Relapse prevention in bipolar disorder

John Donoghue

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Objectives

- To review outcomes and clinical need in bipolar disorder
- To review evidence for relapse prevention
- To review the relationship between treatment adherence and outcome in bipolar disorder
- To consider how better medicines management could aid adherence to treatment

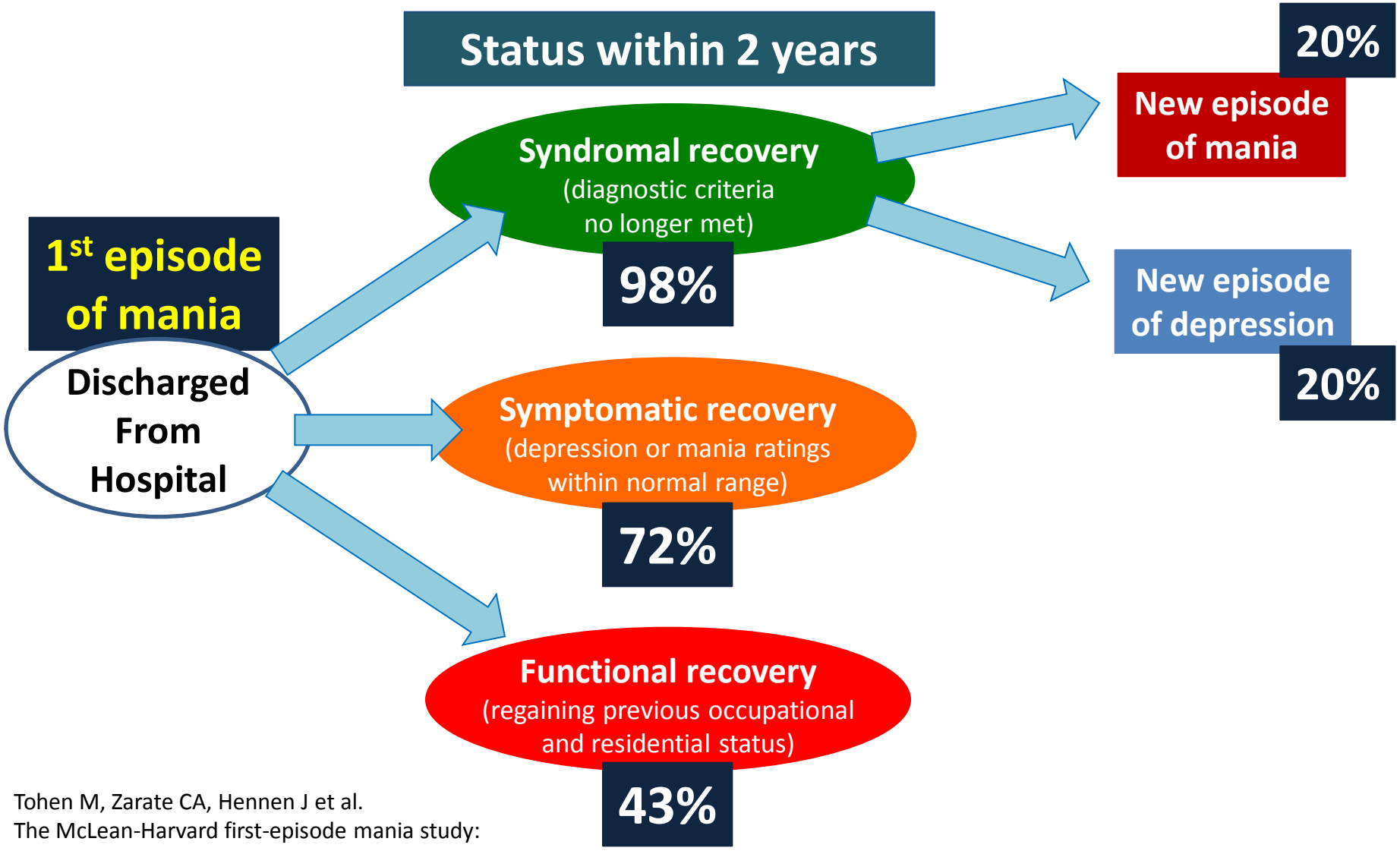
Bipolar Disorder

- Lifetime prevalence approx 1%
- Using estimates of
  - Years of life lost
  - Years lived with disability

  BPD ranked by WHO as **6th** leading cause of disability worldwide

National Collaborating Centre for Mental Health
Bipolar disorder: the management of bipolar disorder in adults, children and adolescents, in primary and secondary care.
National Clinical Practice Guideline Number 38, Full Guideline
The British Psychological Society & The Royal College of Psychiatrists, London, 2006.

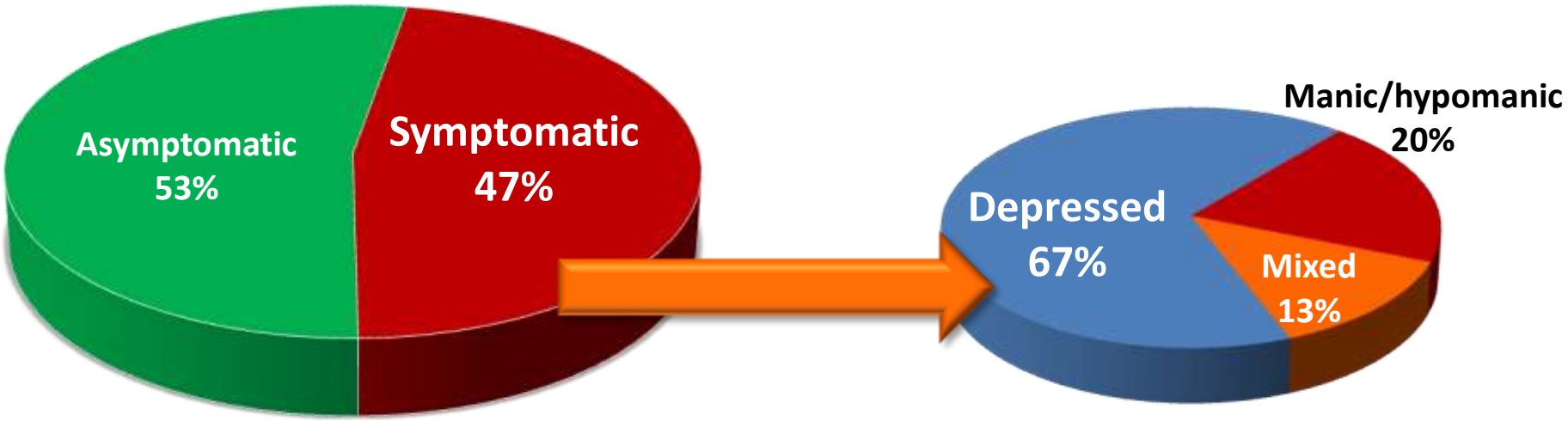
Outcomes after first episode of mania



Tohen M, Zarate CA, Hennen J et al.
The McLean-Harvard first-episode mania study:
Prediction of recovery and first recurrence.
Am J Psychiatry 2003;160:2099-2107

Long-term symptomatic status

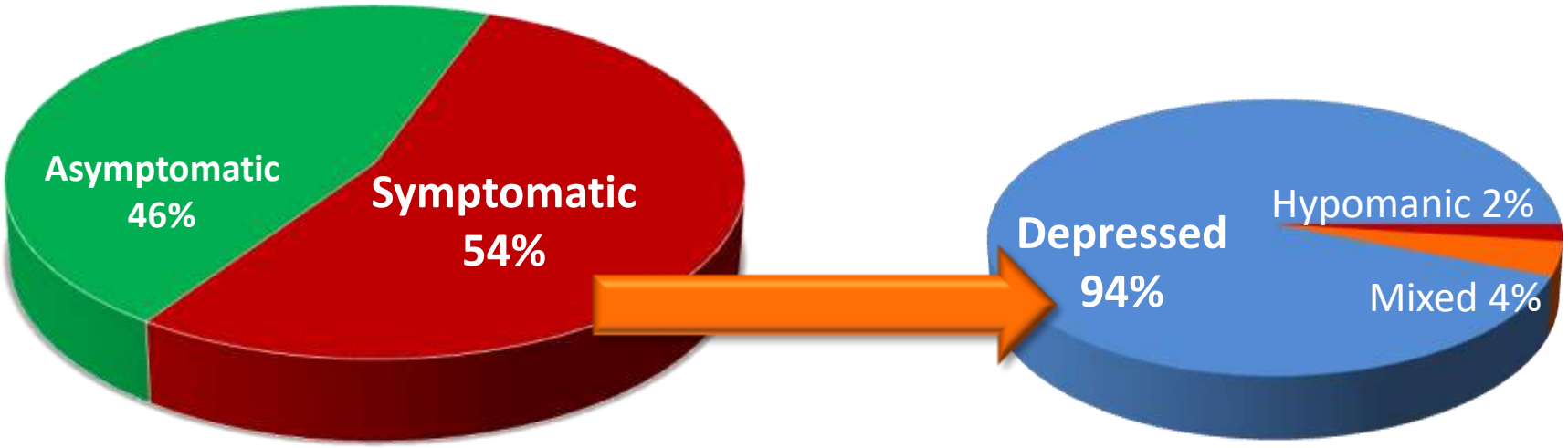
Bipolar-1



Judd LL, Akiskal HS, Schettler PJ et al.
The long-term natural history of the weekly symptomatic status of Bipolar I Disorder
Arch Gen Psychiatry 2002;59:530-37

Long-term symptomatic status

Bipolar-2



Judd LL, Akiskal HS, Schettler PJ et al.
A prospective investigation of the natural history of the long-term weekly symptomatic status of Bipolar II Disorder
Arch Gen Psychiatry 2003;60:261-269

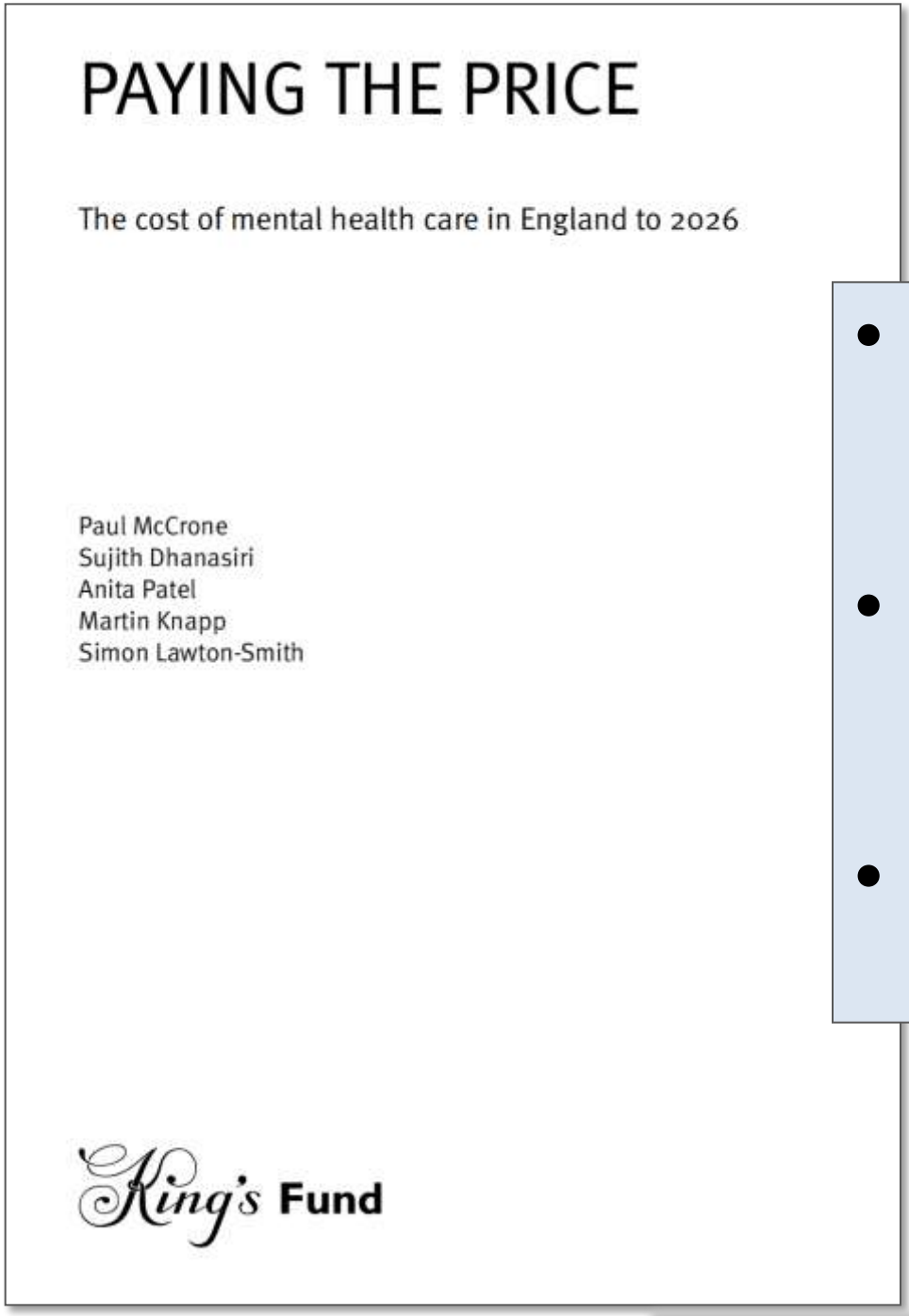
Premature death

- Standardised mortality ratio in bipolar disorder for death by natural causes
  - Males = 1.9
  - Females = 2.1

