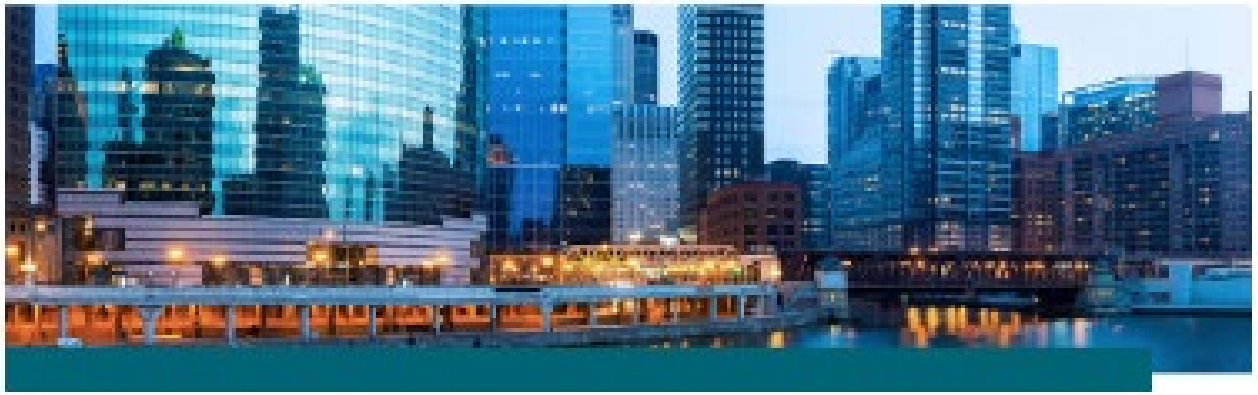
PostENDO Symposium – August 31st 2023

ENDO 2023
JUNE 15–18, 2023 CHICAGO, IL



Pituitary - Update

PD Dr Georgios Papadakis

Prof. Peter Kopp

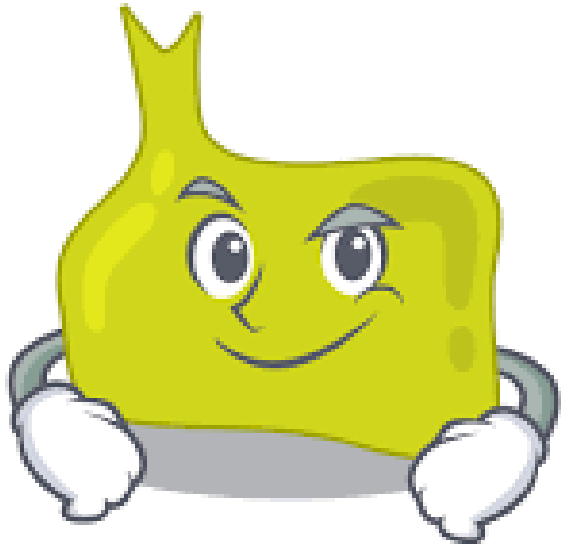
Service of **E**ndocrinology, **D**iabetes & **M**etabolism

CHUV

Unil
UNIL | Université de Lausanne
Faculté de biologie et de médecine

Today's Menu

- AVP deficiency – Diabetes insipidus
- Oxytocin deficiency
- Osmotic Demyelination syndrome (hypoNa)
- Acromegaly – Paltusotine
- Immune checkpoint inhibitors hypophysitis
- Hypogonadism (TRAVERSE trial)



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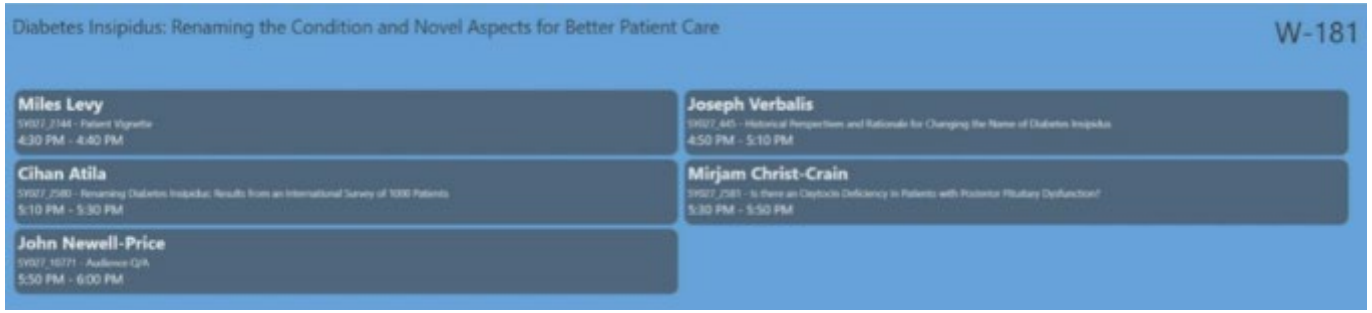
Diabetes insipidus

Change in nomenclature



Patient testimonials :

- ✓ confusion with sugar diabetes
- ✓ healthcare community unawareness

how rare actually does mistaking diabetes insipidus for diabetes mellitus occur?

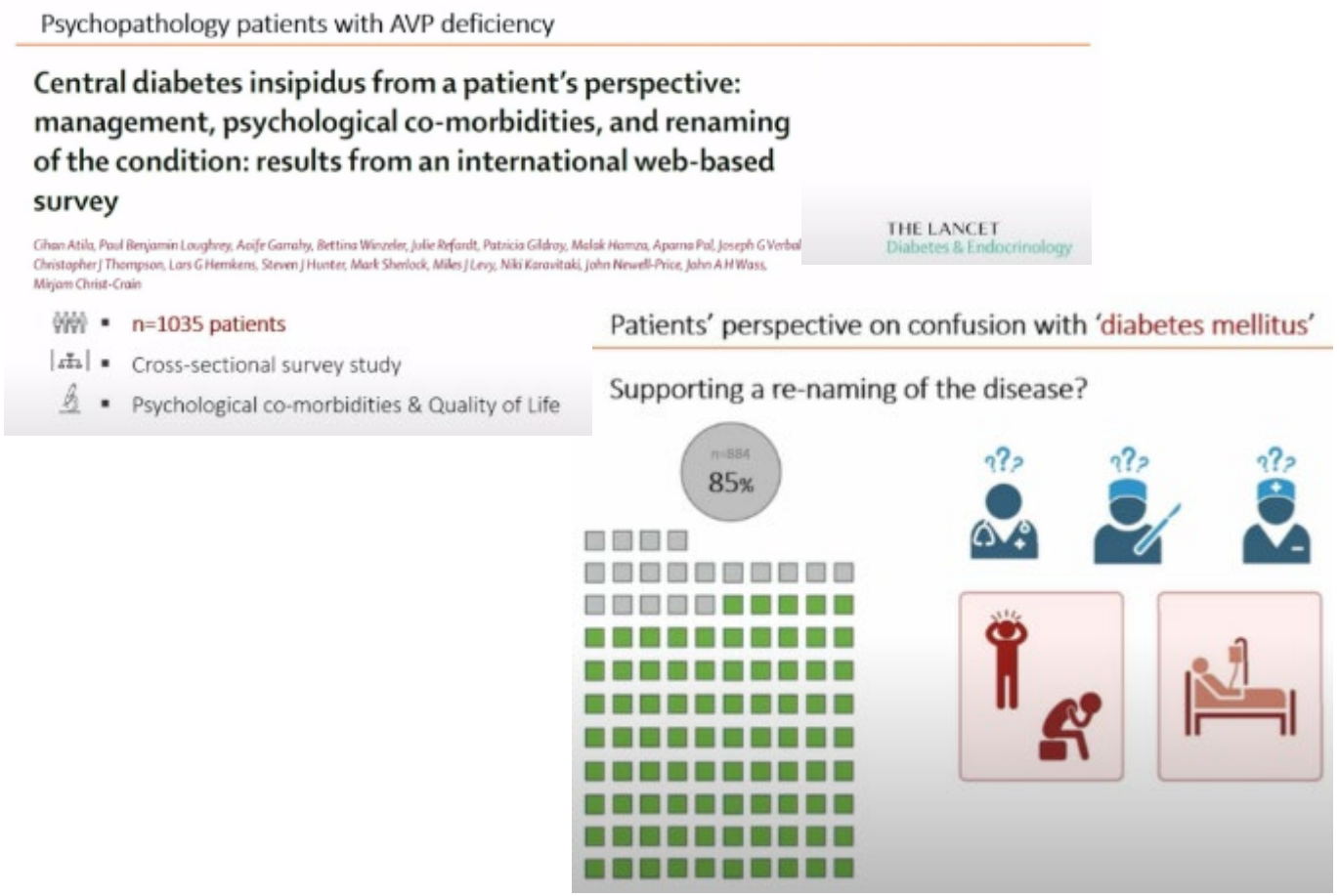
data from U.K. National Health Service, 2009-2015:

471 adverse events involving desmopressin (dDAVP) use:

12% incorrect dose
16% dose omission

4 cases of desmopressin dose omission resulted in death from severe dehydration

Behan LA, et al. *Eur J Endocrinol*. 172:243-50, 2015



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Diabetes insipidus

Change in nomenclature

Position Statement | H Arima and others | Changing the name of diabetes insipidus | 187:5 | P1–P3

Changing the name of diabetes insipidus: a position statement of The Working Group for Renaming Diabetes Insipidus

The Working Group for Renaming Diabetes Insipidus, Hiroshi Arima[1,2], Timothy Cheetham[3,4], Mirjam Christ-Crain[5,6], Deborah Cooper[7], Mark Gurnell[6,8], Juliana B Drummond[9,10], Miles Levy[11,12], Ann I McCormack[13,14], Joseph Verbalis[15,16], John Newell-Price[16,17] and John A H Wass[18,19]

summary: DI name change

our proposal has been published in an editorial in multiple endocrine journals, and has been endorsed by international endocrine societies

our recommendation going forward is to include the previous name in parentheses:

"This patient has vasopressin deficiency (central diabetes insipidus)."

"This patient has vasopressin resistance (nephrogenic diabetes insipidus)."

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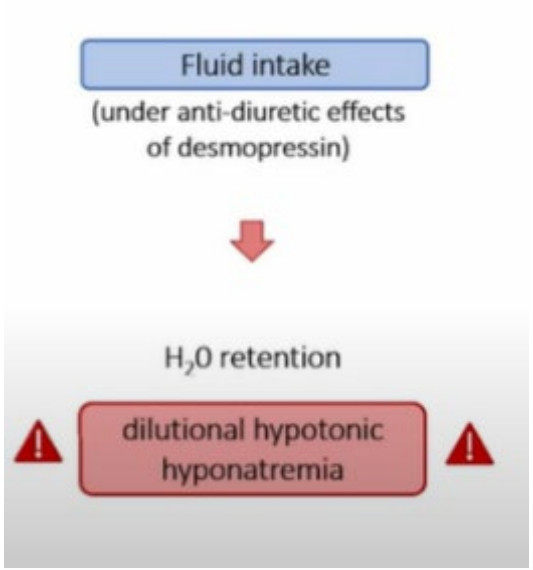
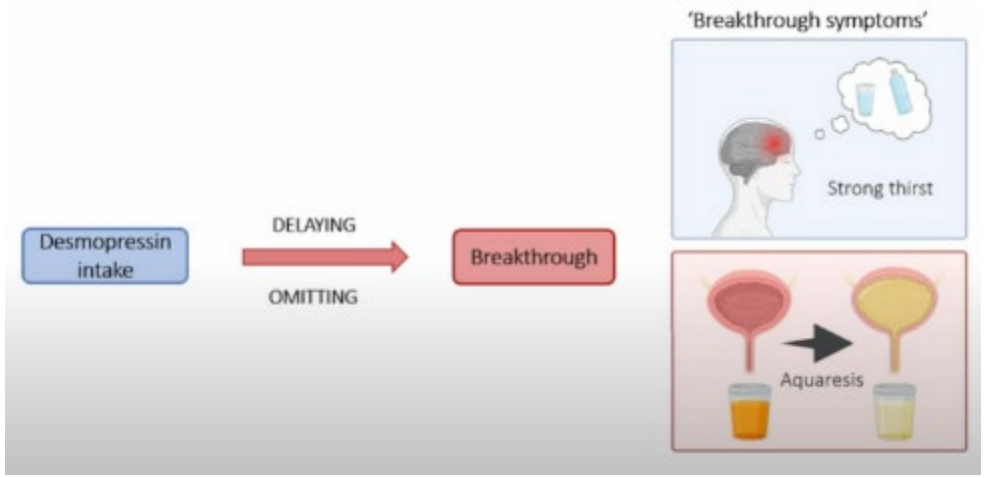
AVP deficiency

Desmopressin escape





Central diabetes insipidus from a patient's perspective: management, psychological co-morbidities, and renaming of the condition: results from an international web-based survey

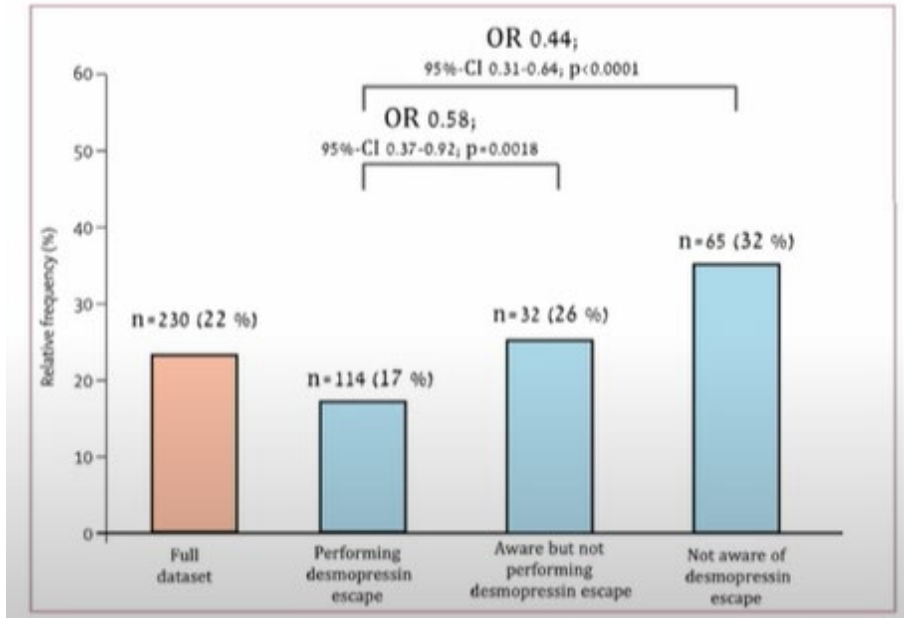
Cihan Atila, Paul Benjamin Loughrey, Aoife Garrahy, Bettina Winzeler, Julie Refardt, Patricia Gildroy, Malak Hamza, Aparna Pal, Joseph G Verbalis, Christopher J Thompson, Lars G Hemkens, Steven J Hunter, Mark Sherlock, Miles J Levy, Niki Karavitaki, John Newell-Price, John A H Wass, Mirjam Christ-Crain

