Bipolar disorder : diagnosis and short term treatment

Guy Goodwin
University of Oxford

Conflicts of interest

- Grants — Sanofi-Aventis, Servier
- Honoraria — AstraZeneca, BMS, Lundbeck, Servier
- Shares — P1vital
- Paid positions — University of Oxford
- Advisory boards — AstraZeneca, BMS, Cephalon Lundbeck, P1Vital, Servier
- Expert witness — Eli Lilly

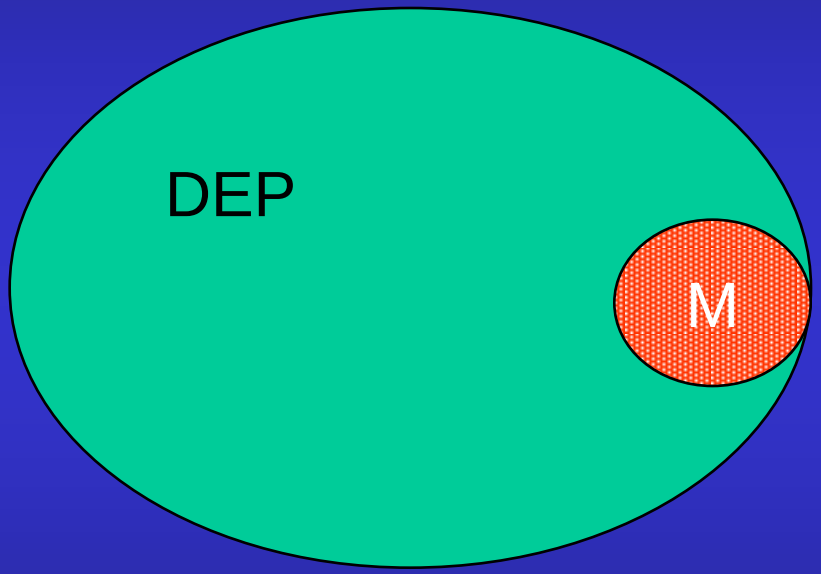
Objectives

- Why diagnose – what's in a name?
  - Why is it missed
  - Why might it come to be over-diagnosed in childhood (as in USA)
- When does bipolar disorder start
- Short term treatment

The sub-groups of Bipolar disorders : DSM-5

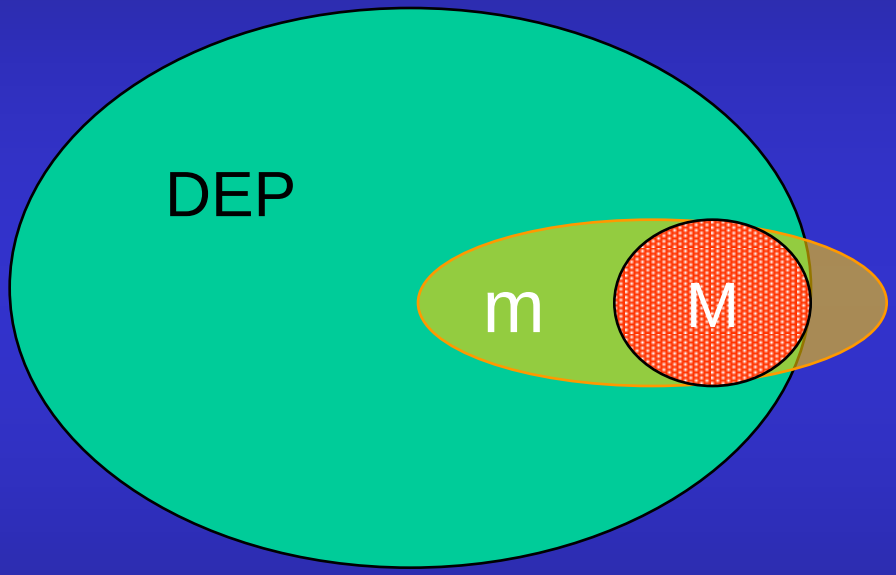
- Bipolar I
  - Defined by mania = mood elevation with impairment
- Bipolar II
  - Defined by major depression PLUS hypomania = mood elevation, no impairment
- Other Specified Bipolar and Related Disorders (Bipolar NOS)

The bipolar phenotype
DSM-IV



Kraepelin's manic-depressive insanity (and paranoia)

The bipolar phenotype DSM-5



The bipolar phenotype
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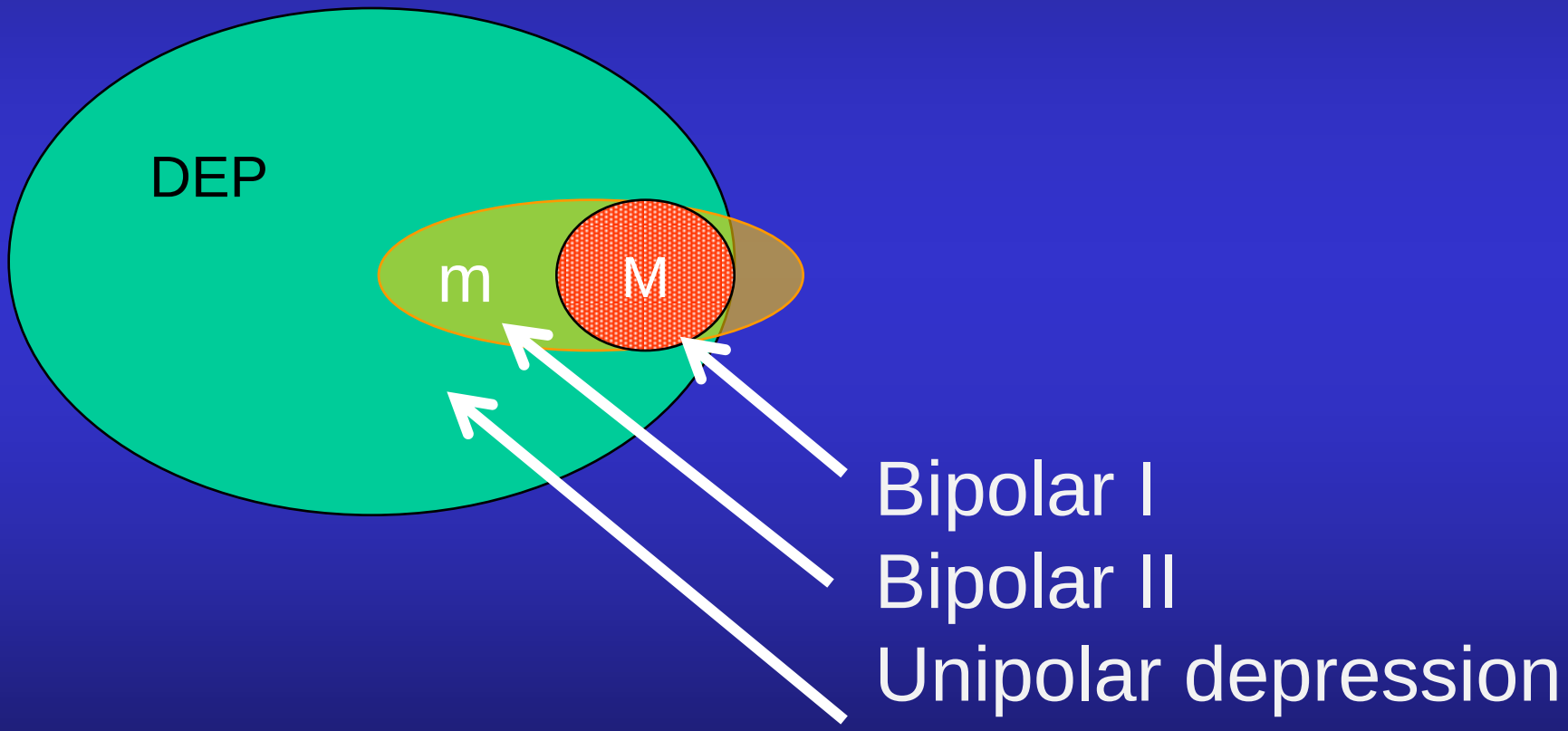
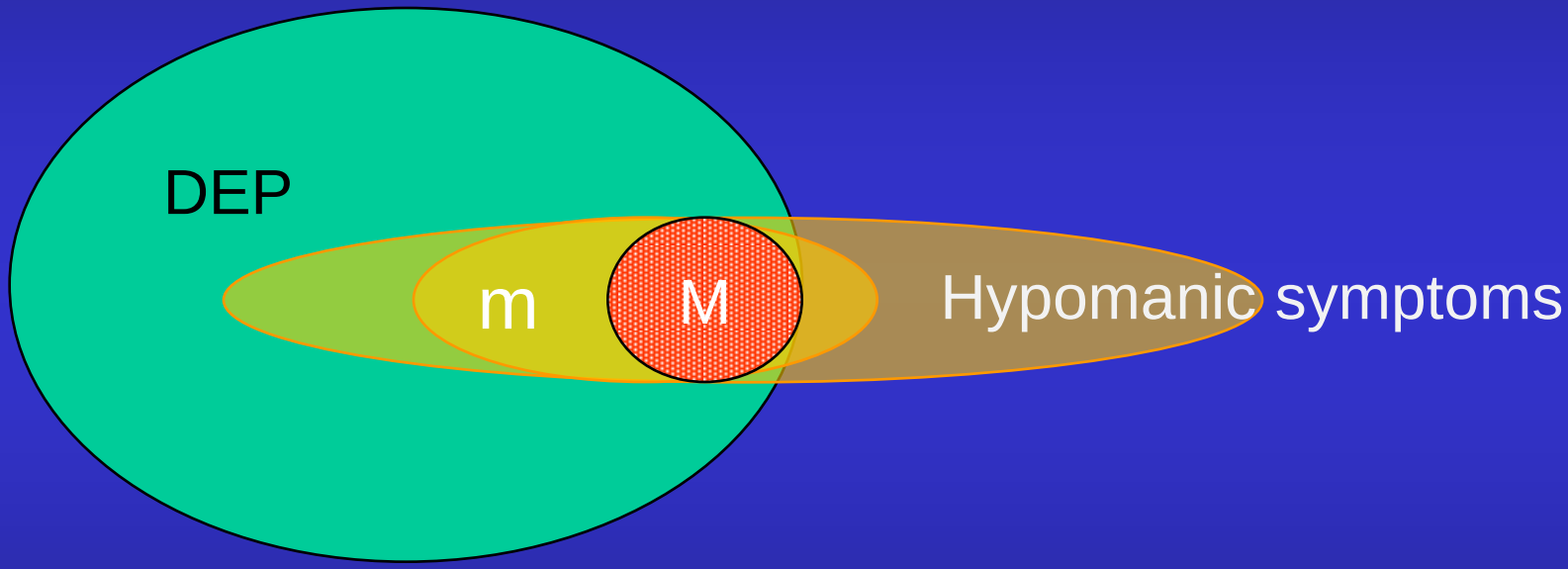


