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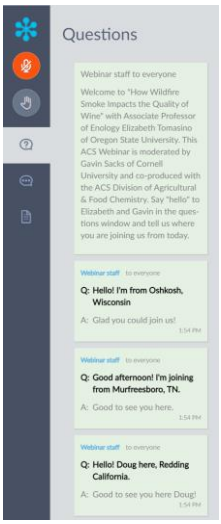

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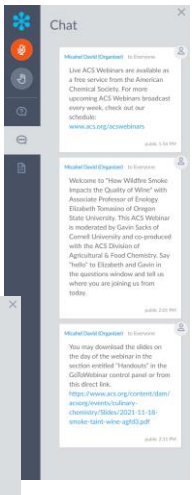

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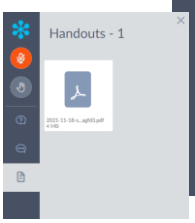

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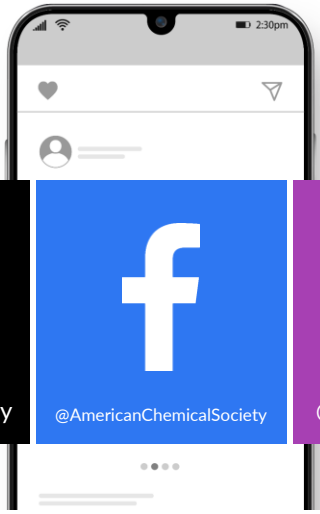

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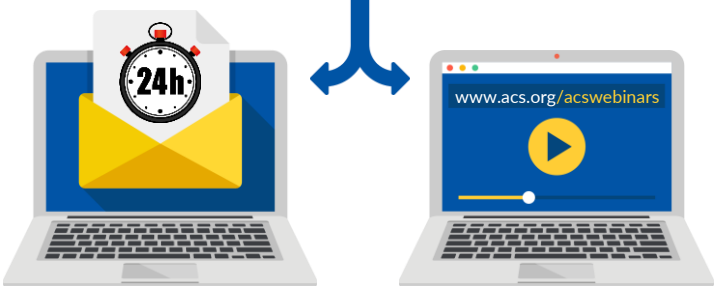

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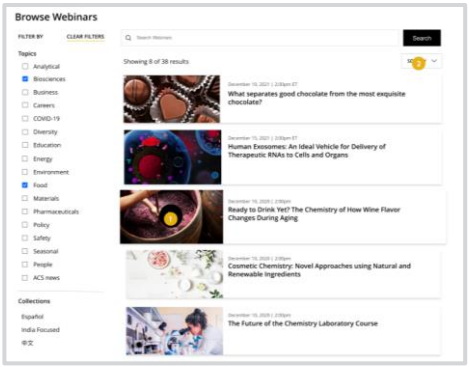

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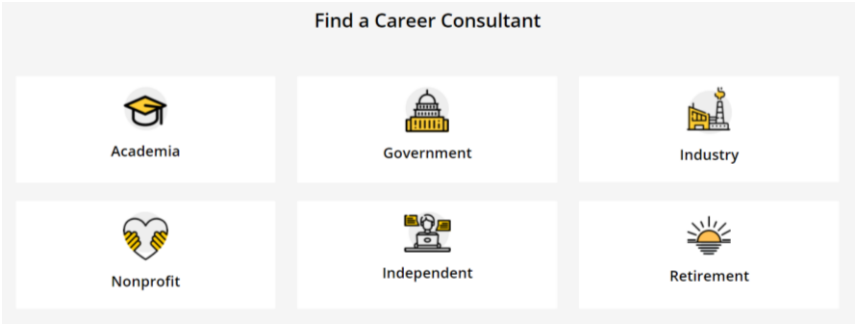
6

6

Career Consultant Directory



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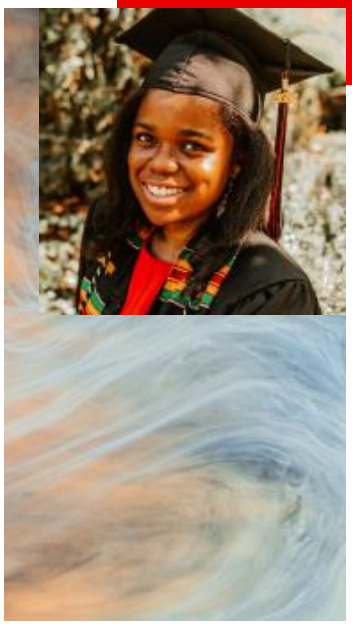

ACS Scholar Adunoluwa Obisesan

BS, Massachusetts Institute of Technology, June 2021
(Chemical-biological Engineering, Computer Science & Molecular Biology)

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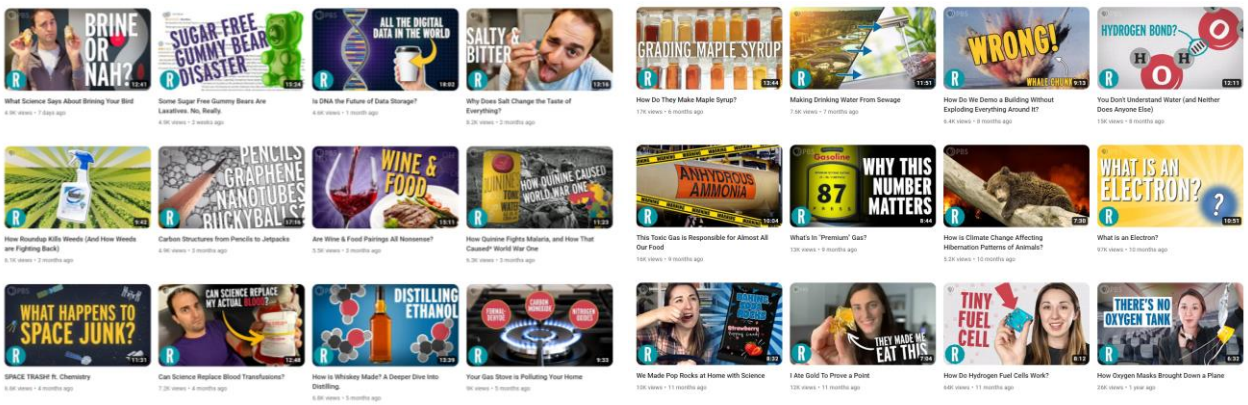

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11

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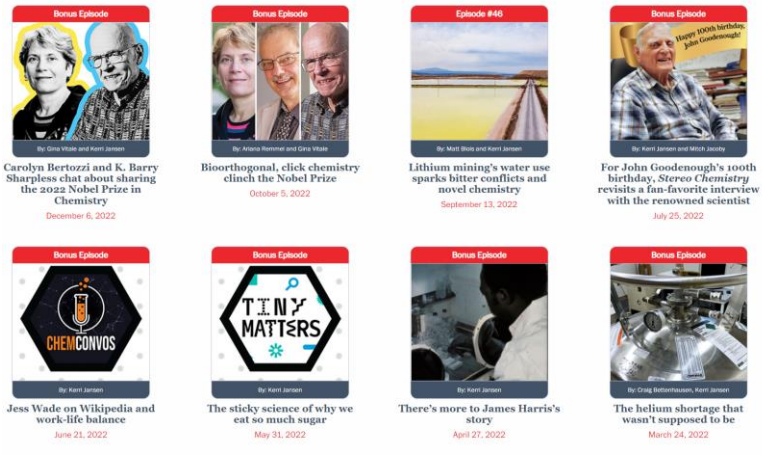

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12

12

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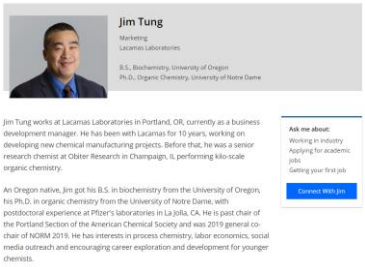

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15

15

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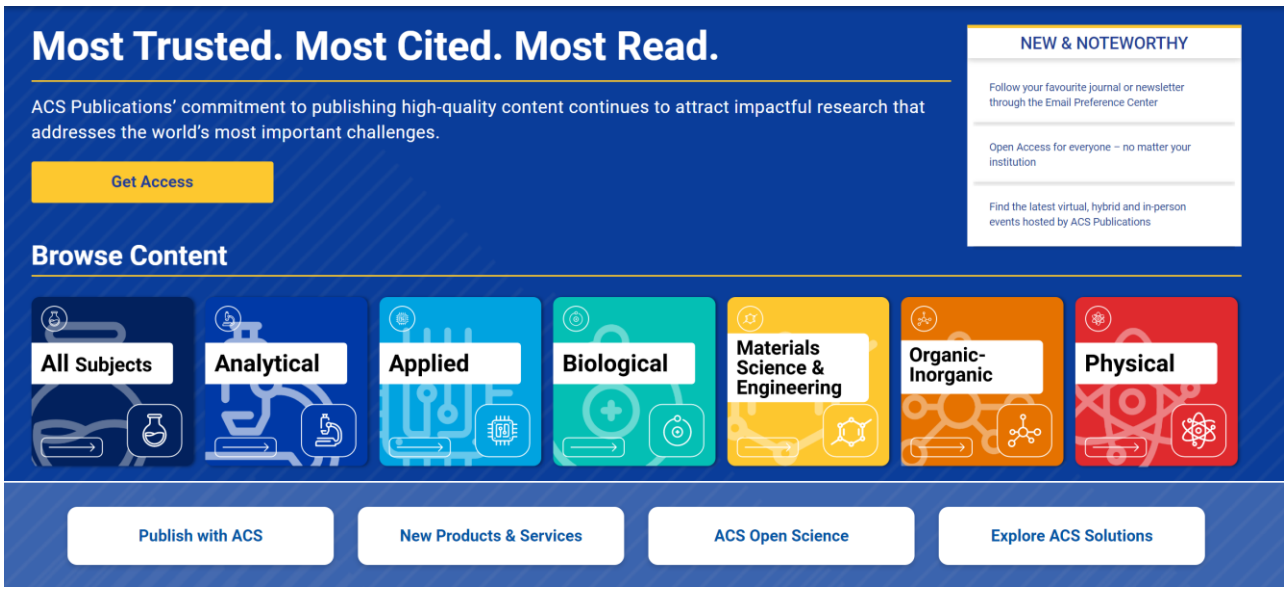

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16

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Advancing ACS' Core Value of Diversity, Equity, Inclusion and Respect

Resources

Inclusivity Style Guide
Designed to help staff and members use language and images that respect diversity in all its forms.

ACS Webinars on Diversity
Covering diversity and inclusion at the workplace

ACS Publications DEIR Hub
See what ACS Publications is doing for fostering inclusivity in scholarly publishing

ACS Volunteer and ACS Meetings Code of Conduct
Fostering a positive and welcoming environment for attendees, volunteers and staff.

C&EN Trailblazers
C&EN highlights scientists from different backgrounds who are making an impact in chemistry.

NEW! Download DEIR Educational Resources
Download this educational guide for additional recommendations on videos, articles, books, podcasts, and more on diversity, inclusion, and related topics.

Quick Guide: Inclusion Moments
Learn more about what Inclusion Moments are and see ideas to host them during your meetings.

Quick Guide: How to host inclusive in-person events
Recommendations and best practices to ensure that your events can accommodate everyone.

Diversity, Equity, Inclusion, and Respect
**Adapted from definitions from the Ford Foundation Center for Social Justice:

Equity**
Seeks to ensure fair treatment, equality of opportunity, and fairness in access to information and resources for all. We believe this is only possible in an environment built on respect and dignity. Equity requires the identification and elimination of barriers that have prevented the full participation of some groups.

Diversity**
The representation of varied identities and differences (race, ethnicity, gender, disability, sexual orientation, gender identity, national origin, tribe, caste, socio-economic status, thinking and communication styles, etc.), collectively and as individuals. ACS seeks to proactively engage, understand, and draw on a variety of perspectives.

Inclusion**
Builds a culture of belonging by actively inviting the contribution and participation of all people. Every person's voice adds value, and ACS strives to create balance in the face of power differences. In addition, no one person can or should be called upon to represent an entire community.

