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DETOUR

Mapping Medications: New Routes and Detours

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ON THE ROAD TO DIABETES EDUCATION BEST PRACTICES
WASHINGTON STATE AADE 2011 Conference
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Disclosures

JN receives research grant support from Amylin, Johnson & Johnson, Merck and Novartis.


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Objectives

1. Discuss medications that can affect blood glucose levels or mask the symptoms of hypoglycemia;
2. Describe and discuss recent reports and controversies regarding the safety of medications for the treatment of diabetes; and
3. Outline new and emerging therapies for the treatment of diabetes and discuss the potential pros and cons of these agents

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Discuss medications that can affect blood glucose levels or mask the symptoms of hypoglycemia



A cartoon illustration of a yellow character with a face, wearing a red shirt that says "SUGAR" and "HAPPY". The character is riding a roller coaster track that is shaped like a roller coaster. The character is at the peak of a hill, looking happy. The background is a simple landscape with green grass and a blue sky.

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Medication-Induced Hyperglycemia



A photograph showing a person's hand holding a blue glucose meter. A small drop of blood is being applied to a test strip that is inserted into the meter. The meter has a small screen and several buttons.

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Diuretics

- Thiazide diuretic-induced hyperglycemia thought to be due to a reduction in total body potassium
- Dose-dependent and reversible
 - Potassium replacement
 - Drug discontinuation
- Loop diuretics (furosemide, torsemide etc.) also implicated
- Thiazides did not increase risk of DM development in a prospective study

Luna B et al. JAMA. 2001;286:1945-8.

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Protease Inhibitors

- Known to contribute to:
 - Hyperglycemia
 - Hypercholesterolemia
 - Lipodystrophy
- Hyperglycemia reported in 3%-17% on PIs
- Mechanism thought to be:
 - Increased insulin resistance
 - Impaired β -cell function
- Discontinuation not recommended to alleviate hyperglycemia

Luna B et al. JAMA. 2001;286:1945-8.

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Atypical Antipsychotics

- Significant weight gain observed with treatment
 - Insulin resistance
- Cases of new-onset DM in the absence of weight gain have been reported
- Increases in insulin and C-peptide observed with clozapine treatment supports insulin resistance theory

Luna B et al. JAMA. 2001;286:1945-8.

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Antipsychotics: ADA Screening Recommendations

Assessment(s)	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually
Personal family history; physical exam	X					X
Weight (BMI)	X	X	X	X	X	X
Height	X					
Waist Circumference	X					X
Blood Pressure	X			X		X
Fasting Plasma Glucose/ A1C	X			X		X
Fasting Lipid Profile	X			X		X

American Diabetes Association. Antipsychotic medications and the risk of diabetes and cardiovascular disease. [http://professional.diabetes.org/admin/UserFiles/Files/CE/AntiPsych%20Med%20Professional%20Tool%20%231\(1\).pdf](http://professional.diabetes.org/admin/UserFiles/Files/CE/AntiPsych%20Med%20Professional%20Tool%20%231(1).pdf)

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Medication-Induced Hypoglycemia




A close-up photograph showing a person's hands using a glucometer. The person is holding a test strip and a finger, with the glucometer device positioned to read the strip. The background is slightly blurred, showing what appears to be a medical or pharmacy setting.

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Alcohol

- Highest risk in those receiving SU's and/or insulin
- Alcohol believed to:
 - Inhibit gluconeogenesis
 - Indirectly increases endogenous insulin secretion
- Counsel to monitor BG closely
 - Can confuse symptoms of hypoglycemia with mild alcohol intoxication



A photograph of a glass mug filled with a golden beer, topped with a white head of foam. The glass is set against a plain white background.

Weathermon R et al. Alcohol Research & Health. 1999;23:40-54.
Field JB et al. Journal of Clinical Investigation. 1962;42:497-506.
White JR et al. Endocrinology and Metabolism Clinics of North America. 2000;29:789-802.

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Alcohol and Sulfonylureas

- Study involving people with T2DM receiving 20mg glyburide daily
 - Performed two 24h fasts at least 1 week apart
 - During hours 14 and 15 of fast, received ethanol or placebo infusion (~ equivalent to 1 alcoholic beverage)
 - Subjects experienced significantly lower BG levels after the ethanol infusion compared to saline infusion

Burge MR. Diabetes Care 1999;22:2037-2043.

