Can Treating Obesity Fix the Brain?

Tom Ransom

Endocrinology, Capital Health, Nova Scotia

thomas.ransom@nshealth.ca

May 7, 2022

Disclosures relevant to this presentation

- I have received speaking honoraria, attended advisory board meetings and have been involved in clinical trials with Novo Nordisk
- All pharmacological use mentioned in this talk is off label

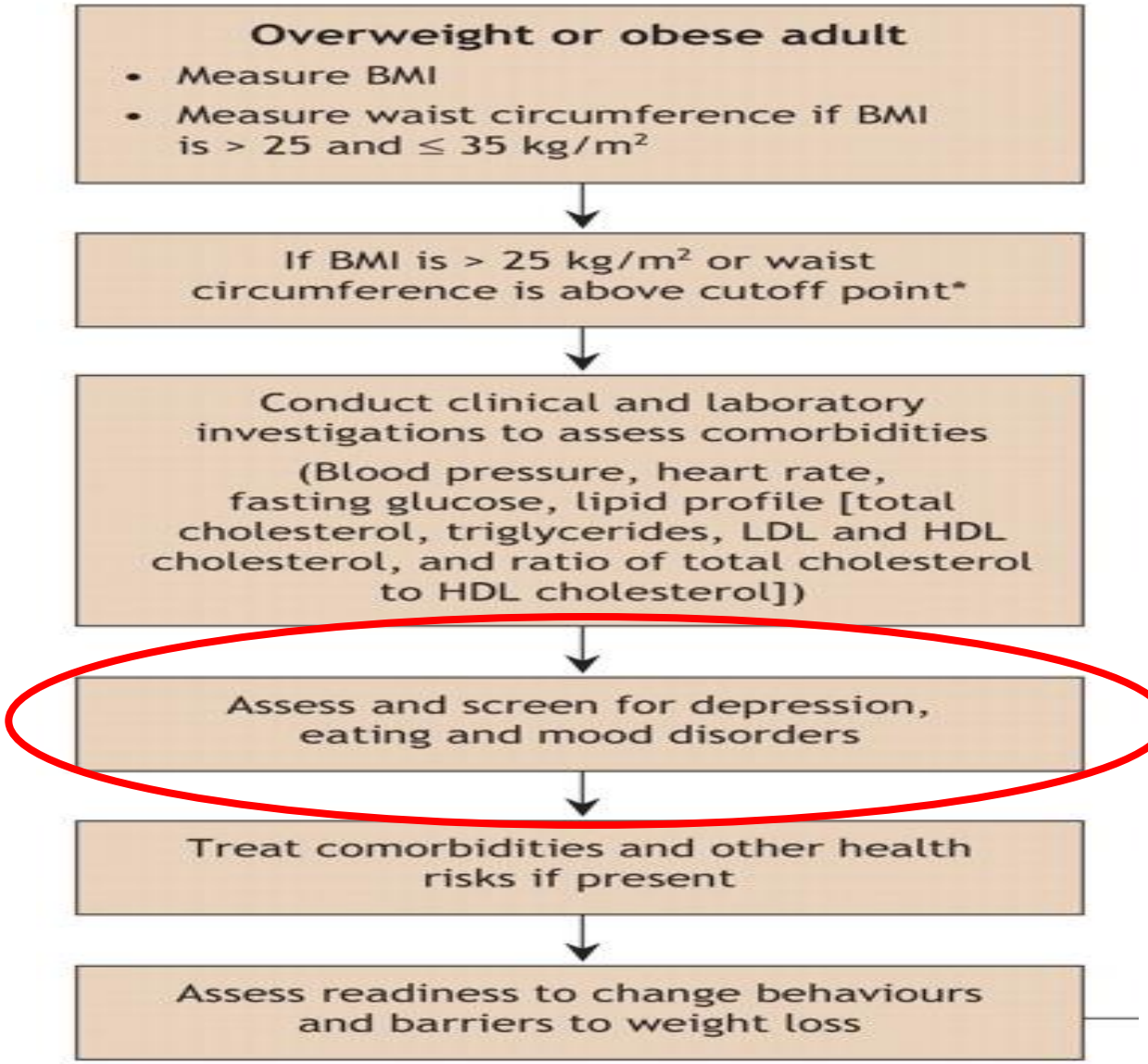
Objective

- After this presentation the attendee will understand that:
  - Insulin resistance (IR) that is often associated with obesity can alter brain function
  - Such altered brain function can worsen psychiatric illnesses such as bipolar disorder
  - Reversing IR can ameliorate bipolar disorder
  - The proposed mechanism relates to blood brain barrier (BBB) permeability

Outline

- Obesity → IR → worse outcomes for patient with bipolar disorder
- A trial of treating IR to improve outcomes
- BBB leakage may be the target

Algorithm for the assessment and stepwise management of the overweight or obese adult



RC PSYCH ROYAL COLLEGE OF PSYCHIATRISTS
The British Journal of Psychiatry
BJPsych

Insulin resistance and outcome in bipolar disorder

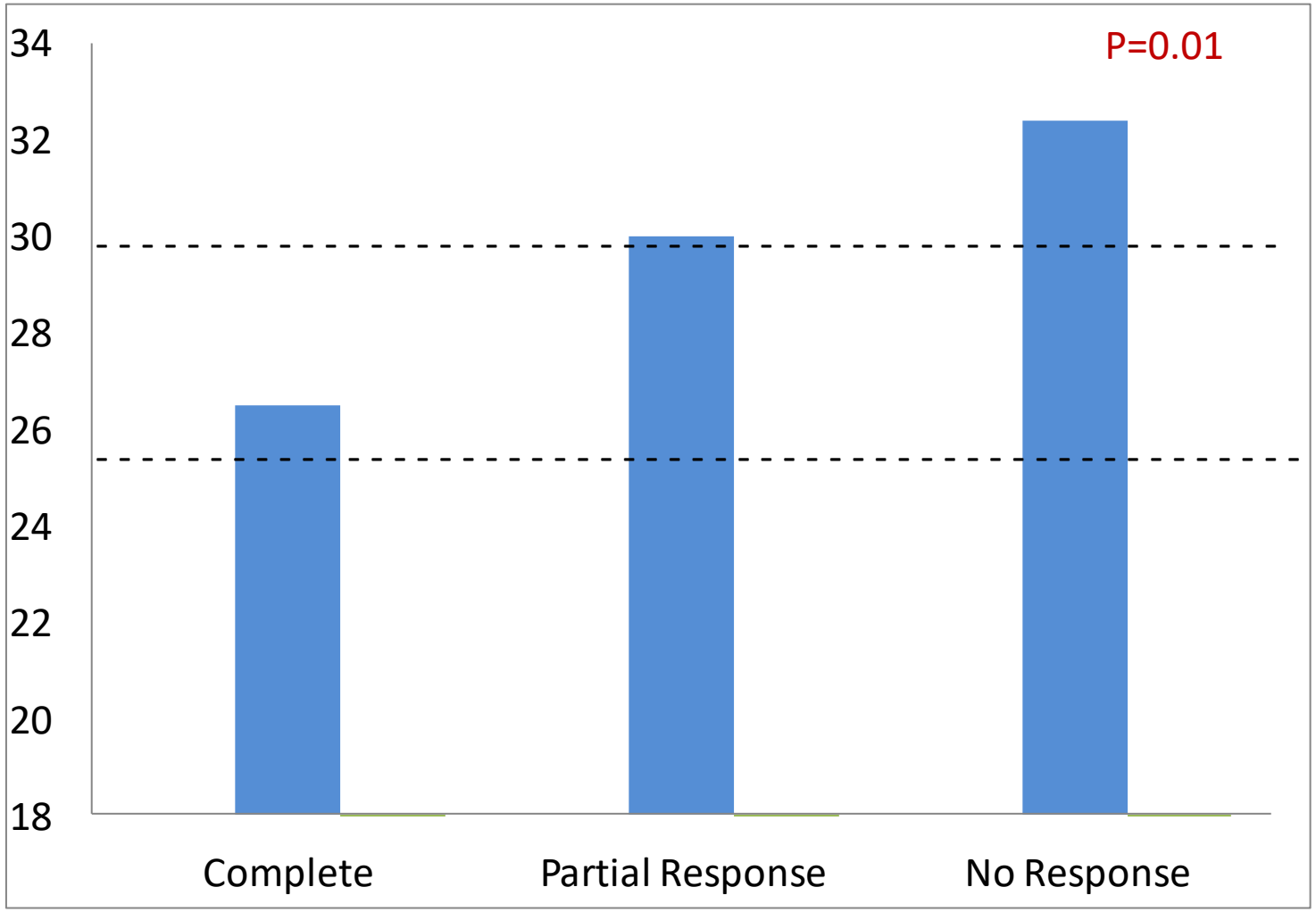
Cynthia V. Calkin, Martina Ruzickova, Rudolf Uher, Tomas Hajek, Claire M. Slaney, Julie S. Garnham, M. Claire O'Donovan and Martin Alda

