Nutrient Stimulated Hormones (NuSHs): Current and Upcoming Treatment Options and Clinical Insights Regarding Use and Co-Management

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EXPLORE
HEALTHCARE SUMMIT

Disclosures

- Speaker for Rhythm Pharmaceuticals

2

Objectives

1. Definition of NuSh
2. Major mechanism of action of FDA-approved and phase 3 NuSHs
3. Safety issues
4. Potential Side-Effects & How to Reduce
5. Co-Managing with other Clinicians
6. Future Treatment Options on Horizon
7. Holistic Approach
8. Summary

3

NuSHs: What Are They?

Nutrient Stimulated Hormones (NuSH): Term refers to the "dynamic interaction between dietary components [or endogenous hormones or peptides] and the endocrine system, leading to the modulation of hormone secretion and subsequent metabolic changes." [1]

- 11-B HSD1 inhibitor
- Adipolytic peptide
- Amylin analogue
- Apelin analogue
- CalcR-pvh agonist
- Cannabinoid R Inh
- Central spermine bile acid
- CGCRa
- CMA
- DGAT1 inhibitor
- DSM33407
- Enteropeptidase inhibitor
- FGF-21 modulator
- Gastric & pancreatic lipase inhibitor
- GDF-15 agonist
- GDNF RA
- GIP antagonist
- GIP RA
- GLP-1 RA
- GOAT inhibitor
- GOAT SRI
- K+/ATP agonist
- LA ANP agonist
- Leptin RA
- Leptin sensitizers
- MC4R agonist
- MGAT2 inhibitor
- MOTS-c analogue
- MTTPi
- Myostatin inhibitor
- NPY2 RA
- Opioid receptor antagonist
- Pan-AMPk activator
- Paraoxonase 1 modulator
- PYY agonist
- SCD1 inhibitor

Other Categories
- SGLT2i/SGCT2i
- Transporter of molecular O2
- TRI
- 5-HT2C RA
- Lipidated IL-22
- Mitochondrial ox-phos decoupler

See Slides Phase I, Phase II, and Phase III clinical trials for source

Current FDA-Approved Options for Obesity

GLP-1 Ra
- Semaglutide (Wegovy ®)
- Liraglutide (Saxenda ®)

GLP-1 RA + GIPRa
- Tirzepatide (Zepbound ®)

MC4Ra (This is why we can't call everything a GLP1)
- Setmelanotide (Imcivree ®)

See Slides Phase I, Phase II, and Phase III clinical trials for source

Phase III Clinical Trial Monotherapies and Combination Therapies

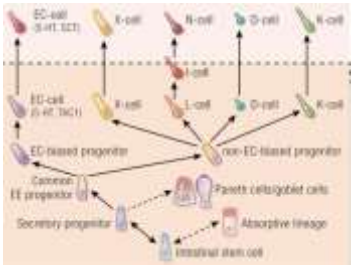
Company	Drug	Type	Route
BI	survodutide	GLP1/GCG RA	SC
Eli Lilly	mazdutide	GLP1/GCG RA	SC
Eli Lilly	orforglipron	GLP1	Oral
Eli Lilly	retatrutide	GIP/GLP1/GCG RA	SC
LG-Chem	LB54640	MC4R agonist	Oral
Novo	semaglutide 50 mg	GLP-1 agonist	Oral
Novo	cagrilintide/semaglutide	GLP-1/amylin agonist	SC
Sciwind	ecnoglutide	GLP1	SC

GIP, GLP1, GCG, MC4R

Anatomy & Physiology

7

Cell Differentiation of Intestinal Enteroendocrine Cells



Reference 12

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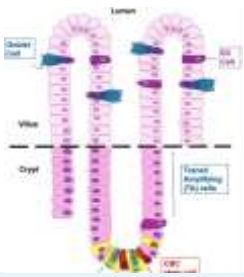
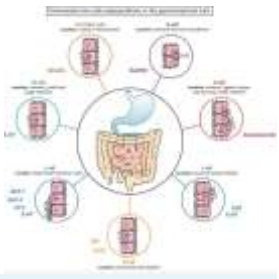
Enteroendocrine Cells, Location, & Function





