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האוניברסיטה העברית בירושלים
THE HEBREW UNIVERSITY OF JERUSALEM

המרכז הרפואי
שערי צדק
SHAARE ZEDEK
MEDICAL CENTER



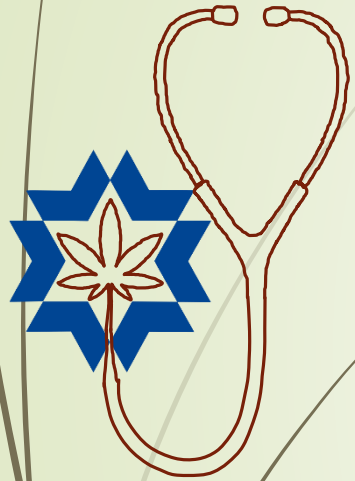


Grant/Research Support: *BOL pharma, National Institute of Psychobiology in Israel*

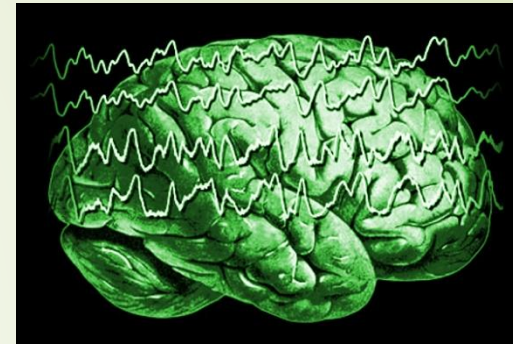
Consultant: *BOL pharma*

I will be discussing “off-label” uses of medical cannabis

Research Interests




**1. Cannabinoids &
endocannabinoid system
in autism spectrum disorder**



**2. Biomarkers &
Early Diagnosis of Autism
in Risk-groups (CEDAR/ אתג"ר)**



Center for Early Diagnosis of
Autism in Risk-groups (CEDAR)
Shaare Zedek Medical Center 

Cannabis for autism



ENDOCA news



mothers advocating medical marijuana for autism



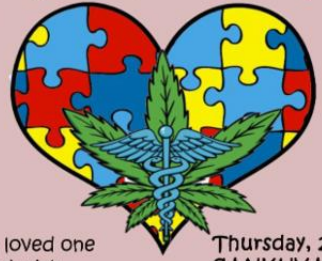
MEDICAL CANNABIS for AUTISM

CANNABIS IS GETTING NEW LIFE AS A PSYCHOTHERAPEUTIC DRUG TO COMBAT PSYCHOLOGICAL AND MENTAL SYMPTOMS.



PHILLY NORML presents...

Medical Marijuana for Treating Autism



Have you or a loved one been diagnosed with Autism Spectrum Disorder?

Thursday, 2/1/2018 @ 8PM
SANKHYA Yoga East Pa
3502 Scotts Lane
Building 16, Suite 1612
Philadelphia, PA 19129

Did you know that autism is one of the 17 qualifying conditions for medical marijuana treatment in Pennsylvania?

Register at <http://conta.cc/2F4JB7F>

Looking to be a medical marijuana patient in order to access safe, effective and natural medicine?

Suggested donation is \$5 door. Food and refreshments will be provided!

HEALTH

How Does Cannabis Consumption Affect Autism?

JEREMY KOSSEN
May 19, 2016



sophisticated cannabis

CANNABIS RESEARCH



Effects of Cannabis on Autism



Medical cannabis & Autism – clinical studies



**“The plural of anecdote is
not evidence! “**



1972 – Dr. Archie Cochrane

Evidence for the Risks and Consequences of Adolescent Cannabis Exposure.

Levine A. et al. 2017 Mar;56(3):214-225

J Am Acad Child Adolesc Psychiatry.



Phytocannabinoids- compounds unique to the cannabis plant

- Δ^9 – tetra-hydro-cannabinol - THC
- Cannabidiol - CBD
- THC is the main psychoactive substance (anxiety, psychosis)
- CBD is non-psychoactive, anti-psychotic, anxiolytic.



