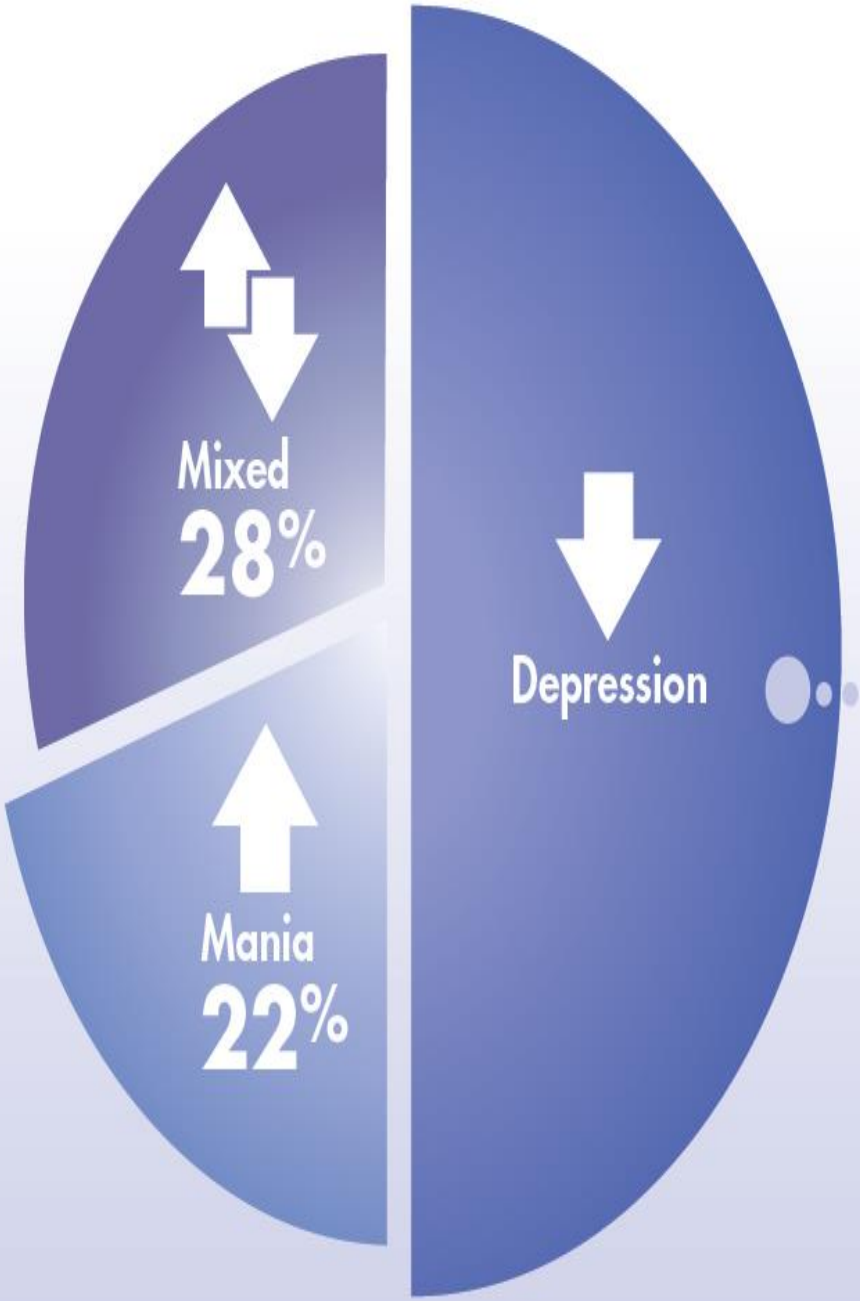
Bipolar Depression – Diagnosis &Management

Dr.Hema Tharoor

Senior Consultant Apollo Spectra Hospitals & SCARF

60%

of adult patients with bipolar disorder who were misdiagnosed **were initially diagnosed with unipolar depression**[1]



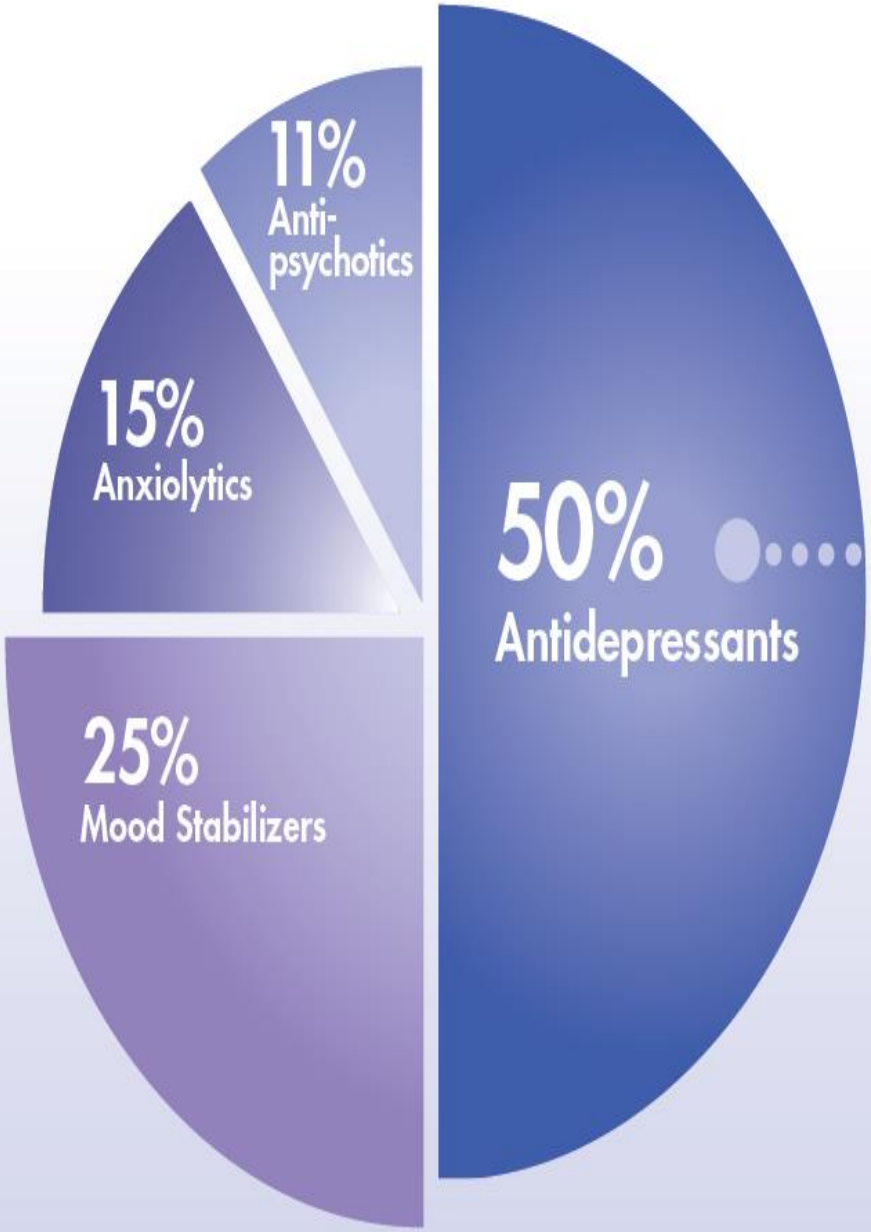
50%

of adult patients with bipolar disorder **experience depression at onset of their symptoms**[6]

Approximately

50%–66%

of patients experience onset during childhood or adolescence[2,3]



Antidepressant monotherapy is prescribed as first-line therapy for ~50% of adult patients diagnosed with bipolar disorder, **2x more often than mood stabilizers**[12]

The numbers in the above chart do not equal 100% due to rounding.

