UNIVERSITY OF OXFORD

Oxford Health
NHS Foundation Trust

Department of Psychiatry
Medical Sciences Division

Long term management of Bipolar Disorder

John Geddes

University of Oxford

Oxford Health Biomedical Research Centre
Improving brain health: the future in mind

NHS
National Institute for Health Research

Disclosure

- Funding from NIHR, MRC, philanthropy

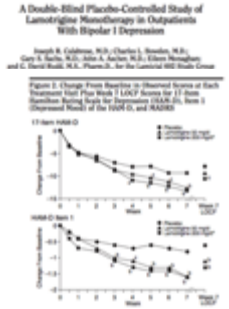
The problem

- Promising beginnings in 1950s
- Slow and uncoordinated
- Small scale, unambitious
- Failure to replicate or conduct key experiments.
- Lack of agreed targets
- Applies to psychological as well as drug therapy

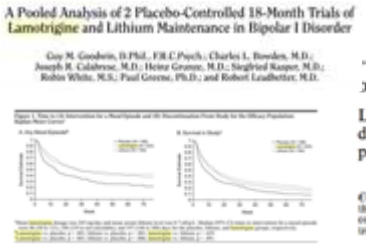
Medicines

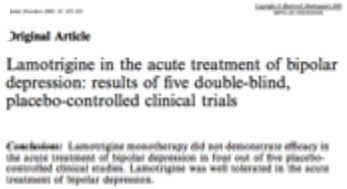
Synthesized

First RCT in BP



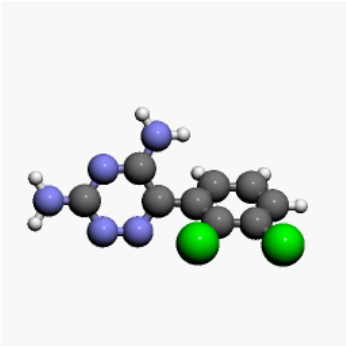
Approved in BP for maintenance





35 years….

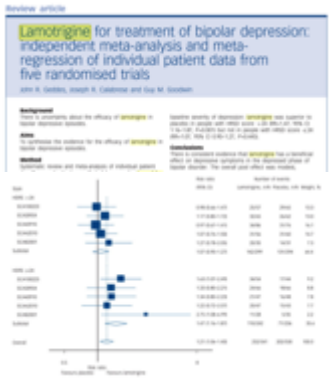
1980 → 1994 → 1999 → 2004 → 2009 → 2015



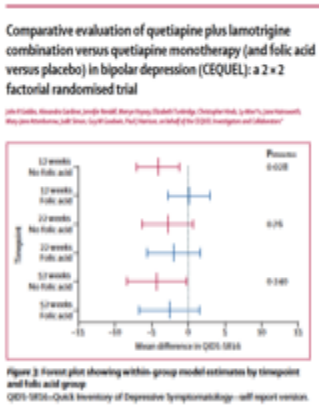
Approved for epilepsy

First report of efficacy in bipolar depression

IPD metaanalysis

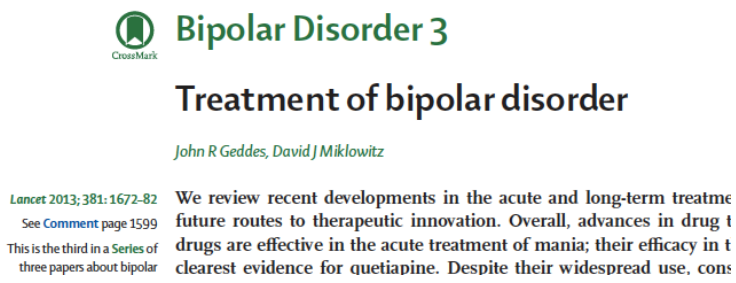


CEQUEL



Lamotrigine

Lithium remains the only bipolar specific drug treatment



Bipolar Disorder 3

Treatment of bipolar disorder

John R Geddes, David J Miklowitz

Lancet 2013; 381: 1672–82

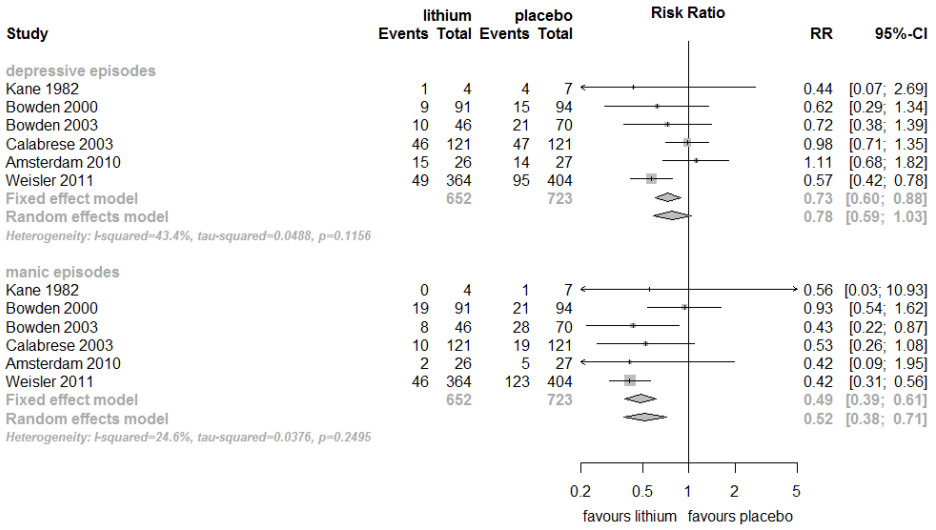
See Comment page 1599

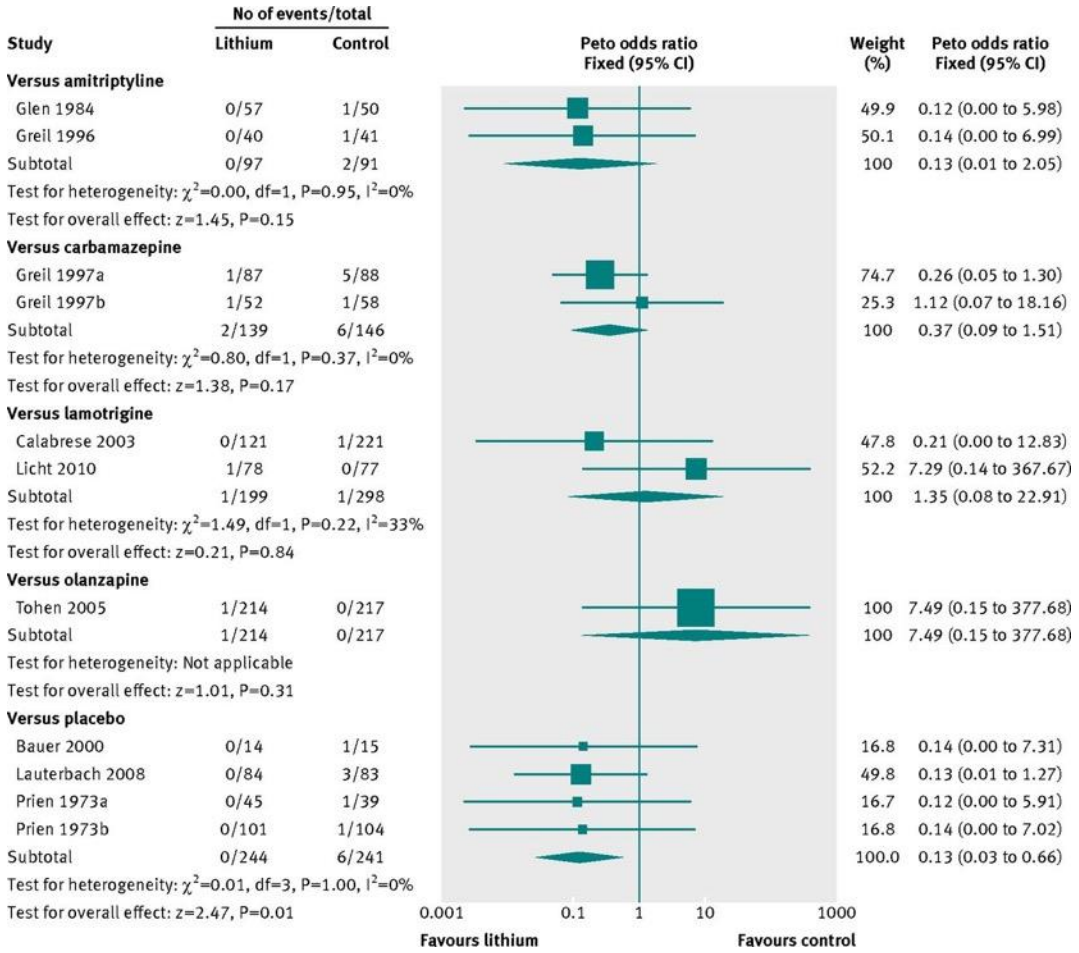
This is the third in a Series of three papers about bipolar

We review recent developments in the acute and long-term treatme future routes to therapeutic innovation. Overall, advances in drug t drugs are effective in the acute treatment of mania; their efficacy in t clearest evidence for quetiapine. Despite their widespread use, cons

- Unknown MOA
- Intracellular signalling
  - Inositol monophosphatase inhibition
  - Glycogen synthase kinase 3 (GSK-3) inhibition
  - Protein kinase C pathway inhihibition

Mania, depression, suicide





Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial

*The BALANCE investigators and collaborators**

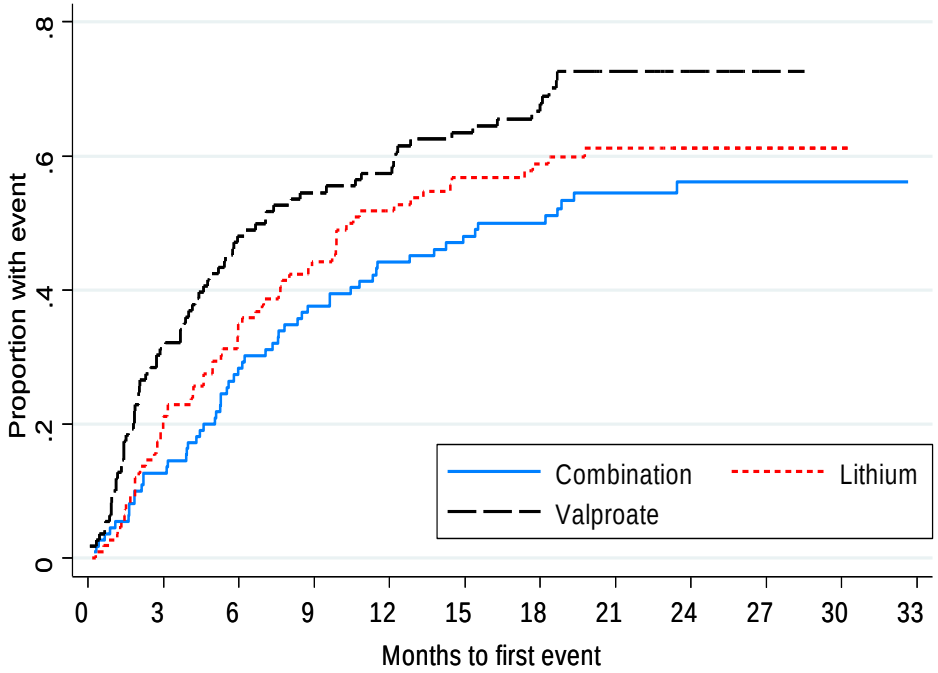
Summary

Background Lithium carbonate and valproate semisodium are both recommended as monotherapy for prevention of relapse in bipolar disorder, but are not individually fully effective in many patients. If combination therapy with both agents is better than monotherapy, many relapses and consequent disability could be avoided. We aimed to establish whether lithium plus valproate was better than monotherapy with either drug alone for relapse prevention in bipolar I disorder.