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β -Blockers

- β -blockers implicated in causing or exacerbating hypoglycemia
 - Some agents also associated with hyperglycemia
- Inhibit hepatic glucose production
- Non-cardioselective agents (propranolol) more likely to be associated with hypoglycemia
- Given the proven CV benefits, benefits are thought to outweigh the risks

White JR et al. Endocrinology and Metabolism Clinics of North America. 2000;29:789-802.
Ma RCW et al. Drug Safety. 2007;30:215-45.
William-Olsson T et al. Acta Med Scand. 1979;206:201-6.

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Quinolone Antibiotics


- Thought to block ATP-sensitive K⁺ channels in β -cells
 - Dose-dependent increase in insulin release
- DM listed as a contraindication for gatifloxacin (dysglycemia risk)
 - Associated with both hypo- and hyperglycemia in literature
- Caution for dysglycemia with other quinolones
- Higher risk in those with renal dysfunction

Maida N et al. Br J Pharmacol. 1996;117:372-6.
Greenberg AL et al. Clin Infect Dis. 2005;40:1210-1.
Cryer PE et al. J Clin Endocrinol & Metab. 2009;94:709-28.

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Salicylates

- Frequently used as a treatment for DM in the early 1900s
- Thought to be due to several mechanisms:
 - Increased insulin secretion
 - Increased insulin sensitivity
 - SU displacement from protein-binding sites
- Risk highest with concomitant SU use
- High dose ASA (4-7 g/day) shown to enhance insulin sensitivity



Williamson RT. BMJ. 1901;1:760-2.
Goldfine AB et al. Ann Intern Med. 2010;152:346-57.
Hundal RS et al. J Clin Invest. 2002;109:1321-6.

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ACE Inhibitor-Induced Hypoglycemia?

- First reported with captopril in 1985
- Proposed mechanisms:
 - Increased glucose uptake in muscle tissue due to vasodilation
 - Decreased hepatic glucose production
 - Suppression of peripheral sympathomimetic overactivity
- Association is controversial

Ferrario M et al. Ann Intern Med. 1985;102:134.
Barne C. J Int Med. 1991;229:119-25.

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Drugs that can Mask Hypoglycemia Symptoms

- Atenolol (Tenormin[®], Tenoretic[®])
- Carteolol (Cartrol[®], Occupress[®])
- Carvedilol (Coreg[®], Coreg[®] Tiltabs[®])
- Clonidine (Duraclon[®], Catapres[®])
- Metoprolol (Lopressor[®], Toprol XL[®])
- Nadolol (Corgard[®])
- Nebivolol (Bystolic[®])
- Pindolol (Visken[®])
- Propranolol (Inderal[®], Inderal LA[®], Inderide[®])
- Timolol (Timoptic[®], Timoptic-XE[®])

Diabetes In Control. <http://www.diabetesincontrol.com/articles/diabetes-news/9625-#hyper>.

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β -Blockers and Hypoglycemia Unawareness

- β -Blockers:
 - May block adrenergic symptoms of hypoglycemia (except for sweating)
 - May blunt return to euglycemia (gluconeogenesis/glycogenolysis mediated by β 2 receptors in the liver)

JR White. Diabetes Spectrum 2007;20:77-80

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SSRIs and Hypoglycemia Unawareness?

- 3 case reports have suggested a link between the development of hypoglycemia unawareness in patients with T1DM (17-21 yo) started on an SSRI (fluoxetine, sertraline, paroxetine)
 - Reports of hypoglycemia unawareness, more frequent hypoglycemia, and severe hypoglycemia (unconsciousness or help required) within weeks of starting SSRI in all 3 cases

JR White. Diabetes Spectrum 2007;20:77-80


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Describe and discuss recent reports and controversies regarding the safety of medications for the treatment of diabetes

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Exenatide: Pancreatitis

- Pancreatitis
 - 30 post-marketing reports of pancreatitis led to the FDA requiring information about acute pancreatitis in the exenatide product label in the US
 - Pancreatic pseudocyst formation in 1 patient resulting in death
 - 22 cases improved after drug withdrawal, 3 cases symptoms recurred after drug reintroduction
 - Pancreatitis reported following the bite of the Gila monster
 - A total of 89 cases of pancreatitis reported as of September 2007, with six cases of hemorrhagic or necrotizing pancreatitis, two cases resulting in death, reported in August of 2008



Bain SC et al. Expert Opin Drug Saf 2008;7:643-644.
FDA Drug Safety Newsletter 2008;1:12-14.
Ahmed SI et al. N Engl J Med 2008;358:1970-1.

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Sitagliptin and Pancreatitis?