International Society of Bipolar Disorders Working Group on Bipolar Depression

- Family history : Positive for bipolar disorder
- Course of illness: Early onset of first depression (<25 years)*
  Multiple prior episodes of depression (≥5 episodes)*
- Symptomatology :Hypersomnia and/or increased daytime napping Initial insomnia/reduced sleep
- Hyperphagia and/or increased weight
- Atypical depressive symptoms such as leaden paralysis
- Psychomotor retardation
- Psychotic features and/or pathological guilt
- Lability of mood

Table

Factors that suggest bipolar depression rather than unipolar depression

- Prepubertal onset of symptoms
- Brief duration of depressed episodes
- High frequency of depressed episodes
- Seasonal pattern
- Postpartum symptom onset
- Multiple antidepressant failures
- Nonresponse to antidepressant treatment[a]
- Rapid response to antidepressant treatment[b]
- Erratic response to antidepressant treatment[b]
- Dysphoric response to antidepressant treatment with agitation and insomnia
- Family history of bipolar disorder
- History of unstable interpersonal relationships
- Frequent vocational problems
- Frequent legal problems
- Alcohol and drug abuse

[a] The correct diagnosis is bipolar disorder.
[b] Because of the development of mania/hypomania.

MDD With Subthreshold Hypomania Tends to Become BPD Over Time

550 patients diagnosed with MDD (mean follow-up duration: 17.5 years)

- 19.6% converted to bipolar disorder during follow-up
- 12.2% developed hypomania without mania
- 7.5% developed mania (59% of these had preceding hypomania)
- Presence of one or more manic symptoms at time of diagnosis correlated to probability of eventual conversion

Fiedorowitz JG, et al.[2]

TABLE 3. Summary of Consensus Recommendations for Antidepressant Use in Bipolar Disorders by International Society for Bipolar Disorders Task Force[10]

Adjunctive AD for major depressive episode	Acceptable for bipolar disorder I or bipolar disorder II if history of positive response to ADs; avoid if 2 or more core manic symptoms in presence of psychomotor agitation or rapid cycling
Adjunctive AD for maintenance treatment	Acceptable if relapse into depressive episode after discontinuing AD
AD monotherapy for major depressive episodes	Avoid in bipolar disorder I; avoid in bipolar disorder I and bipolar disorder II with 2 or more core manic symptoms
AD associated with switch to mania/hypomania, mixed symptoms, or rapid cycling	Discontinue if emergent mania/hypomania or increased psychomotor agitation; discourage if prior AD-associated mania/hypomania or mixed symptoms; avoid if high number of episodes (mood instability) or history of rapid cycling
AD use in mixed states	Avoid during any episode with mixed symptoms; avoid in patients with predominantly mixed states; discontinue if mixed state emerges
AD with increased risk of switch (TCA and SNRI)	Acceptable only if other ADs failed and if patient is monitored closely

AD, antidepressant.

BD -First Line

- Lithium or Lamotrigine. •Antidepressant mono-therapy is not recommended.
- •Life-threatening inanition, suicidality, psychosis, catatonia - ECT.
- •Psychotherapy - used in addition to pharmacotherapy. Inter Personal Therapy (IPT) & Cognitive Behavior Therapy (CBT).
  •Psychotic features require adjunctive - antipsychotics

Contd

- If not responding to 1st line - – Addition of Lamotrigine, Bupropion or Paroxetine.
- • Next step would be - – Newer antidepressants - SSRI’s or Venlafaxine or MAOI.
- • Breakthrough episode - Optimize the dose of maintenance medication. • Antidepressant induced switch into hypomania is low in BPAD II . So can be started on antidepressants early

Antidepressants

- **Do not** stabilize mood, **may worsen** the outcome of the opposite pole of the illness.
- All major guidelines **advise use of mood stabilizer & recommend only as 2nd line, in concurrent with mood stabilizer.**
- Current guidelines stress to use in short term & early discontinuation.
- Inadequate data to favor one over the other.
- But at the same time no strong evidence to avoid them in severe bipolar depression.

Bipolar Symptoms In Children

- Clinicians should consider BPD
  - Acute, dramatic worsening of apparent ADHD
  - Lack of response/negative to stimulants
  - Other symptom "clues"
    - Grandiosity; elated mood
    - Inappropriate sexual behavior
    - Severe mood swings >3/day
    - Significant aggression
- Mixed features predominate
  - Irritability
  - Belligerence
- Euphoria is not as common

BD in children

11 Astonishing Signs of Bipolar Depression in Children

1. Mood elevation
2. Mood drops
3. Mood fluctuation or cycling
4. Anger, rage
5. Difficulty at school
6. Physical complains
7. Change in food habits
8. Fast forward talking and thinking

9. Suicidal tendency
10. Sleep pattern changes
11. Risky behaviour

Comorbidity in Pediatric and Adolescent Bipolar Disorder (BPD)

- ADHD - 40% to 90%
- Conduct or oppositional defiant disorder - 30% to 76%
- Substance use disorders - 30% to 40%
- Anxiety disorders - 36%

Kafantaris V, et al. *J Am Acad Child Adolesc Psychiatry*. 2001;40:1448.; Geller B, Cook EH. *Biol Psychiatry*. 2000;47:605.

Mood Disorders Questionnaire: The Parent/Adolescent Version

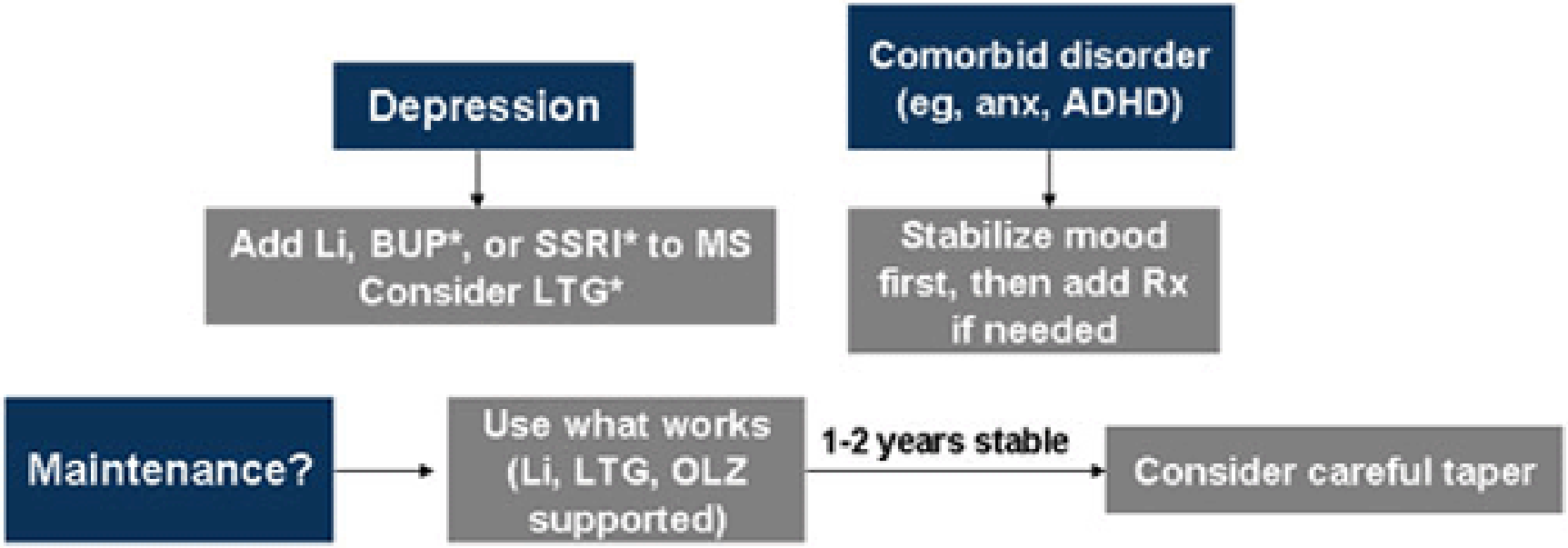
Appendix 1. Mood Disorder Questionnaire-Adolescent Version

