An Update on Bipolar Disorder: Evidence, Challenges, and Solutions

Andrew A. Nierenberg, MD

Thomas P. Hackett, MD, Endowed Chair in Psychiatry,

Director, Dauten Family Center for Bipolar Treatment Innovation,

Co-Director, Center for Clinical Research Education,

Massachusetts General Hospital/MassGenBrigham

Professor of Psychiatry, Harvard Medical School

- **Evidence**
- **Challenges**
- **Solutions**

Evidence

Evidence based medicine

Strengths of EBM

- Better than the alternatives
- Provides scientific foundation for clinical practice
- Increases probability that effective and safe treatments will be given
- Decreases probability that ineffective or unsafe treatments will be given

7 Alternatives to Evidence Based Medicine

Basis of clinical practice

Basis for clinical decisions	Marker	Measuring device	Unit of measurement
Evidence	Randomised controlled trial	Meta-analysis	Odds ratio
Eminence	Radiance of white hair	Luminometer	Optical density
Vehemence	Level of stridency	Audiometer	Decibels
Eloquence (or elegance)	Smoothness of tongue or nap of suit	Teflometer	Adhesin score
Providence	Level of religious fervour	Sextant to measure angle of genuflection	International units of piety
Diffidence	Level of gloom	Nihilometer	Sighs
Nervousness	Litigation phobia level	Every conceivable test	Bank balance
Confidence*	Bravado	Sweat test	No sweat

*Applies only to surgeons.

Isaacs and Fitzgerald. BMJ 1999;319:1618

Limitations of Evidence Based Medicine

- Quality of evidence rarely evaluated
  - Studies of groups have limited information for the care of individual patients
  - Registration trials may not inform care
  - Investigators have varying incentives
  - Subjects differ from patients
  - Outcomes not clinically relevant
  - Raters display bias
- Difficult to implement

Clinical Epistemology

Evidence from Bipolar Guidelines

DOI: 10.1111/bdi.12609

ORIGINAL ARTICLE

WILEY BIPOLAR DISORDERS

Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder

Lakshmi N Yatham[1] | Sidney H Kennedy[2] | Sagar V Parikh[3] | Ayal Schaffer[2] | David J Bond[4] | Benicio N Frey[5] | Verinder Sharma[6] | Benjamin I Goldstein[2] | Soham Rej[7] | Serge Beaulieu[7] | Martin Alda[8] | Glenda MacQueen[9] | Roumen V Milev[10] | Arun Ravindran[2] | Claire O'Donovan[8] | Diane McIntosh[1] | Raymond W Lam[1] | Gustavo Vazquez[10] | Flavio Kapczinski[5] | Roger S McIntyre[2] | Jan Kozicky[11] | Shigenobu Kanba[12] | Beny Lafer[13] | Trisha Suppes[14] | Joseph R Calabrese[15] | Eduard Vieta[16] | Gin Malhi[17] | Robert M Post[18] | Michael Berk[19]

NICE National Institute for Health and Care Excellence

NICE guideline

Bipolar disorder: assessment and management

Clinical guideline
Published: 24 September 2014
Last updated: 2 September 2025

VA/DoD CLINICAL PRACTICE GUIDELINE FOR MANAGEMENT OF BIPOLAR DISORDER

Department of Veterans Affairs
Department of Defense

REVIEW

The CANMAT and ISBD Guidelines for the Treatment of Bipolar Disorder: Summary and a 2023 Update of Evidence

Kamyar Keramatian, M.D., F.R.C.P.C., Nellai K. Chithra, M.B.B.S., M.D., Lakshmi N. Yatham, M.B.B.S., F.R.C.P.C.

DOI: 10.1111/bdi.13036

REVIEW ARTICLE

BIPOLAR DISORDERS WILEY

The 2020 Royal Australian and New Zealand College of psychiatrists clinical practice guidelines for mood disorders: Bipolar disorder summary

Gin S. Malhi[1,2,3] | Erica Bell[1,2,3] | Philip Boyce[4,5] | Darryl Bassett[6] | Michael Berk[7,8] | Richard Bryant[9] | Michael Gitlin[10] | Amber Hamilton[1,2,3] | Philip Hazell[5] | Malcolm Hopwood[11] | Bill Lyndon[1] | Roger S. McIntyre[12] | Grace Morris[1,2,3] | Roger Mulder[13] | Richard Porter[13] | Ajeet B. Singh[14] | Lakshmi N. Yatham[15] | Allan Young[16,17] | Greg Murray[18]

