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Psychobiology Research Group

A Critical Review of Current Guidelines for Bipolar Disorder

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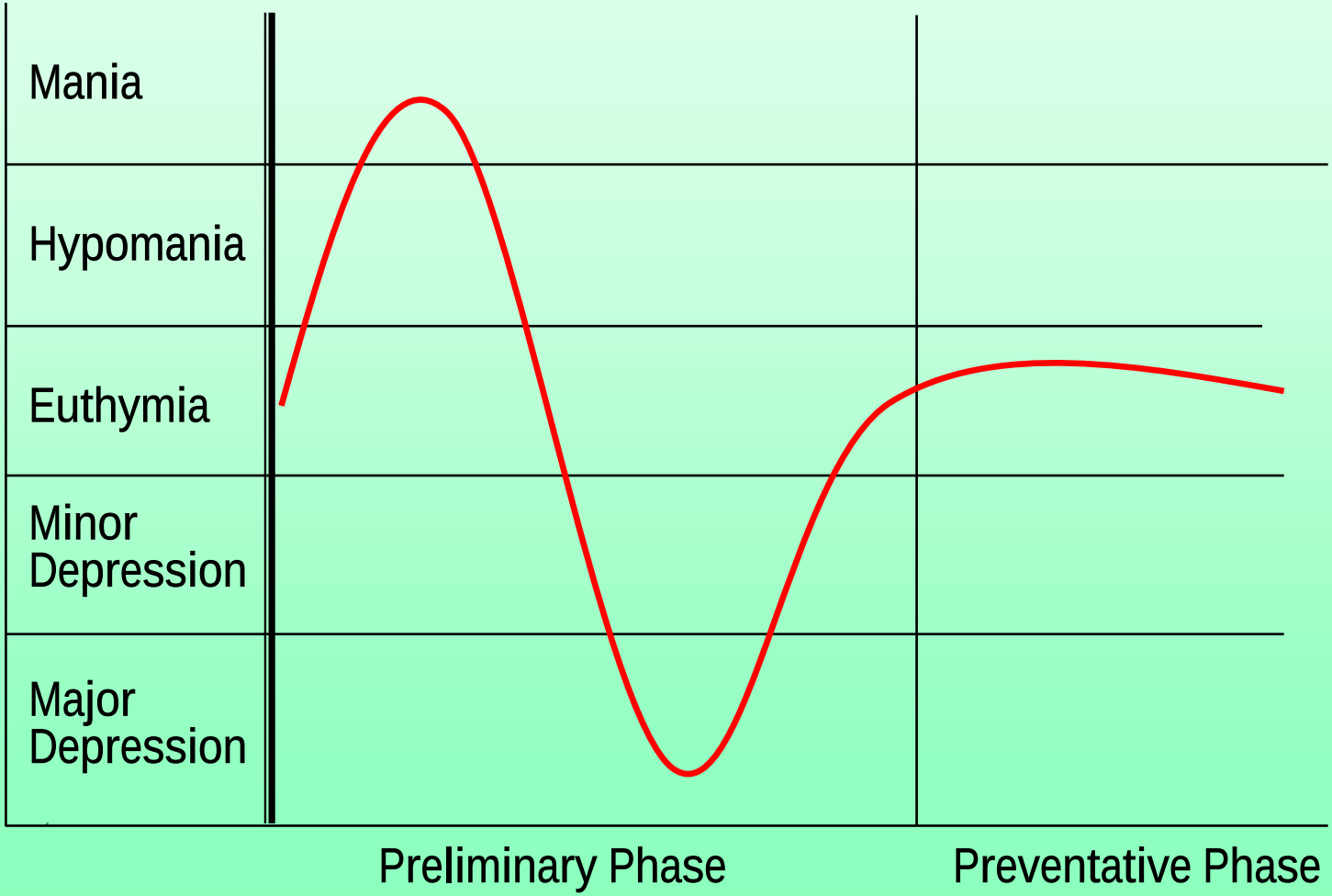
Remit: Guidelines

- Focus on:
  - British Association of Psychopharmacology (BAP)
    - Goodwin et al. 2003, J.Psychopharm.
- Compare with:
  - American Psychiatric Association (APA)
  - Texas Implementation of Medication Algorithms (TIMA)
  - Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines
  - NICE 2nd draft bipolar guidelines

Remit: Patients and Treatments

- Bipolar I and II (and bipolar spectrum)
- Adults of working age
- Will not cover comorbidity and treatment in special situations (e.g. pregnancy)
- Focus on pharmacotherapy but will mention other treatment modalities

The course of Bipolar Disorder



Agenda

- Guidelines
  - BAP
  - APA
  - TIMA
  - CANMAT
  - NICE
- Acute mania
- Acute Depression
- Maintenance

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Guidelines

BAP Guidelines for the Management of Bipolar Disorder

G.M. Goodwin “Evidenced based guidelines for treating bipolar disorder: recommendations from the BAP.” J Psychopharmacology 17(2) 2003 149-173

Methodology

- Meeting on 24th May 2002.
- Brief presentations on key areas
  - emphasis on systematic reviews and randomised controlled trials (RCTs).
  - discussion to identify consensus and uncertainty
- Review and recommendations circulated to participants (2 iterations, Nov, 2002, Feb 2003).
- Feedback as far as possible incorporated into the final version of the guidelines (Feb 2003)

Guidelines

- The principle **recommendations** usually apply to the *average* patient.
- Recommendations may be expected to apply about 70% of the time so we have used expressions like “Clinicians *should* consider…..”
- However, there will be occasions when adhering to such a recommendation unthinkingly could do more harm than good.

STRENGTH OF EVIDENCE AND RECOMMENDATIONS

TREATMENT

- Ia: meta-analysis of RCTs
- Ib: at least one RCT
- IIa-b: at least one controlled or exptl. study (no R)
- III: descriptive studies
- IV: expert committee reports, opinions and/or clinical experience

OBSERVATIONAL

- I: large representative population samples
- II: small, limited samples
- III: non-representative surveys, case reports
- IV: expert committee reports, opinions and/or clinical experience

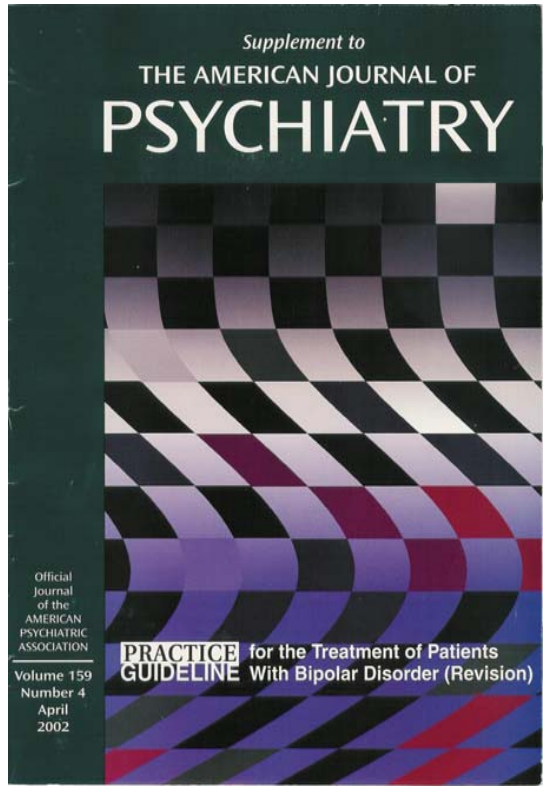
Outline

- Guidelines
  - 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
- Review
- Appendix

Welcome to the
American Psychiatric Association
www.psych.org
The American Psychiatric Association -- the world's largest psychiatric organization -- represents over 38,000 psychiatric physicians from the U.S. and around the globe.

Practice Guidelines for the Treatment of Patients with Bipolar Disorder

Hirschfeld et al., Am. J. Psychiatry 2002



Methodology

- Developed by psychiatrists who are active in clinical practice
- Some contributors primarily involved in research or other academic activities
- Issues re conflicts of interest
  - Extensively reviewed by members of APA
  - Objective evaluation of evidence
  - C.of I. notified to APA Dept. of Quality Improvement and Psychiatric Services and discussed with work group chair and chair of Steering Committee on Practice Guidelines
- Multiple drafts and widespread review
- Approval by the APA Assembly and Board of Trustees

Guidelines

- "These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome in every case."
- "The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the psychiatrist…"

STRENGTH OF EVIDENCE AND RECOMMENDATIONS

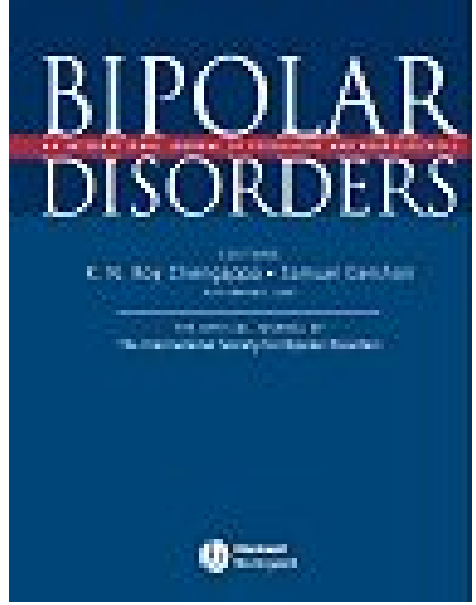
I: Recommendation with substantial clinical confidence

II: Recommendation with moderate clinical confidence

III: May be recommended on the basis of individual circumstances

Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies

Yatham et al. 2005 Bipolar Disorders 7(suppl. 3) 5-69



Methodology

- Update of guidelines published in 1997
- Little information regarding methodology
  - Guideline Committee, Section Leaders and Co-Chairs (Yatham & Kennedy) identified
  - Invited experts from outside Canada to comment
  - Supported by an unrestricted educational grant from Lilly, AstraZeneca and Janssen-Ortho
- Modified criteria for rating strength of evidence
- Produced treatment algorithms