Reference 12

9

Phases of Digestion

Source 15

10

Review of NuSH Types

11

Current Approved and Phase 3 NuSHs & Mechanism of Action

Glucose-dependent Insulinotropic Polypeptide (GIPRa) (formerly Gastric Inhibitory Peptide)

- GIP made from the K cells in the duodenum and upper jejunum
- GIP release is stimulated by: **TG >>> Carbs=glucose=saturated FA >> fructose=protein/AA**
- GIP increases LPL (helps FA uptake) and lipogenesis from FA esterification
- Genetically deleting GIP receptors leads to weight loss with a high-fat diet.
- GIP also increases de novo lipogenesis from glucose.
- "Both GIPRa and antagonism have been described to reduce body weight and prevent diet-induced obesity." Antagonism is less effective once an individual already had pre-existing obesity but may still improve insulin sensitivity. Long-acting agonism may act as a partial antagonist by downregulating receptors.
- Gasbjerg et al. were able to demonstrate with receptor blockade techniques that GIP is responsible for more incretin effect than GLP-1.
- Little to no effects on gastric emptying and hypoglycemia
- Tirzepatide showed equal affinity for the GIPR compared with native GIP but binds the GLP-1R with approximately 5-fold weaker affinity than native GLP-1. Also acts centrally to reduce nausea.

Reference 4, Reference 13, Reference 14

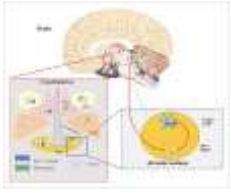
12

Current Approved and Phase 3 NuSHs & Mechanism of Action

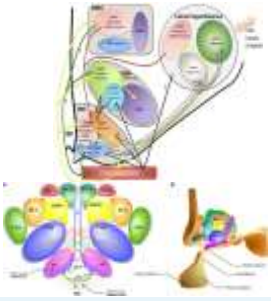
Glucagon-like Peptide 1 (GLP-1 RA)

- Released by L cells in the distal small intestine, colon, and rectum
- GLP1 release stimulated by: **TG**>>> **Carbs = glucose** >> **fructose = protein = AA= short-chain fatty acids**
- Centrally-mediated mechanisms & slowing of gastric emptying and intestinal transit.
- Delayed gastric emptying blunting insulin response & incretin effect.
- "Propulsive peristalsis" when GLP-1 acts as an ileal break.
- Gastric emptying is subject to tachyphylaxis in weeks to months
- Gustducin (sweet taste receptors) and BAs can also increase release of GLP-1
- At pharmacologic GLP-1 doses, insulin wasn't released at glucose was below 66 mg/dL. Little to no risk of hypoglycemia.
- GLP-1 may inhibit glucagon at euglycemia or hyperglycemia but allow glucagon release with hypoglycemia.
- Decreased dietary intake has been found with pharmacologic but not physiologic levels

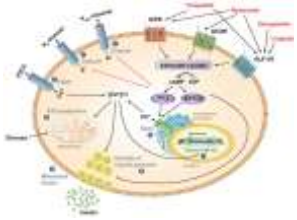
Reference 4 13

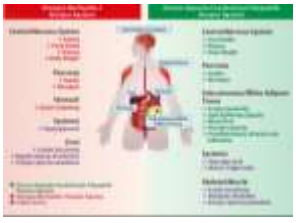


VMH: Ventromedial Hypothalamus;
DMH: Dorsomedial Hypothalamus;
PVH: Paraventricular hypothalamus;
ARC: Arcuate nucleus;
LH: Lateral Hypothalamus;
VTA: Ventral Tegmental Area



Reference 4, Reference 16 14





"Incretin hormones are ineffective in initiating an insulin secretory response, which requires membrane depolarization, for example, as triggered by hyperglycemia and the subsequent closure of K-ATP channels."