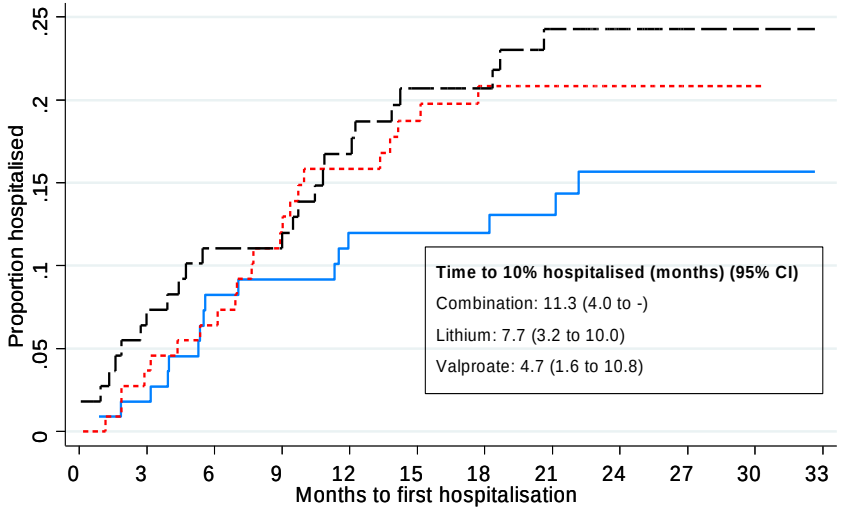
Methods 330 patients aged 16 years and older with bipolar I disorder from 41 sites in the UK, France, USA, and Italy were randomly allocated to open-label lithium monotherapy (plasma concentration 0·4–1·0 mmol/L, n=110), valproate monotherapy (750–1250 mg, n=110), or both agents in combination (n=110), after an active run-in of 4–8 weeks on the combination. Randomisation was by computer program, and investigators and participants were informed of treatment allocation. All outcome events were considered by the trial management team, who were masked to treatment assignment. Participants were followed up for up to 24 months. The primary outcome was initiation of

Published Online December 23, 2009
DOI:10.1016/S0140-6736(09)61828-6
See Online/Comment DOI:10.1016/S0140-6736(09)61970-X

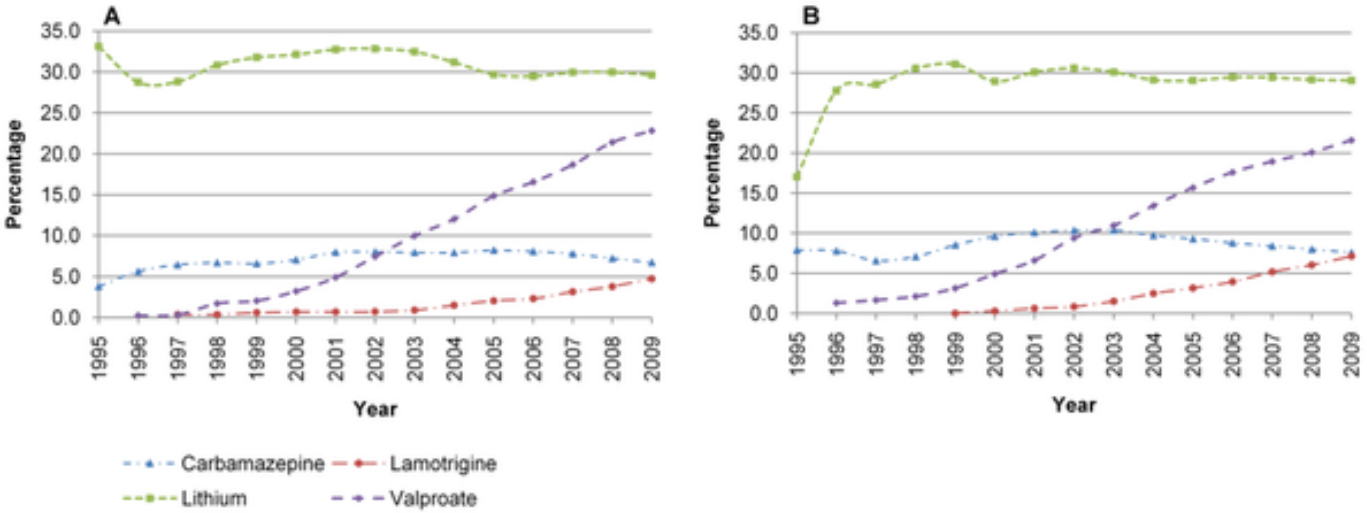
*Members listed at end of paper
Correspondence to: Prof John R Geddes, Oxford Clinical Trials Unit for Mental Illness, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford OX3 7JX, UK

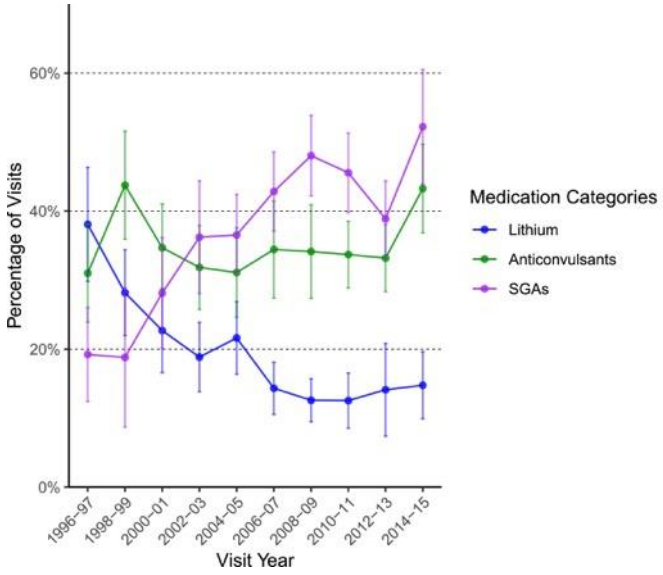


At risk (events):												
Combination	110 (14)	96 (17)	77 (10)	67 (7)	59 (4)	53 (2)	47 (4)	36 (1)	20 (0)	2 (0)	1 (0)	0
Lithium	110 (23)	86 (15)	70 (10)	59 (8)	50 (5)	43 (2)	39 (2)	30 (0)	12 (0)	1 (0)	1 (0)	0
Valproate	110 (34)	74 (18)	56 (7)	48 (3)	42 (6)	36 (3)	29 (5)	17 (0)	6 (0)	1 (0)	0 (0)	0



At risk (events):												
Combination	110 (2)	108 (7)	99 (1)	98 (3)	93 (0)	89 (0)	81 (1)	69 (2)	29 (0)	2 (0)	1 (0)	0
Lithium	110 (4)	105 (3)	101 (6)	92 (4)	87 (3)	81 (2)	71 (0)	61 (0)	21 (0)	2 (0)	1 (0)	0
Valproate	110 (8)	100 (4)	96 (0)	95 (6)	85 (4)	78 (0)	70 (3)	57 (0)	22 (0)	3 (0)	1 (0)	0





Hayes J, Prah P, Nazareth I, King M, Walters K, et al. (2011) Prescribing Trends in Bipolar Disorder: Cohort Study in the United Kingdom THIN Primary Care Database 1995–2009. PLOS ONE 6(12): e28725. https://doi.org/10.1371/journal.pone.0028725 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0028725

Lin, Mojtabai, Goes, Zandi,

Trends in prescriptions of lithium and other medications for patients with bipolar disorder in office-based practices in the United States: 1996–2015, Journal of Affective Disorders, 276, 2020, 883-889

Lithium toxicity profile: a systematic review and meta-analysis

Rebecca F McKnight, Marc Adida, Katie Budge, Sarah Stockton, Guy M Goodwin, John R Geddes