- Prescribing information revised in September 2009 for sitagliptin (Januvia) and sitagliptin/metformin (Janumet)
- FDA cited 88 cases of acute pancreatitis reported between October 2006 and February 2009
 - 2 cases of hemorrhagic or necrotizing pancreatitis
- Recommendations from FDA:
 - Monitor patients carefully for pancreatitis after initiation of therapy or dose increases
 - Use cautiously and with appropriate monitoring in patients with a history of pancreatitis

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm143390.htm>

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Retrospective Claims Data

- US health insurance database (2005-2008)
- Followed new users of exenatide or sitagliptin and matched metformin or glyburide users for 1 year
- Risk factors not reported

	N	Frequency (%)		RR (95% CI)
		GLP-1	Metformin/glyburide	
Exenatide	27,996	0.13	0.13	1.0 (0.6-1.7)
Sitagliptin	16,276	0.12	0.12	1.0 (0.5-2.0)

Dore et al. Curr Med Res Opin. 2009;25:1019-27.

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Liraglutide: pancreatitis data

- Pancreatitis in clinical trial program:
 - 7 cases of pancreatitis in participants receiving liraglutide
 - 5 cases of acute pancreatitis
 - 2 cases of chronic pancreatitis
 - 1 of the 7 cases associated with necrosis and led to death
 - 1 case in control groups

<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM202063.pdf>

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Pancreatitis with Saxagliptin?

- Overall incidence in a pooled clinical Phase 2b/3 trial population was:
 - 0.2% in 3,422 participants treated with saxagliptin
 - 0.2% in 1,066 controls
- Prescribing information does not currently include a warning for pancreatitis
- Post marketing surveillance data are not yet robust

<http://www.fda.gov/downloads/advicorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugs/advicorycommittees/ucm148589>

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Incidence of Pancreatitis Increased in Patients with T2DM

- Retrospective claims database
- 337,067 patients with T2DM and equal number of age/sex-matched controls without T2DM
- Participants included if enrolled for at least 12 months and followed ≥ 1 month
- **RR: 2.83 95% CI (2.61-3.06)**
- Data on other risk factors not available

Noel et al. Diabetes Care 2009;32:834-8.

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Liraglutide: REMS Recommendations


- Patients using liraglutide should be counseled about the symptoms of pancreatitis, such as severe abdominal pain that may radiate to the back, possibly with nausea and vomiting
- If patients experience symptoms of pancreatitis, they should contact their health care provider immediately
- Patients must be provided a *Medication Guide* that provides information about pancreatitis that includes the following:
 - Conditions that may place patients at greater risk for pancreatitis, such as a prior history of pancreatitis, gallstones, excessive use of alcohol, or very high triglyceride levels
 - Symptoms of pancreatitis and what to do if these symptoms occur
- Liraglutide should be used cautiously in those with a history of pancreatitis

<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM202063.pdf>

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Overall Conclusions - Pancreatitis

- Mechanism for pancreatitis is not understood
- FDA recommends:
 - Suspicion for patients with suggestive symptoms
 - Against restarting incretin-based therapies in patients with confirmed pancreatitis



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**Incretin Mimetics:
Decreased Renal Function?**


- Warning of post marketing incidences of altered renal function added to exenatide prescribing information in 2009
 - 78 case reports to FDA from April 2005 to October 2008
 - 62 cases of acute renal failure
 - 16 cases of renal insufficiency

www.fda.gov/safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm188703.htm

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**Incretin Mimetics:
Decreased Renal Function?**

- Case series of 4 instances noted all patients on stable doses of ACE inhibitors and diuretics
- Theory: nausea and vomiting causes hypovolemia that results in decreased renal perfusion
- Concern with liraglutide???




Weisse WJ, et al. Diabetes Care. 2009;32(2):e22-e23.

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WARNING: RISK OF THYROID C-CELL TUMORS
See full prescribing information for complete boxed warning.

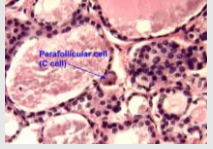
- Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in rodents. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies.^{1,2,3,4}
- Victoza® is contraindicated in patients with a history of thyroid disease, including thyroid cancer or nodular goiter, or in patients with Multiple Endocrine Neoplasia type 2 (MEN2).



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C-cell Hyperplasia

- C-cells account for ~1% of the total thyroid
- C-cell density is 22- and 45-fold higher in mouse and rat thyroid glands compared to humans
- C-cells secrete calcitonin



Knutzen et al. Endocrinology 2010;151:1473-86.