The bipolar phenotype including the spectrum



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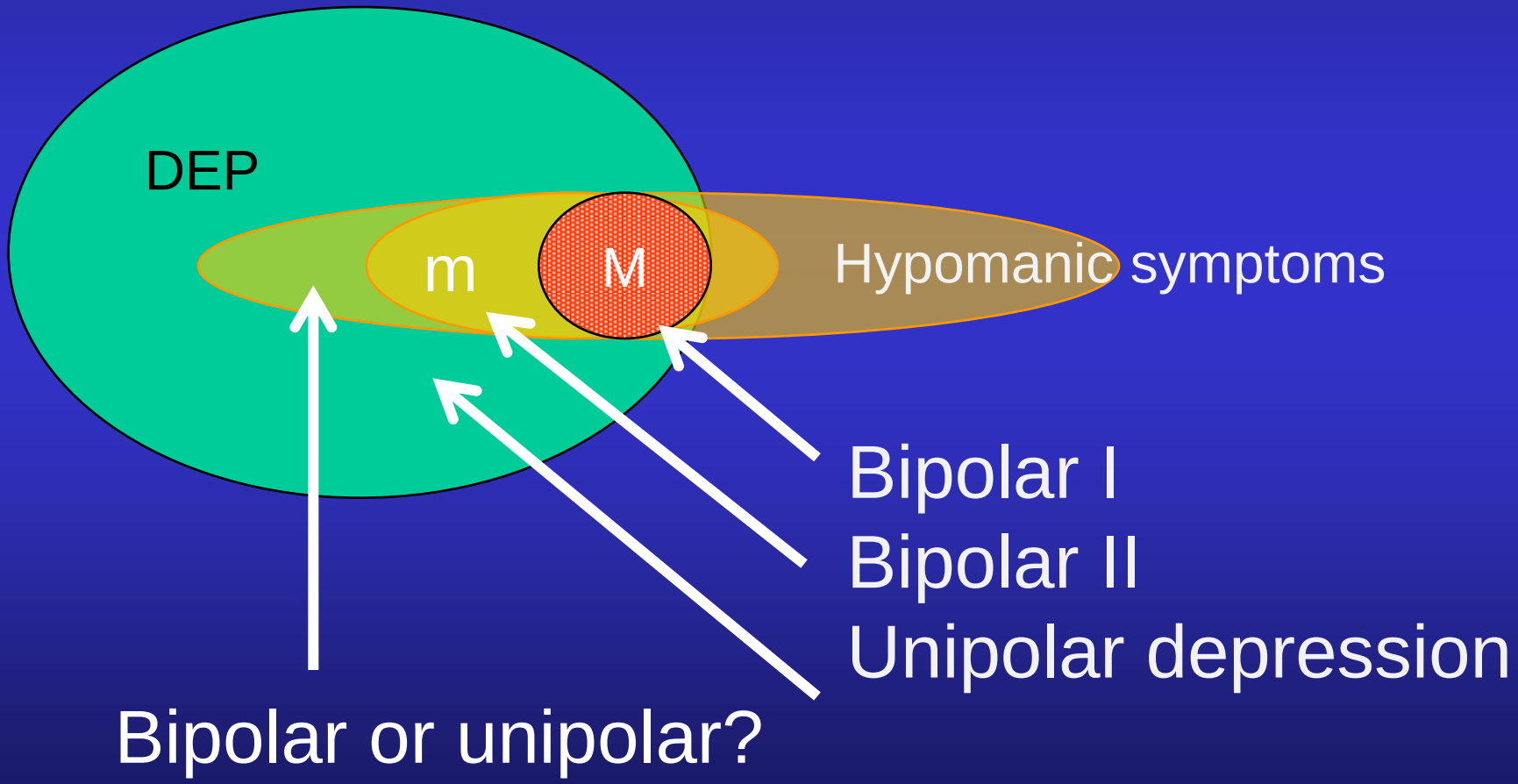

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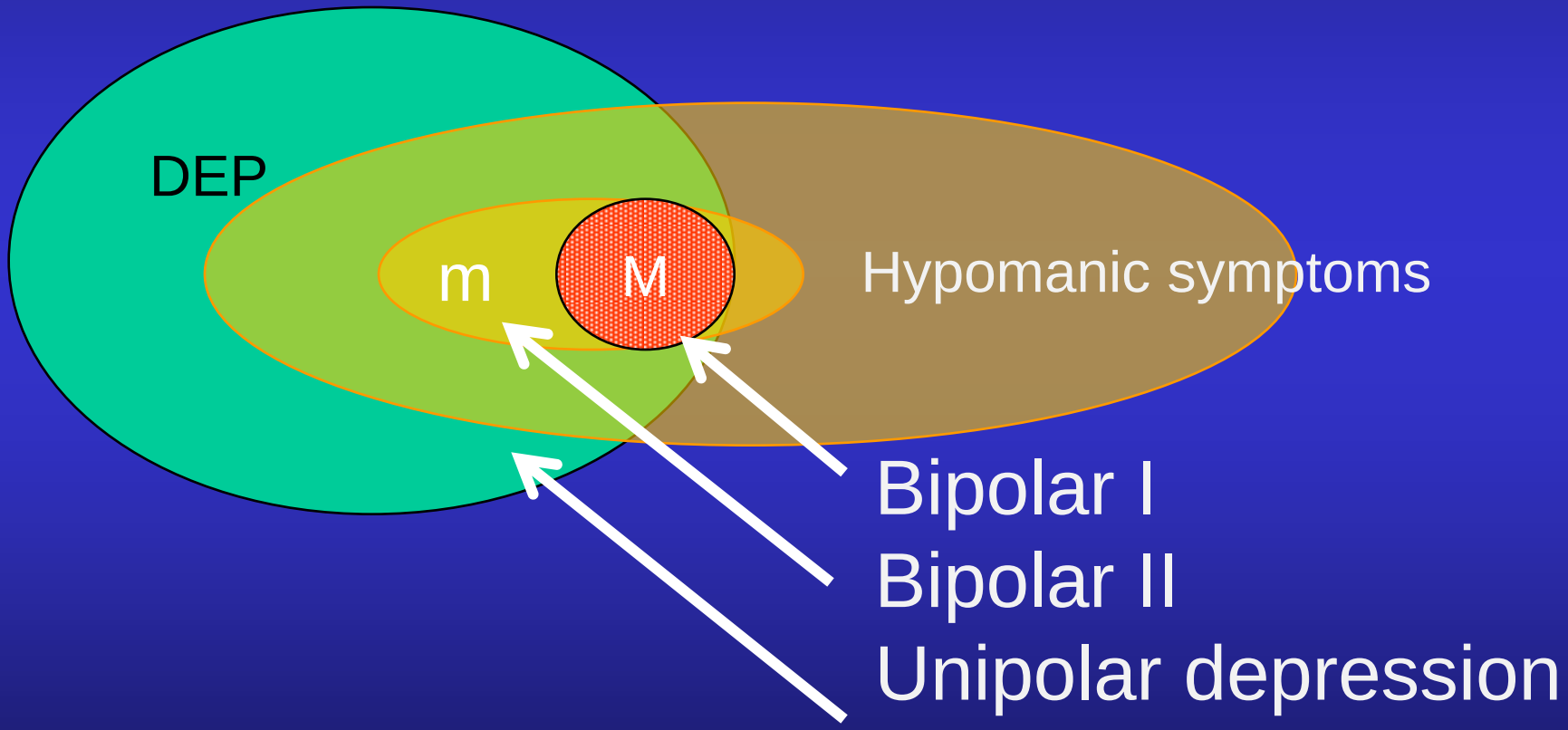

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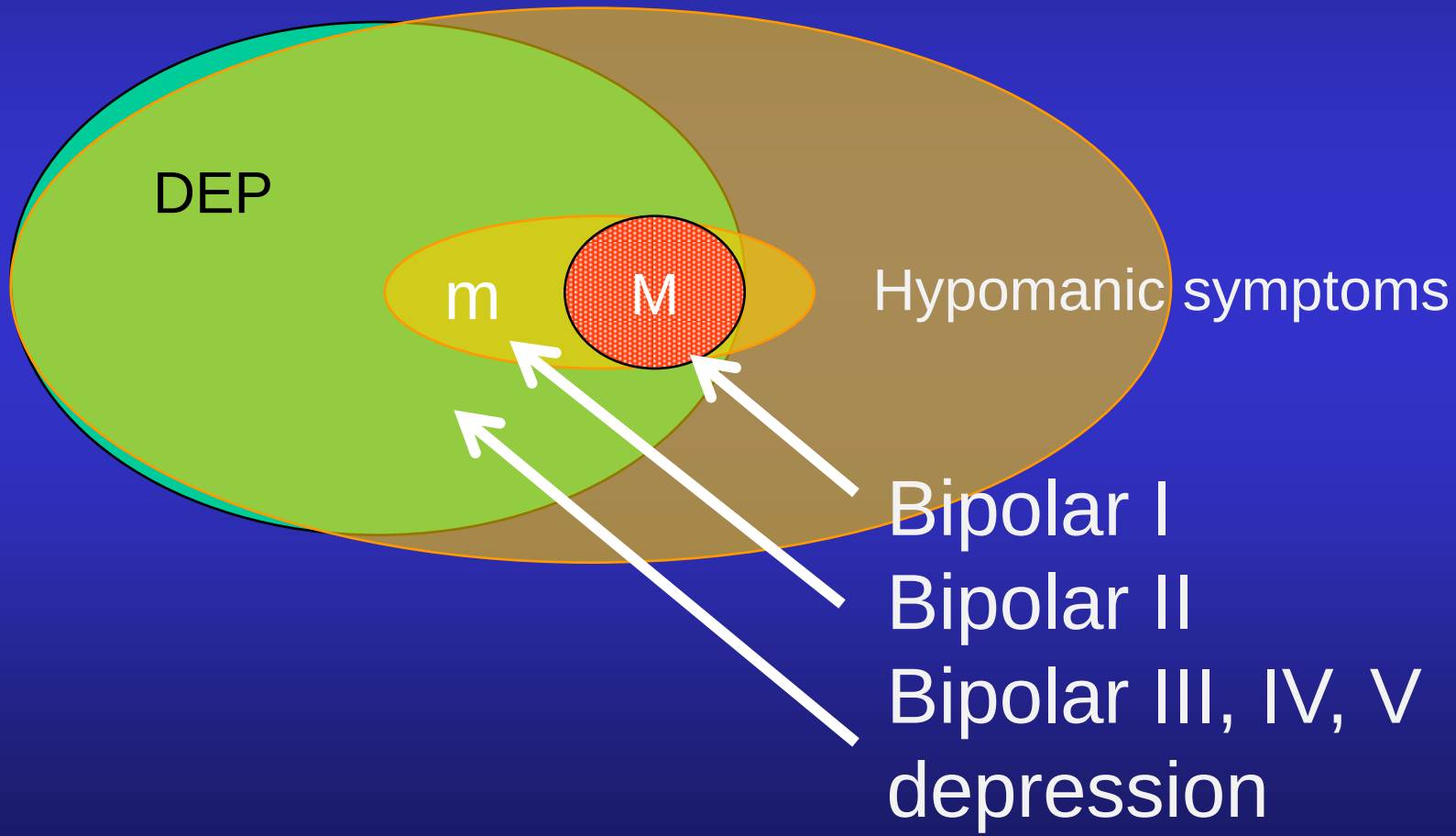

Conclusions: diagnosis

- BP-I, mania diagnosis is uncontroversial
- BP-II, other BP
  - Boundaries depend on definition of hypomania
- What has DSM-5 added?

Criterion A for mood elevation

- "a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy."

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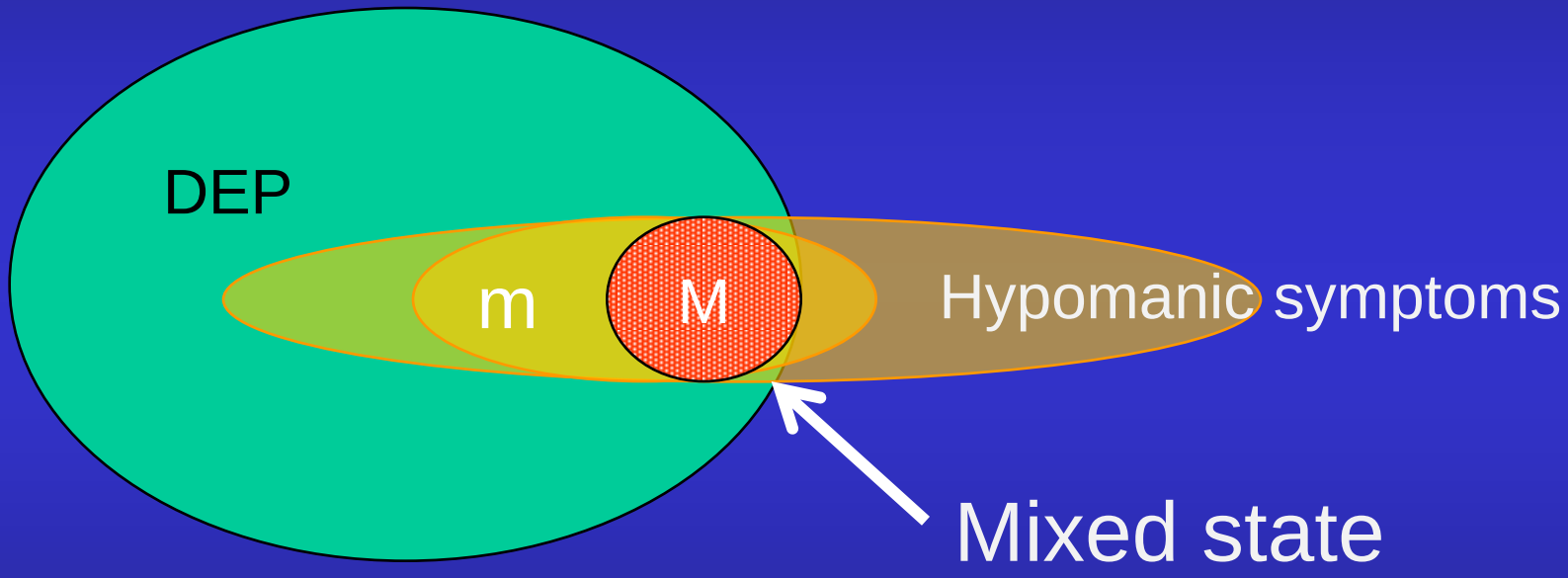
Mixed state (DSM-IV-TR)

- The criteria are met both for a manic episode and for a major depressive episode (excluding duration) nearly every day for at least 1 week
- The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others or to necessitate hospitalization to prevent harm to self or others, or the mood disturbance has psychotic features

The potential range of bipolar episodes: DSM-IV



Mixed state (DSM-5)

- DSM-IV mixed state very rare
- Extend the concept of mixed mood beyond BP-I disorder – as a specifier
- Thus, full criteria for primary mood (depression, mania or hypomania) and three or more symptoms of the other mood pole (excluding those common to both poles)

Mood elevation plus 3 of which depressive symptoms?