Lancet 2012; 379: 721–28

Published Online January 20, 2012 DOI:10.1016/S0140-6736(11)61516-X

See Comment page 690

Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford

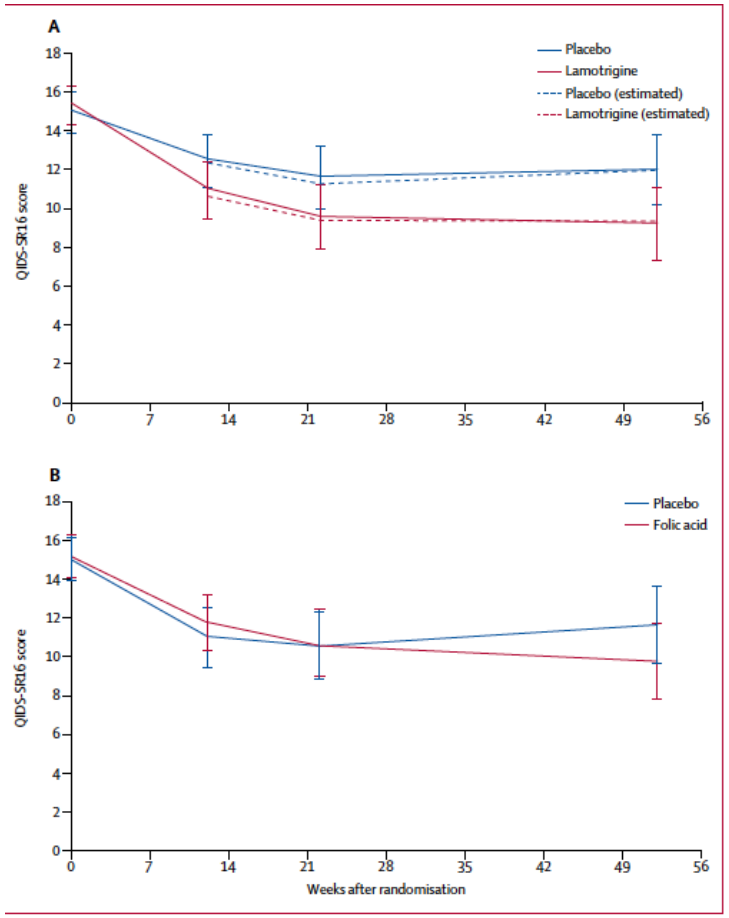
Summary

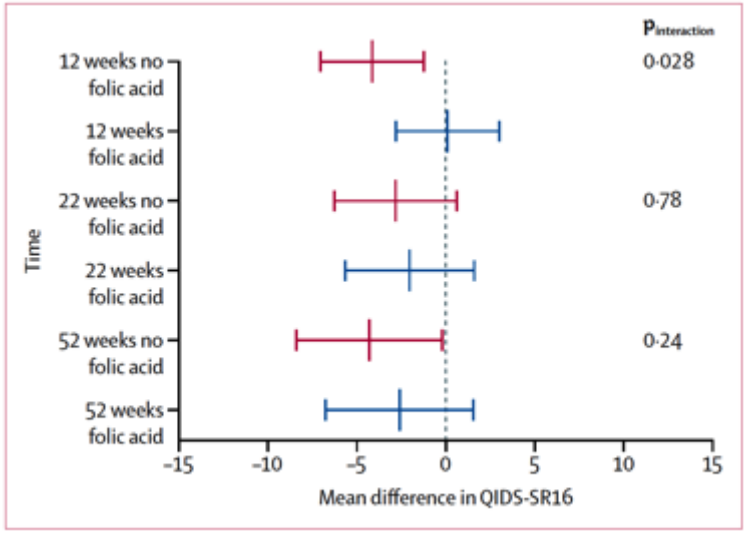
Background Lithium is a widely used and effective treatment for mood disorders. There has been concern about its safety but no adequate synthesis of the evidence for adverse effects. We aimed to undertake a clinically informative, systematic toxicity profile of lithium.

Methods We undertook a systematic review and meta-analysis of randomised controlled trials and observational studies. We searched electronic databases, specialist journals, reference lists, textbooks, and conference abstracts. We used a hierarchy of evidence which considered randomised controlled trials, cohort studies, case-control studies, and case reports that included patients with mood disorders given lithium. Outcome measures were renal, thyroid, and

Comparative evaluation of quetiapine plus lamotrigine combination versus quetiapine monotherapy (and folic acid versus placebo) in bipolar depression (CEQUEL): a 2 × 2 factorial randomised trial

*John R Geddes, Alexandra Gardiner, Jennifer Rendell, Merryn Voysey, Elizabeth Tunbridge, Christopher Hinds, Ly-Mee Yu, Jane Hainsworth, Mary-Jane Attenburrow, Judit Simon, Guy M Goodwin, Paul J Harrison, on behalf of the CEQUEL Investigators and Collaborators**





Long term treatments – large scale evidence of uncertain quality

Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis

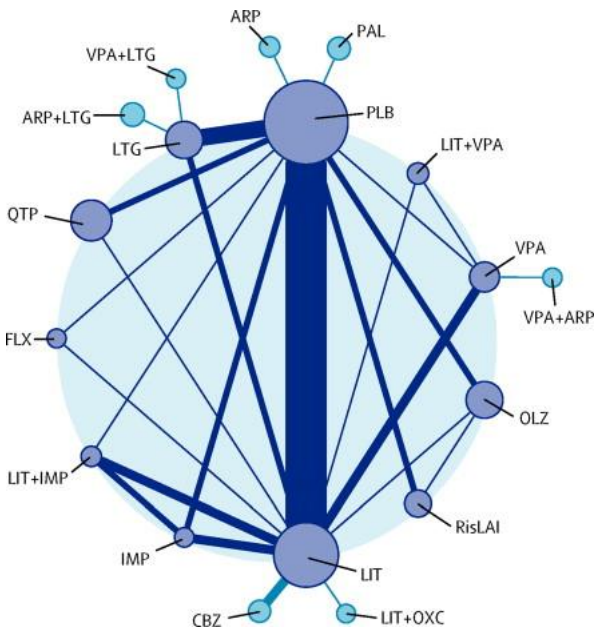
Tomofumi Miura, Hisashi Noma, Toshi A Furukawa, Hiroshi Mitsuyasu, Shiro Tanaka, Sarah Stockton, Georgia Salanti, Keisuke Motomura, Satomi Shimano-Katsuki, Stefan Leucht, Andrea Cipriani, John R Geddes, Shigenobu Kanba

Summary

Background Lithium is the established standard in the long-term treatment of bipolar disorder, but several new drugs have been assessed for this indication. We did a network meta-analysis to investigate the comparative efficacy and tolerability of available pharmacological treatment strategies for bipolar disorder.

Lancet Psychiatry 2014; 1: 351–59

Published Online September 16, 2014



- 522 trials
- 116477 participants

Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis

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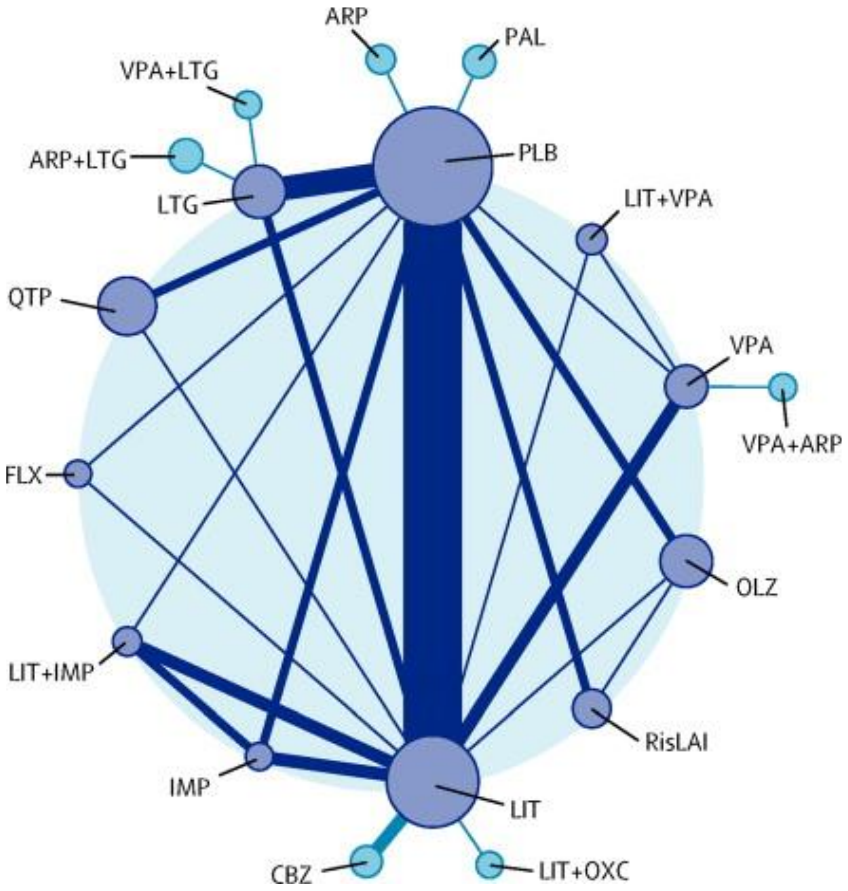
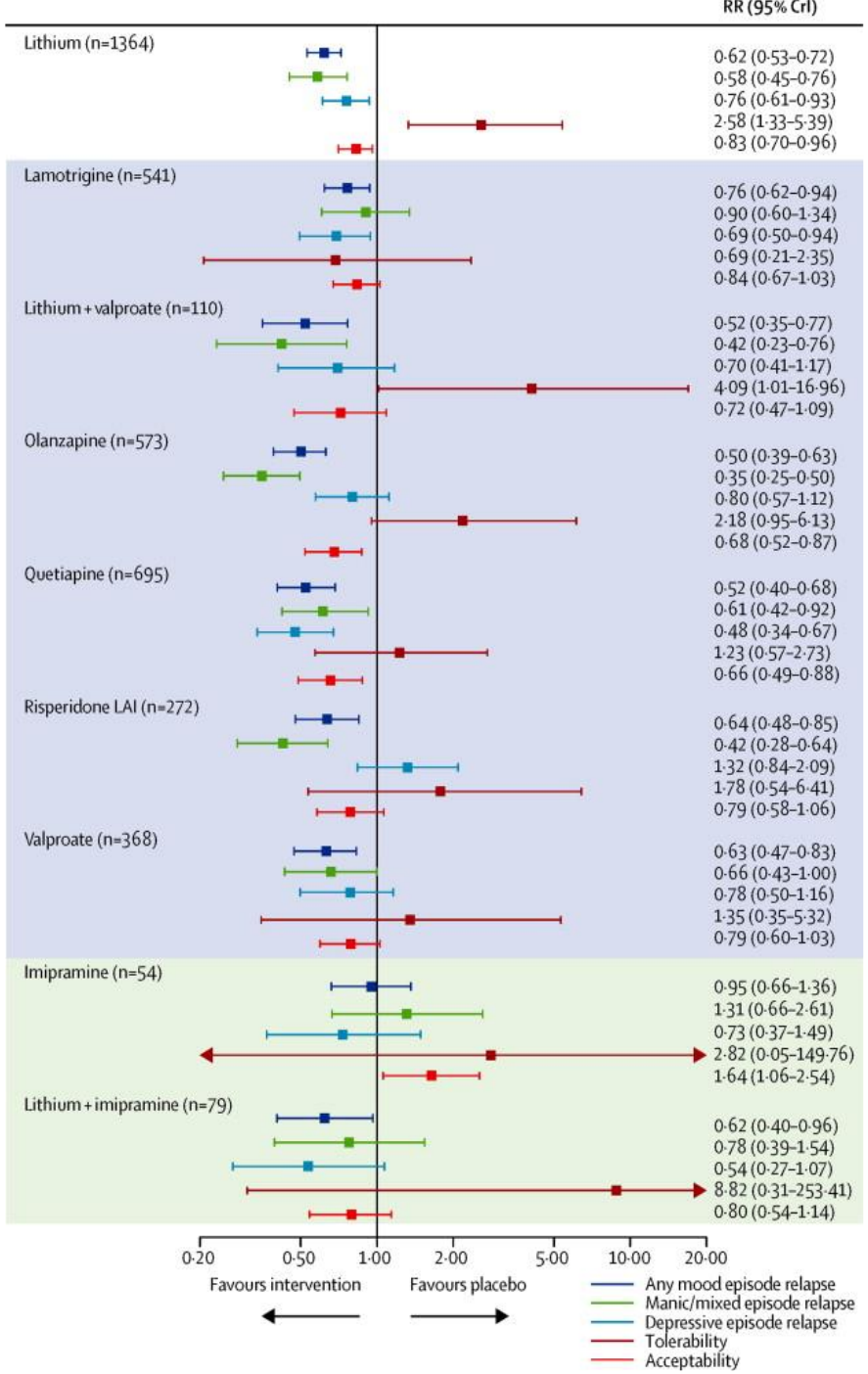
Summary