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Liraglutide: Thyroid Carcinoma?

- Preclinical data from rodent models linked liraglutide with dose-dependent and treatment-duration-dependent thyroid C-cell tumors
- Benign C-cell adenomas observed in animal studies at plasma drug levels similar to those seen in humans at approved doses
- GLP-1 receptor agonists stimulate calcitonin in rat, but not human C-cell lines
- Incidence of medullary thyroid cancer ~600 cases per year

Sjorne Knudsen L, et al. Endocrinology. 2010;151(14):1473-1486.
Limal Y, et al. FEBS Lett. 1996;393(2-3):248-252.
Parkin M, et al. N Engl J Med. 2010;363(9):774-777.
Knutzen et al. Endocrinology. 2010;151:1473-86.

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Exenatide

- No surveillance data available on calcitonin levels
- No cases of medullary thyroid carcinoma currently reported in humans
 - 4500 patients in clinical trials
 - 3854 subject-years
 - Post-marketing reporting

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Conclusions

- Clinical relevance of rodent data in humans remains unknown
- Long-acting GLP-1 based therapies shouldn't be used in patients at increased risk for MTC
- Ongoing surveillance and research is needed



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Rosiglitazone REMS: 2010

- Rosi will be available for patients who are not already receiving the drug only if they are unable to achieve glycemic goals using other medications and cannot take pioglitazone for medical reasons
- Current users of rosi can continue to use it if they appear to be benefitting from therapy and acknowledge that they understand the potential risks of continued use
- Physicians will be required to attest to and document patient eligibility for rosi therapy, and patients will be required to review statements describing the cardiovascular safety concerns for rosi

Woodcock J, et al. N Engl J Med. 2010;363(16):1489-1491.

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Metformin and B12 Deficiency

- Malabsorption of B12 in ~30% of metformin users
 - B12 not absorbed in the terminal ileum
 - Metformin effect on calcium-dependent membrane action
 - Dose and duration-dependent
 - Takes 12-15 years to totally deplete B12 stores
 - On the verge of an epidemic?

Nathan et al. Diabetes Care. 2009;32:193-203.
Bell. South Med J. 2010;103(3):286-7.

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Metformin and B12 Deficiency

- Recommendations:
 - Calcium supplementation?
 - Annual B12 level?
 - Annual 1000 mcg injection of B12?




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Outline new and emerging therapies for the treatment of diabetes and discuss the potential pros and cons of these agents

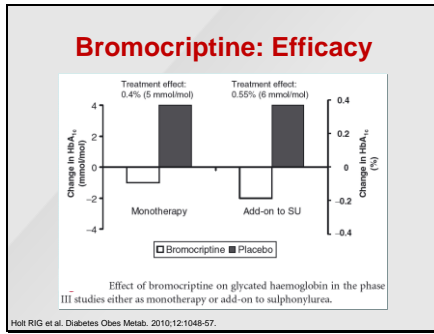
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Bromocriptine (Cycloset)

- Approved in 2009 by FDA to treat T2DM
- Once daily in AM with food and is a quick release, low dose (0.8 mg) formulation
- Acts on CNS to improve insulin resistance and glucose tolerance – resets neuroendocrine rhythms




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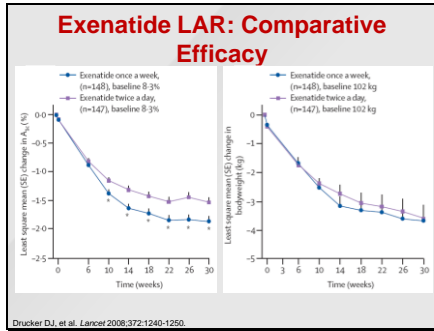
Exenatide LAR (Bydureon)

- Once-weekly administration
- Consists of microspheres
 - Exenatide within a poly(lactide-co-glycolide) matrix
 - Following injection exenatide is slowly released from the microspheres via diffusion and erosion



Kim D, et al. Diabetes Care 2007;30:1487-1493.