Evidence criteria and strength of recommendations

Evidence Criteria

1. Meta-analysis or replicated double-blind RCT (DBRCT) that includes placebo
2. At least one DBRCT with placebo or active comparator
3. Prospective uncontrolled trial with 10+ subjects
4. Anecdotal reports or expert opinion

Treatment recommendations

First line – level 1 or 2 evidence plus clinical support for efficacy and safety

Second line – Level 3 or higher evidence plus clinical support for efficacy and safety

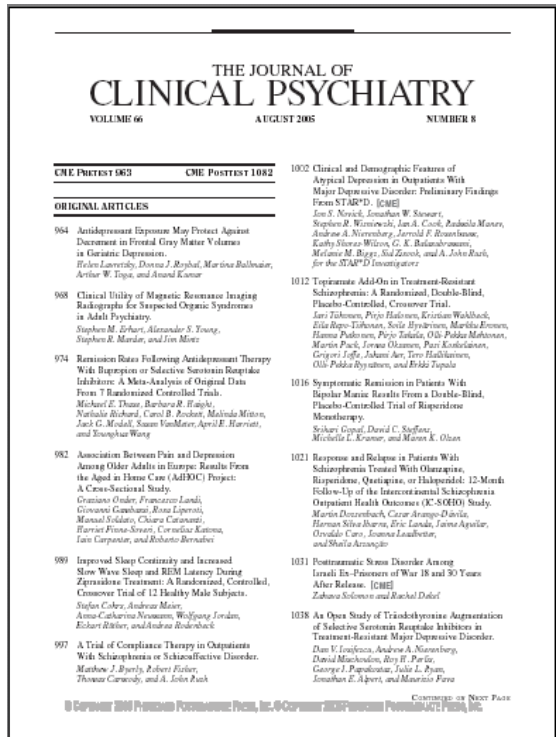
Third line - Level 4 or higher evidence plus clinical support for efficacy and safety

Not recommended – Level 1 or 2 evidence for lack of efficacy

TEXAS
Department of State Health Services

The Texas Implementation of Medication Algorithms (TIMA): Update to the algorithms for treatment of bipolar I disorder

Suppes et al. 2005 J. Clin. Psychiatry 66:870-886



THE JOURNAL OF
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VOLUME 66 AUGUST 2005 NUMBER 8

CME PRETEST 963 CME POSTTEST 1082

ORIGINAL ARTICLES

964 Antidepressant Exposure May Protect Against Decrement in Frontal Gray Matter Volumes in Geriatric Depression.
Helen Lavretsky, Donna J. Reynal, Martina Ballmaier, Arthur W. Toga, and Anand Kumar

968 Clinical Utility of Magnetic Resonance Imaging Radiographs for Suspected Organic Syndromes in Adult Psychiatry.
Stephen M. Erhart, Alexander S. Young, Stephen R. Marder, and Jim Mintz

974 Remission Rates Following Antidepressant Therapy With Bupropion or Selective Serotonin Reuptake Inhibitors: A Meta-Analysis of Original Data From 7 Randomized Controlled Trials.
Michael E. Thase, Barbara R. Haight, Nathalie Richard, Carol B. Rockett, Melinda Mitton, Jack G. Modell, Susan VanMeter, April E. Harriett, and Youonghua Wang

982 Association Between Pain and Depression Among Older Adults in Europe: Results From the Aged in Home Care (AdHOC) Project: A Cross-Sectional Study.
Graziano Onder, Francesco Landi, Giovanni Gambassi, Rosa Liperoti, Manuel Soldato, Chiara Carassanti, Harriet Finne-Soveri, Cornelius Katona, Iain Carpenter, and Roberto Bernabei

989 Improved Sleep Continuity and Increased Slow Wave Sleep and REM Latency During Ziprasidone Treatment: A Randomized, Controlled, Crossover Trial of 12 Healthy Male Subjects.
Stefan Cohrs, Andreas Maier, Anna-Catharina Neumann, Wolfgang Jordan, Eckart Rüther, and Andrea Rodenbeck

997 A Trial of Compliance Therapy in Outpatients With Schizophrenia or Schizoaffective Disorder.
Matthew J. Byerly, Robert Fisher, Thomas Carmody, and A. John Rush

1002 Clinical and Demographic Features of Atypical Depression in Outpatients With Major Depressive Disorder: Preliminary Findings From STAR*D. [CME]
*Jon S. Nevick, Jonathan W. Stewart, Stephen R. Wisniewski, Ian A. Cook, Rashida Manev, Andrew A. Nierenberg, Jerrold F. Rosenbaum, Kathy Shores-Wilson, G. K. Balasubramani, Melanie M. Biggs, Sid Zisook, and A. John Rush, for the STAR*D Investigators*

1012 Topiramate Add-On in Treatment-Resistant Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial.
Jari Tiihonen, Pirjo Halonen, Kristian Wahlbeck, Eila Repo-Tiihonen, Soile Hyvärinen, Mariska Rimmen, Hanna Pohjonen, Pirjo Tolaka, Olli-Pekka Mahonen, Martin Puch, Jorma Oksanen, Pasi Koskelainen, Grigori Joffe, Juhani Aer, Tero Hallikainen, Olli-Pekka Ryynänen, and Pekka Tupala

1016 Symptomatic Remission in Patients With Bipolar Manic Results From a Double-Blind, Placebo-Controlled Trial of Risperidone Monotherapy.
Srihari Gopal, David C. Steffens, Michelle L. Kramer, and Manon K. Olson

1021 Response and Relapse in Patients With Schizophrenia Treated With Olanzapine, Risperidone, Quetiapine, or Haloperidol: 12-Month Follow-Up of the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) Study.
Martin Dossenbach, Cesar Arango-Dávila, Hernan Silva Ibarra, Eric Landa, Jaime Aguilar, Osvaldo Caro, Joanna Laudbetter, and Sheila Arcangelo

1031 Posttraumatic Stress Disorder Among Israeli Ex-Prisoners of War 18 and 30 Years After Release. [CME]
Zahava Solomon and Rachel Dekel

1038 An Open Study of Triiodothyronine Augmentation of Selective Serotonin Reuptake Inhibitors in Treatment-Resistant Major Depressive Disorder.
Dan V. Iosifescu, Andrew A. Nierenberg, David Mischoulon, Roy H. Perlis, George I. Papakostas, Julie L. Ryan, Jonathan E. Alpert, and Maurizio Fava

CONTINUED ON NEXT PAGE

Methodology

- Texas expert consensus panel
- Updating previous algorithms published in 2001
- 2 day meeting with bipolar experts, pharmacists, community and inpatient physicians, advocates and consumers
- Reviewed data presented at meetings as well as that published in peer review journals
- No industry support, individuals declarations of interest made in the publication

Strength of Evidence

A – randomised, blind, placebo-controlled trials

B – open, controlled trials, large case series, large retrospective analyses

C – preliminary but unconfirmed findings, case reports and series, expert consensus

- Algorithms based on quantity and quality of data of efficacy and effectiveness, expert opinion, consumer input and safety and tolerability issues

NICE Clinical Guideline
Second Draft, Feb 2006

NHS
National Institute for Clinical Excellence

Bipolar Disorder: The management of bipolar disorder in adults, children and adolescents, in primary and secondary care

Methodology

- Funded by NICE
- 23 member Guideline Development Group
  - Convened by the National Collaborating Centre for Mental Health (RCPsych CRTU and BPS equivalent)
  - Chair – Nicol Ferrier
  - Psychiatrists (adult and CAMS), Psychologists, Pharmacists, OT, Nurses, Users and Carers, Reviewers and Economists
  - Special Advisors consulted
- 2 drafts sent to stakeholders for comments (Nov 2005, Feb 2006)
- Final version due July 2006
- N.B. multiple versions (2nd draft: 77 and 341 pages)

NHS
National Institute for Clinical Excellence

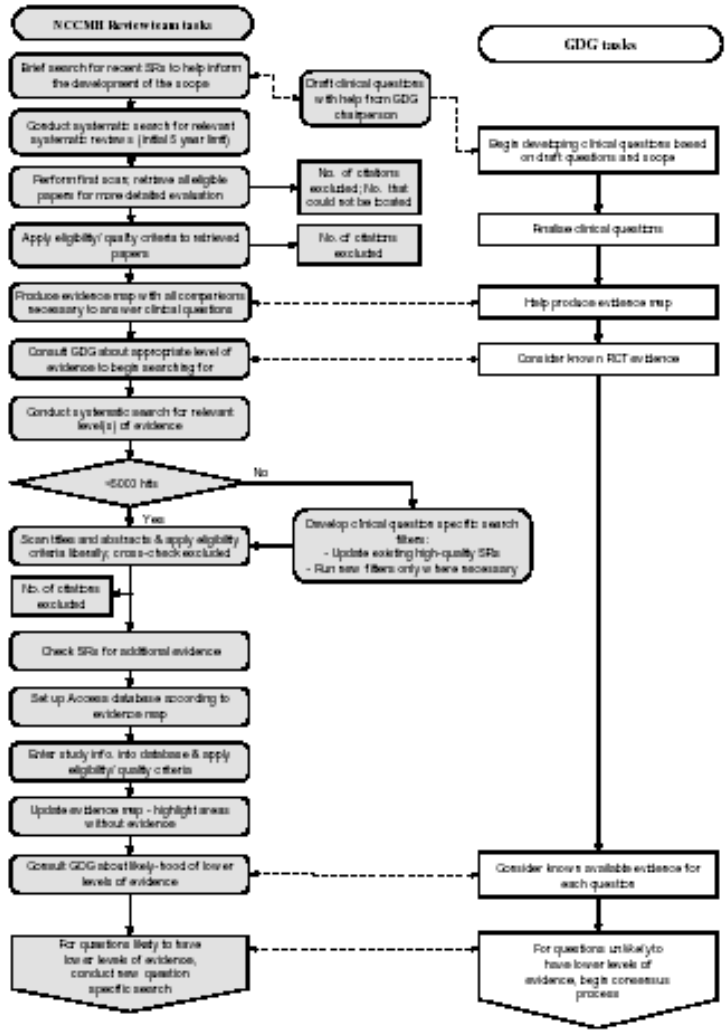
NICE Guidelines

- Full guideline 341 pages
  - 10 pages of contents – comprehensive guidelines!
  - 25 pages of methodology – thorough / obsessional guidelines!