Respect
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19

19

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Harnessing the Power of Natural Polymers

Co-produced with the ACS Green Chemistry Institute

Thursday, February 29, 2024| 2-3:15pm ET

Sustainable Biomanufacturing at Scale

Co-produced with the ACS Committee on Science

Thursday, March 7, 2024| 2-3:15pm ET

The Art of Self-Reinvention

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21

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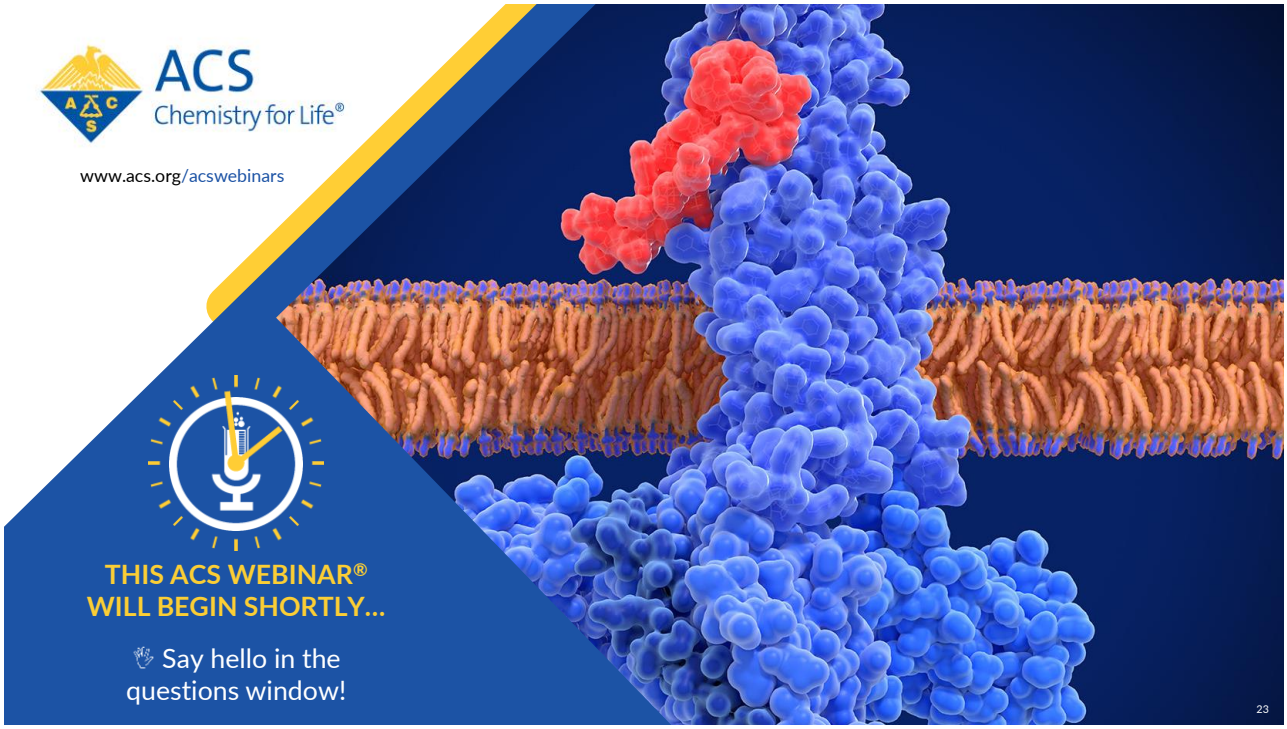
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The GLP-1 Revolution:
From Diabetes and Obesity to Alzheimer's and PCOS
RICHARD WYSE, MBE
Director of Research and Development, The Cure Parkinson's Trust
LEILA PARAND, PhD, MD
Neurobehavior Specialist, UCLA Memory Clinic, David Geffen School of Medicine
Melanie G. Cree, PhD, MD
Physician Scientist, Pediatric Endocrinologist and Associate Professor, University of Colorado Anschutz and Children's Hospital Colorado
CAROLINE HOPKINS, MS
Health & Science Reporter, Precision Medicine Online and GenomeWeb
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24

24

The GLP-1 Revolution

From Diabetes and Obesity to Alzheimer's and PCOS

Thu, Feb 22nd, 2024

Dr Richard Wyse
Director of Clinical Development
Cure Parkinson's

richard@cureparkinsons.org.uk

25

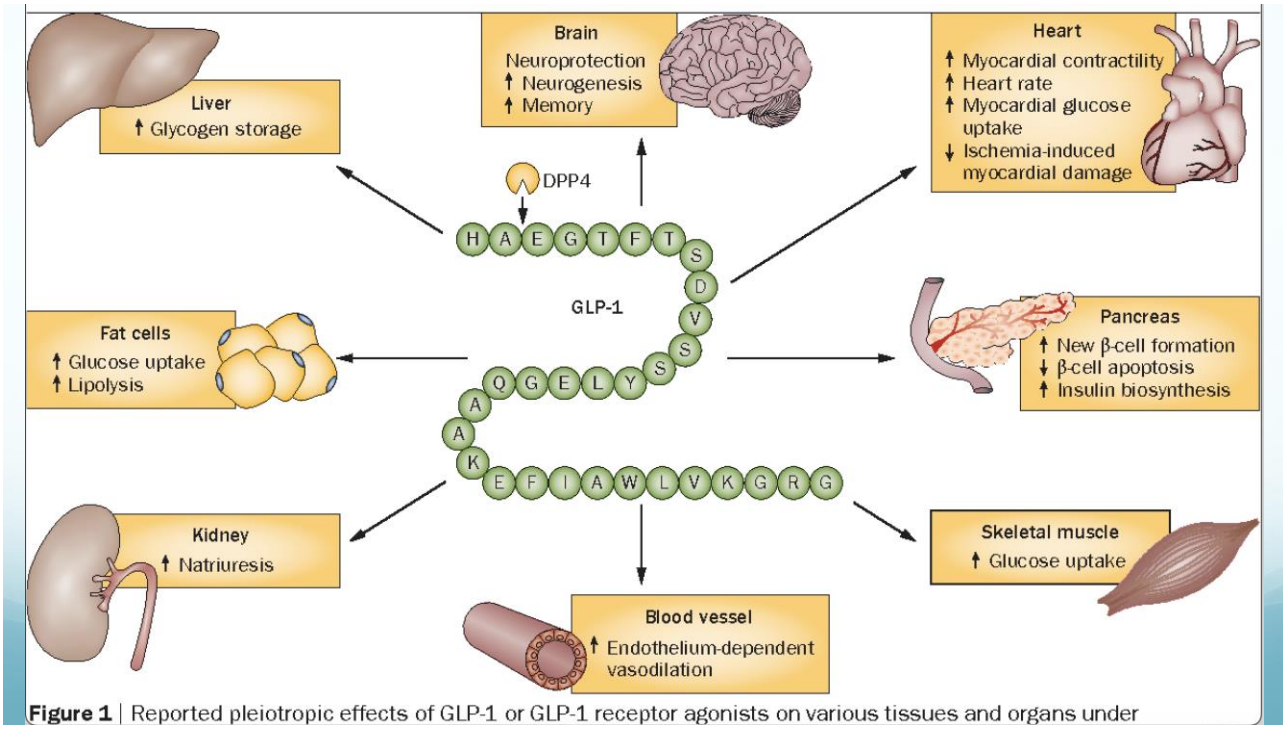
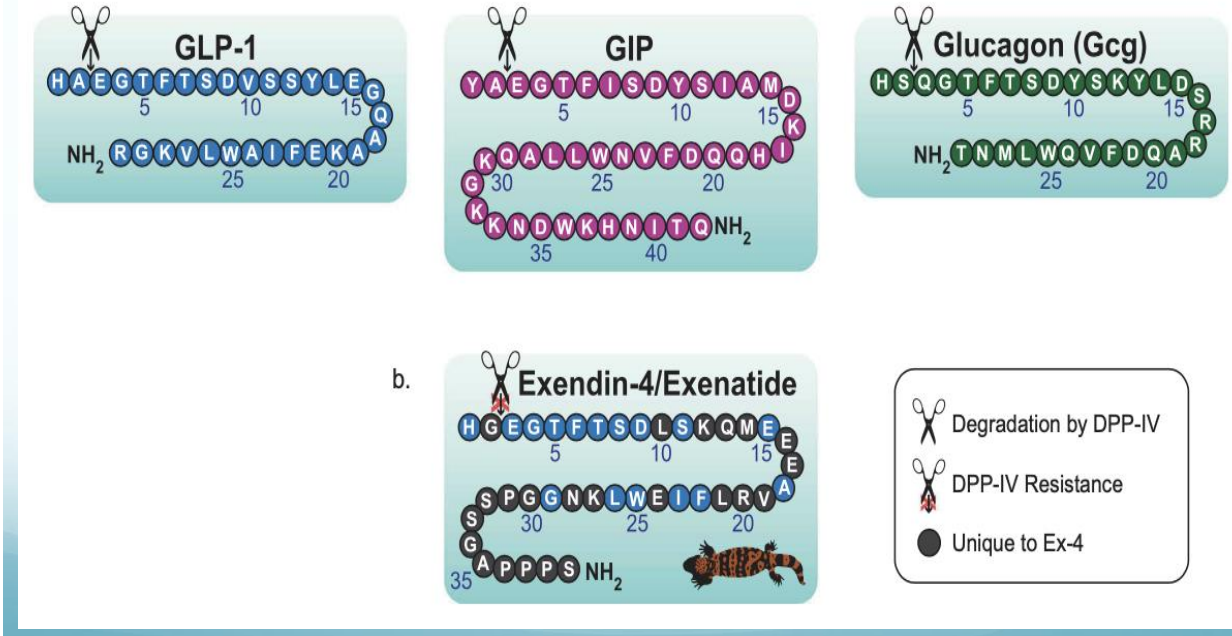


Figure 1 | Reported pleiotropic effects of GLP-1 or GLP-1 receptor agonists on various tissues and organs under

26


GLP-1
HAEGTFTSDVSSYLEGQAA
NH2 RGKVLWAIFEKA
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GIP
YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQ NH2
5
10
15
20
25
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Glucagon (Gcg)
HSQGTFTSDYSKYLDSRRAQDFVQWLMNT NH2
5
10
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b.
Exendin-4/Exenatide
HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS NH2
5
10
15
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Degradation by DPP-IV
DPP-IV Resistance
Unique to Ex-4

27

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Currently Parkinson's patients have :

Symptomatic therapies, with many imperfections

NOTHING to stop year-on-year neurodegeneration

What do we need?

33

What do we need?

We need symptomatic medications that work better

We need disease-modifying medications that work

34

International PD Linked Clinical Trials Initiative

The Brief

To evaluate, prioritise and repurpose existing and new, developing medications that may have benefit in Parkinson's

The Cure Parkinson's Trust

The Cure Parkinson's Trust is a registered charity in England and Wales (1111816) and Scotland (SCO44368) and a company limited by guarantee - company number 5539974

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Received: 23 July 2018 | Revised: 10 September 2018 | Accepted: 21 September 2018

DOI: 10.1111/ejn.14175

SPECIAL ISSUE ARTICLE

WILEY EJN European Journal of Neuroscience FENS

The Linked Clinical Trials initiative (LCT) for Parkinson's disease

Patrik Brundin[1] | **Richard K. Wyse**[2]

[1]Center for Neurodegenerative Science, Van Andel Research Institute, Grand Rapids, Michigan

[2]The Cure Parkinson's Trust, London, UK

Correspondence
Patrik Brundin, Center for Neurodegenerative Science, Van Andel Research Institute, 333 Bostwick Ave. N.E., Grand Rapids, MI.
Email: patrik.brundin@vai.org and r@cureparkinsons.org.uk

Funding information
The Cure Parkinson's Trust and Van Andel Institute; Michael J Fox Foundation; JP Moulton Charitable Foundation; Horizon 2020 (European Union)

Abstract

The Linked Clinical Trials (LCT) initiative is a drug repurposing programme specifically aimed at identifying drugs that can slow the progression of Parkinson's disease (PD). Tom Isaacs was one of the key people behind the idea of LCT in 2011. He ensured it became a priority of The Cure Parkinson's Trust (CPT), a philanthropic funding body based in the UK which Tom had co-founded 7 years earlier. During the latter 6 years of his life, Tom Isaacs was heavily involved in the LCT initiative and held the programme dear to his heart. This article describes the genesis of LCT and how the LCT scientific committee evaluates candidate drugs. From 2012, this committee has met annually to prioritise drugs suitable for repurposing in PD. This article does not catalogue every clinical trial within the LCT programme, but describes the 10 clinical trials that emerged either directly, or as an offspring from discussions, at the first meeting of the LCT scientific committee. Some, but not all, are funded by CPT, and all 10 trials are now either completed or ongoing. These trials use drugs developed to address one of the four therapeutic targets: glucagon-like peptide 1 receptor, iron, and c-abl tyrosine kinase. We conclude the LCT programme has already sparked a large number of promising clinical trials aimed at slowing PD progression. In doing so, it is a major legacy of Tom Isaacs, carrying the torch he once lit and conveying a sense of urgency for new and life-transforming therapies for people with PD.

36

International PD Linked Clinical Trials Initiative

This unique worldwide initiative was designed rapidly to develop the many on-going discoveries and breakthroughs that involve an ever-increasing number of PD-relevant biological targets.

The aim is specifically to evaluate, prioritise new, and repurposed regulatory-approved, medications that may also have direct therapeutic disease-modifying benefits for patients with Parkinson's disease.

To accomplish this, a large International PD Linked Clinical Trials Committee of acknowledged global PD experts was formed in 2012.

Our 1 year progress was described in Journal of Parkinson's Disease, 2013.