Different strains- completely different impact

Most medical strains are high THC low CBD

For ASD we try high CBD low THC strains



CBD

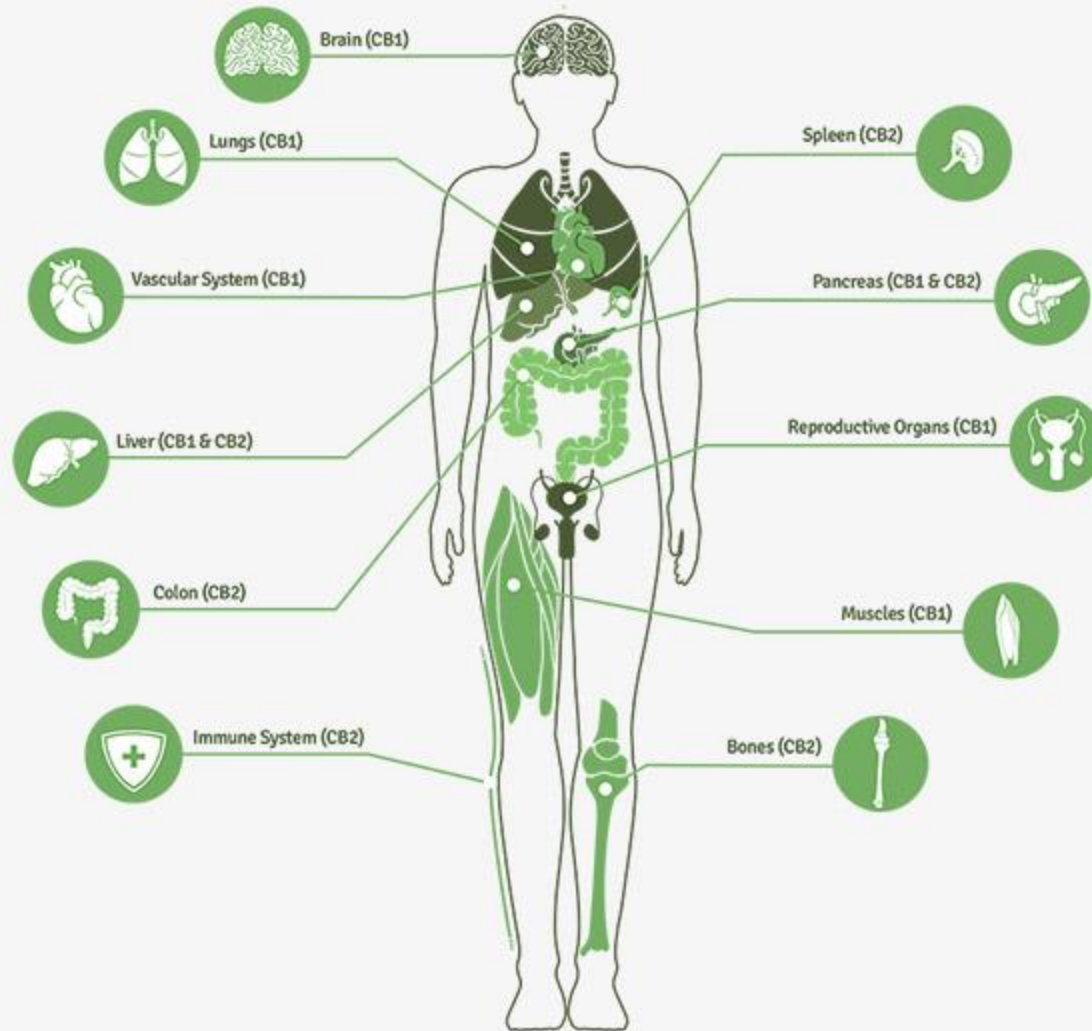


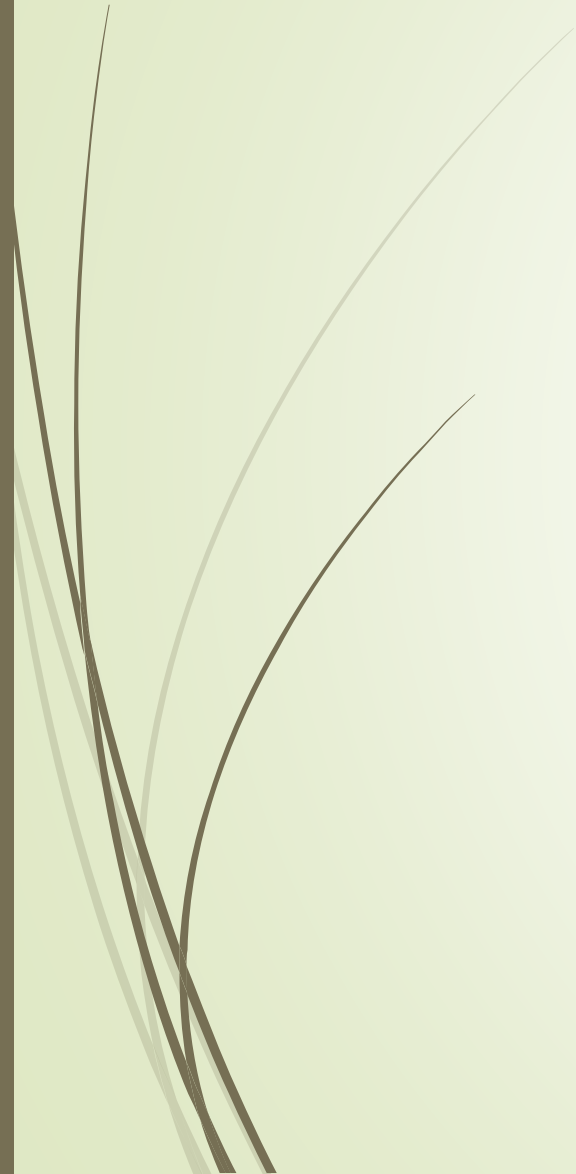
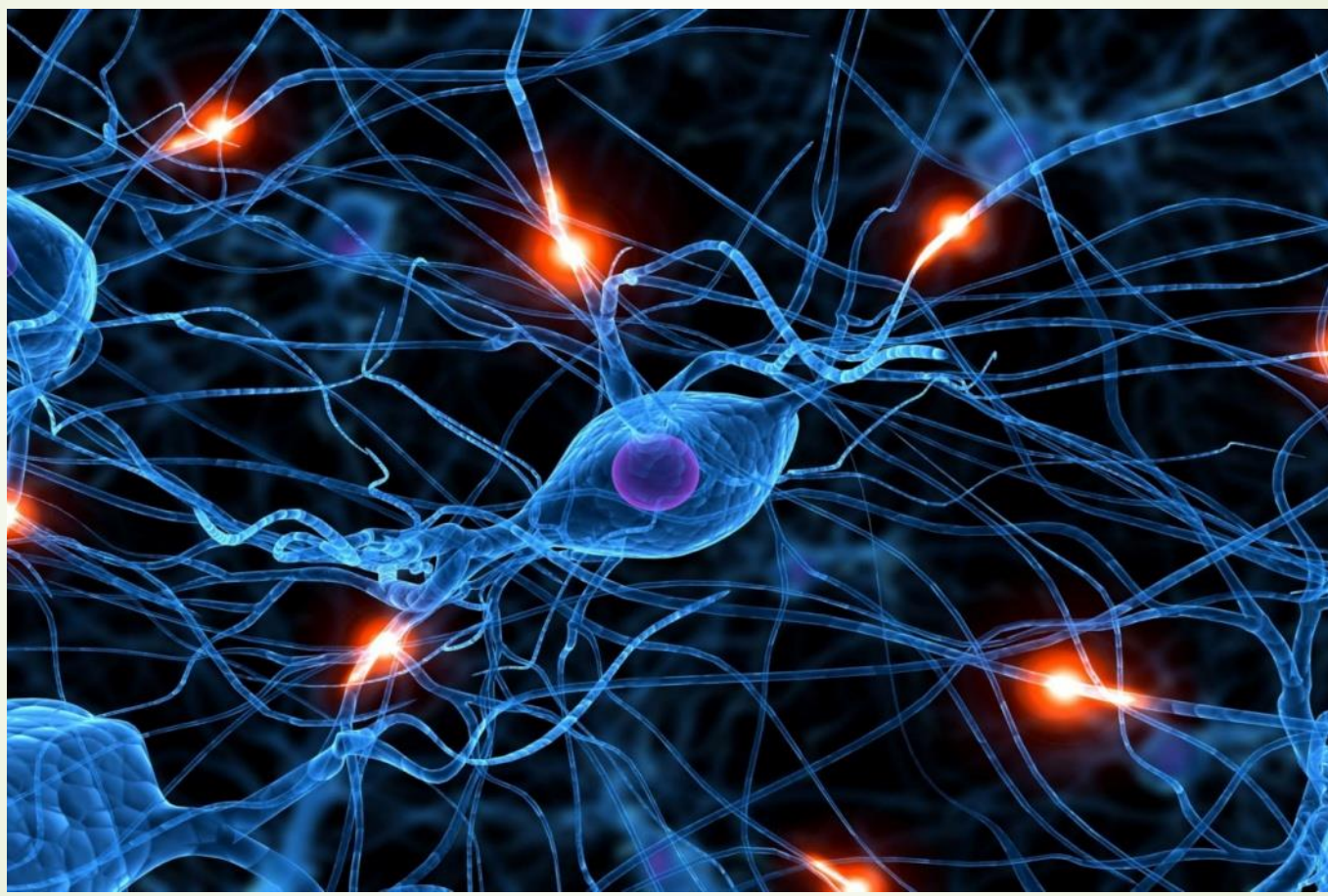
THC