SUICIDE

- Bipolar 1
  - About 17% of sufferers will attempt suicide
- Bipolar 2
  - About 24% of sufferers will attempt suicide
- Standardised mortality ratio
  - 15 for men
  - 22.4 for women
- Most suicide attempts occur in depressive phase

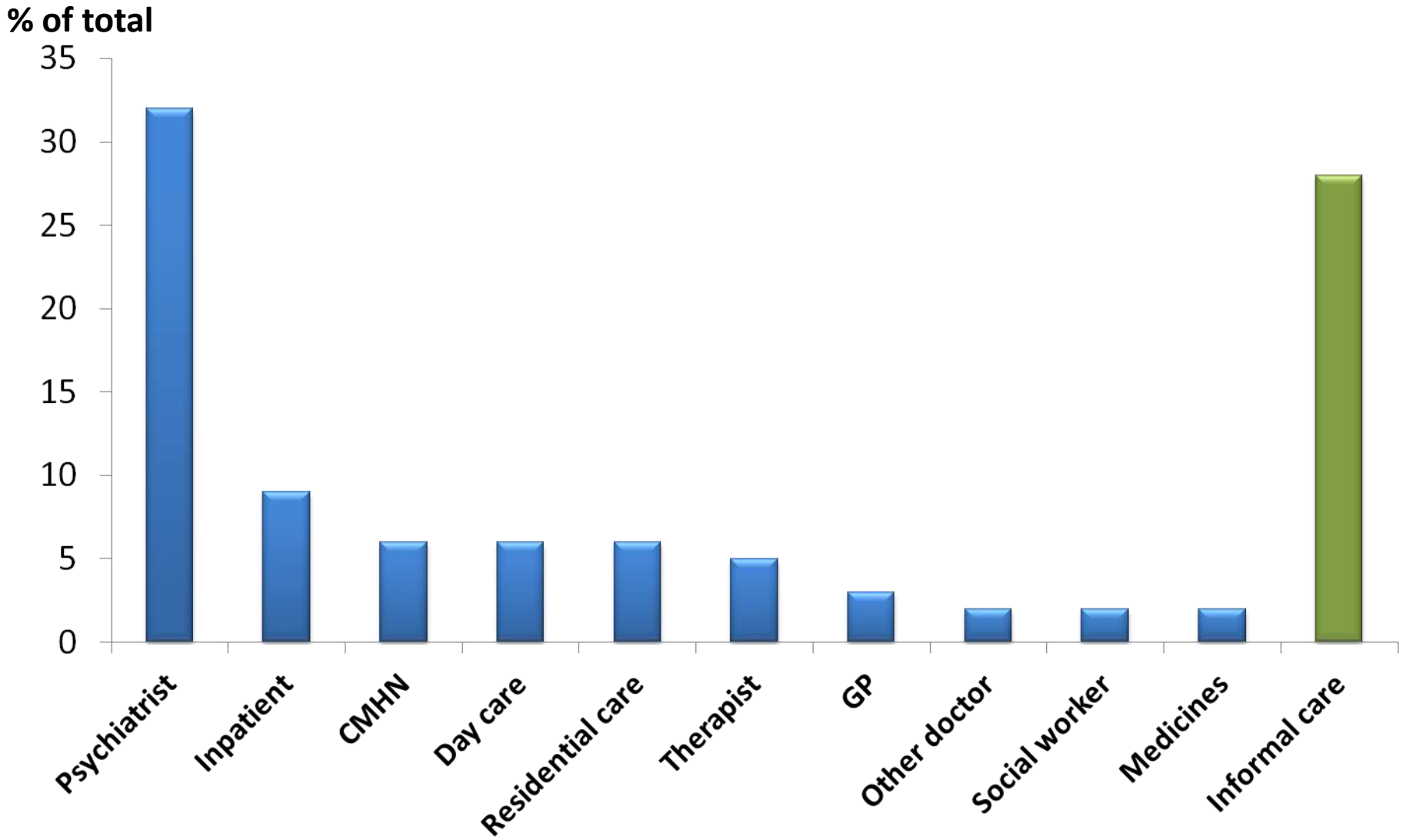
National Collaborating Centre for Mental Health
Bipolar disorder: the management of bipolar disorder in adults, children and adolescents, in primary and secondary care.
National Clinical Practice Guideline Number 38, Full Guideline
The British Psychological Society & The Royal College of Psychiatrists, London, 2006.



Costs of BPD

- Annual cost to UK economy **£5.2 billion** (2006 prices)
- Greatest costs associated with unemployment & loss of productivity
- NHS costs approx **£1.6 billion**

Bipolar Disorder: Cost of Care



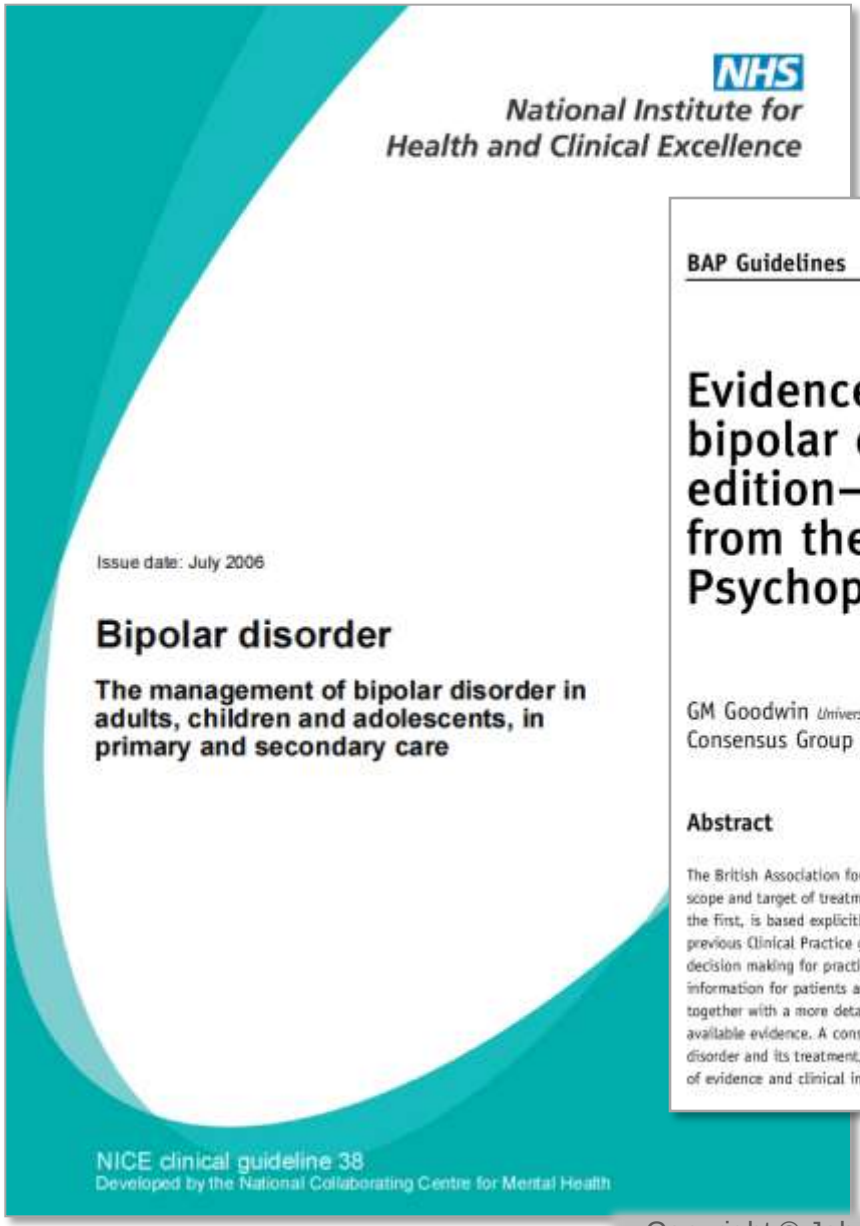
McCrone P, Dhanasiri S, Patel A, et al.
Paying the price: the cost of mental health care in England to 2026
London, King's Fund, 2008

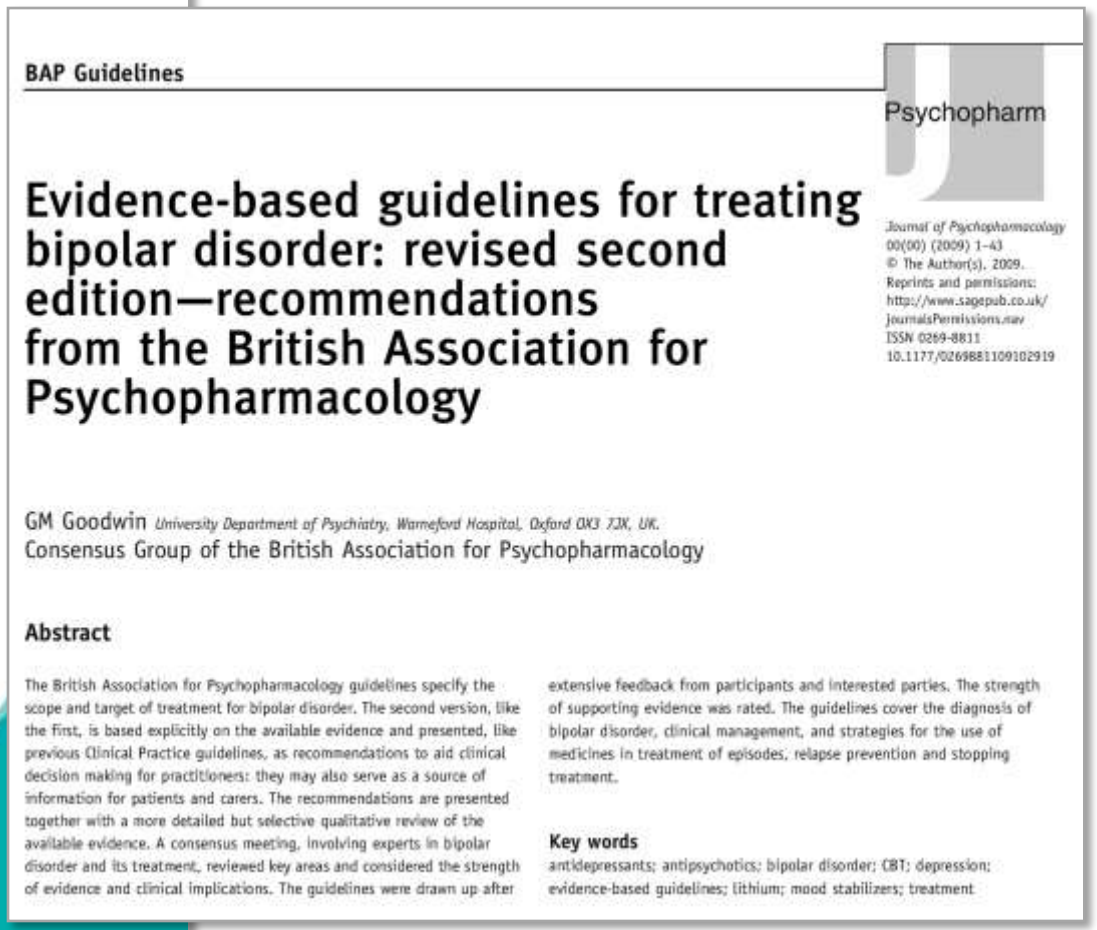
Clinical need in bipolar disorder

- Effective treatment for acute episodes
  - Mania
  - Hypomania
  - Depression

- Which is also effective in preventing relapse:
  - Mania / hypomania
  - Depression

What do treatment Guidelines tell us?