NHS
National Institute for Clinical Excellence

NICE Review Process

Flowchart 1: Guideline Review Process



NHS
National Institute for Clinical Excellence

Nature of NICE guidelines

- Guidelines are…'systematically developed statements that assist clinicians and patients in making decisions about appropriate treatment for specific conditions (DOH 1996)
- From best available evidence reviewed using pre-determined and systematic methods
- "This guideline does not….the individual responsibility of health care professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or carer."
- In addition to clinical evidence, cost effectiveness also taken into account

NICE Strength of Recommendations

NHS
National Institute for Clinical Excellence

Level	Type of evidence	Grade	Evidence
I	Evidence obtained from a single randomised controlled trial or a meta-analysis of randomised controlled trials	A	At least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence level I) without extrapolation.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation	B	Well-conducted clinical studies but no randomised clinical trials on the topic of recommendation (evidence levels II or III); or extrapolated from level I evidence.
IIb	Evidence obtained from at least one other well-designed quasi-experimental study		
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies		
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities	C	Expert committee reports or opinions and/or clinical experiences of respected authorities (evidence level IV). This grading indicates that directly applicable clinical studies of good quality are absent or not readily available.
		GPP	Recommended good practice based on the clinical experience of the GDG.
NICE	Evidence from NICE clinical guideline or technology appraisal	NICE	

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Acute Mania

Acute Manic or Mixed Episodes

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

- Initiate oral administration of an (atypical) antipsychotic or valproate (A)
- The lowest doses necessary should be employed (A). Do not escalate the dose of antipsychotic simply to obtain a *sedative* effect (S).
- For less ill manic patients lithium or carbamazepine may be considered as a short term treatment (A).
- To promote sleep consider adjunctive benzodiazepine (B)
- Antidepressants should be tapered and stopped (B)
- Treatment choice guided by patient preference (S)

Acute Manic or Mixed Episodes

For patients who suffer an episode while on long term treatment:

- Ensure highest well-tolerated dose / lithium in therapeutic range (A)
- Start antipsychotic or valproate as above
- Use same principles as above
- Consider if current episode is due to poor adherence
  - Consider more tolerable regimen
  - If episode due to lithium discontinuation, use of lithium may not be indicated (B)

Acute Manic or Mixed Episodes

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).
  - 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).

Acute Mania

- First line Li + antipsychotic or Valproate + antipsychotic [I]
  - Less severe, Li, valproate or antipsychotic [I]
- Otherwise almost exactly the same as BAP guidelines

Acute treatment of mania

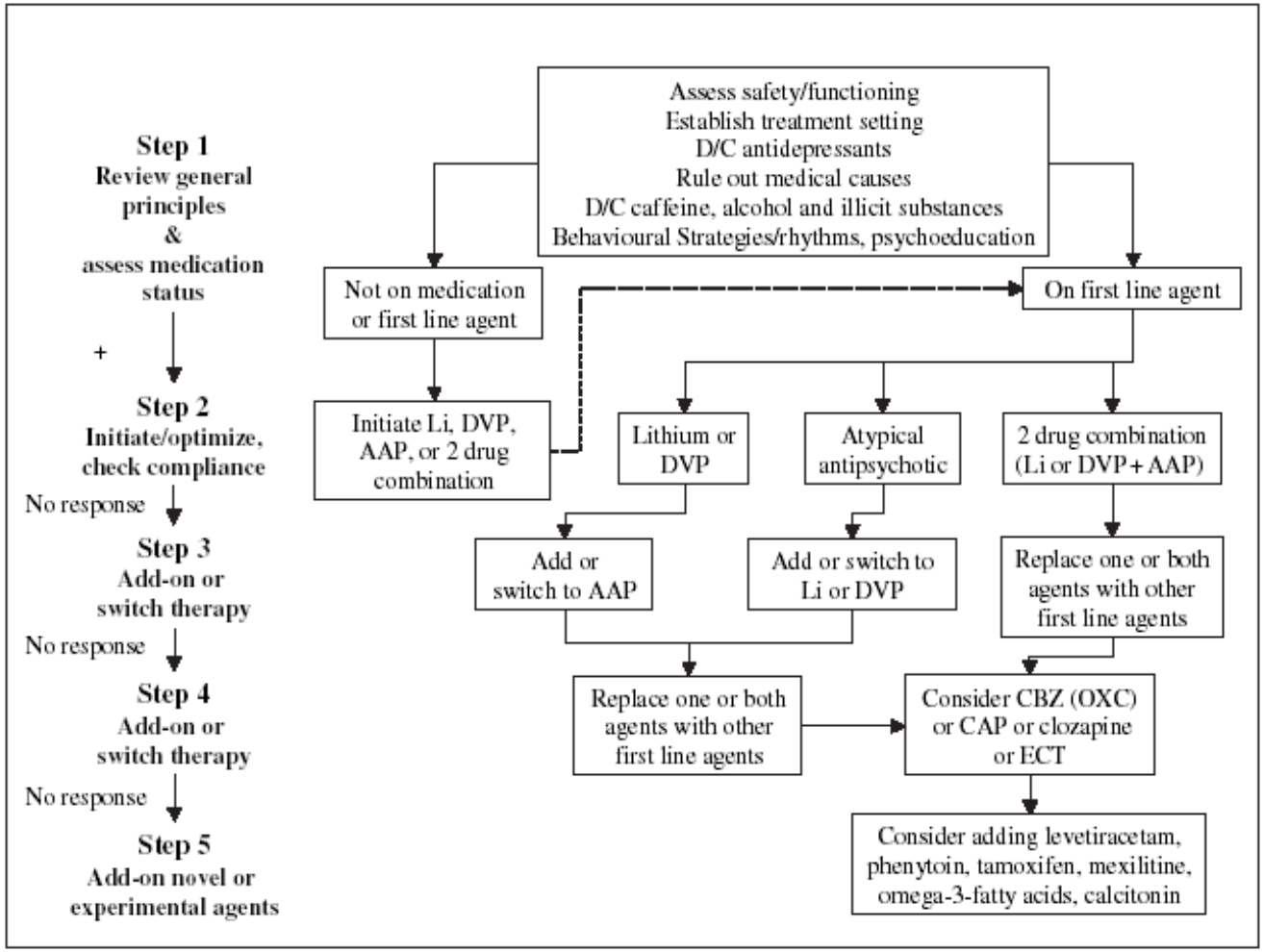
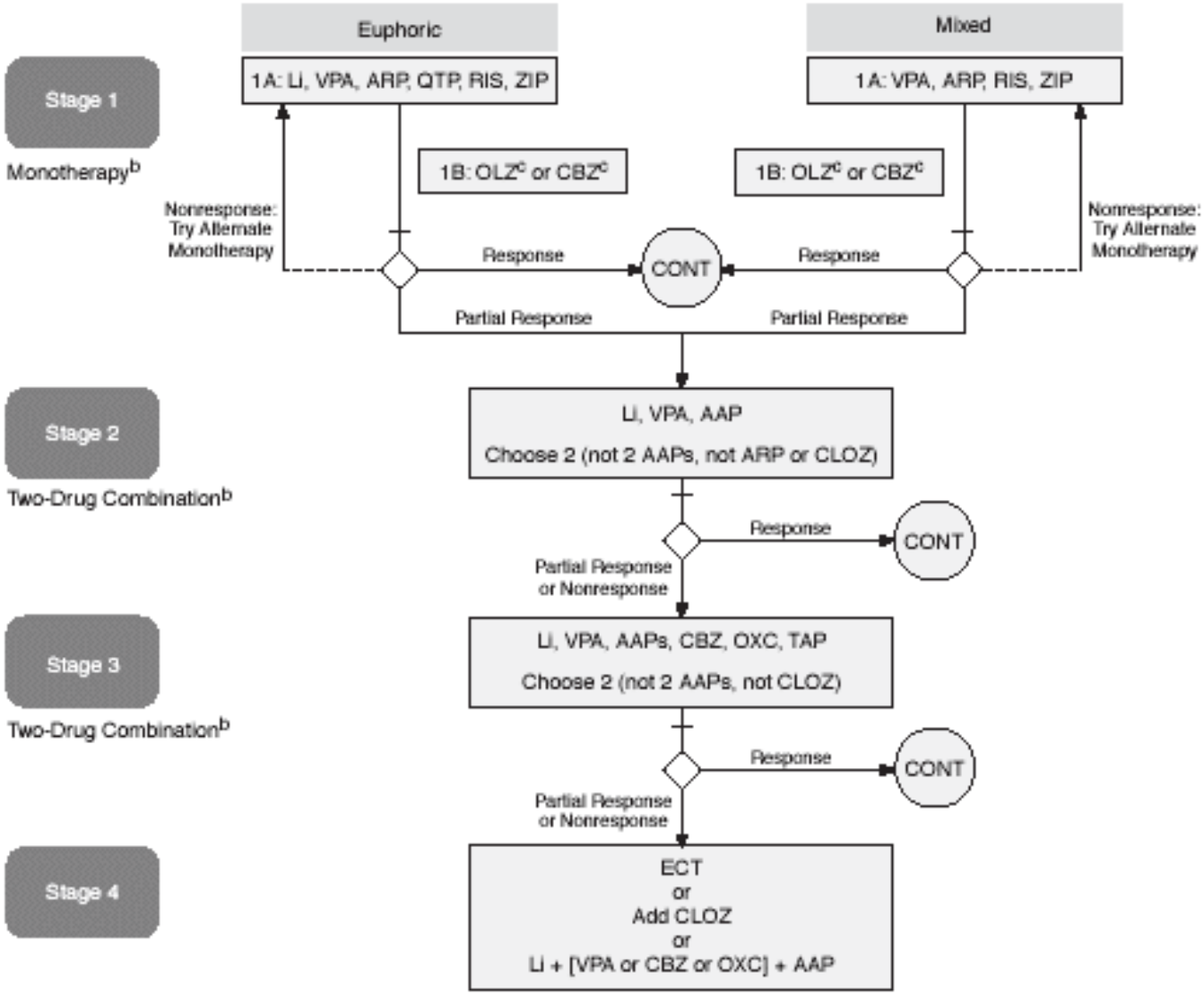


Fig. 3.1. Treatment algorithm for acute mania. AAP = atypical antipsychotic; CBZ = carbamazepine; CAP = conventional antipsychotic; DVP = divalproex; ECT = electroconvulsive therapy; Li = lithium; OXC = oxcarbazepine.

