Clinical Updates on Neurotherapeutics: Disease State

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SGAs versus Mood Stabilizers: The Paradigm Shift in Core Treatment for Bipolar Disorder

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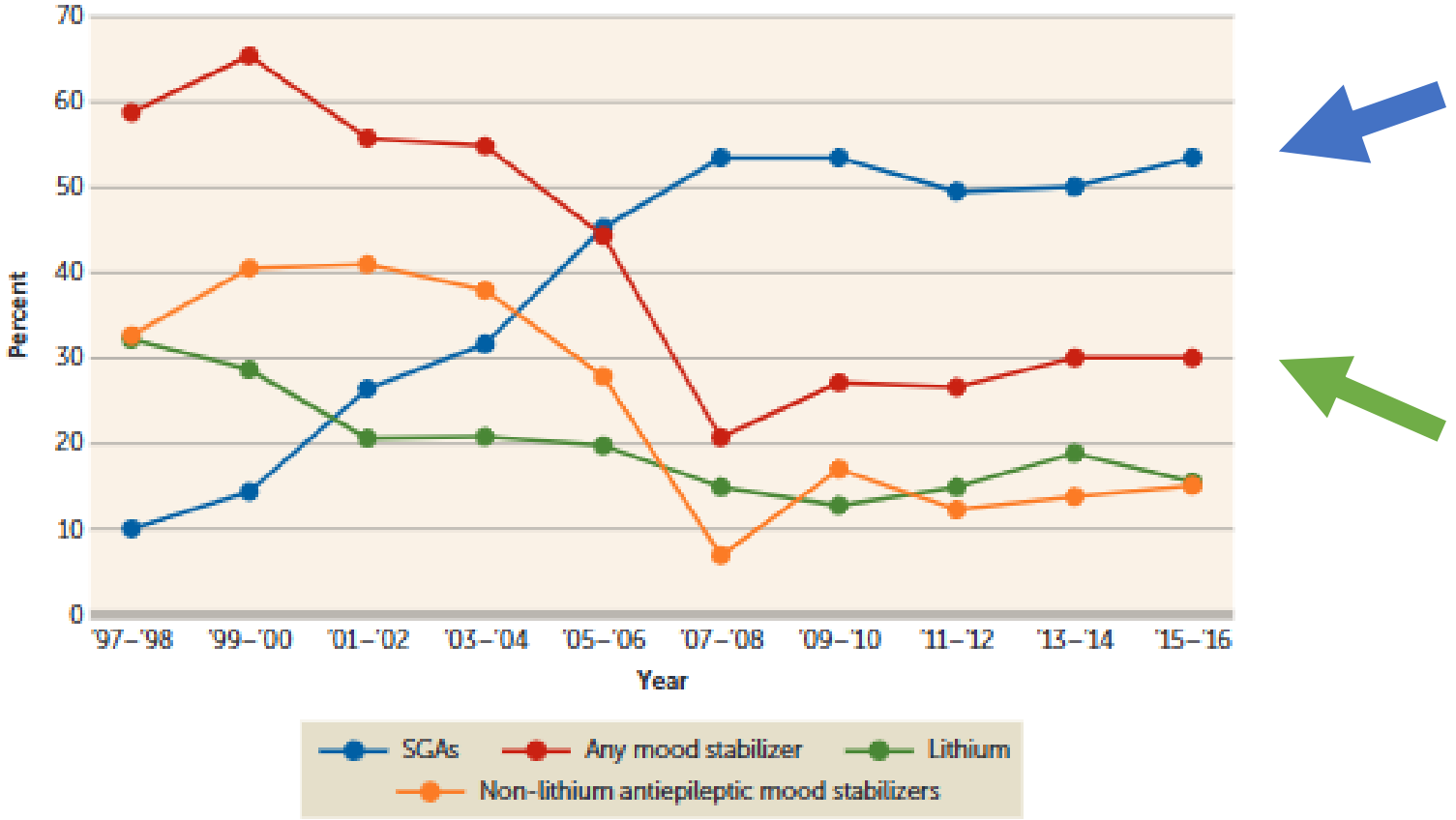
Disclosures

Entity	Role
Abbvie	Consultant
Alvogen	Consultant
Alkermes	Consultant
Almatica	Advisory board
Axsome	Consultant
American Psychiatric Publishing	Royalties
Bristol Myers Squibb	Consultant, Speakers bureau
Cambridge University Press	Royalties
Genomind	Consultant
Johnson and Johnson	Speakers bureau
Luye Pharmaceuticals	Advisory board
Neurelis	Advisory board
Neumora	Advisory board
Otsuka	Consultant
Seaport Therapeutics	Consultant, advisory board
Vanda Pharmaceuticals	Speakers bureau

The Uptick in Antipsychotics and the Downtick in Mood Stabilizers For Bipolar Disorder

Prescribing Trends for Second Generation Antipsychotics and Mood Stabilizers
In the Treatment of Bipolar Disorder in Office-Based Visits to Psychiatrists, 1997-2016*



[a] Data are from the National Ambulatory Medical Care Survey, 1997–2016.

Rhee et al., *Am J Psychiatry* 2020; 177: 706-715

Financial Considerations

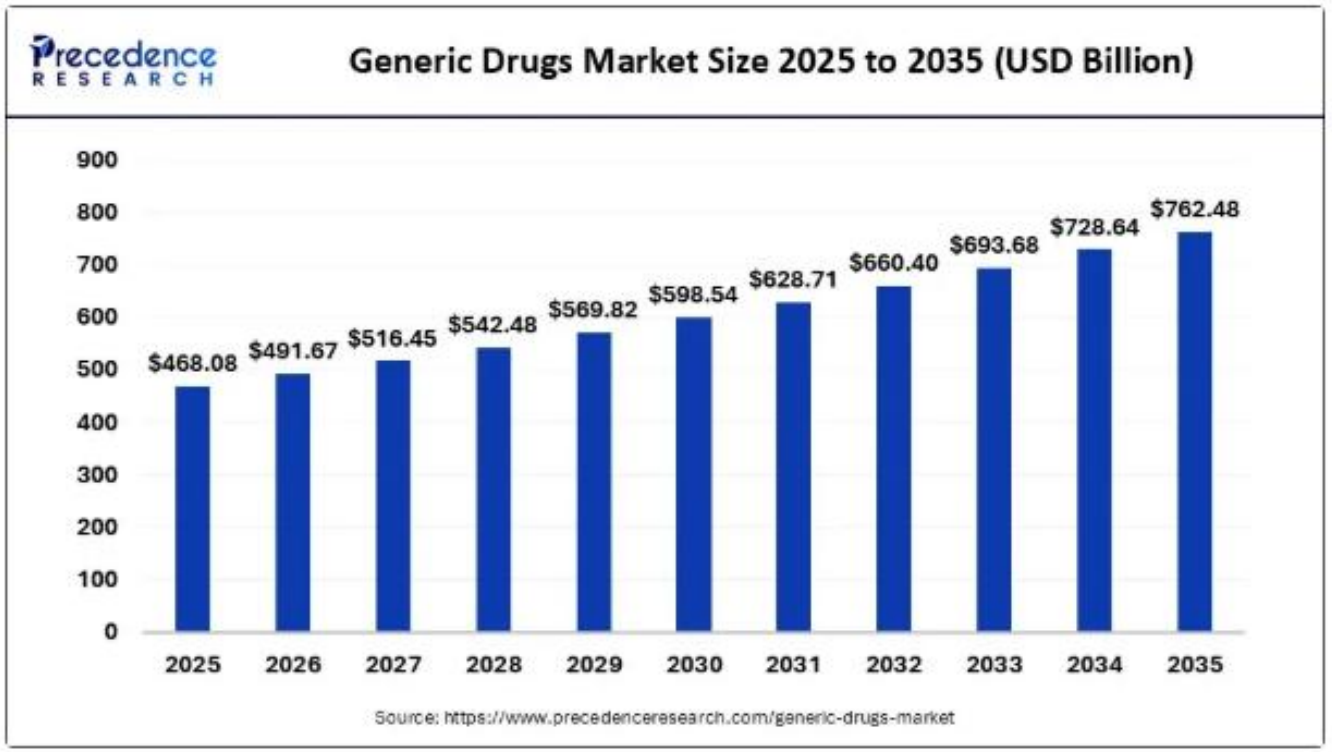
Agent	Loss of US Market Exclusivity	US Sales – 2025
Lithium carbonate (ER)	~1995	$3.7-3.9B
Divalproex	2008	$1.2-1.3B
Carbamazepine (ER)	2014	$372M
Lamotrigine	2008	$600M
Oxcarbazepine	2007	$350-450M
Licarbazepine	2025	Not disclosed
Eslicarbazepine	2025	$395M
Topiramate	2008	$350-500M
Gabapentin	2004	$700-800M
Gabapentin Enacarbil	2016	~$200M
Pregabalin	2019	$600-800M