Has there ever been a time for a week or more when your adolescent was not his/her usual self and…	Yes	No
…felt too good or excited?	❑	❑
…was so irritable that he/she started fights or arguments with people?	❑	❑
…felt he/she could do anything?	❑	❑
…needed much less sleep?	❑	❑
…couldn't slow his/her mind down or thoughts raced through his/her head?	❑	❑
…was so easily distracted by things?	❑	❑
…had much more energy than usual?	❑	❑
…was much more active or did more things than usual?	❑	❑
…had many boyfriends or girlfriends at the same time?	❑	❑
…was more interested in sex than usual?	❑	❑
…did many things that were foolish or risky?	❑	❑
…spent too much money?	❑	❑
…used more alcohol or drugs?	❑	❑
If you checked YES to more than one of the above, have several of these ever happened to your adolescent during the same period of time?	❑	❑

How much of problems did any of these cause your adolescent—like school problems, failing grades, problems with family and friends, legal troubles? Please circle one response only.

No problem Minor problem Moderate problem Serious problem

Treatment Issues in Pediatric Bipolar Disorder



Madaan V et al. *Expert Opin Pharmacother.* 2007;8:1801-1819.

*Not FDA approved for this indication

Medscape from WebMD

DBT in adolescent bipolar disorder

- When compared to "treatment as usual" controls, teens receiving DBT
  - Attended significantly more therapy sessions
  - Experienced significantly less depressive symptoms
  - Were 3X more likely to experience reduction in suicidal ideation

Goldstein TR et al. *J Child Adolesc Psychopharmacol*. 2015;(25)2:140-49

Percent of Bipolar Patients Who Met Criteria for an Anxiety Disorder

	Lifetime % (n)	Current % (n)
Anxiety disorders	42 (122)	30 (87)
Panic disorder/agoraphobia	20 (58)	9 (27)
Social phobia	16 (47)	13 (36)
Simple phobia	10 (30)	8 (24)
OCD	9 (27)	8 (22)
PTSD	7 (19)	4 (12)
Generalized anxiety disorder	3 (8)	3 (8)
Other anxiety disorders	3 (8)	2 (6)

McElroy SL, et al. *Am J Psychiatry*. 2001;158:420-426.

Comorbidity Occurs Frequently and Can Complicate Diagnosis

- 65% of bipolar patients have a current comorbid axis I condition.
  - Almost a quarter have 3 or more.
- Substance abuse (lifetime prevalence: 61%) and anxiety disorders (lifetime prevalence :42%) are the most common.
- Comorbid conditions can mimic mood symptoms, mask them, or exacerbate them.

McElroy SL et al. *Am J Psychiatry*. 2001;158:420-426.

BPD & Bipolar depression

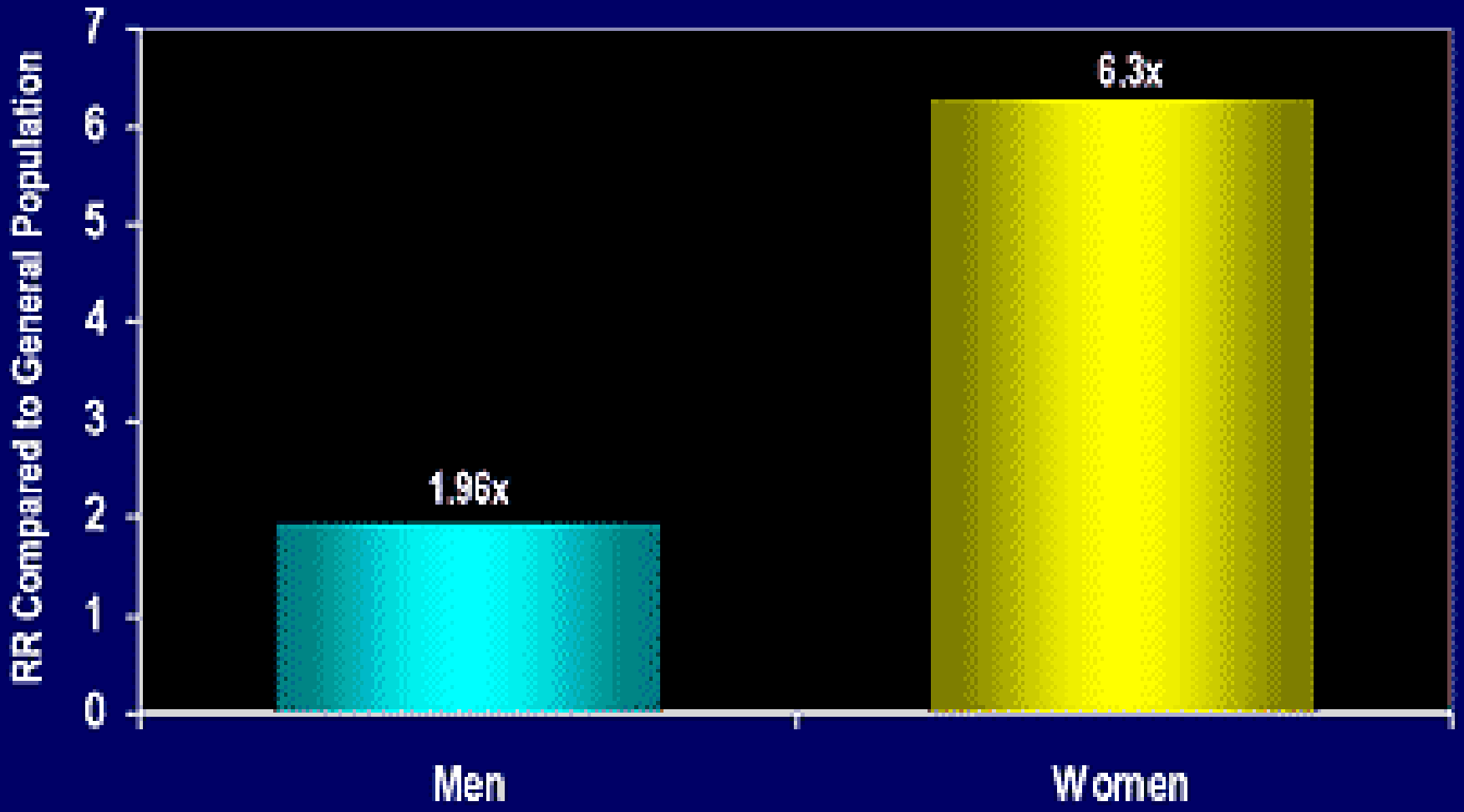
- **Impulsiveness** is an important aspect of both disorders and that there is a compounding effect associated with a diagnosis of bipolar II disorder with comorbid BPD.
- Oxcarbmazepine
- Flupenthixol

Substance Use & Epilepsy

Clinical Presentation and Treatment Response: Bipolar Disorder and Substance Abuse

1. Earlier age of bipolar illness onset
2. Increased healthcare utilization
    - ER visits
    - Hospitalization
3. Higher rates
    - Mixed states
    - Rapid cycling
    - Impulsivity
    - Aggression
    - Suicidality
4. Treatment response
    - Slower time to recovery
    - Decreased lithium response
    - Decreased treatment adherence

Greater Risk of Alcohol Comorbidity in Women With Bipolar Disorder than Men



RR=Relative risk.