Figure 1. Algorithm for Treatment of Acute Hypomanic/Manic/Mixed Episodes in Patients With Bipolar I Disorder[a]



Acute Mania:
Those not on anti-manic treatment

NHS
National Institute for Clinical Excellence

- Atypical antipsychotic (olanzapine, risperidone, quetiapine) for those with severe mania
  - If ineffective consider adding Li or valproate
- Valproate or Li if previous good response and compliance
  - Avoid valproate in women of child baring potential
  - Li only if less severe
- Don’t use carbamazepine routinely and avoid gabapentin, lamotrigine and topiramte

Acute Mania:
Those on anti-manic treatment

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- Optimise treatment
  - Li level 0.8-1.0
  - Valproate to max. licensed dose (depending on SEs)
  - Don’t generally increase carbamazepine
- Add olanzapine, risperidone or quetiapine

Acute Mania: Summary

- Fair degree of consensus:
  - Li, valproate and atypicals all considered first line treatments
- BAP argue Li only for less severe mania
- NICE suggest atypicals main choice (N.B. beware valproate in women)
- TIMA express concern re olanzapine
- APA tends to be aggressive and go for combination treatment early

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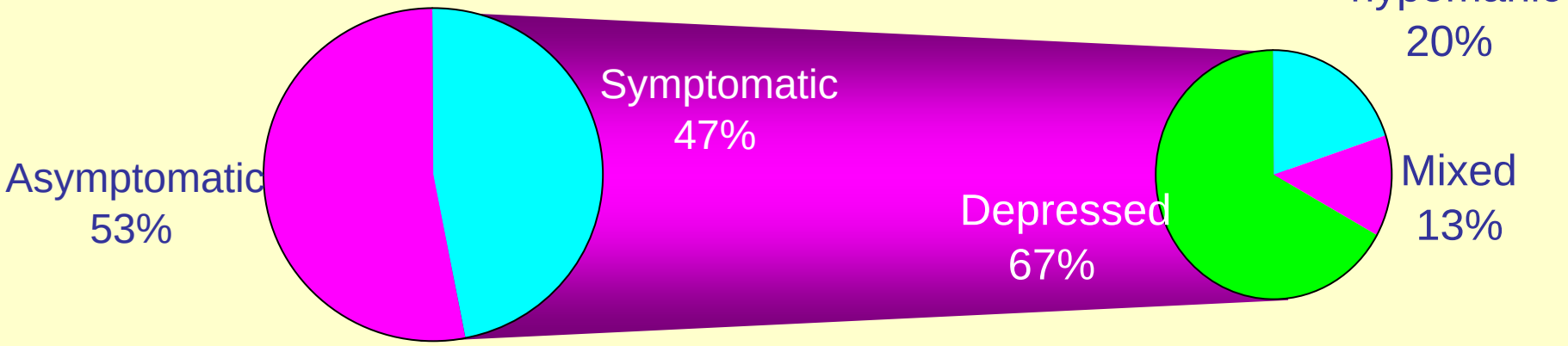
Acute Depression

Depression is THE Problem

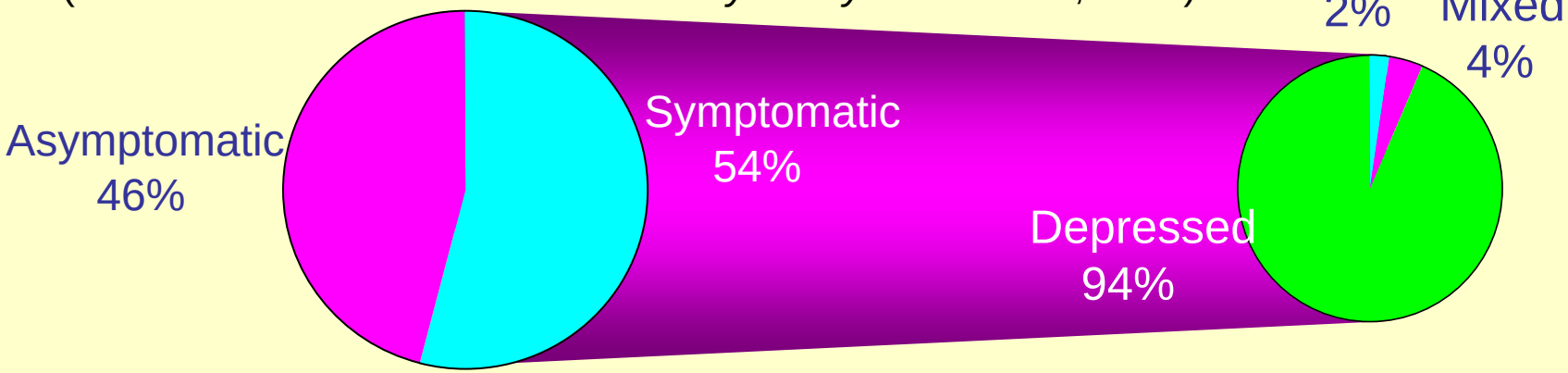
Bipolar I

(Judd et al. *Archives of General Psychiatry* 59:530-537, 2002)

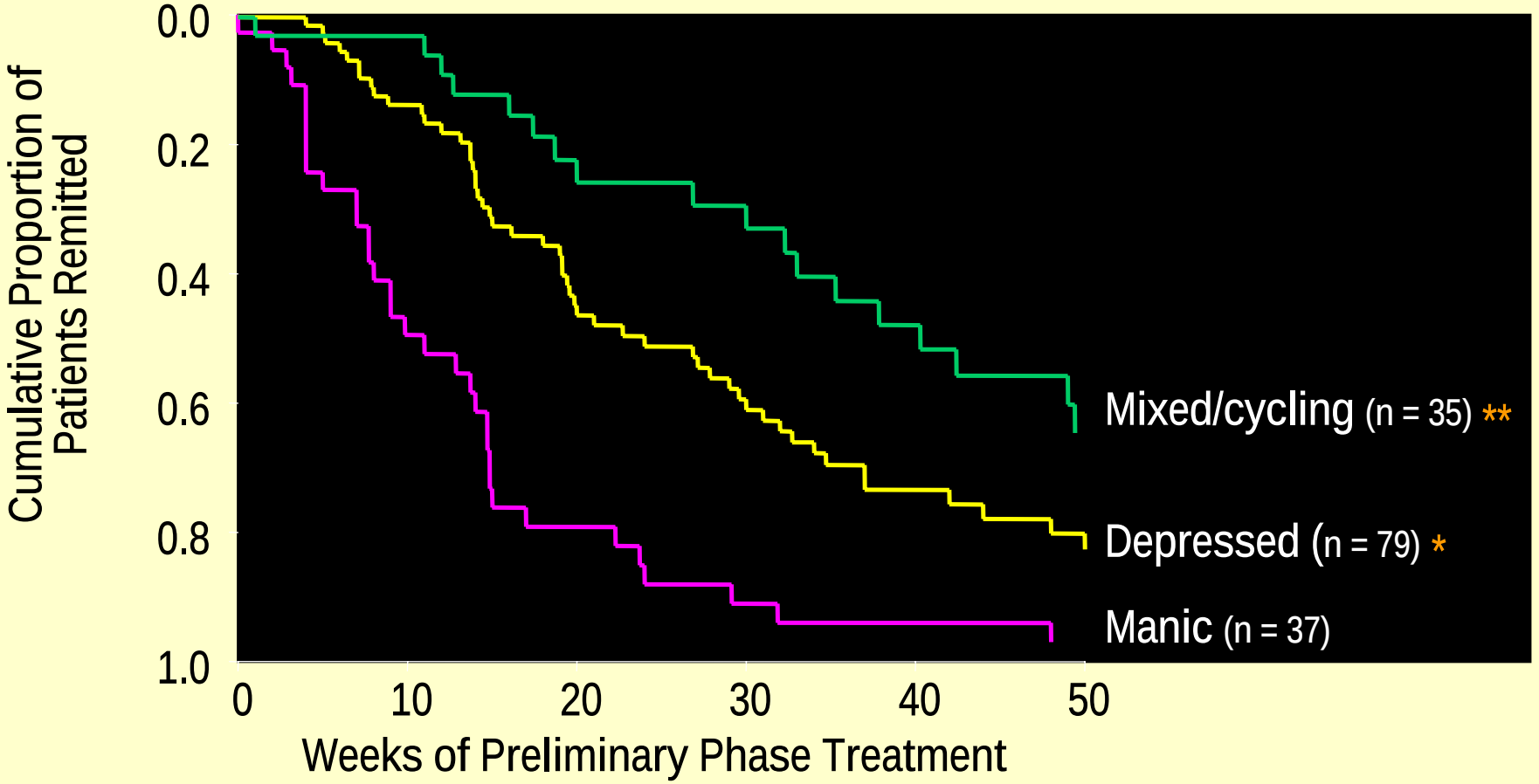


Bipolar II

(Judd LL et al. *Archives of General Psychiatry* 60:261-269, 2003)



Bipolar Depressive and Mixed Episodes are Difficult to Treat



*p < 0.0001 vs Manic; **p<.0001 vs Manic and p < 0.05 vs Dep

Kupfer DJ et al. *Acta Neuropsychiatrica* 12:110-114, 2000

Acute Depression

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

- Treat with an antidepressant (e.g. SSRI) and an anti-manic drug (e.g. lithium, valproate or an antipsychotic) together (B).
- Antidepressant monotherapy is not recommended for patients with a history of mania (B).
- Consider adding antipsychotic especially if psychotic symptoms present (A)
- Consider ECT for patients with high suicidal risk, psychosis, severe depression during pregnancy or life-threatening inanition (A).