Lancet Diabetes Endocrinol 2022; 10: 700–09
Published Online August 22, 2022

Summary

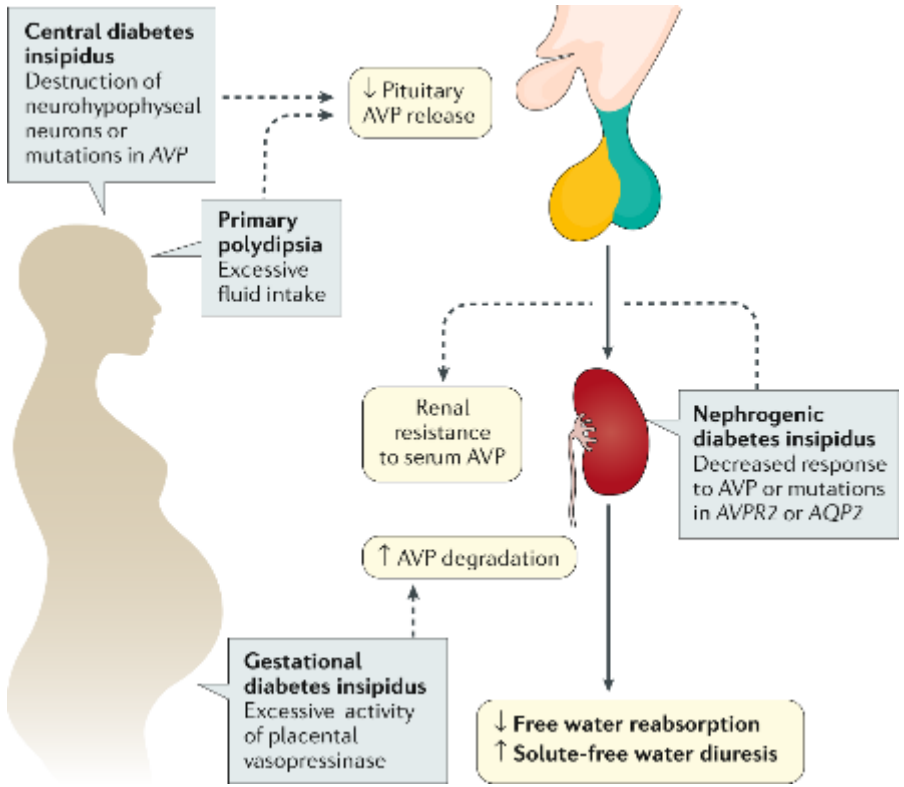
Background Central diabetes insipidus is a rare neuroendocrine condition. Data on treatment-associated side-effects, psychological comorbidities, and incorrect management are scarce. The aim of this study was to investigate patients' perspectives on their disease.

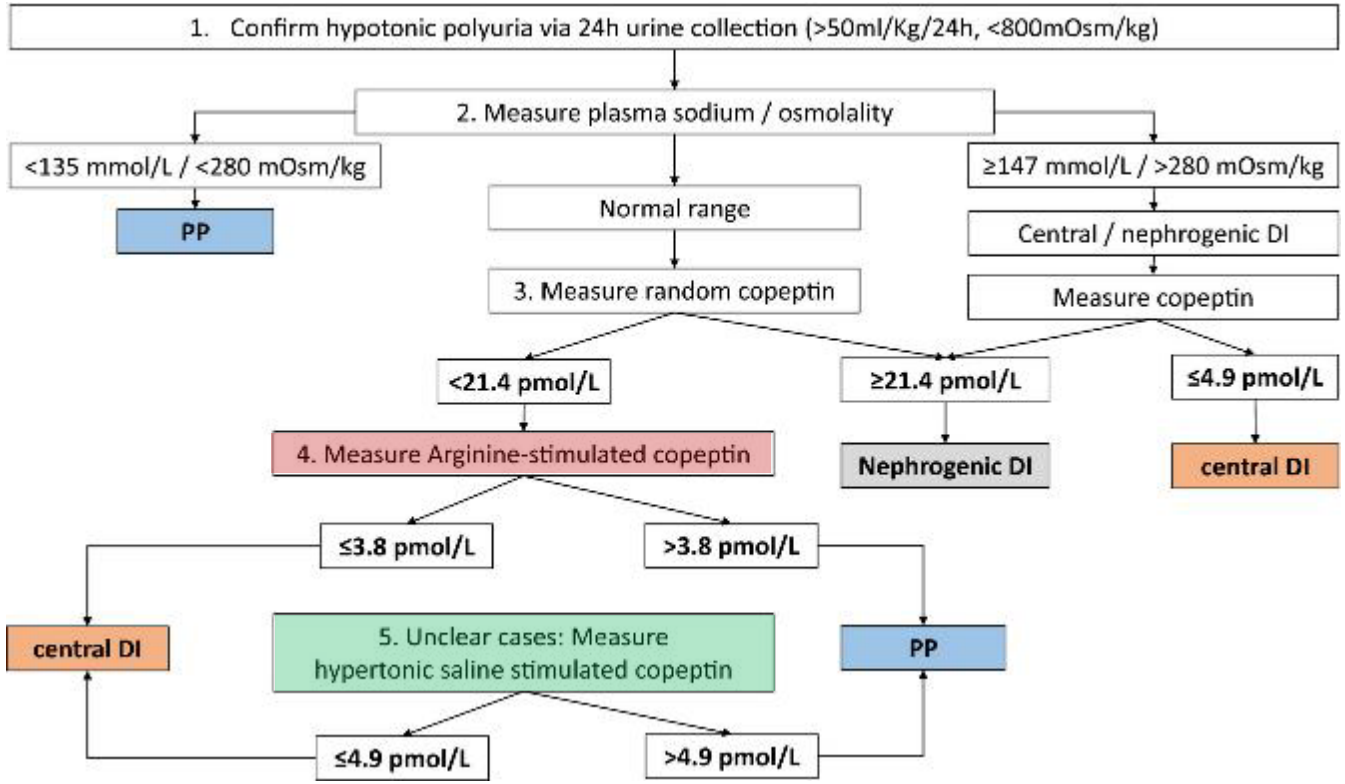
Hyponatremia in the outpatient setting



AVP deficiency

Differential diagnosis





Arginine-stimulated copeptin : cut-off at 3.8 pmol/l
93% diagnostic accuracy (sensitivity 92%, specificity 93%)

Hypertonic saline-stimulated copeptin : cut-off at 4.9 pmol/l
97% diagnostic accuracy (sensitivity 93%, specificity 100%)

Christ-Crain et al, *Nature Rev Primer* 2019
Christ-Crain et al, *Journal of Internal Medicine* 2021

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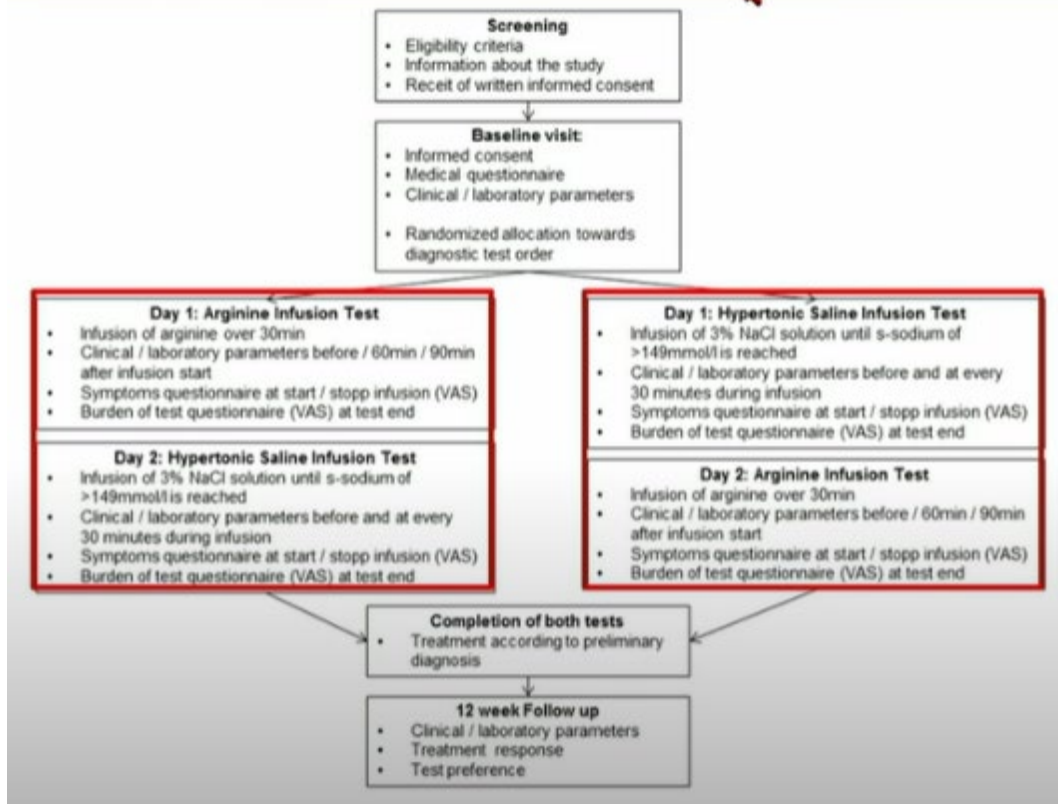
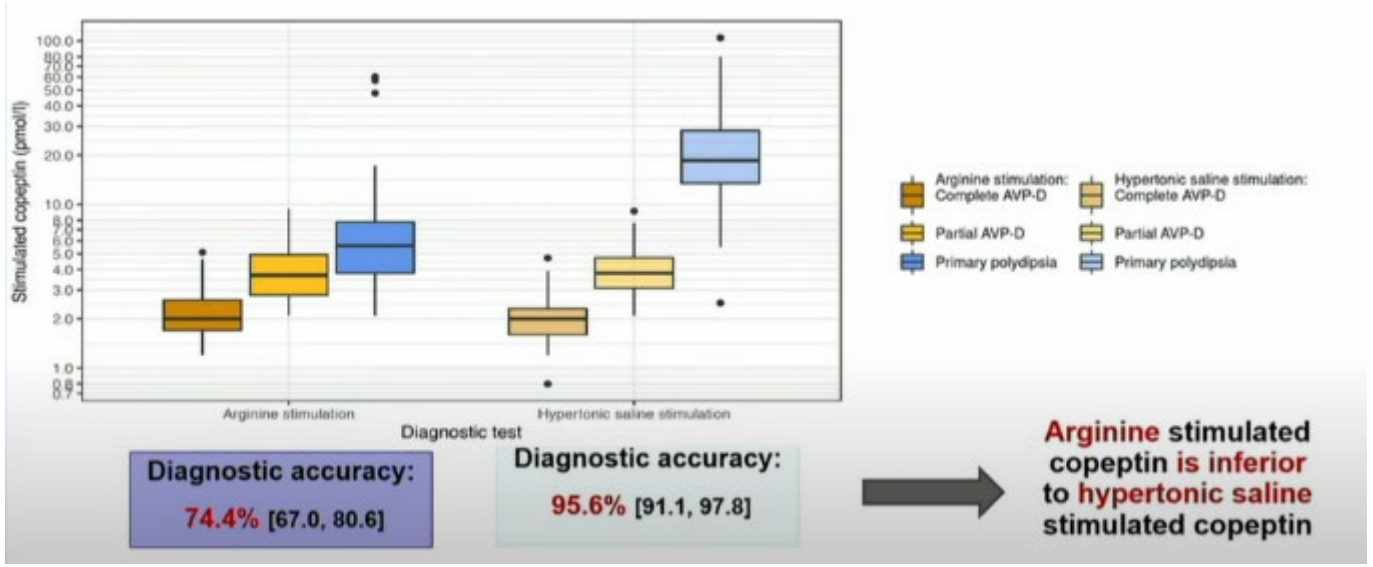
Diabetes insipidus

Differential diagnosis

Prospective Head-to-Head comparison





To diagnose AVP-deficiency			To diagnose primary polydipsia		
Threshold	Specificity	Sensitivity	Threshold	Specificity	Sensitivity
2.2	98.9	36.3	4.2	78.3	70.2
2.3	97.8	40.6	4.4	79.8	69.0
2.4	97.8	42.1	4.5	81.2	69.0
2.5	96.6	46.4	4.6	82.7	69.0
2.6	95.5	49.3	4.7	85.6	66.7
2.7	95.5	52.2	4.9	87.0	64.4
2.8	94.3	53.7	5.0	88.5	63.3
2.9	90.9	56.6	5.1	89.9	58.7
3.0	90.9	59.5	5.2	91.4	56.4
3.1	87.4	60.9	5.4	92.8	54.1
3.2	86.3	66.7	5.5	92.8	51.8
3.3	84.0	66.7	5.6	94.3	50.6
3.4	81.7	66.7	5.9	94.3	49.5
3.5	81.7	69.6	6.2	94.3	46.0
3.6	79.4	71.1	6.3	94.3	42.6
3.7	75.9	72.5	6.4	94.3	41.4
3.8	75.9	74.0	6.6	94.3	39.1
3.9	73.6	75.4	6.7	95.7	39.1
4.0	73.6	76.9	6.9	95.7	38.0
4.1	71.3	78.3	7.0	95.7	33.4