Guideline	First-Line Mania	Key Distinguishing Features
CANMAT/ISBD 2018	lithium, valproate, quetiapine, aripiprazole, risperidone, asenapine, paliperidone, and cariprazine; mood stabilizer + antipsychotic	Broadest first-line list; hierarchical ranking across illness phases
VA/DoD 2023	lithium, valproate, carbamazepine, olanzapine, quetiapine, aripiprazole, risperidone, or ziprasidone	Emphasizes "breadth of effectiveness"
NICE	antipsychotics as first-line monotherapy (haloperidol, olanzapine, quetiapine, risperidone)	Lithium as second line
RANZCP 2020	lithium and valproate as monotherapy, with antipsychotics added for combination therapy	Uses a "Choice" and "Alternative" framework. Emphasizes tailoring by severity

Guideline	First-Line Depression	Key Distinguishing Features
CANMAT/ISBD 2018	Quetiapine, lurasidone (mono or adjunctive to Li/DVP), lithium, lamotrigine	Broadest first-line list; uniquely includes lithium and lamotrigine as first-line despite mixed RCT data; downgraded adjunctive antidepressants from first-line (2013) to second-line
VA/DoD 2023	Quetiapine (monotherapy)	Most restrictive — only quetiapine receives a strong first-line recommendation; lamotrigine monotherapy considered ineffective
NICE	Quetiapine, olanzapine/fluoxetine (moderate-severe, secondary care); olanzapine or lamotrigine monotherapy	Severity-stratified approach — psychotherapy alone for mild; pharmacotherapy reserved for moderate-severe in secondary care
RANZCP 2020	SGA (quetiapine, lurasidone, olanzapine) or mood stabilizer (lithium, lamotrigine, valproate)	Unique stepwise algorithm; most permissive regarding antidepressant use (with caution);

Guideline	First-Line Maintenance	Key Distinguishing Features
CANMAT/ISBD 2018	Lithium, quetiapine, divalproex, lamotrigine, asenapine, aripiprazole (mono or combo)	Broadest first-line list; hierarchical ranking across illness phases
VA/DoD 2023	Lithium, quetiapine, olanzapine (prevent both poles); lamotrigine (depression prevention)	Emphasizes "breadth of effectiveness" — agents preventing both mania and depression preferred
NICE	Lithium preferred; valproate, olanzapine, or quetiapine if lithium not tolerated	Strongest preference for lithium as first choice
RANZCP 2020	Tailored by dominant polarity: lamotrigine (depression), lithium/olanzapine (mania), quetiapine (both)	Unique polarity-based approach

Recently Approved Medications for Bipolar Disorder: Heavily “Me Too”

Compound	Approval Year	Indication	Primary Target
Bysanti — milsaperidone	2026	Acute manic or mixed episodes in bipolar I disorder	D2 / 5-HT2A antagonist
Uzedy — risperidone ER injectable	2025	Maintenance treatment of bipolar I disorder, monotherapy or adjunctive to lithium/valproate	D2 / 5-HT2A antagonist
Fanapt — iloperidone	2024	Acute manic or mixed episodes in bipolar I disorder	D2 / 5-HT2A antagonist
Abilify Asimtufii — aripiprazole LAI	2023	Maintenance treatment of bipolar I disorder	D2 partial agonist / 5-HT modulation

Sources: FDA/label and company approval announcements for Abilify Asimtufii, Fanapt, Uzedy, and Bysanti.

Selected Compounds in Clinical Testing for Bipolar Disorder: More Mechanistic Diversity

Compound	Target Population	Development Status	Primary Target
ABX-002 / elunetirom	Bipolar depression, adjunctive	Phase II	CNS-directed TRβ agonist
RAP-219	Bipolar I mania	Phase II	TARPγ8-selective AMPA receptor NAM
LB-102	Bipolar I depression	Phase II	D2 / D3 / 5-HT7 antagonist
NRX-101	Suicidal / treatment-resistant bipolar depression	Phase IIb/III completed	D-cycloserine + lurasidone
BHV-7000	Bipolar I mania	Phase II/III completed; negative topline	Kv7.2/7.3 potassium-channel activator

ClinicalTrials.gov NCT06869187, NCT07046494; Autobahn Therapeutics, 2025; Rapport Therapeutics, 2026; Nierenberg et al., Int J Bipolar Disord, 2023; Biohaven/Psychiatric Times, 2025.

Challenges

Challenges

Guidelines difficult to implement.