1.5.1.2 Lithium, olanzapine or valproate should be considered for long-term treatment of bipolar disorder. The choice should depend on:

- response to previous treatments
- the relative risk, and known precipitants, of manic versus depressive relapse
- physical risk factors, particularly renal disease, obesity and diabetes
- the patient's preference and history of adherence
- gender (valproate should not be prescribed for women of child-bearing potential)
- a brief assessment of cognitive state (such as the Mini-Mental State Examination) if appropriate, for example, for older people.

National Institute for Health and Clinical Excellence
Bipolar disorder: the management of bipolar disorder in adults, children and adolescents, in primary and secondary care.
NICE Clinical Guideline 38, July 2006

BAP Guideline 2009

Maintenance treatment

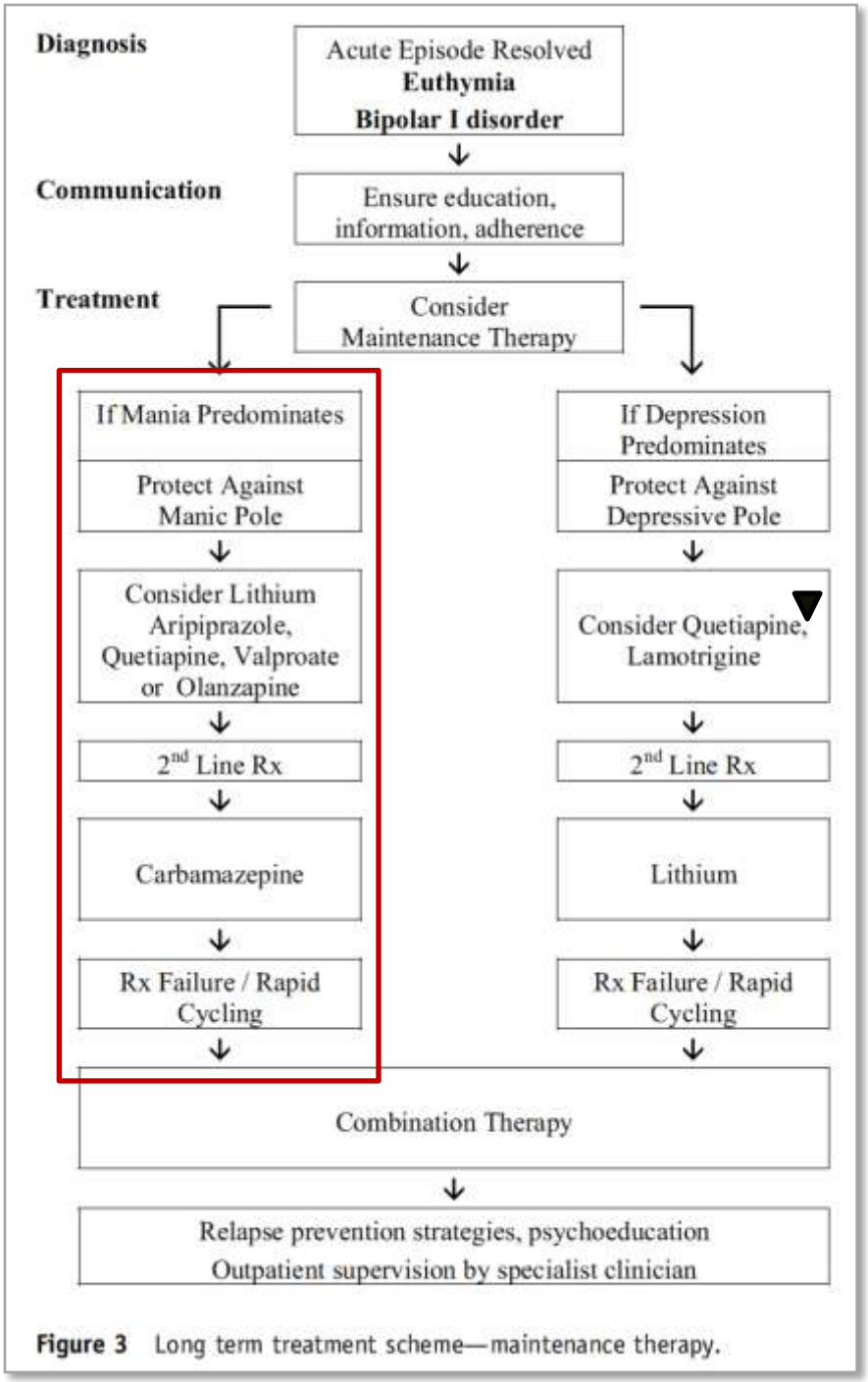
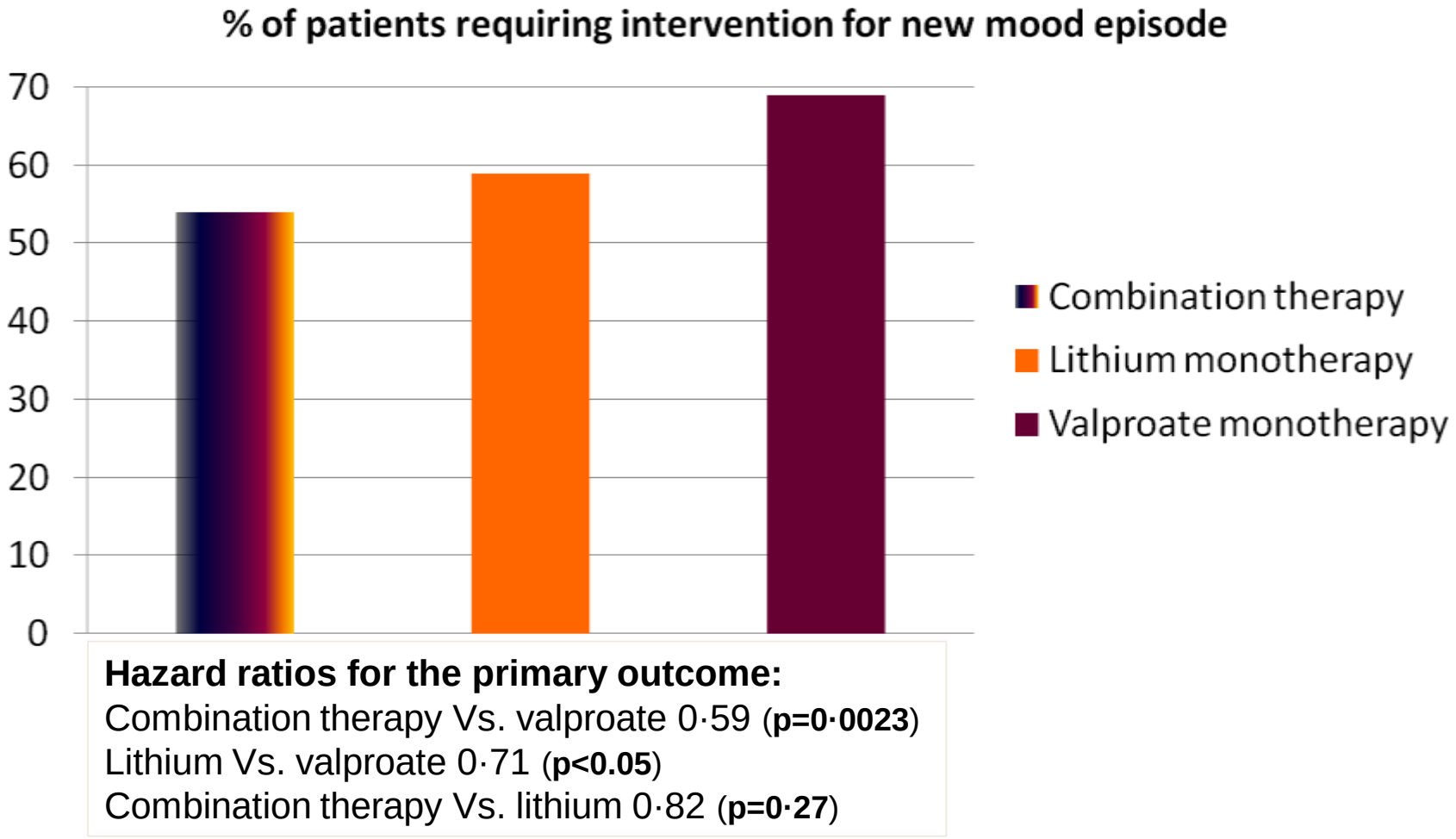


Figure 3 Long term treatment scheme—maintenance therapy.

Intensive monitoring requested only for BP depression and preventing recurrence in BP disorder

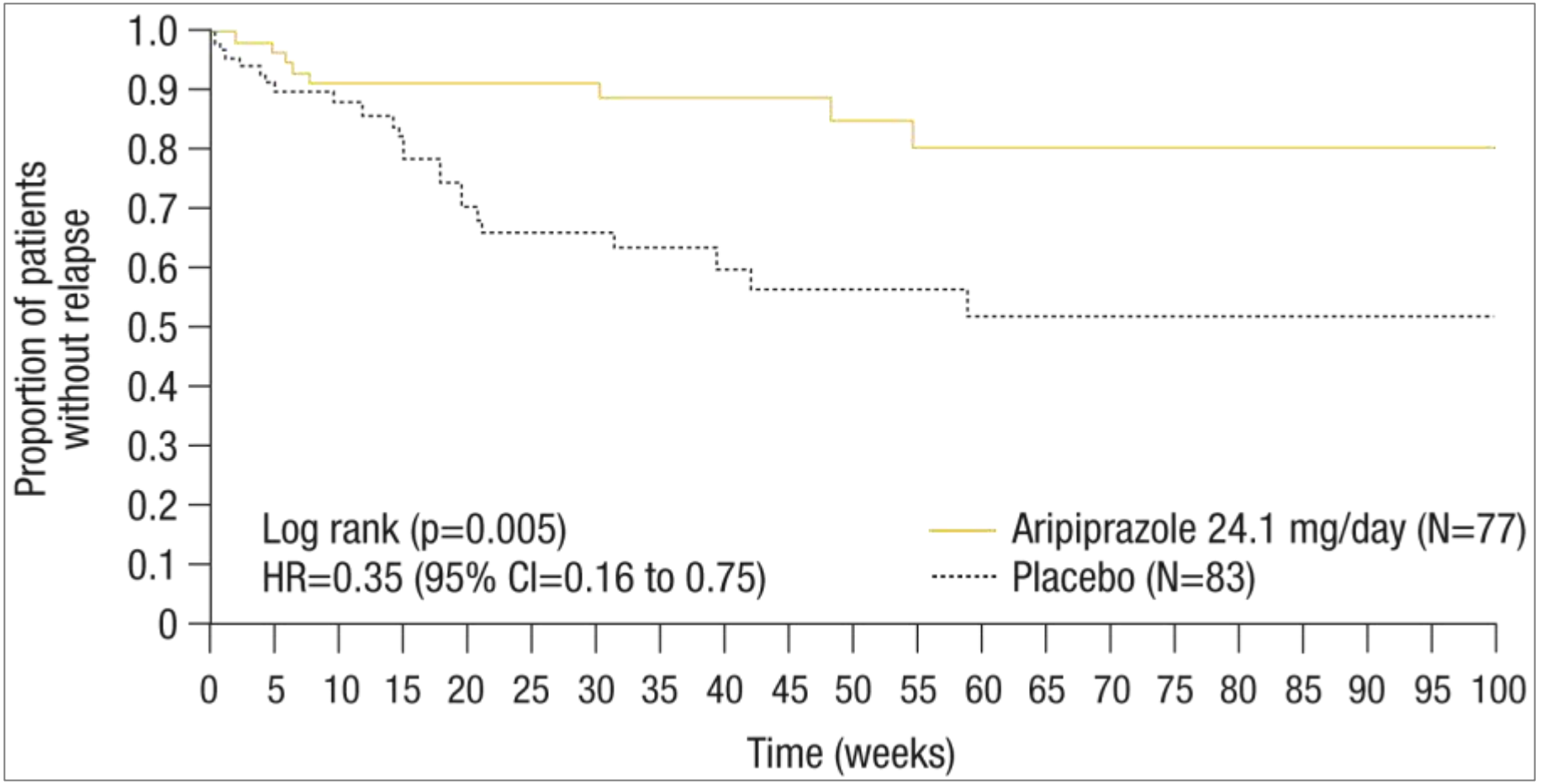
Mood stabilisers in bipolar-1: the *BALANCE* trial