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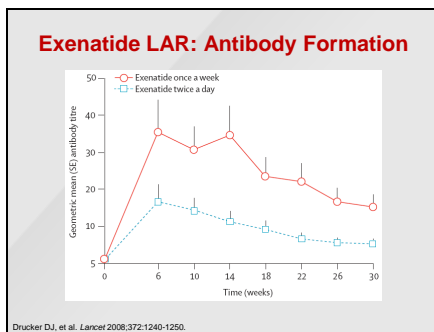
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Exenatide LAR: Adverse Events Compared to IR

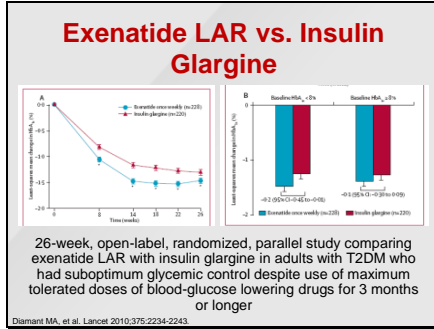
	2.0 mg exenatide once a week (N=148) n (%)	10 µg exenatide twice a day (N=145) n (%)
Nausea	39 (26.4)	50 (34.5)
Vomiting	16 (10.8)	27 (18.6)
Injection site pruritus	26 (17.6)	2 (1.4)
Upper respiratory tract infection	12 (8.1)	25 (17.2)
Diarrhoea	20 (13.5)	39 (26.9)
Constipation	16 (10.8)	9 (6.2)
Injection site bruising	7 (4.7)	15 (10.3)
Urinary tract infection	15 (10.1)	12 (8.3)

Drucker DJ, et al. Lancet 2008;372:1240-1250.

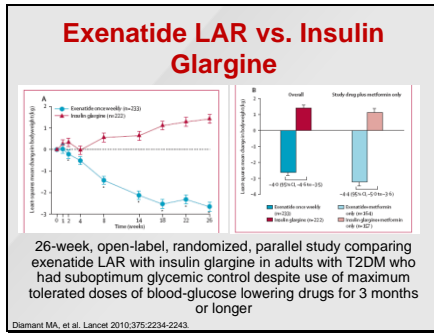
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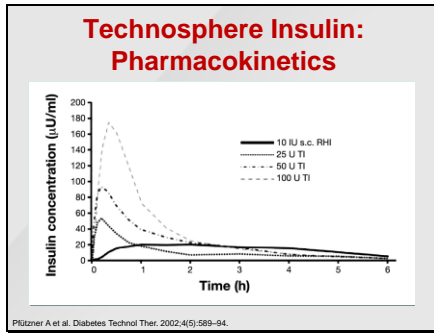


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Technosphere Insulin




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Technosphere Insulin: Pros and Cons



- Potential Pros:
 - Prandial coverage without injection
 - "Very" rapid acting insulin
 - Less weight gain?
 - Less hypoglycemia?
- Potential Cons/Considerations:
 - Safety concerns? (lung carcinoma)
 - Use in smokers/COPD?
 - Respiratory AEs
 - Usability?
 - Acceptance?
 - Price?

Neumiller JJ et al. Am J Pharmacotheor 2010;44:1231-1239.

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Insulin Degludec

- Ultra-long acting basal insulin
- Has the potential to be used less than once daily
- Demonstrated efficacy in both type 1 and type 2 diabetes
- Lower hypoglycemia when compared to insulin glargine when used once daily

Weeks since randomization	Insulin Degludec	Insulin Glargine	Insulin Glargine QD
0	0.0	0.0	0.0
4	-0.4	-0.2	-0.1
8	-0.5	-0.3	-0.2
12	-0.6	-0.4	-0.3
16	-0.7	-0.5	-0.4

Figure 1—Mean change from baseline in A1C. Data are mean (last observation carried forward) for each time point.

Heise T et al. Diabetes Care. 2011;34:669-74.
Birkeland KI et al. Diabetes Care. 2011;34:681-5.

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SGLT-2 Inhibitors

90% of filtered glucose is reabsorbed through SGLT2 transporters in the early proximal tubule. 10% is reabsorbed by SGLT1 transporters in the late proximal tubule. (Note: SGLT1 is also present in the small intestine.)

Inhibition of SGLT2 transporters in the proximal tubule blocks the reabsorption of filtered glucose = increased glucose excretion via urine.

Adapted from Idris I, Donnelly R. Diabetes Obes Metab. 2009.

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SGLT-2 Inhibitors: Pros and Cons

- **Potential Pros:**
 - Unique MOA (A1C reduction ~0.5-1%)
 - Useful in T2DM and T1DM
 - Potential weight loss (~2.5 kg)
 - Modest decrease in BP
 - Low risk of hypoglycemia
- **Potential Cons:**
 - Risk of UTI/Genital infections
 - Electrolyte imbalances with long-term treatment?
 - Exacerbation of urinary urgency?
 - Cost?

Neumiller JJ et al. Drugs 2010;70(4):377-385.

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