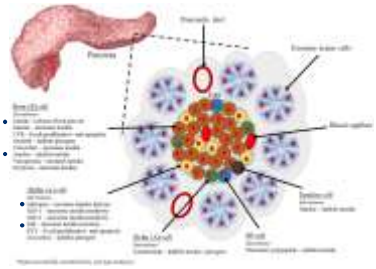
GLP1 improves satiety in the brain, slows gastric emptying initially, improves insulin sensitivity and decreases ectopic fat accumulation.
GIP decreases food intake centrally, improves insulin sensitivity, reduces inflammation, reduces and nausea, and decreases ectopic lipid accumulation

References 2 and 4 15

Reference 4

16

Pancreatic Cells



https://ordinesstre.club/2021-club.html

17

Current Approved and Phase 3 NuSHs & Mechanism of Action

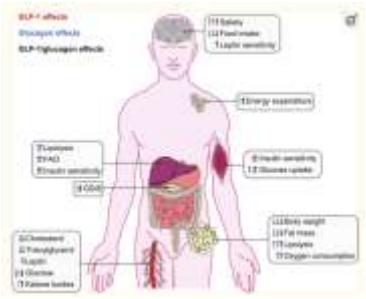
Glucagon Receptor Agonist (GCGRa)

- Glucagon made by alpha cells in pancreas. Glucagon secretion is inhibited by insulin. Therefore, in insulin resistance there is decreased receptor activation of endogenous insulin and relative hyperglucagonemia. (AKA, IR causes low insulin activation and high relative glucagon)
- GCG effect may vary on concentration as GCG activates GLP-1 receptor in double-digit picomolar ranges but is more specific to GCGR at <1 pM range.
- Coupling Proteins: Move hydrogen ions from inner membrane space into matrix and couple it with synthesis of ATP. UN-coupling proteins, like UCP1 allow hydrogen ions to move hydrogen using kinetic energy from intermembrane space to matrix and produce heat. Brown fat > beige fat >white fat contains more uncoupling proteins (thermogenin).
- GCGRa increases UCP1-dependent interscapular brown adipose tissue (iBAT)→increased thermogenesis. Therefore, GCGR agonism reduces body weight by increasing energy expenditure and might positively affect lipid metabolism, increasing fatty acid oxidation, and resulting in lowering of plasma and liver triglycerides and plasma cholesterol.
- In UCP-1 knock out mice, GCG still decreased intake. This could be from increased GABA-ergic MBH signaling or GCGR-expressing hepatic vagal nerve afferents may project to the ARC in the hypothalamus and affect food intake via this pathway.
- Retatrutide is being studied as triagonist of GLP1/GIP/GCG

Reference 5

18

GCG…
Increases satiety
^ Energy expend.
^ Lipolysis
^ O2 uptake



Reference 5

19

Current and Phase 3 NuSHs & Mechanism of Action

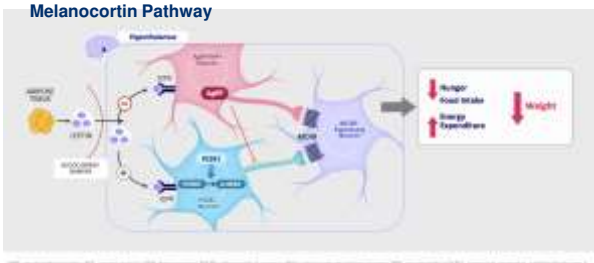
Amylin agonist

- Made from pancreatic beta cells, stomach cells, spinal ganglia, and brain.
- Improves satiation by activating noradrenergic neurons in the Area Postrema (AP) of the medulla oblongata. May also act on NTS and LPBN.
- Inhibits postprandial glucagon secretion through direct and indirect effects on alpha-cells.
- Slows gastric emptying
- Inhibits digestive enzymes
- May improve leptin sensitivity in obesity
- May have vasodilatory effect in vasculature
- Cagrilinitide (studied as CagriSema with semaglutide) is a stable lipidated non-selective long-acting amylin analog

Reference 10

20

Melanocortin Pathway



Yazdi et al.

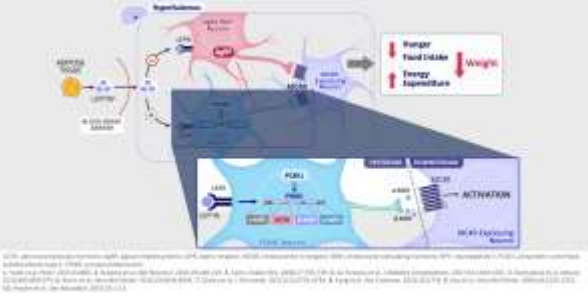
21

Current Approved and Phase 3 NuSHs & Mechanism of Action

MC4R agonist

- Only FDA-approved current option is Setmelanotide (Imcivree ®) approved for homozygous PCSK1 deficiency, homozygous POMC deficiency, homozygous LEPR deficiency, and BBS.
- LG-Chem is developing an oral LB-54640 selective MC4R agonist.
- Acts by bypassing pathway and directing stimulating end of pathway receptor MC4R. This results in increase in alpha-MSH.
- Alpha-MSH stimulates orexin in the lateral hypothalamus.
- End result: decreases hunger and increases energy expenditure via MC4R activation