Refardt J et al., in preparation

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Diabetes insipidus

Key messages

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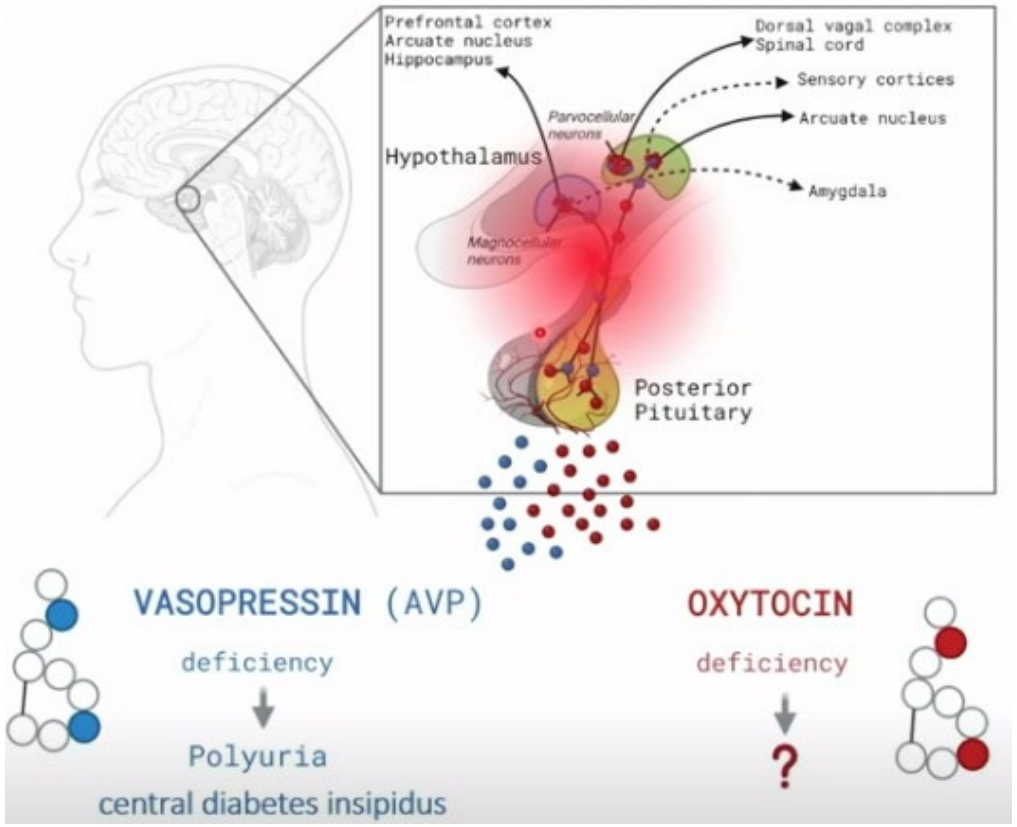
AVP deficiency ~~Diabetes insipidus~~

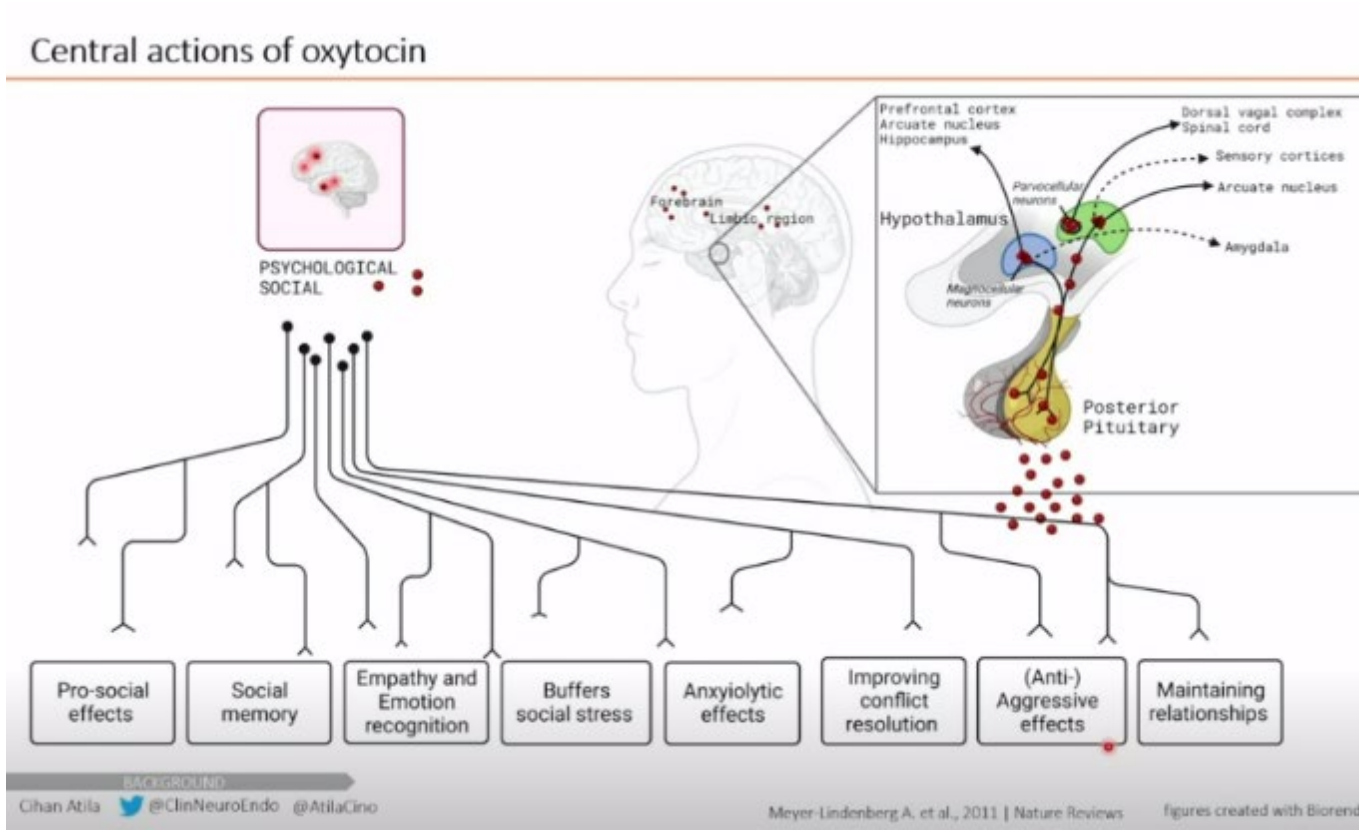
Key messages

- ✓ New disease name to integrate in daily practice
- ✓ Convincing evidence to suggest desmopressine escape strategy as a mean to reduce risk of dilutional hyponatremia
- ✓ Stepwise diagnostic exploration: need to refer complex cases with borderline copeptin results in arginine stimulation for hypertonic saline testing

Oxytocine deficiency

in patients with AVP deficiency





Meyer-Lindenberg et al, *Nat Rev Neurosci* 2011

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Oxytocine deficiency

in patients with AVP deficiency

Psychopathology patients with AVP deficiency

Central diabetes insipidus from a patient's perspective: management, psychological co-morbidities, and renaming of the condition: results from an international web-based survey

Cihan Atila, Paul Benjamin Loughrey, Aoife Garrahy, Bettina Wenzler, Julie Refardt, Patricia Gildroy, Melak Hamza, Aparna Pal, Joseph G Verbalis, Christopher J Thompson, Lars G Hemkens, Steven J Hunter, Mark Sherlock, Miles J Levy, Niki Karavitaki, John Newell-Price, John A H Wass, Mirjam Christ-Crain

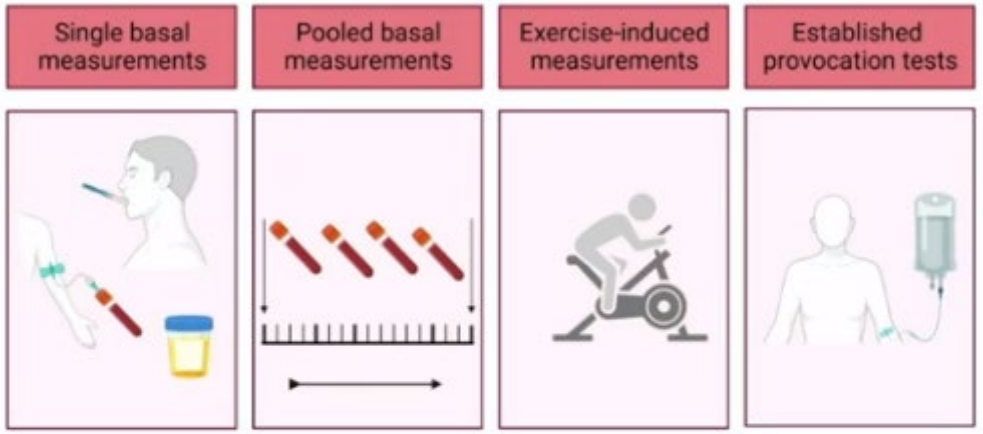
- n=1035 patients
- Cross-sectional survey study
- Psychological co-morbidities & Quality of Life

THE LANCET Diabetes & Endocrinology

	Full dataset (n=1034)	Participants with isolated posterior pituitary dysfunction (n=488)	Participants with anterior and posterior pituitary dysfunction (n=546)
Psychological problems or changes since diagnosis	369 (36%; [33–39])	173 (35%; [31–40])	196 (36%; [32–40])
Heightened anxiety	258 (25%; [22–28])	115 (24%; [20–27])	143 (26%; [23–30])
Sleep disturbance	263 (25%; [23–28])	113 (23%; [19–27])	150 (27%; [24–31])
Depressed mood	239 (23%; [21–26])	99 (20%; [17–24])	140 (26%; [22–29])
Stress management disturbance	181 (18%; [15–20])	86 (18%; [14–21])	95 (17%; [14–21])
Change in eating habits	168 (16%; [14–18])	82 (17%; [13–20])	86 (16%; [13–19])
Change in personality	124 (12%; [10–14])	51 (10%; [8–13])	73 (13%; [11–16])
Documented psychological condition after the diagnosis	111 (11%; [9–13])	41 (8%; [6–11])	70 (13%; [10–16])

Data presented in median [IQR] and n (%; [95%-CI]).

Table 2: **Psychological comorbidities**



...are not sufficient to identify an oxytocin deficiency

... 36% recognized psychological changes & problems (subjectively related to their Vasopressin deficiency) with heightened **anxiety** levels, **depressed** mood, impairment in **social** domains, and overall **reduced QoL (64%)**

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Oxytocine deficiency

MDMA provocation test

Novel oxytocin provocation test

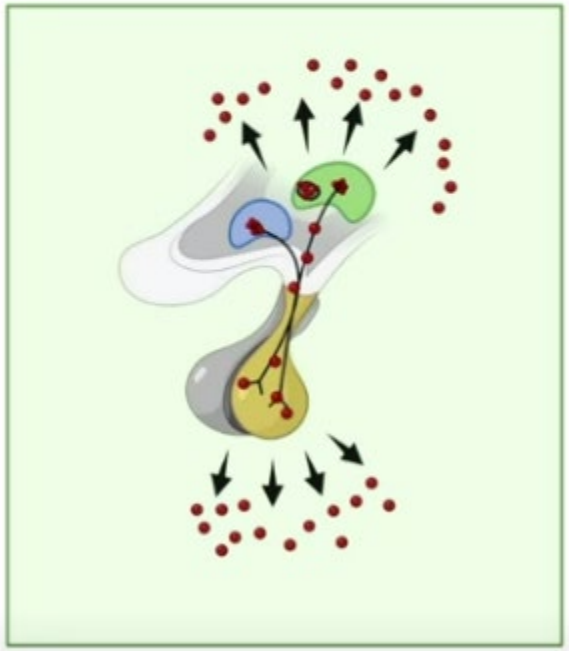
Atila C et al. 2023 | The Lancet *Diabetes & Endocrinology*

Oxytocin in response to MDMA provocation test in patients with arginine vasopressin deficiency (central diabetes insipidus): a single-centre, case-control study with nested, randomised, double-blind, placebo-controlled crossover trial

Cihan Atila, Friederike Holze, Rakithan Murugesu, Nikki Rommers, Nina Hutter, Nimmy Varghese, Clara O Sailer, Anne Eckert, Markus Heinrichs, Matthias E Liechti, Mirjam Christ-Crain

Oxytocin measurements

Psychoactive and biochemical provocation test is needed



Study design and methods

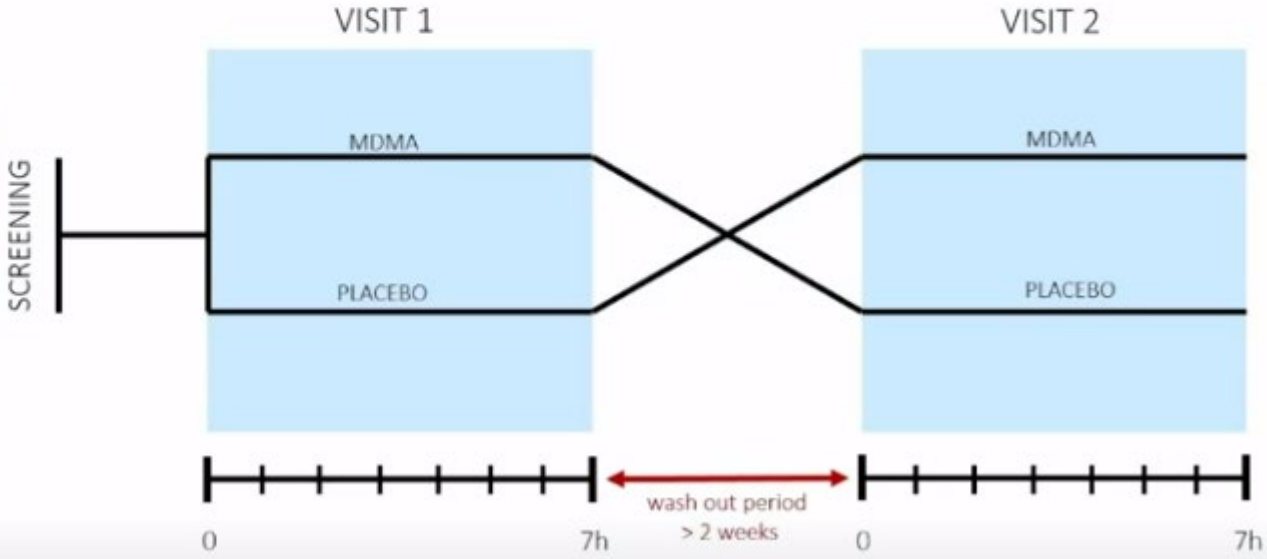
Case-control trial with nested randomized, placebo-controlled, double-blind, cross-over

MDMA (100mg) vs. Placebo

Central diabetes insipidus (Vasopressin deficiency) (*n*=15)