Hazard ratios for the primary outcome:
Combination therapy Vs. valproate 0·59 (**p=0·0023**)
Lithium Vs. valproate 0·71 (**p<0.05**)
Combination therapy Vs. lithium 0·82 (**p=0·27**)

Geddes JR, Goodwin GM , Rendell J, et al.
Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial.
Lancet. 2010;375:385-95

Aripiprazole vs placebo in prevention of manic relapse (100 Weeks)



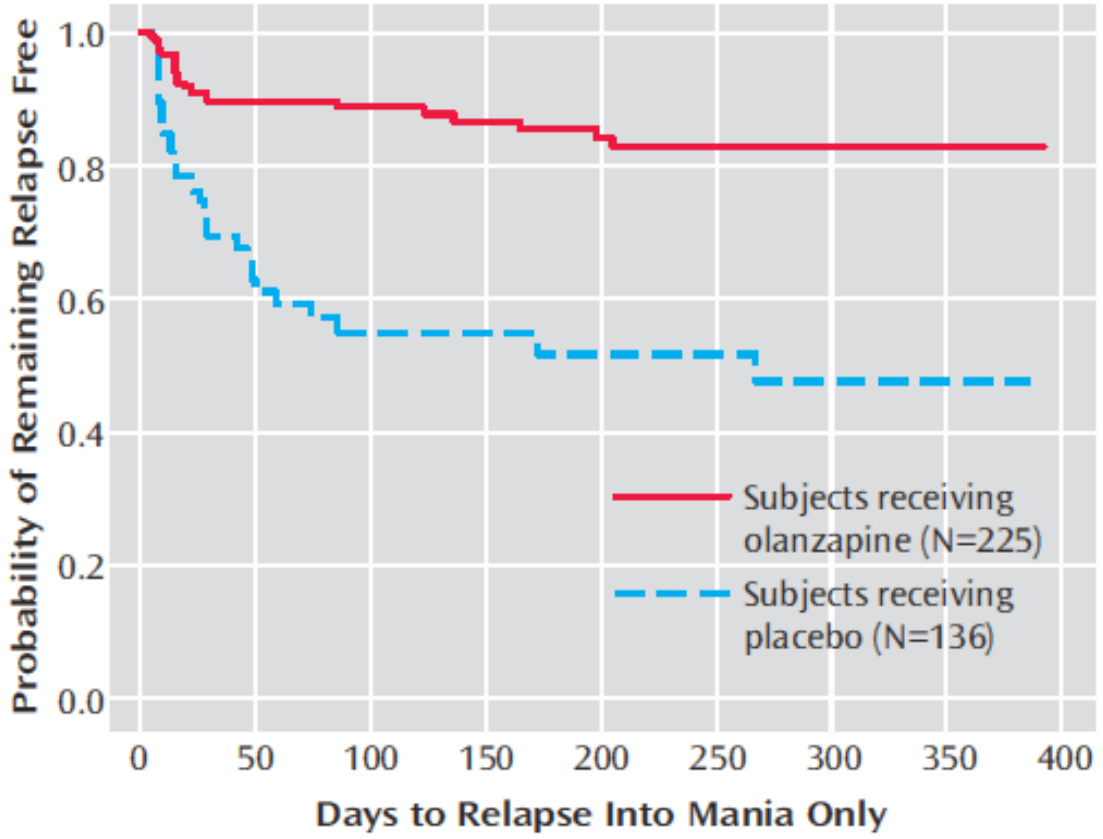
Relapse = Discontinuation of the study attributed to lack of efficacy indicated by hospital admission because of a manic episode or addition to or increase in psychotropic medication other than study drug for manic and/or depressive symptoms. Mean dose of aripiprazole during last 7 days of treatment, whenever that occurred, was 24.1 mg/day HR = hazard ratio (safety sample); CI = confidence interval

Keck PE, Calabrese JR, McIntyre RS et al.
Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo.
J Clin Psychiatry 2007;68:1480–1491.

Olanzapine vs placebo in prevention of manic relapse:

(48 Weeks)

FIGURE 2. Kaplan-Meier Survival Analysis of Time to Symptomatic Relapse Into Mania Only for Bipolar I Disorder Patients in the Double-Blind Maintenance Phase of a Study of Olanzapine in Relapse Prevention[a]

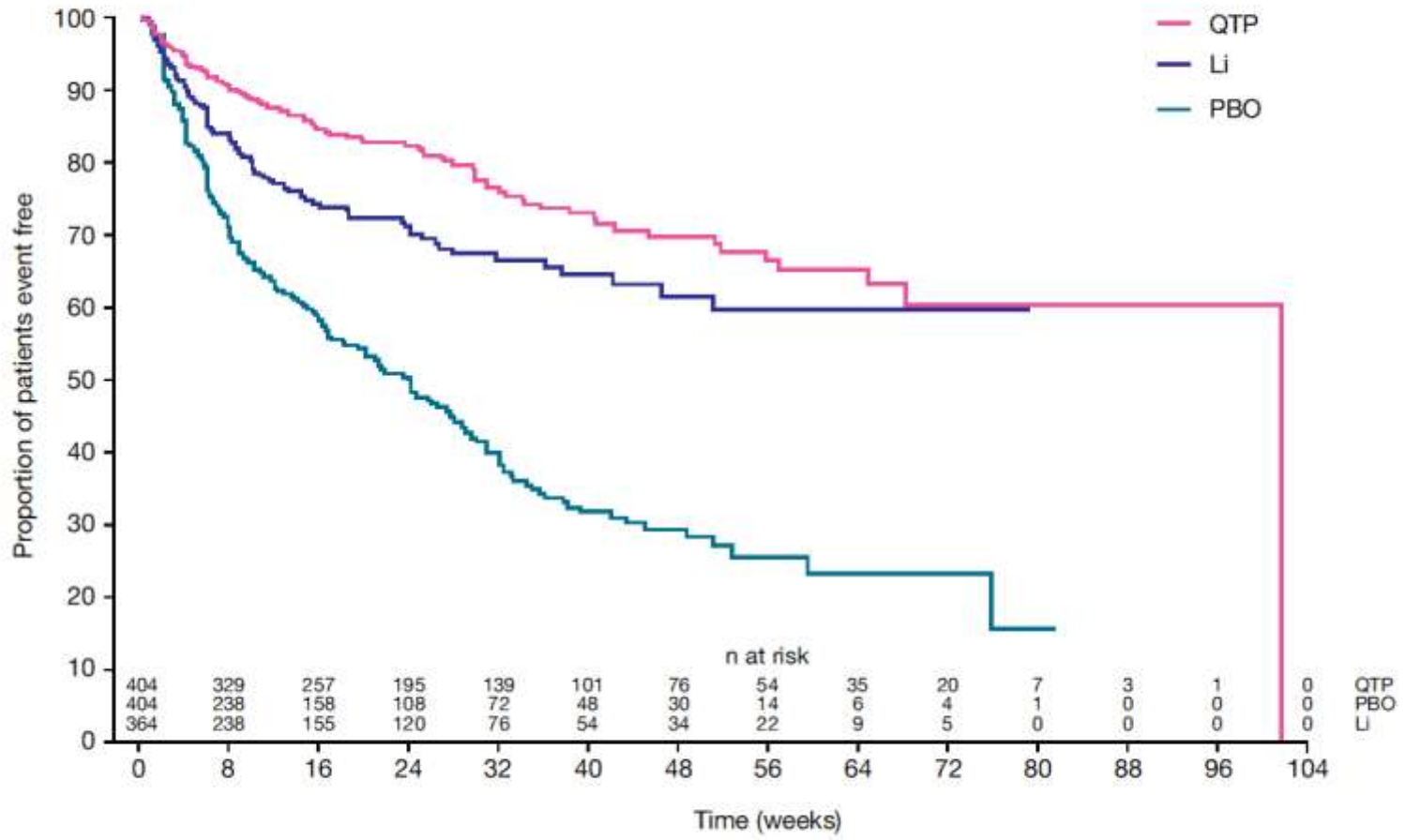


[a] Relapse based on Young Mania Rating Scale score ≥15 and 21-item Hamilton Depression Rating Scale score <15, or hospitalization for mania. Estimated 25th percentile time to relapse was not calculable for olanzapine patients and was 26 days for placebo patients (log-rank χ^2=35.6, df=1, p<0.001; hazard ratio=3.90, 95% CI=2.40–6.33).

Tohen M, Calabrese J, Sachs G et al.
Randomized, Placebo-Controlled Trial of Olanzapine as Maintenance Therapy in Patients With Bipolar I Disorder Responding to Acute Treatment With Olanzapine
Am J Psychiatry 2006; 163:247–256

Quetiapine vs lithium & placebo in prevention of recurrence: (104 Weeks)

Figure 2. Time to recurrence of any mood event during randomized phase (Kaplan-Meier curves, ITT population)



Weisler R, Nolen W, Neijber A et al.
Quetiapine or lithium versus placebo for maintenance treatment of bipolar I disorder after stabilization on quetiapine
Poster presented at the 8th International Conference on Bipolar Disorder 2009, Pittsburgh, USA

Number needed to treat analyses of drugs used for maintenance treatment of bipolar disorder

Dina Popovic · Maria Reinares · Benedikt Amann · Manel Salamero · Eduard Vieta

Received: 30 July 2010 / Accepted: 8 October 2010

Abstract
Rationale Due to the episodic and chronic nature of bipolar disorder (BD), maintenance therapy represents a critical part of treatment; however, there is a paucity of studies comparing effectiveness of available long-term treatments.
Objective The aim of this study is to determine and compare the efficacy of pharmacological treatments for maintenance treatment of BD by means of the number needed to treat (NNT).
Methods The efficacy of drugs used for maintenance treatment of BD, as emerging from the results of randomized controlled trials, was assessed using the size effect measure of NNT. PubMed searches were conducted on English-language articles published until May 2010 using the search terms "bipolar disorder," "mania," "mixed episode," or "bipolar depression," cross-referenced with trial characteristic search phrases and generic names of medications. The search was supplemented by manually reviewing reference lists from identified publications.
Results In 15 studies, aripiprazole, olanzapine, quetiapine, risperidone long-acting injection, lithium, lamotrigine, and divalproex proved effectiveness in terms of NNTs (≥10% advantage over placebo) for prevention of relapse into any mood episode. Quetiapine, lithium, risperidone long-acting injection, aripiprazole, and olanzapine are effective in manic recurrence prevention. Lamotrigine, quetiapine, and lithium present significant NNTs for prevention of depressive relapses.
Conclusions All of the pharmacological agents assessed were effective in the prevention of any kind of mood episode; however, different efficacy profiles were found for prevention of manic and/or depressive relapses. The comparison of NNT values of the available agents may represent a useful tool in clinical settings, in order to facilitate implementation of long-term pharmacological interventions in patients with BD.