22



Yazdi et al.; Cone; da Fonseca et al; Bochukova et al; Burns et al; Doche et al; Yang et al; Seo et al; Heydet et al.

23

Potential Safety Concerns of NuSHs Discussed Thus Far

MEN II-a or II-b Syndrome or Medullary Thyroid Cancer
- "Mean numbers of C-cells/mm^2 of thyroid tissue have been found to be approximately 10 ± 26 in humans, whereas mice and rats have 22 to 45 times greater the amount (216 ± 62 and 449 ± 222 number of C-cells/mm 2of thyroid tissue, respectively)."

heAOM
- Not everyone needs or qualifies for this class of medication

Double contraceptive methods in first month
- Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation with MOUNJARO

MC4Ra
- Hyperpigmentation and melanotic lesions; derm check

References 21, 22, 23, 24

24

Potential Side-Effects

GLP1 Monotherapy as Reported for Semaglutide in Clinical Trials

Table 1. Adverse Reactions in Placebo-Controlled Trials Reported in ≥5% of OZEMPIC-Treated Patients with Type 2 Diabetes Mellitus

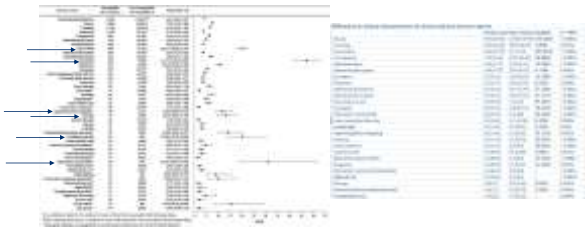
Adverse Reaction	Placebo (N=262) %	OZEMPIC 0.5 mg (N=260) %	OZEMPIC 1 mg (N=261) %
Nausea	6.1	15.8	20.3
Vomiting	2.3	5.8	9.2
Diarrhea	1.9	8.5	8.8
Abdominal pain	4.6	7.3	7.7
Constipation	1.5	5.0	5.1

Reference 19

25

Potential Side-Effects

GLP1 Monotherapy as Reported for Semaglutide in Post-Marketing Surveillance



Reference 18

Reporting Odds Ratio

26

Potential Side-Effects

GLP1 + GIP as Reported for Tirzepatide in Clinical Trials

Table 1: Adverse Reactions in Pool of Placebo-Controlled Trials Reported in ≥5% of MOUNJARO-treated Adult Patients with Type 2 Diabetes Mellitus

Adverse Reaction	Placebo (N=238) %	MOUNJARO 5 mg (N=237) %	MOUNJARO 10 mg (N=240) %	MOUNJARO 15 mg (N=241) %
Nausea	4	12	15	18
Diarrhea	9	12	13	17
Decreased Appetite	1	5	10	11
Vomiting	2	5	5	9
Constipation	1	3	6	7
Dyspepsia	3	5	6	5
Abdominal Pain	4	5	5	5

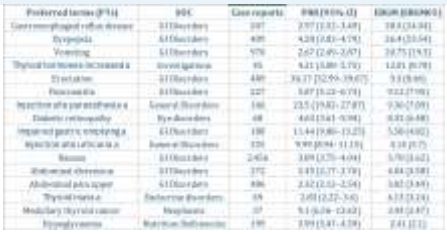
Note: Percentages reflect the number of patients who reported at least 1 occurrence of the adverse reaction.