Healthy Controls (*n*=15)

matched
- BMI
- Sex
- Age
- Contraceptives/ Menopause



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Oxytocine deficiency

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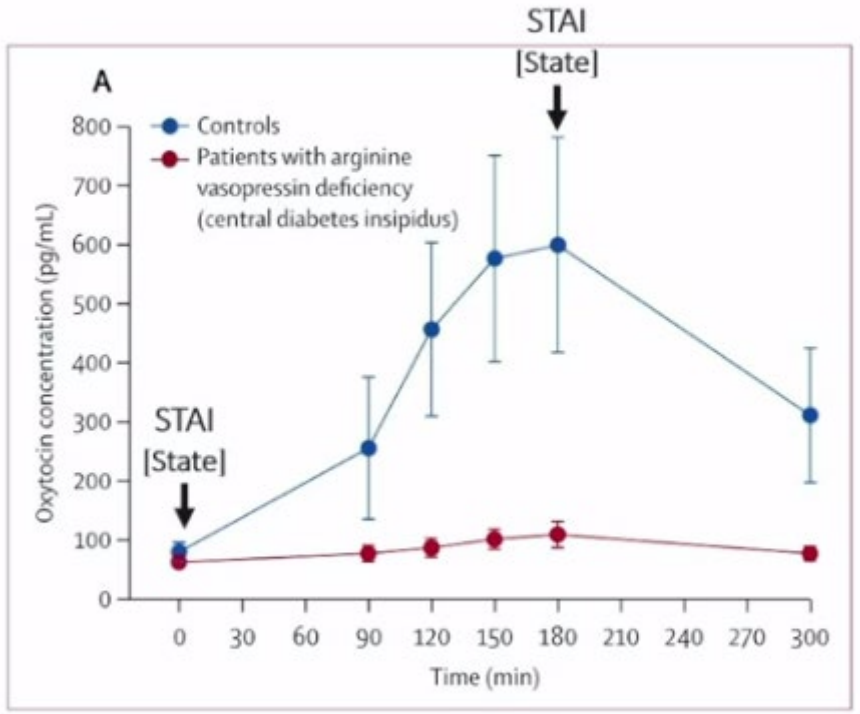
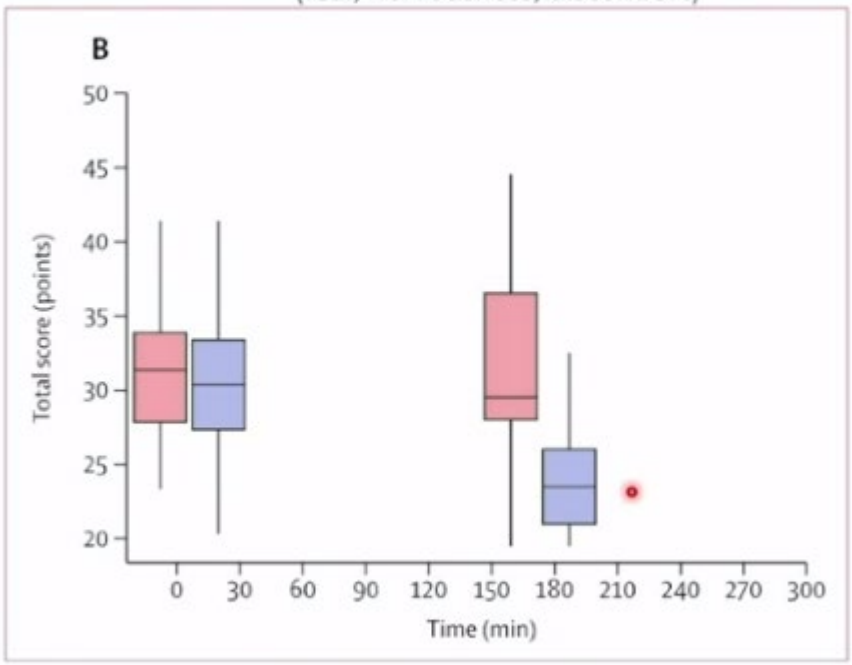
Oxytocin in response to MDMA



STAI [State]= measure of acute anxiety (fear, nervousness, discomfort)



... no acute anxiolytic effects of MDMA in patients as compared to healthy controls

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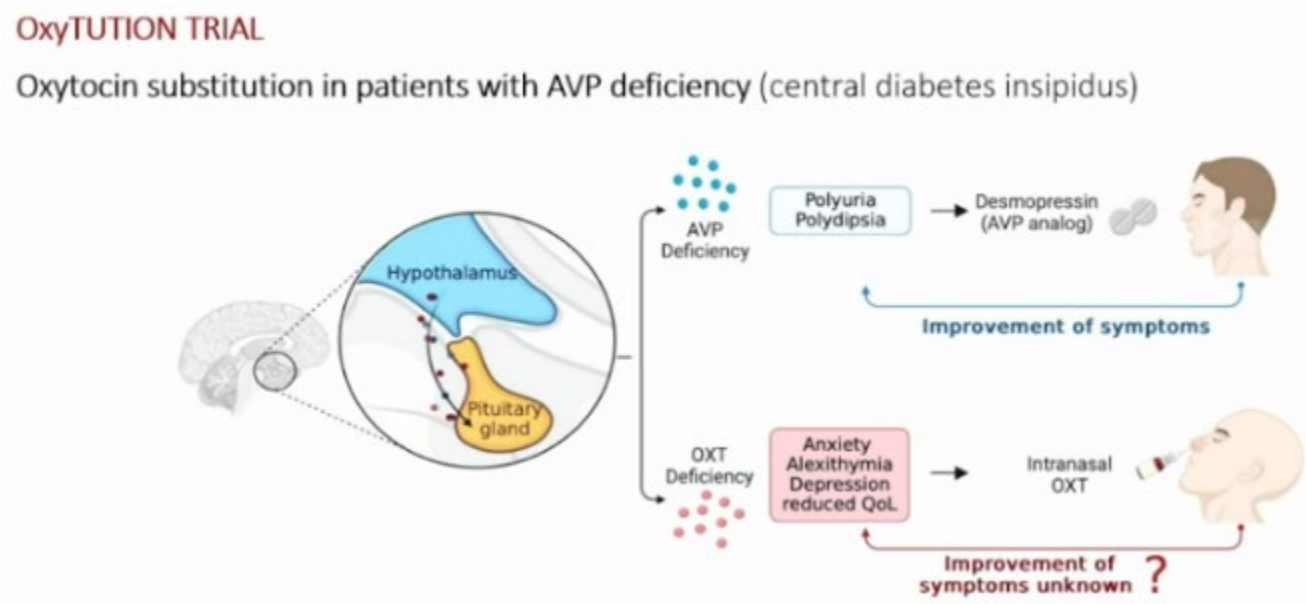
Oxytocine deficiency

Key messages

- ✓ MDMA provocation test is able tor detect oxytocin deficiency in patients with AVP deficiency (diabetes insipidus)

- ✓ Oxytocin deficiency is associated with relevant psychopathologic findings and could account in part for the decreased quality of life in patients with AVP deficiency



Hyponatremia/SIADH

Osmotic demyelination syndrome

DIAGNOSIS AND MANAGEMENT OF HYPONATREMIA

Joseph G. Verbalis, MD
Professor of Medicine and Physiology
Chief, Endocrinology and Metabolism
Director, Georgetown-Howard Universities Center for Clinical and Translational Science
Georgetown University
Washington, DC USA

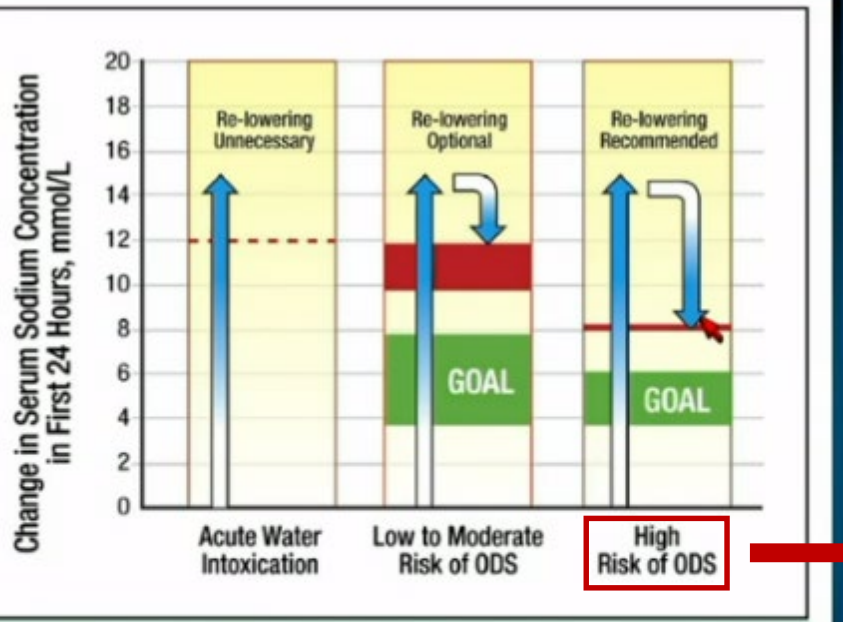


Figure 3 Recommendations for relowering of serum sodium concentration ($[Na^+]$) to goals (green) for patients presenting with serum $[Na^+] < 120$ mmol/L who exceed the recommended limits of correction (red) in the first 24 hours. Abbreviations: L = liter; mmol = millimole; ODS = osmotic demyelination syndrome.

Table 3 Factors That Place Patients at High Risk of Developing the Osmotic Demyelination Syndrome with Correction of Chronic Hyponatremia

High Risk of Osmotic Demyelination Syndrome

- Serum sodium concentration $\leq$105 mmol/L
- Hypokalemia*
- Alcoholism*
- Malnutrition*
- Advanced liver disease*

L = liter; mmol = millimole.

*Unlike the rate of increase in serum sodium concentration, neither the precise level of the serum potassium concentration nor the degree of alcoholism, malnutrition, or liver disease that alters the brain's tolerance to an acute osmotic stress have been rigorously defined.

Verbalis et al, *Am J Med* 2013

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Hyponatremia/SIDAH

Osmotic demyelination syndrome

DIAGNOSIS AND MANAGEMENT OF HYPONATREMIA

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Director, Georgetown-Howard Universities Center for Clinical and Translational Science
Georgetown University
Washington, DC USA

What are the risk factors for rapid Na^+ correction and osmotic demyelination in patients with an initial serum Na^+ <120 mEq/L?

CJASN Clinical Journal of American Society of Nephrology

Methods and Cohort

- 1490 patients
- Serum Na^+ <120 mEq/L
- 7 hospitals in Geisinger Health System, 2001-2017
- Retrospective cohort study

Results

Na^+ → 606 patients

Rapid Na correction >8 mEq/L in 24 h

Increased risk

- Younger age
- Female
- Schizophrenia
- Lower initial serum Na^+
- Initial urine Na <30 mEq/L

Incident osmotic demyelination → 8 patients

- Na^+ 7 with rapid Na^+ correction
- 5 with beer potomania
- 5 with hypokalemia

Conclusions Among patients presenting with severe hyponatremia, rapid correction occurred in 41%. Nearly all patients with incident osmotic demyelination had a documented episode of rapid correction.

Jason George, Waleed Zafar, Ion Dan Bucaloiu, and Alexander Chang. ***Risk Factors and Outcomes of Rapid Correction of Severe Hyponatremia.*** doi: 10.2215/CJN.13061117

increase in [Na^+] >8 mmol/L/24h: 606/1490 = 41%
osmotic demyelination by MRI: 8/1490 = 0.5%

George et al, *Clin J Am Soc Nephrol* 2018

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Hyponatremia/SIDAH

Osmotic demyelination syndrome

DIAGNOSIS AND MANAGEMENT OF HYPONATREMIA

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NEJM Evidence

Published March 23, 2023
NEJM Evid 2023; 2 (4)
DOI: 10.1056/EVIDoa2200215

ORIGINAL ARTICLE

Osmotic Demyelination Syndrome in Patients Hospitalized with Hyponatremia

Thomas E. MacMillan, M.D., M.Sc.,[1,2] Saeha Shin, M.P.H.,[3] Joel Topf, M.D.,[4] Janice L. Kwan, M.D., M.P.H.,[1,5] Adina Weinerman, M.D., M.H.Sc.,[1,6] Terence Tang, M.D., M.Sc.,[1,7] Afsaneh Raissi, B.Sc.(Hon.),[3] Radha Koppula, M.B.B.S.,[3] Fahad Razak, M.D., M.Sc.,[1,3,8] Amol A. Verma, M.D., M.Phil.,[1,3,8] and Michael Fralick, M.D., Ph.D.[1,5]

22,858 hospitalizations over 10 years with serum [Na^+] <130 mmol/L:
17.7% had a correction >8 mmol/L/24h (n=3,632)
incidence of ODS (by MRI) was 0.05% (n=12)

- ✓ 89% of patients had Na ≥ 120 mmol/l
- ✓ ODS incidence 2.5% in patients with Na < 110 mmol/l
- ✓ Ascertainment of ODS only by MRI is not sufficiently sensitive to detect all cases

Treatment Guidelines for Hyponatremia
Stay the Course

*Richard H. Sterns,[1,2] Helbert Rondon-Berrios,[3] Horacio J. Adrogué,[4] Tomas Berl,[5] Volker Burst,[6] David M. Cohen,[7] Mirjam Christ-Crain,[8] Martin Cuesta,[9] Guy Decaux,[10] Michael Emmett,[11] Aoife Garrahy,[12] Fabrice Gankam-Kengne,[13] John K. Hix,[2] Ewout J. Hoorn,[14] Kamel S. Kamel,[15] Nicolaos E. Madias,[16] Alessandro Peri,[17] Julie Refardt,[8] Mitchell H. Rosner,[18] Mark Sherlock,[19] Stephen M. Silver,[2] Alain Soupart,[10] Chris J. Thompson,[19] and Joseph G. Verbalis,[20] on behalf of PRONATREOUS Investigators**

Abstract

International guidelines designed to minimize the risk of complications that can occur when correcting severe hyponatremia have been widely accepted for a decade. On the basis of the results of a recent large retrospective study of patients hospitalized with hyponatremia, it has been suggested that hyponatremia guidelines have gone too far in limiting the rate of rise of the serum sodium concentration; the need for therapeutic caution and frequent monitoring of the serum sodium concentration has been questioned. These assertions are reminiscent of a controversy that began many years ago. After reviewing the history of that controversy, the evidence supporting the guidelines, and the validity of data challenging them, we conclude that current safeguards should not be abandoned. To do so would be akin to discarding your umbrella because you remained dry in a rainstorm. The authors of this review, who represent 20 medical centers in nine countries, have all contributed significantly to the literature on the subject. We urge clinicians to continue to treat severe hyponatremia cautiously and to wait for better evidence before adopting less stringent therapeutic limits.