37

Journal of Parkinson's Disease 3 (2013) 231–239
DOI 10.3233/JPD-139000
IOS Press

Review

Linked Clinical Trials – The Development of New Clinical Learning Studies in Parkinson's Disease Using Screening of Multiple Prospective New Treatments

Patrik Brundin[a,1,*], Roger A. Barker[b,1], P. Jeffrey Conn[c,1], Ted M. Dawson[d,1], Karl Kieburtz[e,1], Andrew J. Lees[f,1], Michael A. Schwarzschild[g,1], Caroline M. Tanner[h,1], Tom Isaacs[i], Joy Duffen[i], Helen Matthews[i] and Richard K.H. Wyse[i]
[a]*Center for Neurodegenerative Science, Van Andel Institute, MI, USA*
[b]*Cambridge Centre for Brain Repair, Cambridge, UK*
[c]*Vanderbilt Center for Neuroscience Drug Discovery, Vanderbilt University Medical Center, Nashville, TN, USA*
[d]*Johns Hopkins University, Institute for Cell Engineering, Baltimore, MD, USA*
[e]*University of Rochester Medical Center, Center for Human Exp. Therapeutics, Rochester, NY, USA*
[f]*Reta Lila Weston Institute of Neurological Studies, University College London, London, UK*
[g]*Department of Neurology, Massachusetts General Hospital, Boston, MA, USA*
[h]*The Parkinson's Institute and Clinical Center, Sunnyvale, CA, USA*
[i]*The Cure Parkinson's Trust, UK. The Pavilion, Mickelfield Hall, Sarratt, Herts, UK*

38

Current Composition of International PD Linked Clinical Trials Committee

- Professor Patrik Brundin, Van Andel Institute, Michigan, USA (chairman)
- Professor Andrew Lees, Institute of Neurology, London, UK
- Professor Ted Dawson, Johns Hopkins University, Baltimore, USA
- Professor Michael Schwarzschild, Harvard University, Boston, USA
- Professor Carlie Tanner, University of California, San Francisco, USA
- Professor Karl Kieburtz, University of Rochester, New York, USA
- Professor Roger Barker, University of Cambridge, UK
- Professor Jeff Conn, University of Nashville, Tennessee, USA
- Professor Howard Federoff, University of California, Irvine, USA
- Professor David Simon, Massachusetts General Hospital, Boston, USA
- Professor John Trojanowski, University of Pennsylvania, USA
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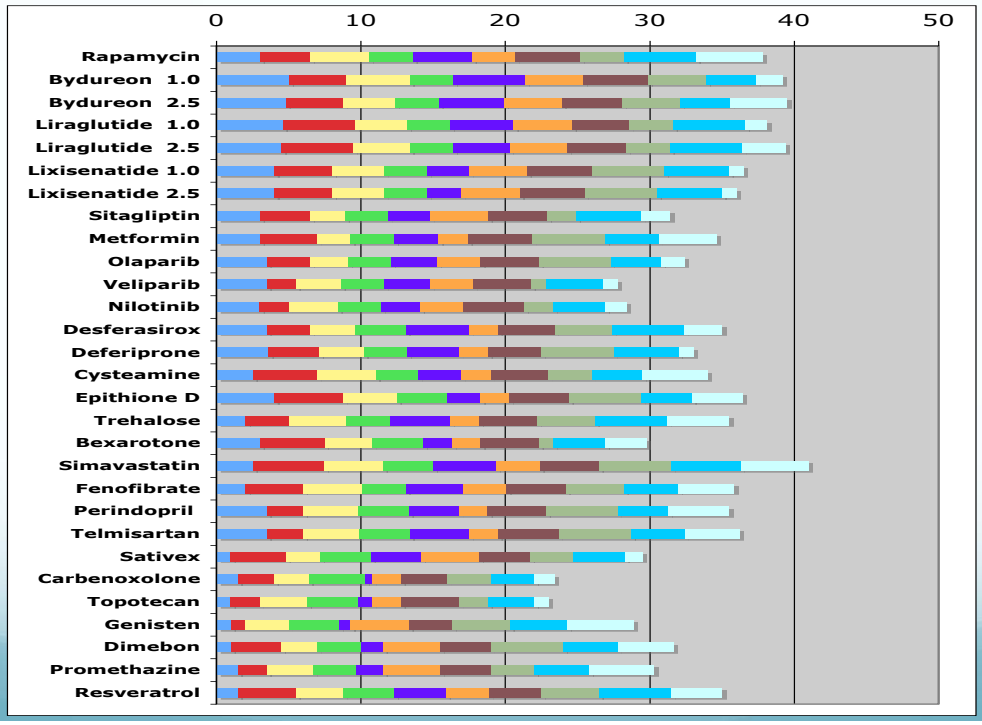
39



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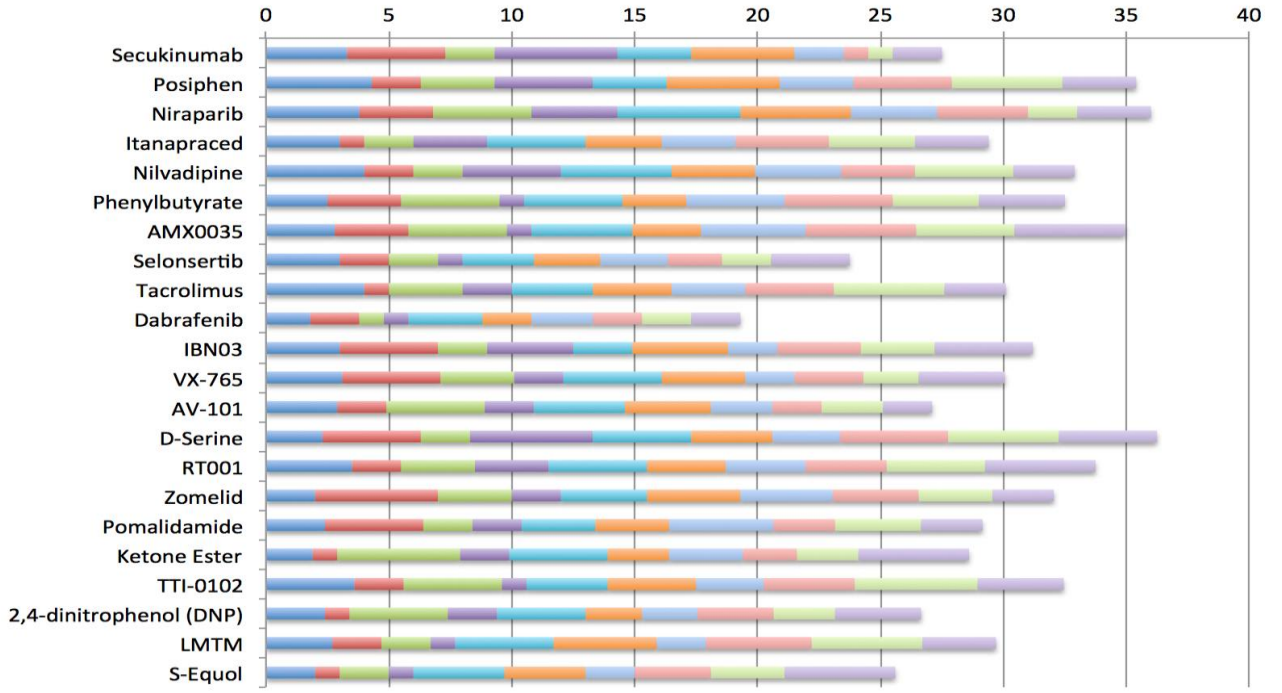
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Secukinumab
Posiphen
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Phenylbutyrate
AMX0035
Selonsertib
Tacrolimus
Dabrafenib
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41


Linked Clinical Trials
VAN ANDEL INSTITUTE
The Cure Parkinson's Trust
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42

International PD Linked Clinical Trials (LCT) Program

VARI - The Cure Parkinson's Trust: Phase II and Phase III Linked Clinical Trials Initiatives

2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022

Exenatide 44 pts & Bydureon 60 patients	Completed	Phase III 200 patient, 2 year trial starts Oct 2019 GLP-1 agonist Wearables & imaging sub studies
Ambroxol	Completed	GBA therapeutic Planning next clinical stage. CPT funded GBA & idiopathic patients RAPSODI and FRONTLINE-PD
EPI-589	Completed	New mitochondrial (oxidoreductase) therapeutic USA, UK and German centers. Idiopathic & genetic PD patients
Simvastatin	230/198 recruited	2 year trial CPT part-funded Multiple biological targets Multiple sub-studies.
Deferiprone: Sky, FAIRPARK II	335/338 recruited	Iron chelation approach. 338 de-novo patients, Pan-European centers. EU funded Sky = Apo Pharma dose finding study
Liraglutide	Almost fully recruited	GLP-1 agonist PD pts with & without insulin resistance 54 weeks on Liraglutide. Cognition & motor end points
Lixisenatide	76/158 recruited	GLP-1 agonist Early stage PD patients. 21 French hospitals CPT/VARI/French Government funded
UDCA	29/30 randomised	Proof of concept study. Novel imaging & wearables. Mitochondrial mode of action. Started 2019 CPT funded
Nilotinib	Completed	cAbl inhibitor Funding from MJFF & CPT & VARI 76 patients Results released December 2019
K-0706	Completed	Safety, tolerability Ph I study involving 32 patients No serious ADRs at highest dose (384mg)
K-0706	Completed	PK/dose finding study. CSF levels in humans similar to those found for efficacious doses in mouse models
K-0706	504 PD patients	cAbl inhibitor Multinational Phase II trial started 2019
Nortryptiline		ADepT-PD 408 PD patients To start in Q4 2019 Alpha-synuclein mode of action
Azathioprine		Anti-inflammatory mode of action Trial starts in 2019
Australia – Drug 1		Phase II, 3 treatment arms + placebo arm 300 PD patients, Extensive additional biomarker studies. All 3 trials simultaneously to start in Q2 2020 Drug over-encapsulation of all treatment arms Australian federal government funded (APM)
Australia – Drug 2		
Australia – Drug 3		

Completed LCT trials, or entering Phase III

Active LCT Phase II trials

Phase III LCT trials due to be launched in 2019/2020

43

GLP-1 Agonists – the facts

What are GLP-1 Agonists and why are these drugs important to CPT's research?

Liraglutide, Lixisenatide and Exenatide (the synthetic form of Exendin-4) belong to a group of drugs called Glucagon-like peptide (GLP-1) agonists designed to mimic the action of human gut hormones (incretins). GLP-1's are currently used to treat diabetes and in recent years there has been research based evidence to suggest that they show

Latest

The October Club Fundraising Dinner

The October Club Dinner Auction Lots

Team CPT at the Royal Parks Foundation Half Marathon 2016

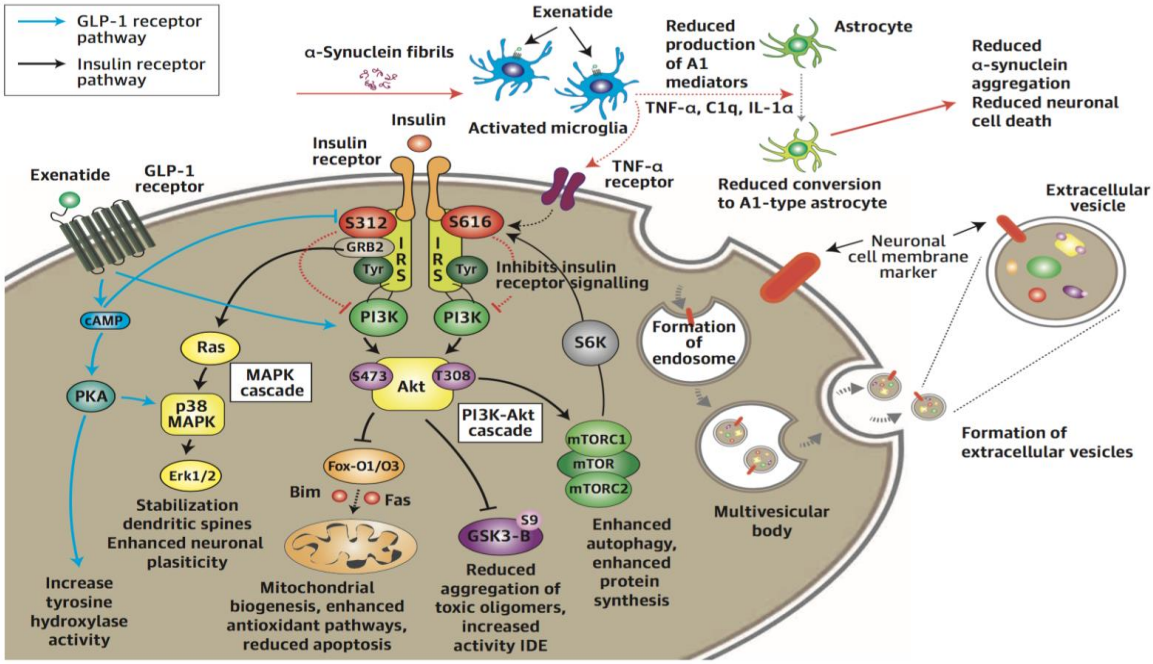
The Grouse & Grape Fundraising Luncheon

Parkinson's MOVEMENT
The Cure Parkinson's Trust

Parkinson's Movement

44

Proposed Scheme for the Neuroprotective Effects of Glucagon-Like Peptide 1 (GLP-1) in Neurons