Reference 20

27

Potential Side-Effects

GLP1 + GIP as Reported for Tirzepatide in Post-Marketing Surveillance



Empirical Bayes Method

Reference 17

28

Co-Management with Other Clinicians

- If you want to take over a medication, make sure needing a prior authorization won't cause a delay in care
- Don't resume most patients beyond 2 weeks off the medication. Make sure they know not to jump around on doses or hold for extended periods.
- If needing to convert to another medication due to insurance or supply, don't re-titrate over if patient is actively on medication, instead convert to equivalent dose
- Counsel prior to surgical procedures they may need to hold 7-14 days
- Don't prescribe DPP4 or sulfonylurea if on GLP1Ra medication
- Consider holding or reducing Metformin if another clinician is increasing NuSHs
- Consider prescribing PPI if patient contacts you regarding dyspepsia in setting of a NuSH prescribed by another physician.
- Monitor for nutritional deficiencies, especially common ones like folate or B12 deficiency
- Screen for decreased mood or sex drive
- Ask about GI side-effects
- Make sure they aren't losing TOO quickly or undereating, especially if elderly
- If complaining of hair loss, push protein and adequate PO intake of calories
- Ensure annual dermatologic assessment for patients on MC4Ra along if prescribing physician
- If they are plateauing, push behavior before dose increase
- If they have an allergic reaction to one NuSH, they may still do well with another, don't give up until all options are exhausted if you and patient feel comfortable trying

29

Ways to Reduce Side Effects

Factors that affect GI Tolerability

- Gastric Irritants: alcohol, frequent NSAIDs, coffee
- High fat (TG) and sugary foods (high glucose)
- Prolonged fasting
- Constipation
- Large Portions
- Anatomical abnormality (e.g. hiatal hernia or presbyesophagus)

30

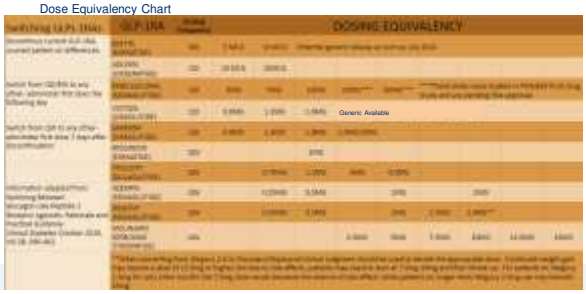
Tips for Patients

	You May Want to Try	You May Want to Avoid
Carbohydrates	Rice, rice cakes, rye or saltine crackers, cold cereal without milk, dry toast, boiled potatoes	Croissants, doughnuts, pancakes, very sweet foods
Dairy	Low fat dairy products, skimmed milk in small amounts	Whole milk, milkshakes
Protein	Steamed or baked chicken or turkey breast, lean beef or ham, low fat cottage cheese, plain cheese, salted nuts	Strong cheeses, fried or grilled meats, spicy foods, gravies, sauces, peanut butter
Vegetables	Carrots, cucumbers, celery	Broccoli, cabbage, cauliflower, garlic, onions, beans
Fruits	Low fat cream cheese, low fat salad dressing, small portions of butter or margarine	Deep-fried foods (e.g. French fries), mayonnaise
Dessert	Gelatine, fruit, low fat gingerbread	Ice cream, pastries, rich cakes or puddings or custards
Liquids	Unsweet tea, sugar-free ginger ale	Coffee, tea, cola, root beer, beer