Medical cannabis & Autism – Pre-clinical studies



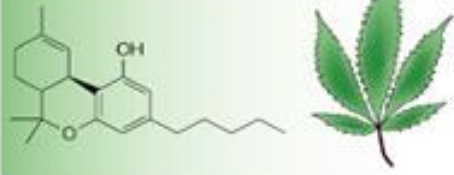
THE BODY'S ENDOCANNABINOID SYSTEM





Plant-derived cannabinoid

Δ^9 -Tetrahydrocannabinol (THC)

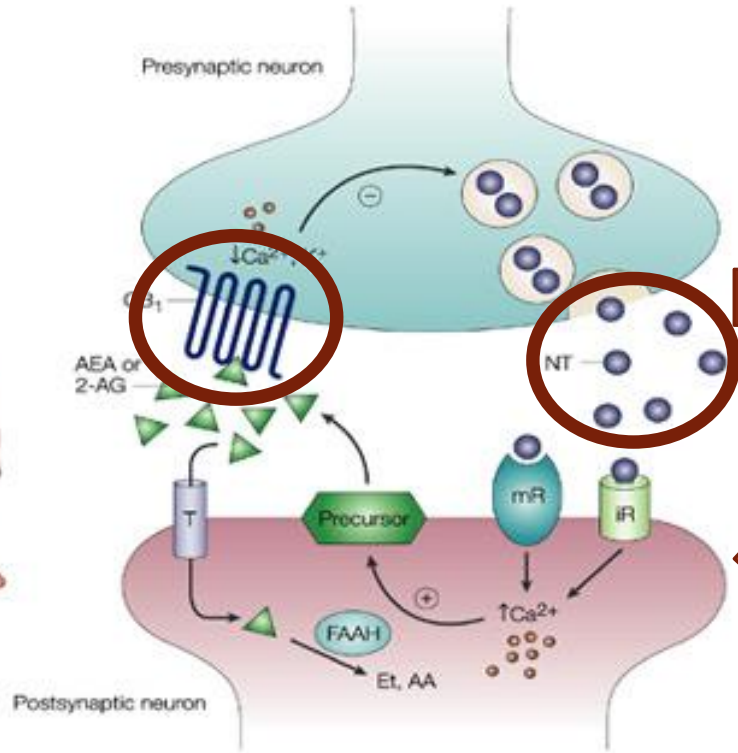


Endogenous cannabinoids

Anandamide (AEA)



