to receptor downregulation, but responsiveness may return once glucose regulation is under better control. In animals, a GIP antagonist (developed at the University of Ulster) has shown potential for promoting weight loss. A GIP agonist (also developed at the University of Ulster) has shown efficacy in animal models of diabetes.



Not ready for prime time players – cont.

- ✦ Two other endogenous hormones appear to act more centrally on the CNS.
 - **Enterostatin** is a selective inhibitor of dietary fat intake. In humans, this compound has been administered only via IV injection – with discouraging results. Animal models show a more robust response when the agent is administered into the cerebral ventricles – something not easily accomplished in humans.
 - **GM-CSF** is a cytokine that has many properties similar to leptin. It appears to act centrally to reduce fat intake and promote weight loss. Currently, a form of this cytokine is used to increase white cell production in patients on myeloablative chemotherapy. As with enterostatin, the need for central delivery makes it problematic.

Neither of these two compounds appears to be in active commercial development for obesity or diabetes management.



Will patients choose multiple pills daily to treat their diabetes and obesity, or pick a once-weekly injection to treat both?

- ✦ While there is a lot of research activity in this space, these incretins and gut hormones have the potential to treat both diabetes and obesity, making them attractive drugable targets.
- ✦ The success of **Byetta** demonstrates that SQ injections may become increasingly acceptable, especially if longer-acting formulations are available.

It has long been the belief that an oral, once-daily formulation is the optimum way to deliver pharmacotherapy. With patients finding themselves taking a whole handful of pills each day, perhaps that paradigm is shifting. Several drugs have been formulated to allow for once-weekly, even once-monthly administration. Would a once-weekly SQ injection be preferable to daily multipill dosing? Would injectable formulations to treat a combination of diseases be more acceptable to physicians than combo pills? It is hard to say at this point, but it is an important issue for the future.



Dual (α and γ) PPARs – Are they dead or alive?

- ✦ This time last year, we were looking forward to the launch of one or more of the dual PPAR agents within the next year or two (**muraglitazar** by BMS and **tesaglitazar** by AstraZeneca). Since then, there have been disappointing results and safety concerns about fluid retention and edema in diabetic patients with heart failure.

- ✦ The dual PPARs confer many benefits:
 - Positively impact lipids and glucose homeostasis
 - Prevent inflammation
 - Improve beta-cell function
 - Beneficial activity at vascular wall
 - Improves endothelial function
 - Inhibits matrix metalloproteins and tissue factor



Dual PPARs – Down but not out...

- ✦ ...But fluid retention and edema are troubling.
 - In preclinical trials, there were carcinogenicity issues as well as cardiac events.
 - In clinical studies, the gamma component is believed to be responsible for edema, which may lead to weight gain and/or heart failure.
 - The alpha component has been associated with myopathy and high levels of homocysteine levels and may impact creatinine and renal function.
- ✦ Some interesting observations:
 - The fluid retention that is problematic in heart failure is in the pulmonary space and jugular venous distension; less problematic is the peripheral fluid accumulation. The glitazars (dual PPARs) seem to be correlated only with peripheral edema.
 - Clinical studies have shown that **amiloride** can blunt the weight gain caused by these agents.

It has been suggested that the glitazars may actually “unload” the heart by moving fluid from the pulmonary to the peripheral space.



Dual PPARs – A prototype poly-pill?

- ✦ While the PPARs have been dealt a serious blow, they may not be dead yet.
 - **Metformin** also carries a CHF contraindication, yet this has not significantly affected its use in diabetics without CHF.
 - Combination therapy with **amiloride** might improve the safety profile with regard to edema.
 - Other adverse effects seem to be molecule-related, not class-related
- ✦ Most current PPARs still have a predominant γ activity. Perhaps a more balanced α versus γ activity would have a more acceptable risk versus benefit ratio.

Again, we are dealing with a single pill to treat two separate conditions, even though it is a single molecular entity. We think physicians will accept this dual-action therapy – could it pave the way for future combination therapies used to treat multiple conditions?



Poly-Pill: For today? Tomorrow? Beyond?

- ✦ Increasingly, diseases such as obesity, dyslipidemia, and cardiovascular disorders are hot topics at diabetes meetings. Whether or not the “metabolic syndrome” exists, there is little doubt that these diseases do tend to cluster.
- ✦ It is clear that we have a number of successful marketed products in the armamentarium to treat these diseases as well as numerous developmental products poised to fill in any gaps in the market.
- ✦ The question for us today is whether the marketplace is ready for that “poly-pill” that will treat several conditions with one convenient pill (or injection?).

MJG is here to help you answer that question by providing a full range of services from product forecasting and market research, brand optimization, and product life cycle management to scientific assessments and product in- and out-licensing.



I hope this little summary was informative. If you would like further information, or have an RFP concerning one of the issues discussed here (or others), I can be reached at:

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