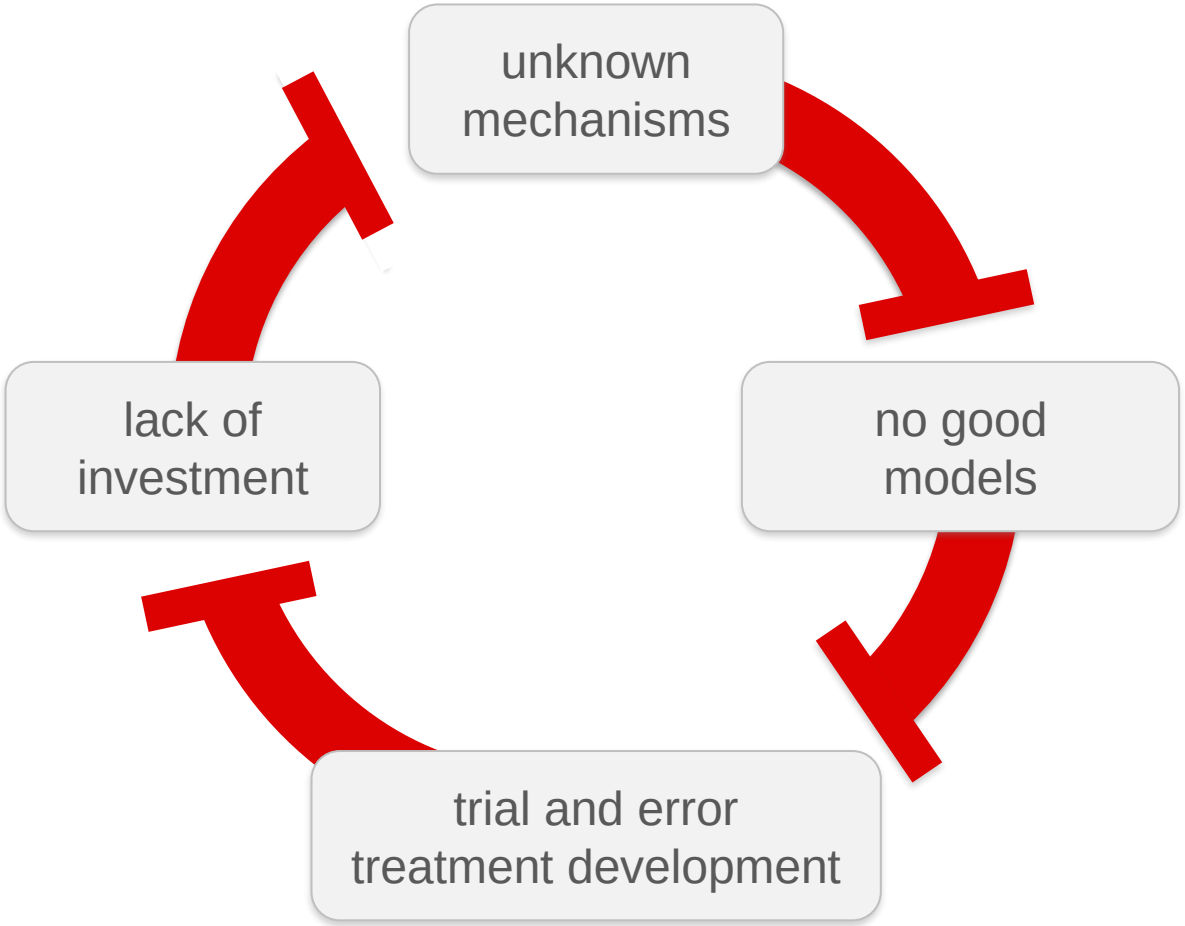
Background Lithium is the established standard in the long-term treatment of bipolar disorder, but several new dı have been assessed for this indication. We did a network meta-analysis to investigate the comparative efficacy tolerability of available pharmacological treatment strategies for bipolar disorder.

Methods We systematically searched Embase, Medline, PreMedline, PsycINFO, and the Cochrane Central Regi of Controlled Trials for randomised controlled trials published before June 28, 2013, that compared active treatm

