Understanding the issues on TZDs, DPP4s, GLP-1 agonists

How we got the pharmaceutical industry we deserve

Edwin Gale
Declaration of Interests

I consulted for the pharmaceutical industry prior to 2000, earning £25-30k/yr

Since then no consultancies, shares, or any other form of income from the industry (two offers of covert funding refused)

I have acted as an expert witness in drug-related litigation in the USA (troglitazone, pioglitazone and exenatide)
Personal Background

1976: “Can phenformin-induced lactic acidosis be prevented?” (BMJ)

1990s: Clinical Expert for Eli Lilly, European regulatory submissions for Humalog and Humalog mixes


2006 -2012: Chair, Special Advisory Group (SAG) for Diabetes and Endocrinology of EMEA (now EMA)
• Ethics
• Science
• Authority
• Commerce
- Companies
- Regulators
- Guideline Makers
- Physicians
- The Patient
The abdication of the physician?
“Best thing since sliced bread”

“Wouldn’t give it to a politician”

“Useful in selected patients”
Surrogate end-points

Safety concerns

Hard outcomes
Long term safety
Surrogate end-points

UGDP 1968

Hard outcomes
Long term safety

CV safety of SUs still debated

Safety concerns
Drug Safety Issues: Diabetes

Phenformin
Human insulin
Troglitazone
Rosiglitazone
Rimonabant
Sibutramine
Inhaled insulin
Insulin glargine
Exenatide (Liraglutide)
DPP-4 inhibitors
What the record shows

Serious adverse events not identified at approval for 20% of drugs handled by FDA, and 20% of these withdrawn in consequence

Serious adverse events in 1/3 drugs granted fast-track approval

Average 10 year response time

Moore TJ, Arch Intern Med Oct 8th 2012
Many potent drugs have serious side effects but some continue to be used because they offer a unique benefit that outweighs the risk. This is not the case with phenformin...
UGDP Study: Increased mortality with phenformin

Diabetes, 1975
Guilt by Association

• The US launch of metformin was delayed by 20 years (to March 1995), mainly due to safety concerns related to phenformin
• Now universally accepted as first line drug of choice in diabetes
• Appears to improve cardiovascular safety
• Millions of Americans could have benefited had it been available
The Troglitazone Story

On May 17 1998, Audrey LaRue Jones, a 55 year-old school teacher with IGT, died of acute liver failure weeks after starting troglitazone in an NIDDK-sponsored trial*.

Her death was ascribed to the drug, and the trial was stopped on June 4th 1998.

* Panel chaired by a man who held two patents for troglitazone use
Troglitazone Time-Line

1996 (Nov) FDA medical officer concludes Rezulin unfit for approval. He is replaced.

1997 (March) Rezulin launch in US

1997 (October) Rezulin launched in UK, withdrawn after 29 days when US safety reports received

Troglitazone: the lesson that nobody learned: Diabetologia 2006
http://www.troglitazone-story.net/
Troglitazone Time-Line

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Sir Richard Sykes, CEO Glaxo-Wellcome

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1998 (May) death of Audrey LaRue Jones

1999 (June) American Endocrine Society endorses Rezulin

2000 (March) Rezulin withdrawn

Troglitazone: the lesson that nobody learned: Diabetologia 2006
http://www.troglitazone-story.net/
The fall of troglitazone

• Was largely due to a Pulitzer-winning journalist from the Los Angeles Times

• And the actions of “the termites” - 2 FDA officials who alerted US Senator Waxman to the problem

• And were disciplined by FDA for so doing
“Describing the Agency he works for as incapable of stopping dangerous drugs from coming to and staying on the market, David Graham told the senators...”

Newsweek, 2004
“The most striking thing about the story is that the medical community remained resolutely silent on the subject of patient safety. No prominent physician, anywhere in the world, ever stood up to say that a pill for diabetes is not worth dying for”

Troglitazone: the lesson that nobody learned
Diabetologia (2005)
“Media reports sensationalizing the risks associated with Rezulin therapy have created a climate in which patients and physicians have been simply unable to make informed decisions regarding the safety and efficacy of Rezulin”

*Warner-Lambert, March 2000*
Troglitazone Time-Line

“Media reports sensationalizing the risks associated with Rezulin therapy have created a climate in which patients and physicians have been simply unable to make informed decisions regarding the safety and efficacy of Rezulin”

Warner-Lambert, March 2000

“The rate of ALF estimated at 1/1000 users ... cumulative incidence increased with time ... enzyme monitoring ineffective and poorly performed ... “point of no return” reached when liver enzymes still normal ...”