Agent	Loss of US Market Exclusivity	US Sales - 2025
Cariprazine	2029	$1.02B
Lumateperone	2029	$680M
Iloperidone	2027	$117M
Aripiprazole LAI	2033	$3.8B
Olanzapine	2010	$425M (cf. $2.5B in 2010)
Quetiapine IR	2011	$300M (cf. $3B in 2011)
Quetiapine XR	2017	<$100M (cf. $1.1B in 2017)

Generic Drugs Market Size to Reach USD 762.48 Billion by 2035 Driven by Rising Chronic Disease Burden and Cost-Control Focus

Precedence Research

February 6, 2026 • 15 min read



Fact Sheet : Ensuring Patient Safety Through Reform of Direct-to-Consumer Pharmaceutical Advertisement Policies

Return to the press release.

In 1997, the FDA established a loophole that has enabled pharmaceutical companies to run direct-to-consumer (DTC) advertisements without fully disclosing information on side effects or patient harm. The explosion of DTC pharmaceutical advertising following 1997 has led to (1) public deception from patient confusion, (2) patient harm via inappropriate demand for medications and misalignment of therapeutic choices with actual patient needs, and (3) harm to the public finances via misallocation of healthcare resources, including government spending.

ChatGPT

Is there evidence that doctors or other healthcare providers are especially gullible to prescribing medicines in response to manufacturers' promotional advertising?

Yes — there is substantial published evidence that pharmaceutical marketing influences physicians' prescribing behavior. But framing physicians as simply "gullible" would oversimplify the evidence and the psychology involved.

The research literature generally supports three conclusions:

1. Physicians are influenced by pharmaceutical marketing.
2. Many physicians underestimate their own susceptibility to influence.
3. The mechanisms of influence are often subtle, reciprocal, and unconscious rather than overt persuasion.

A major systematic review published in the *Annals of Internal Medicine* evaluated 36 studies and found a highly consistent association between industry payments and physician prescribing. Across 101 analyses, 89 showed a positive association between receiving payments and increased prescribing of the sponsoring company's drugs, higher prescribing costs, or greate[illegible] of branded medications. The review also found evidence of dose-response relationships and temporal associations, which strengthen the argument for causality. PMC

What Is a "Mood Stabilizer"? An Evidence-Based Response

Mark S. Bauer, M.D.

Landis Mitchner, M.D.

Objective: The term "mood stabilizer" is widely used in the context of treating bipolar disorder, but the U.S. Food and Drug Administration (FDA) does not officially recognize the term, and no consensus definition is accepted among investigators. The authors propose a "two-by-two" definition by which an agent is considered a mood stabilizer if it has efficacy in treating acute manic and depressive symptoms and in prophylaxis of manic and depressive symptoms in bipolar disorder. They review the literature on the efficacy of agents in any of these four roles to determine which if any agents meet this definition of mood stabilizer.

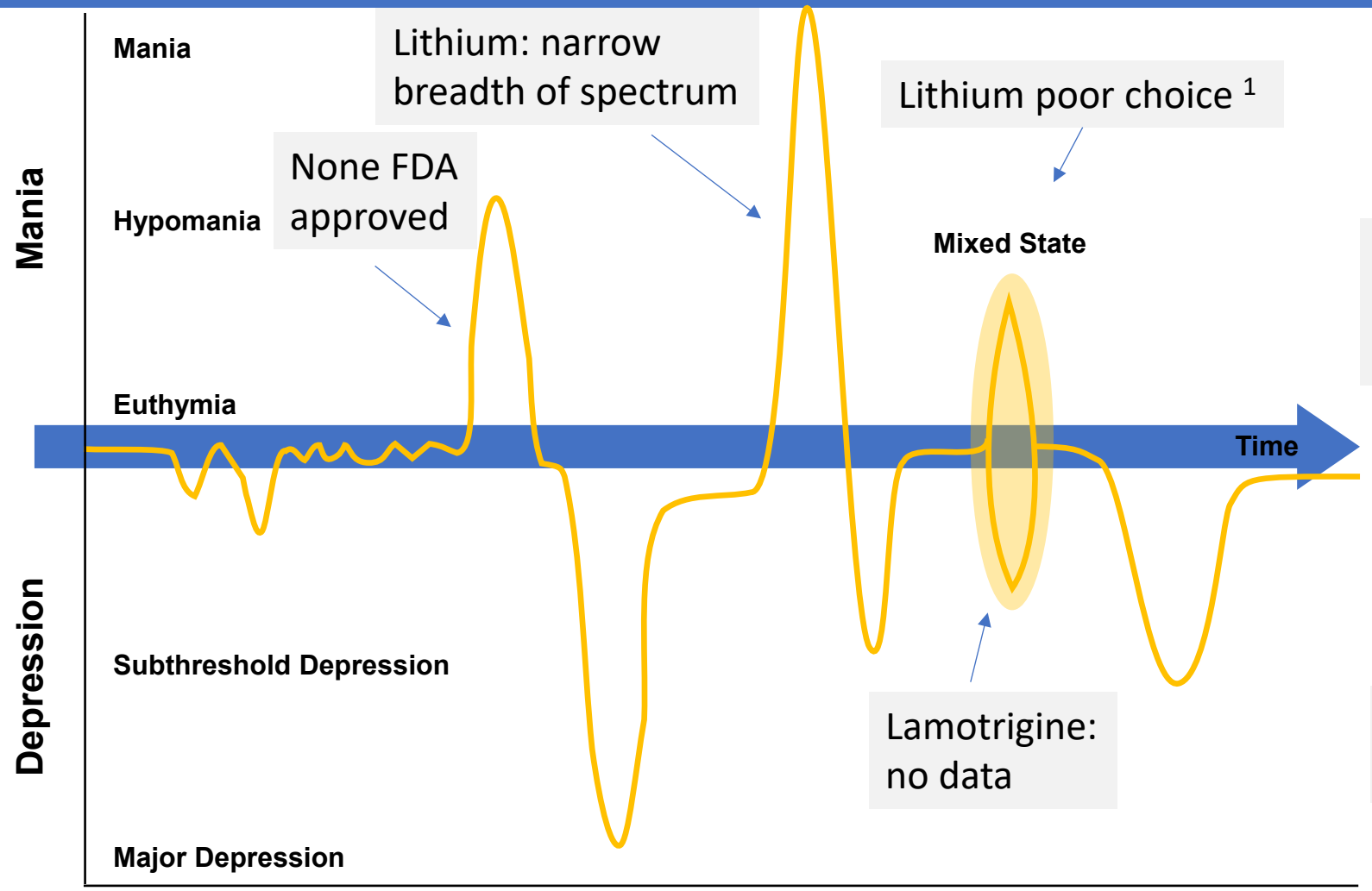
Method: The authors conducted a comprehensive review of English-language literature describing peer-reviewed, U.S. Agency for Healthcare Research and Quality class A controlled trials in order to identify agents with efficacy in any of the four roles included in their definition of a mood stabilizer. The trials were classified as positive or negative on the basis of primary outcome variables. An "FDA-like" criterion of at least two positive placebo-controlled trials was required to consider an agent efficacious. The authors also conducted a sensitivity analysis by raising and relaxing the criteria for including trials in the review.