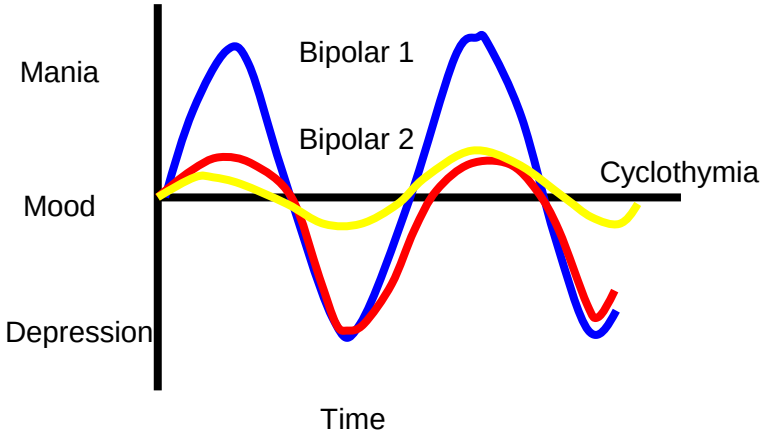


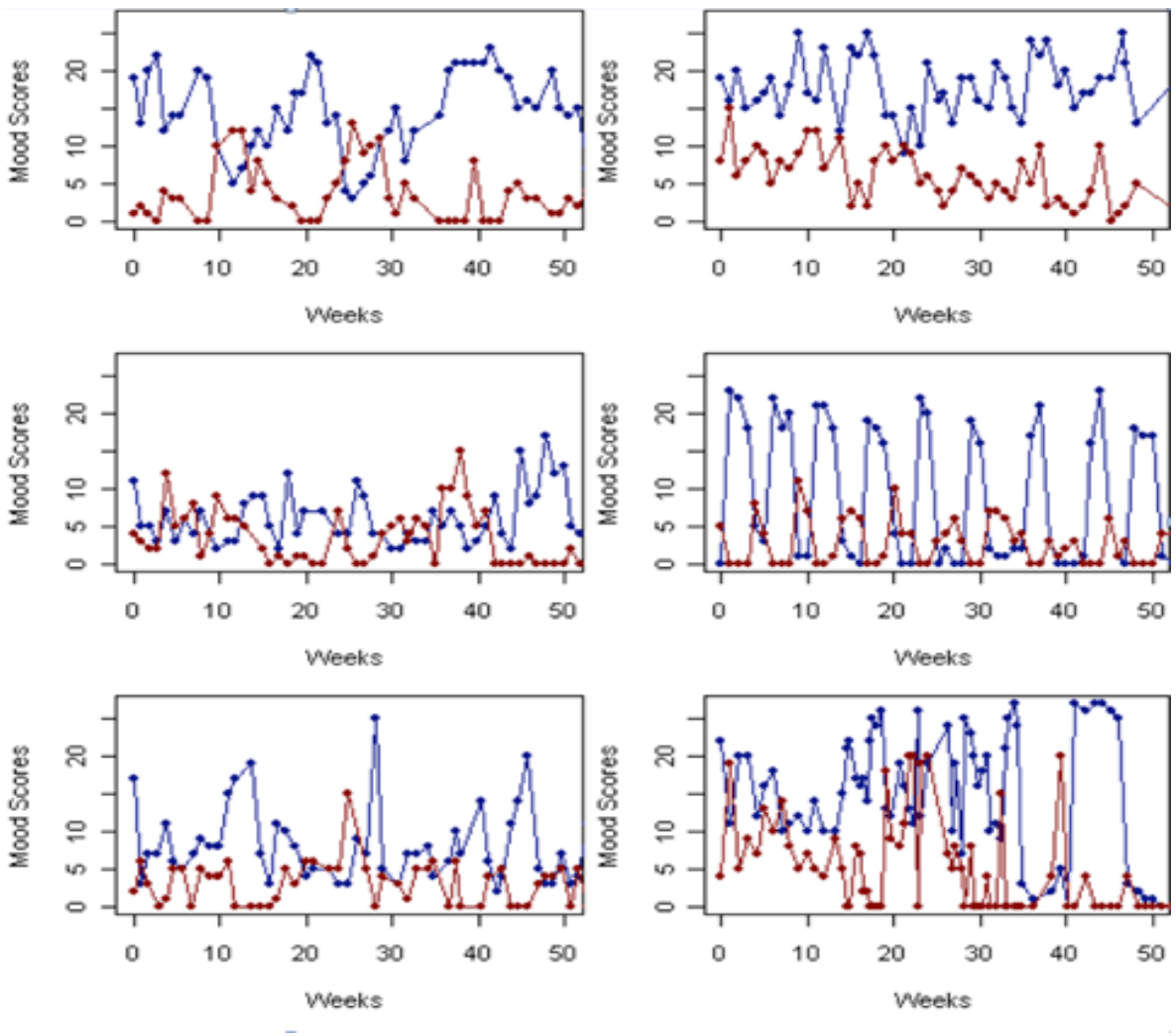


Experimental medicine for bipolar disorder

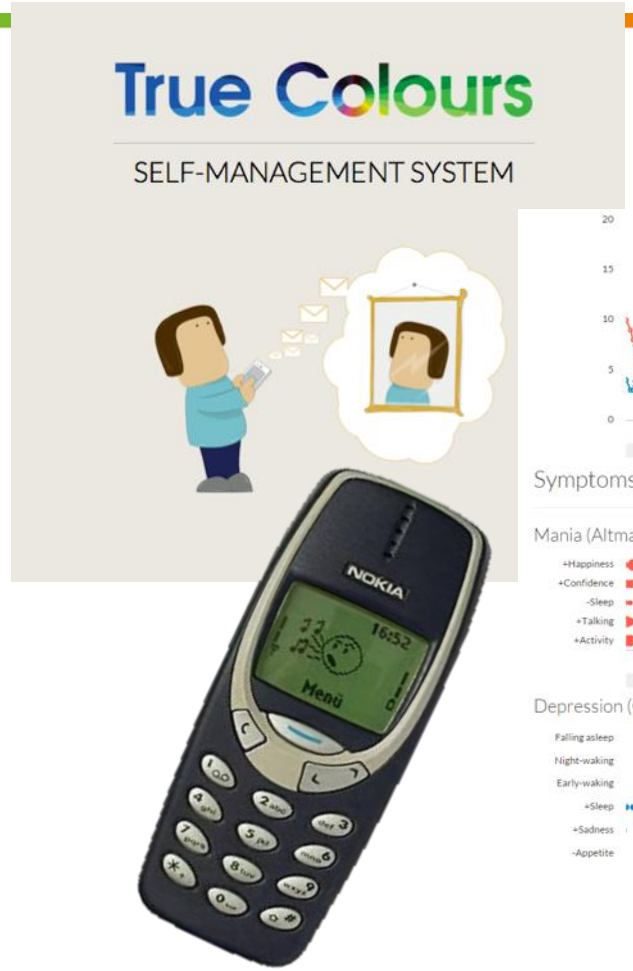


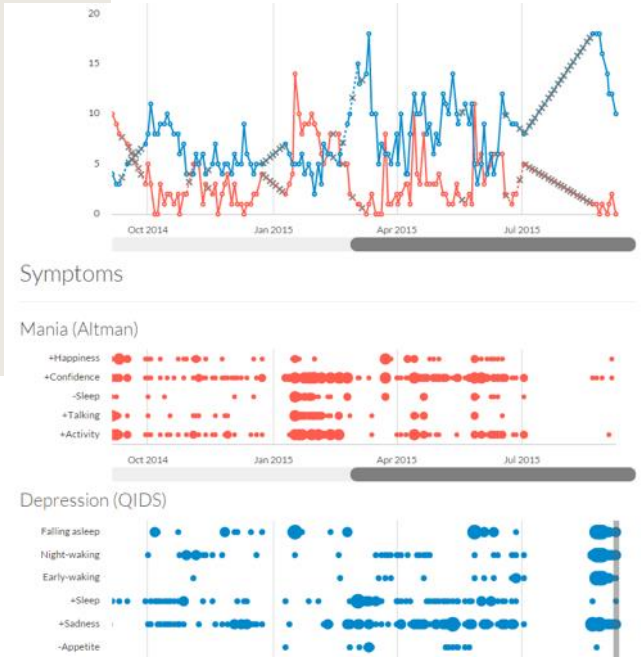
True Colours
SELF-MANAGEMENT SYSTEM

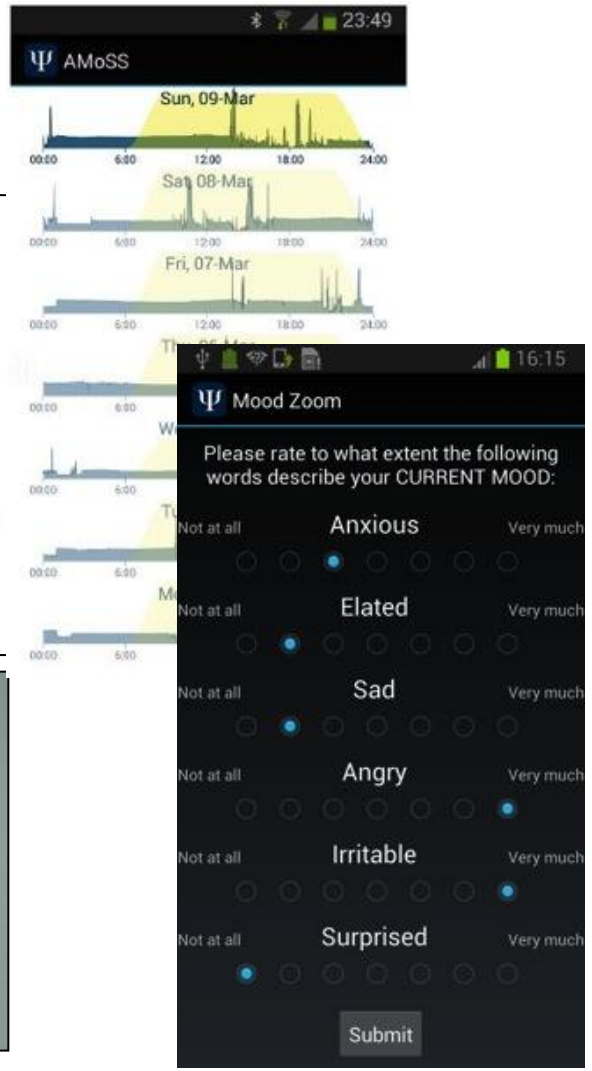

Mania
Mood
Depression
Bipolar 1
Bipolar 2
Cyclothymia
Time


Mood Scores
Weeks
0
5
10
20
30
40
50

Enhanced phenotypes: Remote data collection



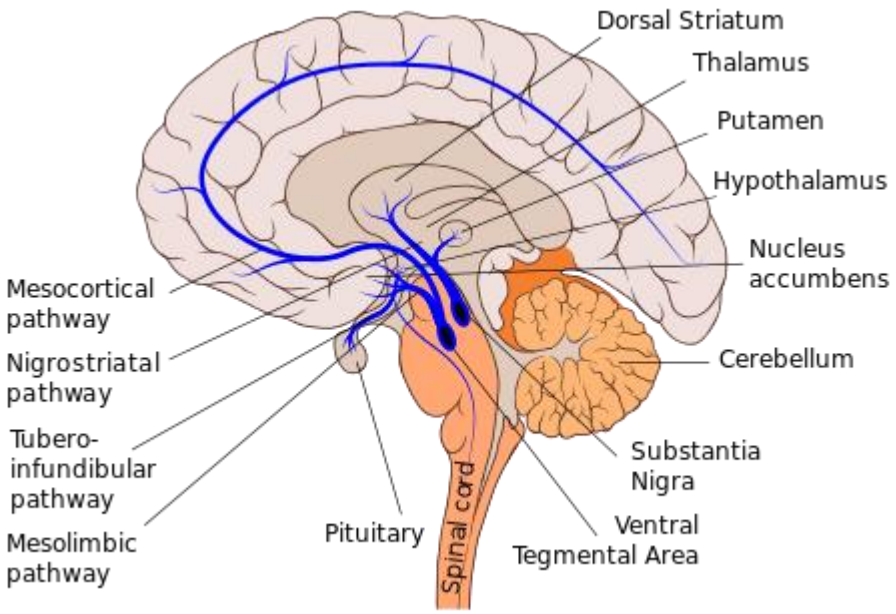




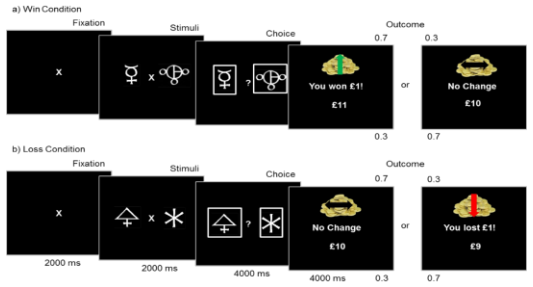
>35,000 patients, >1M measures, Research studies, Trials, Clinical practice, extended beyond MH

PAX-D - Pro-dopaminergic therapy in treatment resistant depression

- Dopaminergic neurons project from central nuclei (VTA, SN) to the striatum and cortex



Models to Tease Apart Effects of Dopamine

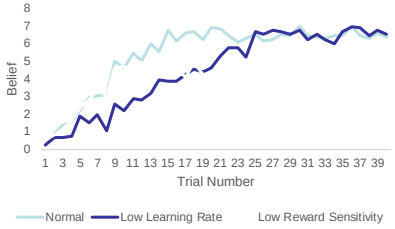


Prediction Error

$$belief_{(i+1)} = belief_{(i)} + \alpha * ((\lambda * outcome_{(i)}) - belief_{(i)})$$

Learning Rate

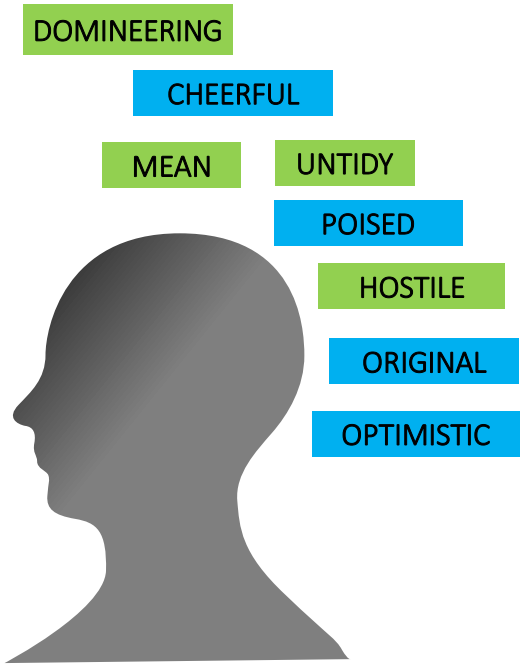
Reward Sensitivity



Innovation in methods of evaluating treatment effects

- Optimising use of existing randomized data
- Digital Phenotyping
- Large, simple trials with mechanistic/mediation analyses
- Experimental medicine in humans – determine effects quickly

An experimental medicine model for depression



Emotional memory

Facial expression perception

- Negative bias in depression: increased attention, perception and memory for negative vs positive information (see Roiser and Sahakian 2014)

Saunders et al. Trials (2016) 17:116
DOI 10.1186/s13063-016-1230-7

Trials

STUDY PROTOCOL Open Access

Oxford Lithium Trial (OxLith) of the early affective, cognitive, neural and biochemical effects of lithium carbonate in bipolar disorder: study protocol for a randomised controlled trial

Kate E. A. Saunders[1], Andrea Cipriani[1], Jennifer Rendell[1], Mary-Jane Attenburrow[1], Natalie Nelissen[1], Amy C. Bilderbeck[1], Sridhar R. Vasudevan[2], Grant Churchill[2], Guy M. Goodwin[1], Anna C. Nobre[1], Catherine J. Harmer[1], Paul J. Harrison[1] and John R. Geddes[1*]