Frye MA, et al. *Am J Psychiatry*. 2003;160(5):883-889.

Epilepsy + BD

- Watch for Leviracetam induced mood changes
- Missed especially if premorbidly has cluster b traits or epileptic personality

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Effect of sleep patterns on levetiracetam induced mood changes☆

Randip Taneja [a], Krystal Hunter [b], Evren Burakgazi-Dalkilic [a,c], Melissa Carran [a,c,*]

[a] Department of Neurology, Cooper University Hospital, 1 Cooper Plaza, Camden, NJ 08103, United States
[b] Cooper Research Institute, Cooper University Hospital, 1 Cooper Plaza, Camden, NJ 08103, United States
[c] Department of Neurology, Cooper Medical School of Rowan University, 3 Cooper Plaza, Suite 320, Camden, NJ 08103, United States

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ABSTRACT

A common side effect of levetiracetam is the onset of neuropsychiatric symptoms such as mood changes including depression, anxiety, agitation, and sometimes psychosis. We performed a retrospective analysis to examine the effect of sleep pattern and chronotype on individual susceptibility to levetiracetam-induced mood changes. We reviewed records of 110 adults with epilepsy presenting to our clinic during a 3-month period, and categorized them into those currently on levetiracetam, and those no longer taking it because of mood-related adverse effects. Patients were administered Morningness–Eveningness Questionnaire (MEQ), Beck's Depression Inventory-II, and Neurological Disorders Depression Inventory in Epilepsy. Using various statistical methods, we analyzed the comparison of these 3 different scales amongst one another and between those subjects who tolerated levetiracetam and those who did not. Of 110 patients, 74 (67%) tolerated levetiracetam and 36 (33%) did not tolerate it because of mood changes with chronotype being a significant determining factor. Of those who tolerated the drug, 62% were intermediate chronotypes and 20.3% and 17.6% were morning and evening chronotypes, respectively. For those intolerant, 86.1% were morning chronotypes, 13.9% were intermediate chronotypes, and none were evening chronotypes ($p < 0.001$). Thirty-two percent of morning chronotypes, 100% of evening chronotypes, and 90.2% of intermediate chronotypes were tolerant of levetiracetam ($p < 0.001$). Chronotype significantly affected toleration of levetiracetam. Chronotype, but not depression, was a significant factor in determining tolerability of mood-altering side effects of levetiracetam, via statistically significant trend for an increasing ability to tolerate levetiracetam as chronotype would shift from morning to intermediate to evening. Additional research may help establish if this is related to possible underreporting of poor mood with evening chronotypes, and morning chronotypes having more stringent sleep schedules, genetic factors, or other reasons.

1. Introduction

Levetiracetam is one of the safest and most widely used anticonvulsants. The most frequently encountered and troubling side effect is the onset of neuropsychiatric symptoms such as mood changes of depression, anxiety, agitation, and sometimes psychosis [1,2]. This causes problems for patients and their family members, and often necessitates discontinuation of the medication. The ability to predict which patients will not tolerate levetiracetam would have a major impact on clinical decisions to successfully treat epilepsy.

Chronotype refers to the circadian rhythm of a given organism that determines if alertness and productivity are greater in the hours of early morning or later in the day [3]. When identifying a chronotype, three broad categories are often used: Morning type (informally known as "Lark"), Evening type (informally known as "Owl"), and Intermediate type [4]. The purpose of this study was to determine if there is a relationship between a patient's sleep pattern, i.e., chronotype, and their susceptibility to the mood deteriorating side effects of levetiracetam. We hypothesize that the individual chronotype may predict tolerance of the medication.

In his thesis *Charting Individual Daily Rhythms* [5], O. Oquist from University of Goteborg, Sweden, Department of Psychology, introduced a questionnaire with the aim to separate "morningness" and "eveningness" [6]. This questionnaire was modified by Ostberg and Horne, who in 1976 had published the 19-item Morningness–Eveningness (ME) Questionnaire (MEQ) [4], which has been widely used in medical research. The scoring for the MEQ consists of a scale from 16 to 86, based on which an individual is determined to have one of five chronotypes: Definite Evening, Moderate Evening, Intermediate, Moderate Morning, or Definite Morning [Table 1].

There is accumulating research suggesting a link between chronotype and mood. Some studies show higher association with depression or

☆ Statistical analysis was conducted by Krystal Hunter, MBA, Cooper Medical School of Rowan University, Statistician II — Cooper Research Institute, Cooper University Hospital.

* Corresponding author at: Cooper Medical School of Rowan University Hospital, 3 Cooper Plaza, STE 320, Camden, NJ 08103, United States.
E-mail addresses: Randymd1@hotmail.com (R. Taneja), Hunter-krystal@cooperhealth.edu (K. Hunter), Burakgazi-dalkilic-evren@cooperhealth.edu (E. Burakgazi-Dalkilic), Carran-Melissa@cooperhealth.edu (M. Carran).

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1525-5050/

Levetiracetam in the Management of Bipolar Depression: A Randomized, Double-blind, Placebo Controlled Trial

Aybala Saricicek, MD; Kathleen Maloney, BA; Boris Lorberg, MD;
Anjana Muralidharan, BA; Barbara Ruf, BA; Hilary Blumberg, MD;
Gerard Sanacora, MD, PhD; Brian Pittman, MS;
Jian Hu, MD; Zubin Bhagwagar, MD, PhD, MRCPsych
Department of Psychiatry, Yale University, New Haven, CT

NCDEU
New Research Approaches for Mental Health Interventions
2009

This poster is presented in columns for online reading.
You may also see the poster in its original format.

Evolving Role of PKC

Association of PKCε with the risk of suicide[1]

Role of **PKC-Zeta** in bipolar disorder susceptibility[2]

Excessive activation of PKC dramatically impairs cognitive function[3]

Inhibitors of PKCε are useful in reducing **ethanol consumption and anxiety.**[4]

PKC inhibition blocks the development of **cocaine** CPP.[5] PKC also has role in blocking **cannabis and morphine** preferences

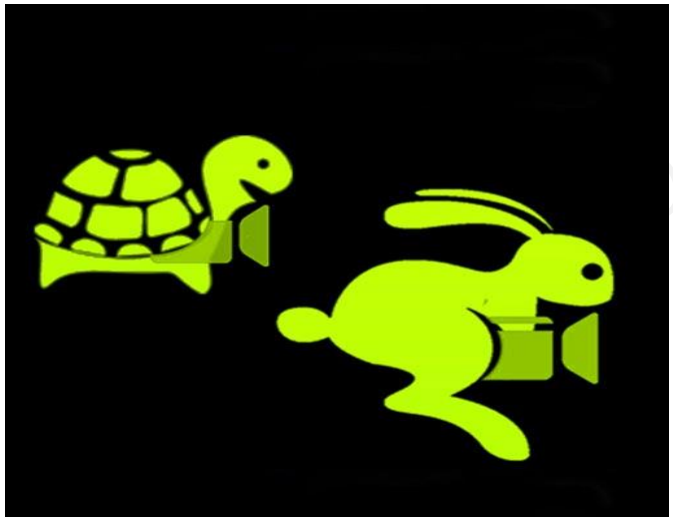
* The pictures are not of actual patients and are for representation purpose only.