Acute Depression

For patients who suffer a depressive episode while on long term treatment

- Optimize doses of medicines and serum levels of lithium (B). Address current stressors, if any (B).
- Ensure current long-term treatment will prevent manic relapse (e.g. lithium, valproate, antipsychotic) (A).
- If the patient fails to respond to optimization of long-term treatment, and especially if depressive symptoms are significant, initiate an antidepressant (or consider augmentation or change of antidepressant) (A).

Acute Depression

Choice of antidepressant

- Antidepressants work in bipolar disorder (Ia)
- There is a risk of switch to mania or mood instability during treatment for depression (I).
  - Antidepressants less likely to induce mania when added to lithium, valproate or antipsychotic (IIa).
  - Tricyclic antidepressants more likely (Ia) and not recommended except for treatment resistant patients (C).
  - Consider lamotrigine, esp. if an antidepressant has previously appeared to provoke mood instability (A).

Acute depression

- Start either lithium [I] or lamotrigine [II]
- If on long term treatment – optimise this [II]
- Don’t use antidepressant monotherapy
  - Consider Li + antidepressant [III]
- Consider ECT [I]
- If fails first line therapy consider adding lamotrigine [I], buproprion [II] or paroxetine [II]
  - Alternatives: another SSRI [II], venlafaxine [II] or an MAOI [II]

Acute treatment of depression

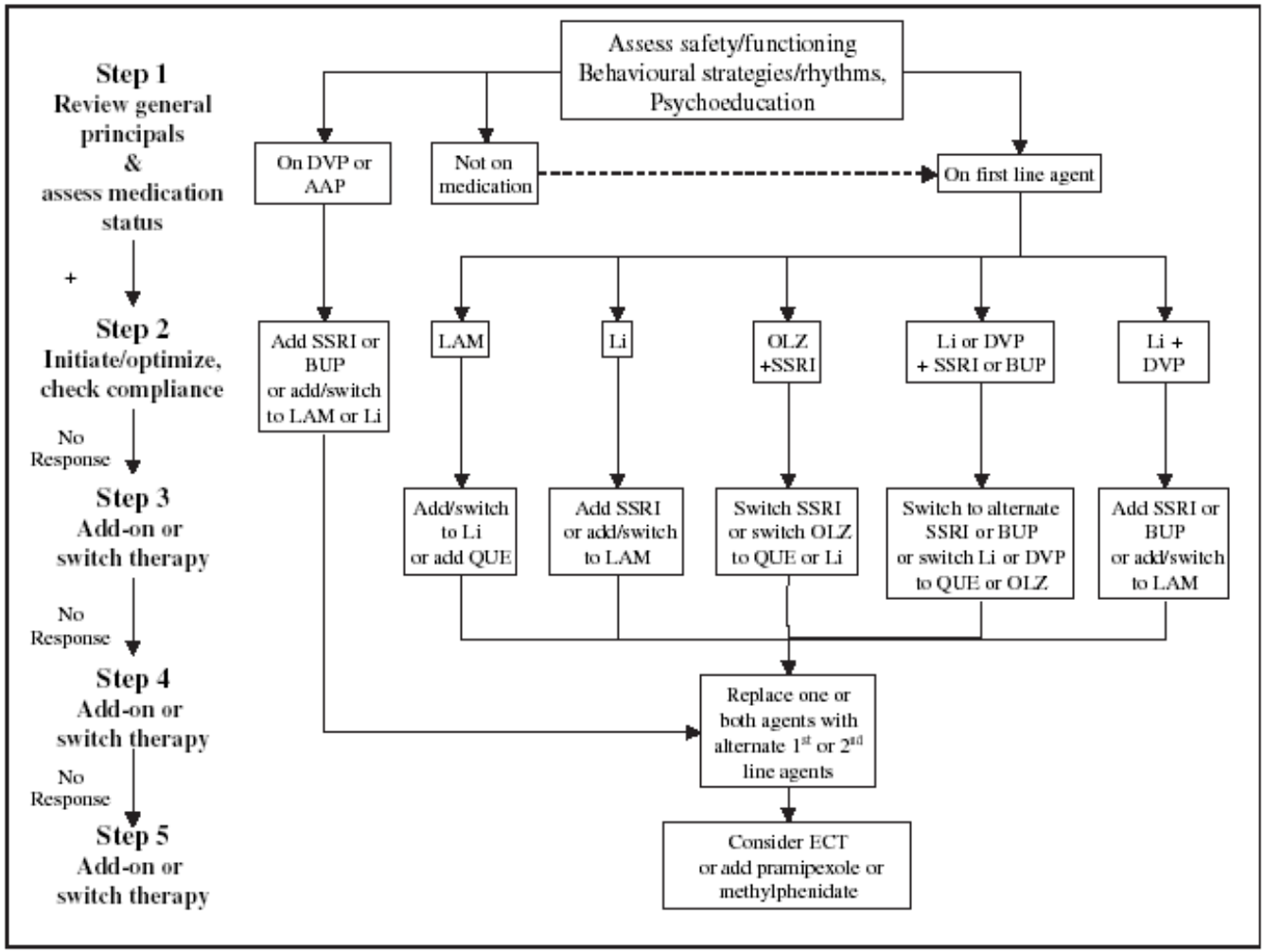
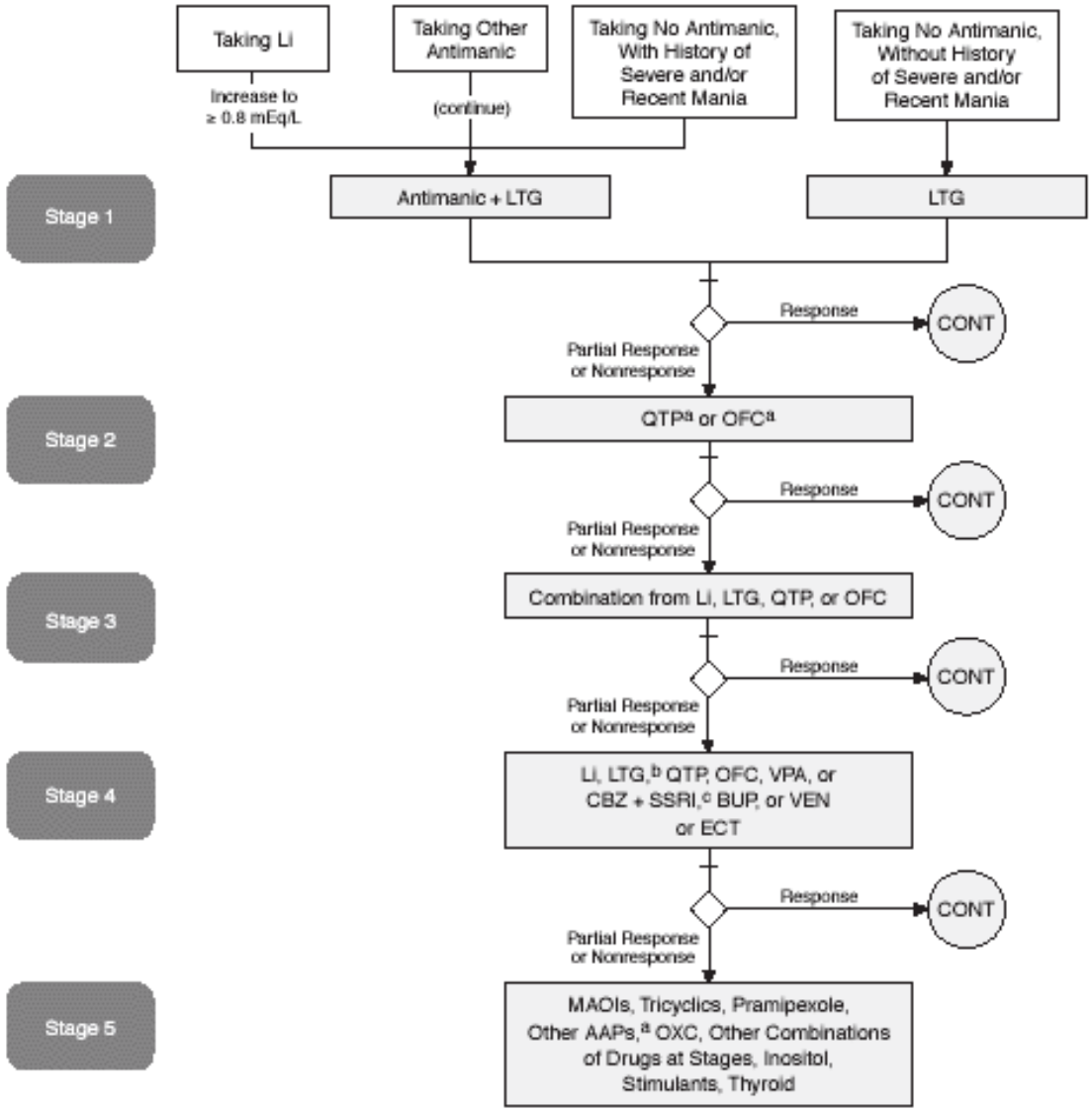


Fig. 4.1. Treatment algorithm for the management of bipolar depression. AAP = atypical antipsychotic; BUP = bupropion; DVP = divalproex; ECT = electroconvulsive therapy; LAM = lamotrigine; Li = lithium; OLZ = olanzapine; QUE = quetiapine; SSRI = selective-serotonin reuptake inhibitor.