FDA Final Report NDA 29-720 Dec 19 2000
The Panalba Paradigm

*Panalba* (1957-1970) was an antibiotic combination shown to be more dangerous and less effective than competing agents.

*Presented with this clear evidence, the board of Upjohn voted to keep the drug on the market, and to fight its withdrawal through the courts*
The Panalba Paradigm

*Panalba* (1957-1970) was an antibiotic combination shown to be more dangerous and less effective than competing agents.

*Presented with this clear evidence, the board of Upjohn voted to keep the drug on the market, and to fight its withdrawal through the courts.*

Prof Scott Armstrong presented these data to his MBA students. 97% considered the company behaviour to be unethical.

In role-playing exercises, however, 79% opted to do the same as Upjohn

The Moralization Gap

“It’s not just that there are two sides to each dispute. It’s that each side *sincerely* believes its version of the story, namely that it is an innocent and long-suffering victim and the other side a malevolent and treacherous sadist. And each side has assembled a historical narrative and database of facts consistent with its sincere belief”

Steven Pinker
*The Better Angels of our Nature*
Drugs for Diabetes: Special Considerations

• Well-established and much cheaper alternatives
• Lack of unbiased head-to-head comparisons
• Lack of outcome studies
• Lack of cardiovascular benefit
• Gradient of risk within the treated population
• The boundless possibilities of the new versus the suboptimal performance of the old
The constraints on industry

20 year licence, ~12 yrs on the market
“High compression” marketing
Pressure to produce blockbusters
Heavy reliance on shareholder confidence
Vulnerable giants
Drug development

Working clinical knowledge
Drug development

Independent evaluation

Regulators
Cochrane
NICE, etc

Working clinical knowledge

Publication bias?
Head to head?
Outcome studies?
Long term safety?
Rosiglitazone: clinical summary document to support formulary applications

References 57
Product related 22
“Data on file” 6
Abstracts 12
Papers:
  • Pharmacokinetic 2
  • Clinical trials 2
Rosiglitazone in combination with, and in place of, Metformin

HbA1c over weeks

-4 4 8 12 20
Rosi 4 mg bd
MF 2.5 gm
MF + Rosi

(FDA website)
Rosiglitazone in combination with, and in place of, Metformin

LDL Chol

mM/L

(FDA website)
Role playing exercise
The marketing manager
The Drug Narrative

- Drug development
- Independent evaluation
- Managed perception
- Working clinical knowledge
Construction of a drug narrative

1. Identify the problem for which your drug is the solution
2. Promote clinical awareness of this problem
3. Accentuate the positive
4. Downplay the negatives
5. Discredit the alternatives
6. Add some “blue sky”
Insulin resistance

Don't worry about this.
be a doctor
be an architect of the future

AVANDIA
4mg once daily rosiglitazone
Resensitising makes sense
Insulin resistance

KOLs
Insulin resistance

Sulfonylureas
Metformin

KOLs

be a doctor
be an architect of the future

Resensitising makes sense

AVANDIA
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Sulfonylureas
Metformin
Insulin resistance

KOLs

Sulfonylureas
Metformin
The Narrative becomes the Evidence

- Managed perception
- Drug development
- Independent evaluation
- Working clinical knowledge

The Narrative
Incretin effect
Incretin effect

KOLs

Do more than lower blood glucose. Grab diabetes by the roots.

New once-daily Victozan goes deep to impact many parts of type 2 diabetes, with significant and sustained:
- Reductions in HbA1c up to 2.74%**
- Reductions in weight: -4.8 kg
- Reductions in systolic blood pressure: -6.7 mm Hg
- Improvements in beta-cell function**
Incretin effect
Incretin effect

KOLs

Sulfonylureas
Insulin
Incretin effect

Sulfonylureas
Insulin

KOLs
Launching New Agents: the Evidence Gap

- No outcome studies
- Few head-to-head studies
- Cost-benefit unknown
- Long term safety unknown
- Selective publication of results
- Inadequate post-marketing surveillance
Launching New Agents: the Evidence Gap

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- Long term safety unknown
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Evidence-based medicine cannot function without the evidence
GLP-1 Based Therapies

DPP4 Inhibitors
- Sitagliptin
- Saxagliptin
- Vildagliptin

GLP Analogs
- Exenatide
- Liraglutide

High physiological levels

Pharmacological levels
Questions

1. Is GLP-1 deficiency a factor in the pathogenesis of diabetes?
“There is little evidence to suggest that impairments in incretin secretion play a major role in the pathogenesis of type 2 diabetes ...