1. Pandey GN, *et al*. *Int J Neuropsychopharmacol*. 2021;24(5):400–408.
2. Kandaswamy R, *et al. Am J Med Genet B Neuropsychiatr Genet*. 2012;159B(2):201–9.
3. Birnbaum SG, *et al. Science*. 2004;306(5697):882–4.
4. Olive MF, Messing RO. *Mol Neurobiol*. 2004;29(2):139-154.
5. Zarate CA, Manji HK. *CNS Drugs*. 2009;23:569–82

CCP: Conditioned place preference; PKC: Protein kinase C.

Bipolar & PKC

Mania



PKC

International Guidelines Bipolar Disorders

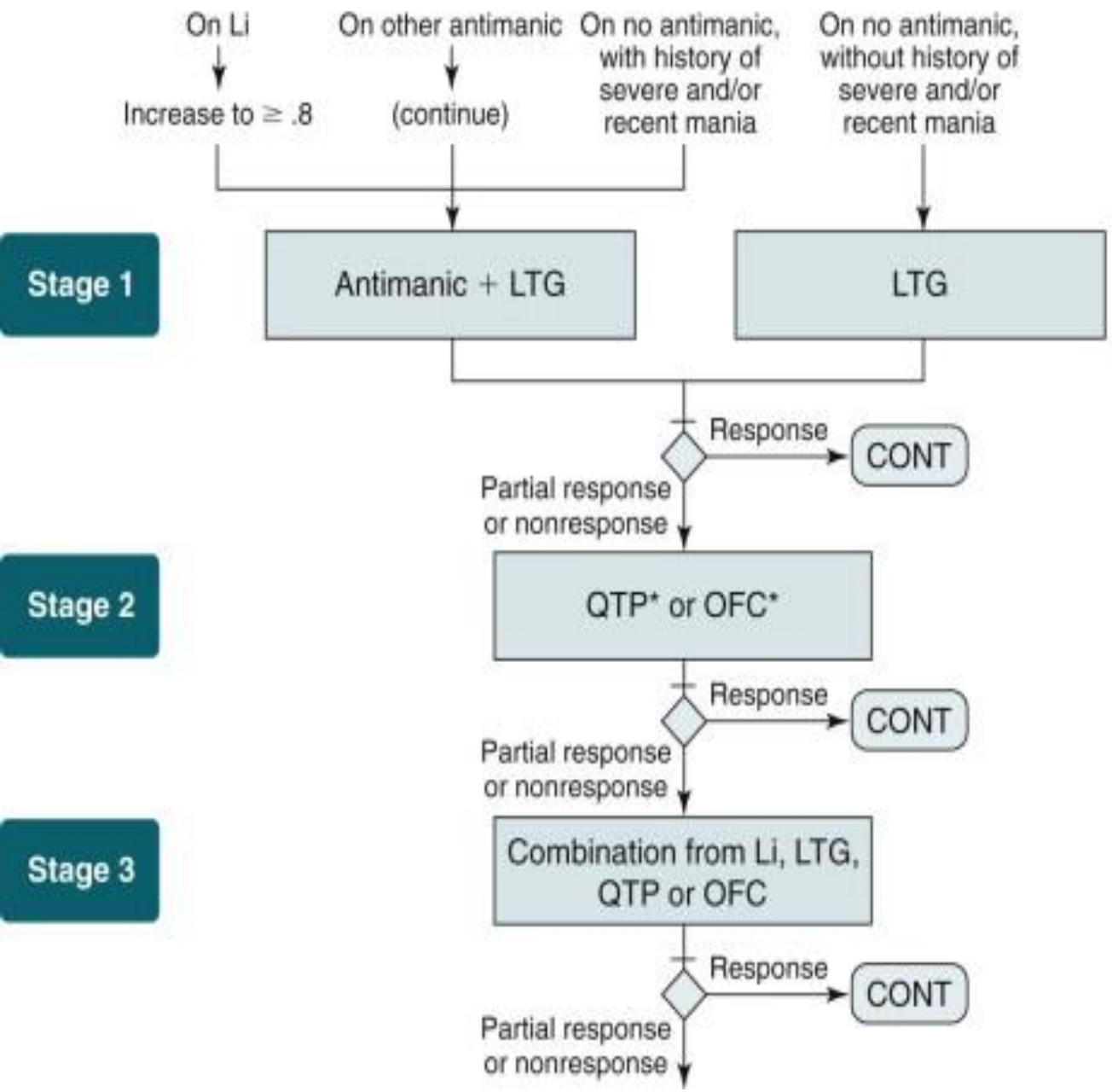
- American Psychiatric Association (APA):
  Practice Guideline for the Treatment of Patients with Bipolar Disorder[1]
- Canadian Network for Mood and Anxiety Treatments (CANMAT):
  Guidelines for the Management of Patients with Bipolar Disorder[2,3]
- British Association for Psychopharmacology (BAP):
  Evidence-based guidelines for treating bipolar disorder[4]
- World Federation of Societies of Biological Psychiatry (WFSBP)
  WFSBP Treatment Guidelines on Bipolar Disorders[5,6,7]
- NICE Guideline
  The management of bipolar disorder in adults, children and adolescents, in primary and secondary care[8]

[1]Hirschfeld et al. 2002, [2]Yatham et al. 2005, [3]Yatham et al. 2006, [4]Goodwin et al. 2009, [5]Grunze et al. 2002, [6]Grunze et al. 2004, [7]Grunze et al. 2009, [8]The British Psychological Society and The Royal College of Psychiatrists 2006

Controlled Trials of Mood Stabilizers for the Acute Treatment of Bipolar Depression

- Lithium: 9 studies; modest effects
- Divalproex: 1 study; modest effect
- Olanzapine: 1 study; modest effect
- Lamotrigine: 2 studies; robust effects
- Quetiapine and olanzapine + fluoxetine: 1 study each; robust effects, but mood stabilization not yet demonstrated

ALGORITHM FOR THE TREATMENT OF BIPOLAR DISORDER I—CURRENTLY DEPRESSED



Antimanic = Li, valproex

Li = lithium

LTG = lamotrigine

QTP = quetiapine

OFC = olanzapine + fluoxetine combination

CONT = continue

Approved for BD

- OFC - single modality
- Quetiapine – single modality
- Lurasidone -single & adjunct to li + Divalproex
- **The overall effect size of the 3 treatments in mitigating depressive symptoms is similar**.

BOLDER (BipOlar DEpRession) I & II trials & EMBOLDEN (Efficay of Monotherapy Quetiapine in BipOLar DEpressioN)

- BOLDER I & II - 8 week, DBRCT, comparing 300mg & 600mg, significant improvement in MADRS scores over placebo. • Response rates - 58% & Remission rates - 53%. • EMBOLDEN- Quetiapine was significantly more effective than Lithium in improving MADRS score at 8 weeks. • Low incidence of emergent mania. • Adverse effects - dry mouth, sedation, somnolence, dizziness & constipation.