- Subjective depression
- Worry
- Self-reproach/guilt
- Negative evaluation of self
- Hopelessness
- Suicidal ideation or behaviour
- Anhedonia
- Fatigue
- Psychomotor retardation

Examples of Mixed Features from the DSM-5: Hypomania (mixed mood)

- Patient with bipolar II meets the diagnostic criteria of hypomania (the primary mood) PLUS:
  - Anhedonia
  - Inappropriate guilt
  - Recurrent thoughts of death
- EXCLUDES distractability, irritability, insomnia, indecisiveness

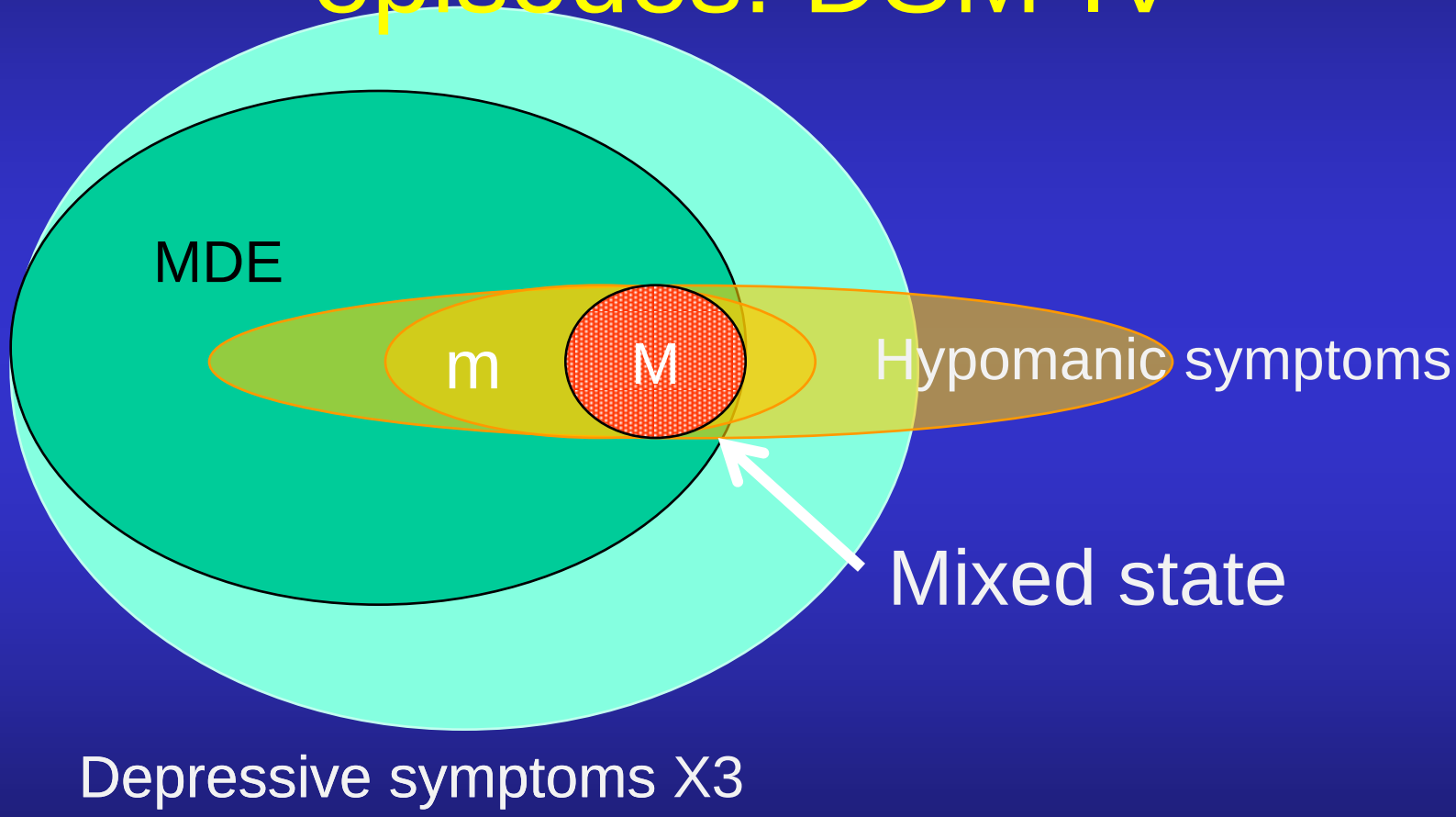
Major depressive episode plus 3 of which symptoms of mood elevation?

- Elevated mood
- Decreased need for sleep
- Goal-directed activity
- Increased energy and visible hyperactivity
- Grandiosity
- Accelerated speech
- Racing thoughts

Unipolar Depression (mixed mood)

- Major depressive episode, depression is the predominant mood
- PLUS nearly every day during this episode
  - Inflated self-esteem
  - Racing thoughts
  - Increased goal-directed activity
- EXCLUDES distractability, irritability, insomnia, indecisiveness

The potential range of bipolar episodes: DSM-IV



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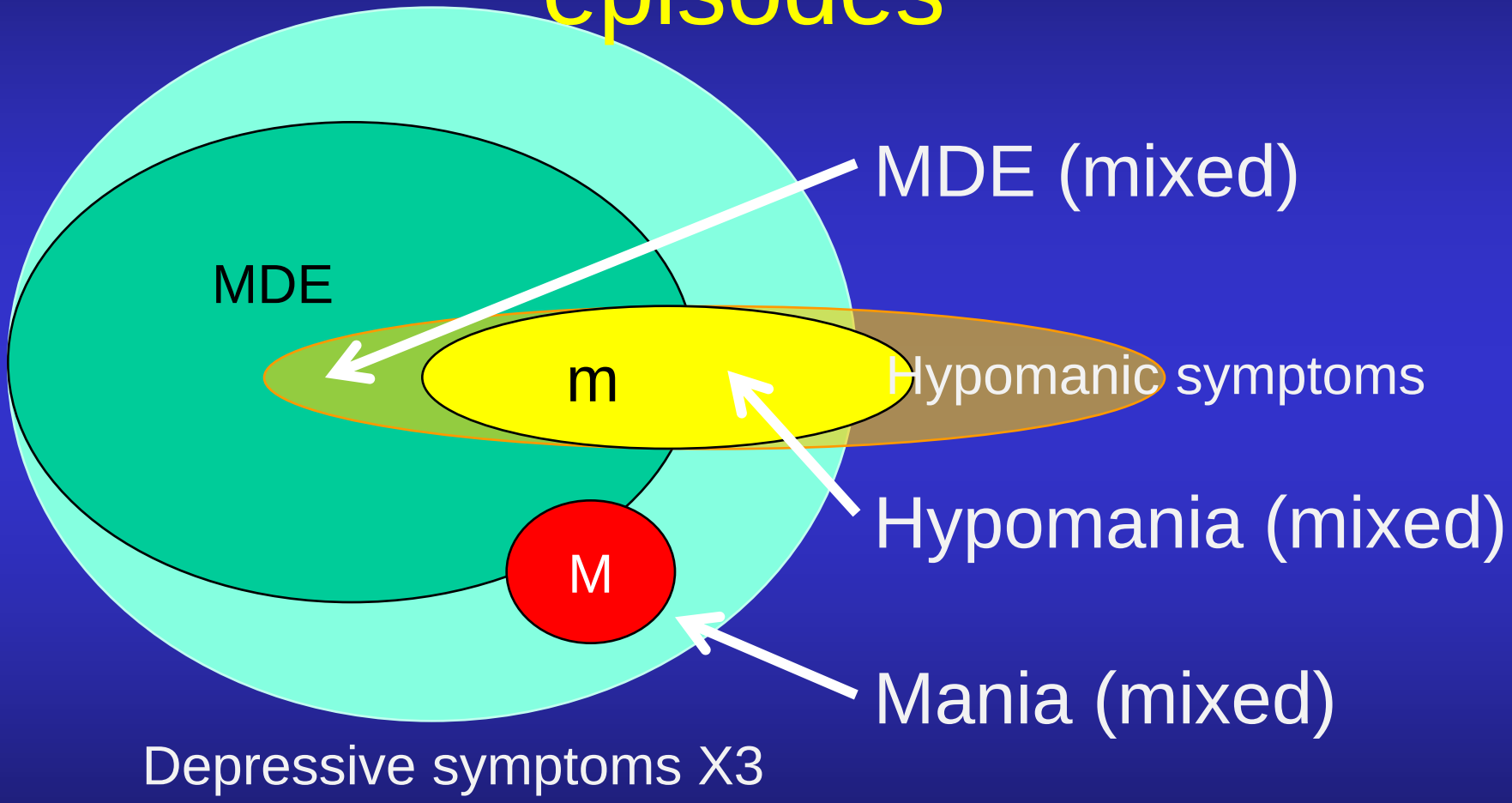

Risks

- Diagnosis inflation
  - CHILDREN
- Inappropriate extrapolation of treatment options from BP-I to milder or non-bipolar conditions
- Confusion with borderline personality disorder

Age at onset

Childhood bipolar disorder

Diagnosis of Bipolar disorder in childhood and adolescence

- Regarded as
  - Important, because of the emphasis on early diagnosis, especially from patient groups
  - Difficult
  - Controversial
  - BUT increasingly common

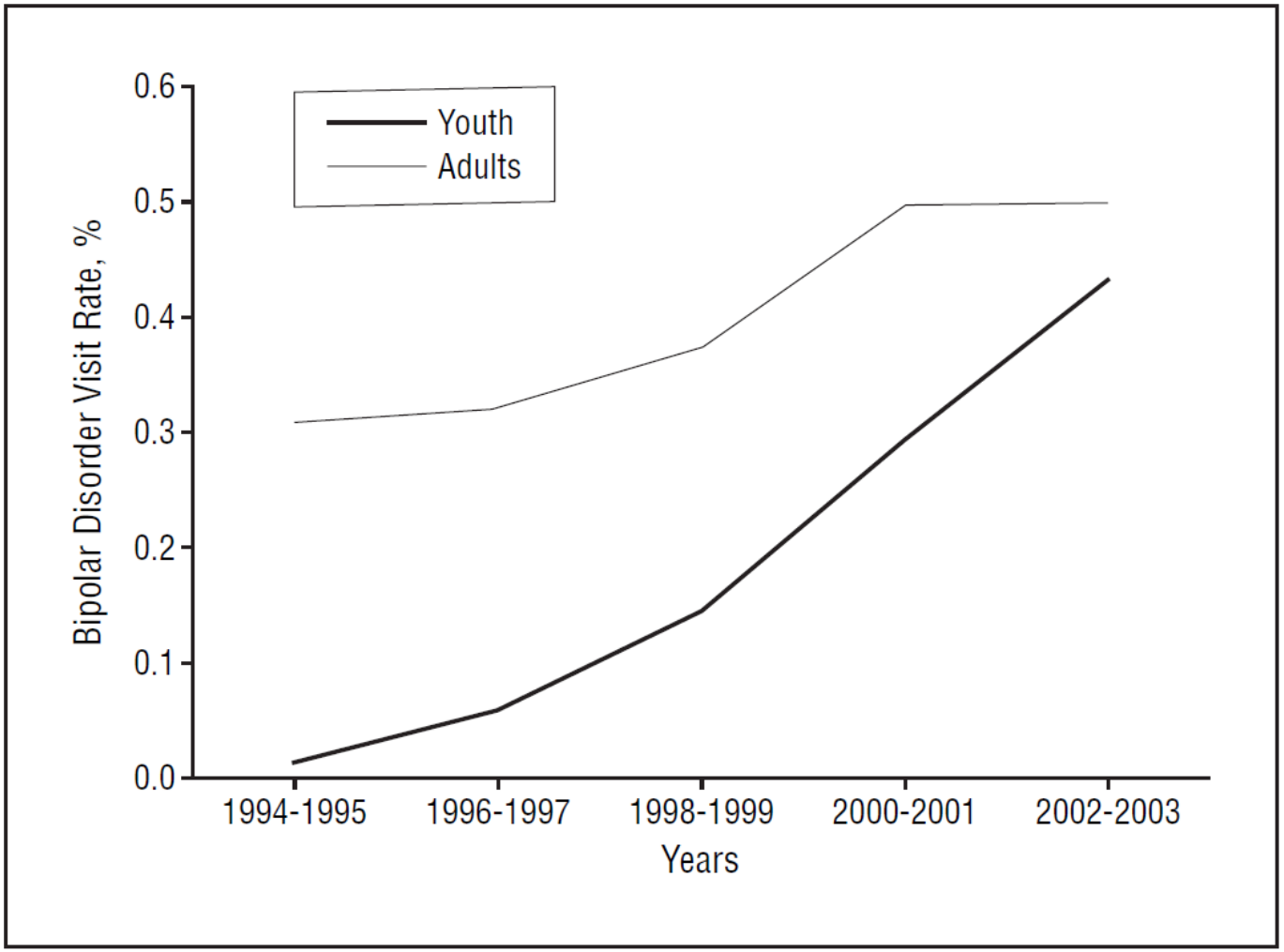

Figure. National trends in visits with a diagnosis of bipolar disorder as a percentage of total office-based visits by youth (aged 0-19 years) and adults (aged ≥20 years).