... the reduction of the incretin effect in patients with diabetes may simply be an epi-phenomenon of chronic hyperglycemia, independent of any primary defect in GIP or GLP-1 action.”

Meier & Nauck, Diabetes 2010;59:1117-25
Questions

1. Is GLP-1 deficiency a factor in the pathogenesis of diabetes?
2. How do GLP-1 analogues work?
Who am I?

I suppress appetite
I delay gastric emptying
I reduce weight

I inhibit glucagon

I reduce post-prandial glycaemia
Pramlintide!

I suppress appetite

I delay gastric emptying

I reduce weight

I inhibit glucagon

I reduce post-prandial glycaemia
An enterogastrone?

- Appetite suppression
- Delayed gastric emptying
- Weight reduction
- Glucagon inhibition
- Reduction in post-prandial glycaemia

Horowitz & Nauck, Gut, 2006;55:148-150
Questions

1. Is GLP-1 deficiency a factor in the pathogenesis of diabetes?
2. How do GLP-1 analogues work?
3. Where do they act?
**Where does GLP-1 act?**

<table>
<thead>
<tr>
<th>Tissue/Cell Type</th>
<th>Function/Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular tissue</td>
<td>Cardioprotective?</td>
</tr>
<tr>
<td>CNS</td>
<td>Huntington’s?</td>
</tr>
<tr>
<td>Bone</td>
<td>Anabolic</td>
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<tr>
<td>Proximal renal tubule</td>
<td>Mild diuretic</td>
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<td>Gut</td>
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<tr>
<td>Beta cell</td>
<td>Secretion, proliferation?</td>
</tr>
<tr>
<td>Location</td>
<td>Function</td>
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<td>------------------------------------------</td>
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<tr>
<td>Thyroid C cells</td>
<td>Growth factor?</td>
</tr>
<tr>
<td>Exocrine pancreas</td>
<td>Growth factor?</td>
</tr>
</tbody>
</table>
GLP-1 receptor expression in exocrine ducts

Tornehave D et al., J Histochem Cytochem (2008)

Impact of GLP-1 therapy in rodents in-vivo
“Notwithstanding the uncertainty about whether rodent or human acinar and ductal cells express a functional GLP-1R, older rodent pancreatic ductal cells retain the capacity to proliferate following GLP-1R activation. Indeed, a 3-fold increase in ductal proliferation was observed after a 7 day course of exendin-4 in three 7 month old mice...”

Drucker DJ, Diabetes 2013;62:3316-23
Questions

1. Is GLP-1 deficiency a factor in the pathogenesis of diabetes?
2. How do GLP-1 analogues work?
3. Where do they act?
4. How effective are they?
ABCD Audit of ~4,400 patients

**HbA1c**

- Baseline: 9.5%
- Latest: 8.8%

Decrease: 0.73%

**Wt**

- Baseline: 115 kg
- Latest: 109 kg

Decrease: 5.9 kg
ABCD Audit of ~4,400 patients

- **HbA1c**: 0.73% decrease
- **Wt**: 5.9 kg decrease
- 20% dropout
Effect upon HbA1c: Exenatide once weekly

Weekly exenatide produced similar reduction in HbA1c (~1.5%) and weight loss (~2kg) as compared with metformin at 26 weeks

Superior to sitagliptin

Russell-Jones et al, Diabetes Care 2012;35:252-8
Questions

1. Is GLP-1 deficiency a factor in the pathogenesis of diabetes?
2. How do GLP-1 analogues work?
3. Where do they act?
4. How effective are they?
5. How cost-effective are they?
Relative Costs of GLP-1 Based Therapies

Cost per year's treatment, £GBP

Metformin, Glipizide, Sitagliptin, Saxagliptin, Exenatide, Liraglutide

British National Formulary 2012
Questions

1. Is GLP-1 deficiency a factor in the pathogenesis of diabetes?
2. How do GLP-1 analogues work?
3. Where do they act?
4. How effective are they?
5. How cost-effective are they?
6. How safe are they?
The challenge of pleiotropic agents

- Traditional drugs are antagonists
- TZDs and incretins are agonists
- Complex networked effects, phenotypic modification
- Long term consequences uncertain
Drug safety? Ask an Investor

