Promising New Approaches to Clinical Interventions Aimed at Reducing Obesity and Preventing Progression and Complications of Diabetes

John Buse, MD, PhD
Verne S. Caviness Distinguished Professor
Chief, Division of Endocrinology
Director, NC Translational and Clinical Sciences Institute
Executive Associate Dean, Clinical Research
University of North Carolina School of Medicine
Diabetes complications are preventable today!

What is the spectrum of diabetes complications?
- Microvascular complications (eye, kidney, nerve)
- Macrovascular complications (myocardial infarction, stroke, peripheral vascular disease)
- Emerging complications (cancer, liver disease, arthritis, dementia, heart failure . . .)
- Uncertain impact of type 2 diabetes in youth

What would it take to accomplish eradication of early disability and death from classical complications of diabetes at a population level?
- Detect prediabetes and type 2 diabetes by screening
- Treatment per guidelines (lifestyle, education, medications [glycemia, BP, statins, etc])
  - Individualized care delivered in a patient-centered way
  - Access to care
  - Avoid therapeutic inertia
  - Creative and opportunistic team-based care with social/societal support

*Sweden A1c, glycosylated hemoglobin

† US
Every day, >1000 people die prematurely or are disabled as a result of diabetes in the US

What are the barriers to avoiding these poor outcomes to care?

• Access to care
• Other poorly understood drivers of health outcome “disparities”
• Lack of systems of care (with notable exceptions)
  • Non-adherence by patients
  • Non-adherence of providers
• Focus of payors on short-term costs as opposed to long-term benefits
• Insanity in the marketplace regarding pricing for goods and services
• Regulatory imbalance (drugs, devices, diagnostics, payors)
  • Poor pipeline of discovery to implementation
    • Prediabetes
    • Diabetes indications
    • Obesity
• In fact, it is in obesity management where the opportunities for benefit have been least developed
20-year History of Chronic Weight Management Therapeutics

Number of classes of antihyperglycaemic agents

0 drugs in phase III

Antihypertensive Therapeutics

- Angiotensin II receptor blockers
- ACE Inhibitors
- Calcium channel blockers
- \(\beta\)-blockers
- Diuretics
- Central \(\alpha\)-2 agonists
- Peripheral \(\alpha\)-1 blockers
- Adrenergic neuronal blockers

Antihyperglycemic Therapeutics

- Soluble insulin
- Intermediate-acting insulin
- Sulfonylurea

Thiazolidinedione
- Metformin
- Human insulin
- Sibutramine
- Orlistat
- Liraglutide 3mg
- Lorcaserin
- Phentermine

Phentermine+Topiramate
- Naltrexone+Bupropion

0 drugs in phase III
## Medications Approved for Obesity - 2016

<table>
<thead>
<tr>
<th>Medication</th>
<th>Average Weight Loss*</th>
<th>Mechanism of Action</th>
<th>Potential Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine† (Adipex™, Ionamin™)</td>
<td>~ 5%</td>
<td>Adrenergic</td>
<td>Tachycardia, hypertension</td>
</tr>
<tr>
<td>Phentermine / Topiramate (Qsymia™)</td>
<td>10%</td>
<td>Adrenergic, CNS</td>
<td>Tachycardia, hypertension, cognitive dysfunction, neuropathy, teratogenicity</td>
</tr>
<tr>
<td>Liraglutide (Saxenda™)</td>
<td>7%</td>
<td>GLP-1 agonist</td>
<td>Nausea</td>
</tr>
<tr>
<td>Bupropion / Naltrexone (Contrave™)</td>
<td>4.5%</td>
<td>CNS; opioid antagonism</td>
<td>Seizures, confusion, anxiety, opiate withdrawal</td>
</tr>
<tr>
<td>Lorcaserin (Belviq™)</td>
<td>3.5%</td>
<td>Serotonergic (5HT&lt;sub&gt;2C&lt;/sub&gt;)</td>
<td>Headache</td>
</tr>
<tr>
<td>Orlistat (Xenical™)</td>
<td>3%</td>
<td>Lipase inhibitor</td>
<td>Steatorrhea, incontinence</td>
</tr>
</tbody>
</table>

* Beyond placebo  † Only approved for short-term use