

## What's New on the Horizon: Diabetes Medication Update



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## Outline of Talk

- Newly released and upcoming medications: the incretins, DPP-IV inhibitors, and what's coming
- Revised ADA/EASD and AACE guidelines: focus on potency, safety, cost
- Update on insulin therapeutic regimens: self-titration regimens and creative simplified bolus mealtime dosing

## The Diabetes Toolbox 2010

Drug Class (First in Class)	FDA Approval
Insulin	1922 (first use)
Sulfonylurea (chlorpropamide)	1958
Biguanides (metformin)	1995
Alpha-glucosidase inhibitor (acarbose)	1995
Thiazolidinedione (troglitazone)	1997
Meglitinide (repaglinide)	1997
Incretins (exenatide)	2005
DPP-IV Inhibitors (sitagliptin)	2006

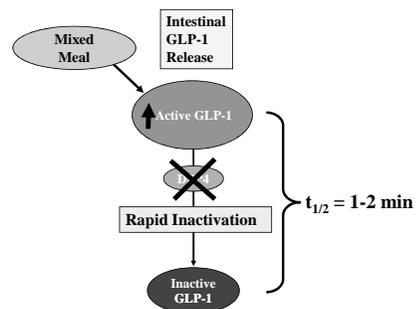
## What's New and What's Coming

- Incretins: GLP-1 agonists and analogs
- Incretins: DPP-IV inhibitors
- Bile acid sequestrants: colesevelam
- Sodium-Glucose Transport Proteins-2 (SGLT-2) inhibitors: Dapagliflozin

## Glucagon-Like Peptide-1

- Glucagon-like peptide-1 is an incretin, a gut hormone that increases the release of insulin
- Many effects of GLP-1:
  - Increases insulin sensitivity
  - Inhibits glucagon release
  - Inhibits gastric emptying
  - Increases satiety and decreases food intake
- Native GLP-1 improves glucose control but the short half-life limits its use (needs pump)

## GLP-1 Agonists and DPP-IV Inhibitors



### **GLP-1 Agonists and Analogs**

- Exenatide: GLP-1 receptor agonist (BID)
- Liraglutide: GLP-1 analog (QD)
- Under development:
  - Once-weekly exenatide long-acting release (LAR)
  - Taspoglutide
  - Lixisenatide
  - Others in various stages

### **GLP-1 Inhibitors: Exenatide**

- Modification of GLP-1 to prevent degrading
- Modest benefit in HbA1c 0.7-1.1%
- Significant nausea (52% vs 8% for insulin) and emesis; RJ Heine et al, Ann Int Med 2005
- Some weight loss as well (see further slide)
- Significant heterogeneity in response in clinical experience (some all-stars, some fail)
- Safety warnings about pancreatitis, kidneys

### **Liraglutide**

- Approved January 2010; once-daily injection
- Associated with similar modest decrease in HbA1c of 0.7% - 1.1% with *slightly* more reduction in one trial (LEAD-6)
- Less renal limitations than exenatide
- Possible association with pancreatitis and there is suggestion of rare thyroid tumors in rats so special warnings for medullary thyroid cancer

### **GLP-1 Inhibitors: Exenatide LAR**

- Sustained release form of exenatide that will likely be given once-weekly
- Similar A1c benefit to twice-daily exenatide and similar weight reduction with somewhat less nausea (26% vs 50%)
- Device not finalized; path to approval not yet clear

### **DPP-IV Inhibitors**

- Sitagliptin (Januvia) and saxagliptin (Onglyza)
- Associated with modest decrease in HbA1c of 0.6% - 0.8%; can be dosed with ESRD
- Minimal side effects (possible more minor infections)
- Both are pregnancy Category B – unclear why
- Minimal long-term safety data – possible off-target interactions with diverse DPP-IV targets

### **Colesevelam**

- Bile acid sequestrant, initially approved to lower LDL cholesterol; trade name Welchol
- Approved for DM2 in 2008; modest efficacy of 0.4-0.5%
- Previously required a large number of pills, now approved in powdered suspension
- Modest efficacy, probably best suited for patients needing small LDL and A1c reductions

## SGLT-2 Inhibitors

- Sodium-glucose cotransporter-2 is a protein that aids in glucose reabsorption from the kidney
- Inhibition of this protein leads to increased glucosuria – in early studies appears to reduce A1c and body weight, with possible side effect of increased UTIs and yeast infections
- Several in development (dapagliflozin, remogliflozin, sergliflozin), none near release

## Final Thoughts on New Therapies

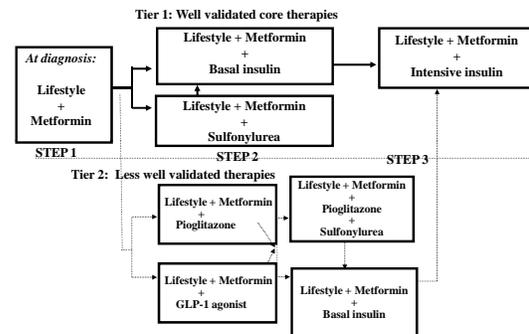
- None of these have been in wide use for long
- Lessons of rosiglitazone: hemoglobin A1c is a surrogate endpoint, not the true goal of care
- None of these have any microvascular or macrovascular endpoints (trials underway)
- All of these drugs cost upwards of \$6/day
- Hence their place in ADA/EASD paradigm