BJP 2015 Jan;206(1):52-7.DOI: 10.1192/bjp.bp.114.152850

Glucose status (n=121)	n	%
euglycemic	56	46
IR/GI	39	32
T2D	26	22

40% diagnosed in Mood & Metabolism Program

BMI and Response to Lithium

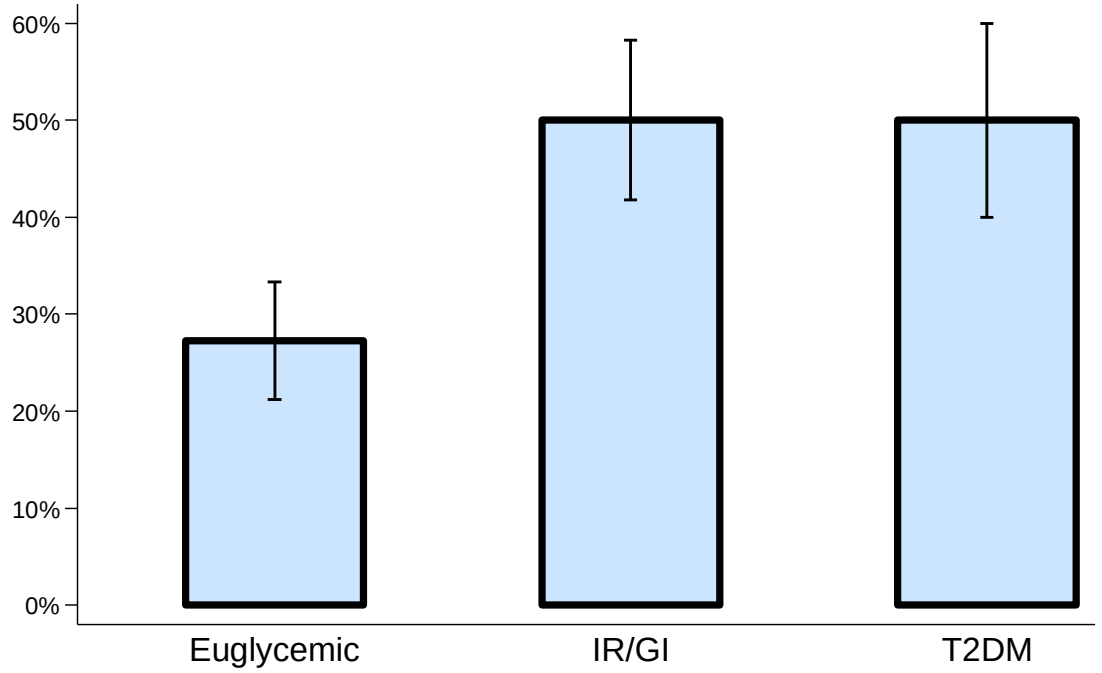


Calkin et al, Bipolar Disorders 2009

Insulin resistance and outcome in bipolar disorder

Course of illness

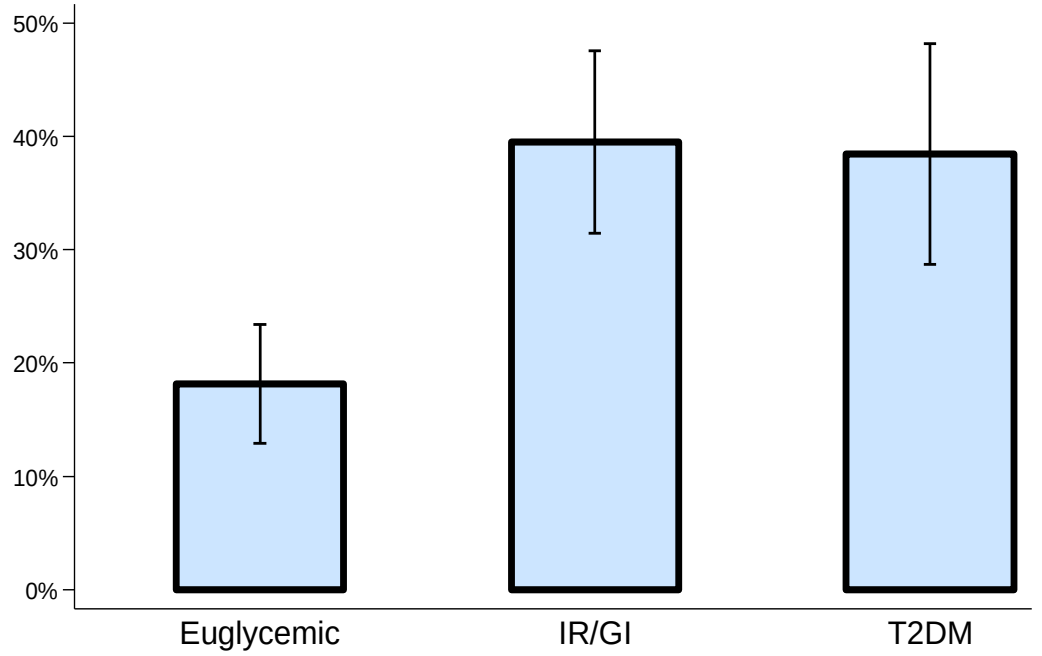
Variable n=121	Episodic	Chronic
Euglycemic	72.7%	27.3%
IR/GI	50.0%	50.0%
T2D	50.0%	50.0%



OR = 3.07 (95%CI 1.35 to 6.95, p=0.007), adjusted for age and sex

Rapid cycling

Variable n=121	Absent	Present
Euglycemic	81.8%	18.2%
IR/GI	60.5%	39.5%
T2D	61.5%	38.5%