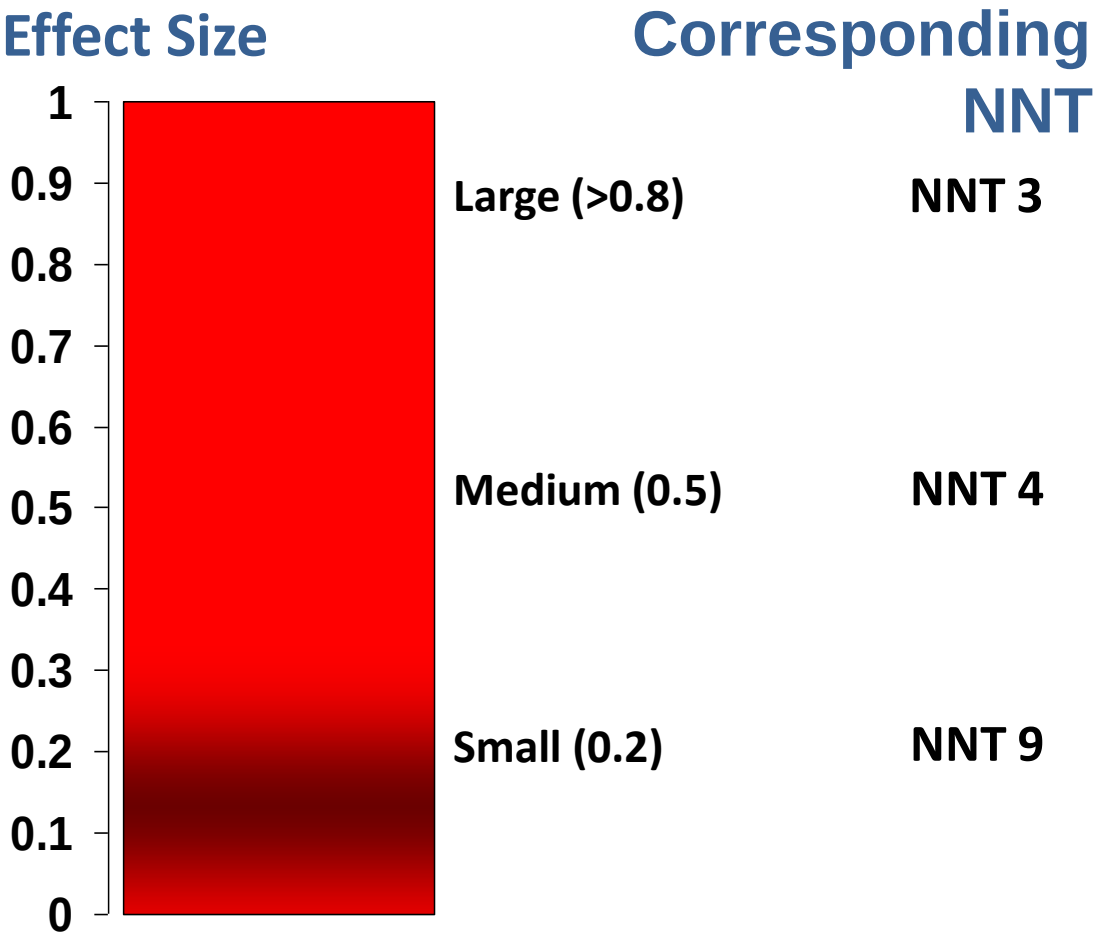
Keywords Bipolar disorder · NNT · Treatment efficacy · Maintenance treatment

Number Needed To Treat: NNT

- Based on absolute difference in outcomes between treatments
- The **NNT** is an **estimate** of the number of patients that would need to be given a treatment for **one additional patient** to achieve the desired outcome who **would not have achieved it with a control treatment**.
- NNTs express the "*therapeutic effort*" needed to achieve the desired outcome

Interpreting NNTs

- Only NNTs <10 are clinically meaningful
- Lower NNTs reflect larger differences between treatment groups



Popovic D, Reinares M, Amann B et al.
Number needed to treat analyses of drugs used for maintenance treatment of bipolar disorder
Psychopharmacology 2011;213:657-667

NNTs for prevention of manic episode

(vs placebo)

Drug	NNT	95% CI
Lamotrigine *	24	5 - infinity
Lamotrigine	59	10 - infinity
Lamotrigine	26	8.6 - infinity
Lithium	4	2.5 - 6.4
Lithium	8	4.6 - 16.3
Lithium	6	3 - 26.4
Lithium	14	6.3 - infinity
Lithium	69	7.5 - infinity
Lithium	3	2.2 - 2.7
Valproate	22	6.8 - infinity

Popovic D, Reinares M, Amann B et al.
Number needed to treat analyses of drugs used for maintenance treatment of bipolar disorder
Psychopharmacology 2011;213:657-667

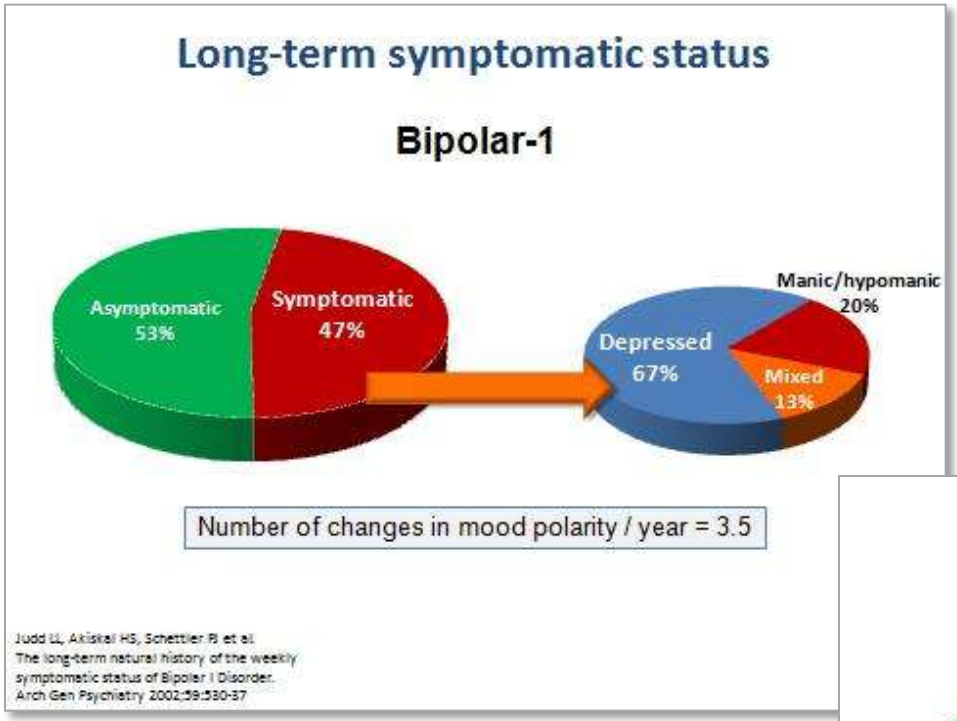
*Lamotrigine is licensed in the prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes

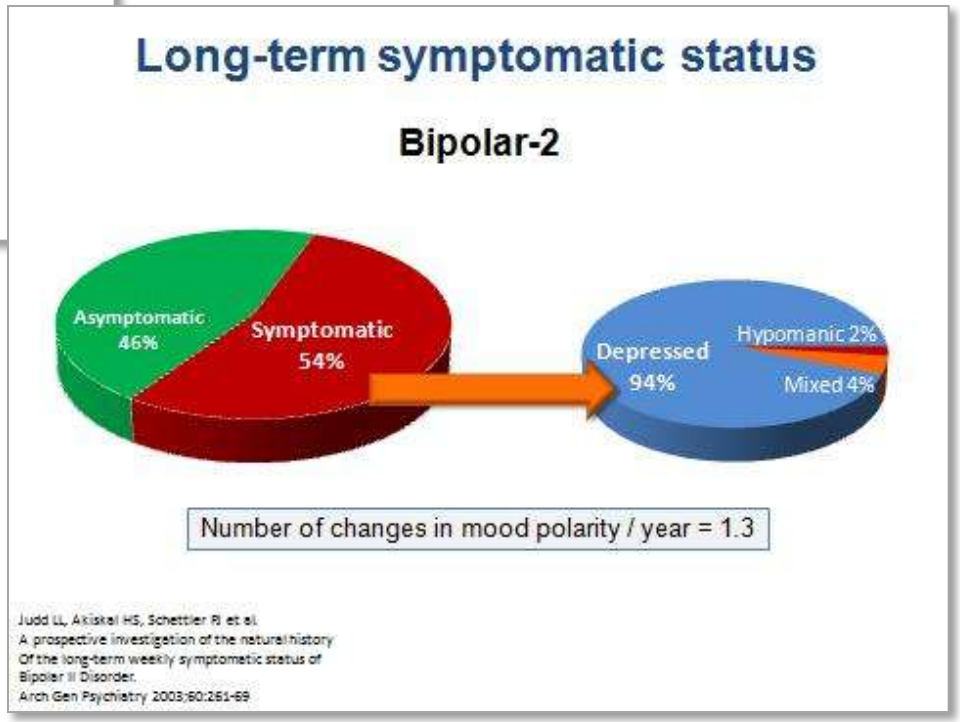
NNTs for prevention of manic episode

	Duration (weeks)	NNT	95% C.I.
Aripiprazole			
Monotherapy vs placebo	**100**	**7**	3.6 – 24.9
Olanzapine			
+ MS vs placebo + MS	**48**	**12**	3.4 - infinity
Monotherapy vs placebo	**72**	**5**	3.4 – 8.8
Quetiapine			
+ MS vs placebo + MS	**104**	**7**	4.8 – 10.1
+ MS vs placebo + MS	**104**	**9**	5.7 - 14
Monotherapy vs placebo	**104**	**3**	2 – 2.8

Popovic D, Reinares M, Amann B et al.
Number needed to treat analyses of drugs used for maintenance treatment of bipolar disorder
Psychopharmacology 2011;213:657-667

Inevitable switch to bipolar depression?





Treatment for chronic and recurrent depressive symptoms

1.5.1.9 The following treatments should be considered, in discussion with the patient, for people who have an established diagnosis of bipolar disorder and chronic or recurrent depressive symptoms, but who are not taking prophylactic medication and have not had a recent manic or hypomanic episode:

- long-term treatment with SSRIs at the minimum therapeutic dose in combination with prophylactic medication
- cognitive behavioural therapy (16–20 sessions) in combination with prophylactic medication
- quetiapine*, or
- lamotrigine*.