Moreno et al. Arch Gen Psychiatry. 2007;64(9):1032-1039

Table 2. Treatment Provided to Youth and Adult Patients With Bipolar Disorder During Office-Based Physician Visits, 1999-2003[a]

Treatment	Youth Bipolar Disorder Visits (n=154)[b]		Adult Bipolar Disorder Visits (n=808)[b]	
	No. (%)	95% CI	No. (%)	95% CI
Any psychotropic medication	141 (90.6)	82.3-95.2	713 (86.4)	82.5-89.6
Mood stabilizer	93 (60.3)	49.7-70.0	538 (64.1)	59.6-68.5
Lithium	21 (12.4)[c]	7.2-20.6	185 (23.2)	19.6-27.3
Any anticonvulsant	75 (49.0)	37.5-60.5	379 (43.5)	38.9-48.2
Valproate	44 (30.6)	21.2-42.0	185 (20.9)	17.1-25.2
Other	31 (18.4)	11.7-27.6	194 (22.6)	18.6-27.2
Antidepressant	55 (34.0)	26.5-42.4	411 (46.5)	41.6-51.4
Antipsychotic	74 (47.7)	36.0-59.7	286 (33.7)	28.0-39.9
Benzodiazepine	8 (5.2)[c]	2.2-11.6[d]	219 (27.6)	23.1-32.6[d]
Stimulant	57 (36.0)	25.9-47.5[d]	45 (5.2)	3.4-8.1[d]
Any psychotropic combination	104 (62.7)	51.0-73.1	525 (60.9)	55.3-66.2
Mood stabilizer + antidepressant	38 (23.6)	16.9-31.9	295 (31.1)	27.0-35.6
Mood stabilizer + antipsychotic	36 (24.7)	16.8-34.9	195 (22.6)	18.4-27.3
Antipsychotic + antidepressant	26 (16.7)[c]	10.4-25.6	146 (16.4)	13.1-20.2
Psychotherapy	62 (41.7)	29.2-55.4	440 (48.4)	41.1-55.8

Abbreviation: CI, confidence interval.

[a] Data are based on the National Ambulatory Medical Care Survey. Youth are defined as aged 0 to 19 years and adults are defined as aged 20 years and older. Percentages are based on weighted sampling. See the text for definition of the medication grouping.

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47%

33.7%

24%

22.6%

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NICE perspective

- **A narrow Phenotype - bipolar I disorder in children**
- Key symptom is *euphoria* +/- grandiosity
  - which should be present most days, most of the day
  - at other times the clinical picture may be dominated by irritability
- BUT mania should not be based on irritability alone
- Episode duration should be relatively short but distinct

DSM-5

- Also
  - anxiety dimension
  - suicide assessment dimension

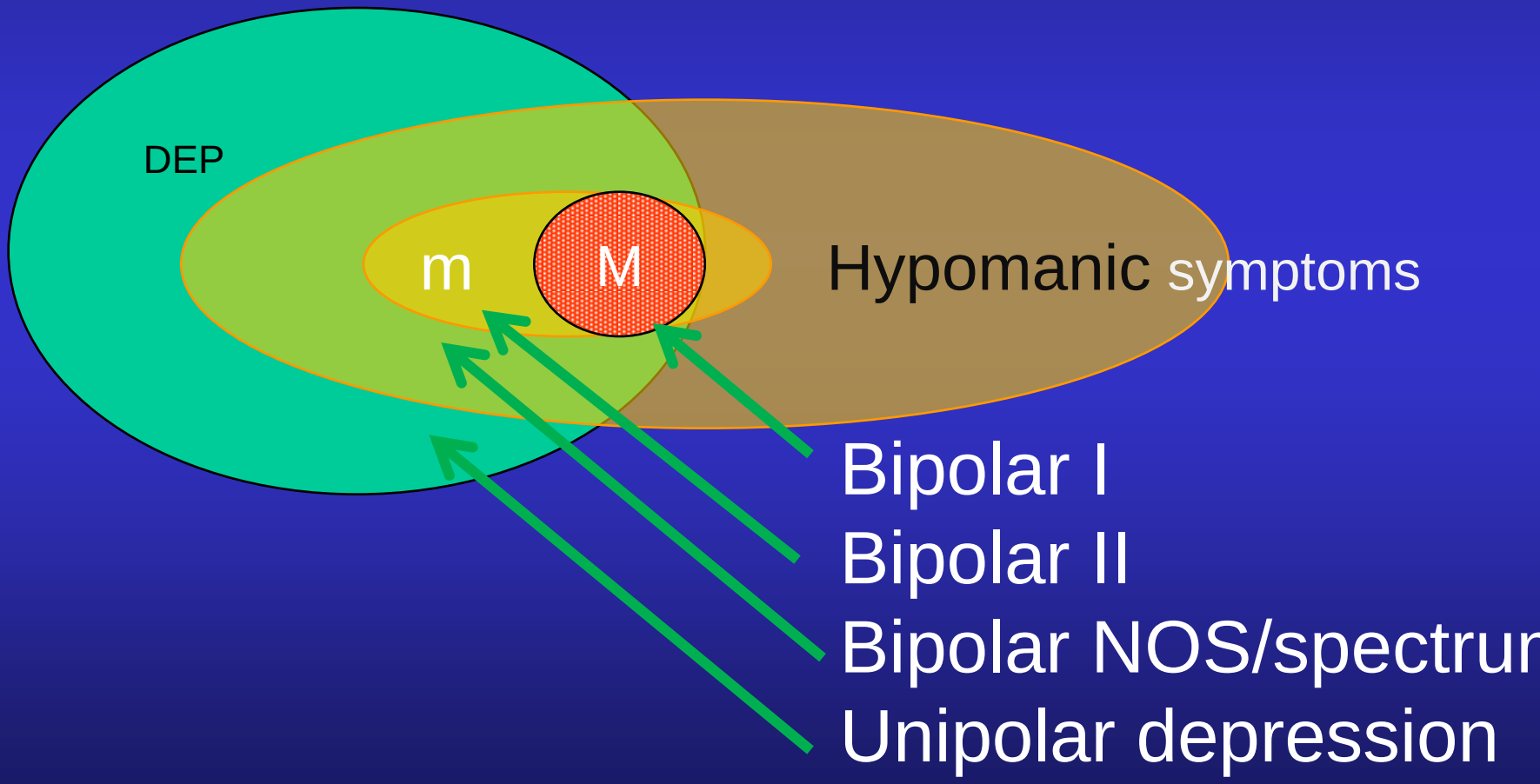
across all mood disorder categories

- Temper Dysregulation Disorder with Dysphoria – to narrow the Bipolar diagnosis

But what then is core psychopathology?