Results: The authors identified 551 candidate articles, yielding 111 class A trials, including 81 monotherapy trials with 95 independent analyses published through June 2002. Lithium, valproate, and olanzapine had unequivocal evidence for efficacy in acute manic episodes, lithium in acute depressive episodes and in prophylaxis of mania and depression, and lamotrigine in prophylaxis (relapse polarity unspecified). Thus, only lithium fulfilled the a priori definition of a mood stabilizer. Relaxing the quality criterion did not change this finding, while raising the threshold resulted in no agents fulfilling the definition.

Conclusions: When all four treatment roles are considered, the evidence supported a role for lithium as first-line agent for treatment of bipolar disorder. The analysis also highlights unmet needs and promising agents and provides a yardstick for evaluating new treatment strategies.

(Am J Psychiatry 2004; 161:3–18)

Mood Stabilizer Shortcomings



Lithium: narrow breadth of spectrum

Lithium poor choice [1]

None FDA approved

Lithium: larger effect against mania than depression [2]

Divalproex: failed maintenance trials [3]

Carbamazepine: No maintenance data

Lamotrigine: no data

Lamotrigine: prevents depression but not mania [4,5]

[1] Swann et al., *Arch Gen Psychiatry* 1997; 54: 37-42; [2] Geddes et al., Am J Psychiatry 2004; 161: 217-222; [3] Bowden et al., *Arch Gen Psychiatry* 2000; 57: 481-489; [4] Calabrese et al., *J Clin Psychiatry* 2003; 64: 1013-1024; [5] Bowden et al., *Arch Gen Psychiatry* 2003; 60: 392-400

Lithium's Narrow Breadth of Spectrum

Mania polarity-proneness [1,2]
Mania as initial episode [2]
Later age at onset [1]
Few episodes [3,4]
Absence of mixed features [5]
Absence of rapid cycling [6]
Absence of psychosis [2]

- Absence of comorbid OCD or alcohol/substance use disorders [2]
- Family history of bipolar disorder [2,7]
- Positive family history of lithium responsivity [8]
- Hyperthymic temperament [9]
- Absence of anxiety [9]

[1] Kleindeinst et al., *Bipolar Disord* 2005; 7: 404-417; [2] Scott et al., *Acta Psychiatr Scand* 2020; 141: 522-533; [3] Gelenberg et al., *N Engl J Med* 1989; 321: 1489-1493; [4] Swann et al., *Am J Psychiatry* 1999; 156: 1264-1266; [5] Swann et al., *Arch Gen Psychiatry* 1997; 54: 37-42; [6] Dunner & Fieve, *Arch Gen Psychiatry* 1974; 30: 229-233; [7] Grof, *Neuropsychobiology* 2010; 62: 27-35; [8] Grof et al., *J Clin Psychiatry* 2002; 63: 942-947; [9] Rybakowski et al., *J Affect Disord* 2013; 145: 187-189

Predictors of excellent response to lithium: results from a nationwide register-based study

Lars Vedel Kessing[a], Gunnar Hellmund[b] and Per Kragh Andersen[b]

The aim of this study was to identify sociodemographic and clinical predictors of excellent response, that is, 'cure' of future affective episodes, to lithium in monotherapy. We used nationwide registers to identify all patients with a diagnosis of bipolar disorder in psychiatric hospital settings who were prescribed lithium from 1995 to 2006 in Denmark ($N=3762$). Excellent lithium responders were defined as patients who after a stabilization lithium start-up period of 6 months, continued lithium in monotherapy without getting hospitalized. The rate of excellent response to lithium in monotherapy was 8.9% [95% confidence interval (CI): 7.9–9.9] at 5-year follow-up and 5.4% (95% CI: 4.4–6.3) at 10-year follow-up. The rate of nonresponse to lithium monotherapy was significantly increased for female patients [hazards ratio (HR)=1.12, 95% CI: 1.04–1.21) and for patients with a depressive index episode compared with patients in remission or with a diagnosis of other or unspecified bipolar disorder before first lithium purchase (HR=1.13, 95% CI: 1.03–1.25). The rate of nonresponse increased by 3% (95% CI: 2–5%) for every psychiatric hospitalization before first purchase of lithium. Patients with somatic comorbidity had increased rates of non-response to lithium compared with patients without somatic comorbidity (HR=1.23, 95% CI: 1.00–1.52).

It is concluded that the prevalence of excellent response to lithium monotherapy is low and such patients are characterized by few earlier psychiatric hospitalizations, a manic index episode before lithium and reduced somatic comorbidity. *Int Clin Psychopharmacol* 26:323–328

International Clinical Psychopharmacology 2011, 26:323–328

Keywords: bipolar disorder, excellent response, lithium

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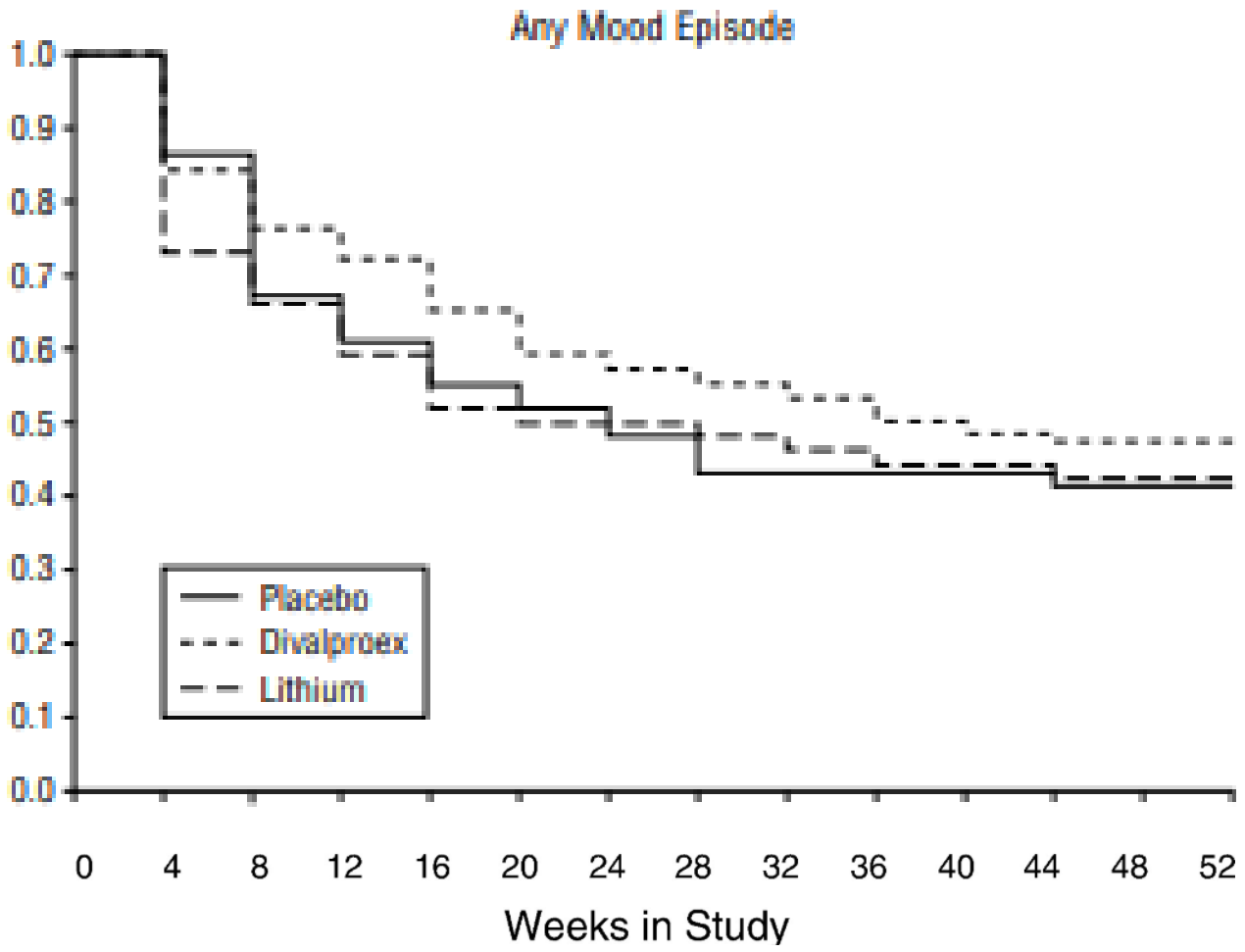
Divalproex: Failed Bipolar Relapse Prevention