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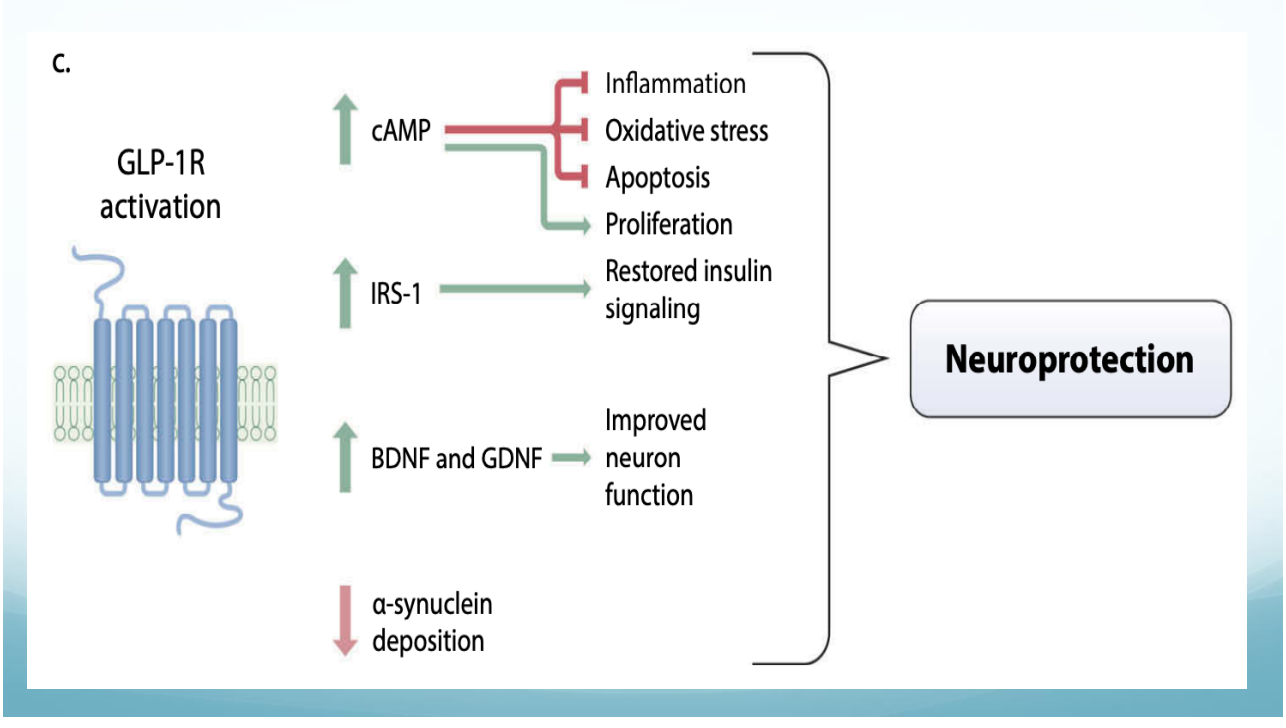

46

doi:10.1093/brain/awaa262 BRAIN 2020: Page 3067 of 3076 | 3067

BRAIN
A JOURNAL OF NEUROLOGY

Diabetes medications and risk of Parkinson's disease: a cohort study of patients with diabetes

Ruth Brauer,[1] Li Wei,[1] Tiantian Ma,[1] Dilan Athauda,[2] Christine Girges,[2] Nirosen Vijiaratnam,[2] Grace Auld,[2] Cate Whittlesea,[1] Ian Wong[1,3] and Tom Foltynie[2]

47

Table 3 Results of the primary and secondary analyses (GTZ, DPP4 and GLP-1 drugs versus other oral drugs used in diabetes)

	GTZ and DPP-4 (n = 58 072)		GTZ (n = 21 175)		DPP4 inhibitors (n = 36 897)		GLP-1 receptor agonists (n = 10 684)	
Type of analysis	Crude IRR (95% CI), P-value	Adjusted IRR (95% CI), P-value	Crude IRR (95% CI), P-value	Adjusted IRR (95% CI), P-value	Crude IRR (95% CI), P-value	Adjusted IRR (95% CI), P-value	Crude IRR (95% CI), P-value	Adjusted IRR (95% CI), P-value
Primary analysis	0.69 (0.55–0.87), <0.01	0.85 (0.66–1.08), 0.206	0.83 (0.64–1.07), 0.143	1.17 (0.76–1.63), 0.467	0.54 (0.41–0.73), <0.01	0.64 (0.43–0.88), <0.01	0.40 (0.24–0.66), <0.01	0.38 (0.17–0.60), <0.01
Additional analyses								
Follow-up time censored	0.56 (0.44–0.72), <0.01	0.58 (0.45–0.76), <0.01	0.66 (0.46–0.91), 0.012	0.52 (0.32–0.73), <0.01	0.48 (0.34–0.66), <0.01	0.52 (0.33–0.74), <0.01	0.24 (0.11–0.52), <0.01	0.16 (0.03–0.3), <0.01
Past use	1.24 (0.92–1.68), 0.160	0.54 (0.40–0.70), <0.01	1.06 (0.78–1.43), 0.729	0.93 (0.50–1.40), 0.777	0.88 (0.53–1.46), 0.633	0.29 (0.14–0.45), <0.01	0.72 (0.38–1.36), 0.311	0.61 (0.07–1.17), 0.179
Duration use								
Up to 12 months	0.6 (0.41–0.88), <0.01	0.75 (0.44–1.08), 0.152	0.73 (0.47–1.14), 0.170	0.75 (0.38–1.14), 0.208	0.39 (0.20–0.76), <0.01	0.44 (0.10–0.78), 0.003	0.35 (0.16–0.74), <0.01	0.26 (0.04–0.48), <0.01
12–36 months	0.72 (0.47–1.10), <0.01	0.89 (0.50–1.31), 0.607	0.67 (0.39–1.17), 0.158	0.68 (0.25–1.13), 0.172	0.80 (0.43–1.48), 0.475	1.20 (0.31–2.14), 0.651	[a]	[a]
>36 months	0.72 (0.56–0.92), 0.132	0.86 (0.65–1.10), 0.269	0.91 (0.68–1.21), 0.502	1.34 (0.76–1.96), 0.248	0.55 (0.39–0.76), <0.01	0.63 (0.37–0.90), 0.015	0.44 (0.23–0.85), 0.01	0.45 (0.11–0.79), <0.01
Age >40 years	0.69 (0.55–0.87), <0.01	0.87 (0.67–1.09), 0.256	0.83 (0.64–1.07), 0.145	1.19 (0.77–1.67), 0.890	0.54 (0.41–0.73), <0.01	0.65 (0.44–0.89), 0.011	0.41 (0.25–0.68), <0.01	0.40 (0.18–0.63), <0.01
Non-smokers	0.59 (0.41–0.86), <0.01	0.82 (0.54–1.16), 0.294	0.74 (0.50–1.12), 0.158	1.16 (0.65–1.77), 0.543	0.42 (0.25–0.71), <0.01	0.54 (0.23–0.88), 0.022	0.42 (0.19–0.94), 0.034	0.42 (0.07–0.80), 0.01
Secondary definition PD	0.73 (0.57–0.94), 0.02	0.87 (0.65–1.13), 0.333	0.86 (0.65–1.15) 0.309	1.14 (0.66–1.67), 0.578	0.59 (0.42–0.81), <0.01	0.69 (0.43–0.92), 0.06	0.37 (0.20–0.67), <0.01	0.28 (0.13–0.64), <0.01
BMI > 30 kg/m2	0.61 (0.43–0.85), <0.01	0.70 (0.47–0.99), 0.072	0.82 (0.56–1.19), 0.293	0.93 (0.55–1.40), 0.759	0.40 (0.25–0.64), <0.01	0.41 (0.21–0.64), <0.01	0.47 (0.27–0.81), <0.01	0.65 (0.28–1.08), 0.13

48


Bydureon® Pen
exenatide extended-release
for injectable suspension
2 mg/pen
Subcutaneous use only.

49


Saxenda®
NUTRICLINIC
liraglutide injection
6 mg/mL (5 x 3 mL pre-filled pen)
Solution for injection, pre-filled pen
Subcutaneous use only
Store in a refrigerator (2° to 8°C). Do not freeze.
After first use of the pen, store at a temperature not above 30°C or in a refrigerator (2° to 8°C).
Do not store with needle attached.
Keep the cap on in order to protect from light.
Discard pen 30 days after first use.
novo nordisk®
Saxenda®

50

Lixisenatide

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mounjaro
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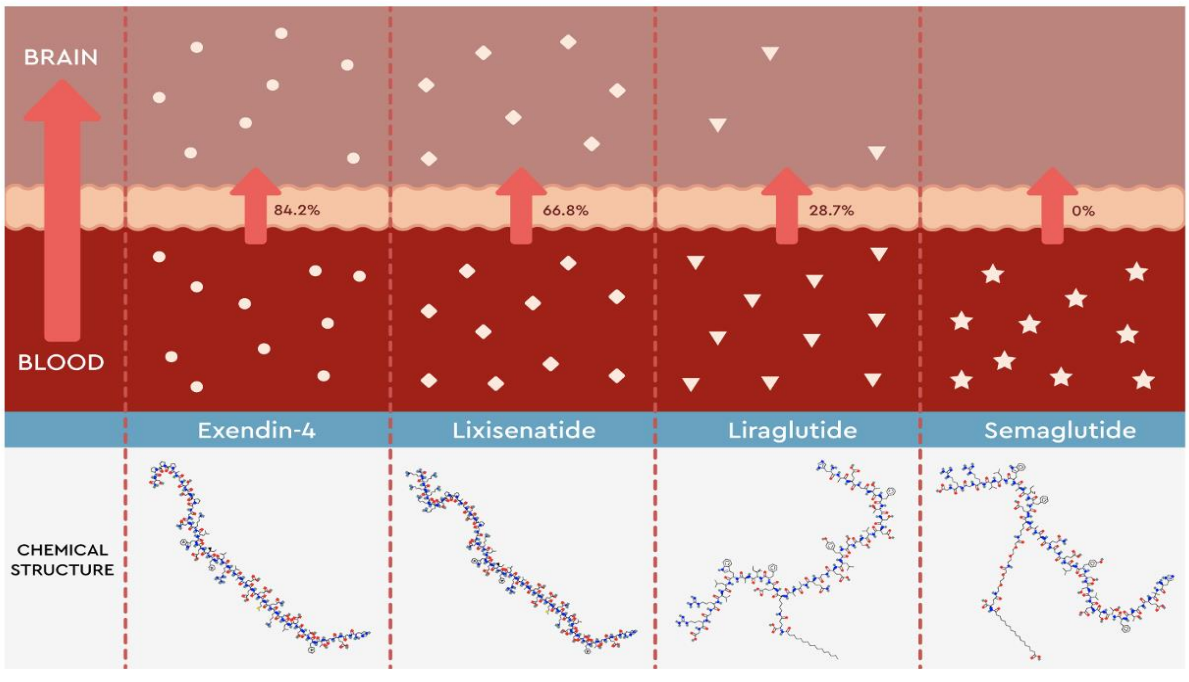

BRAIN
BLOOD
84.2%
66.8%
28.7%
0%
Exendin-4
Lixisenatide
Liraglutide
Semaglutide
CHEMICAL STRUCTURE

54

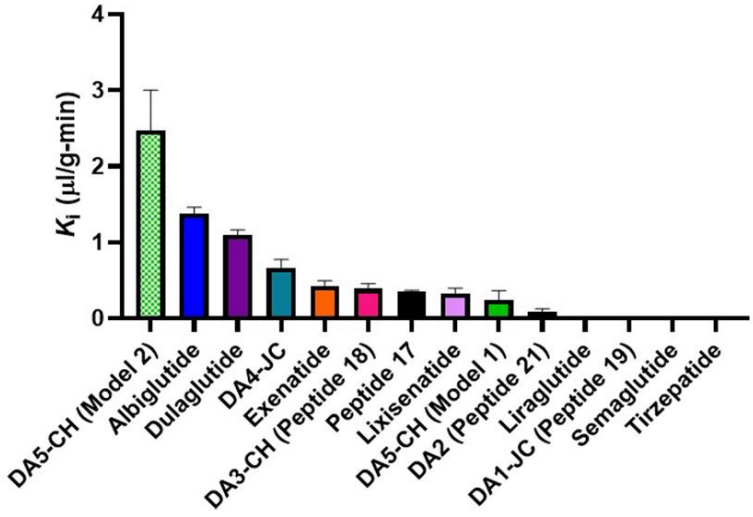
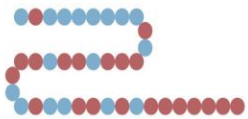
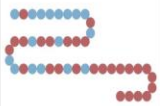
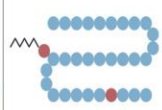
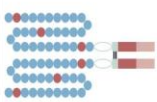
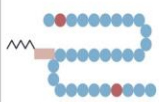
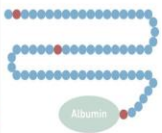


Figure 3. Rate constants (K_i) of $^{125}I/^{14}C$-IRAs transport into whole brain within one hour. The unidirectional influx rates, K_i (slope) and V_r (y-intercept), are listed in Table 3 or in our previous report.[50] $n = 11–14$ per IRA. DA peptides are experimental dual IRA agonists created by Christian Hölscher.[38,62] Peptides 18, 19, and 21 are dual IRAs created by Finan and Ma et al. (2013).[72] numbered as in their Supplementary Fig. S1.

