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Hypertension, depression and bipolar disorder - what's the link?

Daniel Smith

Professor of Psychiatry



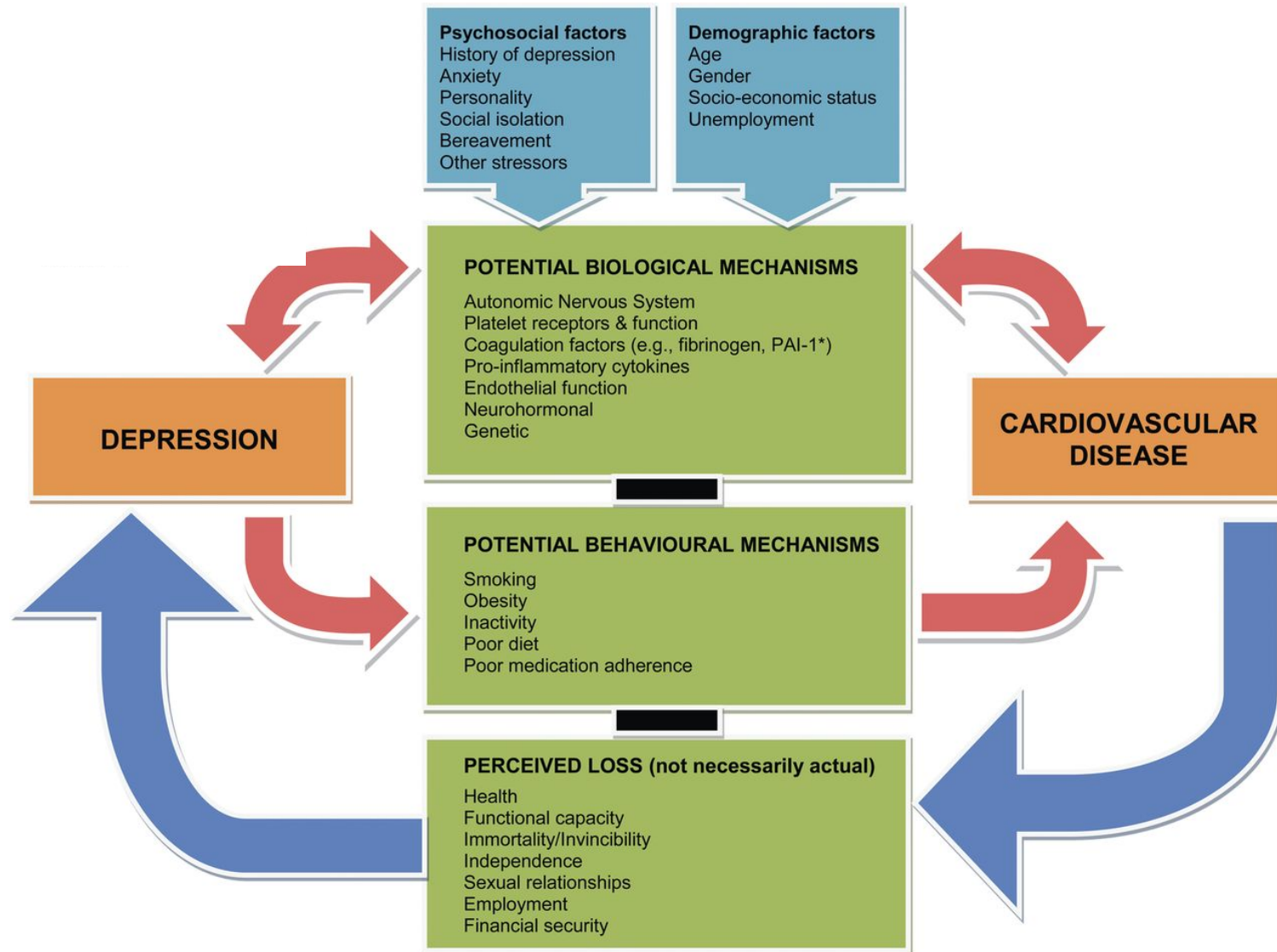


Outline:

- Clinical epidemiology of mood disorders and hypertension
- Is there a shared biology between mood disorders and hypertension?
- Do antihypertensive medications prevent depression?
- Research example: identifying repurposed medications for mood disorders

Depression and cardiovascular disease (CVD):

- Currently the two most common causes of disability in high-income countries
- By 2030, will be the two most common causes of disability globally
- Depression is a risk factor for CVD (and *vice versa*)
- Depression after a heart attack substantially increases risk of death





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High blood pressure and depression – what's the link?