Bipolar BALANCE Trial [2]

Any new episode:

- 54% on combo (HR=0.59, p=.0023 vs divalproex, 0.82, p=ns vs lithium)
- 59% on lithium
- 69% on divalproex

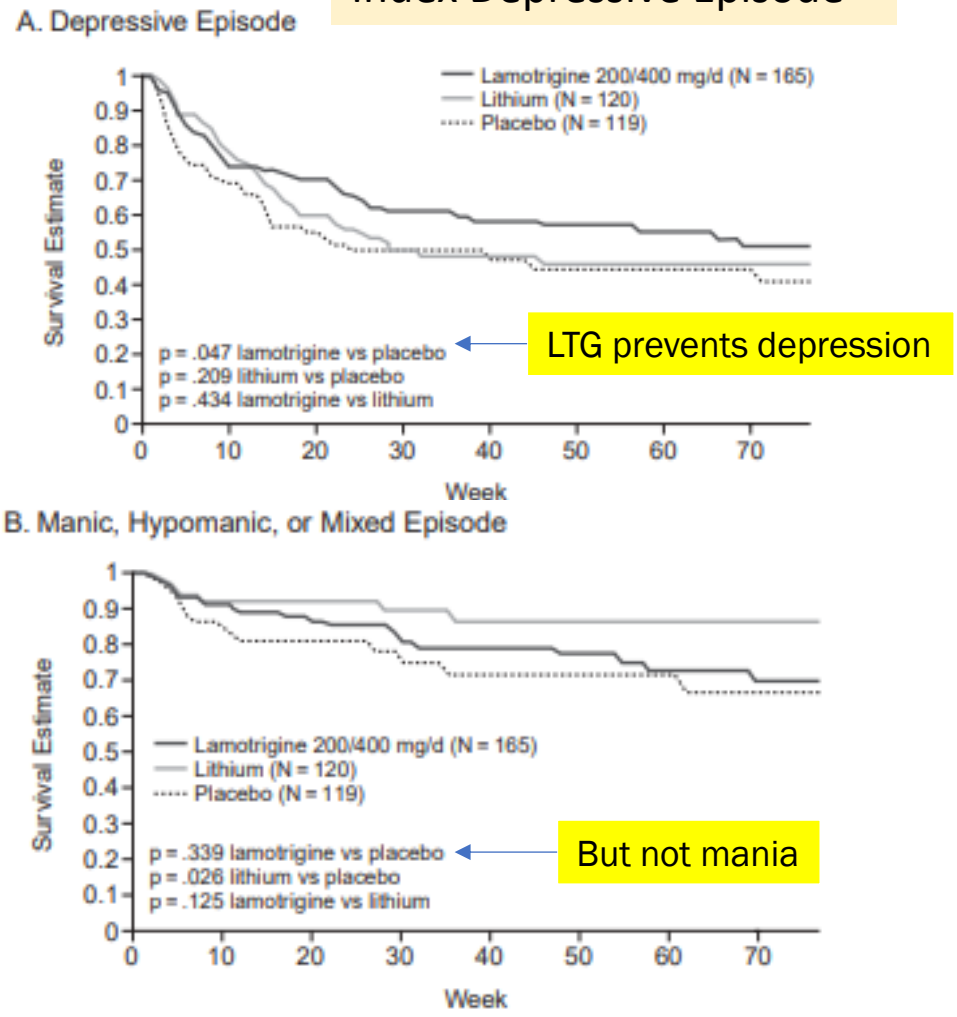
Any new manic episode:

- 27% on combo
- 36% on lithium
- 45% on divalproex

[1] Bowden et al., *Arch Gen Psychiatry* 2000; 57: 481-489; [2] BALANCE Investigators, *Lancet* 2010; 375: 385-395

Lamotrigine in Relapse Prevention

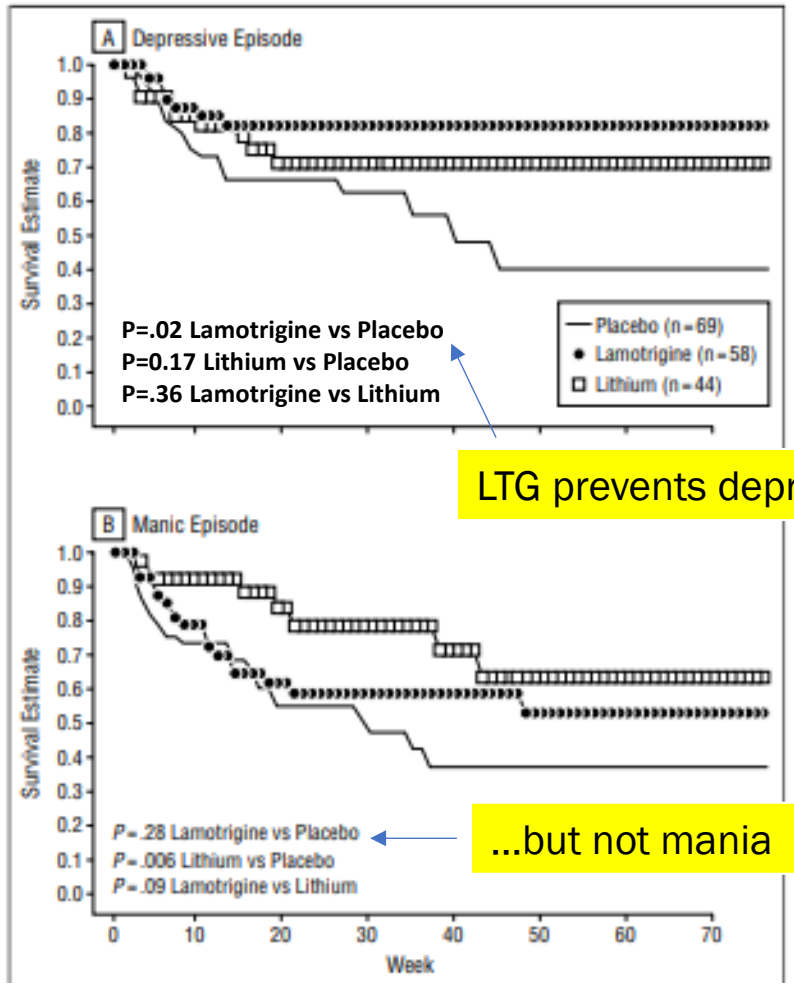
Index Depressive Episode [1]