55

CHARACTERISTICS OF APPROVED GLP-1 RECEPTOR AGONISTS

DRUG	EXENATIDE IMMEDIATE RELEASE	EXENATIDE EXTENDED RELEASE	LIXISENATIDE	LIRAGLUTIDE	DULAGLUTIDE	SEMAGLUTIDE	ALBIGLUTIDE
STRUCTURAL HOMOLOGY ● Human GLP-1 amino acid ● Non-human GLP-1 amino acid							
STRUCTURAL HOMOLOGY	Exendin-4 (53%)		Exendin-4 (50%)	GLP-1 (97%)	GLP-1 (90%)	GLP-1 (94%)	GLP-1 (97%)
DOSAGE (s.c. administration)	2 mg qw	5 µg → 10 µgbd	10 µg → 20 µg qd	0.6 mg → 1.2-1.8 mg qd	0.75–1.5 mg qw	0.25 mg → 0.5–1 mg qw	30, 50mg qw
ELIMINATION HALF LIFE	Not determined	2.4 hours	~3 hours	~13 hours	~1 week	4.5–4.7 days	5 days

S/C = subcutaneous
QW = once weekly
BD = twice daily

56

J Clin Invest. doi:10.1172/JCI68295.

Clinical Medicine

Exenatide and the treatment of patients with Parkinson's disease

Iciar Aviles-Olmos[1], John Dickson[2], Zinovia Kefalopoulou[1], Atbin Djamshidian[3], Peter Ell[2], Therese Soderlund[2], Peter Whitton[4], Richard Wyse[5], Tom Isaacs[5], Andrew Lees[3], Patricia Limousin[1] and Thomas Foltynie[1]

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[2]Department of Nuclear Medicine, University College London Hospitals NHS Trust, London, United Kingdom.
[3]Reta Lila Weston Laboratories, London, United Kingdom.
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[5]Cure Parkinson's Trust, St. Botolph's, London, United Kingdom.

Address correspondence to: Thomas Foltynie, Box 146, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, United Kingdom. Phone: 0203.448.8726; Fax: 0203.448.0142; E-mail: T.Foltynie@ucl.ac.uk.

Published May 20, 2013

57

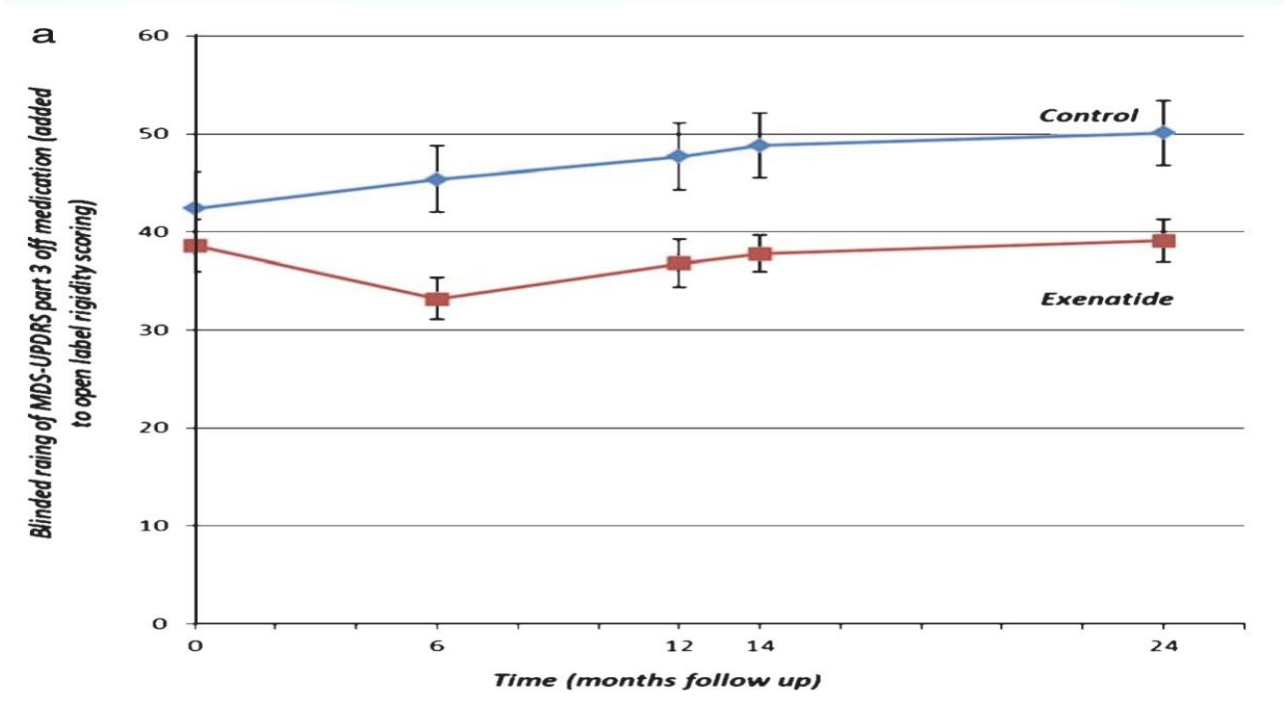
Journal of Parkinson's Disease xx (20xx) x–xx
DOI 10.3233/JPD-140364
IOS Press

Motor and Cognitive Advantages Persist 12 Months After Exenatide Exposure in Parkinson's Disease

Iciar Aviles-Olmos[a], John Dickson[b], Zinovia Kefalopoulou[a], Atbin Djamshidian[c], Joshua Kahan[a], Peter Ell FmedSci[b], Peter Whitton[d], Richard Wyse[e], Tom Isaacs[e], Andrew Lees[c], Patricia Limousin[a] and Thomas Foltynie[a,*]

[a]*Sobell Department of Motor Neuroscience, UCL Institute of Neurology, London, UK*
[b]*Department of Nuclear Medicine, University College London Hospitals NHS Trust, London, UK*
[c]*Reta Lila Weston Laboratories, London, UK*
[d]*UCL School of Pharmacy, London, UK*
[e]*5 The Cure Parkinson's Trust, St. Botolph's, London, UK*

58



59

FOUR PHASE II TRIALS IN PD PATIENTS (LONDON, SWEDEN, SOUTH KOREA & FLORIDA), AND ONE PHASE III TRIAL (200 PD patients, 2 years on medication)

60

Journal of Parkinson's Disease 7 (2017) 451–458
DOI 10.3233/JPD-171192
IOS Press

Is Exenatide a Treatment for Parkinson's Disease?

Dilan Athauda[a], Richard Wyse[b], Patrik Brundin[c] and Thomas Foltynie[a,*]
[a]*Sobell Department of Motor Neuroscience, UCL Institute of Neurology and The National Hospital for Neurology and Neurosurgery, Queen Square, London, UK*
[b]*Cure Parkinson's Trust, London, UK*
[c]*Van Andel Research Institute, Grand Rapids, Michigan, USA*

61

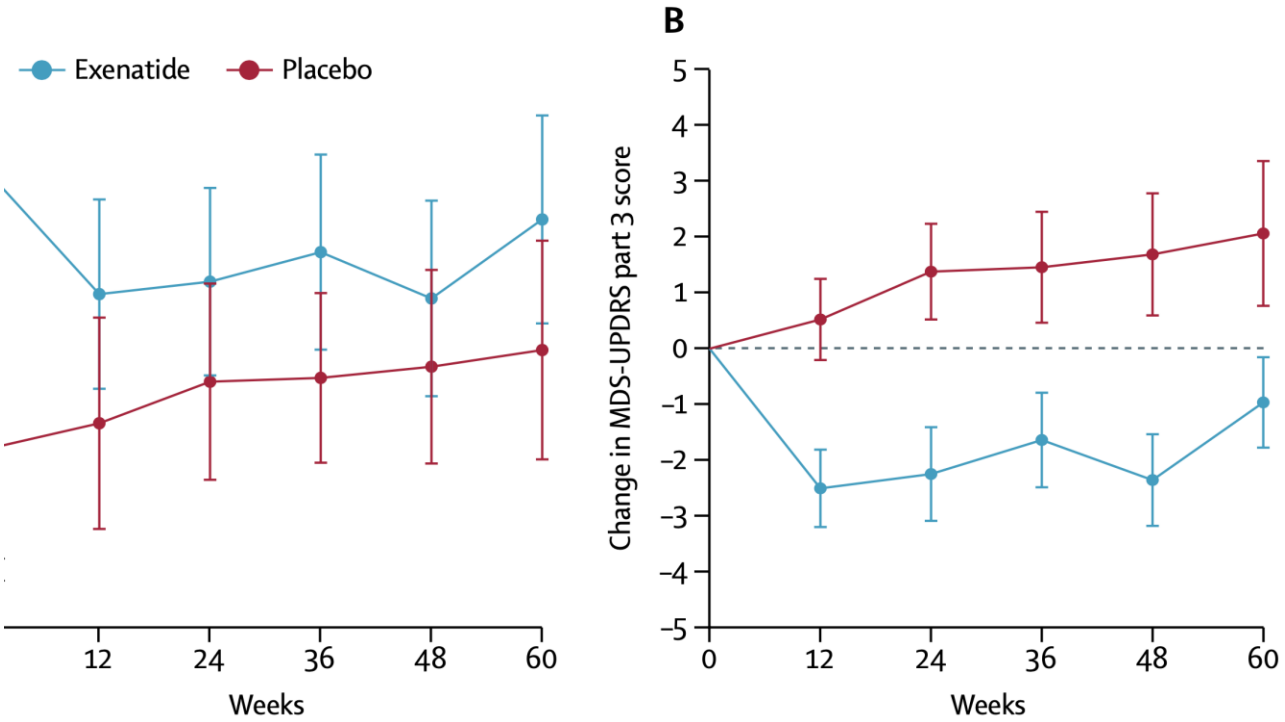
Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial

Dilan Athauda, Kate Maclagan, Simon S Skene, Martha Bajwa-Joseph, Dawn Letchford, Kashfia Chowdhury, Steve Hibbert, Natalia Budnik, Luca Zampedri, John Dickson, Yazhou Li, Iciar Aviles-Olmos, Thomas T Warner, Patricia Limousin, Andrew J Lees, Nigel H Greig, Susan Tebbs, Thomas Foltynie

Summary

Background Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has neuroprotective effects in preclinical models of Parkinson's disease. We investigated whether these effects would be apparent in a clinical trial.

62



63

EXOSOME ANALYSES

JAMA Neurology | Original Investigation

Utility of Neuronal-Derived Exosomes to Examine Molecular Mechanisms That Affect Motor Function in Patients With Parkinson Disease

A Secondary Analysis of the Exenatide-PD Trial

Dilan Athauda, MRCP, PhD; Seema Gulyani, PhD; Hanuma Karnati, PhD; Yazhou Li, PhD; David Tweedie, PhD; Maja Mustapic, PhD; Sahil Chawla, BSc; Kashfia Chowdhury, MSc; Simon S. Skene, PhD; Nigel H. Greig, PhD; Dimitrios Kapogiannis, MD; Thomas Foltynie, MRCP, PhD

64

Presenting a brighter future, both in conventional and regenerative approaches

EXOSOME ANALYSES

CONCLUSIONS AND RELEVANCE The results of this study are consistent with target engagement of brain insulin, Akt, and mTOR signaling pathways by exenatide and provide a mechanistic context for the clinical findings of the Exenatide-PD trial. This study suggests the potential of using exosome-based biomarkers as objective measures of target engagement in clinical trials using drugs that target neuronal pathways.