Depression (MDD), bipolar disorder (BD) and hypertension:

- One third of patients with hypertension report a lifetime history of MDD (compared to 15% in general population)
- Individuals with MDD and BD have increased risk of hypertension (1.5-2.5 times the risk in controls)
- MDD is an independent predictor of new-onset hypertension and *vice versa*
- Side-effects of many antihypertensive medications include alterations in mood (both depression and manic symptoms)



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BRIEF COMMUNICATIONS

nature
genetics

Collaborative genome-wide
association analysis supports a
role for *ANK3* and *CACNA1C* in
bipolar disorder

Manuel A R Ferreira¹⁻⁶, Michael C O'Donovan⁷, Ya

L-type voltage-gated calcium channel; combined $P = 7.0 \times 10^{-8}$, rs1006737). Our results suggest that ion channelopathies may be involved in the pathogenesis of bipolar disorder.

Recent genome-wide association studies (GWAS) have identified

LETTERS

nature
genetics

Large-scale genome-wide association analysis of bipolar
disorder identifies a new susceptibility locus near *ODZ4*

Psychiatric GWAS Consortium Bipolar Disorder Working Group¹



BRIEF REPORTS

Verapamil for the Treatment of Acute Mania: A Double-Blind, Placebo-Controlled Trial

Philip G. Janicak, M.D., Rajiv P. Sharma, M.D.,
Ghanshyam Pandey, Ph.D., and John M. Davis, M.D.

***Objective:** This study investigated the efficacy of verapamil in acute mania. **Method:** The study was a 3-week double-blind, random-assignment, parallel-group, placebo-controlled inpatient trial of verapamil for patients with acute mania. Of the 32 study patients, 15 were given placebo and 17 were given verapamil. **Results:** Mean absolute change scores on the Mania Rating Scale at endpoint, with baseline scores as the covariates, did not differ between the verapamil and placebo groups. There were no significant differences between the two groups in age, sex, and presence of psychosis. **Conclusions:** The investigators found no benefit of verapamil over placebo in treating acute mania.*

(Am J Psychiatry 1998; 155:972-973)



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Brief Report

Pilot investigation of isradipine in the treatment of bipolar depression motivated by genome-wide association

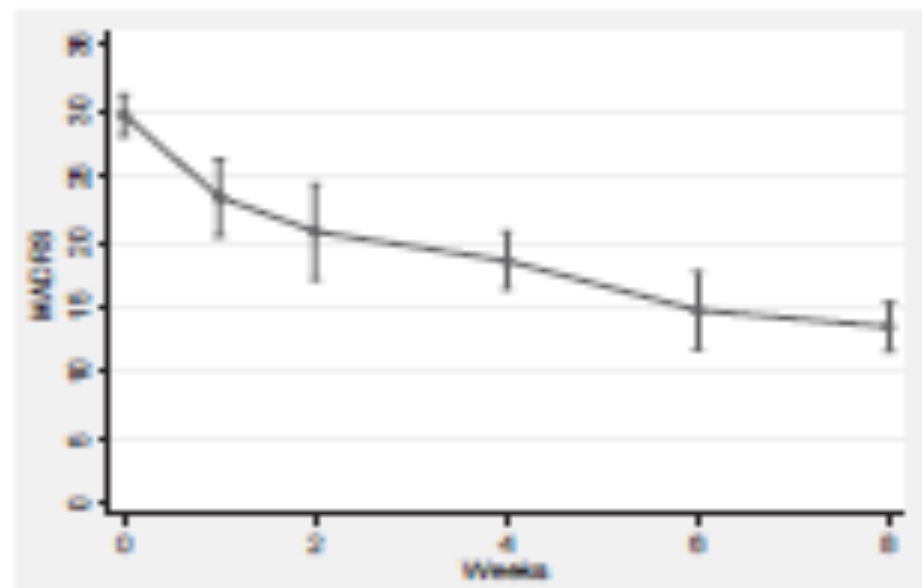
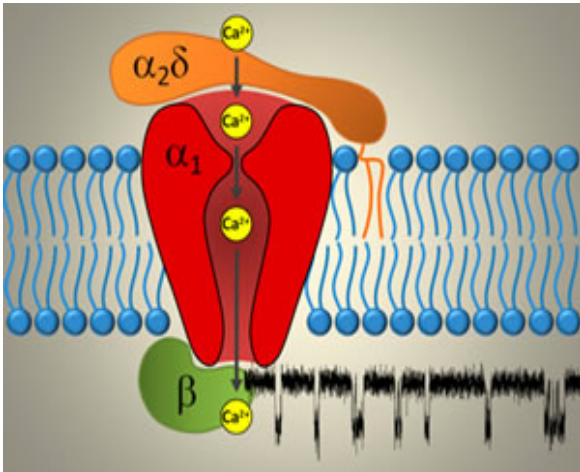