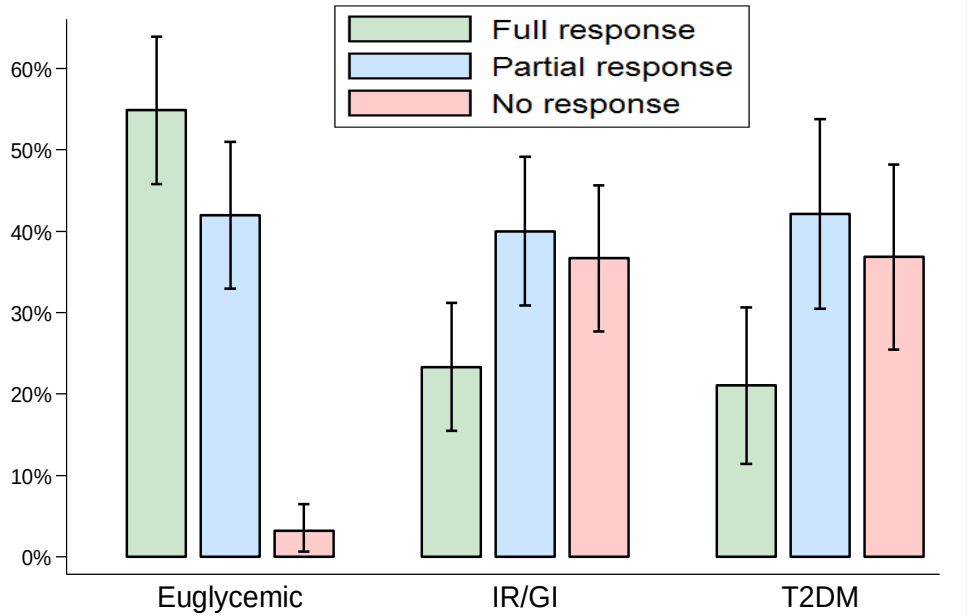
OR = 3.13 (95%CI 1.28 to 7.63, p=0.012), adjusted for age and sex

Calkin et al, B J Psych, 2015

Insulin resistance and outcome in bipolar disorder

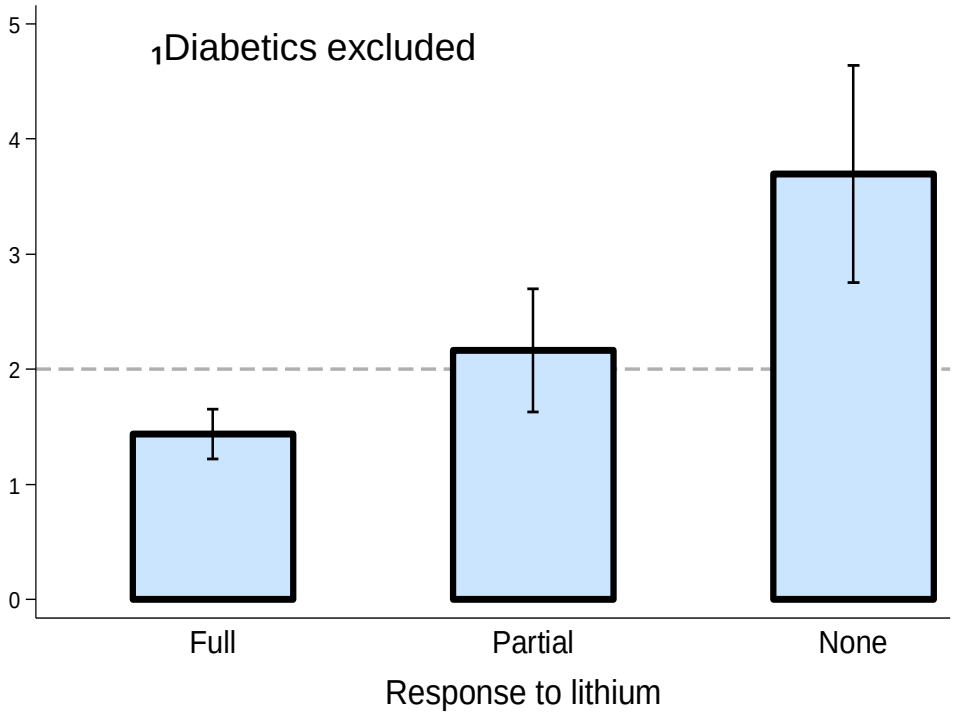
Response to lithium

Variable (n=80)	No response	Partial response	Full response
Euglycemic	3.2%	41.9%	54.8%
IR/GI	36.7%	40.0%	23.3%
T2D	36.8%	42.1%	21.1%



Ordered logistic OR = 8.40 (95% CI 3.03 to 23.3, p<0.0001) Adjusted for age and sex

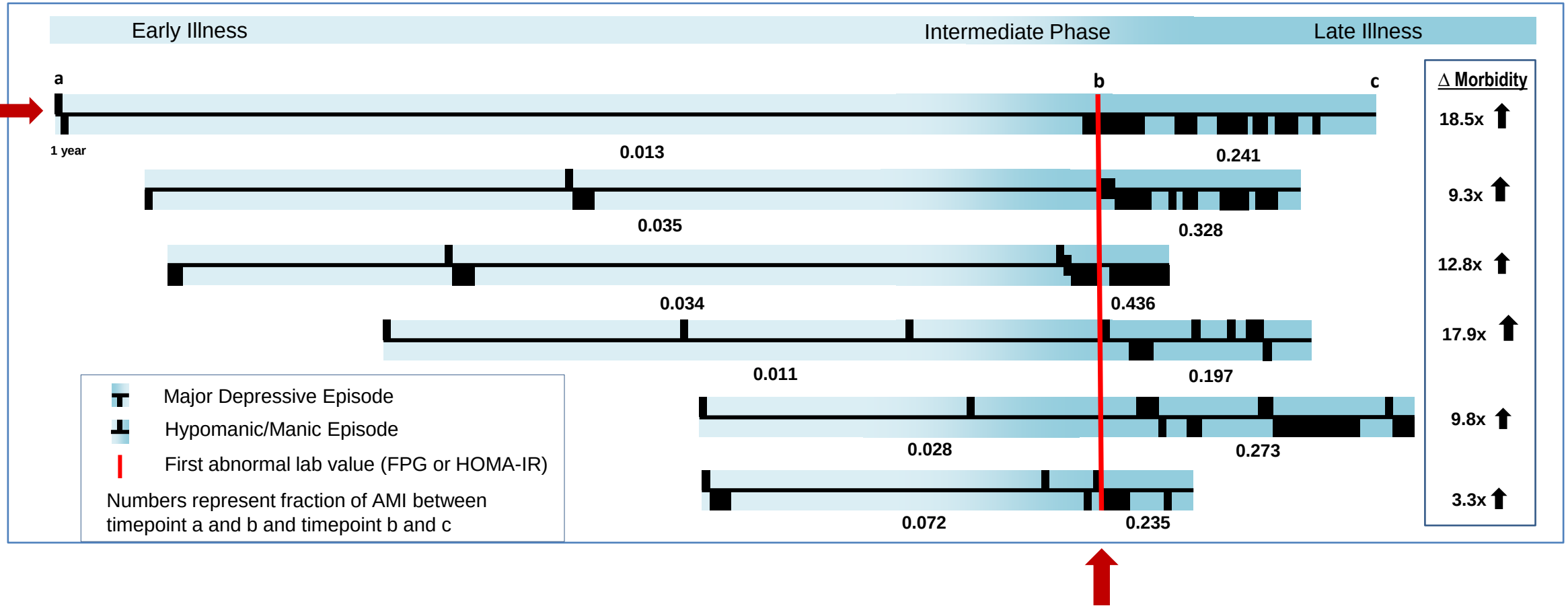
Insulin resistance and response to lithium$_1$