National Institute for Health and Clinical Excellence
Bipolar disorder: the management of bipolar disorder in adults, children and adolescents, in primary and secondary care.
NICE Clinical Guideline 38, July 2006

Not all agents are licensed in this setting in the UK

BAP Guideline 2009

Maintenance treatment

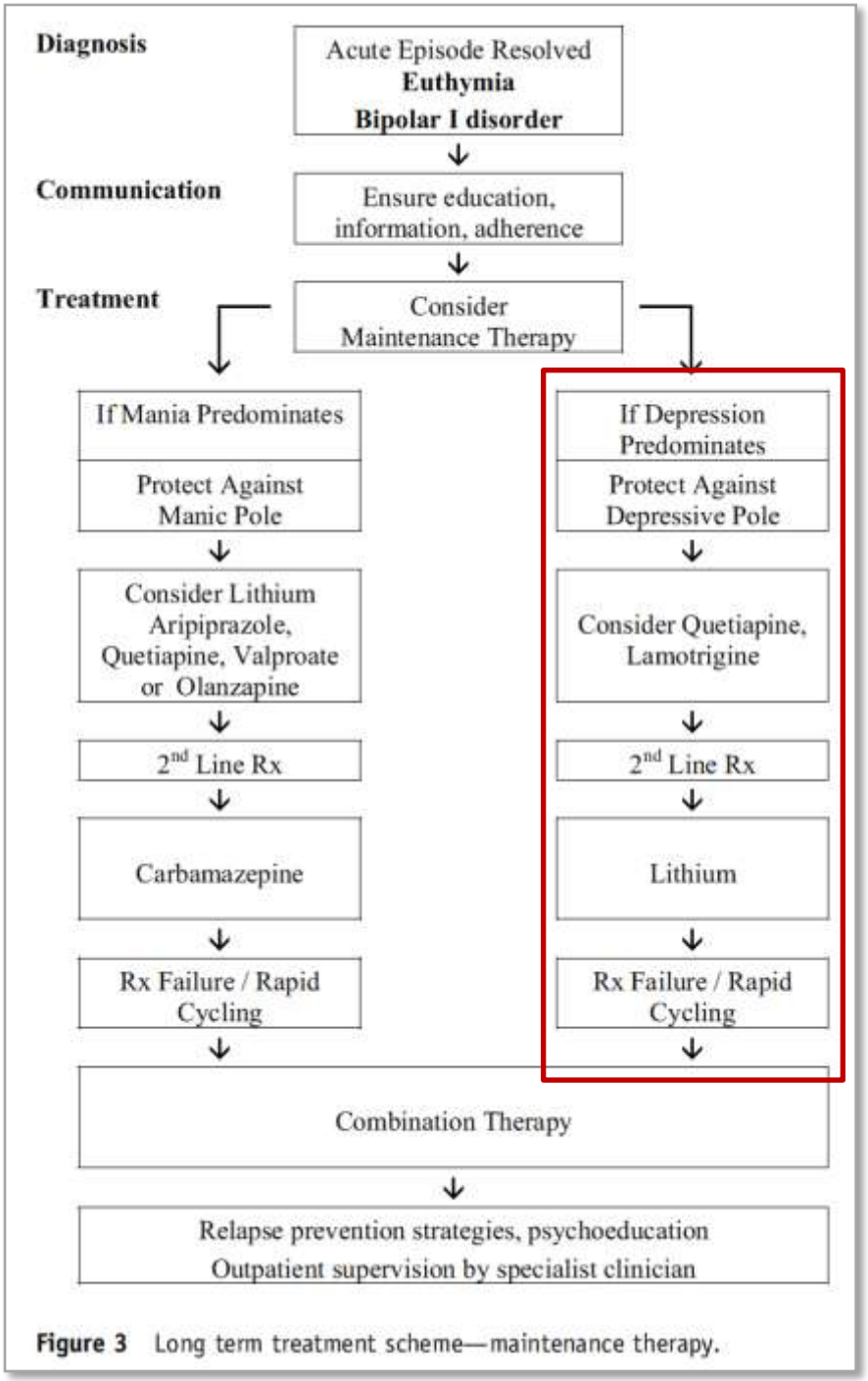


Figure 3 Long term treatment scheme—maintenance therapy.

Lamotrigine

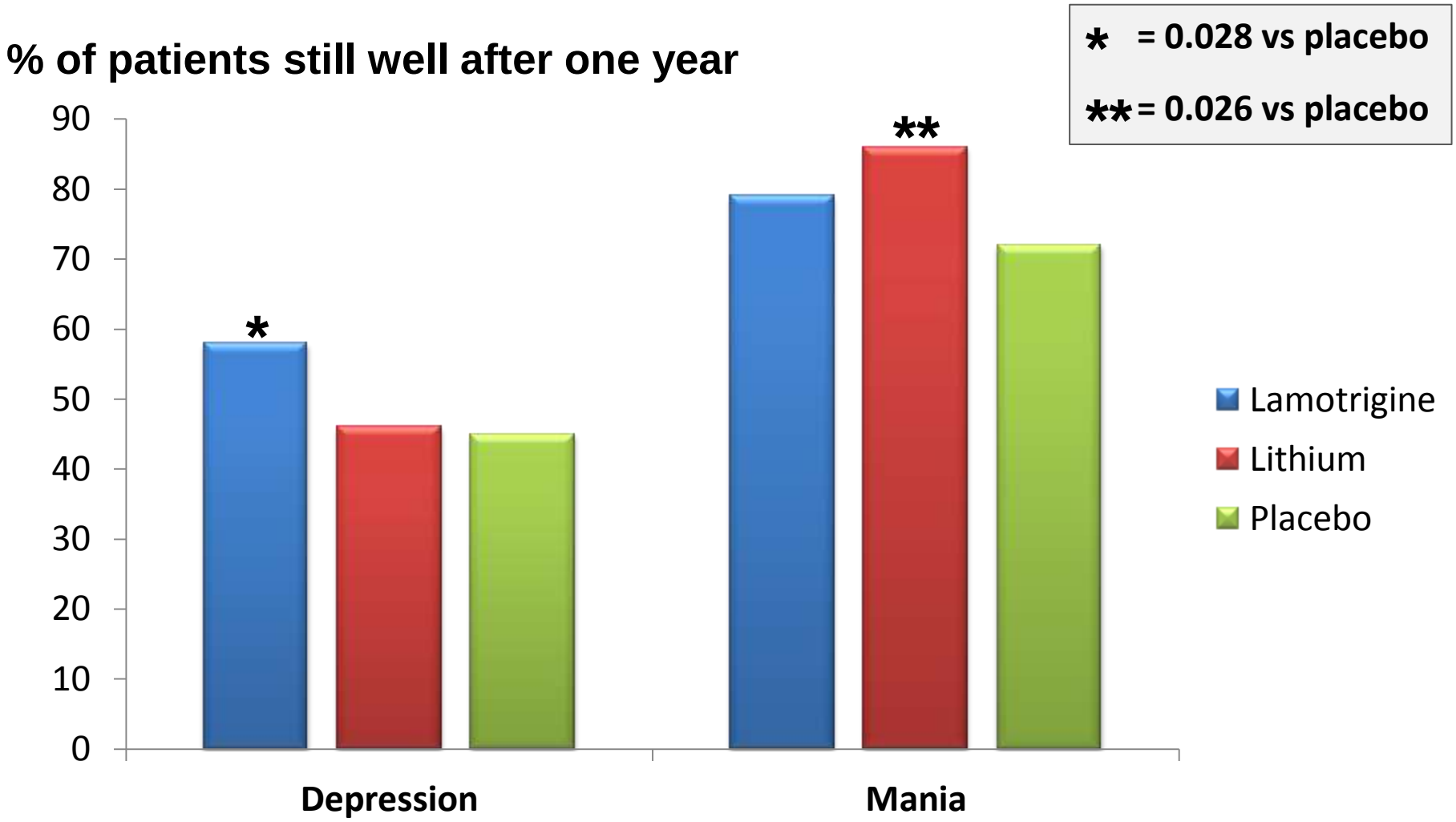
Maintenance after bipolar depression

- Patients recently recovered from major depressive episode
- Randomised, double-blind placebo controlled trial
  - Lamotrigine 50, 200 or 400mg/day n= 221
  - Lithium (0.8 – 1.1 mmol/l) n = 121
    - Mean serum level 0.8mmol/l
  - Placebo n = 121
- Primary outcome measure:
  - Time to intervention with other treatment for mood instability
    - Antidepressant, other mood stabiliser, antipsychotic

Calabrese JR, Bowden CL, Sachs GS, et al.
A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar-I disorder
Journal of Clinical Psychiatry 2003;64:1013-24

Results

Lamotrigine v lithium/placebo in maintenance after bipolar depression



Adapted from: Calabrese JR, Bowden CL, Sachs GS, et al.
A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar-I disorder. J Clin Psychiatr 2003;64:1013-24

Lamotrigine in bipolar depression

- Licensed for prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes
- Not licensed for the acute treatment of bipolar depression in UK
- Slow titration mandatory:
  - Initial dose 25mg once daily for two weeks, then 50mg once daily for two weeks. Then increase dose by a maximum of 50mg-100mg every 1-2 weeks until the optimal response is achieved
  - Effective dose in RCTs: 200mg/day

Neuropsychopharmacology (2008) 33, 2303–2312

www.neuropsychopharmacology.org

N-Desalkylquetiapine, a Potent Norepinephrine Reuptake Inhibitor and Partial 5-HT_{1A} Agonist, as a Putative Mediator of Quetiapine's Antidepressant Activity

Niels H Jensen[1], Ramona M Rodriguiz[2,3], Marc G Caron[4,5], William C Wetsel[2,3,4,5], Richard B Rothman[6] and Bryan L Roth*[,1,7,8]

[1]Department of Pharmacology, University of North Carolina Medical School, Chapel Hill, NC, USA; [2]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA; [3]Mouse Behavioral and Neuroendocrine Analysis Core Facility, Duke University Medical Center, Durham, NC, USA; [4]Department of Cell Biology, Duke University Medical Center, Durham, NC, USA; [5]Department of Neurobiology, Duke University Medical Center, Durham, NC, USA; [6]Intramural Research Program, NIDA, Clinical Psychopharmacology Section, NIH, Baltimore, MD, USA; [7]Department of Psychiatry, Comprehensive Cancer Center, Center for Neurobiology Division of Medicinal Chemistry and Natural Products; [8]NIMH Psychoactive Drug Screening Program, University of North Carolina Medical School, Chapel Hill, NC, USA

Quetiapine is an atypical antipsychotic drug that is also US FDA approved for treating bipolar depression, albeit by an unknown mechanism. To discover the potential mechanism for this apparently unique action, we screened quetiapine, its metabolite *N*-Desalkylquetiapine, and dibenzo[*b*,*f*][1,4]thiazepine-11(10-*H*)-one (DBTO) against a large panel of G-protein–coupled receptors, ion channels, and neurotransmitter transporters. DBTO was inactive at all tested molecular targets. *N*-Desalkylquetiapine had a high affinity (3.4 nM) for the histamine H_1 receptor and moderate affinities (10–100 nM) for the norepinephrine reuptake transporter (NET), the serotonin 5-HT_{1A}, 5-HT_{1E}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_7 receptors, the α_{1B}-adrenergic receptor, and the M_1, M_3, and M_5 muscarinic receptors. The compound had low affinities (100–1000 nM) for the 5-HT_{1D}, 5-HT_{2C}, 5-HT_3, 5-HT_5, 5-HT_6, α_{1A}, α_{2A}, α_{2B}, α_{2C}, H_2, M_2, M_4, and dopamine D_1, D_2, D_3, and D_4 receptors. *N*-Desalkylquetiapine potently inhibited human NE transporter with a K_i of 12 nM, about 100-fold more potent than quetiapine itself. *N*-Desalkylquetiapine was also 10-fold more potent and more efficacious than quetiapine at the 5-HT_{1A} receptor. *N*-Desalkylquetiapine was an antagonist at 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, α_{1A}, α_{1D}, α_{2A}, α_{2C}, H_1, M_1, M_3, and M_5 receptors. In the mouse tail suspension test, *N*-Desalkylquetiapine displayed potent antidepressant-like activity in VMAT2 heterozygous mice at doses as low as 0.1 mg/kg. These data strongly suggest that the antidepressant activity of quetiapine is mediated, at least in part, by its metabolite *N*-Desalkylquetiapine through NET inhibition and partial 5-HT_{1A} agonism. Possible contributions of this metabolite to the side effects of quetiapine are discussed.