2-Arachidonoylglycerol (2-AG)



The endocannabinoid system and ASD

- ▶ Regulation of:

- ▶ Social and emotional reactivity



- ▶ Motivation



- ▶ Learning and memory processes



- ▶ Epilepsy

- ▶ Circadian rhythm regulation

The endocannabinoid system and ASD

- Alterations of the EC system have been found in several animal models of ASD
 - **Monogenic:** Fragile X (Fmr1 knockout), Neuroligin-3 (mutation & knockout)
 - **Polygenic** (idiopathic ASD): BTBR model
 - **Environmental:** prenatal VPA exposure,



Aran et al. *Molecular Autism* (2019) 10:2
<https://doi.org/10.1186/s13229-019-0256-6>


Molecular Autism

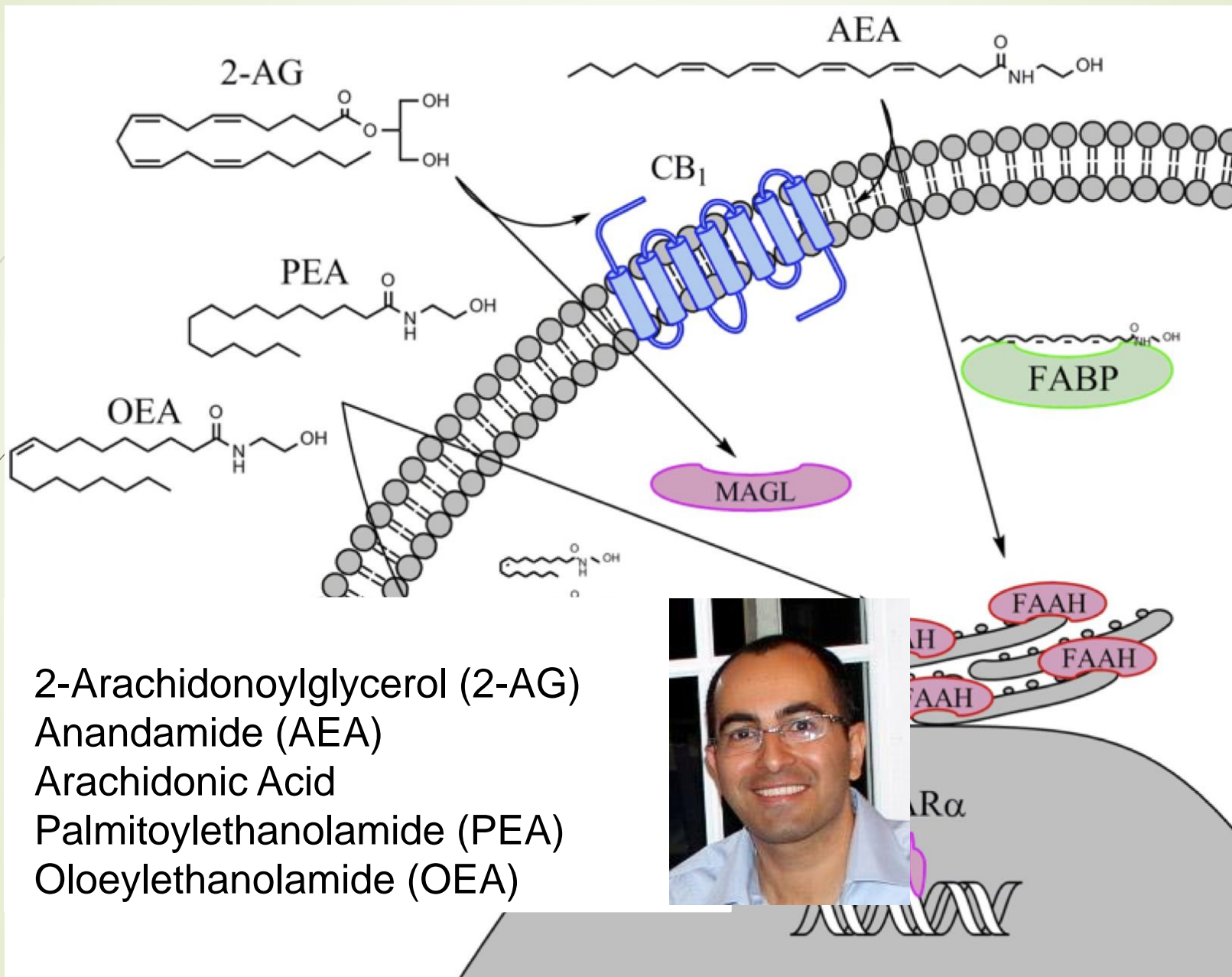
RESEARCH

Open Access

Lower circulating endocannabinoid levels in children with autism spectrum disorder