Ordered logistic OR=1.39 (95% CI 1.07 to 1.80, p=0.013), adjusted for age and sex

Calkin et al, B J Psych, 2015

Morbidity increases 12-fold following the development of IR



IR may modify the course of BD and promote neuroprogression

Cairns et al, J of Psych Res, 2018

TRIO-BD study: Treating insulin Resistance to Improve Outcome in BD

- Parallel-group, intent-to-treat, random-assignment (in a 1:1 ratio to metformin or placebo), quadruple-masked (patient, investigator, outcomes assessor, statistician) study
- Two sites, Halifax, Canada, and Pittsburgh, USA, from February 2016 to October 2019

Calkin et al. J Clin Psych 2022

Hypothesis and Outcomes

- Compared to placebo, metformin would reverse IR significantly among TRBD patients, and the reversal of IR would result in significant improvement of TRBD and associated clinical outcomes

- Primary outcome: change in depression rating scores (MADRS) at 14 weeks between those who no longer met IR criteria (converters) vs those who still did (non-converters).

Calkin et al. J Clin Psych, 2022

Why metformin?

- Metformin is recommended worldwide as the first-line treatment for T2DM and is on the WHO's list of essential medicines

Rojas, Gomes *Diabet Metab Syndr*. 2013; WHO. Model list of essential medicines. 2019

- Increases insulin sensitivity, helps with weight loss, has an established safety profile (including during pregnancy) Rojas, Gomes *Diabet Metab Syndr*. 2013
- Already in use in psychiatric practice as a weight maintenance strategy for patients taking antipsychotics de Silva et al *BMC Psych*. 2016

Inclusion criteria

- Adults aged 18 years or older with DSM-5 BD I or II
- Unremitting depressive symptoms (MADRS score ≥ 15) ≥ 4 weeks despite optimal treatment.
- Optimal treatment = mood-stabilizing monotherapy or medication combinations at stable doses as per CANMAT 2013 guidelines ≥ 4 weeks.
- Insulin resistant, with HOMA-IR ≥ 1.8
- Homeostatic Model Assessment-Insulin-Resistance

$$\text{HOMA-IR} = \frac{\text{FPG (mmol/L) x FSI (µU/mL)}}{22.5}$$

Calkin et al. J Clin Psych, 2022

Treatment

- 500mg metformin (oral immediate-release) or identical-looking placebo x 1 week (1000mg/day), provided in blister packs
- Titrated to 1000mg metformin or placebo twice daily (2000mg/day), if tolerated, for 25 additional weeks.
- Slower titration was permitted for tolerability and all subjects were maintained on a minimum of 1500mg/day.
- Mood stabilizing treatment otherwise remained unchanged
- No subjects withdrew due to tolerability issues or lack of compliance
- Adherence as measured by returned pill counts was 97% for both treatment groups.

Calkin et al. J Clin Psych, 2022

Table 1: Demographic and Illness Characteristics – TRIO-BD Study

	All		Metformin		Placebo	
Number of Subjects	45		20		25	
Men/Women	11/34		6/14		5/20	
Race						
White	42		19		23	
Black	3		1		2	
Other	1		0		1	
	Mean	SD	Mean	SD	Mean	SD
Age in years	47.53	11.53	48.75	10.65	46.56	12.31
Age at onset in years	21.89	9.36	22.85	10.31	21.12	8.68
Duration of illness in years	25.6	11.6	25.9	10.9	25.4	12.2
Number of failed medication trials (lifetime)	8.6	3.6	9.2	4.0	8.2	3.3

Average BMI 34.1

Calkin et al. J Clin Psych, 2022

Results: Illness characteristics

- 91.2% of patients failed drug trials from at least 3 psychotropic drug classes (lithium, anti-epileptics, antipsychotics, antidepressants)
- 55.6% failing drugs from all four drug classes
- MADRS mean scores >28 (moderate, bordering on severe depression)

Müller et al. *J Affect Disord*. 2003

- GAF mean scores <50 (serious symptoms and/or impairment in social/occupational functioning)

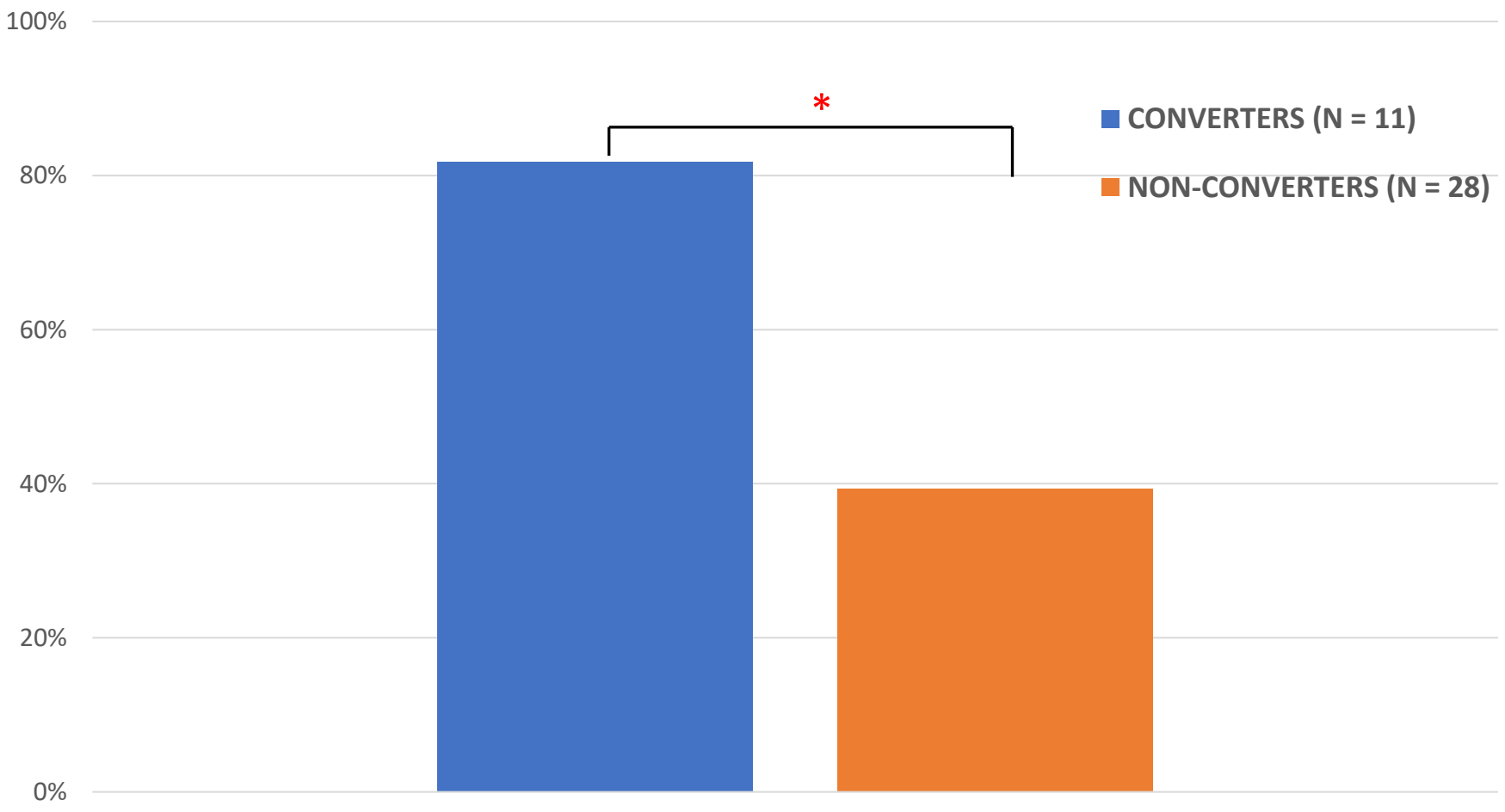
American Psychiatric Association. *DSM-III-R Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed., r.; 1987.