CJASN ■: 1–7, 2023. doi: https://doi.org/10.2215/CJN.0000000000000244

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Hyponatremia/SIADH

Key messages

- ✓ Osmotic demyelination syndrome occurs very rarely in the absence of high risk factors (hypokalemia, malnutrition, liver cirrhosis, alcohol excess)

- ✓ Most experts still suggest caution in patients with chronic hyponatremia & baseline Na levels < 120 mmol/l (correction limit for first 24h: 10-12 mM without risk factors, 8 mM with any risk factor)

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Acromegaly

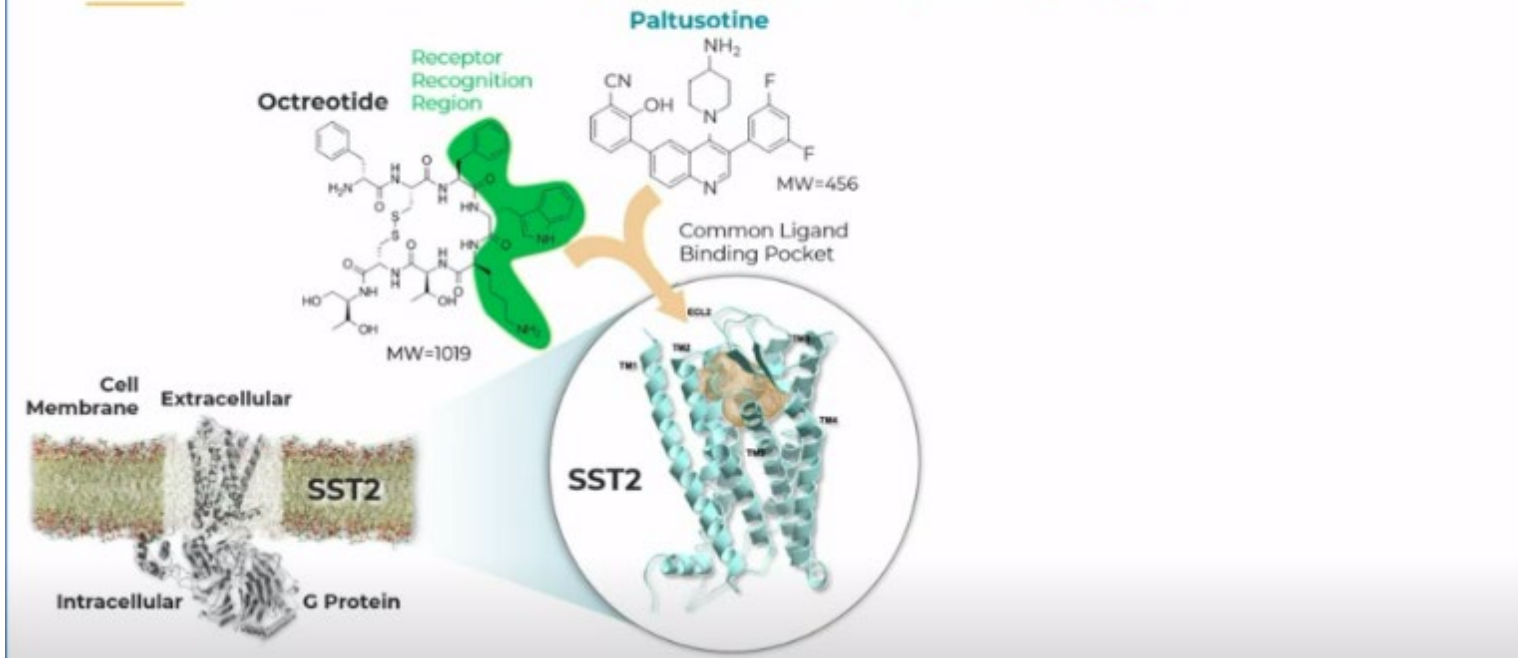
New drug in development

Oral, Once-daily, Paltusotine (Non-peptide Selective Somatostatin Receptor Subtype 2 Agonist) Therapy in Patients With Acromegaly Is Associated With Long-term Biochemical and Symptom Control and Is Preferred Over Injectable Somatostatin-receptor Ligands

Monica R. Gadelha, MD, PhD[1]*; Harpal Randeva, MBChB, FRCP, FAcad TM, PhD[2]; Murray B. Gordon, MD[3]; Mirjana Doknic, MD, PhD[4]; Emese Mezősi, MD, PhD, Dsci[5]; Miklós Tóth, MD, PhD, Dsci[6]; Cesar Luiz Boguszewski, MD, PhD[7]; Christine T. Ferrara-Cook, MD, PhD[8]; Alessandra Casagrande, MD, PhD[8]; Alan Krasner, MD[8]

[1]Neuroendocrinology Research Center/Endocrinology Division—Medical School and Hospital Universitario Clementino Fraga Filho—Universidade Federal do Rio de Janeiro, Brazil; [2]University Hospitals Coventry and Warwickshire NHS Trust, Coventry, United Kingdom; [3]Allegheny Neuroendocrinology Center, Allegheny General Hospital, Pittsburgh, PA, USA; [4]Neuroendocrine Department, Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Center of Serbia, Belgrade, Serbia; [5]University of Pécs Medical School, Pécs, Hungary; [6]Semmelweis University, Budapest, Hungary; [7]SEMPR, Endocrine Division, Department of Internal Medicine, Federal University of Parana, Curitiba, Brazil; [8]Crinetics Pharmaceuticals, Inc., San Diego, CA, USA

Paltusotine Is A Once Daily, Oral, Selectively-Targeted Somatostatin Receptor Type 2 (SST2) Agonist



In Vitro Selectivity at All Five Somatostatin Receptor Subtypes for Paltusotine and Somatostatin

	Human EC_{50} (nM)				
Agonist	SST1	SST2	SST3	SST4	SST5
Paltusotine[1]	>10000	0.25	3300	1100	>10000
Native SS14[2]	0.83	0.14	0.17	0.21	0.065

Oral solution bioavailability[3]*	70%
Observed half life[3]	~30 hours

*Paltusotine administered was as an oral solution in study CRN00808-06. Oral bioavailability for spray-dried dispersion tablet is ~45% administered fasted.

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Acromegaly

Paltusotine, ACROBAT Advance

Oral, Once-daily, Paltusotine (Non-peptide Selective Somatostatin Receptor Subtype 2 Agonist) Therapy in Patients With Acromegaly Is Associated With Long-term Biochemical and Symptom Control and Is Preferred Over Injectable Somatostatin-receptor Ligands

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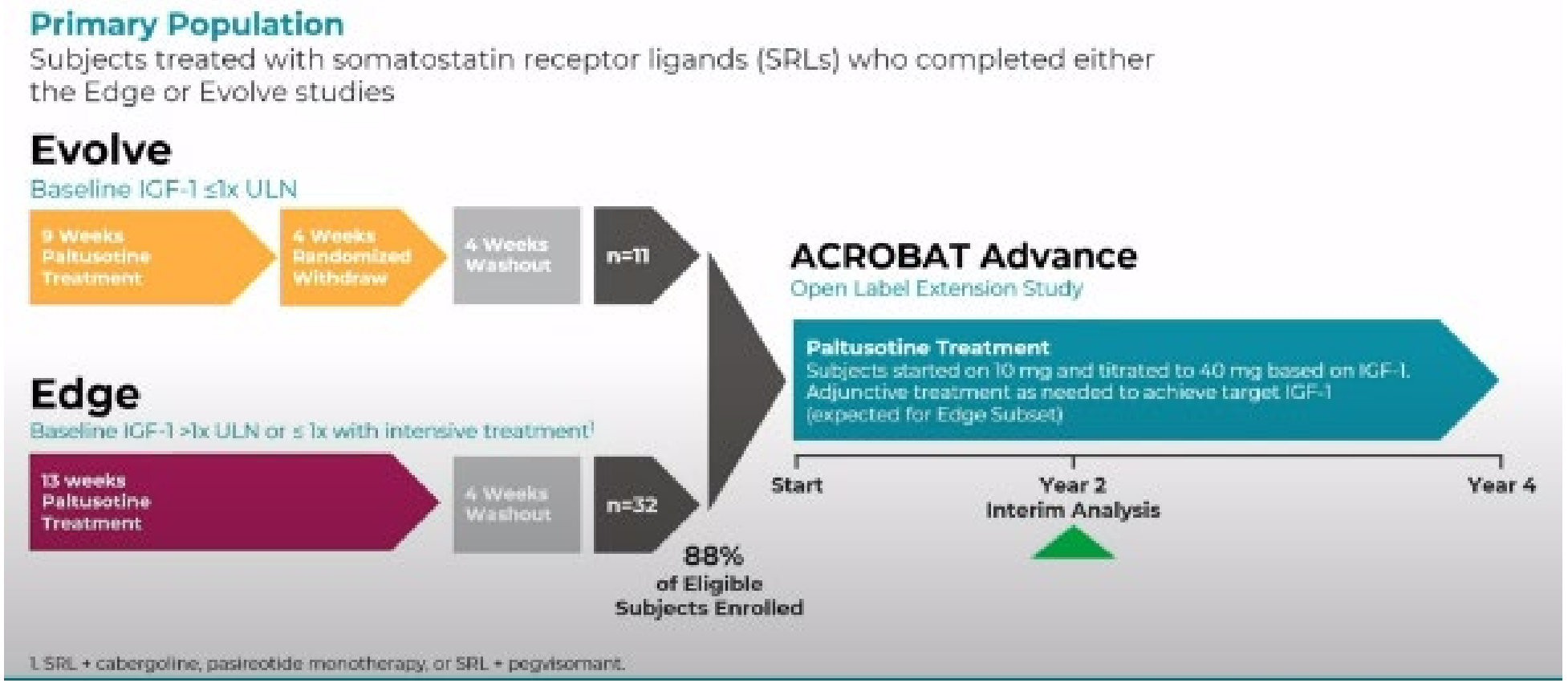

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Acromegaly

Paltusotine, phase III

Oral, Once-daily, Paltusotine (Non-peptide Selective Somatostatin Receptor Subtype 2 Agonist) Therapy in Patients With Acromegaly Is Associated With Long-term Biochemical and Symptom Control and Is Preferred Over Injectable Somatostatin-receptor Ligands

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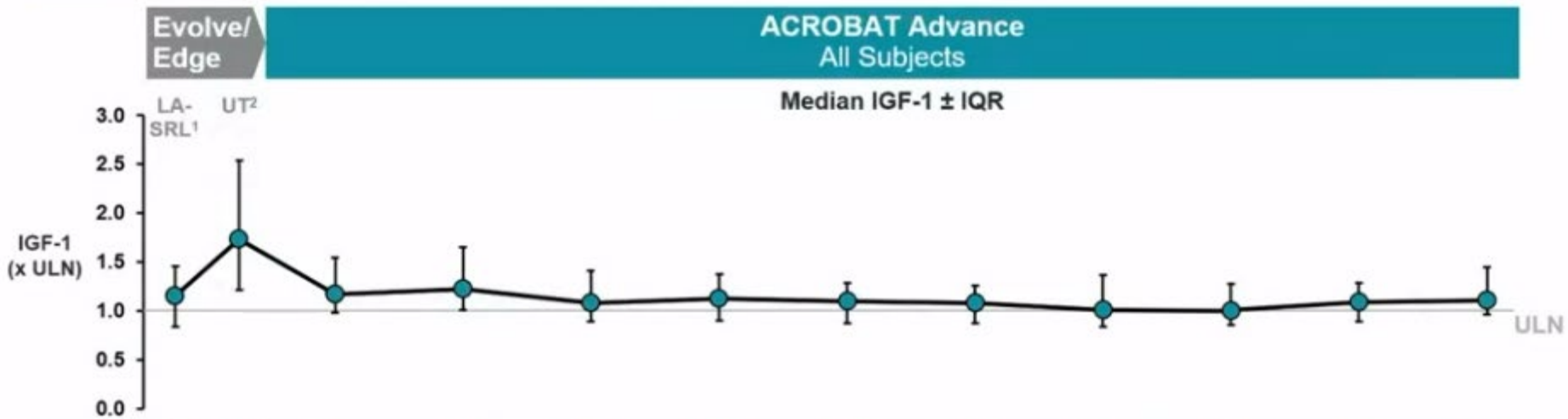
IGF-1 Levels Maintained at Injected LA-SRL Baseline Levels After Switching to Paltusotine



Week		3	15	31	39	47	51	64	77	90	103
N	43 43	43	42	39	37	38	37	31	27	21	10
Cumulative Discons.		0	0	2	3	3	3	5	6	6	6
Med. Paltusotine Dose (mg)		10	30	40	40	40	40	40	40	40	40
Cabergoline Use* (n)		0	1	4	8	14	15	13	11	10	5
Pegvisomant (n)		0	0	0	0	0	0	0	1	1	0

1. Baseline (screening) from Evolve/Edge studies while on injected SRL therapy. 2. End of 4-week wash-out from paltusotine at end of Evolve/Edge studies.
* UT: Untreated

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Acromegaly

Paltusotine, phase III

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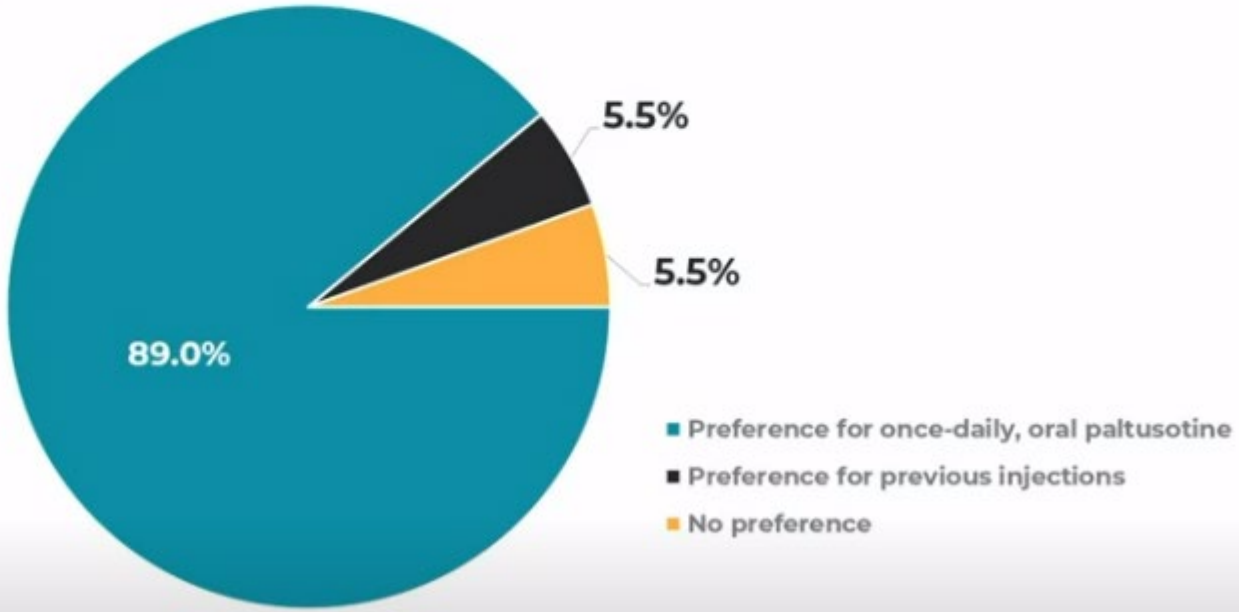
Treatment Preference

- At 52 weeks in the study (or at the last visit for those who discontinued the study), participants were asked to choose their preferred treatment option