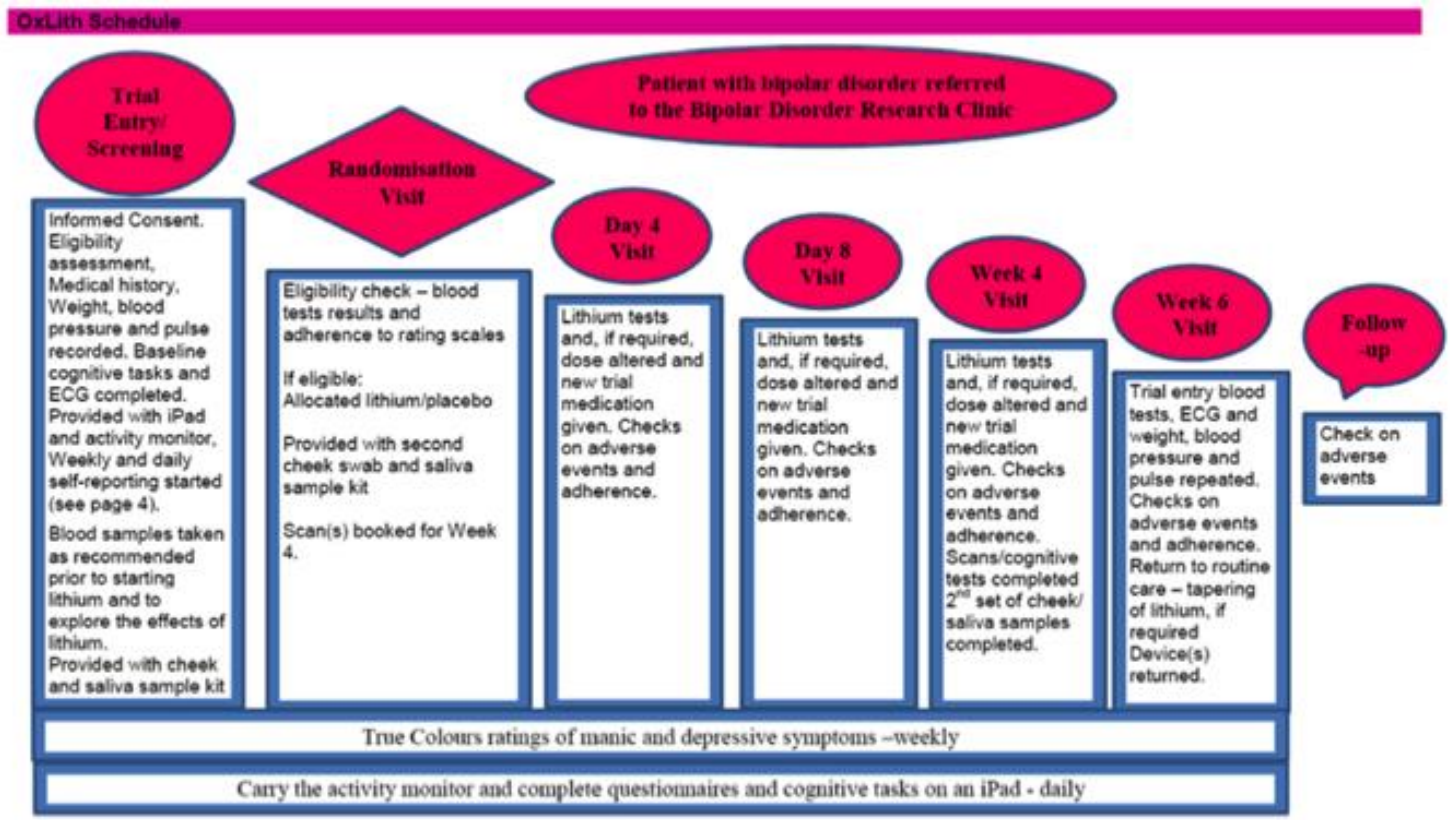
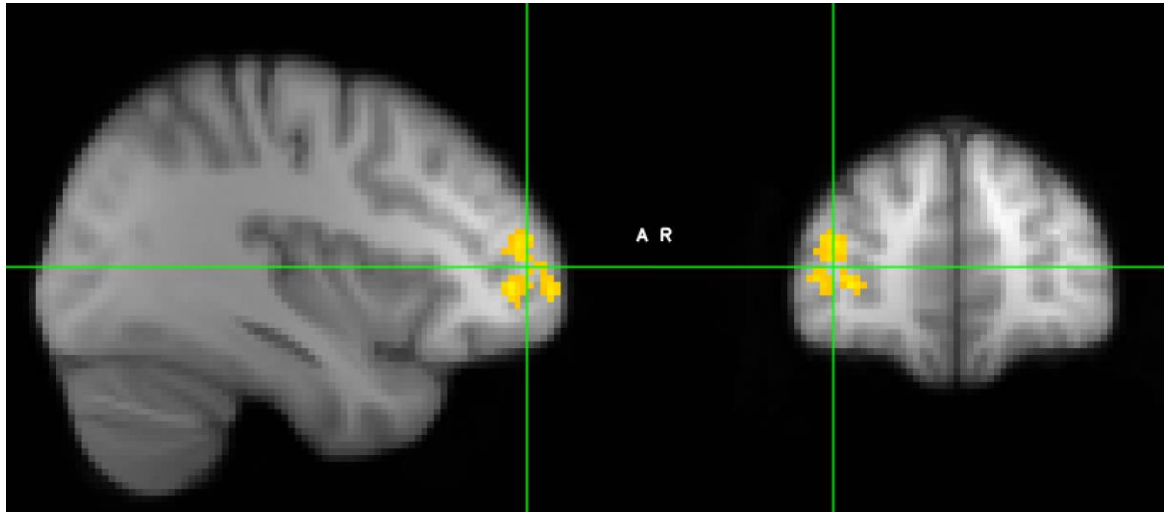


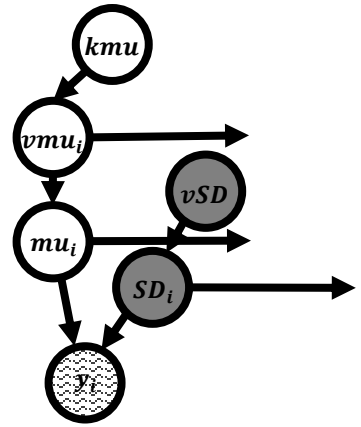
Fig. 1 OxLith trial schedule. ECG electrocardiogram

OxLith – winning a reward

Lithium>Placebo during a win

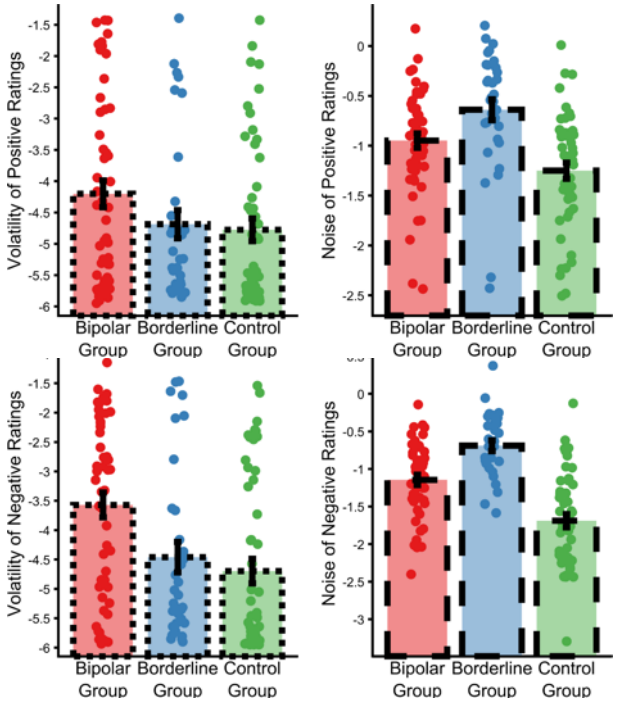


Lithium restores activity in prefrontal part of ‘control network’ compared to placebo during reward

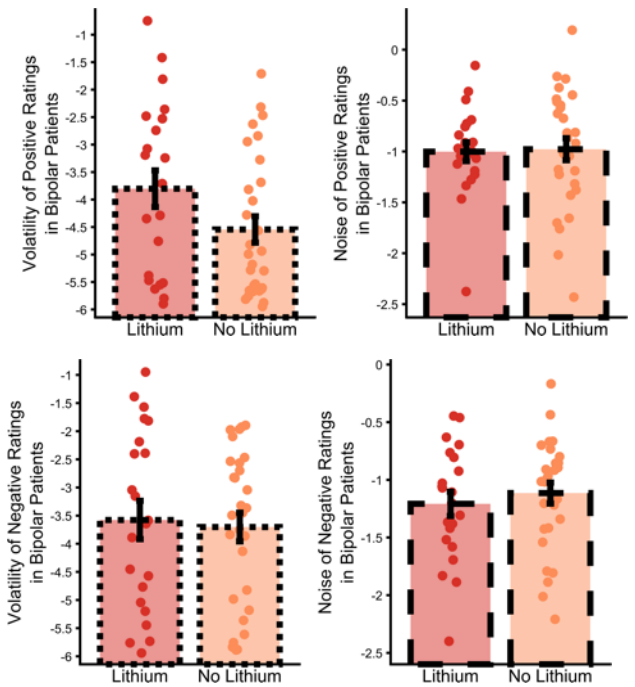


Positive Affect

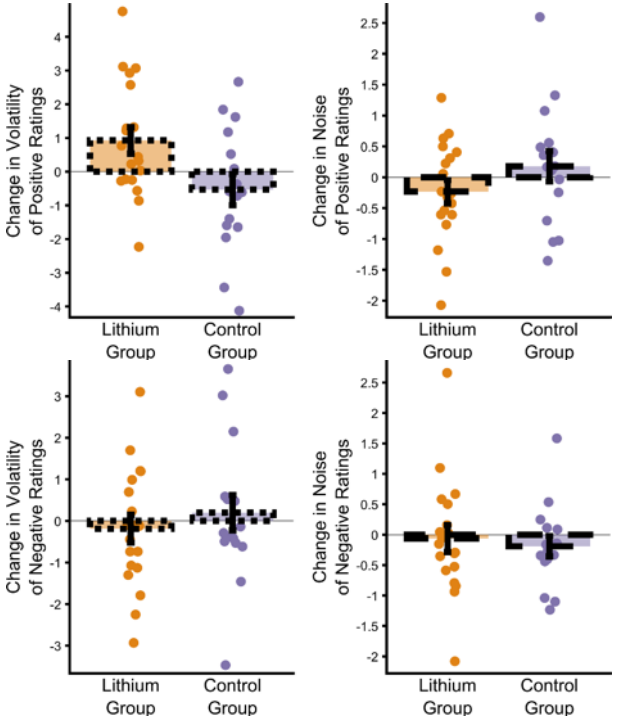
Negative Affect



Bipolar Disorder is associated with increased affective volatility, Borderline Personality Disorder with increased affective noise



Lithium is associated with **increased** volatility of positive affect in a cohort study



Lithium caused **increased** volatility of positive affect in an experimental medicine study

Acceleration of discovery of new treatments for bipolar disorders

- Global collaboration
  - Prioritisation of targets
  - Standardisation of methods, measures, reporting
  - Sharing data, structures, expertise
  - Building on existing national infrastructure, enthusiasms and relationships
  - Extensive and coordinated media briefings
  - Building capacity and developing future leaders
  - Through collaboration leverage increased resource

Target identification

- Genetics
- Phenotypic
- Cognitive/neuropsychology/behavioural
- Immunology
- Sleep and circadian neuroscience
- Repurposing/informatics-driven

L-type calcium channel antagonists

OPEN

Molecular Psychiatry (2016), 1–9
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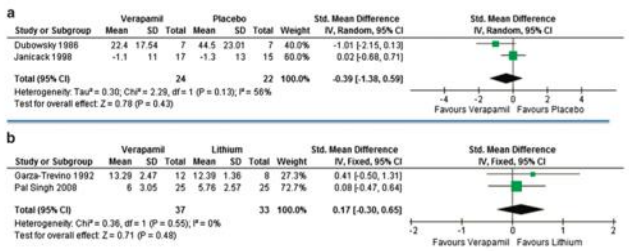
www.nature.com/mp

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 Stefaniak[1], P Panchal[1,2], S Stockton[1,2], TA Lane[1], EM Tunbridge[1,2], JR Geddes[1,2] and PJ Harrison[1,2]