Converters

- Converters were defined as having reversed insulin resistance (HOMA-IR < 1.8)
- Ten metformin-treated patients (50%) no longer met IR criteria (became “converters”) at week 14, the primary outcome endpoint, compared to one (4%) placebo-assigned patient (Fisher exact p=0.0009).

Calkin et al. J Clin Psych, 2022

MADRS Responders by Insulin Resistance Conversion Status at Week 14



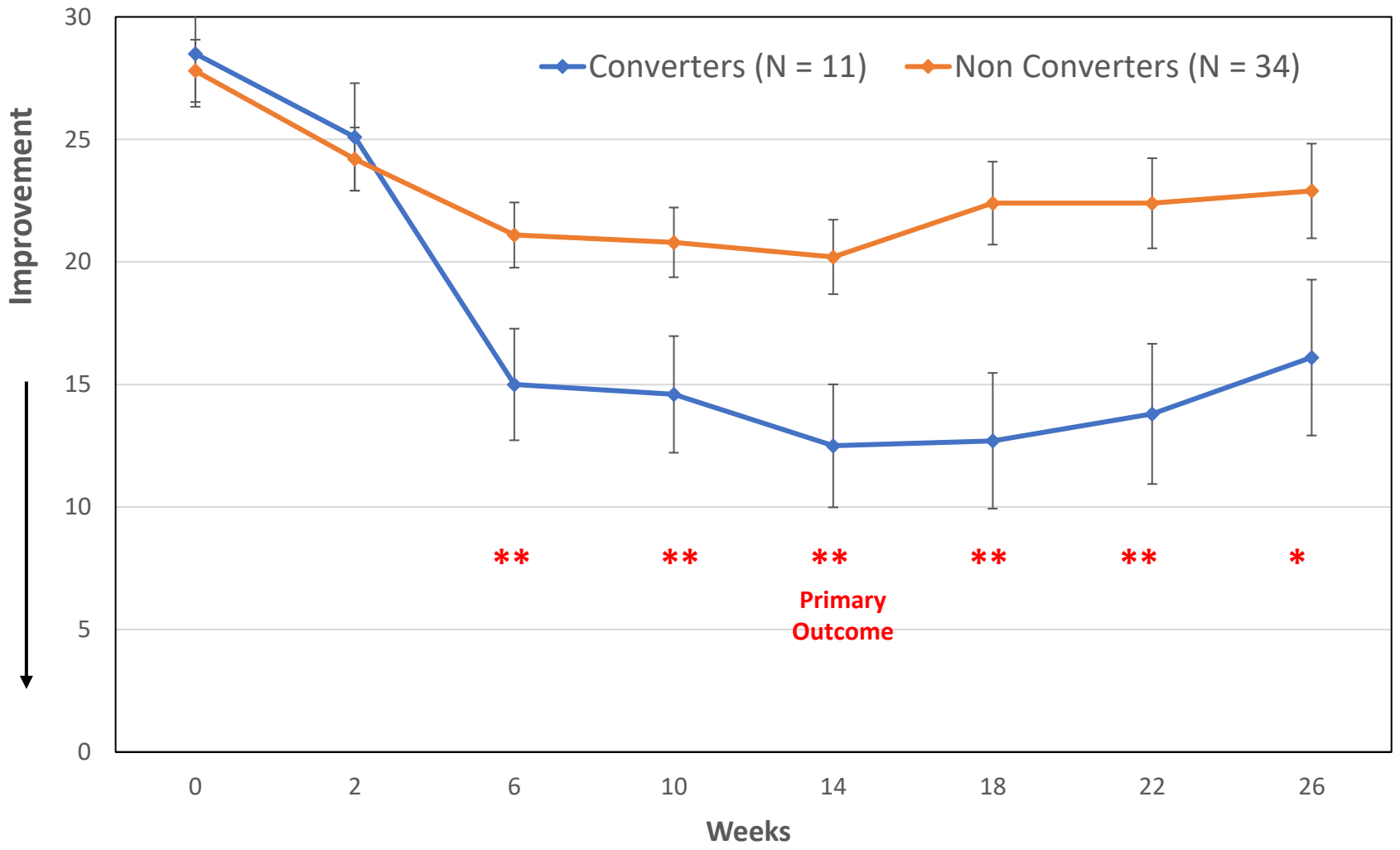
* Fisher's exact test p = 0.031

Responder: ≥ 30% reduction of baseline MADRS total scores by week 14

Calkin et al. J Clin Psych, 2022

TRIO-BD study

Estimated Marginal Mean Changes from Baseline in Montgomery–Åsberg Depression Rating Scale Scores Between Converters and Non-Converters