Neuropsychopharmacology (2008) **33,** 2303–2312; doi:10.1038/sj.npp.1301646; published online 5 December 2007

Keywords: quetiapine; *N*-Desalkylquetiapine; norepinephrine reuptake inhibitor; antidepressant; antipsychotic

A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY WITH ACUTE AND CONTINUATION PHASE OF QUETIAPINE IN ADULTS WITH BIPOLAR DEPRESSION (EMBOLDEN I)

AH Young,[1] S McElroy,[2] W Chang,[4] B Olausson,[3] B Paulsson,[3] M Brecher[4]

A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY WITH ACUTE AND CONTINUATION PHASE OF QUETIAPINE IN ADULTS WITH BIPOLAR DEPRESSION (EMBOLDEN II)

S McElroy,[1] B Olausson,[2] W Chang,[3] A Nordenhem,[3] B Paulsson,[2] M Brecher,[3] AH Young[4]

Objectives

- To evaluate efficacy of quetiapine (300 or 600mg/day) in treatment of depression in bipolar 1 & 2 disorder
- To evaluate quetiapine in time to recurrence of a mood episode (depressive or manic)

Patients

- Outpatients with bipolar 1 or 2
- Rapid cycling NOT excluded
- Major depressive episode
  - Duration $\leq$1 year, onset $\geq$4 weeks

Design

- 8 week double-blind, placebo controlled trial
- Primary outcome measure change in MADRS total score

followed by

- 26-52 week continuation phase

Active control arms

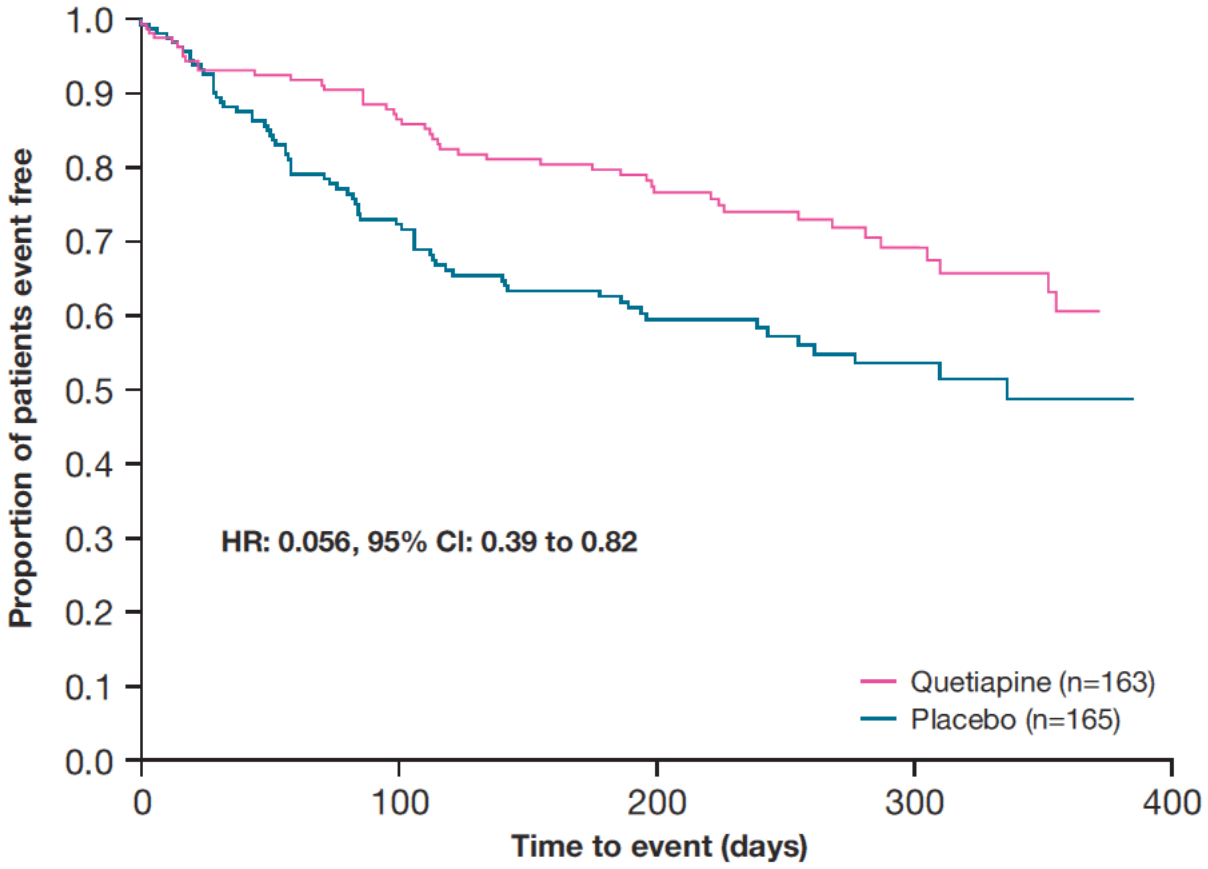
- Lithium (Embolden 1)
- Paroxetine (Embolden 2)

Posters presented at 3rd Biennial conference of Int Soc for Bipolar Disorders, Delhi, Jan 2008

A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY WITH ACUTE AND CONTINUATION PHASE OF QUETIAPINE IN ADULTS WITH BIPOLAR DEPRESSION (EMBOLDEN I)

AH Young,[1] S McElroy,[2] W Chang,[4] B Olausson,[3] B Paulsson,[3] M Brecher[4]

Figure 5. Time to recurrence of a mood event in patients with bipolar I or II disorder (ITT, LOCF; Continuation Treatment Phase)



Poster presented at 3rd Biennial conference of
Int Soc for Bipolar Disorders, Delhi, Jan 2008

A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY WITH ACUTE AND CONTINUATION PHASE OF QUETIAPINE IN ADULTS WITH BIPOLAR DEPRESSION (EMBOLDEN II)

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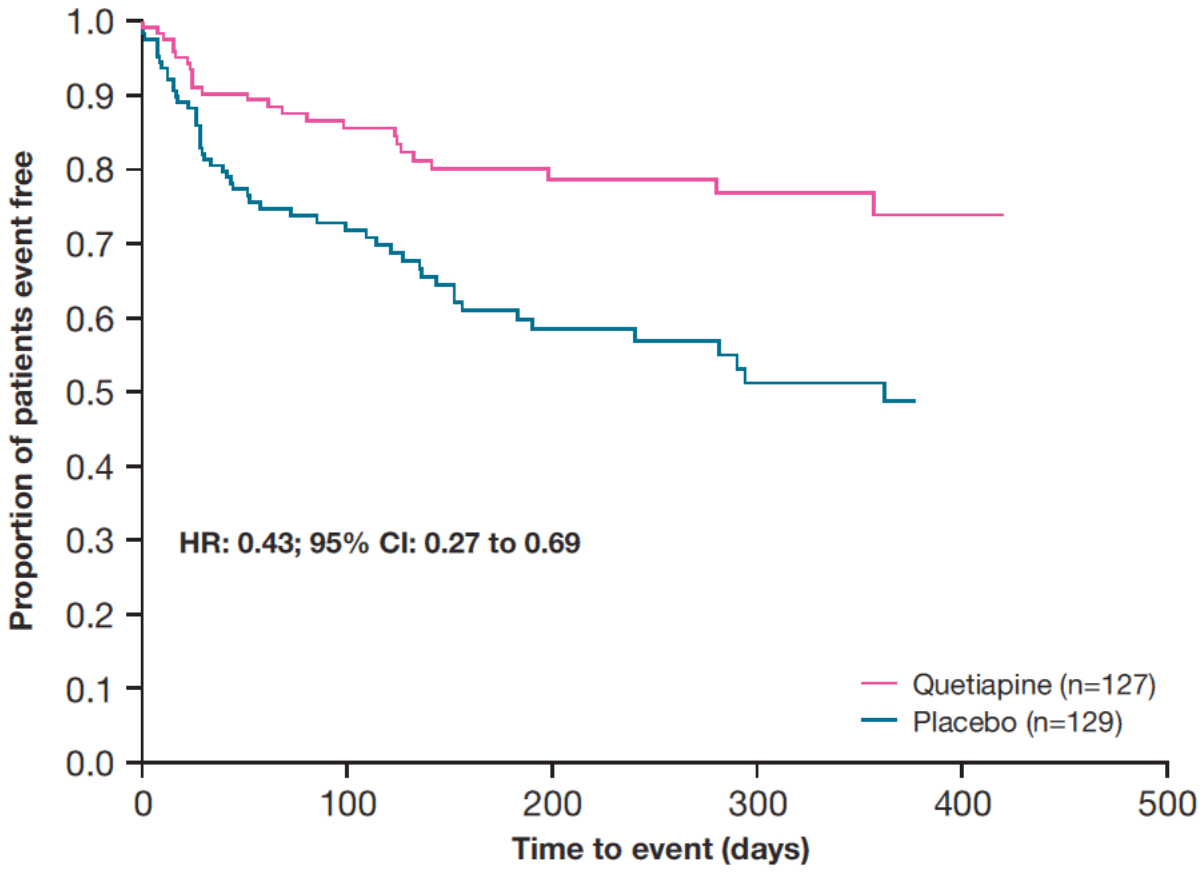
Figure 5. Time to recurrence of a mood event in patients with bipolar I or II disorder (ITT, LOCF; Continuation Treatment Phase)



Poster presented at 3rd Biennial conference of
Int Soc for Bipolar Disorders, Delhi, Jan 2008

NNTs for prevention of depressive episode (vs placebo)

Drug	NNT	95% CI
Lamotrigine	7	3.3 - 38.5
Lamotrigine	28	6.9 - infinity
Lamotrigine	20	7.2 - infinity
Lithium	22	7.6 - infinity
Lithium	49	8.4 - infinity
Lithium	13	4.1 - infinity
Lithium	86	7.4 - infinity
Lithium	17	6.4 - infinity
Lithium	4	2.8 - 4.4
Valproate*	11	5.6 - 74.3

Popovic D, Reinares M, Amann B et al.
Number needed to treat analyses of drugs used for maintenance treatment of bipolar disorder
Psychopharmacology 2011;213:657-667

***Not licensed for prevention of depressive episodes in bipolar disorder in the UK**

NNTs for prevention of depressive episode

	NNT	95% C.I.
Aripiprazole		
Monotherapy vs placebo	50	7.7 – infinity
Olanzapine		
+ MS vs placebo + MS	6	2.6 - infinity
Monotherapy vs placebo	12	5.3 - infinity
Quetiapine		
+ MS vs placebo + MS	**7**	4.9 – 10
+ MS vs placebo + MS	**6**	3.9 – 7.7
Monotherapy vs placebo	**4**	2.8 – 4.2