Fig. 2. Change in Montgomery-Åsberg Rating Scale (MADRS) score with isradipine treatment.

Abnormal calcium signalling in bipolar disorder:



- GWAS findings, eg, CACNA1C.
- Potential use of calcium-channel blockers
- Lithium may act therapeutically by modulating intracellular calcium homeostasis

BUT:

- In animal models, drugs acting on the renin-angiotensin system (such as ACE-inhibitors) have antidepressant properties
- Long history of captopril (ACE-inhibitor) causing mania



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EXPERT REVIEW

A systematic review of calcium channel antagonists in bipolar disorder and some considerations for their future development

A Cipriani^{1,2}, K Saunders^{1,2}, M-J Attenburrow^{1,2}, J Stefaniak¹, P Panchal^{1,2}, S Stockton^{1,2}, TA Lane¹, EM Tunbridge^{1,2}, JR Geddes^{1,2} and PJ Harrison^{1,2}

L-type calcium-channel (LTCC) antagonists as repurposed treatments for bipolar disorder:

- *CACNA1C* locus also shows genome-wide association to working memory and sleep quality
- Other LTCC subunit genes also show genome-wide association to bipolar disorder
- Rare variants in LTCC subunit genes are associated with bipolar disorder
- Neuron-like cells derived from bipolar disorder patients have altered calcium signaling
- Neuron-like cells derived from subjects with the *CACNA1C* risk genotype have increased gene expression and *enhanced calcium signaling*