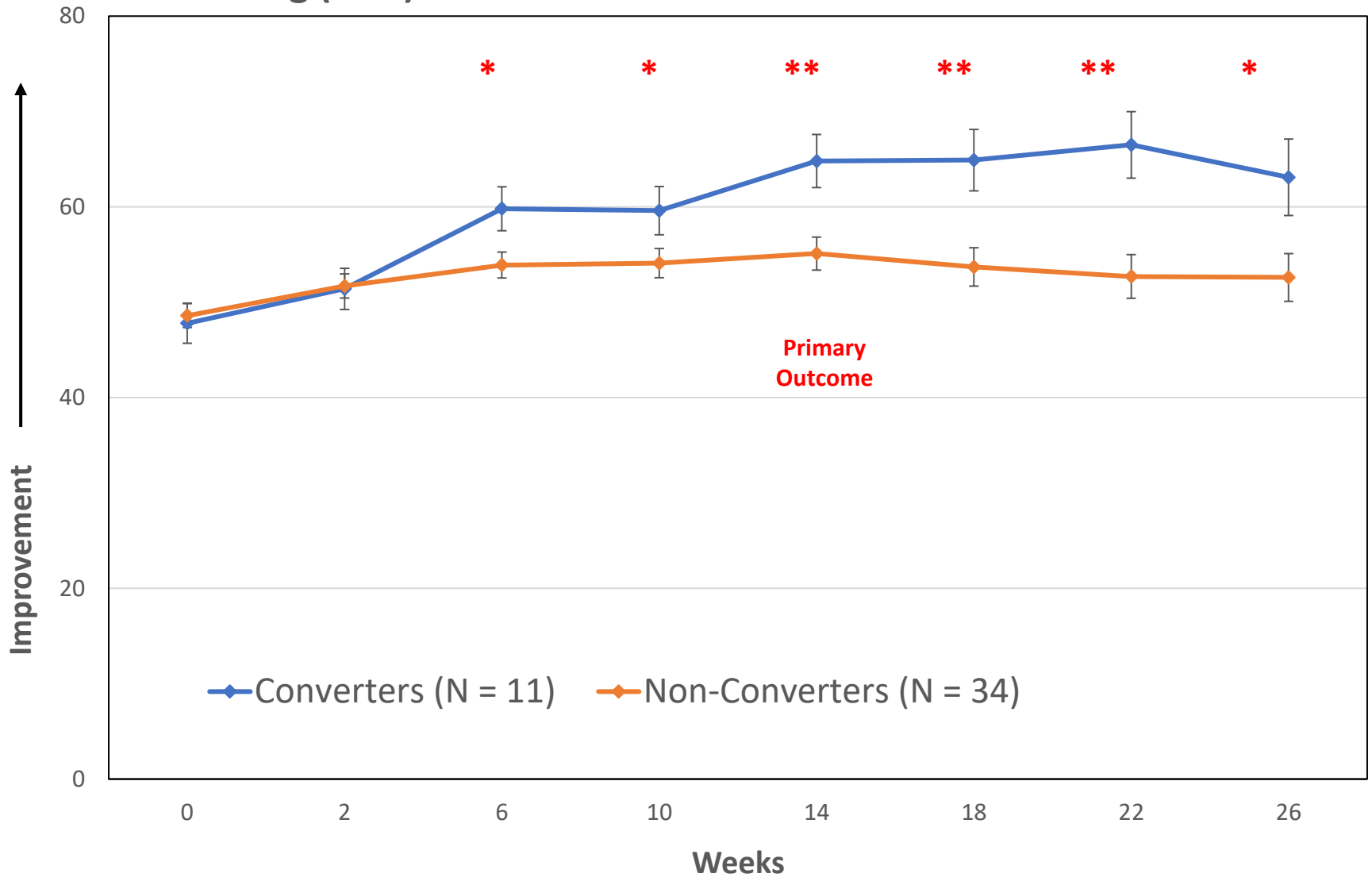
** p = 0.002 to 0.008
* p = 0.031

Mixed model analyses adjusted for treatment, site, age, age at onset, marital status, baseline Montgomery–Åsberg Depression Rating Scale (MADRS) scores, conversion status at week 14, conversion status x weeks of treatment. Bars at time-points represent standard error at each time-point

Calkin et al. J Clin Psych, 2022

TRIO-BD study

Estimated Marginal Mean Changes from Baseline in Global Assessment of Functioning (GAF) Scale Scores Between Converters and Non-Converters



* p = 0.045 to 0.018
** p = 0.002 to 0.008

Mixed model analyses adjusted for treatment, site, age, age at onset, marital status, baseline Global assessment of Functioning (GAF) scores, conversion status at week 14, conversion status x weeks of treatment. Bars represent error bars at each time-point

Calkin et al. J Clin Psych, 2022

Conclusions

Reversal of insulin resistance:

- significantly improves depressive and anxiety symptoms and general functioning in a significant percentage of TRBD patients in both the short and intermediate term

Calkin et al. J Clin Psych, 2022

How might a metabolic problem influence a psychiatric one?

- IR /T2D and BD likely share underlying pathophysiology including genetic and epigenetic mechanisms

Calkin et al Annals of Med 2012

- BD may be a manifestation of a systemic illness; one affecting the brain as well as a number of other organ systems likely mediated by metabolic / immune /inflammatory dysregulation

- Resulting endothelial dysfunction → BBBD

Hypotheses

1. Patients with extensive BBB leakage will also be IR

1. Bipolar patients with extensive BBB leakage will have a more neuroprogressive course of illness

2. Reversing IR will mitigate BBBD and facilitate remission

Research & Innovation

Linking biology and psychiatry

Halifax's world-leading study connects blood-brain barrier leakage and bipolar disorder symptoms

Allison Lawlor
Published: Oct. 15, 2020, 2 p.m.
Updated: Oct. 13, 2020, 6:48 p.m.

Conclusion

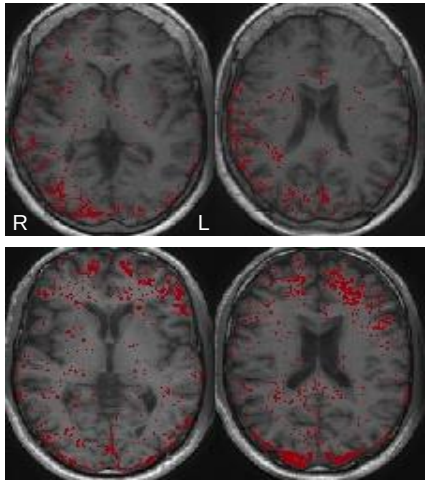
Extensive BBB leakage is a potential mechanism underlying neuroprogression in BD

Kamintsky et al, *Neuroimage: Clinical* 2019

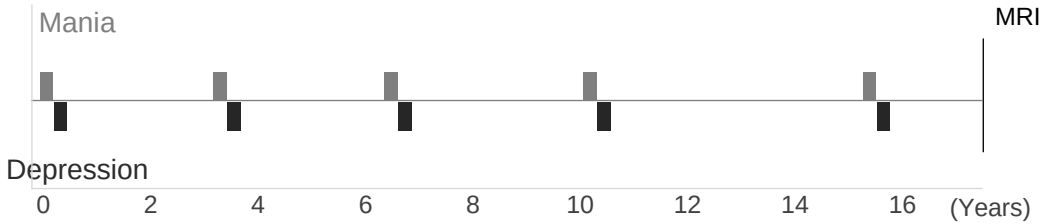
A team at the QEII and Dalhousie University, using research methods and software tools only available in Halifax, found that people with bipolar disorder and more extensive leakage to the blood-brain barrier had more severe depression and anxiety and were more resistant to medicines used to treat the disorder. The high-resolution results of patient scans from the QEII's 3T MRI — funded by the QEII Foundation — allow for precisely detecting blood-brain barrier leakage. – Darren Hubley