31

Expert Opinion*

Dose Equivalency Chart



Future Treatment Options on the Horizon

33

Company	Drug	Type	Route
Amgen	AMG-786	GIP/GLP/GCG agonist	Oral
Amplifier Therapeutics	ATX-304	pan-AMPK activator	Oral
AstraZeneca	AZD-6234	Amylin analogue	SC/IV
AstraZeneca/Eccogene	ECC5004	GLP-1 agonist, GIP antagonist	Oral
BioAge	azelaprag	Apelin analogue	Oral
Biohaven Pharma	taldefgrobep alfa	myostatin inhibitor	SC
Boehringer Ingelheim	BI 1356225	GOAT inhibitor	Oral
Boehringer Ingelheim	BI 1820237	long-acting NPY2 RA	SC
Boehringer Ingelheim	BI 3006337	GLP-1/FGF-21	SC
Bristol-Myers Squibb	BMS-963272	MGAT2/DGAT1	Oral
Carmot Therapeutics	CT-868	GIP/GLP/GCG agonist	Oral
CinRx/Janssen J&J	CIN 109	long-acting GDF-15	SC
CohBar	CB-4211	MOTS-c (MOP) analogue	SC
ConSynance Ther	CSTI-500	5HT/NE/DA reuptake inh	Oral
Cytoki Pharma	CK-0045	lipidated IL-22	SC
D&D Pharmatech	DD-01	GIP/GLP/GCG agonist	SC
Daewoong Pharmaceutical	DWP-306001	SGLT2i/DGCT2	Oral
Eli Lilly	LY-3841136	Amylin analogue	SC
Eli Lilly	LY-3457263	CalcR-PYY agonist	SC
Eli Lilly	[illegible]	NPY RA	SC
Eli Lilly	LY-3971297	long-acting ANP	SC
Enteris	ENT-03	spermine-3A central agonist	SC
ERX Pharmaceuticals	ERX-1000	leptin sensitizer	Oral
Federal Biotech	UBT251	GIP/GLP/GCG agonist	SC
Gila therapeutics	GT-001	PYY agonist	SL
Raynovent Biotech	RAY-1225	peptide of unknown mechanism	SC
Gubra A/S	GUB014295	Amylin analogue	SC

Phase-I Investigational Products[3]

34

Hanmi Pharmaceutical	HM15136	GIP/GLP/GCG agonist	SC
HEC Pharm	HEC-88473	FGF-21 RA	SC
Huadong Medicine	HDM1002	GIP/GLP/GCG agonist	Oral
Inversago Pharma	zevaquenabant	Cannabinoid receptor inhibitor	Oral
LG Chem	LR19021	MC4R	Oral
Lipidio Pharmaceuticals	GED-3899	stearoyl-CoA desaturase 1 inh	Topical
NGM Biopharmaceuticals	NGM 395	Glial-derived neurotrophic factor RA	SC
Novartis	LLF-580	FGF-21 R modulator	SC
Novo Nordisk	NNC-9204-1706	GIP/GLP/GCG agonist	SC
Novo Nordisk	LA-GDF15	GDF-15 modulator	SC
Novo Nordisk	NN-9748	NPY RA	SC
Novo Nordisk	Amycretin	amylin receptor agonist	SC/Oral
OrsoBio	TLC-6740	Mitochondrial protonophore uncoupler	Oral
Otsuka Holdings	HO-[illegible]	peptide of unknown mechanism	Oral
PegBio	PB-119	GIP/GLP/GCG agonist	SC
Regeneron	[illegible]	LEPR agonist	SC/IV
Response Pharmaceuticals	RDX 002	MTTP inhibitor	Oral
Sanofi/[illegible] Medical	SAR[illegible]	GIP/GLP/GCG agonist	SC
Sciwind	XW 014	GIP/GLP/GCG agonist	Oral
Sciwind	XW 004	GIP/GLP/GCG agonist	Oral
Scohia Pharma	SCO-267	GPCR-40 agonist	Oral
Scohia Pharma/Takeda	TAK-094	GIP/GLP/GCG agonist	SC
Sino Biopharmaceutical	GMA-106	GIP/GLP/GCG agonist	SC
Sparrow Pharmaceuticals	SPI-62	11-beta HSD1 inhibitor	Oral
Terns	TERN-601	GIP/GLP/GCG agonist	Oral
Xeno Biosciences	XEN-101	solute transporter of molecule 126	Oral
Zealand	petrelintide	Amylin analogue	SC
Zhejiang Doer	DR-10624	GIP/GLP/GCG agonist	SC

Phase-I Investigational Products Continued[3]