Outcomes have not improved in 20 years

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Contents lists available at ScienceDirect

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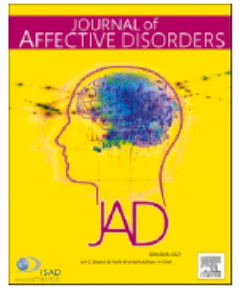
journal homepage: www.elsevier.com/locate/jad



Research paper

Global, regional and national burden of bipolar disorder: An analysis of trends from 1990 to 2021

Xirui Liu [a,1], Qinte Huang [a,1], Yiming Chen [a], Fan Wang [a], Yixia Xie [a], Ningning Chen [a], Shuang He [a], Pinwei Yang [a], Wu Hong [a,b,c,*]

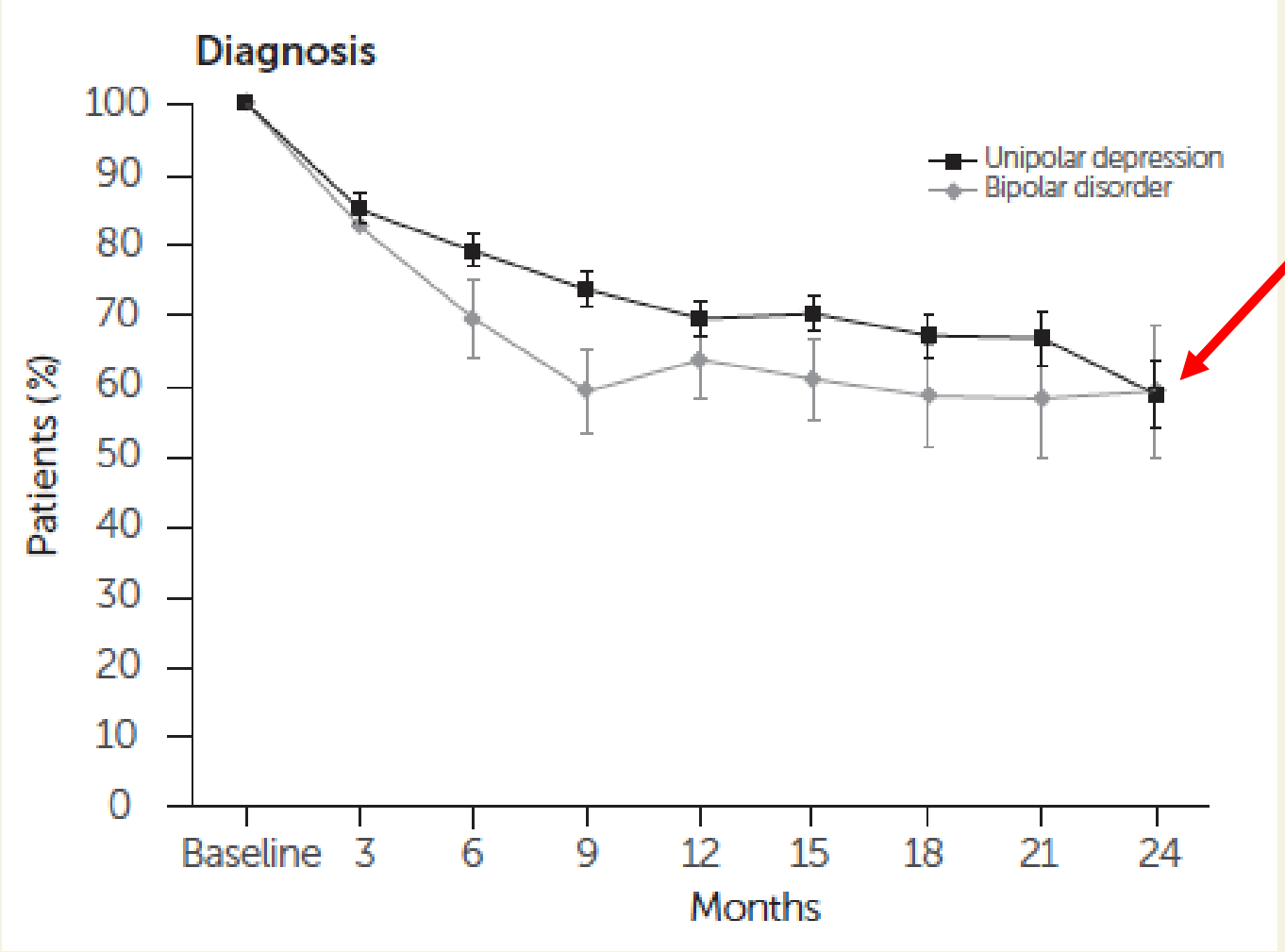
[a] Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, 200030, China
[b] Shanghai Key Laboratory of Psychotic disorders, Shanghai, 201108, China
[c] Mental Health Branch, China Hospital Development Institute, Shanghai Jiao Tong University, Shanghai, China

"...global rates of BP incidence, prevalence, and DALYs are projected to continue to rise through 2035."