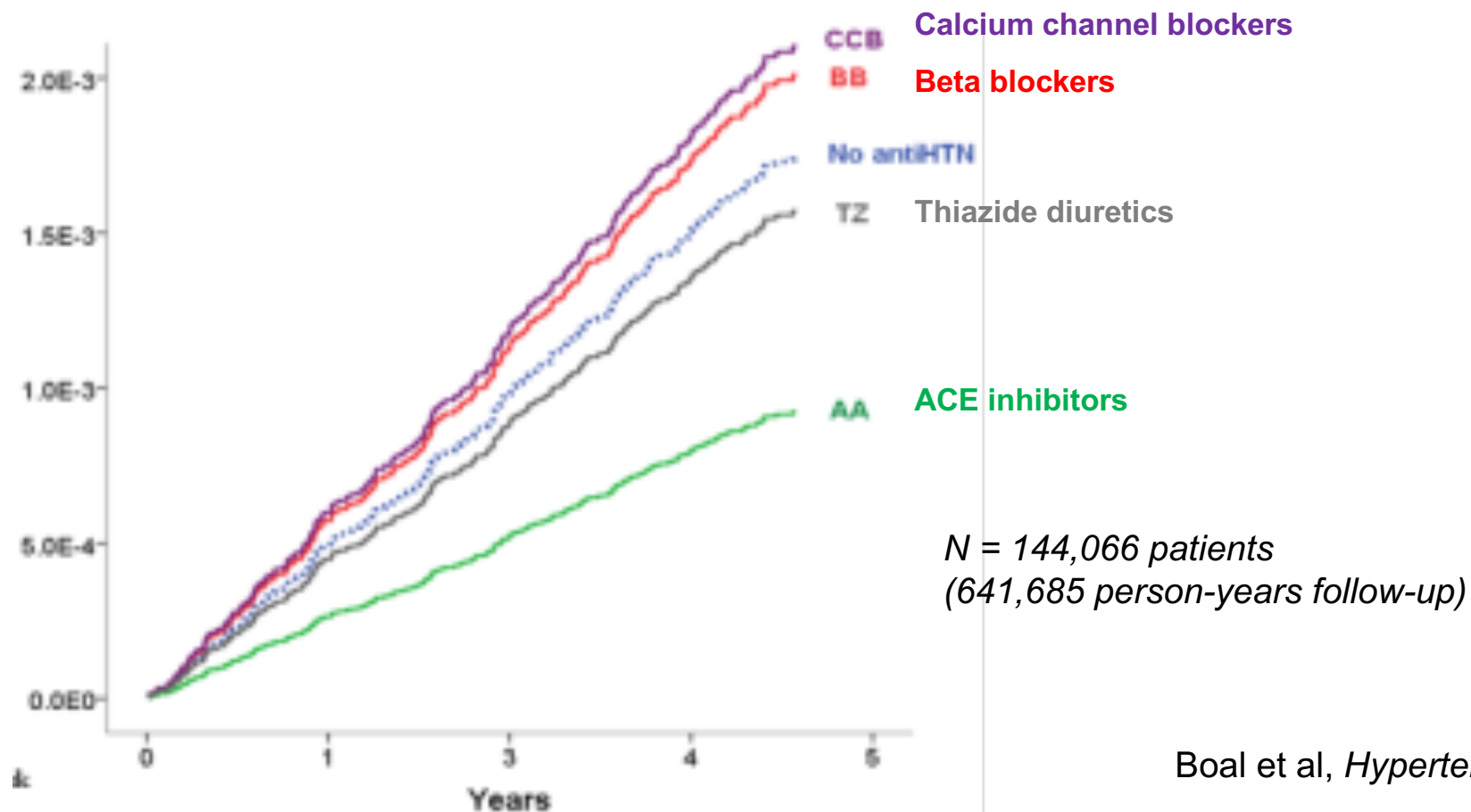
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Monotherapy With Major Antihypertensive Drug Classes and Risk of Hospital Admissions for Mood Disorders

Angela H. Boal, Daniel J. Smith, Linsay McCallum, Scott Muir, Rhian M. Touyz, Anna F. Dominiczak, Sandosh Padmanabhan



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Model	NoAntiHTN	AA	BB	CCB	TZ
Events/total, N	228/111 936	14/10 814	31/11 605	18/5880	8/3831
Person-years follow-up	523 887	38 570	43 343	20 772	15 113
Model 1	1.22 (0.71–2.11)	1	1.93 (1.02–3.63)*	2.28 (1.13–4.59)*	1.29 (0.54–3.09)
Model 2	1.36 (0.79–2.35)	1	2.05 (1.09–3.87)*	2.29 (1.14–4.61)*	1.41 (0.59–3.36)
Model 3	1.89 (1.09–3.26)*	1	2.17 (1.16–4.09)*	2.27 (1.13–4.57)*	1.70 (0.71–4.07)
Model 4	1.63 (0.94–2.82)	1	2.11 (1.12–3.98)*	2.28 (1.13–4.58)*	1.56 (0.65–3.73)

Model 1 adjusted for age and sex

Model 2 adjusted for age, sex, and Charlson comorbidity index

Model 3 adjusted for age, sex, and Elixhauser comorbidity index

Model 4 adjusted for age, sex, and Elixhauser comorbidity index (excluding depression).



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Could your blood pressure pills be making YOU depressed? Common tablets 'double the risk of developing a mood disorder'

- 22% of adults globally suffer from raised blood pressure or 'hypertension'
- Previous research has linked cardiovascular disease to depression
- This study looked at the possible effects of medications on mood disorders
- Found beta blockers and calcium channel blockers increased the risk
- But blood pressure stabilisers ACE inhibitors and ARBs reduced chances

By [KATE PICKLES FOR MAILONLINE](#)

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Taking common blood pressure tablets could increase the risk of depression, a study has warned.