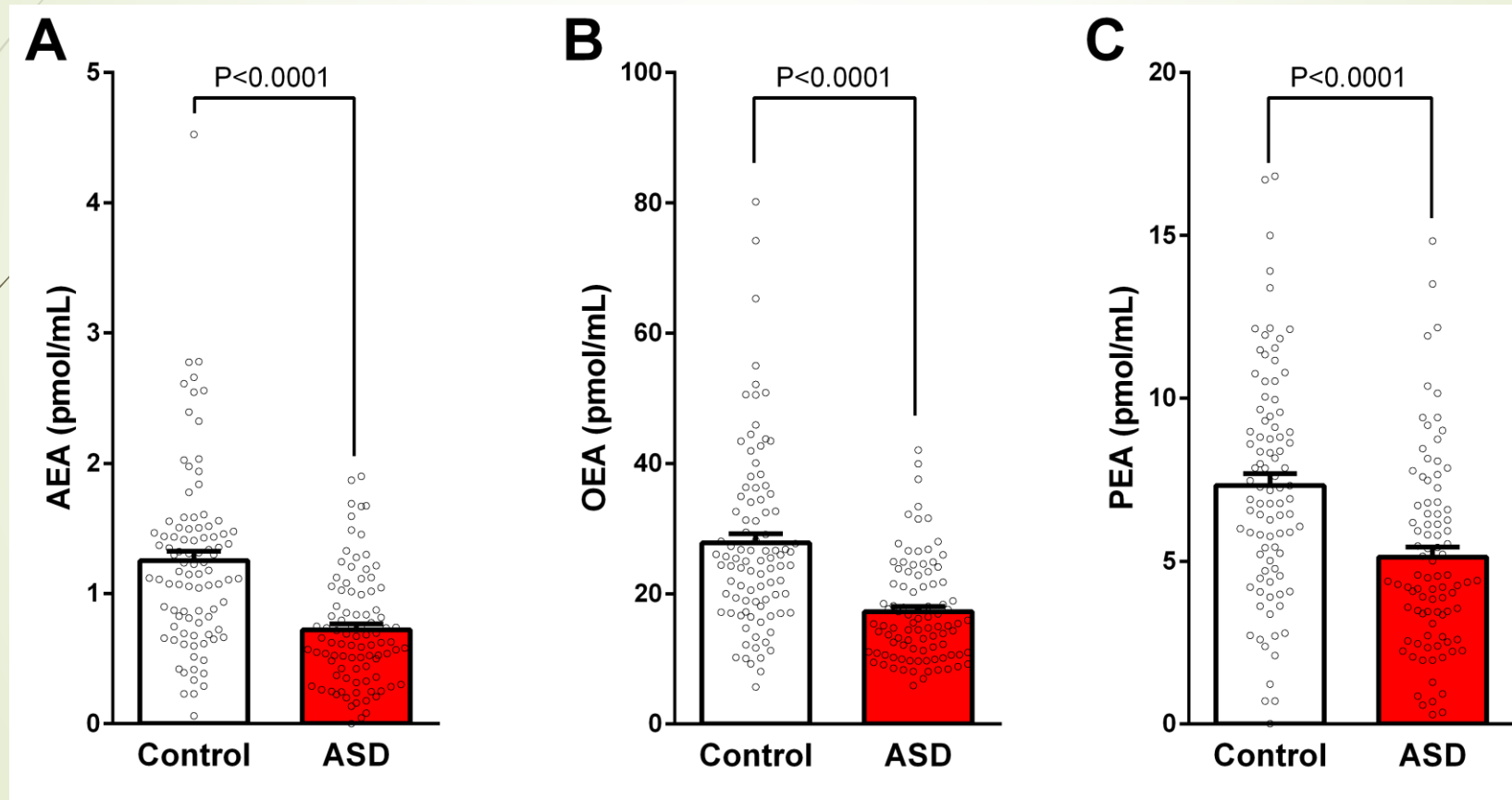


Adi Aran^{1*} , Maya Eylon², Moria Harel¹, Lola Polianski¹, Alina Nemirovski², Sigal Tepper³, Aviad Schnapp¹, Hanoch Cassuto¹, Nadia Wattad¹ and Joseph Tam²



2-Arachidonoylglycerol (2-AG)
 Anandamide (AEA)
 Arachidonic Acid
 Palmitoylethanolamide (PEA)
 Oleoylethanolamide (OEA)

Lower endocannabinoid levels in serum samples of 93 children with ASD compared with 93 age- and sex-matched controls.