65

Cedar's Sinai Hospital, Los Angeles

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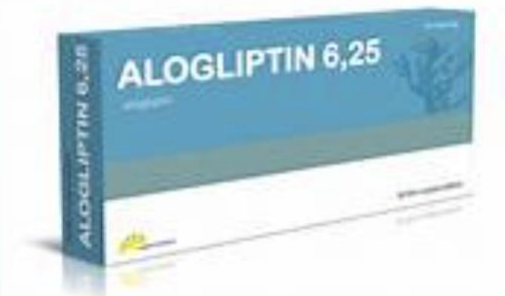
Lixisenatide

21 FRENCH NEUROLOGY CENTERS, 156 Parkinson's patients

67



AUSTRALIAN PARKINSON'S MISSION

68

The GLP-1 Revolution

From Diabetes and Obesity to Alzheimer's and PCOS

Thu, Feb 22nd, 2024

Dr Richard Wyse
Director of Clinical Development
Cure Parkinson's

richard@cureparkinsons.org.uk

69

Glucagon Like Peptide 1 (GLP1)-Receptor Agonists and Alzheimer's Disease

By Leila Parand, MD
Assistant Professor of Neurology at UCLA
David Geffen School of Medicine

70

Outline

- Description of Alzheimer's Disease
- Description of Type 2 Diabetes Mellitus
- Link between Alzheimer's and Type 2 Diabetes Mellitus
- GLP-1 Receptor Agonists
- Clinical Trials including GLP1 Receptor Agonists in relationship to Alzheimer's Disease
- Summary

71

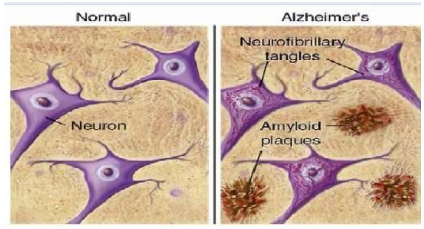
Disclosures

- Primary Investigator for Evoke and Evoke Plus; site is note currently active

72

Alzheimer's Disease

- Alzheimer's Dementia is the most common form of dementia affects ~57 million people worldwide
- Clinical features of Alzheimer's Disease: memory loss, visuospatial difficulties, trouble with orientation
- Pathological markers of Alzheimer's disease include amyloid beta plaques and neurofibrillary tangles
- Other features of Alzheimer's include neuronal loss, neuroinflammation, reduced cerebral glucose metabolism



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Nichols E, Vos T. The estimation of the global prevalence of dementia from 1990–2019 and forecasted prevalence through 2050: An analysis for the Global Burden of Disease (GBD) study 2019. Alzheimers Dement. 2021;17(Suppl 10):e051496.
World Alzheimer's Report 2018
Masters CL, et. al. Alzheimer's disease. Nat Rev Dis Prim. 2015;1:15056.
Google Image Bright Focus Foundation

73

Diabetes Mellitus

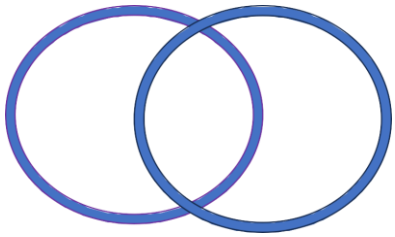
- 537 million adults have diabetes mellitus world-wide (age 20-79)
- 96% are Type 2 Diabetes Mellitus
- Characterized by hyperglycemia and insulin resistance
- Complications include cardiovascular disease, chronic kidney disease, stroke, vision loss
- Associated with cognitive impairment, dementia, and particularly Alzheimer's Disease

https://diabetesatlas.org/#:~:text=Diabetes%20around%20the%20world%20in%202021%3A,%2D%20and%20middle%2Dincome%20countries.
https://collegedunia.com/exams/diabetes-mellitus-types-symptoms-preventions-biology-articleid-6407

74

Relationship between Diabetes Mellitus and Alzheimer's Disease

- Epidemiological and biological studies support the association between Alzheimer's and Type 2 Diabetes
- Diabetes increases the risk of Alzheimer's
- Longer duration of having diabetes has been associated with a higher risk of developing dementia



Amidei, Claduo, et al. "Association Between Age at Diabetes Onset and Subsequent Risk of Dementia. *JAMA.* 2021;325(16):1640-1649
Ott A, et. Al.. Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurology. 1999;**53**:1937–1942.
Akomolafe A, Diabetes mellitus and risk of developing Alzheimer disease: results from the Framingham Study. Arch Neurol. 2006;**63**:1551–1555.
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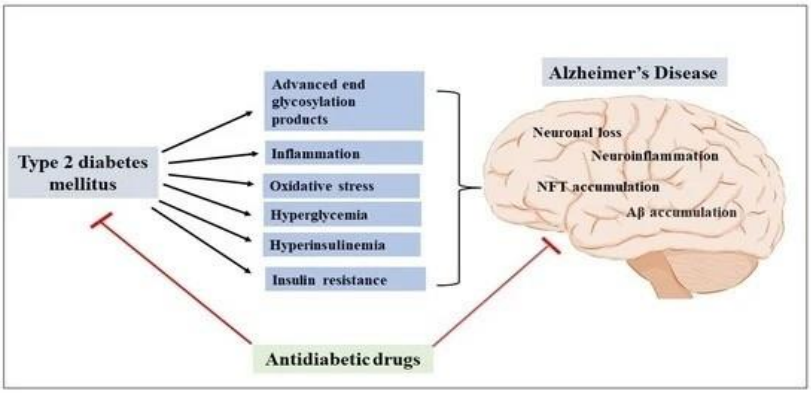
75

Type 2 Diabetes Mellitus Associated with Alzheimer's Dementia



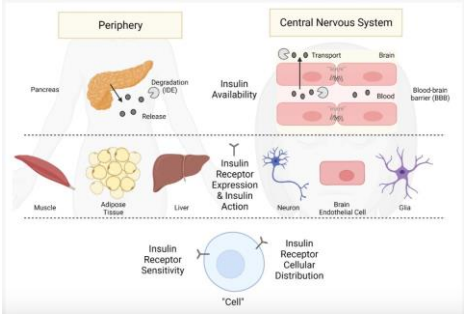
Links between T2DM and AD resulting in repurposing of antidiabetic drugs for AD

Adem, MA, et. Al (2024). "Pharmacological approaches Using Diabetic Drugs Repurposed for Alzheimer's Disease, "Biomedicines, 12(1), 99.

76

Insulin

- Insulin crosses the blood–brain barrier to regulate functioning
- Has a neuroprotective role, plays an important role in the organization and function of the brain
- insulin resistance or deficiency in the brain is a pathological feature in Type II Diabetes and Alzheimer's Disease



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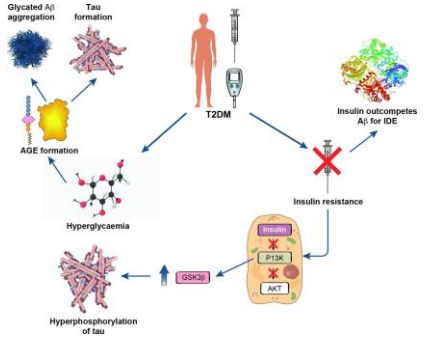
Rhea, EM, et al. Insulin Resistance in Peripheral Tissues and the Brain: A Tale of Two Sites. *Biomedicines* **2022**, *10*(7), 1582

77

Insulin dysfunction in the brain increase pathological markers of Alzheimer's Disease

- Insulin deficient states lead to AD pathogenesis
- Increased Amyloid beta and hyperphosphorylated Tau
- Impaired enzyme system in these models, affecting Amyloid beta and insulin



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Journal of Neurology, Neurosurgery & Psychiatry Published Online First: 30 January 2024.
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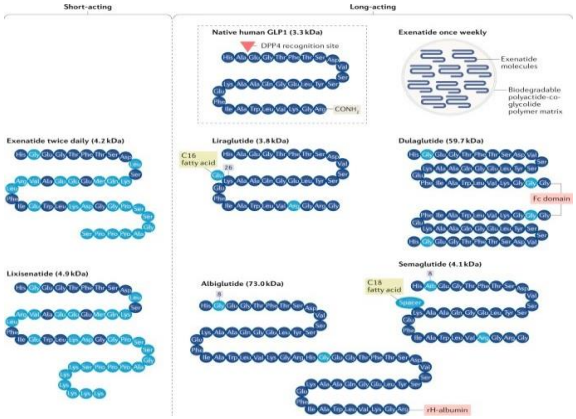
Farris W., Mansourian S., Chang Y., Lindsley L., Eckman E.A., Frosch M.P., Eckman C.B., Tanzi R.E., Selkoe D.J., Guénette S. Insulin-degrading enzyme regulates the levels of insulin, amyloid β-protein, and the β-amyloid precursor protein intracellular domain in vivo. *Proc. Natl. Acad. Sci. USA.* 2003;100:4162–4167. doi: 10.1073/pnas.0230450100.

78

Glucagon-like peptide-1 (GLP1) and GLP1-Receptor Agonists

- Incretin hormone
- induces glucose –dependent insulin secretion to lower blood glucose
- GLP-1 and receptors have been found in the brain and has a benefit in brain functioning



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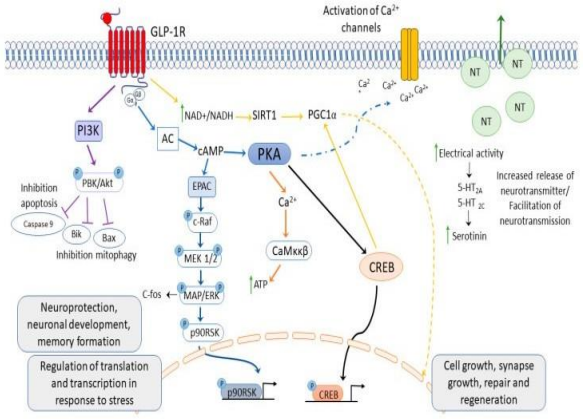
Diz-Chaves Y, Mastooí Z, Spuch C, González-Matías LC, Mallo F. Anti-Inflammatoíy Effects of GLP-1 Receptoí Activation in the Bíain in Neuíodegeneíative Diseases. Int J Mol Sci. 2022 Aug 24;23(17):9583.

79

Beneficial effects of GLP-1 on the brain

- Neuroprotection
- Memory formation
- Neuronal development



Diz-Chaves Y, Mastooí Z, Spuch C, González-Matías LC, Mallo F. Anti-Inflammatoíy Effects of GLP-1 Receptoí Activation in the Bíain in Neuíodegeneíative Diseases. Int J Mol Sci. 2022 Aug 24;23(17):9583.

80

Clinical Trials: Evaluation of Liraglutide in the treatment of Alzheimer's Disease (ELAD)

- 204 adults with mild to moderate AD received subcutaneous injections of either Liraglutide or placebo once daily for 12 months
- Results showed no difference between the treatment and control in terms of the primary endpoint cerebral glucose metabolic rate
- Improved cognitive function in the treated group, measured by ADAS-EXEC (ADAS-Cog with Executive domains of the Neuropsychological Test Battery) as well as MRI volume (temporal lobe and whole MRI volume)

Edison P., Femminella G.D., Ritchie C.W., Holmes C., Walker Z., Ridha B.H., Raza S., Livingston N.R., Nowell J., Busza G. Evaluation of liraglutide in the treatment of Alzheimer's disease. *Alzheimer's Dement.* 2021
Adem MA, Decouít B, Sabbagh MN. Phaímacological Appíoaches Using Diabetic Díugs Repuíposed foí Alzheimeí's Disease. Biomedicines. 2024 Jan 3;12(1):99
McClean P.L., Parthsarathy V., Faivre E., Hölscher C. The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer's disease. *J. Neurosci.* 2011;31:6587–6594.

81

Clinical Trials: Pilot Study of Exenatide Actions on Alzheimer's Disease

- Eighteen participants with high probability of Alzheimer's disease on cerebrospinal fluid (CSF) biomarkers completed the entire study prior to its early termination by the sponsor

- no benefit of exenatide; however, no firm conclusions can be drawn from this study due to its early termination except for a reduction of $A\beta_{42}$ in extracellur vessicles.

Mullins RJ, et al.. A Pilot Study of Exenatide Actions in Alzheimer's Disease. Curr Alzheimer Res. 2019;16(8):741-752.
Adem MA, Decouít B, Sabbagh MN. Phaímacological Appíoaches Using Diabetic Díugs Repuíposed foí Alzheimeí's Disease. Biomedicines. 2024 Jan 3;12(1):99

82

Clinical Trials: Dulaglutide and cardiovascular outcomes in Type II Diabetes (REWIND)

- examined the effect of once weekly subcutaneous injection of either Dulaglutide or placebo in participants aged 50 or more and diagnosed with T2DM on the cardiovascular risks of T2DM, such as non-fatal MI, non-fatal stroke, or death from cardiovascular causes
- Montreal Cognitive Assessment (MoCA) and Digital Symbol Substitution Test (DSST) were done at baseline and follow up to assess cognitive impairment.
- Cognitive impairment was reduced by 14% in the dulaglutide treated arm in comparison to the placebo

Gerstein HC, et. al,; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019 Jul 13;394(10193):121-130
Adem MA, Decourt B, Sabbagh MN. Pharmacological Approaches Using Diabetic Drugs Repurposed for Alzheimer's Disease. Biomedicines. 2024 Jan 3;12(1):99

83

Ongoing Clinical Trials: Evoke and Evoke plus

- Evoke and Evoke + each have ~1840 amyloid-positive participants with MCI or mild AD dementia who have been randomized to receive either daily oral semaglutide (14 mg, escalated via 3 and 7 mg over 8 weeks) or daily oral placebo over a period of 156 weeks
- The difference between the studies is the inclusion of participants with vascular co-pathologies in evoke plus
- Both trials set to be completed in September 2025.