Figure 2. Algorithm for Treatment of Acute Depressive Episodes in Patients With Bipolar I Disorder



Acute Depression

- First line: SSRI plus antimanic agent
- If on antimanic: SSRI or quetiapine (if not on antipsychotic)
- If recent unstable mood: avoid antidepressants – increase antimanic and consider lamotrigine
  - NB avoid lamotrigine as a single first line agent in bipolar I but consider this in bipolar II
- If doesn't respond to SSRI switch to mirtazepine or venlafaxine or add quetiapine or olanzapine if not on an antipsychotic
- Taper antidepressants after symptoms reduced for 8 weeks

Acute Depression: Summary

- Much less consensus:
  - Don’t use antidepressant monotherapy esp. in bipolar I
- BAP use SSRIs and not TCAs
- APA, CANMAT and TIMA: increased use of lamotrigine and buproprion
- CANMAT, TIMA and NICE: increased use of quetiapine

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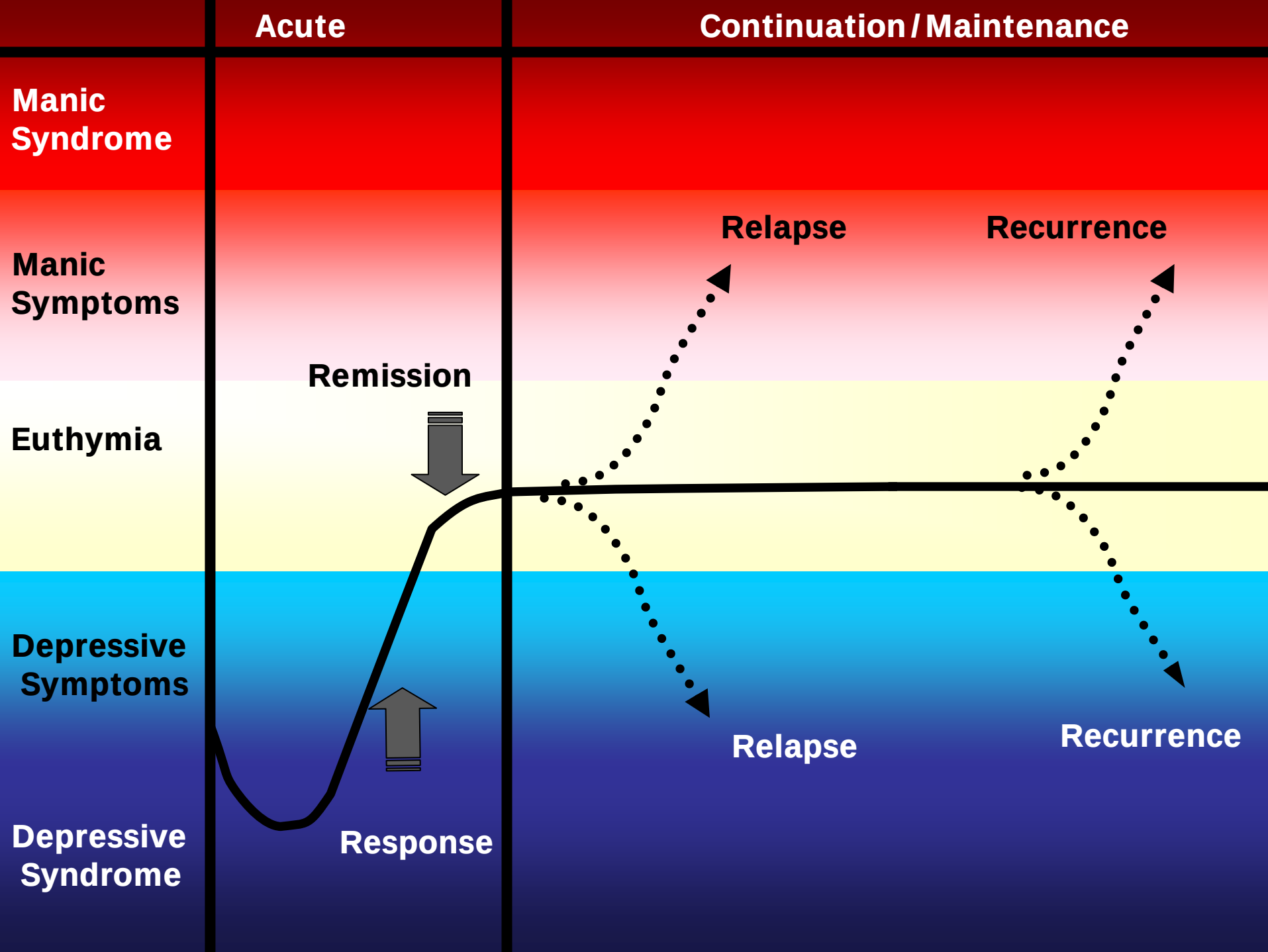
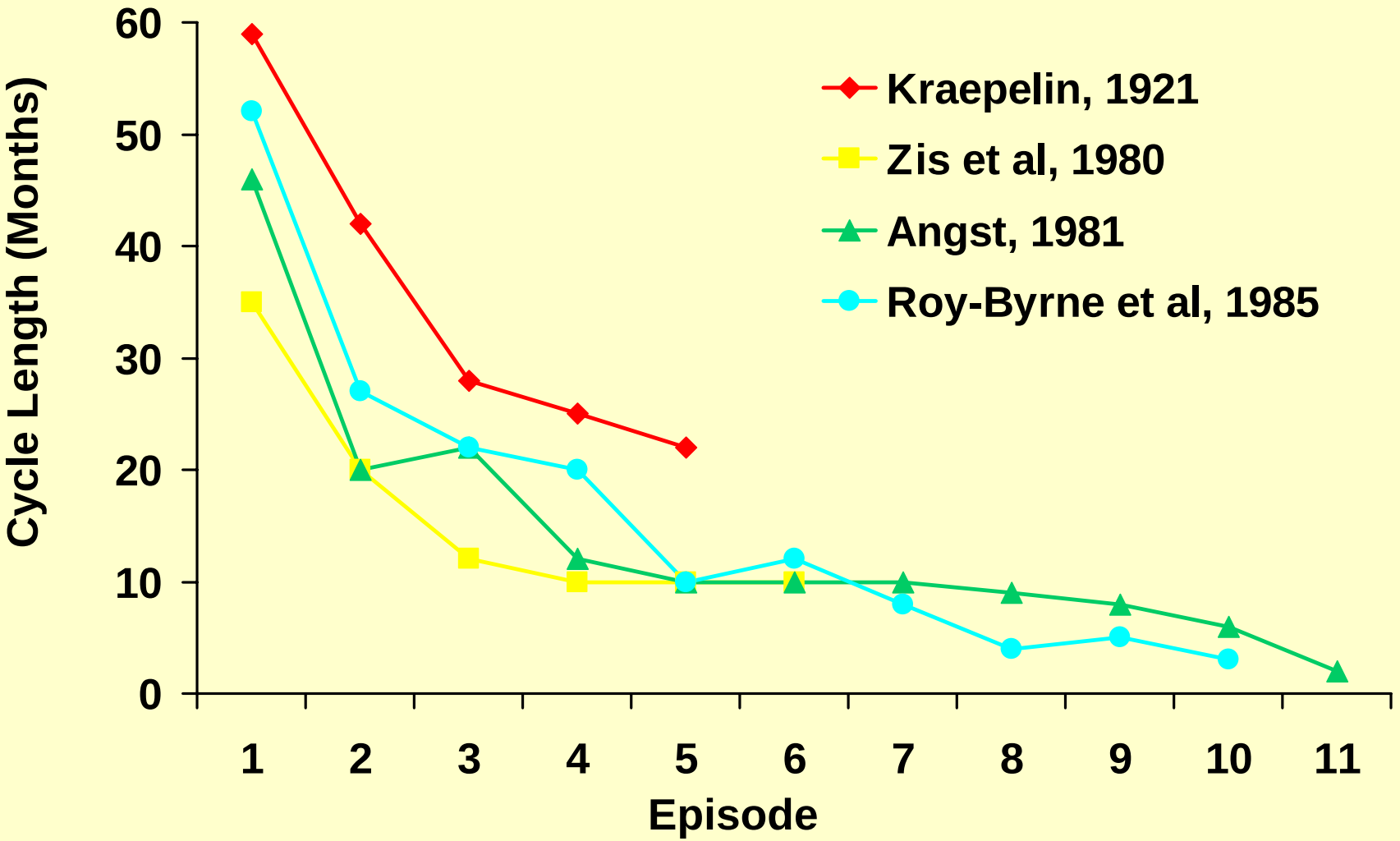
Maintenance

What is a “Mood Stabiliser”

- Treats depression plus mania without making either pole worse and/or has prophylactic effects for both mania and depression
- BAP:
  - An ideal ‘mood stabilizer’ would prevent relapse to either pole of the illness – actually more effective against one pole than the other
- APA and CANMAT:
  - Absence of a consensus definition
- NICE
  - “A term best avoided”


Acute
Continuation / Maintenance
Manic Syndrome
Manic Symptoms
Euthymia
Depressive Symptoms
Depressive Syndrome
Remission
Response
Relapse
Recurrence
Relapse
Recurrence

Relationship between cycle length and number of episodes



Mood Disorders: Risk of relapse

Bipolar Disorder, constant risk of relapse over 40yrs; 0.4episodes/year

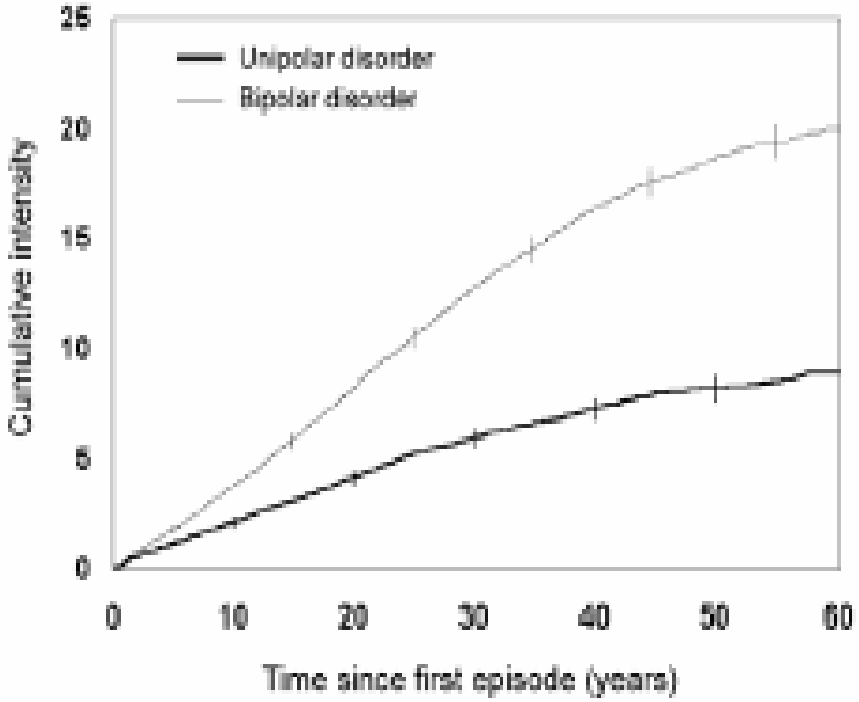


Fig. 1 Bipolar disorder vs. unipolar disorder (vertical bars indicate 95 % confidence intervals)