Comparative Evaluation of QUEtiapine Plus Lamotrigine vs Quetiapine in Bipolar Depression (CEQUEL)

- Quetiapine is efficacious but has a substantial adverse effect burden
- Sedation, weight gain
- Lamotrigine is well tolerated but not particularly efficacious as monotherapy in bipolar depression
- Effective combination

PREVAIL

- **The Program to Evaluate the Antidepressant Impact of Lurasidone .**
- **PREVAIL 1** - 348 depressed bipolar I patients treated with lithium or valproate who were randomized to receive adjunctive lurasidone 20–120 mg/day (*n* = 183) versus placebo (*n* = 165) for 6 weeks.
- **The PREVAIL 2** study included 505 bipolar I depressed patients randomized to 6 weeks of lurasidone monotherapy (20–60 mg/day [*n* = 166] or 80–120 mg/day [*n* = 169]) or placebo (*n* = 170).
- Compared to placebo, lurasidone is associated with a superior rates of response (52.0% vs. 30.2%, NNT = 5) and remission.

Pramiprexole

- D2/D3 dopamine receptor agonist
- Efficacy of pramipexole in the treatment of bipolar depression
- The first report randomized 22 patients with bipolar depression with an inadequate response to existing mood stabilizers, and then added either pramipexole (*n* = 12) or placebo (*n* = 10) for 6 weeks . The **response rate** is **significantly higher in the pramipexole group** than in the placebo group (67% vs. 20%, NNT = 2), **but not in the remission rate** (20% vs. 16%, NNT = 30). Another report randomized 21 patients with bipolar depression with a similar study design and gave a higher response and remission rates in the pramipexole group than in the placebo group (60% vs. 9%, NNT = 2; 40% vs. 9%, NNT = 3, respectively).
- **Pramipexole is generally well tolerated and is not associated with an increased incidence of hypomania/mania.**

Modafinil

Treatment-resistant bipolar depression

- For treatment-resistant acute bipolar depression, the dopaminergic agonist pramipexole and the wakefulness-promoting agent modafinil which have been shown to have efficacy greater than placebo as augmentation to standard treatments

1-Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. *Am J Psychiatry.* 2004; 161:564-566.

2-Frye MA, Grunze H, Suppes T, et al. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. *Am J Psychiatry.* 2007; 164:1242-1249.

Ketamine

- N-methyl-D-aspartate receptor antagonist and targets glutamate.
- Rapid resolution of depression and suicidal ideation after single intravenous infusions of low doses of ketamine has been reported in patients with bipolar depression. **A meta-analysis of 3 double-blind placebo-controlled studies in 69 patients with bipolar depression showed a significant improvement in mean primary depression scores in the ketamine group versus the placebo group** .
- **The onset of antidepressant effects is observed within 40 min and is maintained for several days**

Adjunctive Bright Light Therapy for Bipolar Depression

- 6-week randomized double-blind placebo-controlled trial to investigate the efficacy of adjunctive bright light therapy at midday for bipolar depression.
- The data from this study provide robust evidence that supports the efficacy of midday bright light therapy for bipolar depression.

rTMS & bipolar depression

- Repetitive transcranial magnetic stimulation (rTMS) has been found to be an effective technique in the treatment of unipolar depression & lack of high quality studies on which we can base our conclusions about the effectiveness of rTMS for the treatment of bipolar depression.
- Does not seem to increase the risk that a patient will develop (hypo)mania.
- Tijdschr Psychiatr. 2017;59(10):605-611

tDCS & Bipolar Depression

- April 2002 to November 2016 (systematic review and meta-analysis -382 studies
- 46 patients from 7 studies with depression rating-scale scores pre- and post-tDCS.. Depression scores decreased significantly with a medium effect size after acute-phase of treatment (SMD 0.71 [0.25-1.18]. Six cases of affective switching under tDCS treatment protocols were observed.

- Prog Neuropsychopharmacol Biol Psychiatry. 2017 Aug 1;78:123-131.

THE UNIVERSITY OF MELBOURNE

Department of Psychiatry

LEADING MENTAL HEALTH RESEARCH ACROSS THE LIFESPAN

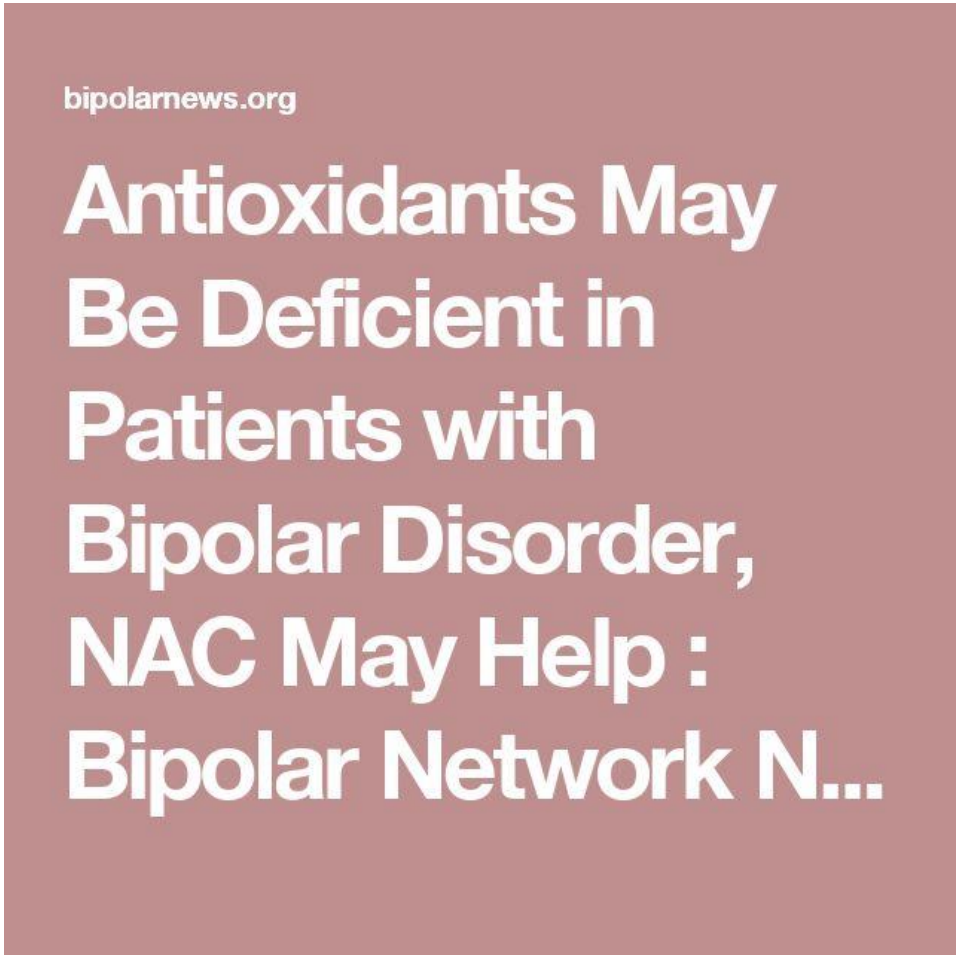
Adjunctive Nutraceutical Treatment of Unipolar & Bipolar Depression

ISAD/ISBD 2016

Dr Jerome Sarris

Senior Research Fellow (CR Roper Fellow)
Head of ARCADIA Mental Health Research Group
Professorial Unit; Department of Psychiatry
The University of Melbourne
jsarris@unimelb.edu.au

NAC & BD


bipolarnews.org
Antioxidants May Be Deficient in Patients with Bipolar Disorder, NAC May Help : Bipolar Network N...