2005 (29 April) Exenatide marketed in the US

2006 (Feb) First case report of pancreatitis

2006 (Oct 2) Bear Stearns warns investors of pancreatitis risk based on FDA data

2006 (Oct 12) Company introduces label change

2007 (Oct) FDA alerts physicians to risk of pancreatitis

Collateral damage: the conundrum of drug safety. Diabetologia 2009
April 2012

Dear Health Care Professional,

... “A review of reports of pancreatitis from post-marketing experience revealed that signs of pancreatitis occurred after the start of saxagliptin treatment and resolved after discontinuation, which is suggestive of a causal relationship. Moreover, pancreatitis has been recognized as an adverse event for other DPP-4 inhibitors... “

Dr Rick Lones
Executive Medical Director, UK and Ireland
Bristol-Myers Squibb Pharmaceuticals Limited
Pancreatic Safety of Incretin-Based Drugs — FDA and EMA Assessment

Animal studies
  Largely negative but healthy animals

Clinical trial data:
  Acute pancreatitis
    Small imbalances in premarketing studies
    Pooled data reassuring
  Subclinical enzyme changes
    “mean levels in the normal range”

CV safety trials
  SAVOR:  12 vs 8
  EXAMINE:  22 vs 16

Observational studies
  “Have yielded inconsistent results”
Pancreatic Safety of Incretin-Based Drugs — FDA and EMA Assessment

Animal studies
Clinical trial data:
  - Acute pancreatitis
  - Subclinical enzyme changes

CV safety trials

[Adverse event reports]

Observational studies

[Human post-mortem studies]
# GLP-1 Agonists: MedWatch Reports

<table>
<thead>
<tr>
<th></th>
<th>Pancreatitis (OR)</th>
<th>Ca Pancreas (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>2327 (30.7)</td>
<td>258 (12.2)</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>888 (94.6)</td>
<td>63 (30.2)</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>718 (38.2)</td>
<td>81 (15.5)</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>125 (51.2)</td>
<td>18 (34.3)</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>43 (84.2)</td>
<td>1 (14.8)</td>
</tr>
</tbody>
</table>

Butler, Elashoff, Gale, 2013
Why the fuss about a few excess cases of acute pancreatitis?
Why the fuss about a few excess cases of acute pancreatitis?

It could mean a much larger number with subclinical inflammation ...
Why the fuss about a few excess cases of acute pancreatitis?

It could mean a much larger number with subclinical inflammation ...

Which means cancer
ALL Phase 3 incretin studies which measured pancreatic enzymes found elevated lipase: Amylase elevated in some

NOT ONE reported this finding, including a study published in the Lancet which was designed specifically to measure pancreatic enzymes

(BMJ investigation)
What about the human pancreas?

8 organ donors on incretins (1 exenatide, 7 sitagliptin), 12 with diabetes on other therapies, 14 controls

All pancreases rated abnormal
Weight increased by 40% on incretin therapy
Increased exocrine dysplasia and PanIN lesions
Marked alpha cell hyperplasia
3 alpha cell microadenomas, 1 neuroendocrine tumour

Strengths of the Butler study

Transplant quality pancreas
World class collection facility
Open access for nPOD users
Superb histopathologist
Critique of the Butler study

Comparison group not well matched with incretin group
Comparison group contained people with type 1 diabetes
Increase in pancreatic weight due to age/BMI
Increase in PanIN lesions secondary to age difference
Changes might be due to hypoxia in intensive care
Alpha cell hyperplasia seen in other type 2 diabetes

Pancreas Weights, nPOD.

A

Pancreas Weight (g)

Pancreas Weights for different conditions:
- No diabetes
- T1D
- T2D
- T2D Incretin

Graph showing the distribution of pancreas weights with statistical significance indicated by asterisks and crosses.
Incretin treatment in humans, proliferation and dysplasia

PanIN 1 and 2 lesions/mm$^2$ tissue $\times 10^3$

Ki67 in whole pancreas section [%]

Butler A, Diabetes (2013)
Beta cell area %

Alpha cell area %

Butler AE et al 2013
Questions for the future

Is something happening in the thyroid?
Is something happening in the exocrine pancreas?
What is happening to the alpha cell?
What is happening to the beta cell?
Questions for the future

Is something happening in the thyroid?
Is something happening in the exocrine pancreas?
What is happening to the alpha cell?
What is happening to the beta cell?

We need:

Imaging studies of the pancreas before and after incretin therapy
Major independent initiative on autopsy findings
Large scale long term analysis of cancer risk
The hand that holds the pen controls the market

We get the pharmaceutical industry we deserve