LTG prevents depression

But not mania

Index Manic Episode [2]



LTG prevents depression

...but not mania

[1] Calabrese et al., *J Clin Psychiatry* 2003; 64: 1013-1024; [2] Bowden et al., *Arch Gen Psychiatry* 2003; 60: 392-400

Mood Stabilizer Shortcomings: Rapid Cycling

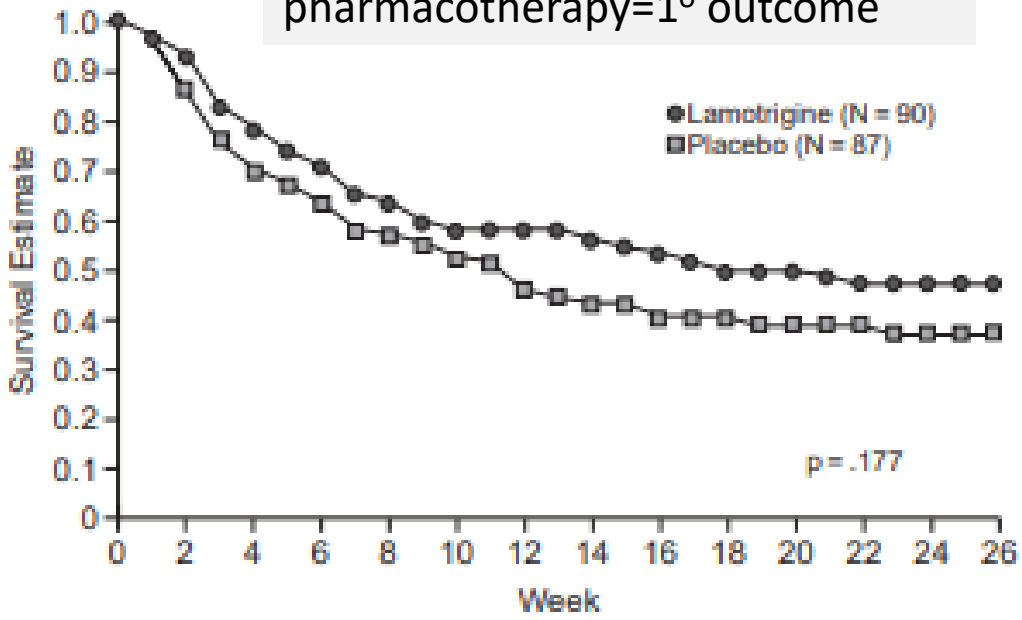
Lithium + Divalproex

Only 24% of RC patients (n=254) stabilized on open label lithium + divalproex, and half of those remained stable when randomized to either monotherapy [1]

1 in 8 chance mood stabilizer monotherapy achieves euthymia in rapid cyclers

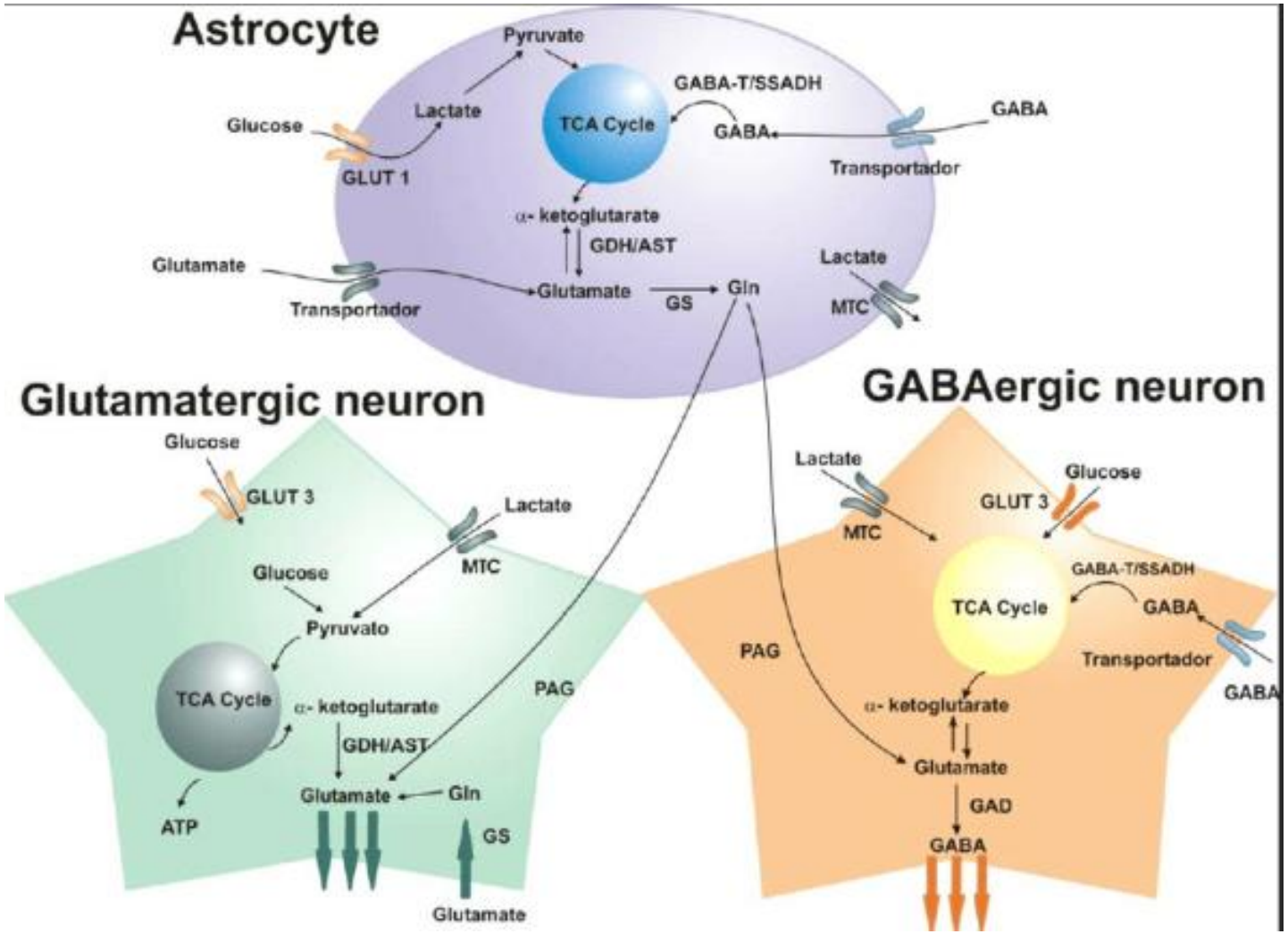
Lamotrigine:

Time until the need for additional pharmacotherapy=1° outcome



[1] Calabrese et al., *Am J Psychiatry* 2005; 162: 2152-2161; [2] Calabrese et al., *J Clin Psychiatry* 2000; 61: 841-850

Rationale For Anticonvulsants in Bipolar Disorder



Mechanistic Considerations: Mood Stabilizers vs. SGAs?

Mechanism	Lithium	DVPX	CBZ	LTG
PKC inhibition	√	√	--	--
BDNF upregulation	√	√	√	√
bcl–2 upregulation	√	√	√	√
GSK3β inhibition	√	√	--	--
MARCKS downregulation	√	√	--	--
GABA upregulation	√	√	√	--
Glutamate downregulation	√	√	√	√
Na^+ channel blockade	√	√	√	√
Ca^{++} channel blockade	--	√	√	√
5-HT2A antagonism	--	--	--	--
5-HT1A partial agonism	?	--	--	--
5-HT1B antagonism, partial agonism or inverse agonism	?	--	--	--
D2 antagonism	?	√	√	--
D3 partial agonism	--	--	--	--
5-HT7 antagonism	--	--	--	--

Goldberg, *FOCUS (Am Psychiatr Publ)* 2019; 17: 218-231

Bipolar Disorders 2006: 8: 15–27

BIPOLAR DISORDERS

Original Article

Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials

Kushner SF, Khan A, Lane R, Olson WH. Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials.
Bipolar Disord 2006: 8: 15–27. © Blackwell Munksgaard, 2006

Objective: To evaluate the efficacy and tolerability of topiramate monotherapy in adults with acute manic or mixed episodes of bipolar I disorder.