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Acromegaly

Paltusotine, phase III

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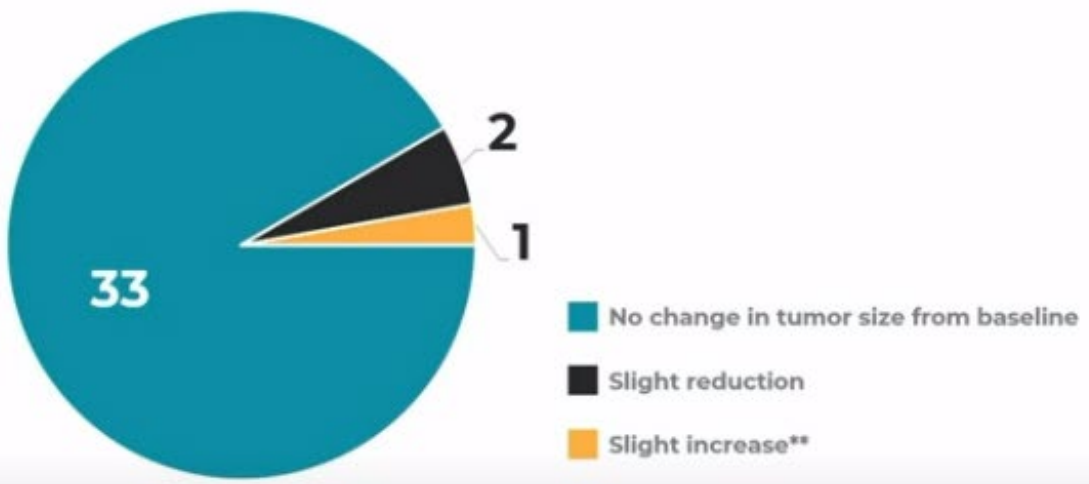
Safety Summary

Treatment-emergent Adverse Events (TEAEs) Occurring in ≥3 Subjects

TEAEs	Any Dose N=43 n (%) m
Headache	13 (30.2) 20
Arthralgia	11 (25.6) 22
Fatigue	8 (18.6) 13
Corona virus infection	7 (16.3) 7
Diarrhea	5 (11.6) 5
Hyperhidrosis	5 (11.6) 7
Myalgia	5 (11.6) 6
Paresthesia	5 (11.6) 8
Anxiety	4 (9.3) 5
Dizziness	4 (9.3) 4
Peripheral swelling	4 (9.3) 9
Hypertension	3 (7.0) 3
Hypotension	3 (7.0) 4

- 6 non-treatment related serious AEs occurred in 5 subjects
- 36 subjects had pituitary MRIs

Pituitary MRI Findings*



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Acromegaly

Key messages

- ✓ Once-daily oral Paltusotine maintained IGF-1 and GH levels to levels comparable to prior injected SRLs up to 2 years

- ✓ Oral Paltusotine was well-tolerated and most subjects preferred this formulation over injected SRLs

- ? No data as a first-line therapy (instead of injected SRLs)
- ? No head-to-head comparison with injected SRLs

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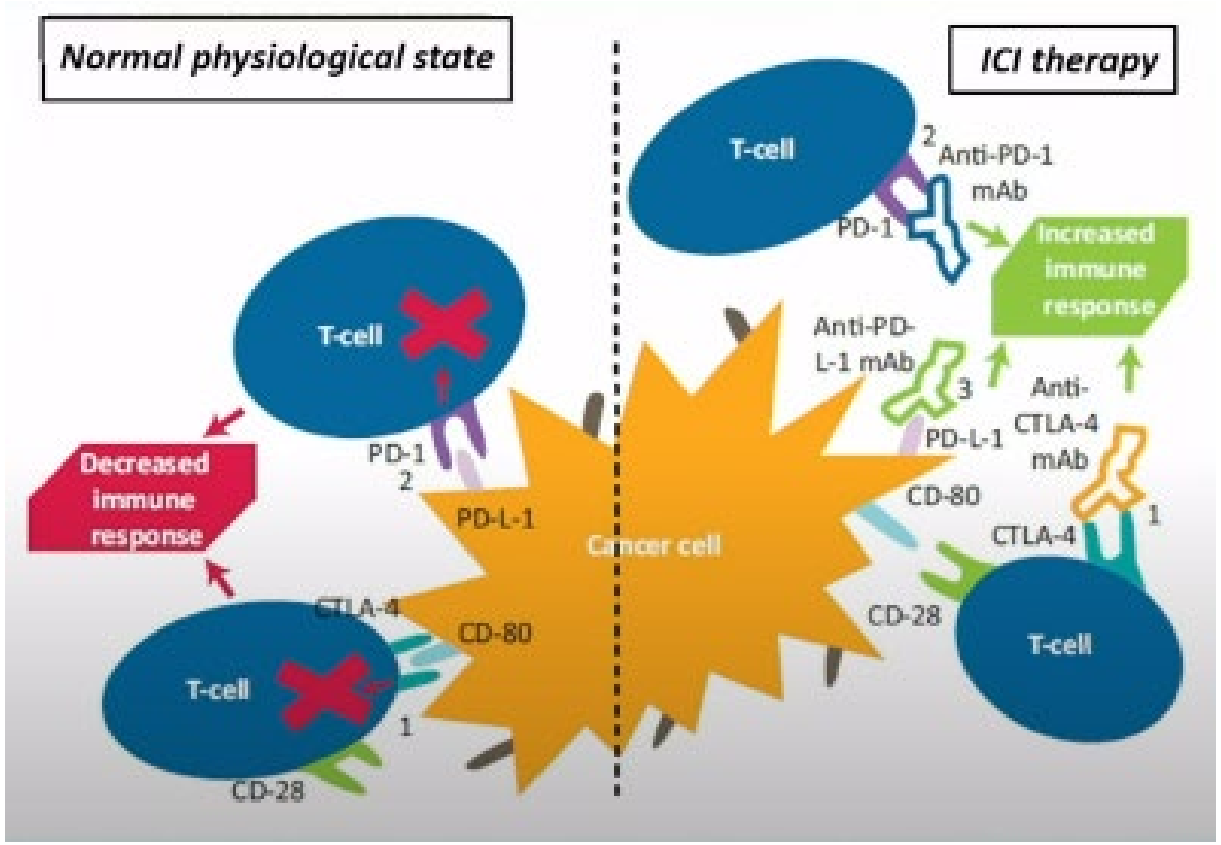
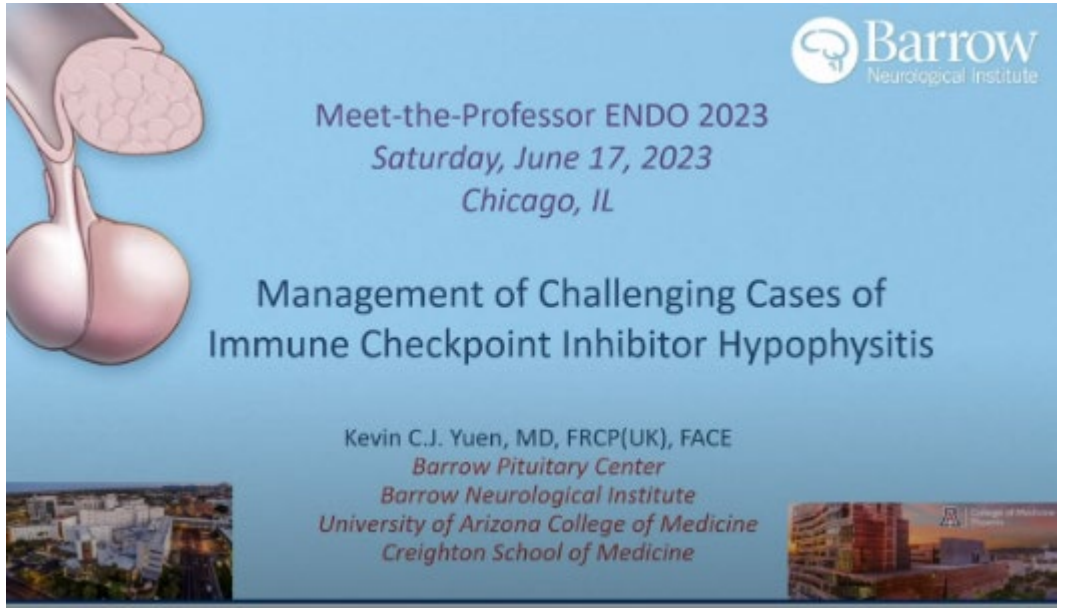
Hypophysitis

Immune checkpoint inhibitors





Hattersley et al, *Clin Med (Lond).* 2021

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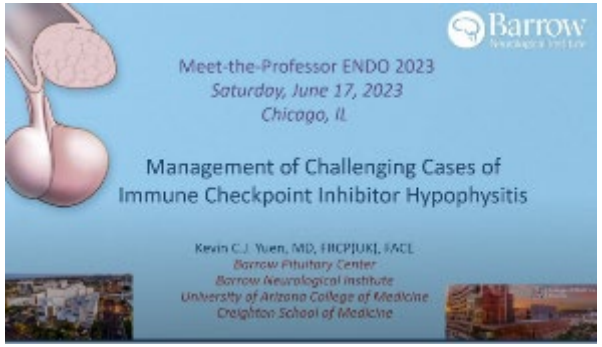
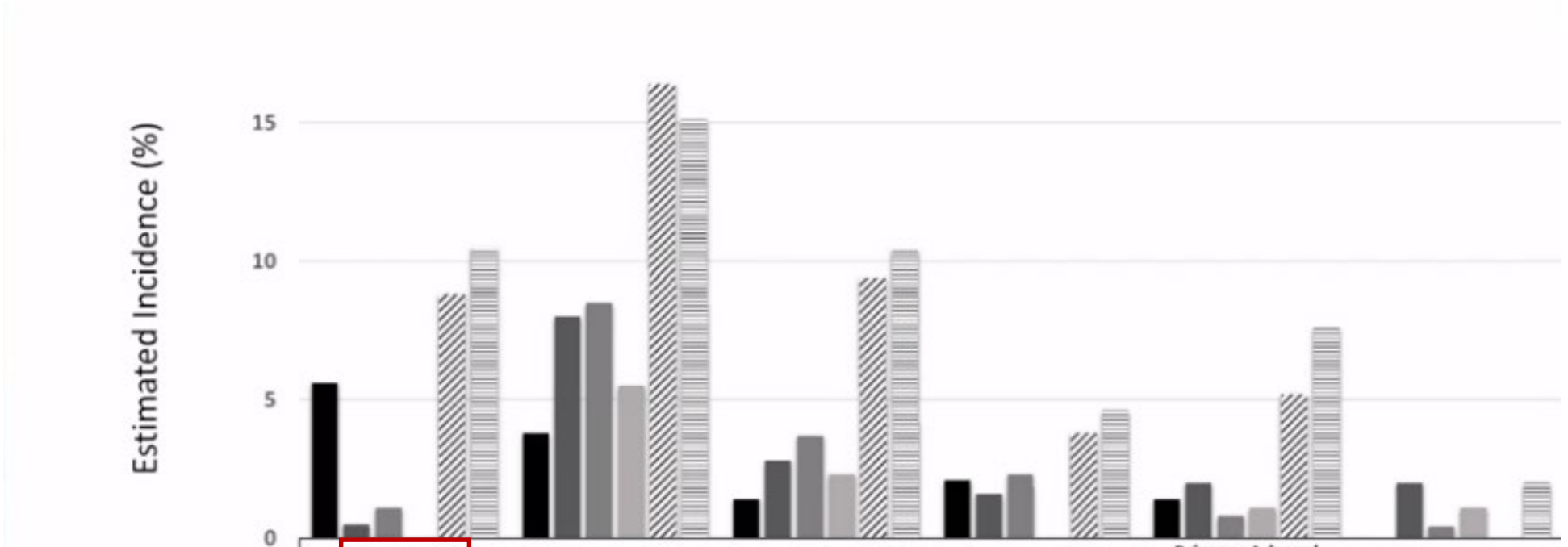
Hypophysitis

Immune checkpoint inhibitors





	Hypophysitis	Hypothyroidism	Hyperthyroidism	Thyroiditis[a]	Primary Adrenal Insufficiency	Diabetes Mellitus[b]
Ipilimumab (CTLA-4)	5.6	3.8	1.4	2.1	1.4	NR
Nivolumab (PD-1)	0.5	8.0	2.8	1.6	2.0	2.0
Pembrolizumab (PD-1)	1.1	8.5	3.7	2.3	0.8	0.4
Avelumab (PD-L1)	NR	5.5	2.3	NR	1.1	1.1
Ipilimumab/Nivolumab	8.8	16.4	9.4	3.8	5.2	NR
Ipilimumab/Pembrolizumab	10.5	15.1	10.4	4.6	7.6	2.0

Yuen KCL et al, *Endocr Practice*. 2022

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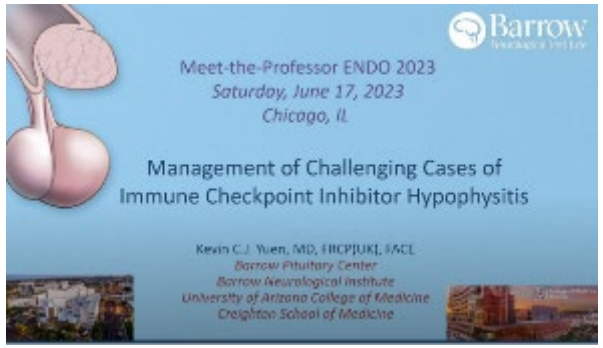
Hypophysitis

Immune checkpoint inhibitors



AACE and ASCO 2022 recommendations for screening and monitoring

Baseline prior to immunotherapy
Comprehensive metabolic panel
TSH and fT4 (TPOAb, TGAb)
HbA1c
8 AM cortisol and ACTH

Yuen KCJ, et al. *Endocr Pract*. 2022 Jun;28:719-731.