## ADA/EASD DM2 Algorithm

- Updated in 2009 based on clinical trials and collective clinical judgment and experience of authors
- Evaluates glucose reductions, non-glycemic effects that could reduce diabetic complications, safety, tolerability, ease of use, and cost of each intervention
- Provides treatment algorithm with intervention tiers

DM Nathan et al, Diabetes Care 2009

## ADA/EASD DM2 Algorithm



DM Nathan et al, Diabetes Care 2009

## Diabetes Interventions by Tiers

- **Tier 1 Interventions ('well-validated core')**
  - Lifestyle changes with diet and exercise (1.0-2.0)\*
  - Metformin (1.0-2.0)
  - Insulin (1.5-3.5)
  - Sulfonylureas (1.0-2.0)
- **Tier 2 Interventions ('less well-validated' core)**
  - Thiazolidinediones (pioglitazone) (0.5-1.4)
  - GLP-1 agonists (exenatide) (0.5-1.0)
- **Others (less A1c lowering, less evidence, or costlier):**
  - $\alpha$ -Glucosidase inhibitors (0.5-0.8), Glinides (0.5-1.5)
  - Pramlintide (0.5-1.0), DPP-IV inhibitors (0.5-0.8)

DM Nathan et al, Diabetes Care 2009

## Comments on Treatment Choices

- Tier 2 options may be considered when weight loss is major goal (exenatide) or when hypoglycemia is major concern (pioglitazone and exenatide, not rosi)
- $\alpha$ -Glucosidase inhibitors, glinides, pramlintide, and DPP-4 inhibitors appropriate for selected patients
- Starting or intensifying insulin preferred to third oral
- Algorithm is cautious in use of newer treatments

DM Nathan et al, Diabetes Care 2009

### AACE Algorithm

- Released by American Association of Clinical Endocrinologists in October 2009
- Stated by AACE to include a variety of choices based on first-line, second-line, and third-line therapies as well as secondary factors (weight, risk of hypoglycemia)
- Emphasizes wider choices
- Ends up somewhat overwhelming algorithm

HW Rodbard et al. Endocrine Practice 2009

### A Broader Toolbox Doesn't Improve All Outcomes

- Diabetes is a progressive disease
- More choices can decrease ability to intensify care (SS Iyengar, 2000)
- Use algorithms as a guideline (joint ADA-EASD consensus statement)
- Individual patients may have specific needs that require tailoring algorithms

### Diabetes Toolbox: A Critical Look

Drug Class	A1C%	Cost/Mo
Sulfonylureas (glimepiride, etc)	1.2-2.0	4-12
Metformin	1.2-2.0	4-12
Thiazolidinediones (pio 45 qday)	0.8-1.4	245
GLP-1 agonist (exenatide 10 bid)	0.8-1.2	271
DPP-IV (sitagliptin 100 qday)	0.6-0.8	193
Human Insulin	No limit	~25
Insulin Analogs (vials)	No limit	~80
Insulin Analogs (pens)	No limit	~100

Drugstore.com

### Indications for Insulin Therapy

- Severe hyperglycemia at diagnosis or at a later point despite aggressive treatment
- To meet glycemic goals - hyperglycaemia despite maximum doses of oral agents
- Decompensation of other organ systems that limits use of other oral agents
- Early cost-effective potent treatment

### Creative Regimens for Insulin

- Empowering through basal self-titration regimens
- Customizing meal dosing based on patient real-world visualization, "the sandwich rule"



### Basal Insulin Self-Titration

- Clinical trial data suggests that patients can self-titrate once-daily basal insulin with excellent success (compared with clinicians)
  - Lowering fasting glucose
  - Lowering hemoglobin A1c
  - Minimal hypoglycemia
- This is seen both with basal insulin glargine and detemir in published clinical trials

### **Simpler Bolus Meal Dosing**

- Not every patient has to move to carb counting
- For Olympia, “carb counting for loggers”
  - 5 units for meal less than a sandwich
  - 10 units for a sandwich-sized meal
  - 15 units for more than a sandwich
  - Can substitute burrito or Hawaiian lunch plate
- This is not full carbohydrate counting, but leads patient to grasp insulin-food connection

### **Conclusion**

- There are interesting new therapies available and on the horizon, but all still have limited long-term safety and hard endpoint data
- The new ADA/EASD guidelines support first-line use of metformin and then either sulfonylureas or basal insulin
- Creative approaches with self-titration basal regimens and mealtime dosing can be designed

### **Questions and Appreciation**



Thanks to Mindy Nichols and WADE for the opportunity to speak today