Recent findings strengthening candidacy of LTCCs as therapeutic targets

- *CACNA1C* locus shows genome-wide association to bipolar disorder, as well as to schizophrenia, major depression, 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 show altered calcium signalling
- Neuron-like cells derived from subjects with *CACNA1C* risk genotype show increased gene expression and enhanced calcium signalling

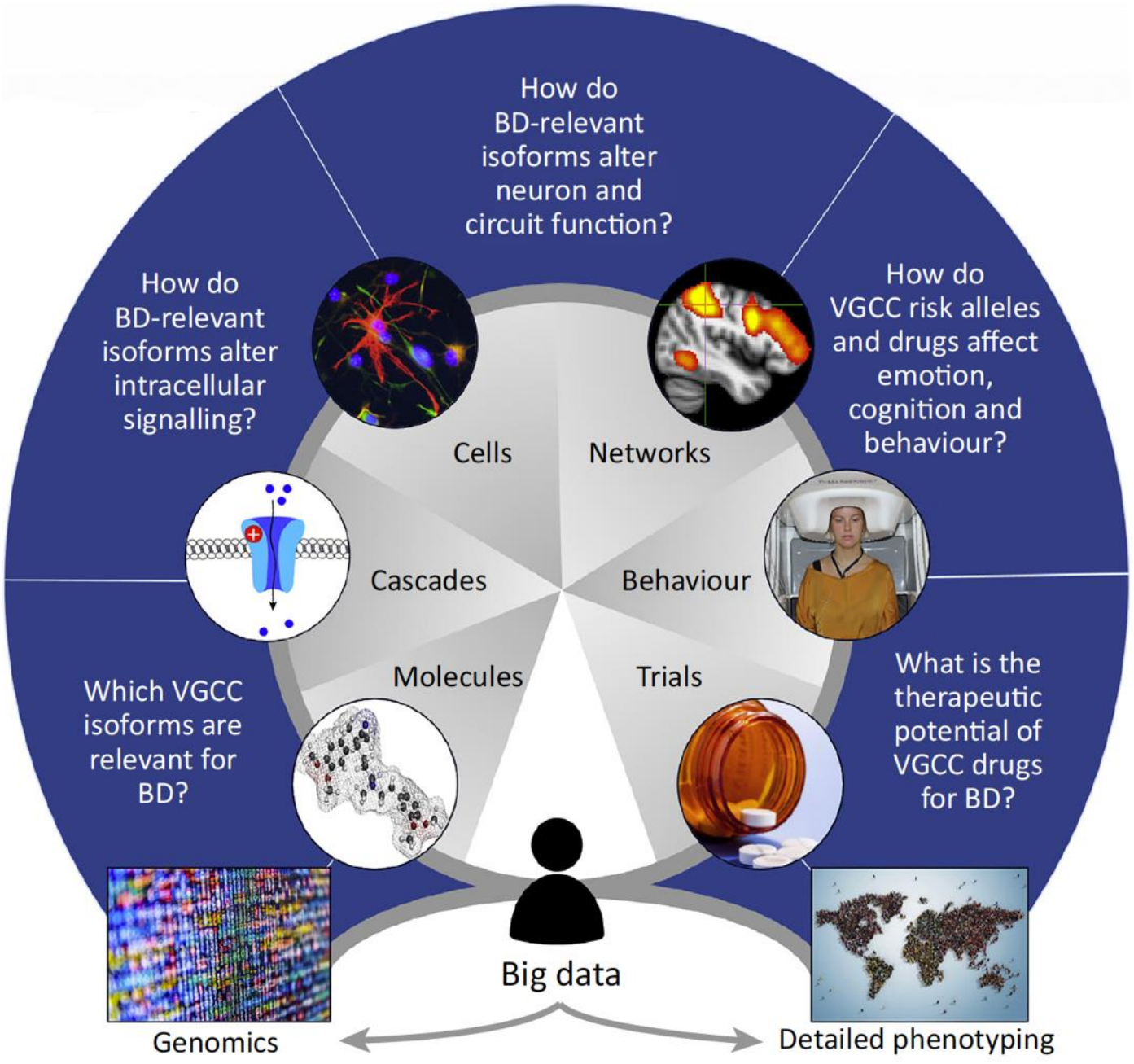
Workflow

Trends in Neurosciences

Review

The Emerging Neurobiology of Bipolar Disorder

Paul J. Harrison,[1,2,*] John R. Geddes,[1,2] and Elizabeth M. Tunbridge[1,2]



Trends in Neurosciences

Adjunctive psychological treatment

JAMA Psychiatry | Original Investigation

Adjunctive Psychotherapy for Bipolar Disorder
A Systematic Review and Component Network Meta-analysis

David J. Miklowitz, PhD; Orestis Efthimiou, PhD; Toshi A. Furukawa, MD, PhD; Jan Scott, MD, PhD; Ross McLaren, BMBCh; John R. Geddes, MD; Andrea Cipriani, MD, PhD

Figure 1. PRISMA Flow Diagram

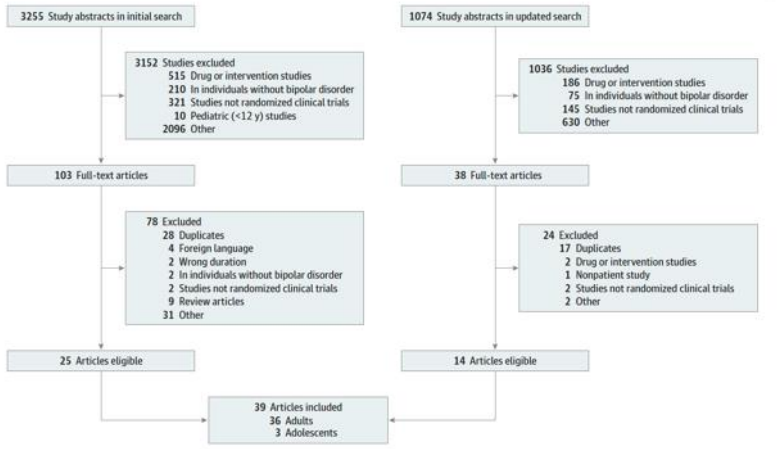
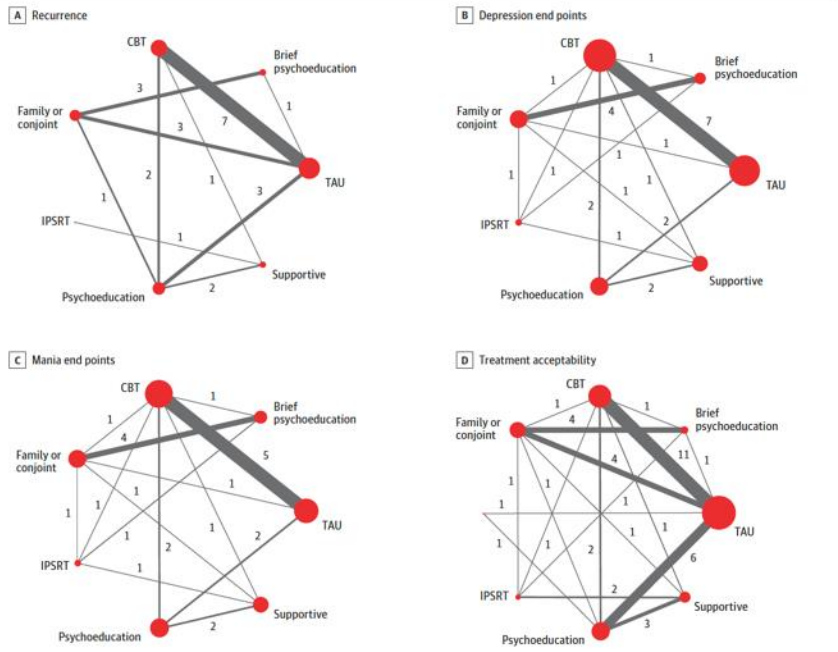


Figure 2. Geometry of Networks for Treatment-Level Comparisons



Network structure for the 4 outcomes examined in this article. Nodes denote treatments, and lines denote trials performing the corresponding treatment comparison. The size of a node is proportional to the number of studies that included the corresponding treatment. The thickness of the lines corresponds to the number of studies performing each comparison (also indicated by the number on each line). CBT indicates cognitive behavioral therapy; IPSRT, interpersonal and social rhythm therapy; and TAU, treatment as usual.

Table 1. Pairwise and Network Meta-analysis for Treatment-Level Comparisons of Recurrence (Odds Ratios)[a]

Brief psychoeducation	NA	1.15 (0.60-2.20)	NA	NA	NA	0.34 (0.08-1.49)
0.66 (0.28-1.55)	CBT	NA	NA	0.89 (0.41-1.95)	0.81 (0.26-2.52)	0.52 (0.32-0.83)
1.15 (0.63-2.09)	1.75 (0.87-3.49)	Family or conjoint therapy	NA	0.51 (0.13-1.92)	NA	0.31 (0.16-0.62)
0.22 (0.04-1.15)	0.34 (0.08-1.46)	0.20 (0.04-0.92)	IPSRT	NA	1.76 (0.49-6.35)	NA
0.66 (0.28-1.58)	1.01 (0.61-1.68)	0.58 (0.29-1.16)	2.96 (0.72-12.11)	Psychoeducation	0.54 (0.28-1.03)	0.51 (0.26-0.99)
0.39 (0.14-1.08)	0.60 (0.30-1.19)	0.34 (0.14-0.82)	1.76 (0.49-6.35)	0.59 (0.33-1.06)	Supportive	NA
0.34 (0.16-0.74)	0.52 (0.34-0.79)	0.30 (0.17-0.53)	1.53 (0.35-6.62)	0.52 (0.32-0.84)	0.87 (0.43-1.76)	TAU

Table 3. Data on Incremental Effectiveness of Treatment Components Regarding Outcome Variables[a]