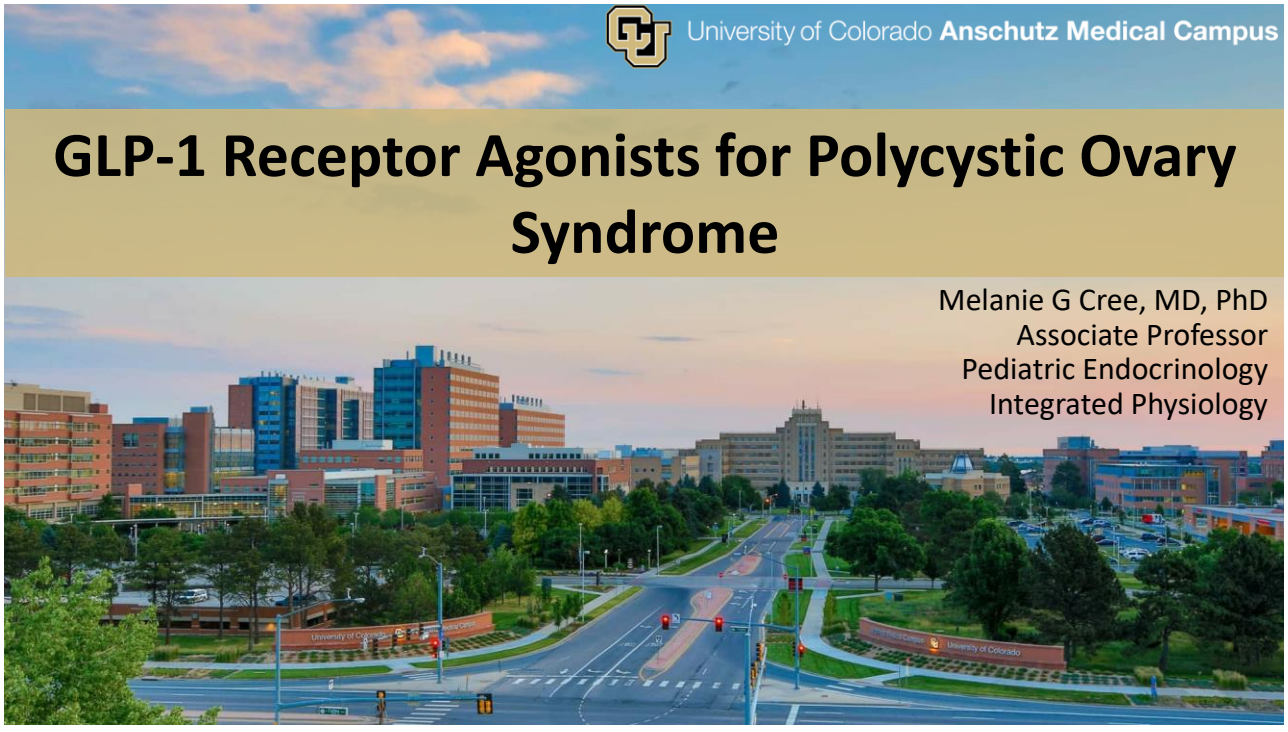
https://classic.clinicaltrials.gov/ct2/show/NCT04777409
Ballard, C.,et al. (2020). Liraglutide and semaglutide: Pooled post hoc analysis to evaluate risk of dementia in patients with type 2 diabetes. *Alzheimer's & Dementia, 16*(S9).

84

Summary

- Type 2 Diabetes and Alzheimer's Disease are associated by clinical and biological changes
- GLP1 Receptor Agonists have been shown in research studies to have a benefit on biological changes associated with Alzheimer's Disease
- GLP1 Receptor Agonists may have a central role in management of Alzheimer's disease in the near future

85



86

No Conflicts
Consultant: Pollie, Inc
Research Scientist: Amino Corp
Will discuss off-label medications

Ludeman Family Center for Women's Health Research

Children's Hospital Colorado

87

Polycystic Ovary Syndrome

PCOS includes
Menstrual cycle irregularities
Elevated testosterone or signs of elevated testosterone
Polycystic ovaries (only adults)

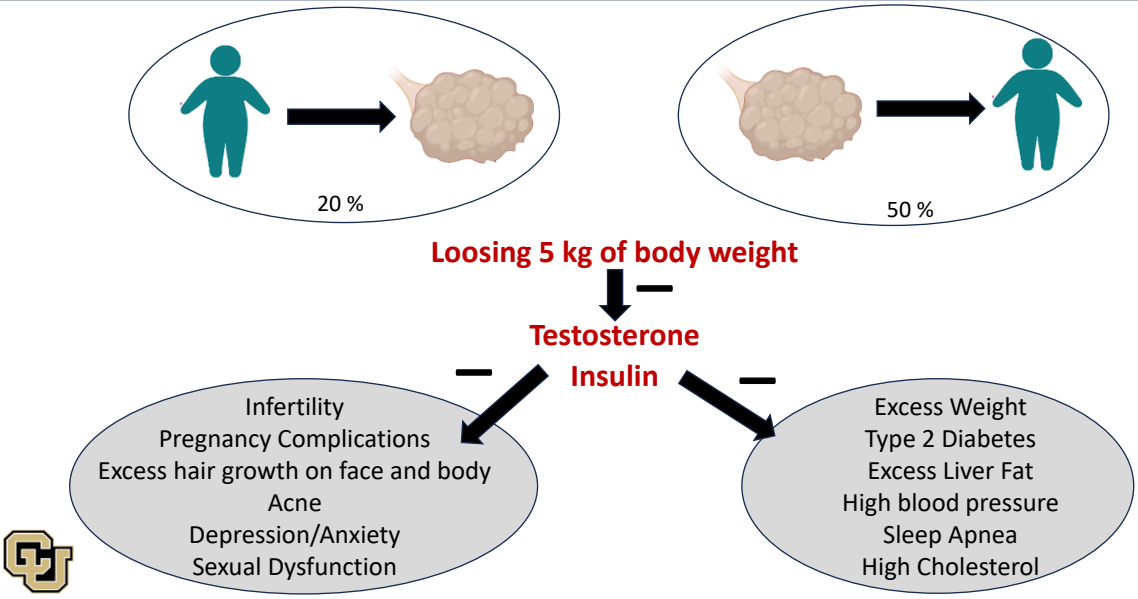
Infertility
Pregnancy Complications
Excess hair growth on face and body
Acne
Depression/Anxiety
Sexual Dysfunction

Excess Weight
Type 2 Diabetes
Excess Liver Fat
High blood pressure
Sleep Apnea
High Cholesterol

PCOS affects 6-15% of women in the United States

88

PCOS and Weight



Figures made with Biorender©

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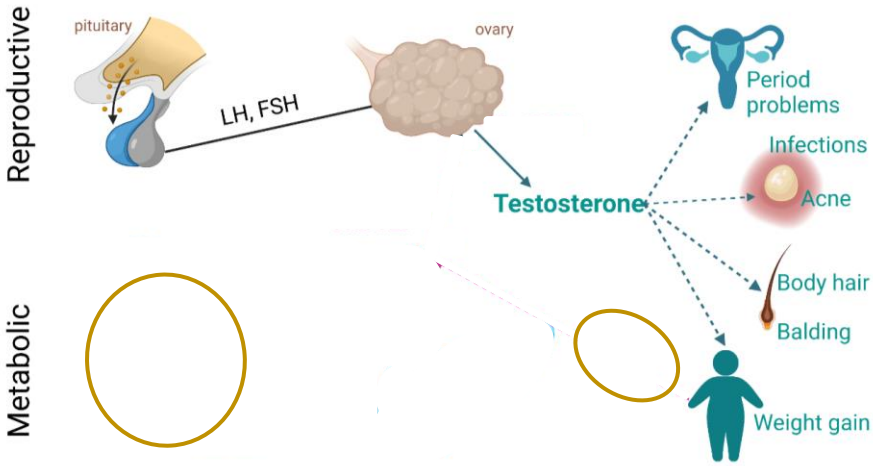
Why does lifestyle matter so much in PCOS?



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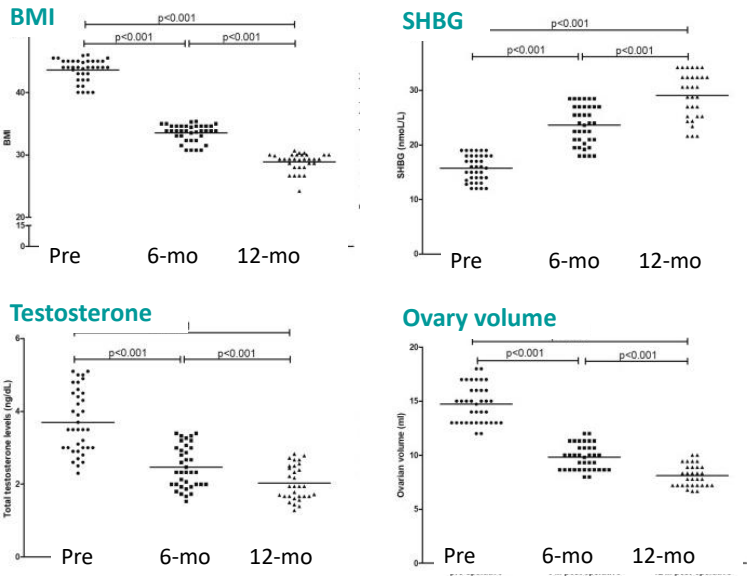
Hormonal Effect of Bariatric Surgery

- 36 women all PCOS
- Age was 27.2 ± 4.2 years
- BMI was 43.6 ± 1.76 kg/m^2
- 61% sleeve gastrectomy, 39% gastric bypass



Saudi Journal of Biological Sciences Vol 28, Issue 9, September 2021, 5048-5052

91

GLP-1RA Treatment in PCOS

- Randomized trial of Exenatide, Exenatid e+ Metformin or Metformin, 24 weeks, 60 women
  - Reproductive:
    - ↓free androgen index
    - ↑ menses
  - Metabolic:
    - ↓ 2 hour glucose on oral glucose tolerance test
    - ↑ Insulin Sensitivity

TABLE 2. Baseline and 24-wk posttreatment clinical, anthropometric, and endocrine parameters and indices of body fat distribution (evaluable patients)

Variable	EX (n = 14)		MET (n = 14)		COM (n = 14)		*P* values
	Baseline	After therapy	Baseline	After therapy	Baseline	After therapy	
Menstrual frequency*	0.22 ± 0.04	0.57 ± 0.08	0.21 ± 0.04	0.49 ± 0.08	0.29 ± 0.037	0.83 ± 0.082	T = 0.0001; I = 0.047; C *vs.* M = 0.018, *vs.* E = 0.091
AG (cm)	120.4 ± 4.5	119.6 ± 4.3	123.4 ± 4.3	123.9 ± 4.4	122 ± 4.4	116 ± 4.3	T = 0.047; I = 0.017; C *vs.* M = 0.04
Absolute weight (kg)	110.5 ± 6	107.3 ± 6	113.4 ± 7	111.8 ± 6	112 ± 8	106.4 ± 6	T = 0.001; I = 0.003; C, E *vs.* M = 0.019
BMI (kg/m^2)	40.3 ± 2	39.3 ± 2	43.3 ± 2	42.3 ± 2	40.9 ± 2	39.2 ± 2	T < 0.0001
T (ng/dl)	75.4 ± 8	65.2 ± 7.4	56.8 ± 8.1	53.2 ± 7.1	59.8 ± 8.1	41.4 ± 7.1	T = 0.02
SHBG (nmol/liter)	17.4 ± 2.4	19.7 ± 6.2	18.5 ± 2.3	18.7 ± 6	22.5 ± 2.3	33.6 ± 6	NS
FAI (U)	16.3 ± 3.5	11.9 ± 1.4	12.6 ± 2.4	11.4 ± 1.3	10.4 ± 2.4	5.7 ± 1.3	T = 0.001; I = 0.016; C *vs.* M = 0.035
DHEAS (μ g/dl)	183.4 ± 20.5	190.7 ± 21.51	142.6 ± 19.6	161.7 ± 20.44	123.9 ± 20.33	121.3 ± 20.32	NS

For *P* values, T = overall effect after all treatments, and I = interaction differences between treatment over trials. C, COM; E, EX; M, MET; NS, not significant.

3.2 1.6 5.6 4.4 1.2 4.8

Elkind-Hirsch K, JCEM 2008

92

GLP-1RA Treatment in PCOS

- Randomized trial of liraglutide, liraglutide + Metformin or Metformin, 12 weeks, 40 women
  - Lira+Met 6.5±2.8 kg loss; Lira 3.8±3.7 kg loss; Met 1.2±1.4 kg loss
  - Reproductive:
    - No change in androgens
    - No change in menstrual frequency
  - Metabolic:
    - ↓ 2 hour glucose on oral glucose tolerance test
    - no change in Insulin sensitivity

Jensterle Sever M, Eur J Endocrinol. 2014

- Randomized trial of liraglutide compared to placebo, 26 weeks, 65 women
  - Lira 5.2 kg loss > placebo
  - ↓Free testosterone, ovary size
  - ↑ SHBG, ↓ liver fat
  - Reproductive:
    - ↓ Free testosterone
    - ↓ ovary size
  - Metabolic:
    - ↓ liver fat

Frossing S, Diabetes Obes Metab. 2018

93

Semaglutide Treatment of Excessive Body Weight in Obese PCOS Patients Unresponsive to Lifestyle Programs

by Enrico Carmina * and Rosa Alba Longo

Medication: 0.5 mg SQ semaglutide

Table 3. Changes in BMI, body weight, fasting glucose, insulin, and insulin resistance (HOMA-IR) (mean ± SD) in 21 obese PCOS women responsive (weight loss > 5%) to semaglutide treatment (0.5 mg subcutaneously once a week).