Effects of *N*-Acetyl Cysteine on Suicidal Ideation in Bipolar Depression

To the Editor: Suicide is the leading cause of death in young adults, and the lifetime risk of suicide for people with bipolar disorder is 15%. A meta-analysis of 15 studies[1] determined prevalence rates of attempted suicide as high as 36.3% in bipolar I disorder and 32.4% in bipolar II disorder. A recent review[2] on suicide in bipolar disorder emphasized the need for further research into how suicidality is generated and how to avert this outcome. Of the available psychotropic agents, only lithium has an evidence base for efficacy in suicide prevention. Effective therapies, including novel therapies, for suicide prevention in bipolar disorder are therefore a clinical imperative.

N-Acetyl cysteine (NAC) has a diversity of actions, including on glutamate, glutathione, oxidative stress, inflammation, and mitochondrial dysfunction, that as a group represent dysregulated pathways in bipolar disorder.[3] Glutamate dysregulation in particular has been implicated in suicide attempts. A recent study[4] reported increased levels of quinolinic acid (an agonist of the glutamatergic *N*-methyl-D-aspartate receptor) in the cerebrospinal fluid of 64 medication-free suicide attempters compared to 36 controls. This study emphasized the importance of inflammation and glutamate neurotransmission in the pathophysiology of suicidal behavior, which has implications for the detection and treatment of suicidal patients. However, no studies have been reported on the reduction of suicidality by NAC to date. NAC is a relatively safe, available, and well-tolerated agent, with efficacy signals in a number of neuropsychiatric disorders.[5]

Method and results. In this light, we conducted a post hoc analysis of the effects of NAC on suicidal ideation in a sample of individuals diagnosed with *DSM-IV* bipolar depression. The data included in this analysis are from a previously conducted 24-week randomized, multicenter, double-blind, placebo-controlled trial[6] (N = 75) of NAC (2 gpp daily) for bipolar depression. The unadjusted Montgomery-Asberg Depression Rating Scale[7] (MADRS) mean (SD) score of item 10 (Suicidality) at baseline was 0.78 (1.3) for placebo and 1.21 (1.5) for the NAC treatment group. At 24 weeks, the MADRS mean score of item 10 was 0.92 (1.4) for placebo and 0.22 (0.52) for NAC. The unadjusted Bipolar Depression Rating Scale[8] (BDRS) mean (SD) score of item 13 (Suicidality) at baseline was 0.41 (0.76) for placebo and 0.55 (0.92) for the NAC treatment group. At 24 weeks, the BDRS mean score of item 13 was 0.44 (0.65) for placebo and 0.04 (0.21) for NAC. These results indicate there was a reduction in suicidal ideation for those taking NAC compared to those taking placebo. Using an intention-to-treat, mixed-effects model, repeated-measures approach (SPSS version 21; IBM, Inc) correcting for the MADRS total score at the start of the trial, we analyzed weeks 0, 4, 8, 12, 16, 20, and 24 of the MADRS suicidality item 10 and found a statistically significant difference in suicidal ideation between NAC and placebo ($P = .039$, CI = −0.476 to −0.013). This result was replicated with BDRS item 13 ($P = .024$, CI = −0.308 to −0.022). This statistically significant difference in suicidal ideation still persisted after adjusting for age and sex.

Conclusion/discussion. In summary, we found a suggestive signal for the reduction of suicidal ideation associated with the use of NAC in a study of bipolar depression. NAC has been shown to be beneficial for bipolar depression, and this study provides a preliminary indication that it might reduce suicidal ideation in this population as an adjunctive therapy. Because this analysis is post hoc, the sample size is limited for the investigation of suicidal ideation. As such, these data are preliminary and can only be taken as directions for future study. Nevertheless, given the severity of the problem of suicide in bipolar disorder,[1,9] the paucity of therapeutic options, and the benign nature of the intervention, use of NAC in this population is a lead worth following.

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Astrid Waterdrinker, MMed, MRCPsych, MSC
astridwater@gmail.com
Michael Berk, MD, PhD
Kamalesh Venugopal, PhD
Marta Rapado-Castro, PhD
Alyna Turner, PhD
Olivia M. Dean, PhD

Author affiliations: North West Area Mental Health Service, Melbourne Health, The Royal Melbourne Hospital (Dr Waterdrinker); Orygen, The National Centre of Excellence in Youth Mental Health (Drs Berk and Rapado-Castro), Parkville, Victoria; IMPACT Strategic Research Centre, Deakin University, School of Medicine, Barwon Health, Geelong (Drs Berk, Venugopal, Turner, and Dean); Department of Psychiatry, University of Melbourne, Royal Melbourne Hospital (Drs Berk, Turner, and Dean); Florey Institute for Neuroscience and Mental Health, University of Melbourne (Drs Berk and Dean), Parkville, Victoria Australia; Department of Psychiatry, Melbourne Neuropsychiatry Centre, The University of Melbourne and Melbourne Health, Victoria, Australia, and Child and Adolescent Psychiatry Department, Hospital General Universitario Gregorio Marañón School of Medicine, Universidad Complutense, Insitituto de Investigacion Sanitaria Gregorio Marañon, IiSGM, CIBERSAM. Madrid, Spain (Dr Rapado-Castro); and School of Medicine and Public Health, University of Newcastle, Callaghan, New South Wales, Australia (Dr Turner).

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Psychotherapy

- CBT
- Mindfulness
- Interpersonal Social rhythm therapy
- Support groups – Chennai has started ….

BD in elderly

Bipolar Disorders: in Older Adults

- Depression usually precedes mania by 20 years
- In general, manic symptoms are milder compared to younger patients
- May present with mixed, manic, dysphoric or agitated states
- More likely to have
  - Irritability,
  - Treatment resistance,
  - Higher mortality rate
- Develop dementia at a higher rate than elderly without bipolar illness

Major Points

- Bipolar states in the elderly are heterogeneous and require careful differential diagnosis.
- Medical assessment is essential.
- Cognitive impairment is a frequent concomitant of bipolar disorders in the elderly.
- Data on pharmacotherapy are limited
- Some data are available to support use of lithium, divalproex, atypical antipsychotics in mania and lithium, lamotrigine, some antidepressants in bipolar depression.