e.g. mood instability

The bipolar phenotype including the spectrum



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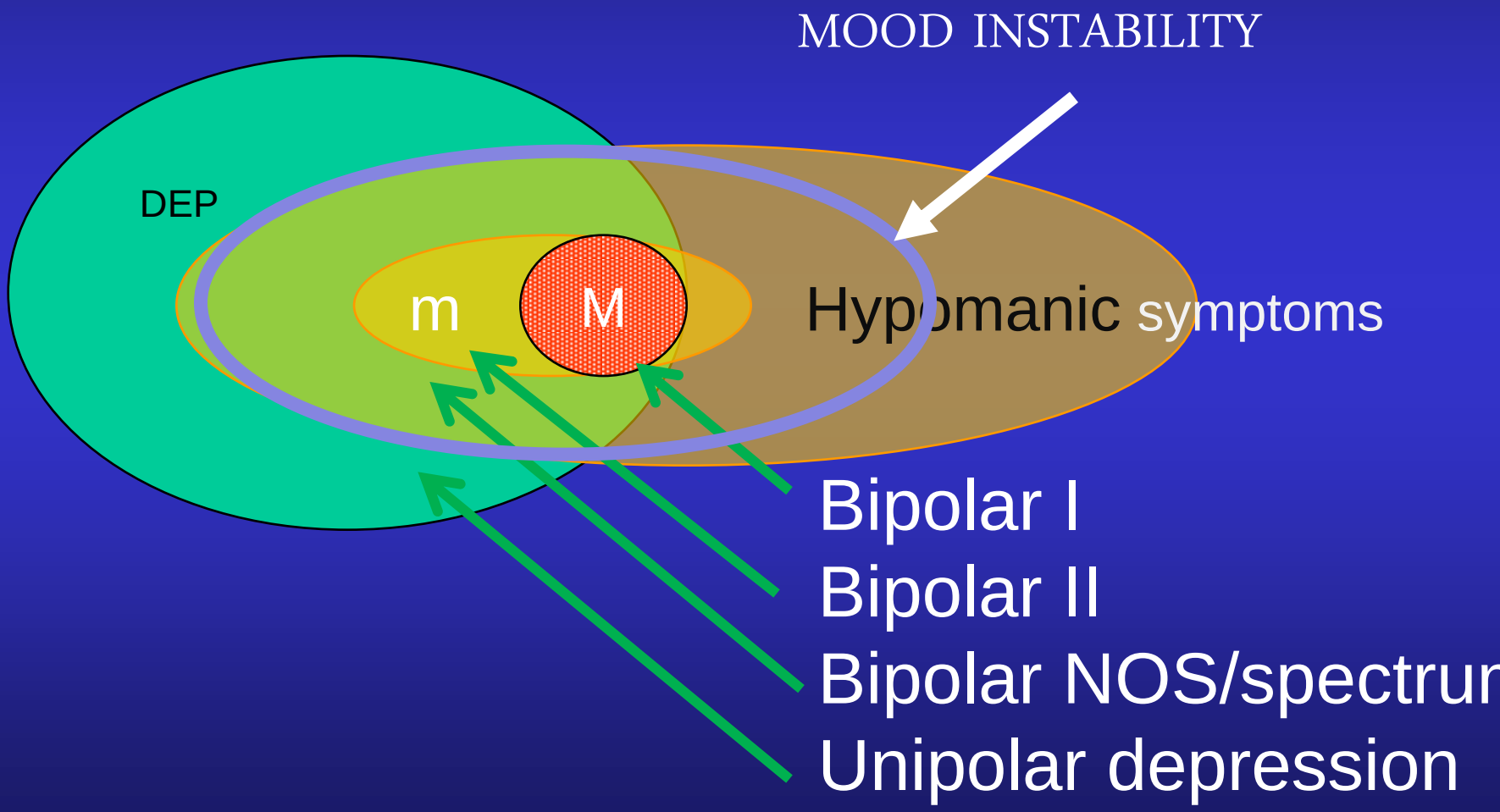
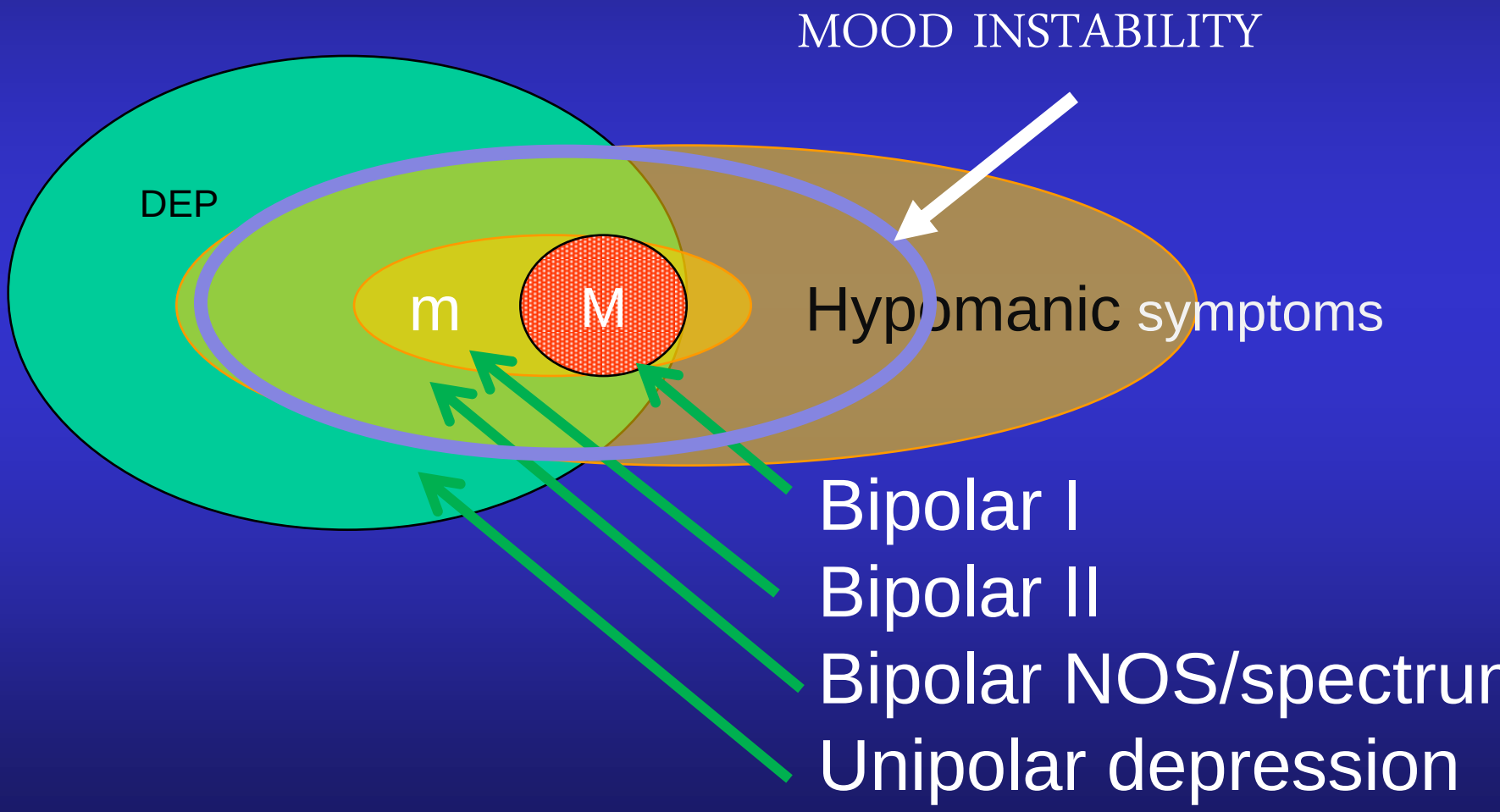
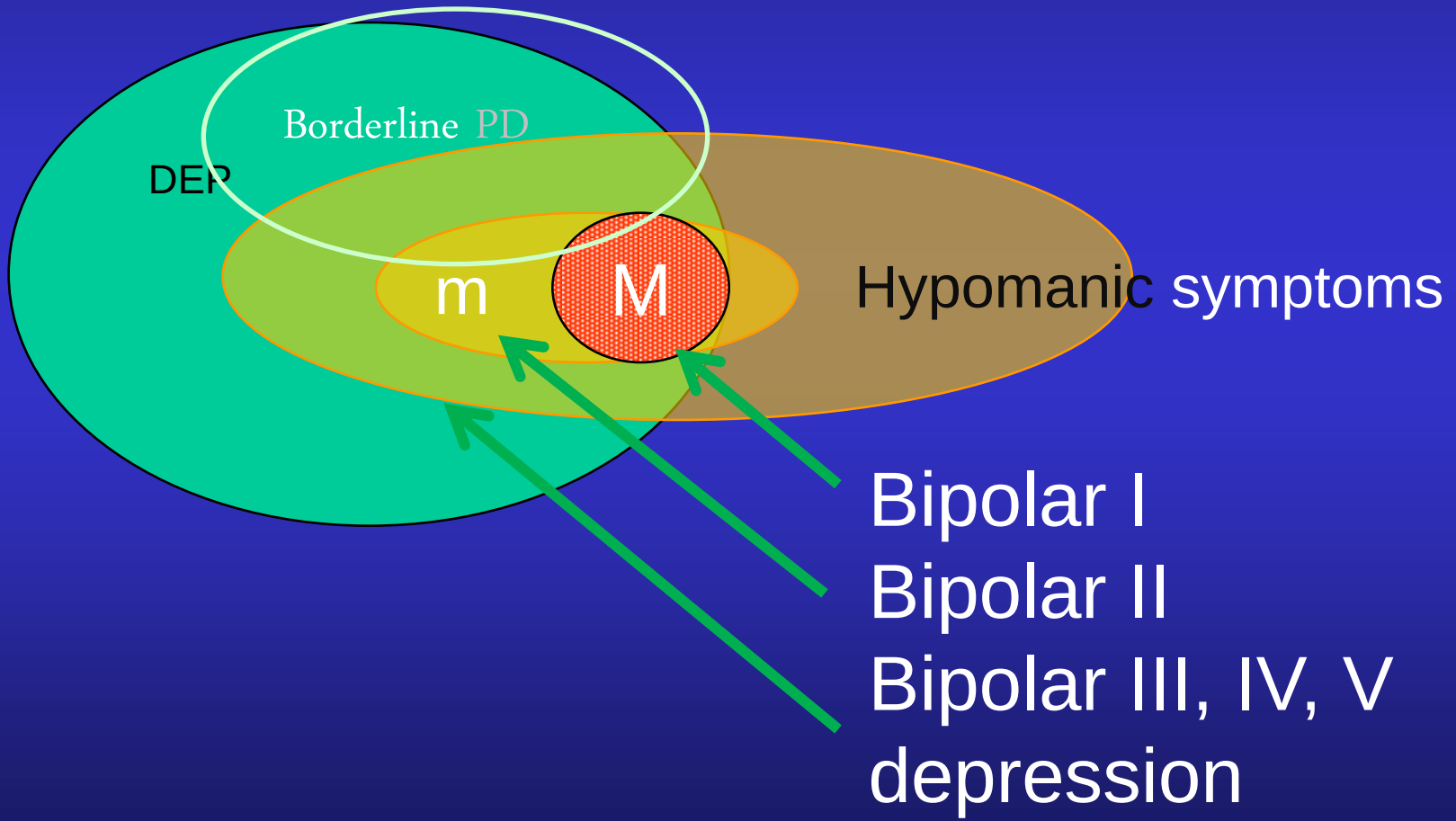


The bipolar phenotype including the spectrum



The bipolar phenotype including the spectrum and BPD?



Borderline or bipolar?

- Both borderline crises and manic (or mixed) bipolar episodes characterised by
  - heightened irritability
  - emotional lability
  - chronic depressive symptoms
  - impulsive behaviours:
- Some co-morbidity but different aetiology and prognosis?
- Different treatment recommendations

Stress sensitivity

Glaser, Van Os, Mengelers MyinGermeys

Psychological Medicine / Volume 38 / Issue 09 / September 2008, pp 1231 1239

- **What if Mood instability is the core**
  - Do we currently measure it?
- Experience sampling methoodology (ESM)
- BPS more sensitive than controls, psychotic patients (and BD)

Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology

GM Goodwin[1], PM Haddad[2], IN Ferrier[3], JK Aronson[4], TRH Barnes[5], A Cipriani[1], DR Coghill[6], S Fazel[1], JR Geddes[1], H Grunze[7], EA Holmes[8], O Howes[9], S Hudson[10], N Hunt[11], I Jones[12], IC Macmillan[13], H McAllister-Williams[3], DR Miklowitz[14], R Morriss[15], M Munafò[16], C Paton[17], BJ Saharkian[18], KEA Saunders[1], JMA Sinclair[19], D Taylor[20], E Vieta[21] and AH Young[22]

Psychopharm

Journal of Psychopharmacology
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Table 1. Traditional evidence categories.

Evidence categories	Treatment studies	Observational studies
I	Meta-analysis of RCTs, at least one large, good-quality, RCT or replicated, smaller RCTs	Large representative population samples
II	Small, non-replicated RCTs, at least one controlled study without randomization or evidence from at least one other type of quasi-experimental study	Small, well designed but not necessarily representative samples
III	Non-experimental descriptive studies, such as uncontrolled, comparative, correlation and case-control studies	Non-representative surveys, case reports
IV	Expert committee reports or opinions and/or clinical experience of BAP expert group	

Randomized Controlled Trials (RCTs) must have an appropriate control treatment arm; for primary efficacy this should include a placebo condition although for psychological treatments this may not be met. BAP: British Association for Psychopharmacology.

Table 2. Grades of recommendation and their relationship with supporting levels of evidence.

Grade of recommendation	Underlying methodology	Symbol
High	RCTs or double upgraded observational studies	****
Moderate	Downgraded RCTs or upgraded observational studies	***
Low	Double downgraded RCTs or observational studies	**
Very low	Triple downgraded RCTs or downgraded observational studies or case series/reports	*

Outline

- Fundamentals of patient management
  - Diagnosis
  - Access to services and the safety of the patient and others
  - Enhanced care
- Treatment of different phases of bipolar illness
  - Acute Manic or Mixed Episodes
  - Acute Depressive episode
  - Long term treatment
  - Treatment in special situations

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  - Acute Depressive episode
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  - Treatment in special situations

Acute Manic or Mixed Episodes

For patients not already on long term treatment for bipolar disorder*

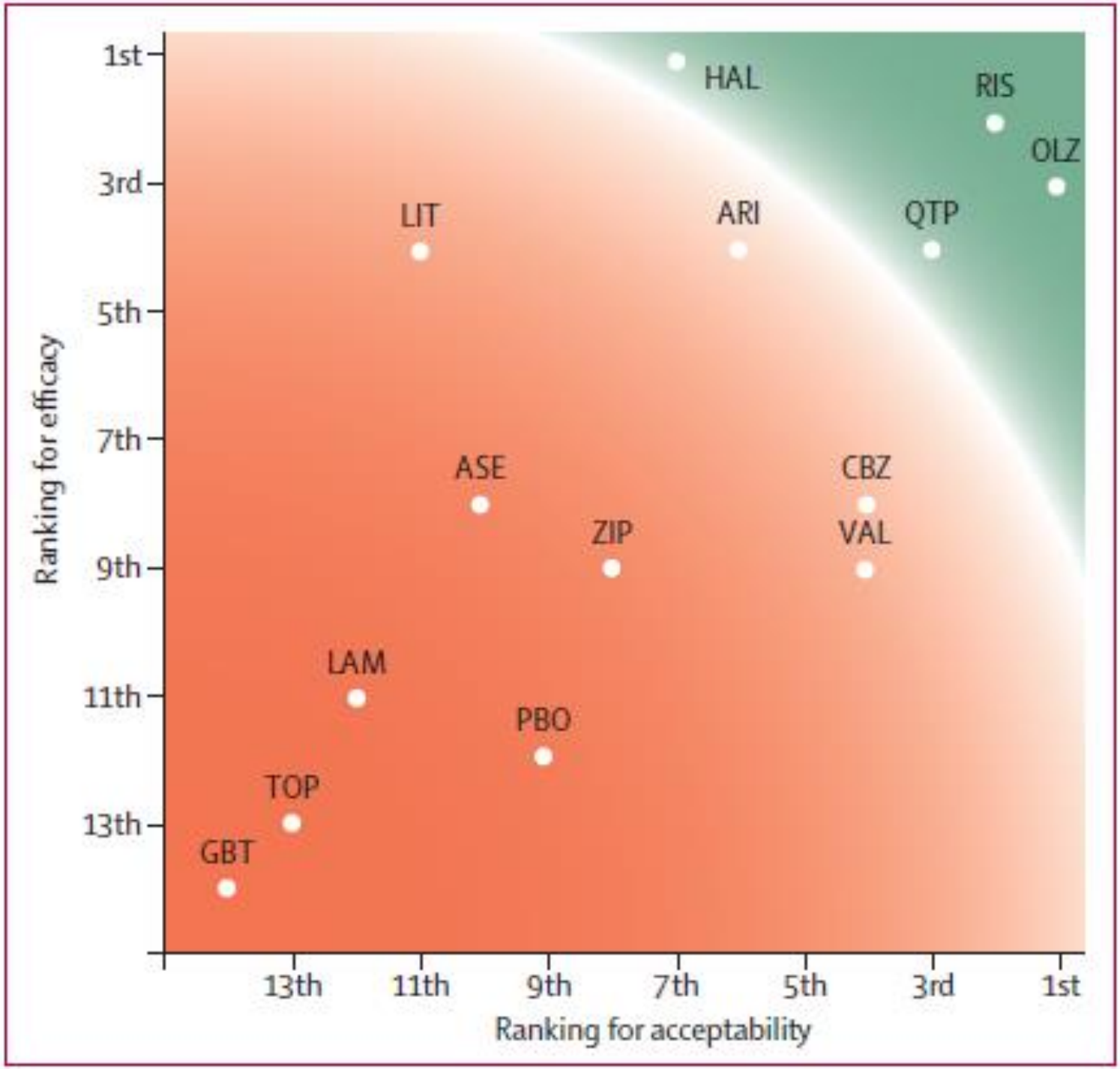
- initiate oral administration of an antipsychotic or valproate
- The lowest doses necessary should be employed (A). Do not escalate the dose of antipsychotic simply to obtain a *sedative* effect (S).