Bipolar Depression: Real World Evidence

National Network Depression Centers Mood Outcomes Program

Proportion of patients With PHQ-9 ≥ 10



60% still depressed after 24 months of treatment

Zandi et al., Psychiatric Services 71:5, May 2020

Solutions


OpenEvidence

REVIEW

THE AMERICAN JOURNAL of MEDICINE®

From Evidence Based Medicine to Medicine Based Evidence

Ralph I. Horwitz, MD, MACP,[a] Allison Hayes-Conroy, PhD,[b] Roberto Caricchio, MD,[c] Burton H. Singer, PhD[d]

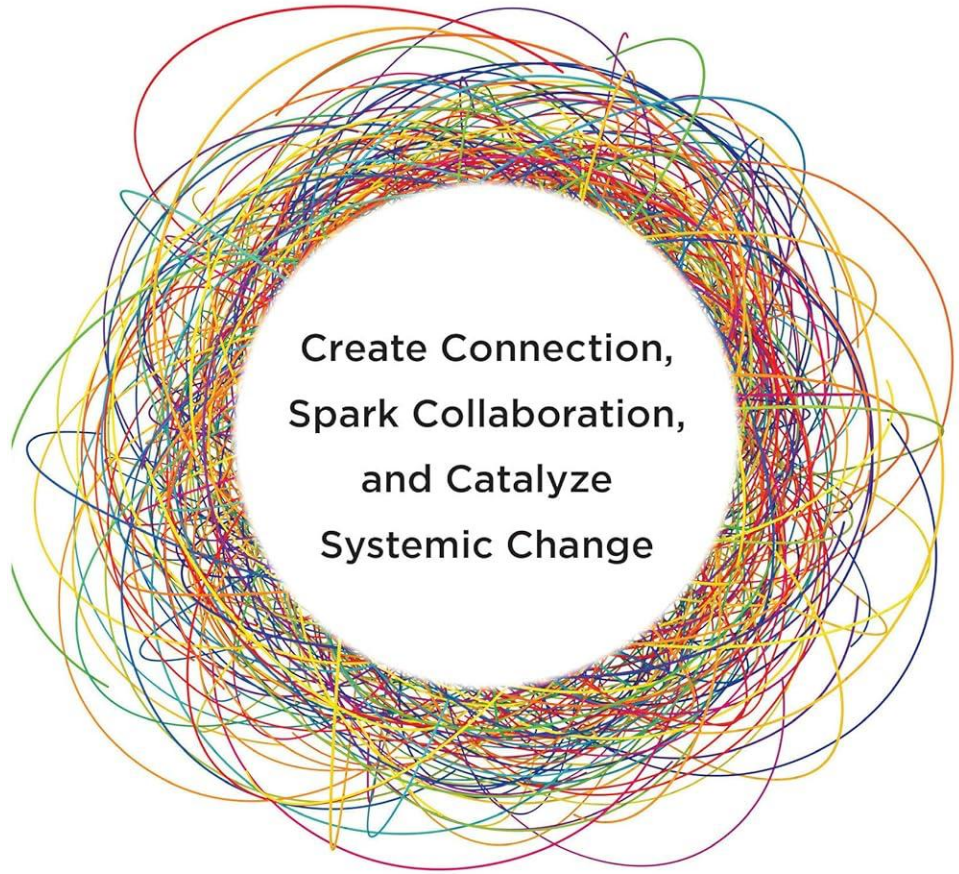
[a]Temple Transformative Medicine Institute; [b]Geography and Urban Studies; [c]Temple Lupus Clinic, Temple University, Philadelphia, Pa; [d]Emerging Pathogens Institute, University of Florida, Gainesville, Fla.

