

GLP-agents with Insulin – No Magic Bullet

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Competing Interests

- None whatsoever. I have no expertise in diabetes.

American College of Chest Physicians Guidelines (2012): evidence appraisal & treatment recommendations led by methodologists in Evidence-Based Medicine.

Specialists in field considered too conflicted to be able to give genuinely unbiased opinions.

Diabetes Hall of Shame

- Phenformin
- Chlorpropamide
- Troglitazone
- Muraglitazar
- Rosiglitazone

Faith, more than Science

- Relentless pursuit of Glucose targets (ignoring law of diminishing returns)
- Multiple surrogate outcomes (which no single drug can cover)
- Paucity of hard outcome data, even with metformin
- Disregard of adverse effects data
- This creates fertile hunting ground for pharma industry – yet another new (expensive) drug, amongst many!

Why GLP agents + insulin?

- Avoid Hypoglycaemia?
- Avoid Weight gain?
- Better Post Prandial Glucose control?
- (Past aim was exenatide to help patients stop insulin, but this failed, so diabetologists moved the goalposts)

Time for Self-Reflection



How do Diabetologists weight up their treatment options?

Psychology of Prescribing in Type II DM

- Self-doubt, Insecurity & Fear of Failure
 - No robust data on beneficial outcomes
 - Clear evidence of harm
 - Dread of using insulin
- Need for self-redemption and salvation
 - Use drugs that apparently reduce adverse effects of other hypoglycaemic agents

GLP-1 agents – panacea for all the ills of insulin!

- Turn back all the horrors brought on by other drugs
 - Promote weight loss
 - Reduce risk of hypoglycaemia
- Clear conscience

Problems with GLP-1 agents

- Do they work? Yes, but only on surrogate measures in short-term
- Are they the best thing since sliced bread?
No, because:
 - Expensive
 - Imagined clinical benefits derived through extrapolation
 - Harmful (exchanging one set of adverse effects for another)

Typical costs per patient

Daily dose of drug	Annual cost
Liraglutide 1.2 mg+ Detemir 40 u	£ 1444
Liraglutide 1.2mg	£ 940
Sitagliptin 100 mg	£ 400
Pioglitazone 30 mg	Generic ?price
Metformin 2g	£ 20

Cost Effectiveness

- Unknown
- Given high annual costs and prevalence of type II DM, likely to need millions of pounds/yr in England
- What for?
 - No reduction in MI/ stroke
 - No decrease in vascular/ neurological complications

GLP agents – RCT data

- Limited to two main trials
 - Exenatide vs. placebo added onto glargine for 30 weeks
 - Detemir vs. nothing in liraglutide users for 26 weeks (unpublished)
- Clever choice of control – guaranteed not to fail in primary HbA1C outcome

Clinical benefit HbA1C

Comparison	Mean change %
Exenatide + Glargine vs. Glargine alone	-0.69 (-0.93 to -0.46)
Detemir + Liraglutide vs. Liraglutide alone	-0.52 (-0.68 to -0.36)

Clinical benefit: Weight

Comparison	Mean change kg
Exenatide + Glargine vs. Glargine alone	-2.7 (-3.7 to - 1.7)
Detemir + Liraglutide vs. Liraglutide alone	+ 0.97 (0.88 - 1.06, $p < 0.001$)*

* I calculated this from unpublished raw data

Adverse Events: Exenatide

Adverse Event	Exenatide (n=137)	Placebo (n=122)	Relative Risk
Withdrawals	13	1	11.6 (1.5– 87)
Nausea	56	10	5.0 (2.7 – 9.3)
Vomiting	25	5	4.5 (1.8– 11.3)
Diarrhoea	25	10	2.2 (1.1-4.4)

Significant increase in constipation and headache also noted.

Hypoglycaemia: Exenatide

- No major differences in exenatide vs. placebo when added to glargine
- Minor hypo: 34/137 (25%) vs. 35/ 122 (29%)
- Exenatide does not significantly reduce hypoglycaemia in glargine users

Adverse Events: Detemir plus Liraglutide

Adverse Event	Detemir/Lira (n=162)	Lira (n=161)	Relative Risk
Serious	17	11	1.5 (0.74– 3.2)
Minor hypo	22	2	10.9 (2.6 – 46)

Detemir still causes significantly more hypoglycaemia even when used together with liraglutide

Intepretation (1)

- Exenatide improves HbA1C in glargine users
- Modest weight loss
- At the cost (or because of) significant GI adverse effects, and treatment withdrawals due to adverse effects

Interpretation (2)

- Detemir improve HbA1C when added to liraglutide
- But at a cost of significantly greater hypoglycaemic episodes
- May reverse some of the weight loss seen with liraglutide alone

Conclusions

- So What?
- GLP agents + insulin reduce HbA1C, no better than any other agent
- Expensive
- Harmful
- Unbridled enthusiasm and perceived advantages are not supported by a cold hard look at the evidence.