NICE guidelines 2014: highlights and lowlights

- Essentially made to conform to DoH policy in many areas
- Written in house
- Stakeholder membership rather wide
- Network meta-analysis fetishists
- The emphasis given to some conclusions is very questionable

Mania

- If not taking an antipsychotic or mood stabiliser, offer haloperidol, olanzapine, quetiapine or risperidone, taking into account any advance statements, the person's preference and clinical context (including physical comorbidity, previous response to treatment and side effects).
- If the person is already taking lithium, check plasma lithium levels to optimise treatment. Consider adding haloperidol, olanzapine, quetiapine or risperidone, depending on the person's preference and previous response to treatment.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ZIP
VAL
LAM
PBO
TOP
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5th
3rd
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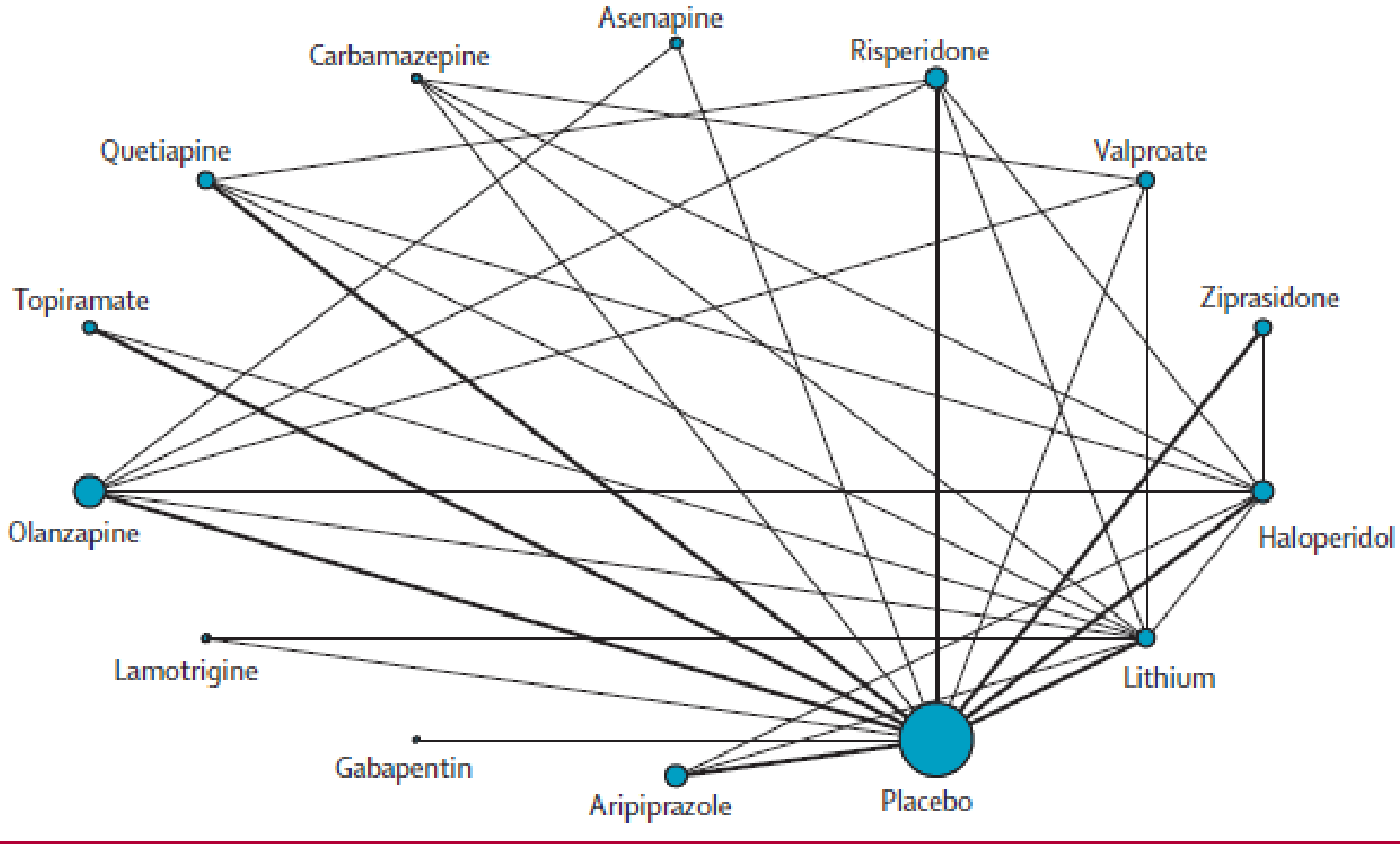
Ranking for acceptability

Cipriani et al. Lancet 2011; 378: 1306–15



If symptoms uncontrolled and/or mania is very severe

- **Add another first-line medicine.**
  - Consider the combination of lithium or valproate with an antipsychotic (A).
  - Consider clozapine in more refractory illness (B).
  - Electro convulsive therapy (ECT) may be considered for manic patients who are severely ill and/or whose mania is treatment resistant and patients with severe mania during pregnancy (C).

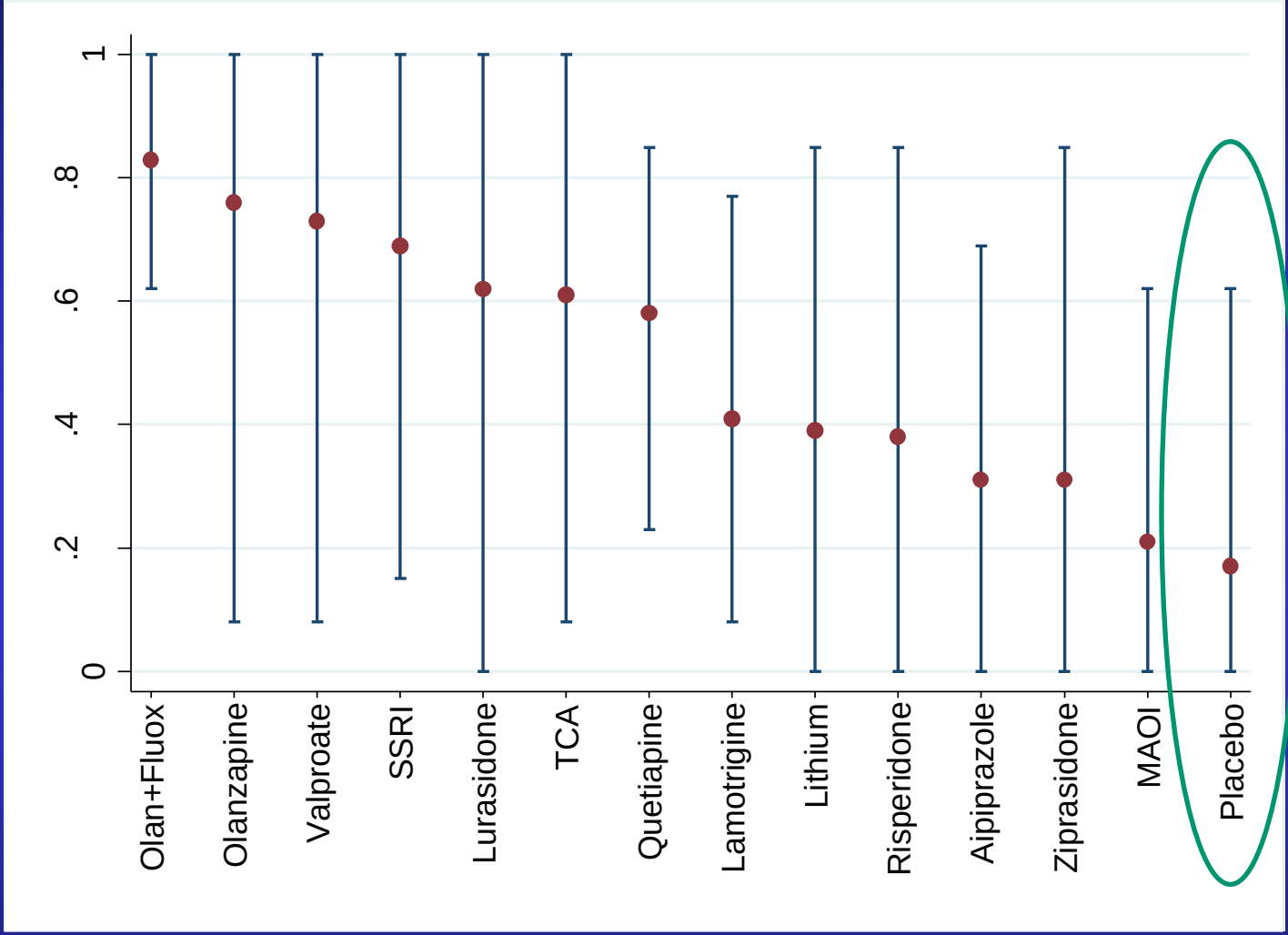
Bipolar depression

- a psychological intervention that has been developed specifically for bipolar disorder and has a published evidence-based manual describing how it should be delivered **or**
- a high-intensity psychological intervention (cognitive behavioural therapy, interpersonal therapy or behavioural couples therapy) in line with recommendations in the NICE clinical guideline on depression *(i.e. by extrapolation).*