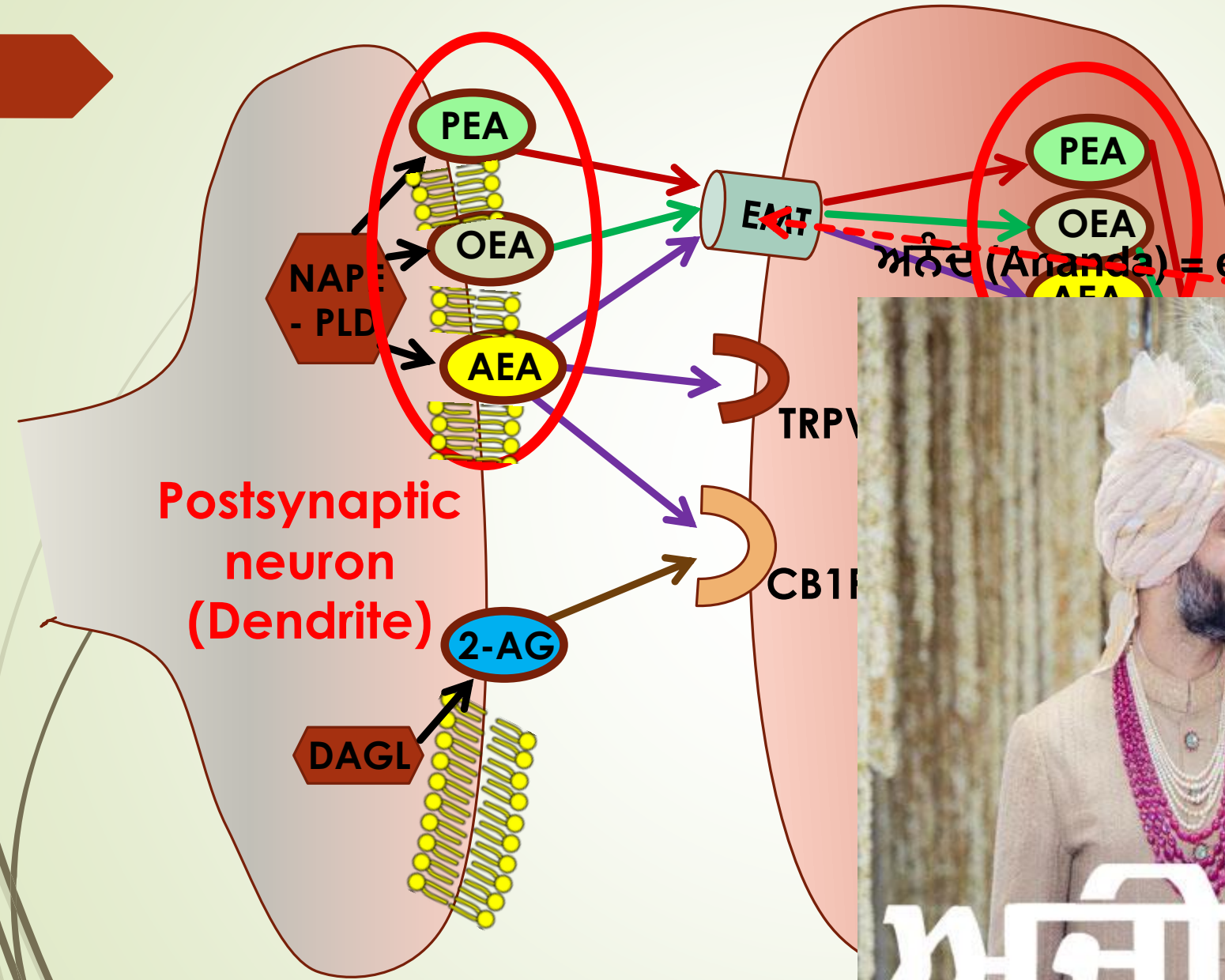
Anandamide (AEA)

Oleoylethanolamine (OEA)

Palmitoylethanolamide (PEA)

ASD

Presynaptic neuron (Axon)




CBD

अनन्द (Ananda) = extreme happiness in Sanskrit






Brief Report: Cannabidiol-Rich Cannabis in Children with Autism Spectrum Disorder and Severe Behavioral Problems—A Retrospective Feasibility Study

Adi Aran¹  · Hanoch Cassuto² · Asael Lubotzky¹ · Nadia Wattad¹ · Esther Hazan¹





Patients and treatment

- ▶ **Children age 5-18 years with ASD**
 - ▶ **Severe behavioral problems (CGI-S = 6 or 7)**
 - ▶ **Failure of proper medical and behavioral treatments**
 - ▶ **Whole plant extracts of CBD-rich cannabis strains**
- 

Results - patients



- **60 children:** age 11.8 ± 3.5 (5.5-17.5 years), 77% low cognitive functioning; 83% boys
- **Follow-up:** 7-13 months

Observational study- adverse events

Adverse event	No of patients (%)
Any adverse event	29 (51%)
Sleep disturbances	8 (14%)
Restlessness	5 (9%)
Nervousness	5 (9%)
Loss of appetite	5 (9%)
Gastrointestinal symptoms	4 (7%)
Unexplained laugh	4 (7%)
Mood changes	3 (5%)
Fatigue	3 (5%)
Nocturnal enuresis	2 (3.5%)
Gain of appetite	2 (3.5%)
Weight loss	2 (3.5%)
Weight gain	2 (3.5%)
Dry mouth	2 (3.5%)
Tremor	2 (3.5%)
Sleepiness	1 (2%)
Anxiety	1 (2%)
Confusion	1 (2%)
Cough	1 (2%)
Serious adverse event	No of patients (%)
Psychotic event	1 (2%)

Overall improvement in behavior as rated by parents on the CGIC scale

➤ Improvement in behavior:

- 21%– None or worse
- 17%– slightly improved - 25-50% reduction
- 34%– **much improved**- 50-75% reduction
- 28%– **Very much improved**- 75-100% reduction



Overall improvement in communication as rated by parents on the CGIC scale

- **Improvement in communication:**
 - 35%– None or worse
 - 17%– slightly improved
 - 25%– much improved
 - 23%– Very much improved