Methods: In four trials, adults hospitalized with acute mania, a diagnosis of bipolar I disorder, history of ≥1 previous manic or mixed episodes, and ≥20 Young Mania Rating Scale (YMRS) score were randomized to double-blind treatment with topiramate (target doses: 200, 400, or 600 mg/day) or placebo; two trials included an active comparator (lithium, 1500 mg/day). The core study duration in all trials was 3 weeks; three trials also had 9-week double-blind extensions. The primary efficacy variable was mean change from baseline in YMRS in the core 3-week study.

Results: Changes in YMRS score during 3 weeks were not significantly different for topiramate versus placebo (mean YMRS reductions, −5.1 to −8.4). Mean YMRS reductions in lithium-treated groups were significantly greater ($p \leq 0.001$ versus placebo and topiramate). A similar pattern was observed after 12 weeks of double-blind treatment in studies with double-blind extensions. Paresthesia, appetite decrease, dry mouth, and weight loss were more frequently associated with topiramate than with placebo.

Stuart F Kushner[a], Akbar Khan[a], Rosanne Lane[a] and William H Olson[b]

[a]Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, [b]Ortho-McNeil Janssen Scientific Affairs, L.L.C., Titusville, NJ, USA

Key words: acute mania – bipolar I disorder – lithium – topiramate – weight loss

Received 13 September 2004, revised and accepted for publication 22 September 2005

Corresponding author: Stuart F. Kushner, MD,

Bipolar Disorders 2000: 2: 249–255
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BIPOLAR DISORDERS
ISSN 1398-5647

Original Article

Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy[1]

Pande AC, Crockatt JG, Janney CA, Werth JL, Tsaroucha G., Gabapentin Bipolar Disorder Study Group. Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy.
Bipolar Disord 2000: 2: 249–255. © Munksgaard, 2000

Objectives: To assess efficacy and safety of gabapentin in the treatment of bipolar disorder.

Methods: This was a double-blind, placebo-controlled trial of adjunctive gabapentin (dosed flexibly between 900 and 3600 mg/day). Patients with a lifetime diagnosis of bipolar disorder (type I), and who were currently suffering from symptoms of either mania, hypomania or a mixed state despite ongoing therapy with lithium, valproate, or lithium and valproate in combination were eligible for inclusion. The primary efficacy measures were the baseline to endpoint change in total score on the Young Mania Rating Scale (YMRS) and the Hamilton Depression Rating Scale (HAM-D).

Results: Both treatment groups had a decrease in total YMRS from baseline to endpoint, but this decrease was significantly greater in the placebo group (-9) than the gabapentin group (-6) ($p < 0.05$). No difference between treatments was found for the total score on the HAM-D. Secondary efficacy measures were not different between treatment groups. More patients in the placebo group had changes made to their ongoing lithium therapy ($n = 12$) compared to the gabapentin group ($n = 4$). When these patients are removed from the efficacy analysis, the YMRS treatment difference still favors placebo, but is no longer statistically significant. Based on gabapentin plasma levels at termination, some patients did not take the study drug as prescribed.

Atul C Pande, Jerri G Crockatt, Carol A Janney, John L Werth, Georgia Tsaroucha and Gabapentin Bipolar Disorder Study Group[2]

Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, MI 48105, USA

Key words: bipolar disorder – clinical trial – gabapentin – mania – placebo-controlled – trial methods

Received 22 July 1999, revised and accepted for publication 22 November 1999

Corresponding author: Atul C Pande, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company

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[Intervention Review]

Oxcarbazepine for acute affective episodes in bipolar disorder

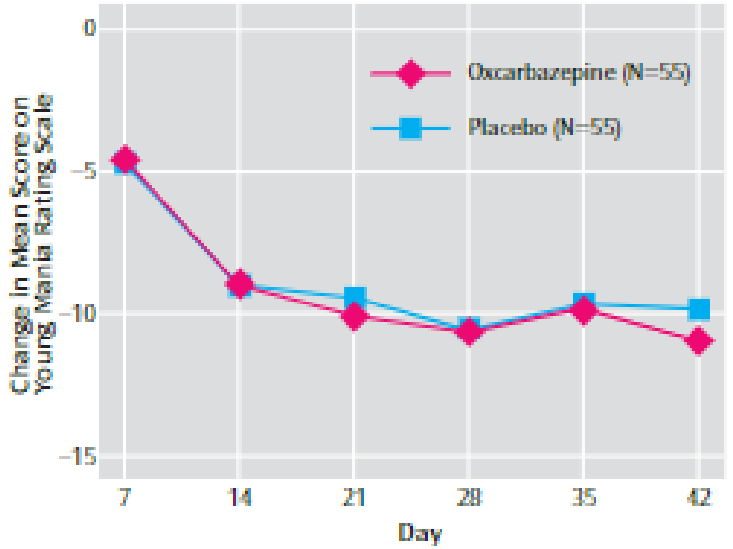
Akshya Vasudev[1], Karine Macritchie[2], Kamini Vasudev[1], Stuart Watson[3], John Geddes[4], Allan H Young[5]

[1]University of Western Ontario, London Health Sciences Centre, Victoria Hospital, London, Canada. [2]Division of Psychiatry, University of Edinburgh, Edinburgh, UK. [3]Department of Psychiatry, Leazes Wing, Royal Victoria Infirmary, Newcastle-upon-Tyne, UK. [4]Department of Psychiatry, University of Oxford/Warneford Hospital, Oxford, UK. [5]Division of Experimental Medicine, Centre for Mental Health, Imperial College London, London, UK

Main results

Seven studies were included in the analysis (368 participants in total). All were on mania, hypomania, mixed episodes or rapid-cycling disorder. Overall, their methodological quality was relatively low.

There was no difference in the primary outcome analysis – a fall of 50% or more on the Young Mania Rating Scale (YMRS) - between oxcarbazepine and placebo (N=1, n=110, OR =2.10, 95% CI 0.94 to 4.73) in one study, conducted in children; no studies were available in adult participants.



Mechanistic Considerations: Mood Stabilizers vs. SGAs?

Mechanism	Lithium	DVPX	CBZ	LTG	SGAs	Antidepressants
PKC inhibition	√	√	--	--	?	?
BDNF upregulation	√	√	√	√	√	√
bcl–2 upregulation	√	√	√	√	?	?
GSK3β inhibition	√	√	--	--	?	?
MARCKS downregulation	√	√	--	--	--	--
GABA upregulation	√	√	√	--	--	?
Glutamate downregulation	√	√	√	√	?	?
Na^+ channel blockade	√	√	√	√	?	√
Ca^{++} channel blockade	--	√	√	√	--	--
5-HT2A antagonism	--	--	--	--	√	√
5-HT1A partial agonism	?	--	--	--	√	√
5-HT1B antagonism, partial agonism or inverse agonism	?	--	--	--	√	?
D2 antagonism	?	√	√	--	√	--
D3 partial agonism	--	--	--	--	√	--
5-HT7 antagonism	--	--	--	--	√	√

Goldberg, *FOCUS (Am Psychiatr Publ)* 2019; 17: 218-231

Molecular Psychiatry (2017) 22, 666–679
www.nature.com/mp

OPEN

REVIEW

The dopamine hypothesis of bipolar affective disorder: the state of the art and implications for treatment