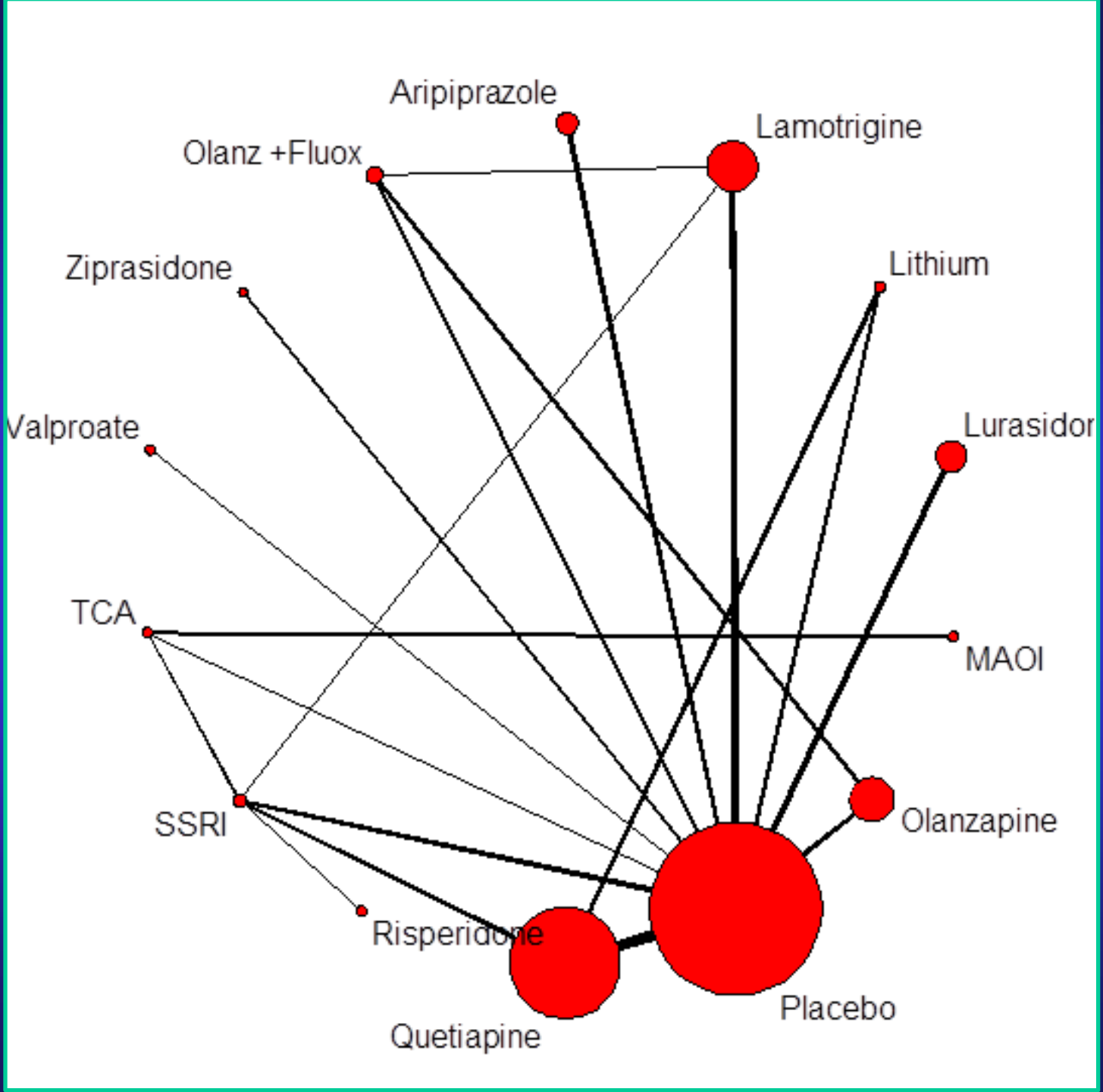
Bipolar depression

- Offer fluoxetine combined with olanzapine, or quetiapine alone
- If the person prefers, consider either olanzapine (without fluoxetine) or lamotrigine
- If there is no response to fluoxetine combined with olanzapine, or quetiapine, consider lamotrigine alone.

SUCRA and 95% CIs for efficacy (SMD) in rank order



SUCRA: surface under the cumulative ranking curve (SUCRA), higher value is favourable


Aripiprazole
Lamotrigine
Olanz +Fluox
Ziprasidone
Lithium
Valproate
Lurasidor
TCA
MAOI
SSRI
Olanzapine
Risperidone
Placebo
Quetiapine

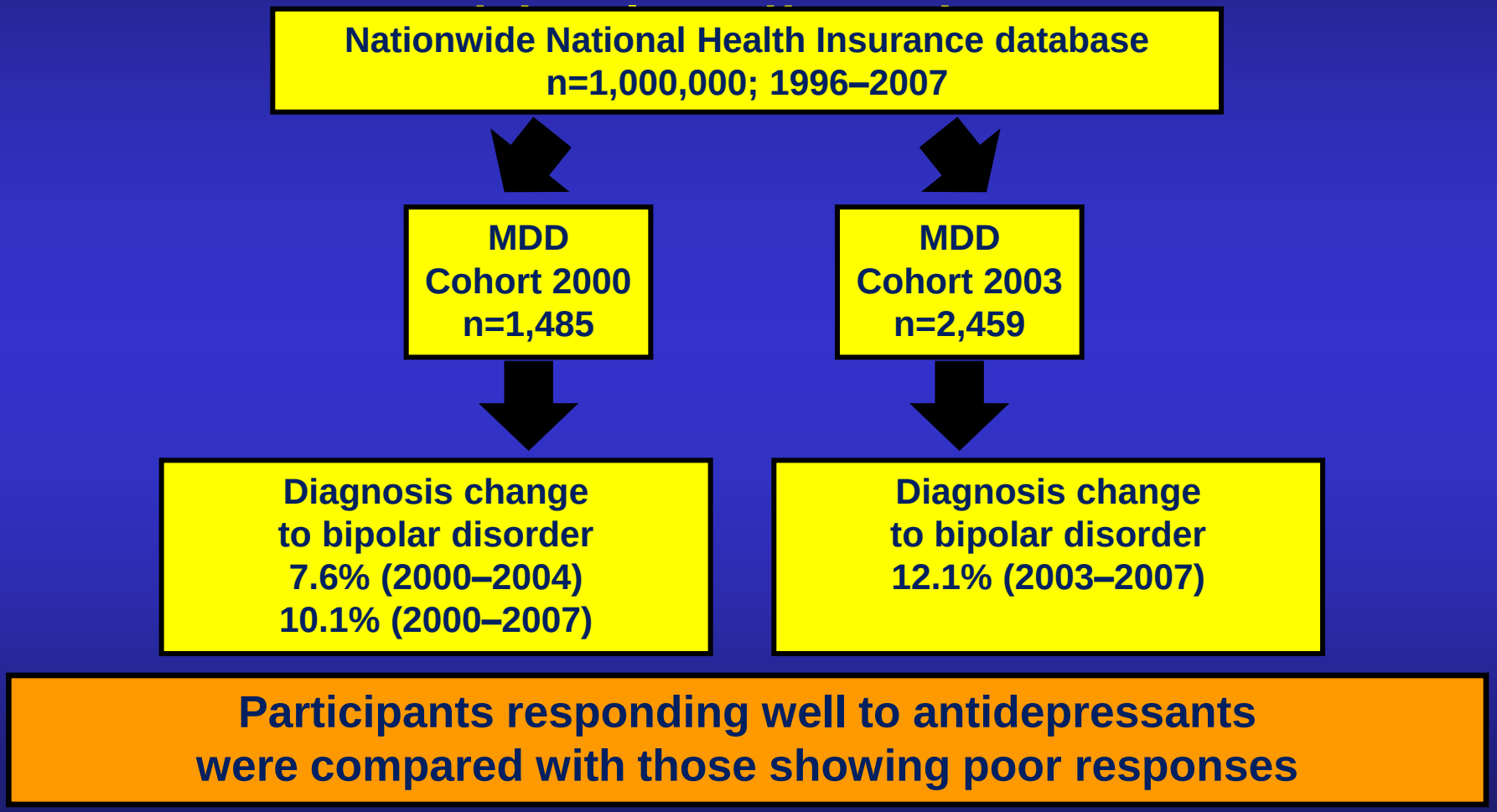
BAP guidelines: recommendations

- Mania
  - As NICE 2014
  - Reasonable choice of effective treatments
- Depression
  - Should we recognize that SSRIs are a class?
  - Should we recognize extrapolation from unipolar experience?
  - Simple problem is paucity of evidence

Table 6. Comparison with NICE guidelines: bipolar depression.

NICE2014	BAP
Offer fluoxetine combined with Olanzapine (OFC), or quetiapine monotherapy	Consider quetiapine, lurasidone or olanzapine monotherapy
Consider either olanzapine (without fluoxetine) or lamotrigine monotherapy	Consider initial treatment with lamotrigine, … usually as an addition to agents preventing recurrence of mania
If there is no response to OFC or quetiapine, consider lamotrigine monotherapy	Consider the use of an antidepressant with an anti-manic drug in bipolar I patients
ECT noticed but not recommended.	Consider ECT in severe or refractory depression
Offer a psychological intervention that has been developed specifically for bipolar disorder	Consider family-focused, cognitive behaviour therapy or interpersonal rhythm therapy *as an additional treatment (not as a primary treatment option)*
Within 4 weeks of resolution of symptoms, discuss …whether to continue treatment for bipolar depression or start long-term treatment	Consider the strategy for long-term treatment as patient recovers

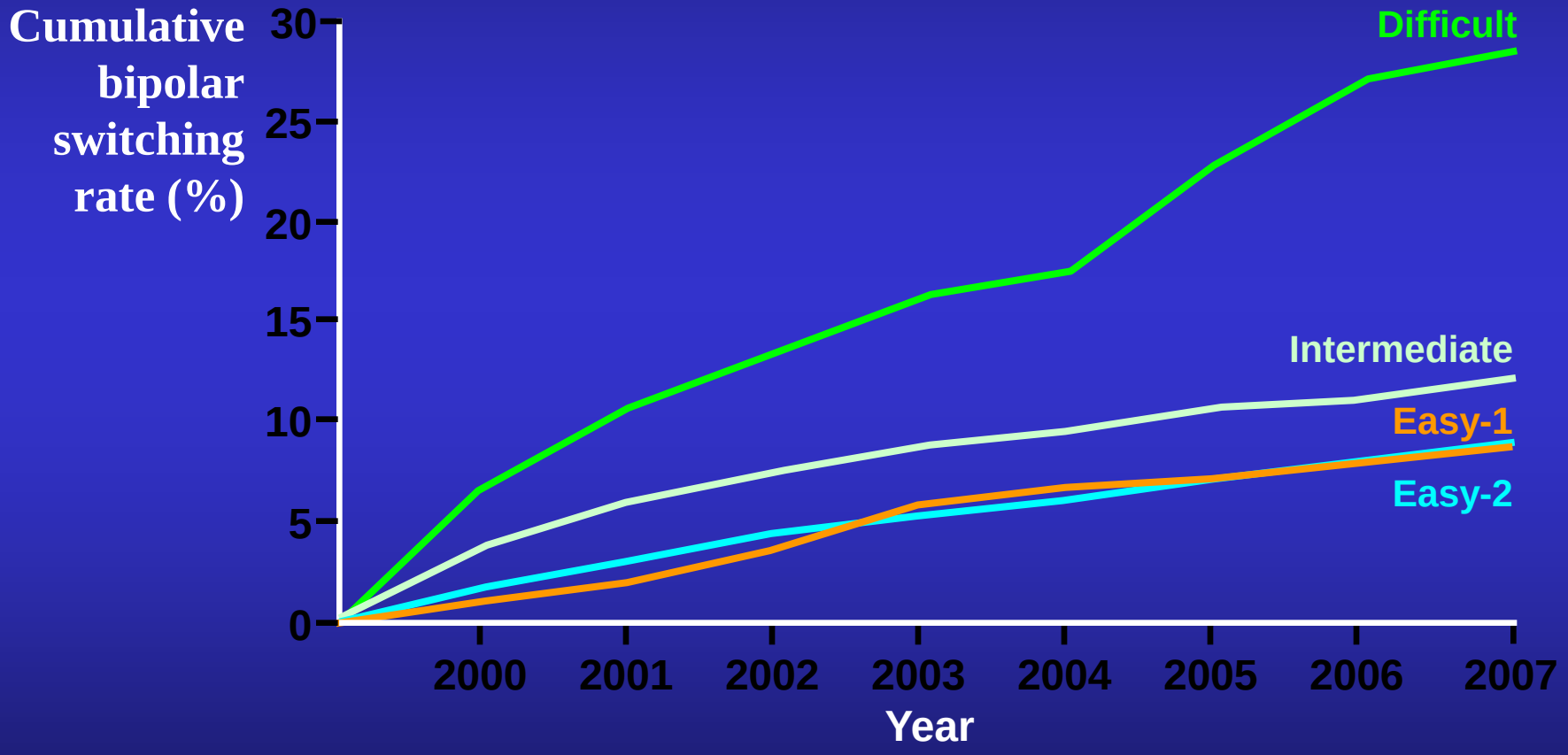
Association between antidepressant resistance in MDD and subsequent