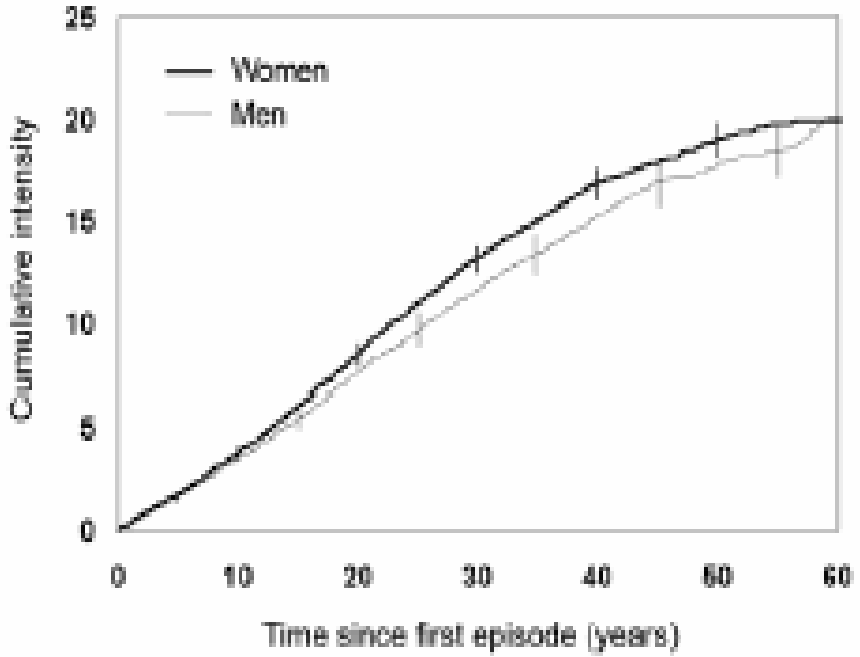


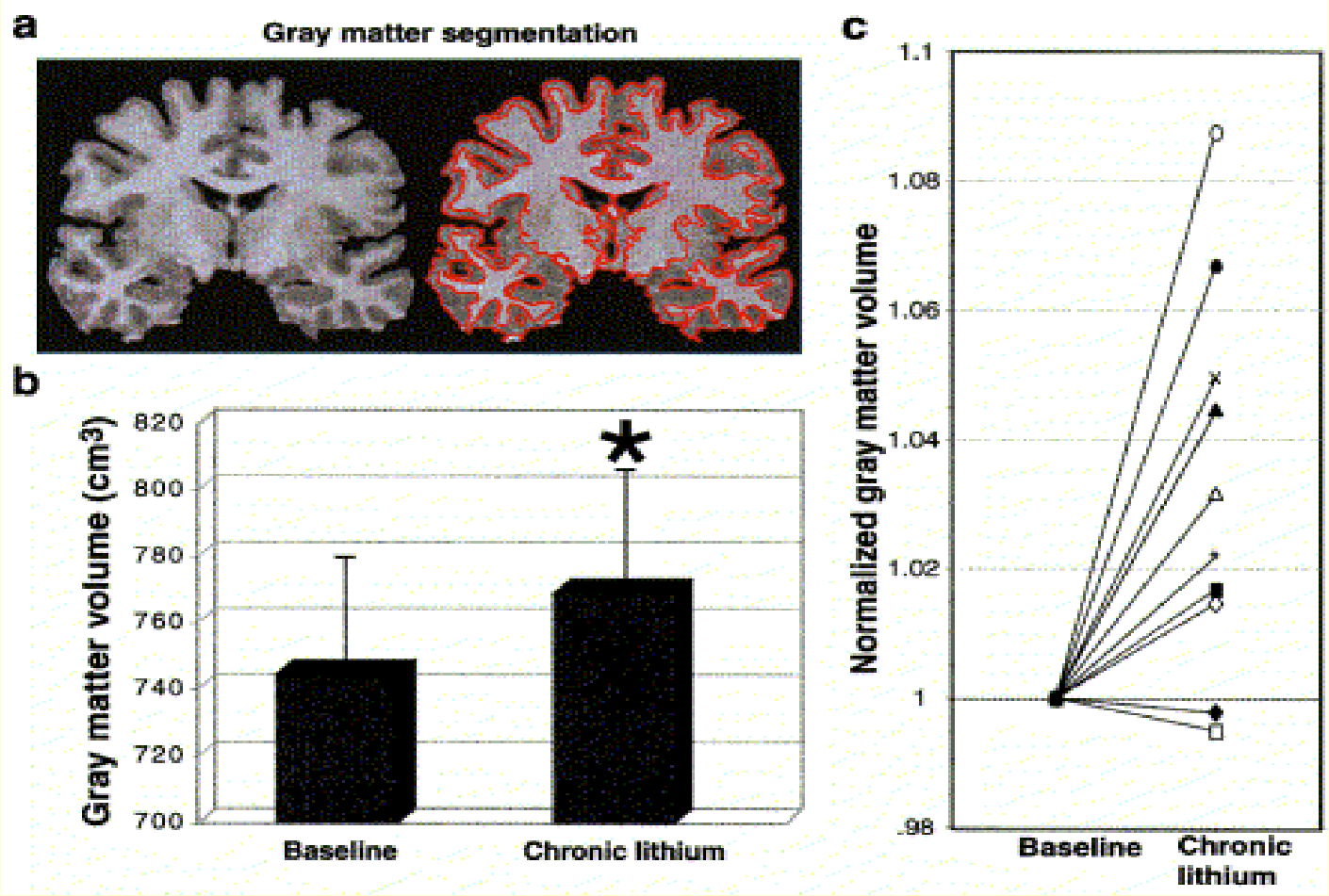
Fig. 3 Bipolar disorders divided into men and women (vertical bars indicate 95 % confidence intervals)

Angst et al. Eur Arch Psychiatry Clin Neurosci. 2003

Long-term treatment: Why?

- High risk of recurrence (Ia)
- Preventing early relapse may lead to a more benign illness course (D)
- High frequency of chronic sub-threshold symptoms (most commonly depressive) (II)
- Cognitive distortions similar to unipolar illness (II)
- Neuropsychological deficits can be disabling and often neglected (II)

Beyond Symptomatic Control?



Moorel et al Lancet 2000

Long-term treatment: When?

Prevention of new episodes

- Consider long term treatment after a single manic episode or as early as acceptable to patient and their family (D).
- Need active acceptance of need for long-term treatment: Consider a wider package of treatment offering enhanced psychological and social support (A).
- Where a patient has done very well, they should be strongly advised to continue indefinitely, because the risks of relapse remain high (A).
- Consider extrapolating above for Bipolar I to II despite absence of good clinical trials (D)

Long-term treatment: How?

Options for long-term treatment

- Continuous rather than intermittent therapy
  - Short term add-ons (e.g. benzos, atypicals) when stressors present or early signs of relapse (esp. sleep disturbance)
  - Consider supplying treatment prospectively to patients (D)
  - Increases dose may sometimes be an alternative to add-ons
  - May help patients comply with their treatment regime

Long-term treatment: What?

Choice of long-term treatments

- Consider lithium monotherapy (A)
  - Lithium protects against both mania and depression, but is more effective at preventing mania (Ia)
  - Long term treatment with lithium decreases the risk of suicide (I)
  - If lithium ineffective or poorly tolerated
    - Valproate protects against mania (and depression) (Ia)
    - Olanzapine protects against mania (and depression) (Ia)
    - Carbamazepine is less effective than lithium (Ib) but may be used especially in non-classical illness (B). Oxcarbazepine has fewer pharmacokinetic interactions
    - Lamotrigine protects against depression (? and mania) (Ia)
    - Gabapentin ineffective (Ib)
  - Acute response to an agent favours its use long term (B)

Long-term treatment: Non-response

If the patient fails monotherapy

- Consider long term combination treatment (C).
  - Where the burden is mania, combine predominantly anti-manic agents (e.g. lithium, valproate, an antipsychotic) (D).
  - Where the burden is depressive, lamotrigine or an antidepressant may be more appropriate in combination with an anti-manic long-term agent (D).
- Maintenance ECT if respond acutely and do badly on oral treatments (D)
- Consider clozapine in treatment resistant patients (C).

Long-term treatment: Rapid cycling

Rapid cycling

- Identify and treat hypothyroidism or substance misuse that may contribute (C)
- Taper and discontinue antidepressants (C)
- For initial treatment consider lithium, valproate or lamotrigine (A)
- Combinations often required. Evaluate over 6 months or more. Discontinue ineffective treatments (D)

Long-term treatment: Stopping

Discontinuation of long term treatment

- Following discontinuation of medicines, the risk of relapse remains, *even after years of sustained remission* (I).
- Discontinuation of any medicine should normally be tapered over at least 2 weeks and preferably longer (A and S). Early relapse to mania is an early risk of abrupt lithium discontinuation (Ia).
- Discontinuation of medicines should not be equated with withdrawal of services to patients (S).