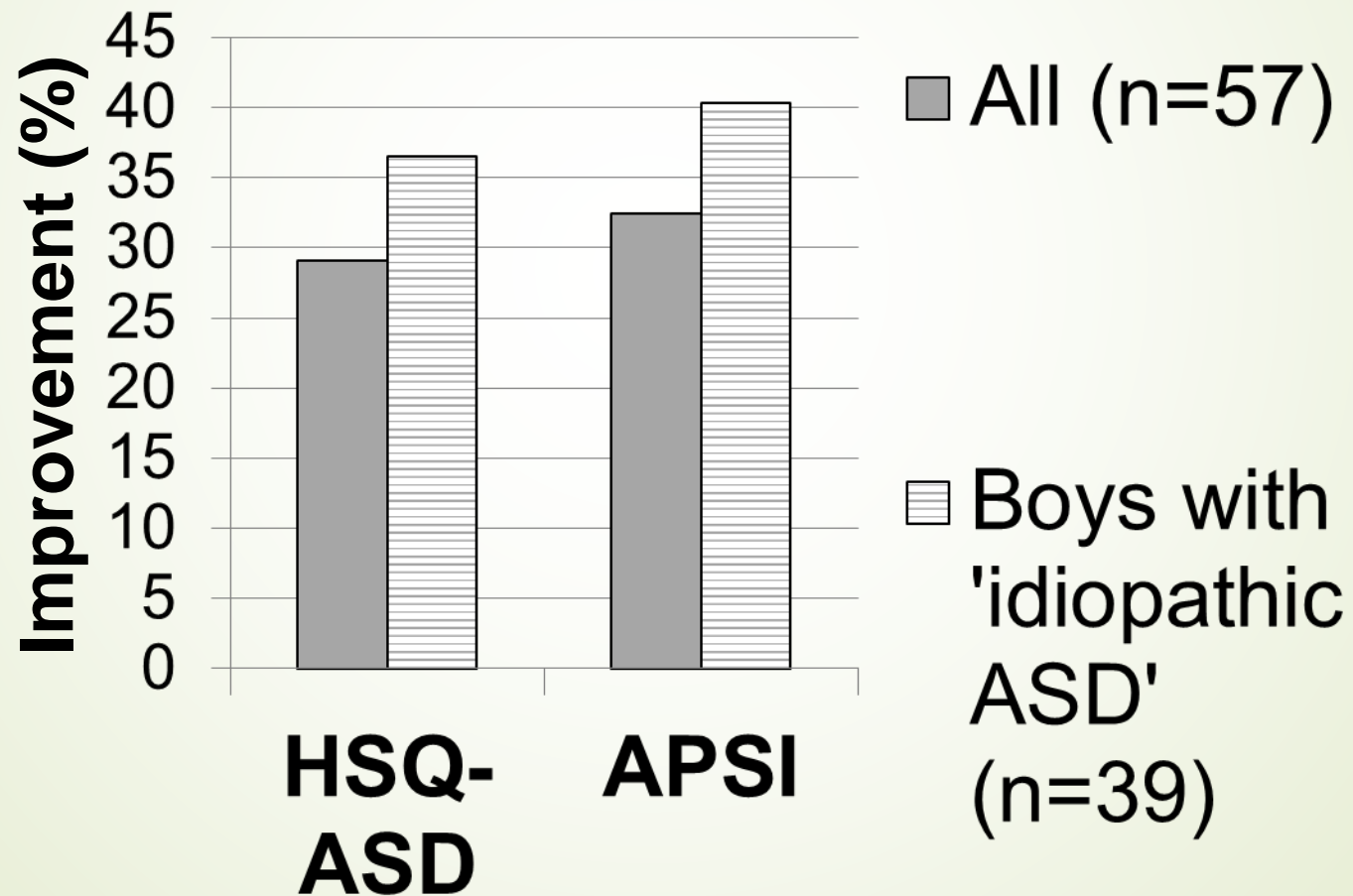
Overall improvement in anxiety as rated by parents on the CGIC scale

➤ Improvement in anxiety:

- 40%– None or worse
- 20%– slightly improved - 25-50% reduction
- **25%– much improved- 50-75% reduction**
- 15%– Very much improved- 75-100% reduction



Improvement in disruptive behavior (HSQ) and parental stress (APSI) following cannabis treatment





Uncontrolled trials should be interpreted cautiously



The NEW ENGLAND JOURNAL of MEDICINE

HOME

ARTICLES & MULTIMEDIA ▾

ISSUES ▾

SPECIALTIES & TOPICS ▾

FOR AUTHORS ▾

ORIGINAL ARTICLE

Lack of Benefit of a Single Dose of Synthetic Human Secretin in the Treatment of Autism and Pervasive Developmental Disorders

Adrian D. Sandler, M.D., Kelly A. Sutton, M.A., Jeffrey DeWeese, B.S., Mary Alice Girardi, P.N.P., Victoria Sheppard, M.D., and James W. Bodfish, Ph.D.

N Engl J Med 1999; 341:1801-1806 | [December 9, 1999](#) | DOI: 10.1056/NEJM199912093412404