Table 3

Clinical considerations in older adults with bipolar disorder

Bipolar manic symptoms may be reduced or attenuated
Bipolar depressive symptoms may be more prominent and exert longer-term impact on functioning
Cognitive deterioration may occur over time
Medical comorbidity is extensive, with 3 to 6 chronic medical conditions being the norm

Source: References 24-27

TABLE 1. Possible contributing factors to treatment-resistant bipolar disorder

- Inability to identify "soft" hypomanic symptoms
- Incorrect diagnosis of bipolar disorder
- Incorrect recognition of bipolar disorder phase
- Patient is poor historian (failure to use collateral sources and prior treatment records)
- Poor patient compliance
- Concurrent alcohol or substance use
- Concurrent use of destabilizing medication (psychiatric and nonpsychiatric)
- Concurrent acute or chronic medical illness
- Inadequate medication supervision by treatment provider
- Inadequate medication trial
- Limiting treatment choices to "evidence-based" medications only
- High starting dose or rapid dose increase of medications
- Failure to recognize bipolar disorder is usually a chronic and recurrent illness

TABLE 2. General medication guideline suggestions

- Do not change more than one medication at a time
- Choose medications for specific target symptoms
- Prioritize treatment of severe, uncomfortable, or disabling symptoms (insomnia, anxiety, panic attacks, psychosis)
- Use benzodiazepines as adjunctive treatment for symptoms of bipolar disorder that do not respond to maintenance mood medications (insomnia, anxiety, panic attacks)
- Consider cost and accessibility of medications
- Educate patient about medication before initiation of treatment (provide literature)
- Provide proactive supervision of medication changes when patient is unstable (frequent phone calls or office visits)
- Be aware that formal treatment guidelines can be helpful, but most have imperfections
- Document rationale for non–FDA-approved medications if not considered standard of care
- Start medications at low doses and increase dose cautiously, especially in elderly patients
- Become familiar with different forms and strengths of bipolar disorder medications (brand vs generic, capsules vs tablets, liquid, compounded, etc)

TABLE 4. Proposed guidelines for treatment options (in order of preference) for the 3 main phases of bipolar disorder

Acute hypomanic/manic and mixed episodes	Major depressive episodes	Continuation/maintenance/preventive treatment
• FDA-approved medications (1-3): lithium, SGA, valproic acid • Monotherapy or adjunctive other FDA-approved medications: carbamazepine, chlorpromazine • Monotherapy or adjunctive other FGA • Other anticonvulsants (adjunctive): oxcarbazepine, pregabalin, gabapentin, levetiracetam • Benzodiazepines (adjunctive) • Other medication families (monotherapy or adjunctive): calcium channel blockers, memantine • Clozapine • ECT	• Lurasidone (FDA approved) and lamotrigine (monotherapy or adjunctive) • Quetiapine (FDA approved) • Lithium (monotherapy or adjunctive) • Asenapine • Aripiprazole (monotherapy or adjunctive) • Anticonvulsants (monotherapy or adjunctive): oxcarbazepine, levetiracetam, carbamazepine • Antidepressants (monotherapy or adjunctive) • Other medications (monotherapy or adjunctive): modafinil or armodafinil, pramipexole, stimulants (methylphenidate), thyroid (T3) • Light therapy • Transcranial magnetic stimulation • ECT • Vagus nerve stimulation • Adjunctive ketamine	• Continue effective medication for acute hypomanic/manic or major depressive episode • Lithium (FDA approved) • Lamotrigine (FDA approved) • FDA-approved SGA (monotherapy or adjunctive) • Non–FDA-approved SGA (monotherapy or adjunctive) • Carbamazepine (monotherapy or adjunctive) • Transcranial magnetic stimulation • Clozapine (monotherapy or adjunctive) • ECT

FGA, first-generation antipsychotic; SGA, second-generation antipsychotic.

Florida Algorithm: Treatment of Acute Bipolar Depression

Consider psychiatric consultation, if possible, prior to psychotherapeutic treatment.

Level 1: Treatments with established efficacy

- Quetiapine* or lurasidone** monotherapy
- Lurasidone adjunctive to lithium or divalproex (bipolar I disorder)

*Only quetiapine has established efficacy for bipolar II disorder

**Lurasidone has a better metabolic profile than quetiapine

Level 2A: Established efficacy, but with safety concerns*

- Olanzapine + fluoxetine (bipolar I disorder)

*Tolerability limitations include weight gain and metabolic concerns.

Level 2B: Better tolerability, but limited efficacy*

Consult a specialist

- Lithium (bipolar I disorder)
- Lithium adjunctive to lamotrigine (bipolar I disorder)
- 2 drug combination of above medications

2015 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults.

Florida Algorithm: Treatment of Acute Bipolar Depression (cont)

Level 3: If levels 1 and 2 are ineffective and/or not well tolerated*

- Electroconvulsive therapy (ECT)

*Consideration is merited due to clinical need, despite even greater efficacy/tolerability limitations than Level 1 and 2 treatments.

Level 4: If levels 1 to 3 are ineffective and/or not well tolerated

- FDA approved agent for bipolar disorder + conventional
- antidepressant*
- Pramipexole
- Adjunctive – modafinil, thyroid, or stimulants
- 3 drug combination
- Transcranial magnetic stimulation (TMS)

*There is inadequate information (including negative trials) to recommend adjunctive antidepressants, aripiprazole, ziprasidone, levetiracetam, armodafinil, or omega-3 fatty acids for bipolar depression.

2015 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults.

Table 2

Suggested provisional guidelines for integrative treatment of bipolar disorder

Manic phase

Use of select natural products as adjuvants to conventional mood stabilizers

Use of magnesium, choline, and branched-chain amino acids as adjuvants in acute manic phase

Use of folate as adjuvant to lithium carbonate in acute manic phase

Use of proprietary nutrient formula as adjuvant to mood stabilizers in mania

Use of *Rauwolfia serpentina* for treatment-refractory bipolar mania with psychosis; adjuvant to lithium for acute manic phase

Depressed phase[a]

Use of omega-3 essential fatty acids as adjuvant to mood stabilizers

Use of *N*-acetylcysteine in stable bipolar disorder as adjuvant to mood stabilizers

[a] Bipolar patients being treated with any conventional or complementary and alternative medicine (CAM) antidepressant should be monitored closely for warning signs of mania; if a patient becomes manic, the conventional or CAM antidepressant should be discontinued immediately.

Antidepressants in Bipolar Disorder: Conclusions

- Maintenance antidepressant efficacy is not established in bipolar disorder.
- Switches and/or cycling on antidepressants demonstrated in 3 randomized placebo-controlled studies.
- Antidepressant monotherapy is contraindicated in bipolar I disorder; bipolar II?
- Antidepressants (with a mood stabilizer) should generally be reserved for severe bipolar depression, or when adjunctive mood stabilizers have failed.
- When antidepressants are used, discontinue them after recovery from depression; maintain them only in those who repeatedly relapse soon after discontinuation (about 20% of bipolar patients)

SN Ghaemi, DJ Hsu, F Soldani, FK Goodwin. *Bipolar Disord*. 2003;5:421-433.

Summary

- The major challenge in long-term management of bipolar disorder is the treatment and prevention of depression.
- Try to use stabilizers that work "from below" without destabilizing, especially lamotrigine.
- Avoid antidepressants if possible; for severe depression, or when 2 stabilizers fail, use antidepressants, but limit dose & duration.
- Lithium is still an important drug, even more so now, given that it is the only stabilizer shown to reduce suicide.

Conclusion

- Mistaking bipolar depression for unipolar depression is common.
- Focusing on a history of objective behaviors associated with mania before investigating mood state increases diagnostic sensitivity.
- Look for clinical features of a depressive episode that are associated with bipolar depression.
- Comorbid conditions can complicate diagnosis and treatment.

psych scene
EXCELLENCE IN PSYCHIATRY

IS IT BIPOLAR DEPRESSION?

W – Worse or wired when taking antidepressants

H – Hypomania, hyperthymic temperament, and mood swings in history

I – Irritable, hostile or mixed features

P – Psychomotor retardation

L – Loaded Family history: bipolar illness, affectivity and mood swings

A – Abrupt onset and/or termination of depressive episodes less than 3 mths

S – Seasonal or postpartum depression

H – Hyperphagia and Hypersomnia

E – Early age of onset

D – Delusions, Hallucinations and Psychotic features

Thank you for listening. Any questions?