Long-term treatment

- Maintenance recommended after a single manic episode [I]
- Consideration of similar maintenance therapy in bipolar II strongly warranted [II]

Long-term treatment: Key differences from BAP guidelines

- If antipsychotic used for the acute episode its ongoing use should be reviewed at the maintenance phase [I]
- Discontinue antipsychotics unless:
  - Required for control of, or persistent, psychosis [I]
  - Prophylaxis against recurrence [III]
- Consider atypicals for maintenance [III] but no definitive evidence as effective as lithium or valproate

Maintenance therapy: when?

- At least one moderately severe manic episode
- If refuse
  - Psychoeducation
  - Continue acute treatments for at least 3-6 months
  - (Antidepressants after 1-3 months)

Maintenance – choice of treatment

- Lithium
  - Best evidence base
  - Antisuicidal effects
  - Treatment of choice for typical bipolar disorder
- Olanzapine and divalproex
  - More suitable for patients with manic relapses
- Lamotrigine
  - Mainly for preventing depressive relapses
  - Avoid monotherapy if history of severe or frequent mania

Maintenance pharmacotherapy of bipolar disorder

- First line
  - Lithium (1), lamotrigine (if only “mild mania”; 1/2), divalproex (2), olanzapine (2)
- Second Line
  - Carbamazepine (2), Li+DVP (2), Li+CBZ (2), Li or DVP+olanz (2), aripirazole (2*), risperidone (3), quetiapine (3), ziprasidone (?), Li+risp or quet (?), Li+lam or SSRI or buproprion (?)
- Third Line
  - Adjunctive phenytoin (3), clozapine (3), ECT (3), topiramate (3), gabapentin (3), omega-3-fatty acids (2), oxcarbazepine (3)
- Not Recommended
  - Benzodiazepines, adjunctive flupenthixol, monotherapy with gabapentin, topiramate, antidepressants

Maintenance

- Different algorithms depending on polarity of most recent episode
  - Much more info re treatment following elevated mood episode
- Maintenance for those stabilised on acute treatment
  - continuation of acute phase treatment
  - followed by simplification of treatment regimes
- Medication changes often made on the basis of sub-syndromal symptoms
- In clinical practice most patients on combinations but evidence base focused on single treatments

Figure 3. Guidelines for Maintenance Treatment: Most Recent Episode Hypomanic/Manic/Mixed

It is an option to remain on well-tolerated, effective, acute-phase treatments. Available evidence supports the options presented for prevention of new episodes or maintenance treatment.

Level I:	Patients With Frequent, Recent, or Severe Mania	Lithium or Valproate
	Patients Without Frequent, Recent, or Severe Mania	Lithium, Valproate, or Lamotrigine
	Alternative	Olanzapine[a]
Level II: Aripiprazole[b]		
Level III: Carbamazepine or Clozapine[a]		
Level IV: Quetiapine,[b] Risperidone,[b] or Ziprasidone[b]		
Level V: Typical Antipsychotics,[a] Oxcarbazepine,[b] ECT		

[a]Safety issues warrant careful consideration of this option for potential long-term use.
[b]Relatively limited information is currently available on this agent in long-term use.

Figure 4. Guidelines for Maintenance Treatment: Most Recent Episode Depressed

It is an option to remain on well-tolerated, effective, acute-phase treatments. Available evidence supports the options presented for maintenance treatment.

Level I:	Patients With Recent and/or Severe History of Mania	Lamotrigine Combined With Antimanic Agent
	All Other Patients	Lamotrigine Monotherapy

Level II: Lithium

Level III: Combination of an Antimanic and Antidepressant That Has Been Effective in the Past, Including Olanzapine-Fluoxetine Combination[a]

Level IV: Valproate, Carbamazepine, Aripiprazole,[b] Clozapine,[a] Olanzapine,[a] Quetiapine,[b] Risperidone,[b] Ziprasidone[b]

Level V: Typical Antipsychotics,[a] Oxcarbazepine,[b] ECT

[a]Safety issues warrant careful consideration of this option for potential long-term use.
[b]Relatively limited information is currently available on this agent in long-term use.

Other issues

- Rapid cycling
  - No specific recommendations
  - Often need combinations
- Bipolar II
  - Clinical considerations coincide with those for bipolar I
  - Evidence for lithium, lamotrigine, valproate and antidepressant monotherapy

Long-term Treatment: When?

National Institute for Clinical Excellence

- Single manic episode with significant risk/consequences
- 2+ episodes in bipolar I
- In bipolar II if:
  - Significant risk
  - Frequent episodes
  - Significant functional impairment

Long-term Treatment: What?

NHS
National Institute for Clinical Excellence

- First line: an atypical antipsychotic
  - Same one used in acute phase or olanzapine
- Second Line:
  - Valproate – esp. if prone to depressive Sx, but N.B. women of child baring potential
  - Lithium
- If fails monotherapy over 6 months
  - Li + valp, Li + olanz, Valp + olanz
- If combination fails
  - Consider lamotrigine (esp. BPII), carbamazepine, referral to tertiary centre
- NOT antidepressants routinely (unless no mania X 5 yrs)
- Normally treat for at least 5 years

Rapid Cycling

- First line: Li + valproate
- Second line: Li
- Avoid antidepressants
- Consider Li or valproate + lamotrigine (esp in BPII)
- Check TFTs (+ antibodies) every 6 months

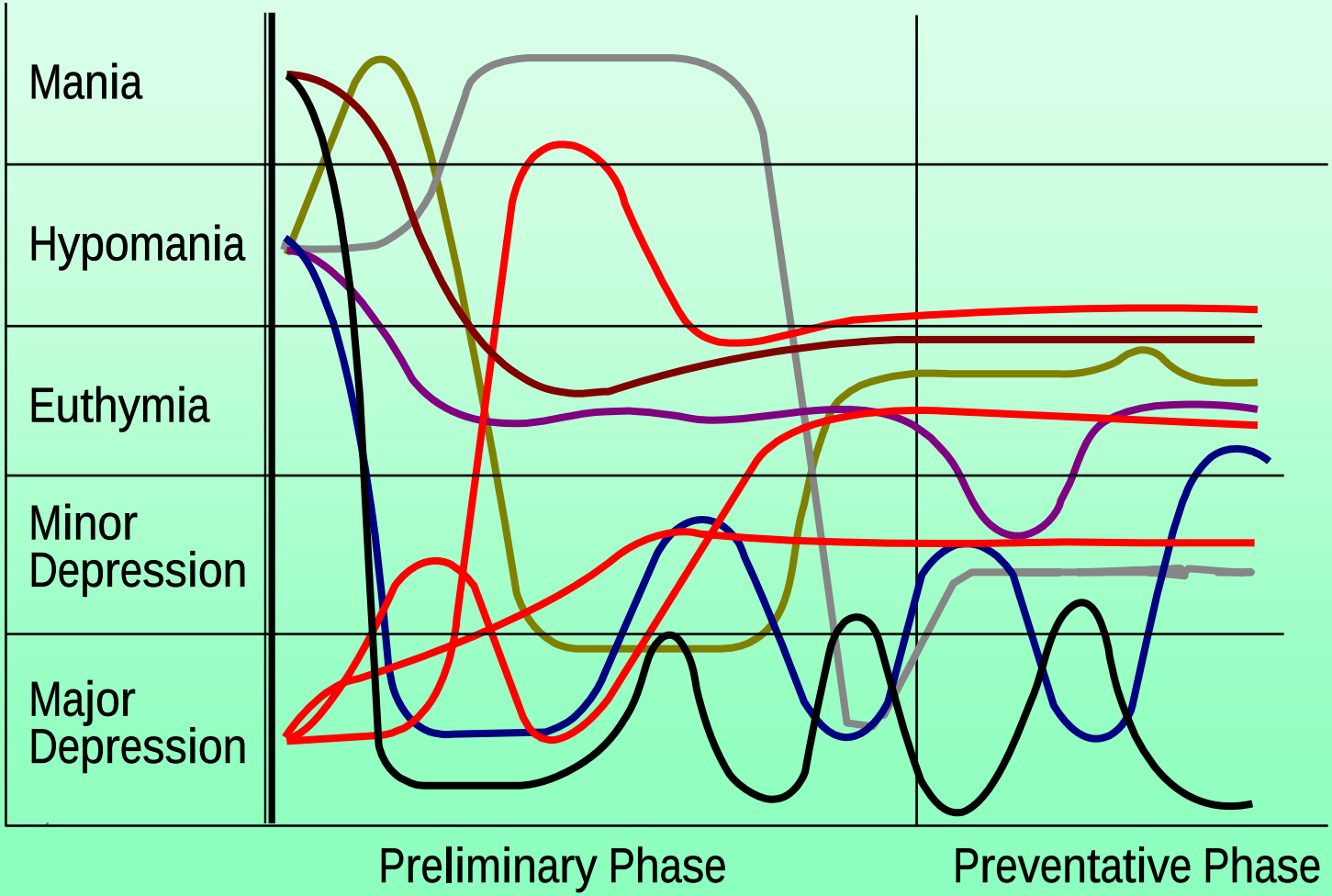
Maintenance: Summary

- Shifts in recommendations evident from APA to NICE
  - Increased recommendations for use of atypicals
  - Increased caution recommended re use of antidepressants
- NICE emphasise the need for physical health monitoring

Finally….

- Shift of olanzapine to stage 1B in TIMA represents acknowledgement that efficacy not the only consideration
  - Singling out olanzapine may be premature
- Acute phase recommendations increasingly being driven by maintenance considerations
- Guidelines limited by evidence base (esp. maintenance)
- Outstanding issues:
  - Is combination of atypical plus “mood stabiliser” better than atypical alone?
  - What is the optimal combination for maintenance?
  - How to balance efficacy with tolerability and safety (esp. for maintenance)?

The course of Bipolar Disorder



Frank E, et al. *Biol Psychiatry.* 2000;48(6):593-604.

“The study of MEDICINE is prosecuted under two relations, namely as a *Science* and as an *Art*”

The Science and Practice of Medicine
W. Aitken
1872