Immunotherapy Initiation

Thyroid
TSH and fT4 every 1-2 cycles

Adrenal
8 AM cortisol and ACTH as indicated by clinical symptoms

Diabetes
FPG every cycle
HbA1C every 2-3 months (prior DM)

Endocrinology Referral if Abnormal

↓TSH ↓fT4
Secondary hypothyroidism
Consider diagnosis of hypophysitis
(DDx: sick euthyroid syndrome)

↓TSH Normal fT4
Evolving thyroiditis (DDx: Graves')
Other tests: TSI, TRAb, TPOAb, TGAb

↓TSH ↑fT4
Thyroiditis (DDx: Graves')
Other tests: TSI, TRAb, TPOAb, TGAb, TG
U/S or thyroid uptake scan if suspect Graves' disease

↑TSH ↓fT4
Primary hypothyroidism
Other tests: TPOAb, TgAb

↑TSH Normal f4
Sub-clinical hypothyroidism
(DDx: recovery of sick euthyroid)
Other tests: Repeat TSH/fT4 in 1-2 weeks

↓Cortisol ↓ACTH
Evolving secondary adrenal insufficiency
Consider hypophysitis
(DDx exogenous glucocorticoids)
Other tests: pituitary laboratory panel with prolactin, sex hormones, IGF-I, for DI serum sodium and osmolality/urine osmolality
MRI if symptoms of mass effect or proven DI

↓Cortisol ↑ACTH
Primary adrenal insufficiency from adrenalitis
(DDx: adrenal metastases)
Other tests: adrenal Ab/21-hydroxylase Ab
ACTH stimulation test if equivocal cortisol
Adrenal imaging if suspect metastases

↑Glucose
New finding of hyperglycemia
>125 mg/dL fasting/>200 mg/dL random
Consider autoimmune DM, new onset Type 2 DM
(DDx: glucocorticoid induced Type 2 DM)
Additional tests[a]: recheck HbA1c, consider C-peptide, islet associated autoantibodies if suspect autoimmune DM, serum ketones and anion gap if concern for DKA

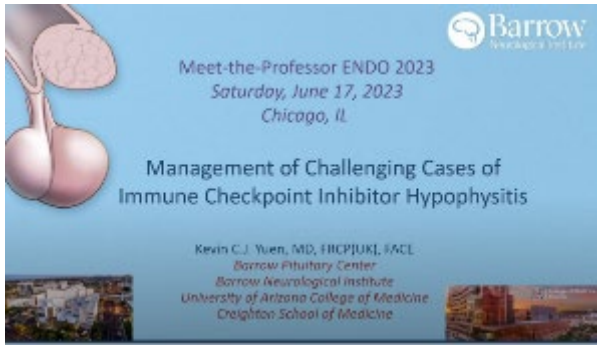
Trend for worsening hyperglycemia/HbA1C
Prior DM diagnosis/previously controlled on therapy, consider evolving autoimmune DM superimposed on Type 2 DM
(DDx: glucocorticoid induced hyperglycemia)
Additional tests: recheck HbA1c, fructosamine (if recent anemia), C-peptide, islet Ab (e.g., GAD Ab)

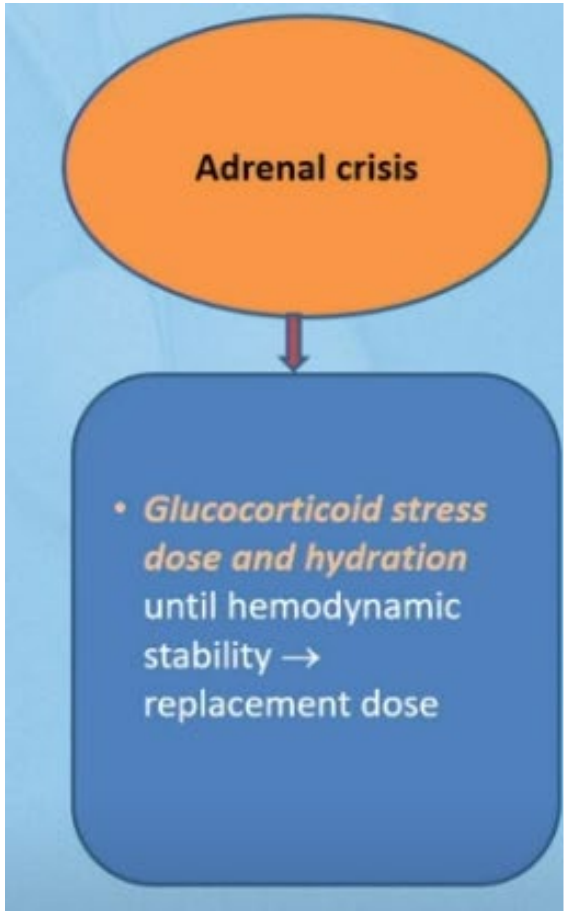
<u>Low threshold for testing</u> of adrenal axes if the clinical status changes (new-onset headache, visual changes, anorexia, and malaise or fatigue)

<u>Other guidelines</u>
Before each ICI dose (especially CTLA-4 inhibitors) for 6-9 months

Hypophysitis

Immune checkpoint inhibitors





≈ 80 nmol/l

≈ 80-420 nmol/l

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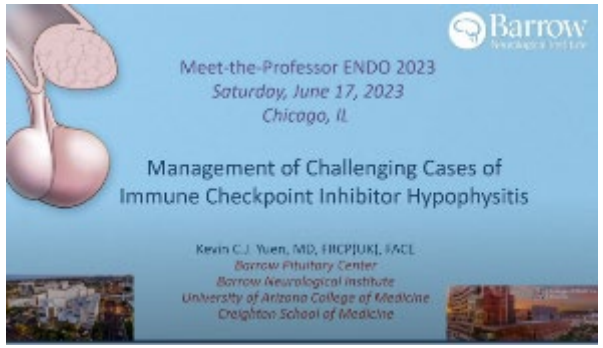
Hypophysitis

Immune checkpoint inhibitors



Diagnostic pearls and pitfalls

What's in a name?

- Hypophysitis with multiple hormone deficiencies usually from CTLA-4
- Isolated ACTH deficiency usually from PD-1/PD-L1

Is MRI sella needed in all cases?

- Perform if mass effect or AVP-D present
- Consider hypopituitarism if diagnosis uncertain
- Persistent pituitary enlargement and AVP-D concerning for metastasis

Role of 250 µg ACTH stimulation if cortisol 3-15 mcg/dL?

- **No:** can be normal in recent-onset secondary AI

Why does hyponatremia occur?

- From SIADH due to increased CRH from secondary AI
- From undiagnosed hypothyroidism

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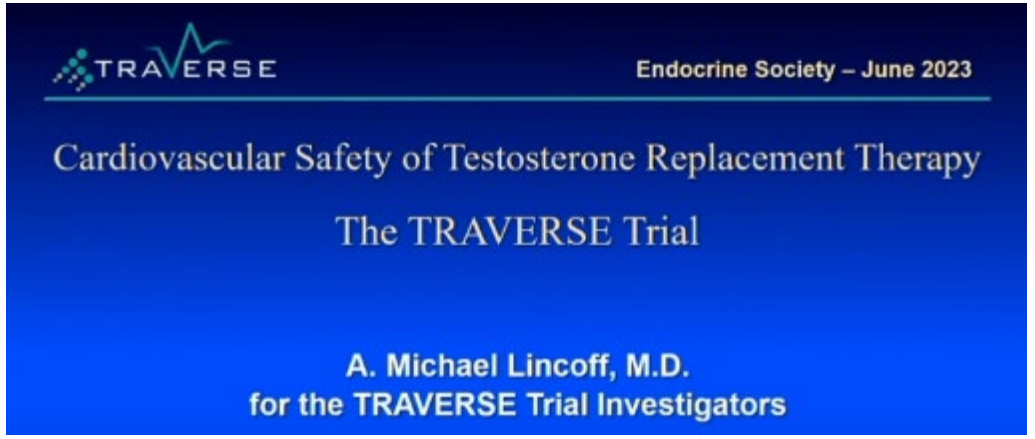
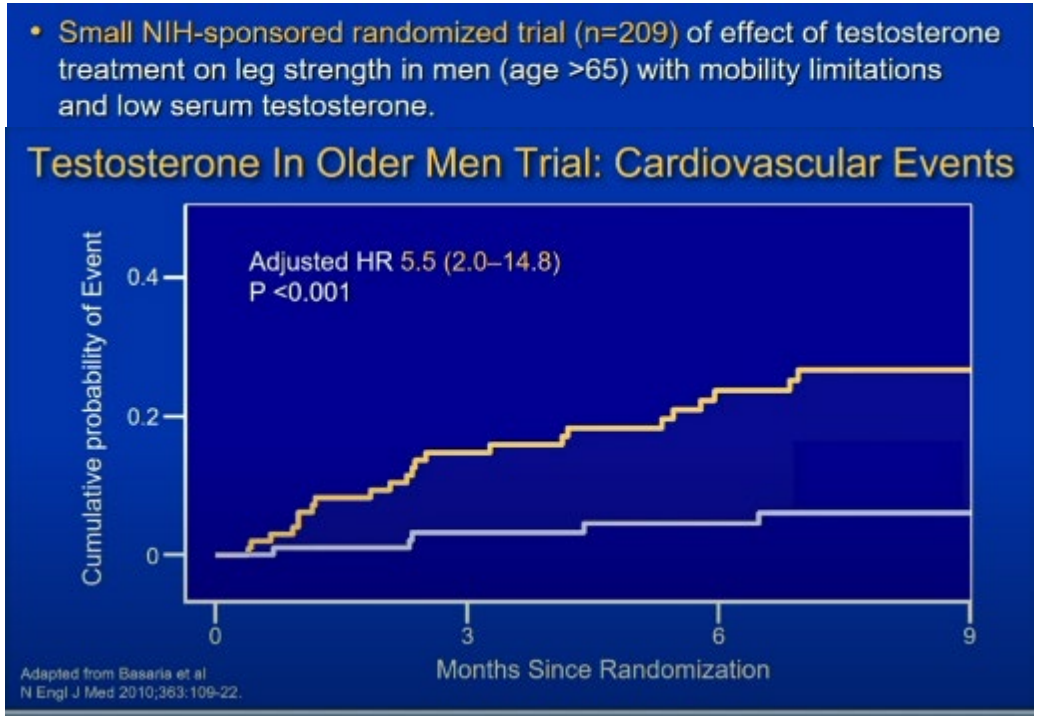
Testosterone replacement

Traverse Trial (CV safety)



FDA alert for all testosterone prescriptions in 2014

1)



2)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 November 2014
EMA/706140/2014

No consistent evidence of an increased risk of heart problems with testosterone medicines

The CMDh[1], a regulatory body representing EU Member States, has agreed by consensus that there is no consistent evidence of an increased risk of heart problems with testosterone medicines in men who lack the hormone (a condition known as hypogonadism). However, the product information is to be updated in line with the most current available evidence on safety, and with warnings that the lack of testosterone should be confirmed by signs and symptoms and laboratory tests before treating men with these medicines.

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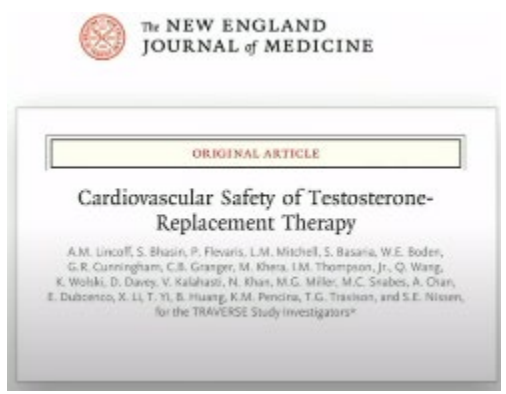
TRAVERSE Trial - Design



- randomized, double-blind, placebo-controlled trial
- non-inferiority
- event driven
- multicenter – 316 sites in the United States

Inclusion Criteria - Hypogonadism

Men, age 45-80 yrs

Symptoms (1 or more) of hypogonadism:

- decreased sexual desire or libido
- decreased spontaneous erections
- decreased energy or fatigue
- low or depressed mood
- loss of axillary or pubic hair or reduced shaving
- hot flashes

Two fasting serum testosterone concentrations <300 ng/dL from blood obtained between 5-11 AM, collected at least 48 hours apart

Inclusion Criteria – Cardiovascular

Pre-existing cardiovascular disease – clinical or angiographic:

- coronary artery disease
- cerebrovascular disease
- peripheral arterial disease

OR

Increased cardiovascular risk – 3 or more risk factors:

- hypertension
- dyslipidemia
- diabetes
- current smoking
- age 65 yr or older
- CKD stage 3
- elevated hsCRP
- Agatston CAC score >75th percentile

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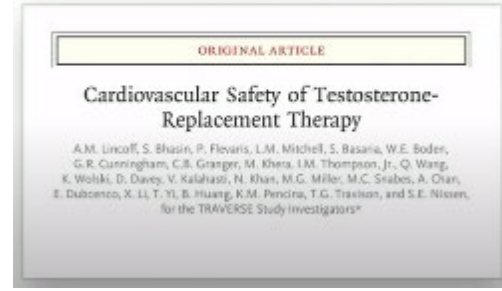
TRAVERSE Trial – Intervention & outcomes



Study Drug Management

Randomized double blind, 1:1 ratio
Stratified by pre-existing CV Disease vs CV Risk Factors

Testosterone 1.62% gel | **Placebo gel**

Patients and trial team blinded to post-baseline testosterone levels measured at central lab*
(*drawn at weeks 2, 4, 12, 26 and months 12, 18, 24, 36, 48)

Dose titrations by automated algorithm to maintain testosterone levels 350-750 ng/dL and Hct ≤54%

Sham titrations in placebo arm to facilitate blinding

Adjudicated Cardiovascular (CV) Endpoints

Primary MACE safety composite
- CV mortality, non-fatal MI, non-fatal stroke

Secondary CV safety composite
- CV mortality, non-fatal MI, non-fatal stroke, or coronary revascularization

Tertiary
- All cause mortality
- Heart failure hospitalization or urgent visit
- Peripheral arterial revascularization
- Venous thromboembolic event