Component	Definition	Groups with component, No.[b]	iOR recurrence (95% CrI)	iSMD depression (95% CrI)	iSMD mania (95% CrI)	iOR dropout (95% CrI)
Psychoeducation: information only	Information giving without skill practice	7-11	0.95 (0.30 to 3.22)	0.25 (−0.57 to 1.06)	0.14 (−1.07 to 1.42)	1.27 (0.65 to 2.86)
Psychoeducation: information plus active skill practice	Information giving with skills development and practice	23-42	0.93 (0.27 to 3.46)	0.01 (−0.94 to 0.87)	−0.03 (−1.58 to 1.56)	1.09 (0.53 to 2.44)
Self-monitoring assignments	Patient tracks moods, prodromal symptoms, sleep, or thoughts	20-33	0.22 (0.04 to 1.35)	−0.13 (−0.71 to 0.58)	−0.17 (−1.25 to 0.95)	1.27 (0.55 to 2.94)
Self-management assignments	Patient learns to implement preventive strategies for managing early warning signs	17-30	1.70 (0.45 to 6.69)	0.38 (−0.36 to 1.07)	0.30 (−0.70 to 1.22)	1.34 (0.61 to 3.39)
Cognitive restructuring	Guided practice in challenging self-defeating thoughts and rehearsing adaptive thinking	10-16	0.64 (0.20 to 2.10)	−1.26 (−2.10 to −0.35)	−1.00 (−2.15 to 0.16)	1.08 (0.35 to 2.66)
Maintaining regular daily rhythms	Patient coached to regulate daily activities and sleep and wake schedules	12-21	1.63 (0.55 to 4.10)	−0.78 (−1.28 to −0.24)	−0.42 (−1.08 to 0.28)	1.15 (0.66 to 1.95)
Behavioral activation assignments	Patient coached to plan pleasurable activities to increase or modulate engagement with environment	3-6	0.69 (0.18 to 2.72)	0.92 (0.11 to 1.71)	0.98 (−0.10 to 2.03)	0.81 (0.30 to 2.18)
Behavioral problem solving	Patient coached on how to identify and define problems and generate, evaluate, and implement solutions	16-28	1.17 (0.39 to 3.22)	0.30 (−0.26 to 0.83)	0.10 (−0.64 to 0.88)	0.88 (0.43 to 1.86)
Interpersonal problem-solving	Patient encouraged to identify interpersonal habits and consider alternative behaviors	7-12	0.81 (0.08 to 8.94)	0.55 (−0.37 to 1.39)	0.73 (−0.47 to 1.90)	0.55 (0.17 to 1.72)
Communication training	Coaching families, couples, or groups on effective speaking and listening skills with in-session rehearsal	5-8	2.46 (0.07 to 74.4)	−0.84 (−1.81 to 0.23)	−0.80 (−2.23 to 0.63)	1.86 (0.46 to 6.49)
Group format	Sessions occur with other patients; includes multifamily groups	10-18	0.94 (0.18 to 4.76)	−0.12 (−0.99 to 0.78)	−0.05 (−1.42 to 1.29)	1.07 (0.49 to 2.16)
Family format	Sessions occur with patient's family members or spouse	11-15	0.16 (0.02 to 1.22)	0.93 (−0.34 to 2.15)	0.76 (−0.96 to 2.45)	0.39 (0.15 to 1.11)
Individual format	Sessions are limited to the individual patient	17-26	1.27 (0.23 to 5.21)	1.01 (−0.12 to 2.07)	0.41 (−1.17 to 1.95)	0.73 (0.29 to 1.95)

Abbreviations: CrI, credible interval; iOR, incremental odds ratios; iSMD, incremental standardized mean differences.

[a] Incremental odds ratios when the component was present vs absent, estimated in association with binary outcomes. Lower iORs indicate lower recurrence rates in treatments with the component. Incremental standardized mean differences when the component was present vs absent, estimated in association with continuous outcomes. Incremental standardized mean differences below 0 indicate that depression or mania scores were lower in treatments with the component.

[b] Number of treatment conditions in which the component was rated as present. There is a range because different numbers of studies qualified for inclusion in analyses of different outcome variables. The lower number refers to the depression and mania analyses, and the upper number to acceptability analyses.

Treatment development in mood disorder

- Create efficient workflow
- Target identification
- Development of human experimental methods
- Replication, fail quickly and definitively, move on
- Coordination
- Collaborative, open science

Global Bipolar Disorder Foundation

- Large-scale coordinated action needed to integrate international big-data approaches with real-world clinical interventions
- Bring government, industry and philanthropy together in common cause and unmet clinical need.
- Build on advances in understanding of the genetic and brain basis of bipolar disorder
- Open science
- Strong involvement of user groups
- Dissemination and public involvement

Mirko Manchia and Ole Andreassen

Examples in bipolar disorder

ENIGMA

IGSLi
International Group for The Study of Lithium Treated Patients

PGC
Psychiatric Genomics Consortium

Learning from COVID-19

- 145 registered trials of hydroxychloroquine
- 32 sample size of ≤100,
- 10 no control group,
- 12 comparative but non-randomised
- Outcome measures vary widely
- 1 provides a protocol

thebmj

BMJ 2020;369:m1847 doi: 10.1136/bmj.m1847 (Published 12 May 2020)

EDITORIALS

Check for updates

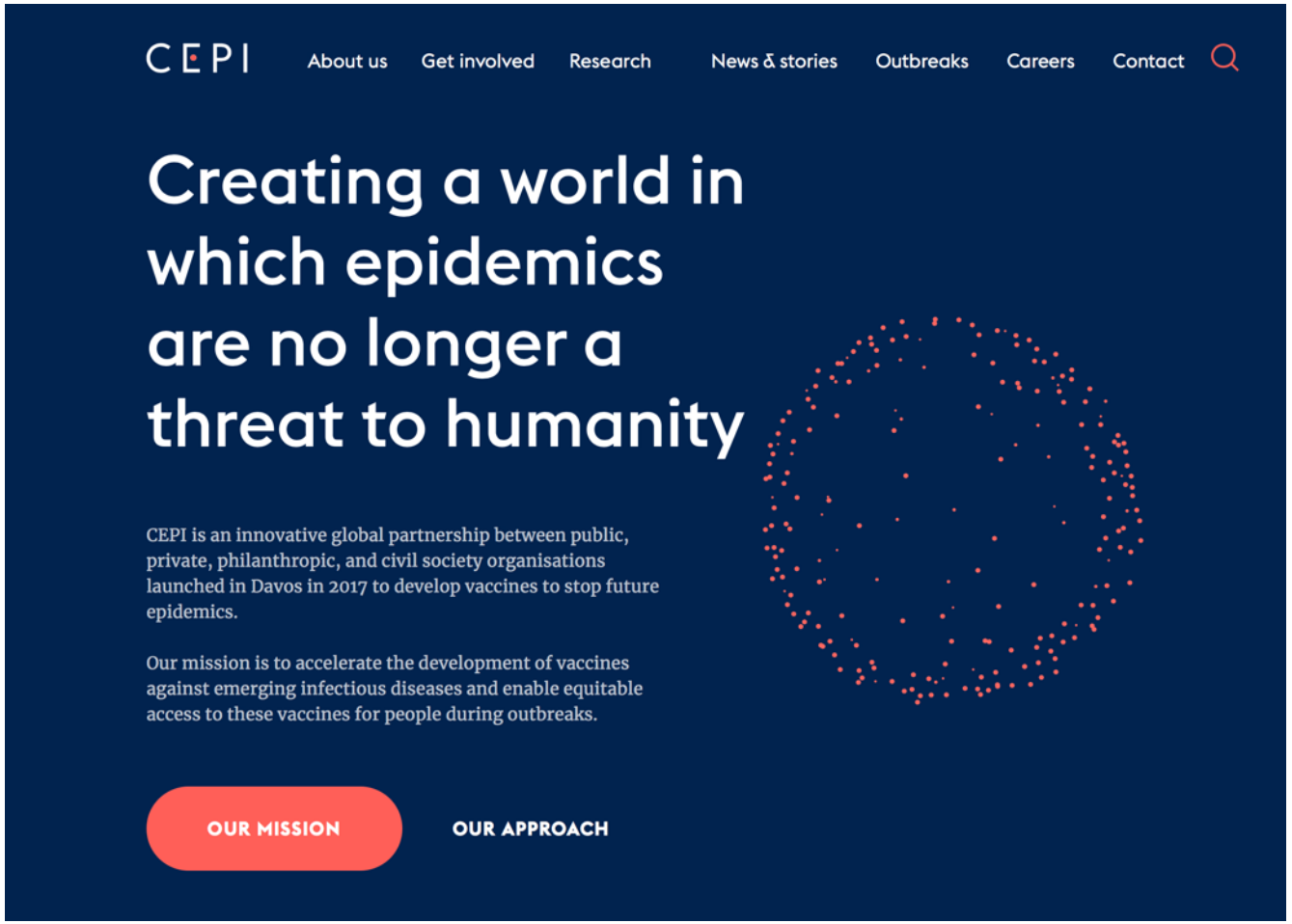
Waste in covid-19 research

A deluge of poor quality research is sabotaging an effective evidence based response

Paul P Glasziou *professor of evidence based medicine*, Sharon Sanders *assistant professor*, Tammy Hoffmann *professor of clinical epidemiology*

Institute for Evidence Based Healthcare, Bond University, Australia

Learning from COVID-19



Learning from COVID-19

RECOVERY
Randomised Evaluation of COVID-19 Therapy

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This national clinical trial aims to identify treatments that may be beneficial for people hospitalised with suspected or confirmed COVID-19

- Lopinavir-Ritonavir (commonly used to treat HIV)
- Low-dose Dexamethasone (a type of steroid, which is used in a range of conditions typically to reduce inflammation).
- Hydroxychloroquine (related to an anti-malarial drug)
- Azithromycin (a commonly used antibiotic)
- Tocilizumab (an anti-inflammatory treatment given by injection)
- Convalescent plasma (collected from donors who have recovered from COVID-19 and contains antibodies against the SARS-CoV-2 virus).

Professor Peter Horby, Professor Martin Landray
RECOVERY trial Co-chairs
Nuffield Department of Public Health
Oxford

28th May 2020

Dear Peter and Martin

RECOVERY trial DMC report

The RECOVERY trial DMC today reviewed the safety and efficacy data that were available on 26th May for the 10755 patients randomised. In the light of these data and the available external data, we saw no cogent reason to modify the protocol or intake to the study. The Committee therefore recommends the trial continue recruitment without interruption until the next scheduled meeting on 11th June.

Yours sincerely

Professor Peter Sandercock, MA, DM, FRCPE, FESO, FWSO
Emeritus Professor of Medical Neurology, Centre for Clinical Brain Sciences
Chairman RECOVERY trial DMC

Cc DMC members, RECOVERY trial office.

Acknowledgements

- OXTEXT/True Colours/CEQUEL participants
- OXTEXT Team – Rebecca McKnight, Guy Goodwin, David Miklowitz, Jean Christensen, Jonathan Price, Jim Davies, Chris Hinds, James Welch, Rebecca Withers, Hannah McMahon, Roshan Baban, Isobel McDonald, Jennifer Rendell, Merryn Voysey, Neil Armstrong, Nicola Williams, Judit Simon, Emily Holmes
- CEQUEL Team – Jennifer Rendell, Alex Gardiner, Judit Simon, Guy Goodwin, Mary Jane Attenburrow, Andrea Cipriani
- conBRIO Team - Paul Harrison, Catherine Harmer, Kia Nobre, Clare Mackay, Mark Woolrich, Kate Saunders, Jim Davies, Andrew McIntosh, Kate Saunders, Matthew Taylor, Steve Smith, Danny Weinberger, Matthew Rushworth, Terry Lyons, Emily Holmes
- BDRN Nick Craddock, Ian Jones, Lisa Jones
- Simon Lovestone; Chas Bountra, Brian Shine, Laurence Leaver, Michael Bauer, Andy Nierenberg, Marion Leboyer, Janssen colleagues,

NHS National Institute for Health Research

MRC Medical Research Council

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