		N=27		N=21	
	Basal	**After 3 Months of Treatment with Semaglutide**		**After 6 Months of Treatment with Semaglutide**	
BMI (kg/m^2)	34.4 ± 5.9	30.8 ± 5 **		29.4 ± 5 **	
Body weight (kg)	85 ±15	76 ± 16 **	7 kg change	73.5 ± 15 **	14 kg change
Fasting glucose (mg/dL)	97 ± 12	90 ± 8 **		90 ± 6 **	
Insulin (mU/mL)	17 ± 7	11 ± 5 **		11 ± 5 **	
HOMA-IR	3.5 ± 2	2.5 ± 1 **		2.4 ± 0.8 **	

** $p < 0.01$ versus basal values.

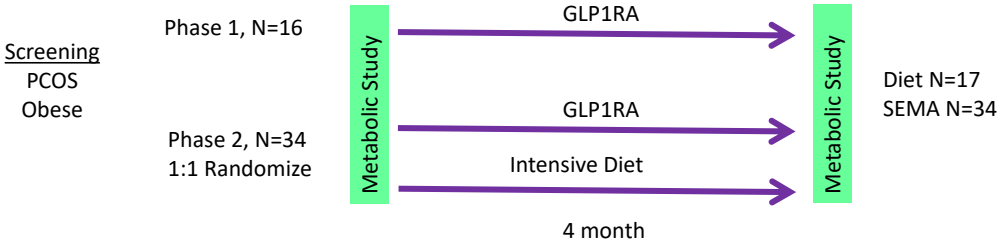
78% Normal Menses

J. Clin. Med. **2023**, *12*(18), 5921; https://doi.org/10.3390/jcm12185921

94

Treating PCOS With Semaglutide vs Active Lifestyle Intervention (TEAL)

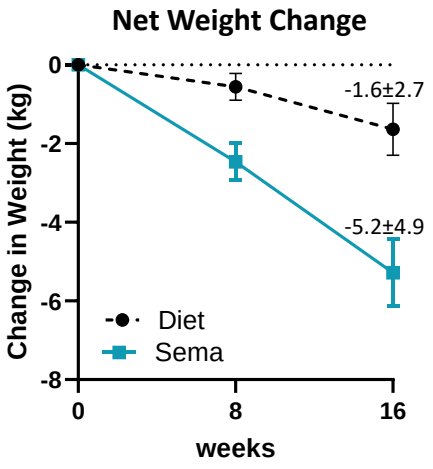
- Effect of oral semaglutide on weight, reproductive and metabolic outcomes in adolescents with PCOS + obesity
- 3 mg x 1 month, 7 mg x 3 months

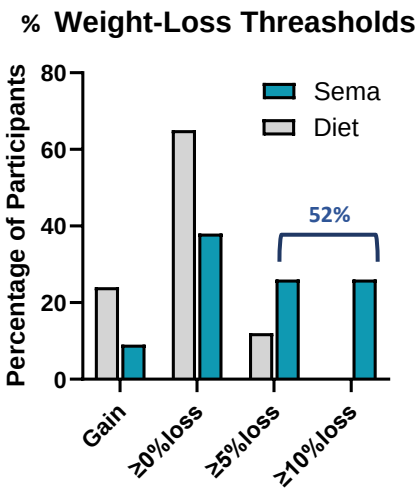


NCT03919929

95

Amount of Weight Loss



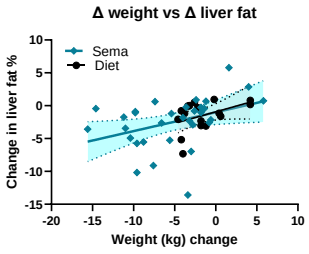


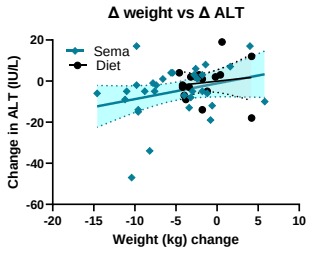
96

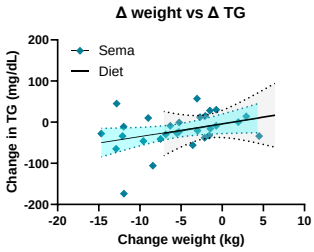
Weight Related Changes

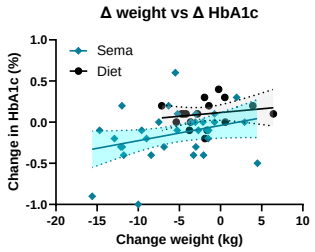
Increase in Menses Frequency

	Sema	Diet
≥10%	78%	
≥5%	56%	100%
≤5%	38%	45%
Gain	33%	25%









97

Reported Side Effects

Symptoms	Nausea	GERD	Abdominal pain	Diarrhea	Constipation	Emesis
Sema pre	16%	18%	13%	8%	3%	5%
Sema post	**66%**	10%	7%	0%	0%	**17%**
Diet pre	24%	24%	0%	0%	0%	0%
Diet post	21%	14%	0%	0%	0%	0%

Safety

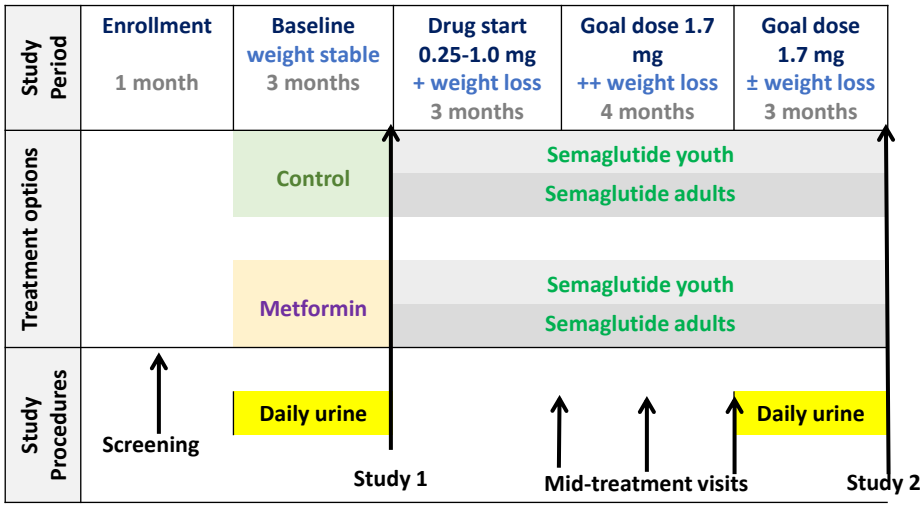
No elevations in ALT or AST
Bun or Cr
1 SI in Sema

Appetite/Mood

Symptoms	RED Appetite Score	CESD-20 Depressive Symptoms
Sema pre	18.0	20.3
Sema post	11.6	18.1
Diet pre	18.8	19.2
Diet post	13.4	18.9

98

Next Steps – GLP1RA for Fertility in PCOS



NCT05819853
NIH NICHD R01

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Summary

- **Overall**
  - Seven mg of oral Semaglutide induces more weight loss than intensive dietary counseling in adolescents
  - GI side-effects are very common, and lead to discontinuation (5%)
- **Safety**
  - No serious events
- **Reproductive**
  - Increased frequency of menses in both groups
  - Similar decreases in testosterone
- **Metabolic**
  - Similar decreases in fasting glucose and HbA1c

100

Next steps to increase access for weight loss therapies for women with PCOS

- Increased National Institutes of Health funding for PCOS
- Increased Foundation funding for PCOS
- Pharmaceutical Industry Interest in GLP1-RA indication for PCOS
  - Concerns for potential birth defects if used in pregnancy
- Classification of PCOS as a complication of obesity, in terms of qualifying for Bariatric Surgery
  - Currently criteria are a BMI of >35 kg/m^2 with type 2 diabetes, excess liver fat and obstructive sleep apnea
  - Otherwise need a BMI of >40 kg/m^2

101

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Participants and their families
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Ludeman Family Center for Women's Health Research
Children's Hospital Colorado
CCTSI
NIH National Institute of Diabetes and Digestive and Kidney Diseases

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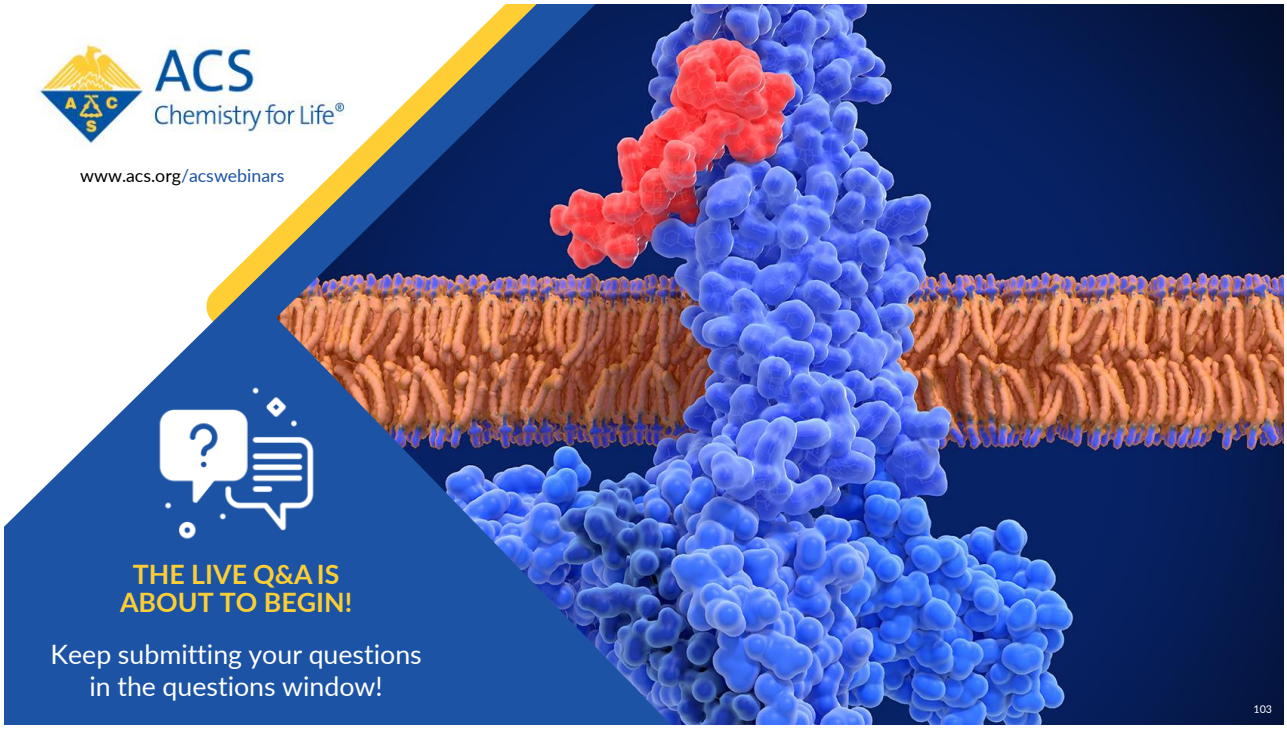
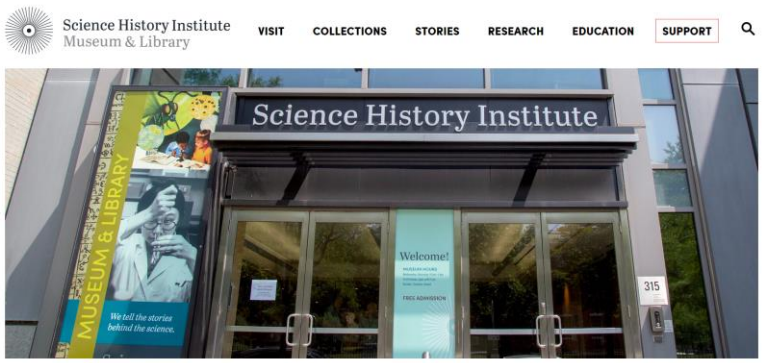
NIH CTSA UL1 TR002535
Childrens Hospital Colorado
Department of Pediatrics, CUAMC

102



103



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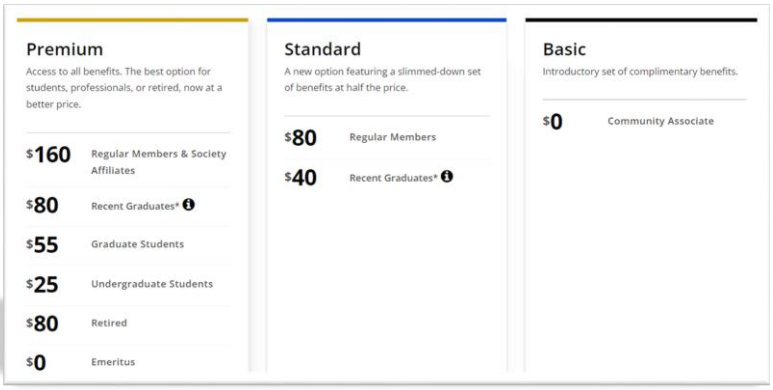

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