The American Journal of Medicine (2017) 130, 1246–1250

A Learning Health Network

- ❑ Relentless focus on outcomes that matter
- ❑ Community - **Everyone** contributes and innovates
- ❑ Data-driven learning and sharing
- ❑ Advanced improvement methods to change systems
- ❑ Multiple healthcare systems learn to improve by sharing outcomes

impact networks



David Ehrlichman

Bipolar *Action* Network

To improve the health and well-being of people with bipolar disorder by fostering collaboration, coproduction, and data-driven improvement, resulting in comprehensive, personalized care solutions that address diverse needs and challenges

JOURNEY TO IMPROVEMENT

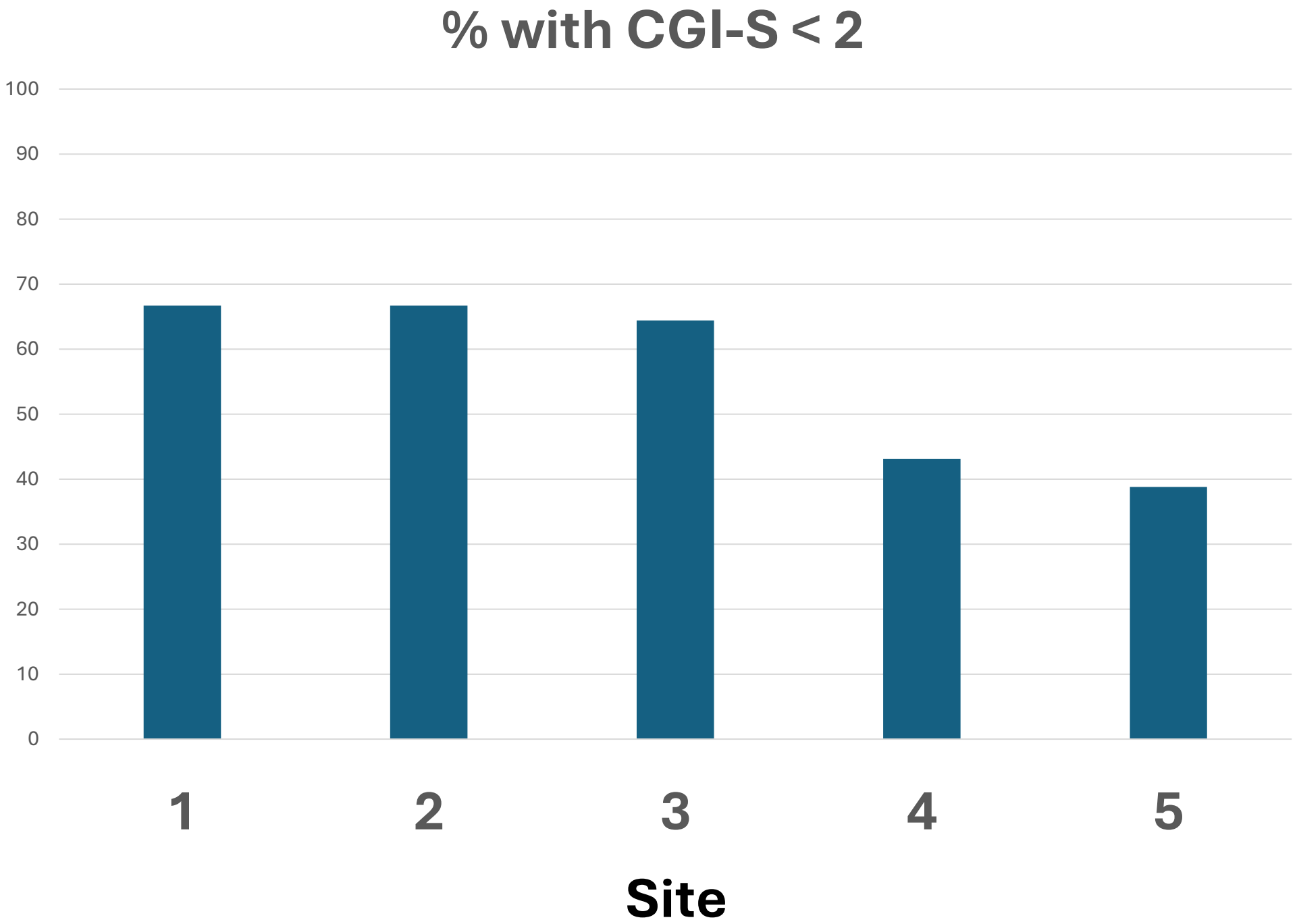
A Team Guide to Systems Change in Education, Health Care, and Social Welfare

Alicia Grunow • Sandra Park • Brandon Bennett

Bipolar *Action* Network

What defines good bipolar care?

- Systematic Diagnosis
- Treatment Selection + Optimization (Treat to Target)
- Routine Monitoring + Stability Assessment
- Relapse and Crisis Planning and Prevention
- Care Coordination
- Safety Monitoring + Side-Effect Management
- Peer & Community Supports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Site

- **Evidence**
- **Challenges**
- **Solutions**