35

Company	Drug	Type	Route
Altimmune	pemvidutide	GLP-1 agonist, GCGRa	SC
Amgen	maridebart cafraglutide	GLP-1 agonist, GIP antagonist	SC
Empros Pharma	orlistat + acarbose	Gastric & Pancreatic lipase inh	Oral
Gedeon Richter	RGH-706	MCHR1 RA	Oral
Glaceum	vutiglabridin	Paraoxonase 1 modulator	Oral
GSK	GSK-1521498	Opioid Receptor Antagonist	Oral
GLWL Research	GLWL-01	SM of GOAT	Oral
[illegible] Biopharm	[illegible] 135	GLP-1 agonist, GIP antagonist	IV
Hanmi Pharm	HM11260C	GLP-1 agonist, GIP antagonist	SC
Merck	Efinopegdutide	GLP-1 agonist, GCGRa	SC
Pfizer	danuglipron	GLP-1 agonist, GIP antagonist	Oral
[illegible] Therapeutics	[illegible]	Adipolytic molecule	Oral
Rivus Pharmaceuticals	HU-6	Controlled metabolic accelerator (CMA)	Oral
Saniona	tesofensine	5HT/NE/DA reuptake inh/B1 ant	Oral
Scohia Pharma/Takeda	[illegible]	Enteropeptidase inhibitor	Oral
Shionogi	S-309309	MGAT2/DGAT1	Oral
Soleno Therapeutics	diazoxide choline	potassium-ATP activator	Oral
Structure	GSBR-1290	GLP-1 agonist, GIP antagonist	Oral
TONIX Pharmaceuticals	oxytocin	CalcR-PYY	Int-Nasal
Transition Therapeutics	pegapamodutide	GLP-1 agonist, GIP antagonist	SC
TRYP	psilocybin, TRP-8803	5-HT2C RA	Oral
Viking Therapeutics	VK-2735	GLP-1 agonist, GIP antagonist	SC
YSOPIA Bioscience	Xla1	Christensenella minuta DSM33407	Oral
YSOPIA Bioscience	Yso-1	christensenella minuta ketone bacteria	Oral
Zealand Pharma	Dapiglutide	GLP-1 agonist, GIP antagonist	SC

Phase-II Investigational Products[3]

At least 41+ unique mechanisms of action

36

Summary

NuSH Summary

Potential Benefits

GIP
- Long-term agonism acts as a partial antagonist
- Reduces inflammation
- Centrally decreases food intake desire
- Improves insulin sensitivity
- Decreases ectopic fat accumulation

Glucagon
- Acts differently at different concentrations and co-activates GLP1
- Increases thermogenesis
- Decreases intake of food centrally

Amylin
- Noradrenergic effect on brain which improves satiety
- Reduces glucagon
- Slows gastric emptying
- Reduces nutrient absorption by inhibiting digestive enzymes
- Improves leptin sensitivity
- Vasodilatory effect

MC4R
- Decreases hunger
- Increases energy expenditure

GLP1
- Slows gastric emptying
- Reduces glucagon during hyperglycemia
- Centrally acts to improve satiety after eating initiated
- Improves insulin sensitivity
- Decreases ectopic fat accumulation.

Summary

- NuSH is a more comprehensive form
- There's no such thing as a "appetite suppressant". We are prescribing anti-obesity medications and ALL of them work via central mechanisms in the brain.
- If prescribing, counsel on how to mitigate side-effects and consider co-morbid diseases
- Screen for side-effects
- Encourage appropriate portions
- Monitor nutritional deficiencies
- Continue to promote behavior change
- Consider prior authorizations if changing therapy or taking over therapy

Appendix

NUSH? Mechanism of Action

Sibutramine + Topiramate

Sibutramine (TRI)

- Selective inhibition of reuptake of 5-HT, NE, and DA which works on CNS to reduce appetite.
- Increases anorexigenic (leptin) to ARC, which also inhibited NPY/AgRP. The former allows alpha-MSH to activate PVH neurons and resists drop in basal energy expenditure that occurs with weight loss. The latter prevents orexin A & B and MCH activation of neurons.
- It may increase thermogenesis with β_3-adrenergic receptor activation (From NE) in peripheral white adipose tissue
- "Weight-reducing effects of sibutramine are largely attributed to its active primary (N-desmethylsibutramine; BTS 54505) and secondary (N-didesmethylsibutramine; BTS 54 354) amine metabolites rather than to the parent compound."
- SCOUT trial showed increased MACE risk by 16%.

Topiramate

synergistic effect: homeostatic intake control + hedonic control

Current and Phase 3 NuSHs & Mechanism of Action

Gastric and Pancreatic Lipase Inhibitor

- Orlistat is FDA-approved and reversibly inhibits gastric and pancreatic lipase which decreases absorption of dietary fats by 30%
- Celistat is being investigated and may increase fecal fat by 3-7 fold.

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Thank you – Questions?

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