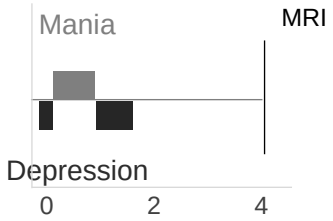
Course of illness and BBB leakage

Normal BBB leakage

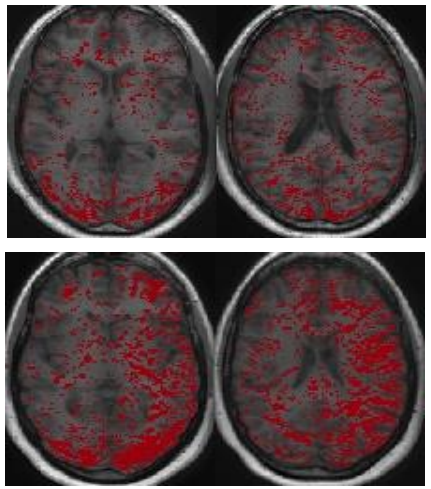


Course of illness

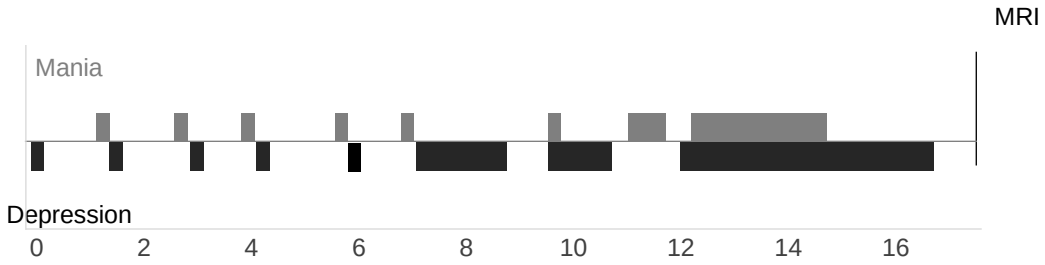


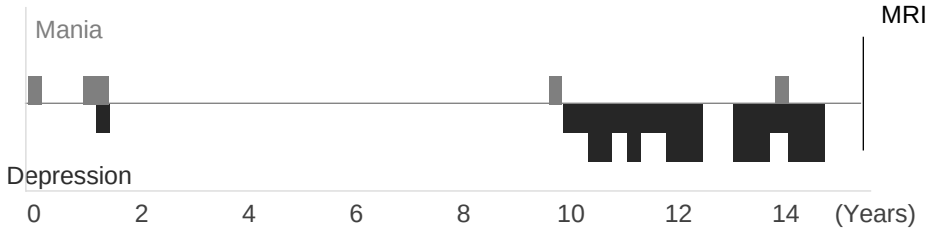


Extensive BBB leakage



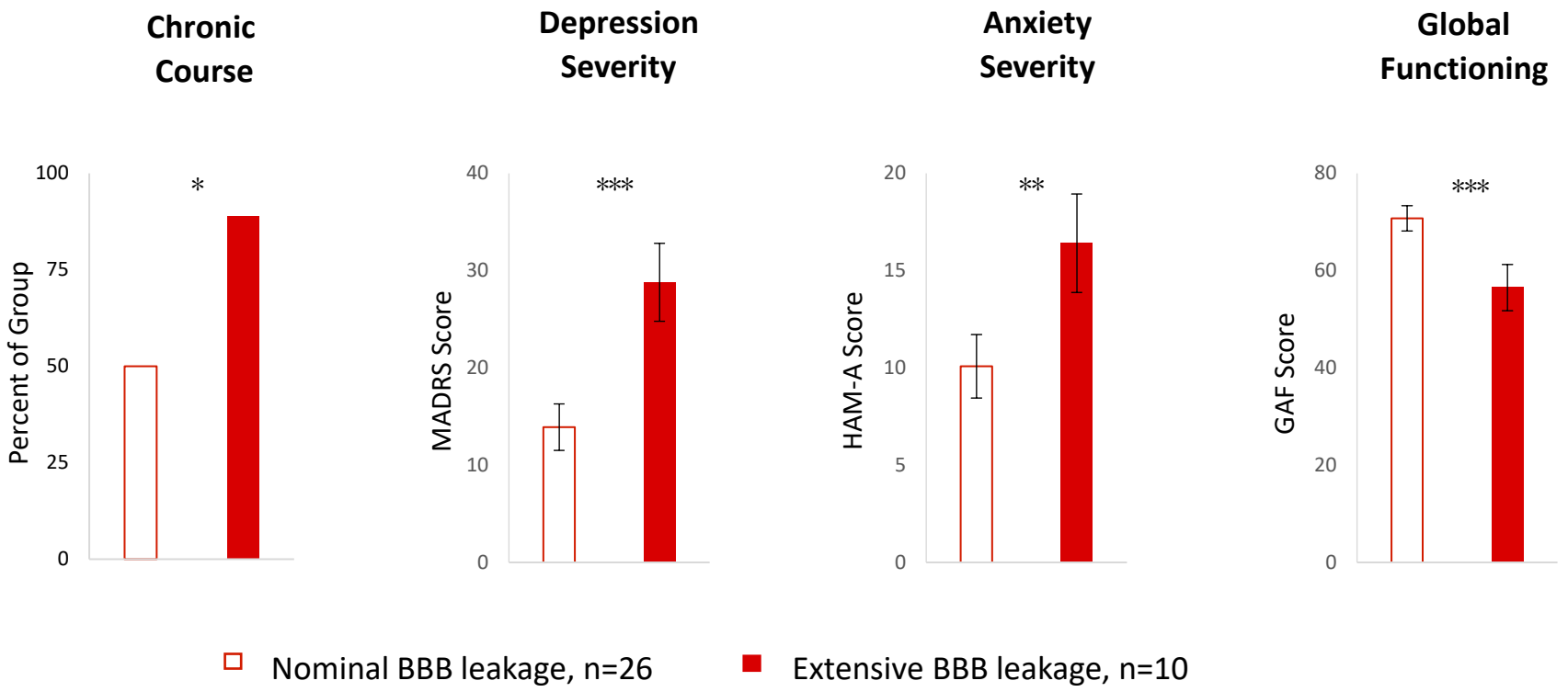
Course of illness





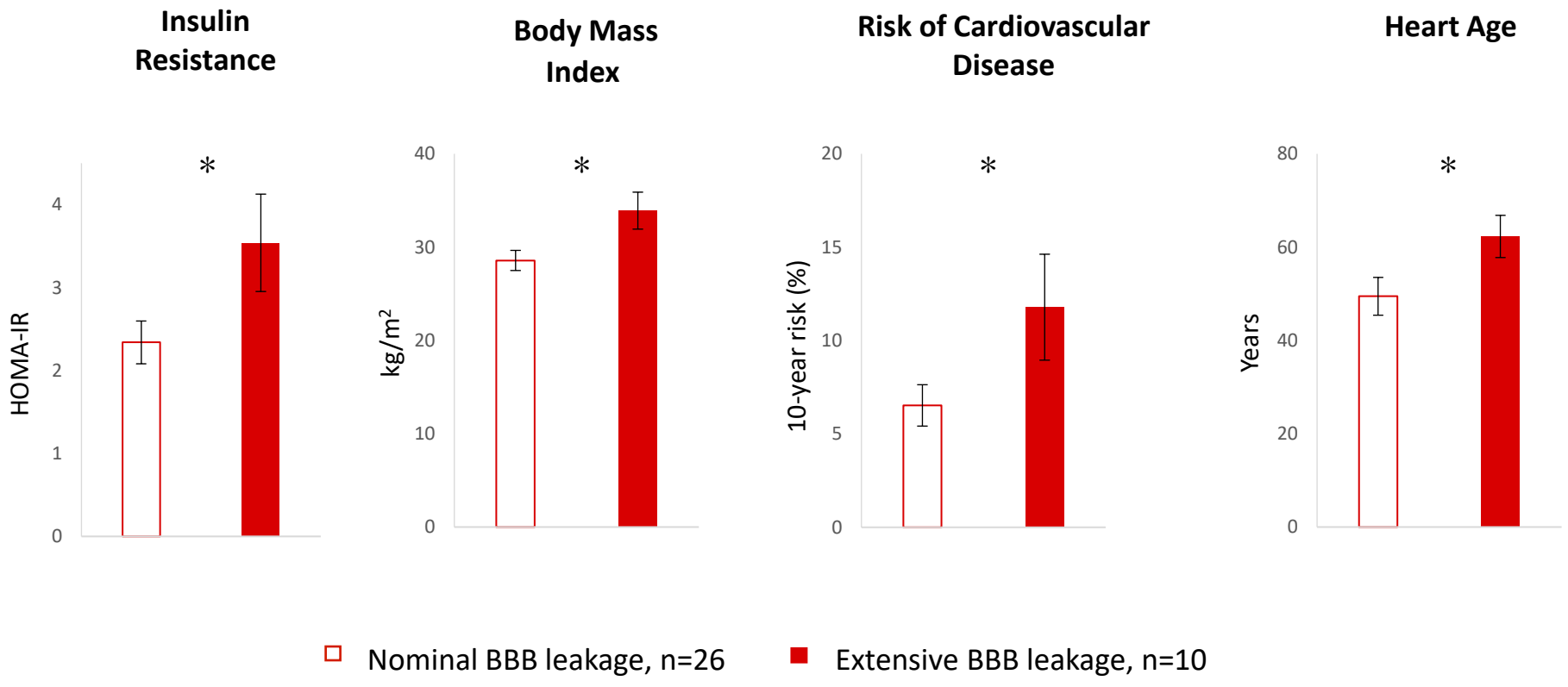
Kamintsky et al, *Neuroimage: Clinical* 2019