UK Biobank achievements so far

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UK Biobank: a global health resource

Genetic study targets smokers, lung disease

UK Biobank achievements so far

Participants

- [Update your contact details](#)
- [BBC – challenge of saving lives with Big Data](#)
- [Find out how the resource is being used](#)
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[General Practice linkage →](#)

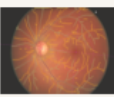
[Imaging study →](#)

[UK Biobank Annual Meeting 2016](#)


Scientists

- [Imaging data on 5,000 now available](#)
- [UK Biobank's cardiovascular MR protocol](#)
- [Video: How to Register and Apply](#)
- [UK Biobank Annual Meeting 2016](#)


News




Assessment measures provide insight into common eye disorders



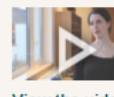
Health and thinking skills linked to same genes, study shows




A broken bone may lead to widespread body pain



New appointments to the UK Biobank Ethics & Governance Council



View the video: Study finds red meat link to bowel cancer



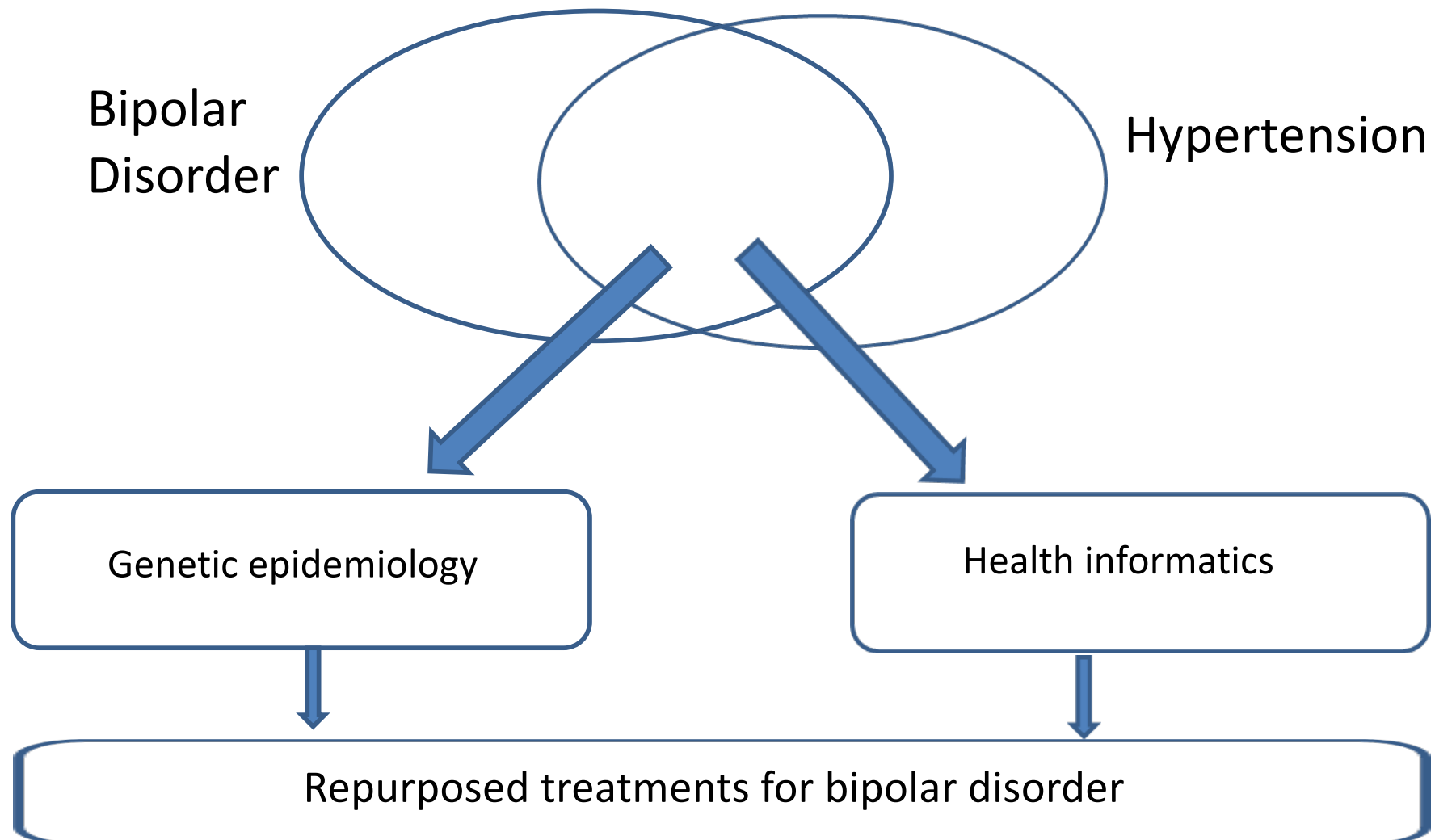
Impact of pregnancy and birth on future health