Cohort study in Taiwan

Li et al 2012

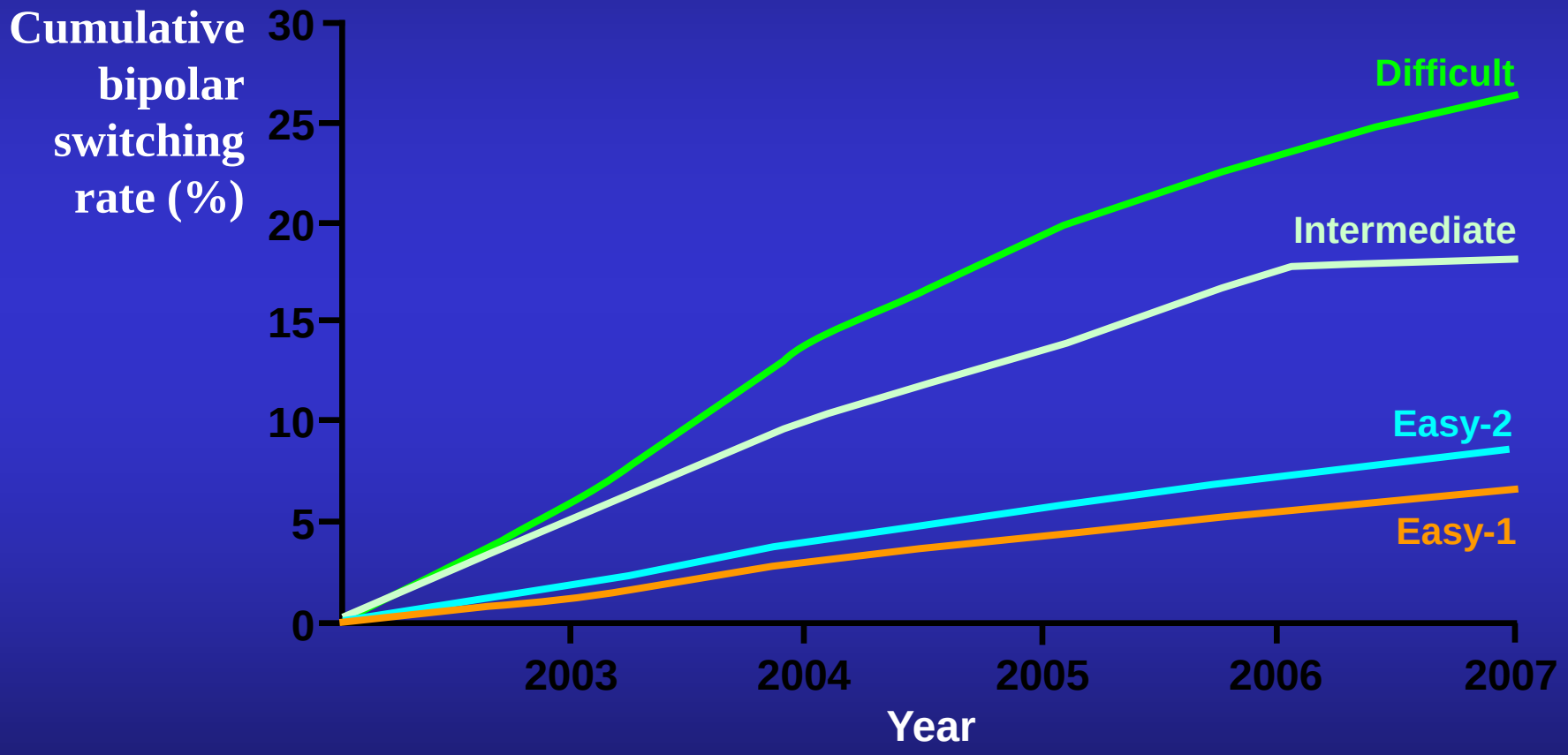
Rates of change from MDD to bipolar disorder Cohort 2000



MDD, major depressive disorder
Cohort 2000, n=1,485

Li et al 2012

Rates of change from MDD to bipolar disorder Cohort 2003



MDD, major depressive disorder
Cohort 2003, n=2,459

Li et al 2012

Bipolar depression and antidepressants

- Unrecognised bipolar disorder is a probable contributor to treatment-resistant MDD
- Patients with MDD should be considered, and prospectively managed, as potentially having bipolar disorder if they
  - Have a pattern of illness suggestive of bipolarity
  - Fail to respond to a first-line antidepressant

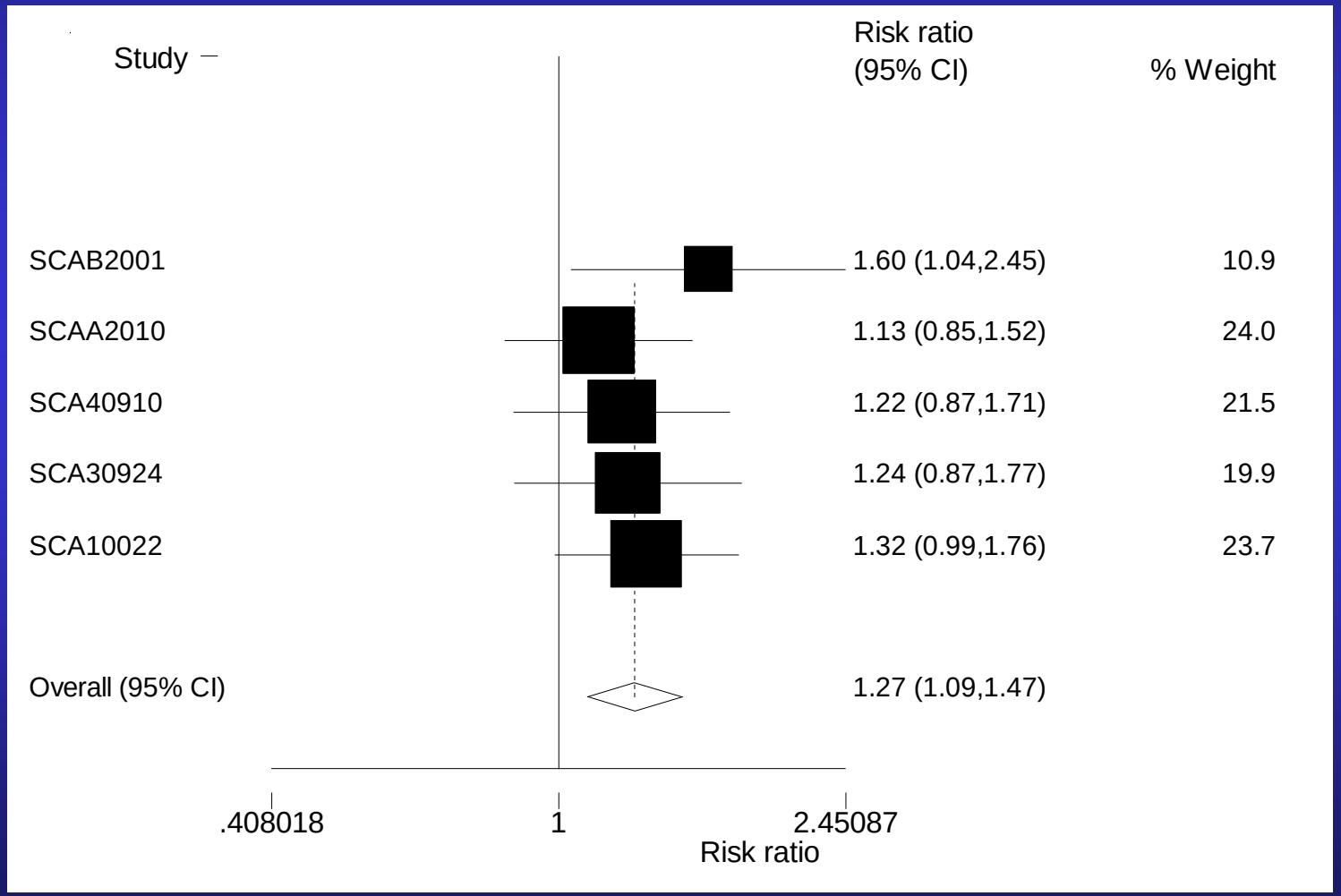
MDD, major depressive disorder

Li et al 2012; Goodwin 2012

Alternatives

- Dopamine/serotonin
  - Olanzapine (plus fluoxetine)
  - Quetiapine
- Lamotrigine
  - Successful in long term treatment
  - Does it work acutely (requires a slow taper)

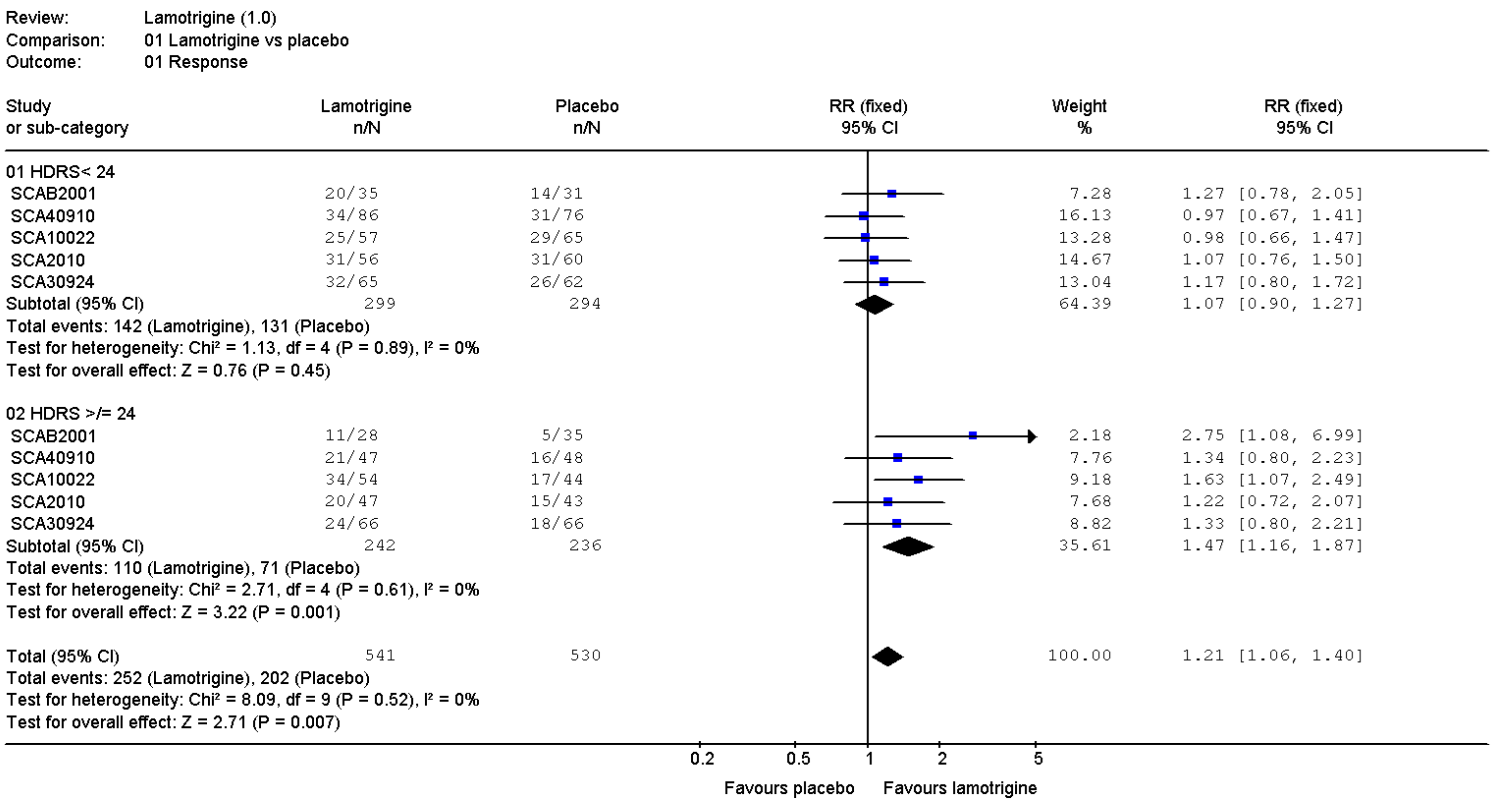
Lamotrigine: Meta-analysis of ‘failed’ acute trials. Ham-D



Why did acute lamotrigine trials fail?

- Seemed paradoxical in view of good long term data
  - How could an ineffective drug MAINTAIN a good effect long term?
- Taper in of lamotrigine dose
- Severity of patients entering the trial
  - Examine in an individual patient data (IPD) analysis of GSK trials

Lamotrigine – meta-analysis of IPD (Geddes *et al* 2009 BJPsych)



The depression challenge

- Antidepressants
  - Less good than we have believed
  - Less bad than some believe
- Atypical antipsychotics
  - interesting
- Lamotrigine
  - Low efficacy, but excellent tolerability
- How to PERSONALISE TREATMENT

Conclusions

- Get the diagnosis right
  - Operational criteria
  - Consistency of assessment
- Scope for pharmacological innovation probably quite limited in short term
- Focus on getting management right