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TRAVERSE Trial

The NEW ENGLAND JOURNAL of MEDICINE

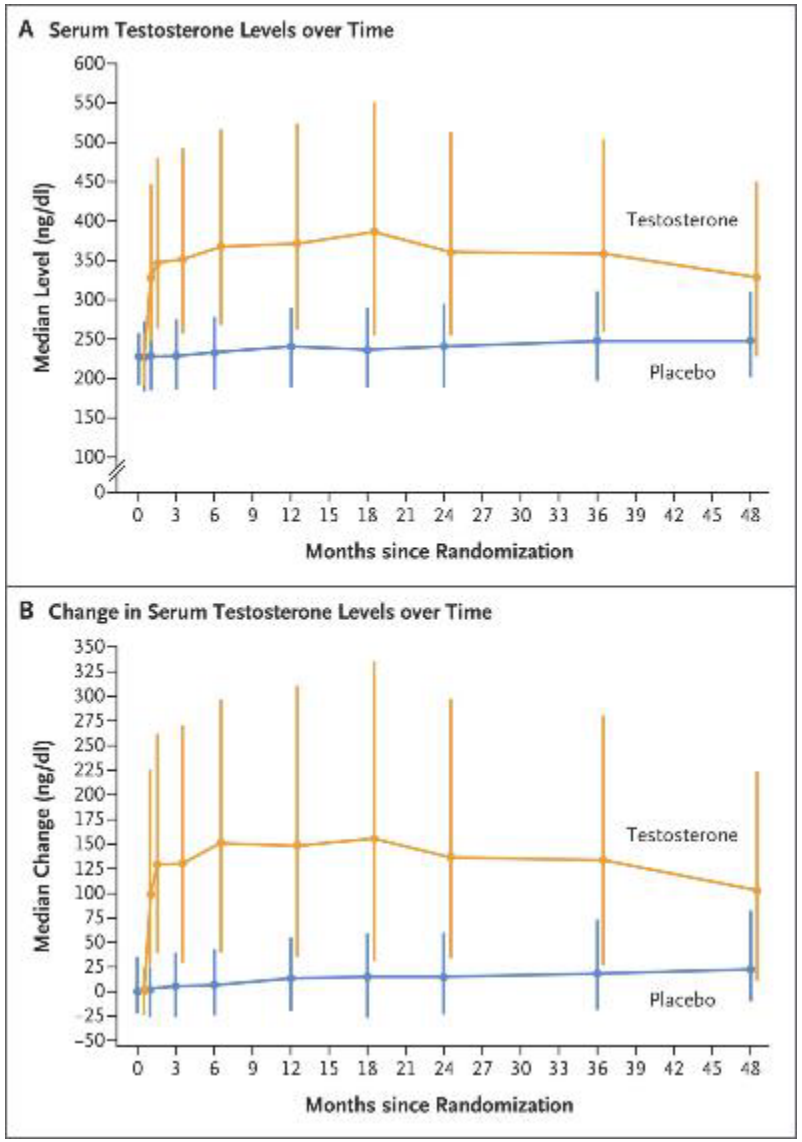
ORIGINAL ARTICLE

Cardiovascular Safety of Testosterone-Replacement Therapy

A.M. Lincoff, S. Bhasin, P. Flevaris, L.M. Mitchell, S. Basaria, W.E. Boden, G.R. Cunningham, C.B. Granger, M. Khera, I.M. Thompson, Jr., Q. Wang, K. Wolski, D. Davey, V. Kalahasti, N. Khan, M.G. Miller, M.C. Snabes, A. Chan, E. Dubcenco, X. Li, T. Yi, B. Huang, K.M. Pencina, T.G. Travison, and S.E. Nissen, for the TRAVERSE Study Investigators*

Table 1. Baseline Characteristics of Patients in the Full-Analysis Population.*

Characteristic	Testosterone Group (N=2601)	Placebo Group (N=2603)
Mean age — yr	63.3±7.9	63.3±7.9
Age ≥65 yr — no. (%)	1241 (47.7)	1211 (46.5)
Race or ethnic group — no. (%)†		
White	2070 (79.6)	2084 (80.1)
Black	445 (17.1)	432 (16.6)
Other	86 (3.3)	87 (3.3)
Hispanic or Latinx	409 (15.7)	439 (16.9)
Body-mass index‡	35.0±5.7	34.8±6.0
Median testosterone level (IQR) — ng/deciliter	227 (189–258)	227 (188–258)
Cardiovascular risk category — no. (%)		
Preexisting cardiovascular disease	1410 (54.2)	1437 (55.2)
Increased cardiovascular risk	1191 (45.8)	1166 (44.8)
History of coronary artery disease — no. (%)	1158 (44.5)	1160 (44.6)
History of cerebrovascular disease — no. (%)	304 (11.7)	318 (12.2)
History of peripheral arterial disease — no. (%)	158 (6.1)	153 (5.9)
Cardiovascular risk factors — no. (%)		
Diabetes, type 1 or type 2	1788 (68.7)	1844 (70.8)
Hypertension	2423 (93.2)	2402 (92.3)
Dyslipidemia	2344 (90.1)	2332 (89.6)
Current smoker	527 (20.3)	534 (20.5)
High-sensitivity C-reactive protein level ≥2 mg/dl	1607 (61.8)	1589 (61.0)
Stage 3 chronic kidney disease	418 (16.1)	393 (15.1)
Elevated coronary calcium score	29 (1.1)	28 (1.1)
Previous testosterone use — no. (%)	5 (0.2)	10 (0.4)
Medication — no. (%)		
Lipid-lowering therapy	2185 (84.0)	2180 (83.7)
Aspirin	1571 (60.4)	1550 (59.5)
Phosphodiesterase-5 inhibitor	170 (6.5)	189 (7.3)
Prostate-specific antigen level — ng/ml	0.91±0.65	0.94±0.68
Hematocrit — %	42±4	42±4
Lipid levels — mg/dl		
HDL cholesterol	41.9±11.2	41.7±10.9
LDL cholesterol	80.2±34.0	79.3±33.9
Median triglycerides (IQR)	154.6 (108.1–227.6)	157.7 (112.5–226.7)



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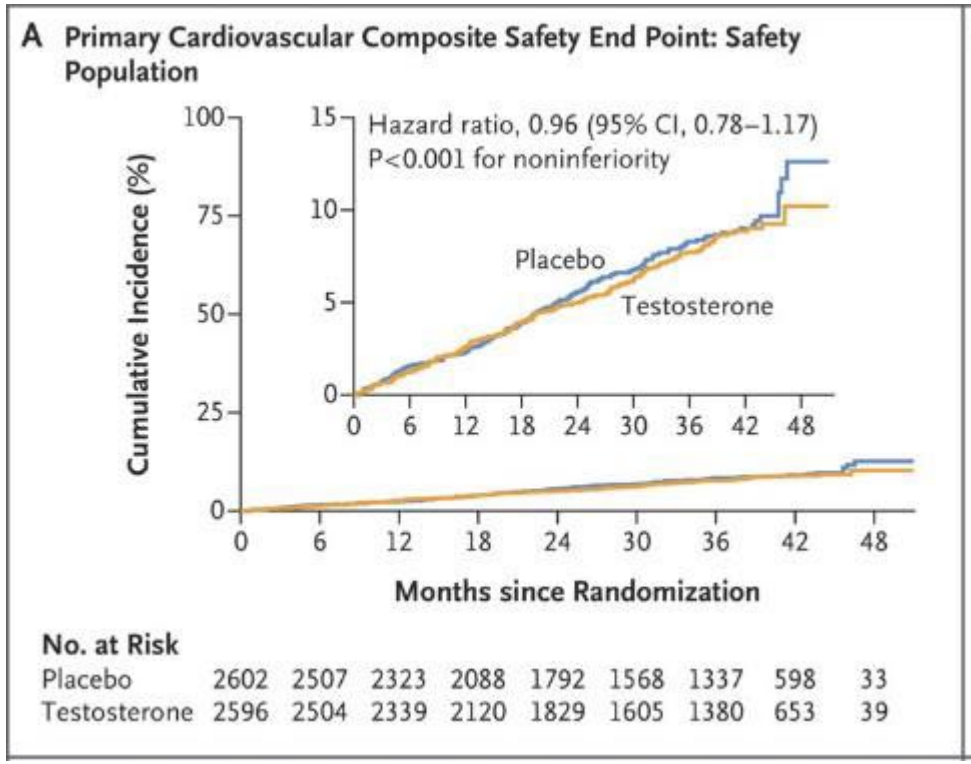
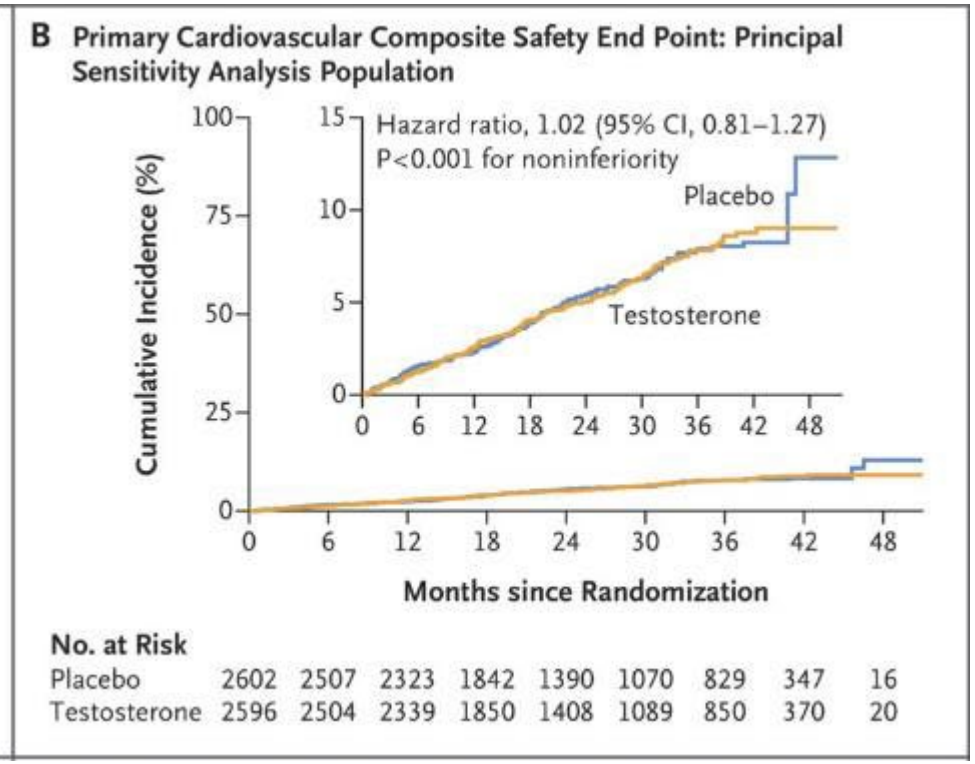
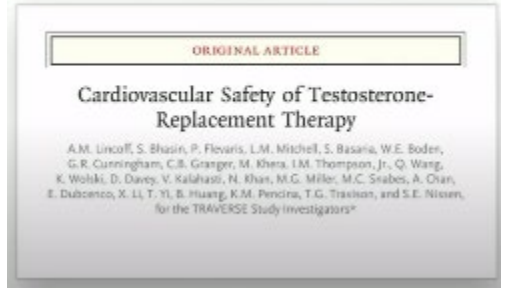
TRAVERSE Trial – Main results







Low retention in both groups

- ✓ Discontinuation rate of 60% higher than in standard CV safety trials but similar to previous trials of testosterone and studies on chronic diseases (obesity, menopause, pain)

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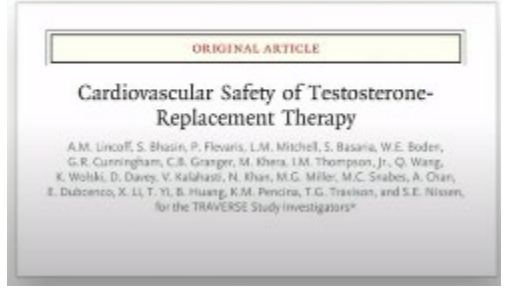
TRAVERSE Trial – Adverse events

The NEW ENGLAND JOURNAL of MEDICINE


ORIGINAL ARTICLE

Cardiovascular Safety of Testosterone-Replacement Therapy

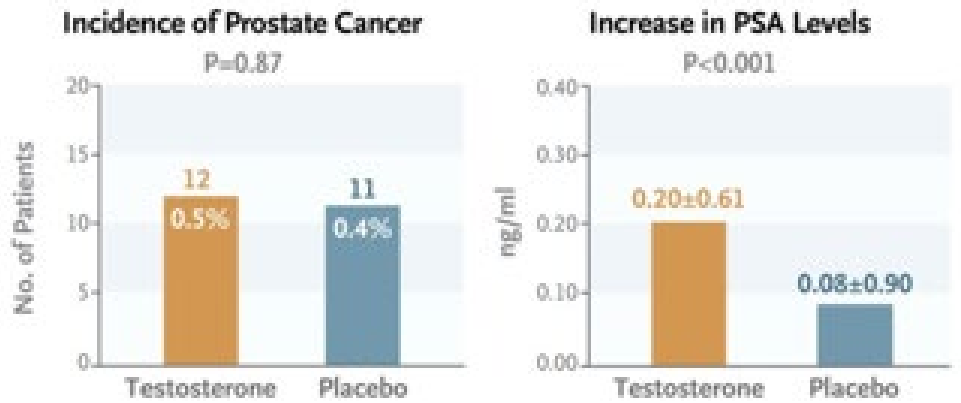
A.M. Lincoff, S. Bhasin, P. Flevaris, L.M. Mitchell, S. Basaria, W.E. Boden, G.R. Cunningham, C.B. Granger, M. Khera, I.M. Thompson, Jr., Q. Wang, K. Wolski, D. Davey, V. Kalahasti, N. Khan, M.G. Miller, M.C. Snabes, A. Chan, E. Dubcenco, X. Li, T. Yi, B. Huang, K.M. Pencina, T.G. Travison, and S.E. Nissen, for the TRAVERSE Study Investigators*

Table 3. Investigator-Reported Adverse Events.*

Event	Testosterone Group (N=2596)	Placebo Group (N=2602)	P Value†
	number of patients (percent)		
Any adverse event	1187 (45.7)	1164 (44.7)	0.47
Serious adverse event	721 (27.8)	697 (26.8)	0.42
Adverse event leading to discontinuation of testosterone or placebo	244 (9.4)	226 (8.7)	0.37
Prespecified adverse events of special interest	196 (7.6)	167 (6.4)	0.11
Hospitalization for unstable angina	44 (1.7)	60 (2.3)	0.12
Nonfatal arrhythmia warranting intervention	134 (5.2)	87 (3.3)	0.001
Cardiovascular disease causing syncope	27 (1.0)	32 (1.2)	0.52
Transient ischemic attack	15 (0.6)	17 (0.7)	0.73
Other adverse events			
Diabetes mellitus	189 (7.3)	213 (8.2)	0.22
Coronavirus disease 2019	121 (4.7)	117 (4.5)	0.78
Atrial fibrillation	91 (3.5)	63 (2.4)	0.02
Pneumonia	64 (2.5)	56 (2.2)	0.45
Acute kidney injury	60 (2.3)	40 (1.5)	0.04
Benign prostatic hyperplasia	45 (1.7)	46 (1.8)	0.92
Acute respiratory failure	52 (2.0)	37 (1.4)	0.11
Urinary retention	50 (1.9)	34 (1.3)	0.08
Cellulitis	35 (1.3)	46 (1.8)	0.22
Congestive cardiac failure	34 (1.3)	41 (1.6)	0.42

* The safety population consisted of all patients who had undergone randomization and received at least one dose of testosterone or placebo. Events are classified according to preferred terms in the *Medical Dictionary for Regulatory Activities*, version 25.0.

† P values were calculated with the use of a chi-square test.



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TRAVERSE trial

Key messages

- ✓ Testosterone gel therapy for a mean duration of 22 months did not increase CV events as compared to placebo in middle-aged and older men with hypogonadism (clinical symptoms and low testosterone)

- ✓ No increase in prostatic cancer, low overall incidence of adverse events

- ? Low retention of participants
- ? Relatively short follow-up


Thank you for your attention