Outline:

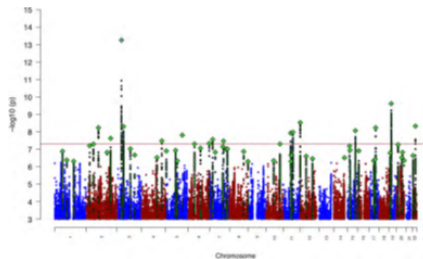
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Investigating the overlap between hypertension and bipolar disorder to identify repurposed medications for bipolar disorder



Genetic epidemiology research questions:

Identification of **genetic risk factors** for bipolar disorder, hypertension and comorbidity →



What is the extent of **shared heritability** between bipolar disorder and hypertension?

↓
Is there evidence of **pleiotropy**?

Which existing treatments can be **repurposed**?

↓
Does **pathway analysis** identify shared biological pathways between bipolar disorder and hypertension?



Health informatics research questions:

1. Does antihypertensive treatment improve psychiatric outcomes for people with bipolar disorder?
2. If yes, which class of antihypertensive?

Datasets:

- National-level routine clinical data linkage (>5m individuals)
- Local NHS cohort of bipolar disorder (n=2,500)

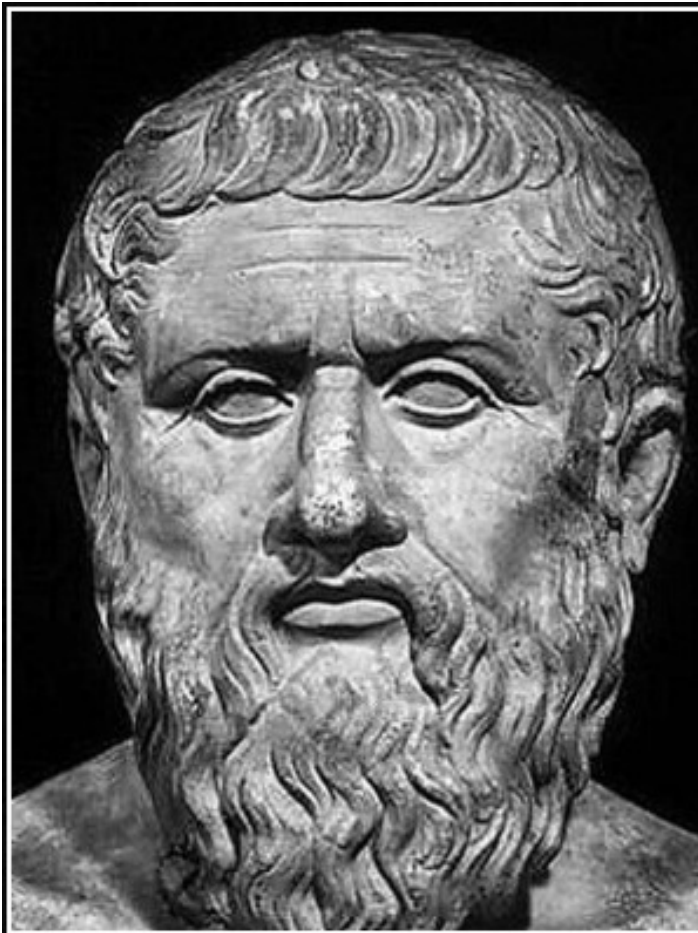


Summary

- Comorbidity between mood disorders and cardiovascular disease is a global public health priority
- The association is complex but is partly genetically-determined
- Understanding the shared clinical and genetic basis of comorbidity may lead to new and/or repurposed treatments for mood disorders



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The greatest mistake in the treatment of diseases is that there are physicians for the body and physicians for the soul, although the two cannot be separated.

— *Plato* —

AZ QUOTES

Thanks

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