AH Ashok[1,2,3,4], TR Marques[1,2,3,4], S Jauhar[1,2,3,4], MM Nour[1,2,3], GM Goodwin[5], AH Young[4,6] and OD Howes[1,2,3,4]

Bipolar affective disorder is a common neuropsychiatric disorder. Although its neurobiological underpinnings are incompletely understood, the dopamine hypothesis has been a key theory of the pathophysiology of both manic and depressive phases of the illness for over four decades. The increased use of antidopaminergics in the treatment of this disorder and new *in vivo* neuroimaging and post-mortem studies makes it timely to review this theory. To do this, we conducted a systematic search for post-mortem, pharmacological, functional magnetic resonance and molecular imaging studies of dopamine function in bipolar disorder. Converging findings from pharmacological and imaging studies support the hypothesis that a state of hyperdopaminergia, specifically elevations in D2/3 receptor availability and a hyperactive reward processing network, underlies mania. In bipolar depression imaging studies show increased dopamine transporter levels, but changes in other aspects of dopaminergic function are inconsistent. Puzzlingly, pharmacological evidence shows that both dopamine agonists and antidopaminergics can improve bipolar depressive symptoms and perhaps actions at other receptors may reconcile these findings. Tentatively, this evidence suggests a model where an elevation in striatal D2/3 receptor availability would lead to increased dopaminergic neurotransmission and mania, whilst increased striatal dopamine transporter (DAT) levels would lead to reduced dopaminergic function and depression. Thus, it can be speculated that a failure of dopamine receptor and transporter homoeostasis might underlie the pathophysiology of this disorder. The limitations of this model include its reliance on pharmacological evidence, as these studies could potentially affect other monoamines, and the scarcity of imaging evidence on dopaminergic function. This model, if confirmed, has implications for developing new treatment strategies such as reducing the dopamine synthesis and/or release in mania and DAT blockade in bipolar depression.

Molecular Psychiatry (2017) **22,** 666–679; doi:10.1038/mp.2017.16; published online 14 March 2017

Post-mortem:

- ↓ DA transporter mRNA
- ↑ D2 mRNA levels in PFC, DLPFC, hippocampus

Imaging: mania:

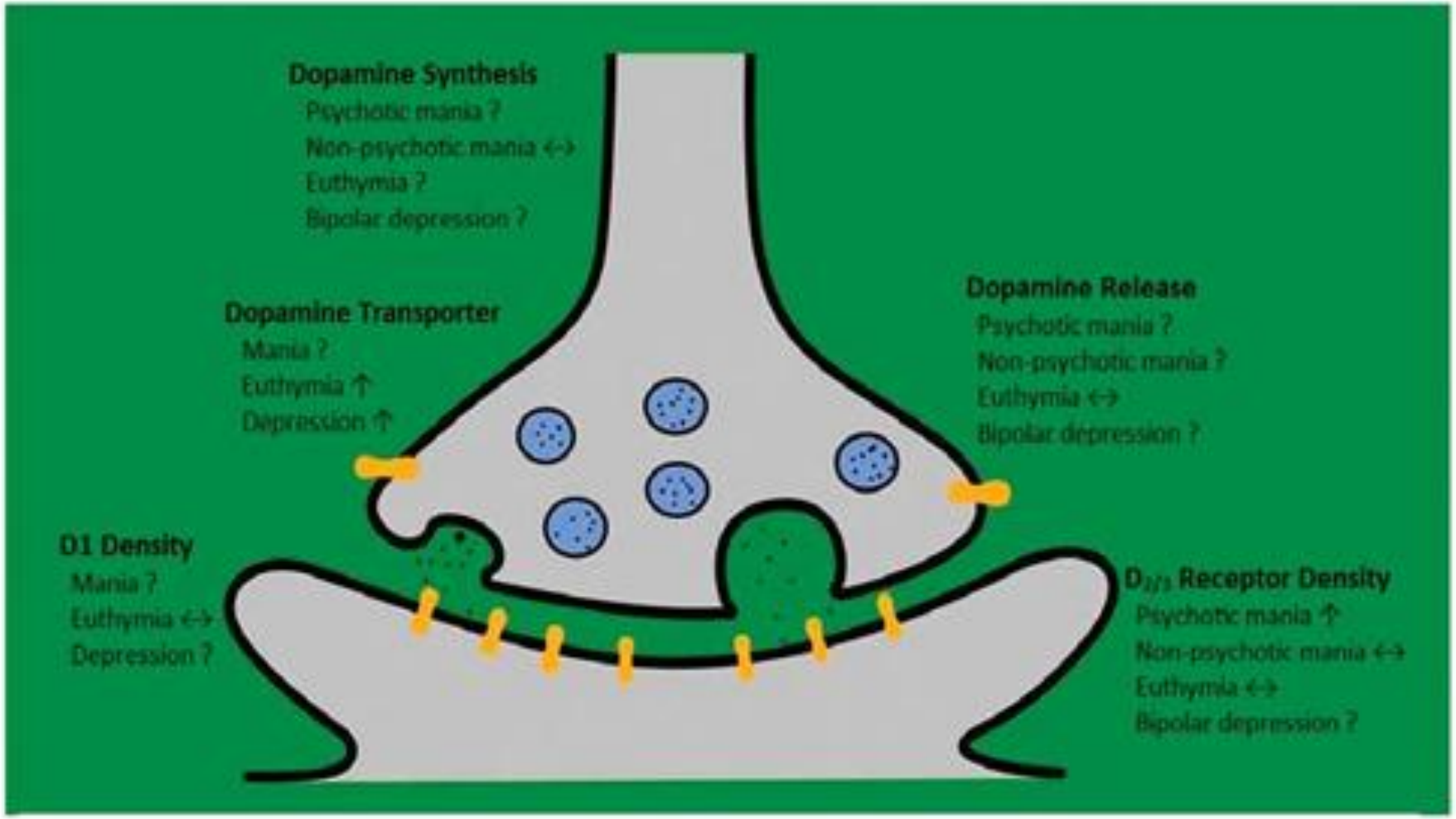
- ↑ D2 density in caudate, putamen

Imaging: depression or euthymia:

- ↑VMAT2 brainstem and thalamus
- ↓ DAT availability in caudate

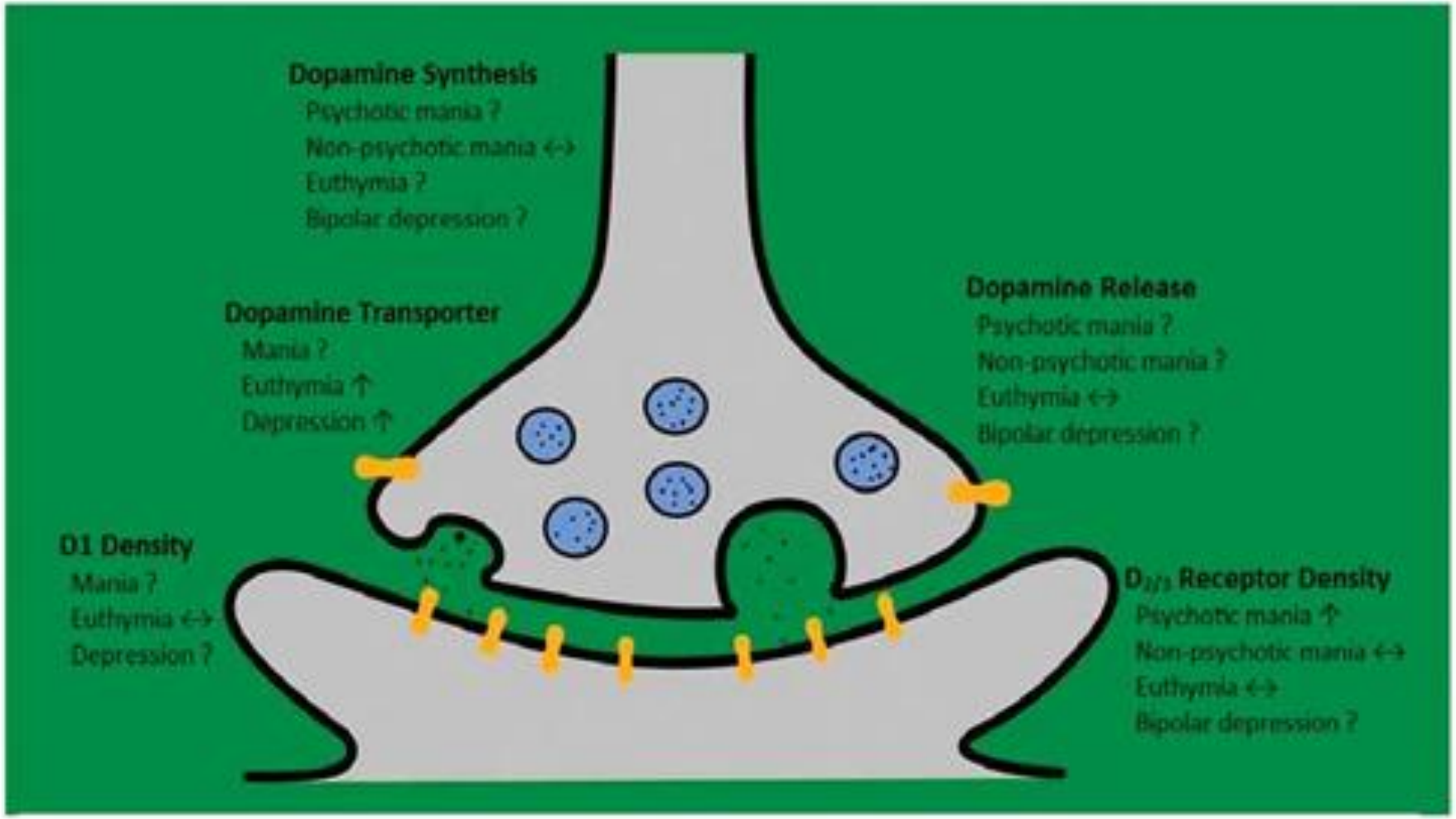
↓D1 density in frontal cortex

Summary of DA Findings in Bipolar Disorder



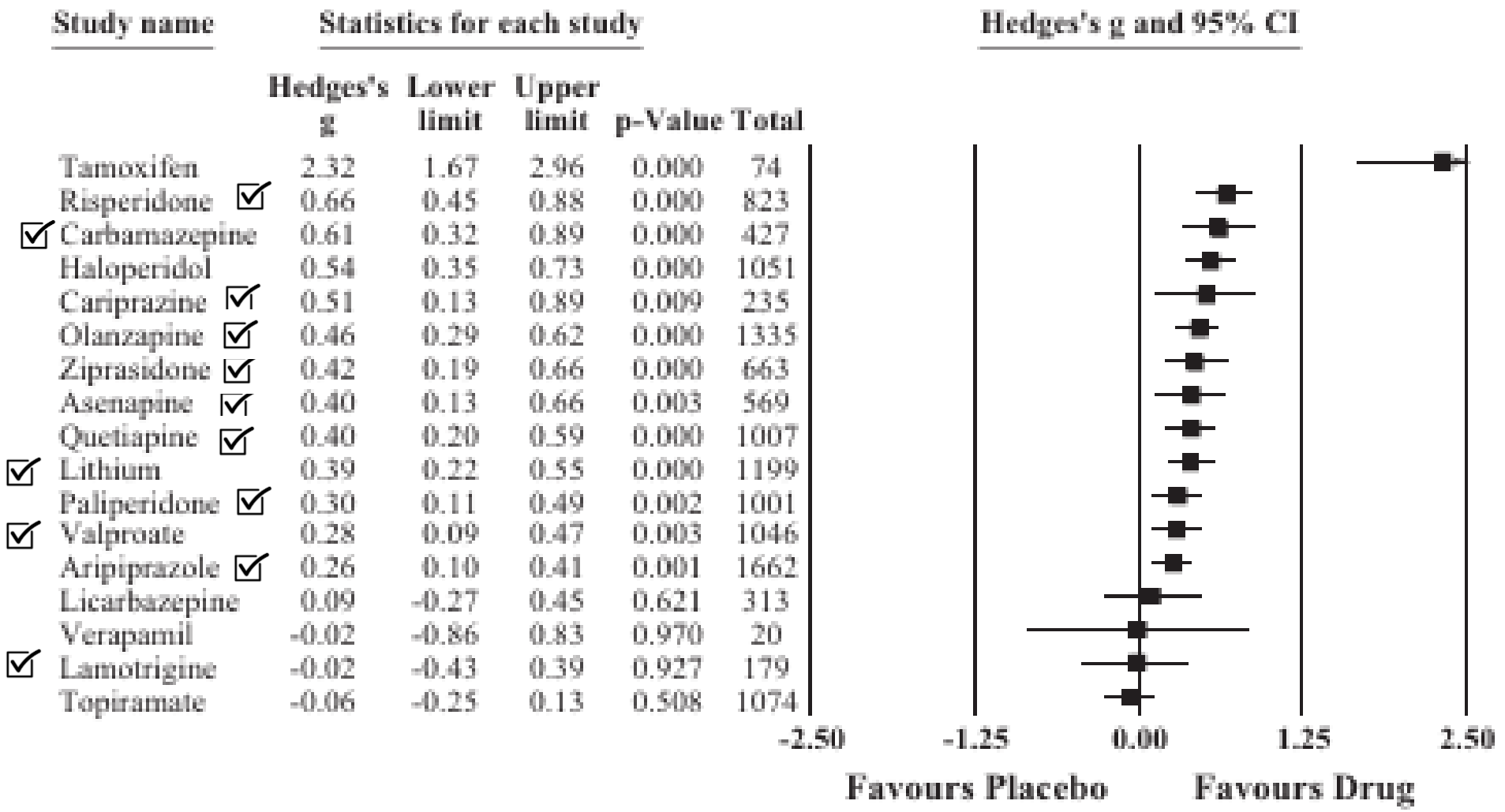
Ashok et al., *Mol Psychiatry* 2017; 22: 666-679

Summary of DA Findings in Bipolar Disorder



Ashok et al., *Mol Psychiatry* 2017; 22: 666-679

Comparative Antimanic Efficacy Across Agents



Yildiz et al., *Neuropsychopharmacology* 2011; 36: 375-389

SGAs: Breadth of Spectrum in Bipolar Disorder

Agent	Mania	Bipolar Depression	Bipolar + Mixed Features	Bipolar Maintenance
Lurasidone	No data	Yes	Yes (BP depressed)	(-) data
Cariprazine	Yes	Yes	Yes (manic or depressed)	No data
Lumateperone	No data	Yes	Yes (BP depressed)	No data
Quetiapine	Yes	Yes	Yes (manic or depressed)	Yes (adjunctive)
Olanzapine	Yes	(Yes w/fluoxetine)	Yes	Yes (bimodal)
Aripiprazole	Yes	(-) data	Yes (mixed mania)	Yes (prevents mania)
Asenapine	Yes	No data	Yes (mixed mania)	Yes (bimodal)
Brexpiprazole	(-) data	No data	No data	No data
Ziprasidone	Yes	(-) data	Yes (mixed mania)	No data
Risperidone	Yes	(-) data	Yes (mixed mania)	Yes (prevents mania)
Iloperidone	Yes	No data	Yes (mixed mania)	No data
Milsaperidone	Yes	No data	Yes (mixed mania)	No data