Not all agents licensed in this setting in the UK

Popovic D, Reinares M, Amann B et al.
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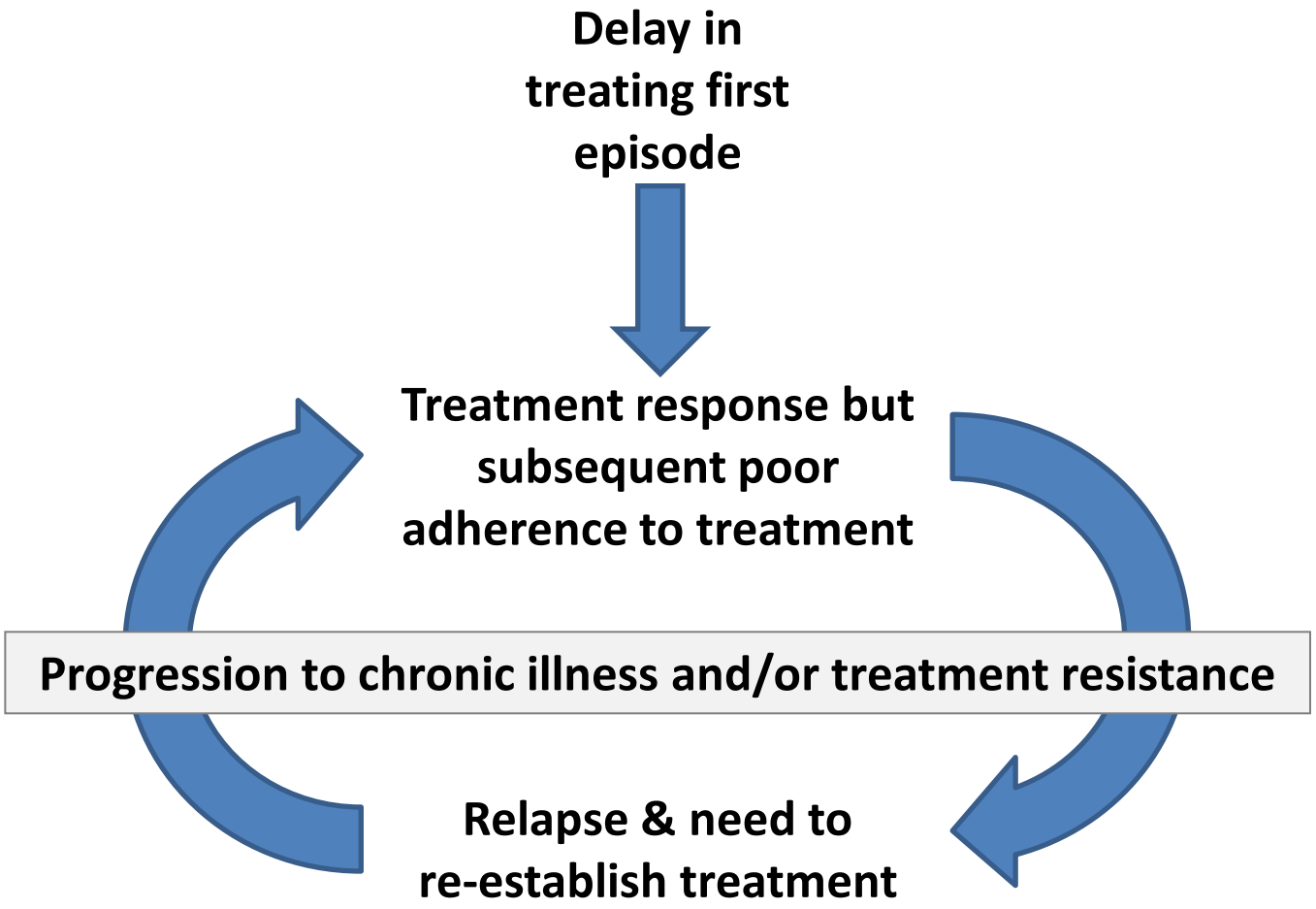
Licensed indications in the treatment of bipolar disorder

Drug	Treatment of acute episodes		Prevention of recurrence		
	Manic episode	Depressive episode	Manic episode	Depressive episode	Mixed episode
ARIPIPRAZOLE	☑	☒	☑	☒	☒
ASENAPINE	☑	☒	☒	☒	☒
OLANZAPINE	☑	☒	☑	☒	☒
RISPERIDONE	☑	☒	☒	☒	☒
QUETIAPINE	☑	☑	☑	☑	☑

SPCs for Abilify®, Sycrest ® ,Zyprexa®, Risperdal®, Seroquel® *, Seroquel XL®
Obtained from Electronic Medicines Compendium www.medicines.org.uk/EMC/

Revolving door = vicious cycle



BPD: Poor treatment adherence

- Rates of non-adherence range from 20%-60% in bipolar disorder
- In one study where 33% of patients showed poor adherence:

Poor adherence

- hospitalisation rates 73%
- average length of hospital stay 37 days

Good adherence

- hospitalisation rates 31%
- average length of hospital stay 4 days

Colom F, Vieta E, Tacchi MJ, et al. Identifying and improving non-adherence in bipolar disorders. Bipolar Disord 2005: 7 (Suppl 5): 24–31.

Is complexity of treatment regimen important in BPD?

- Consider
  - Need for combination treatments
  - Frequency of dosing
  - Intrusion into patient's lifestyle
  - Impact on adherence / outcome

Once-daily dosing improves adherence

Systematic review of MEMS literature 1986 – 2007

(Range of chronic physical & neurological illnesses
No psychiatric illnesses were included in this analysis)

Once daily dosing:

- 13%-26% better adherence than bd dosing
- 22%-41% better adherence than tid dosing

Saini SD, Schoenfeld P, Kaulback K, Dubinsky MC.
Effect of medication dosing frequency on adherence in chronic diseases
Am J Manag Care 2009;15:e22-33

Quetiapine-IR & Quetiapine-XL:
psychiatric hospital admissions in patients with bipolar-1 disorder

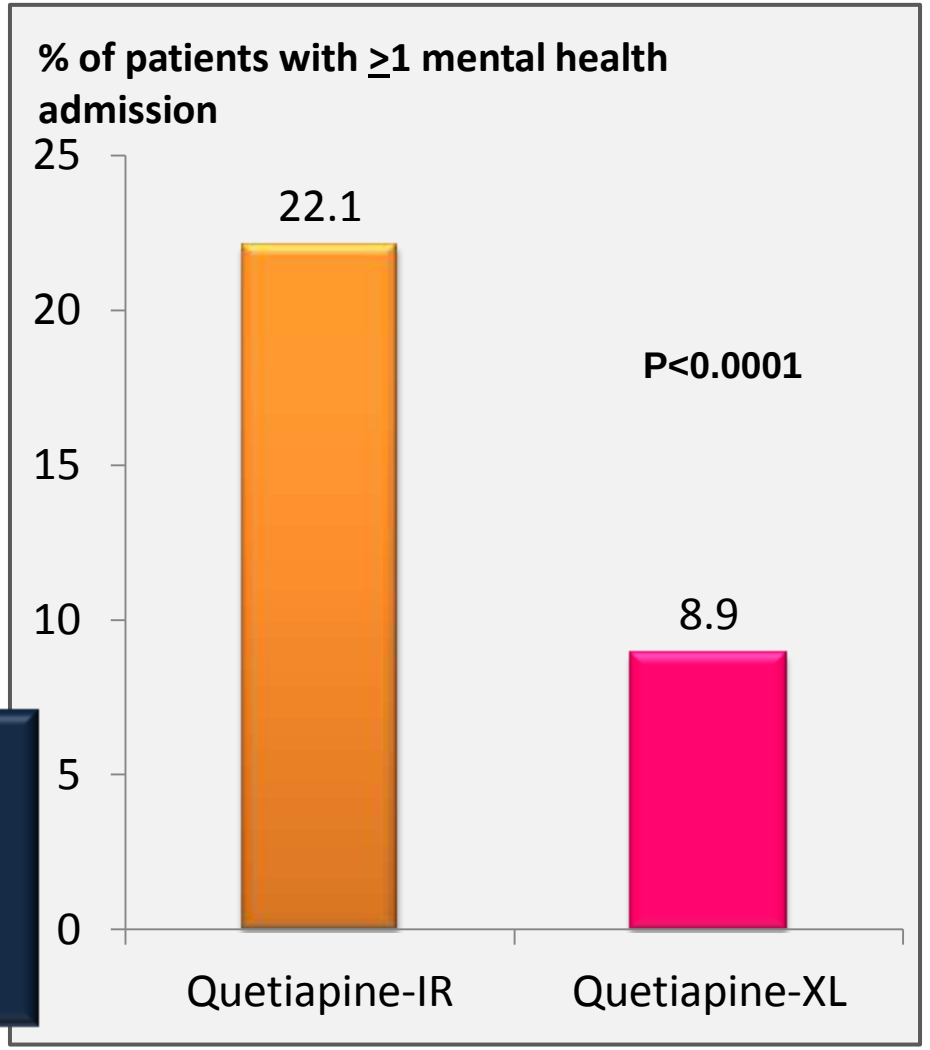
- Retrospective analysis of US managed care database using administrative claims data
- 190 patients with bipolar-1 disorder who had prescription claims data for both Quetiapine-IR and Quetiapine-XL
- 6-month treatment period on Quetiapine-IR
- Followed by 6-month treatment period on Quetiapine-XL
- Differences in hospital admissions and costs pre- and post-switch
- Dose was not recorded in the original protocol

Mean mental health hospital admission costs per patient/6 months:

Quetiapine IR = $2835

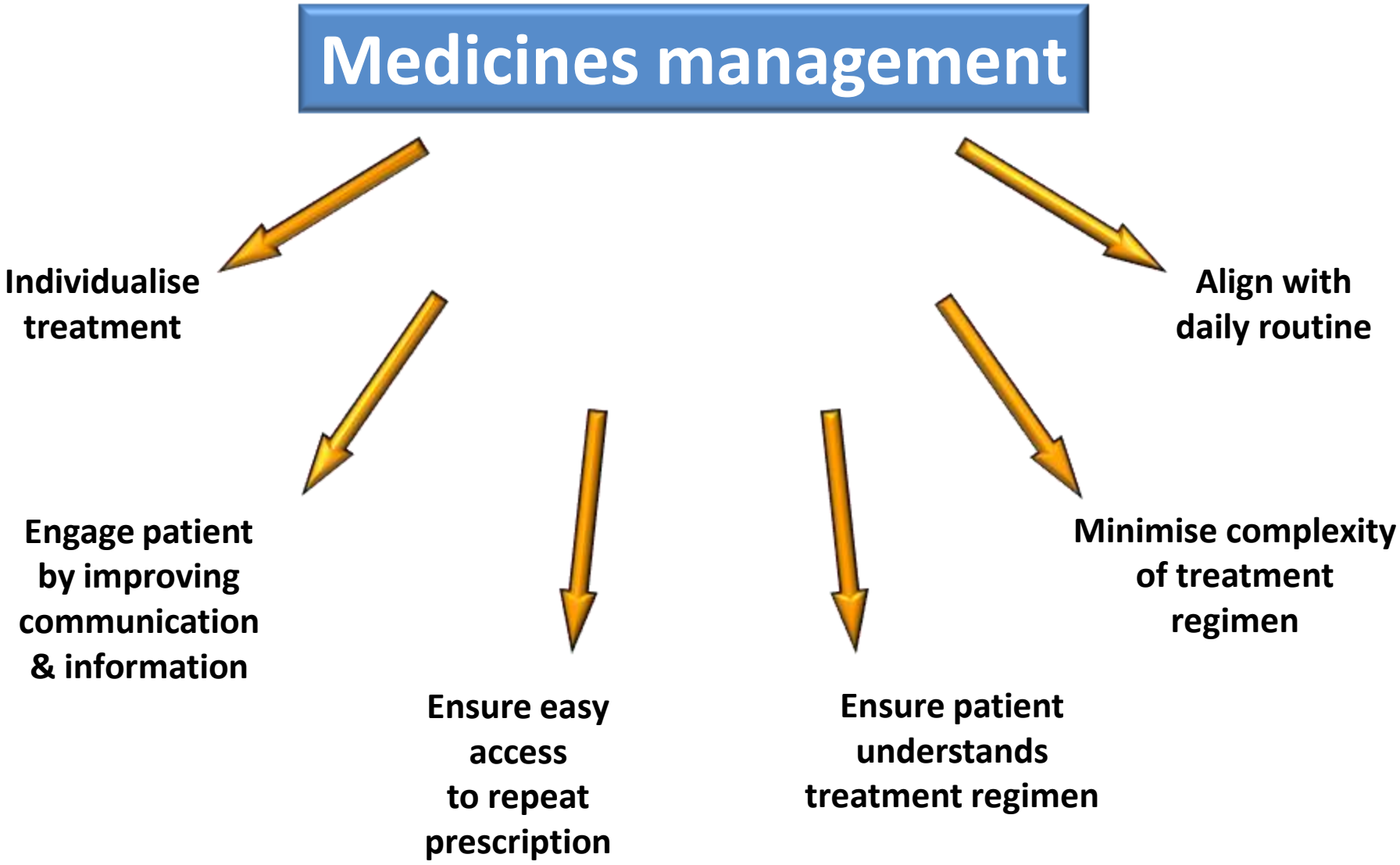
Quetiapine XL = $776

p=0.0019



Adapted from: Hassan M, Pelletier E, Smith D, et al.
Comparison of hospitalisations and costs among bipolar patients who switched to extended-release quetiapine from immediate-release quetiapine.
Poster presented at 163rd Annual Meeting of the American Psychiatric Association, May 22-26th 2010, New Orleans, Louisiana, USA

A strategy for preventing relapse



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Medicines in Mental Health Ltd offers a range of services designed to obtain maximum benefit from medicines in the treatment of severe mental illness.

Thank you

www.mentalmeds.co.uk