Bipolar patients with extensive blood-brain barrier leakage had a more chronic course, and more severe depression, anxiety, and poorer overall functioning.



Kamintsky et al, *Neuroimage: Clinical* 2019

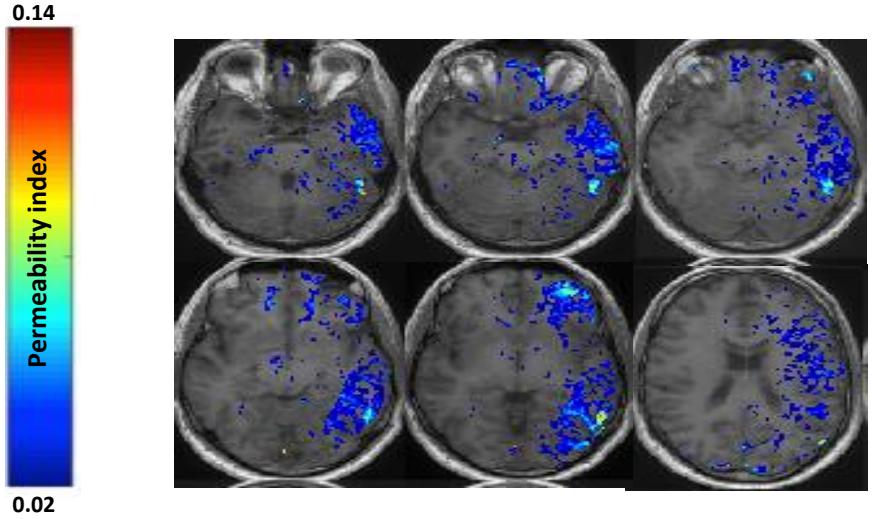
Extensive blood-brain barrier leakage in bipolar patients is associated with insulin resistance, higher BMI, elevated risk of cardiovascular disease, and advanced heart age.



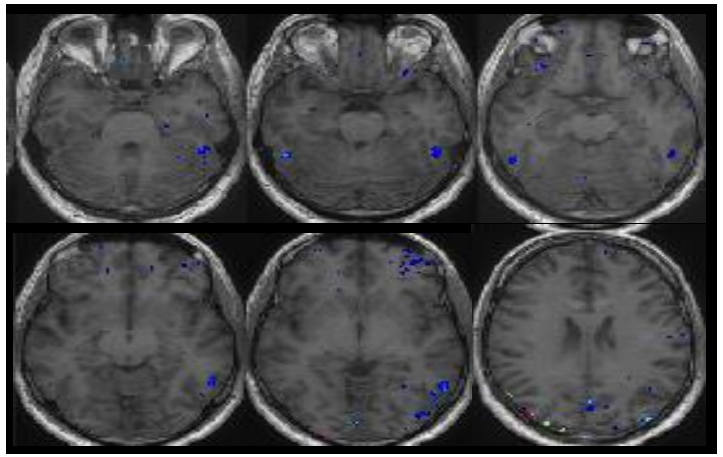
Kamintsky et al, *Neuroimage: Clinical* 2019

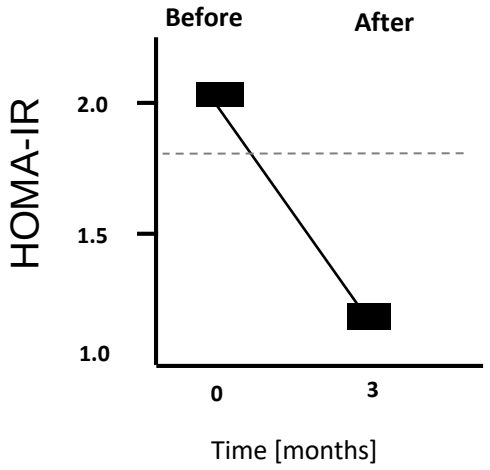
Metformin reverses IR, BBBD and depression in a BD+IR patient with previously non-remitting depression

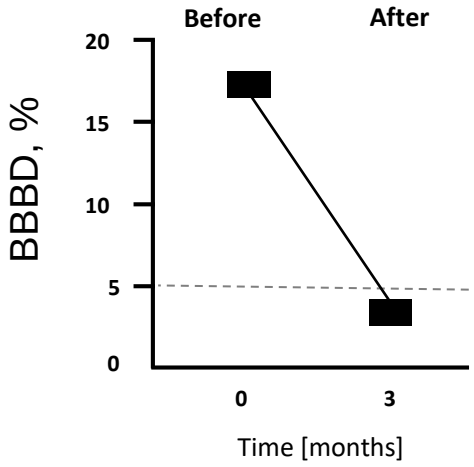
Prior to off-label treatment with metformin

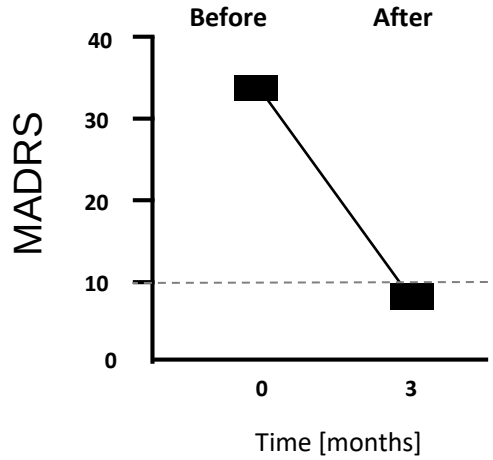


After 3 months treatment with metformin









Calkin et al, Bipolar Disorders, 2022

Future perspectives

- BBB study run in parallel with TRIO-BD study
- We have discovered a mechanism by which BD patients develop neuroprogression, but we also hope to discover an effective treatment

- Can we reduce BBBD/ reverse neuroprogression using:
  - Insulin sensitizing treatment?
  - Weight loss?
  - Vascular-protective drugs?

Our off-label approach to treatment resistant bipolar disorder

- Metformin
- Semaglutide
- Pioglitazone
- Telmisartan