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

MAY 25, 2017

VOL. 376 NO. 21

Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

ARTICLE OPEN ACCESS CLASS OF EVIDENCE

Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome

THE LANCET

Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial

The NEW ENGLAND JOURNAL of MEDICINE


ORIGINAL ARTICLE

Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome

Phase 2- Too many questions



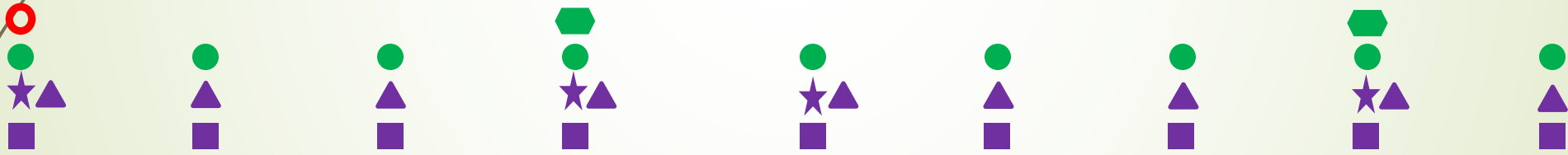
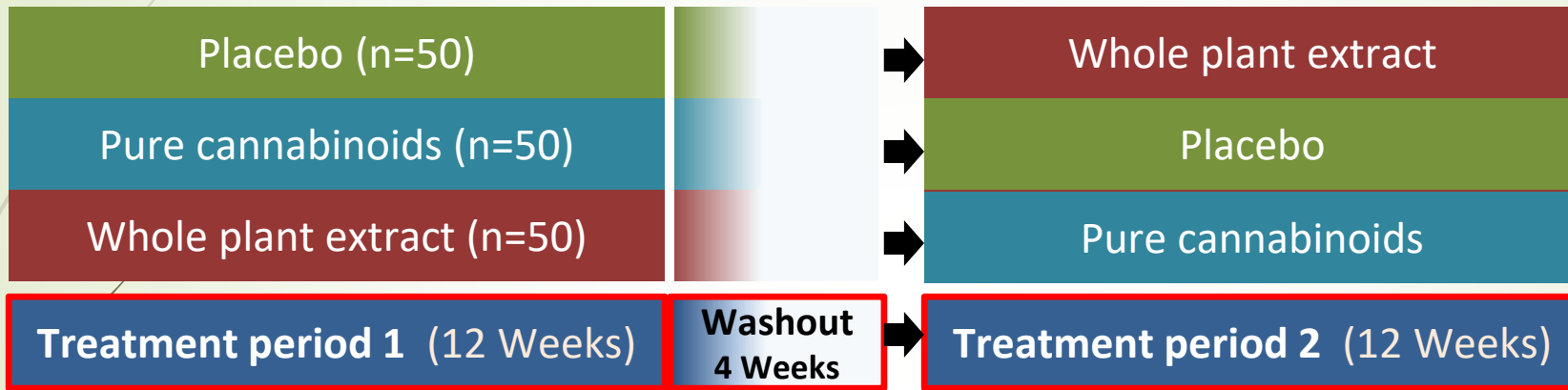
- Should we use **THC**?
 - which **CBD:THC ratio**?
- **Pure** cannabinoids vs. **whole** plant extracts (the entourage effect)
- Total daily **dose**
- **Target population** (age, function, syndromic ASD, environmental risk factors)
- **Treatment targets** (core symptoms, disruptive behavior)



You can never ask too many questions, but you can ask too many questions in a row.

Study Design

Primary
Secondary
Secondary



○ Baseline evaluations

ADOS-2
Vineland-II
CARS-2
SCQ

Primary outcome measures

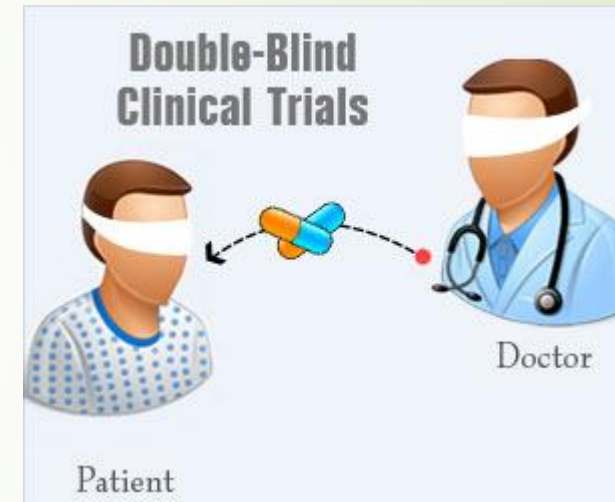
Clinical Global Impression-Improvement
 Home Situation Questionnaire

Secondary outcome measures

Social Responsiveness Scale
 Autism Parenting Stress Index
 Adverse events

Interventional controlled trial

- ▶ 150 participants
- ▶ Double-blind, randomized, placebo controlled trial
- ▶ Three arms and cross over



Arm A

Whole plant extract
20:1 ratio of CBD: THC

Arm B

Placebo

Arm C

Pure cannabinoids
20:1 ratio of CBD: THC



I am not at
liberty to discuss



Can cannabinoids expand our tool box for treating children with ASD?





Are We
There Yet?

Cannabinoids in Children with ASD – A multi-center phase III Study



Evdokia Anagnostou
Bloorview Research Institute
SickKids

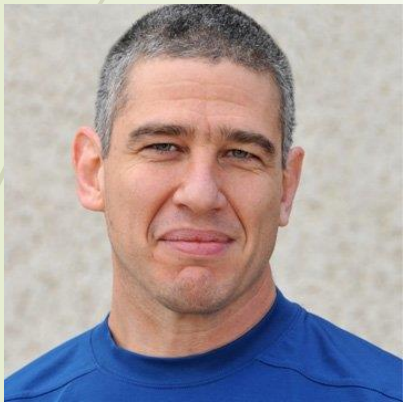


Xavier Castellanos
NYU Child Study Center



Ann Neumeyer
Massachusetts General Hospital
Harvard Medical School

Early Biomarkers in ASD



אלה מנו מנהלת האגף
לשירותי בריאות הציבור
והגיל הרך בעיריית ירושלים



Thank you

