PHARMACOLOGICAL TREATMENT OF BIPOLAR DISORDER : CURRENT EVIDENCE BASE

OUTLINE

- History
- General principles
- Acute mania
- Acute depression
- Prophylaxis

OUTLINE

- Rapid cyclers
- BPAD in pregnancy
- BPAD in children and adolescents
- Summary
- References

HISTORY

- 1871- First use of lithium
- 1949- John Cade re-introduced Lithium
- 1952- CPZ + phenobarbitone
- 1970- Lithium approved by US FDA
- 1994- Abbott study and FDA approval for valproate in mania

HISTORY

- 1960's and 70's- Carbamazepine use in Japan
- 2002- Carbamazepine - acute mania
- 2000- Olanzapine first antipsychotic - mania
- 2003-04 – Lamotrigine and olanzapine - maintenance
- 2017- long acting Aripiprazole and cariprazine

GENERAL PRINCIPLES

- Diagnostic evaluation
- Assess pt. safety and level of functioning and presence of psychotic features
- Establish therapeutic alliance
- Target broad range of symptoms
- Target other substance use/ co-morbidities
- Minimize initial discomfort

GENERAL PRINCIPLES

- Enhance treatment compliance
- Promote regular patterns of sleep and activity
- Anticipate stressors
- Early identification of new episode
- Minimize functional impairment

BPAD- MANIA

ACUTE MANIA

- Severe symptoms, agitated state, risk to self or others- HOSPITALIZATION
- Drugs -mainstay therapy
- Antipsychotics and mood stabilizers
- Antipsychotics + mood stabilizers –

➢ Weigh pros and cons

➢ Recommended in severely ill

ACUTE MANIA

- Basic parameters prior to treatment implementation:
- BMI, waist circumference
- BP
- CBC, LFT, FBS, lipid profile, urea and electrolytes
- Smoking status, alcohol use
- CVD risk
- pregnancy

ACUTE MANIA

Lithium

Baseline
TSH

Serum level
2 levels to establish therapeutic dose, then every 3–6 months

Longitudinal monitoring
- U&E 3–6 monthly
- Ca, white cell count, TSH and weight after 6 months, then annually

Valproate and carbamazepine

Baseline
Hematological and hepatic history

Serum level
2 levels to establish therapeutic dose, then as clinically indicated

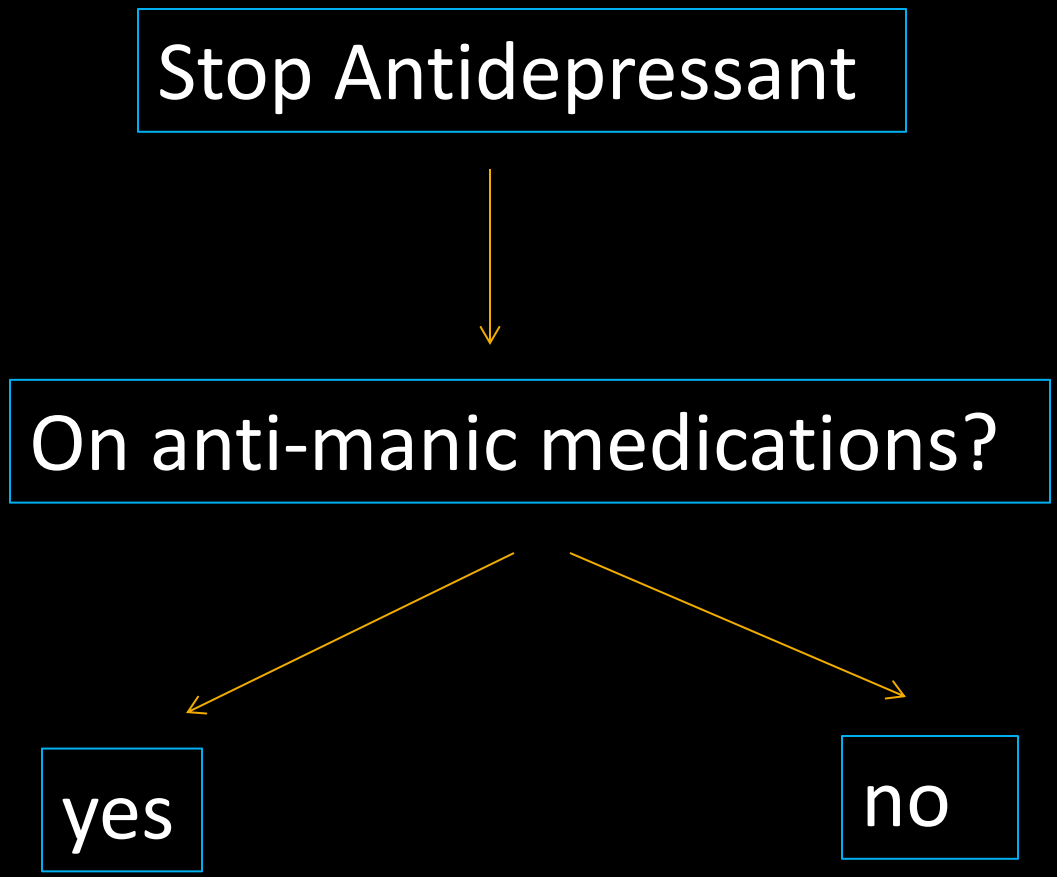
Longitudinal monitoring
- **Valproate:** weight, FBC, LFT, menstrual history every 3 months for first year, then annually; BP, fasting glucose and lipid profile if risk factors; BMD if risk factors
- **Carbamazepine:** FBC, LFT, U&E monthly for first 3 months, then annually; alert to rash especially in first few months of treatment; BMD if risk factors

Atypical antipsychotics

Longitudinal monitoring
- Weight monthly for first 3 months, then every 3 months
- BP and fasting glucose every 3 months for first year, then annually
- Fasting lipid profile after 3 months, then annually
- ECG and prolactin level as clinically indicated

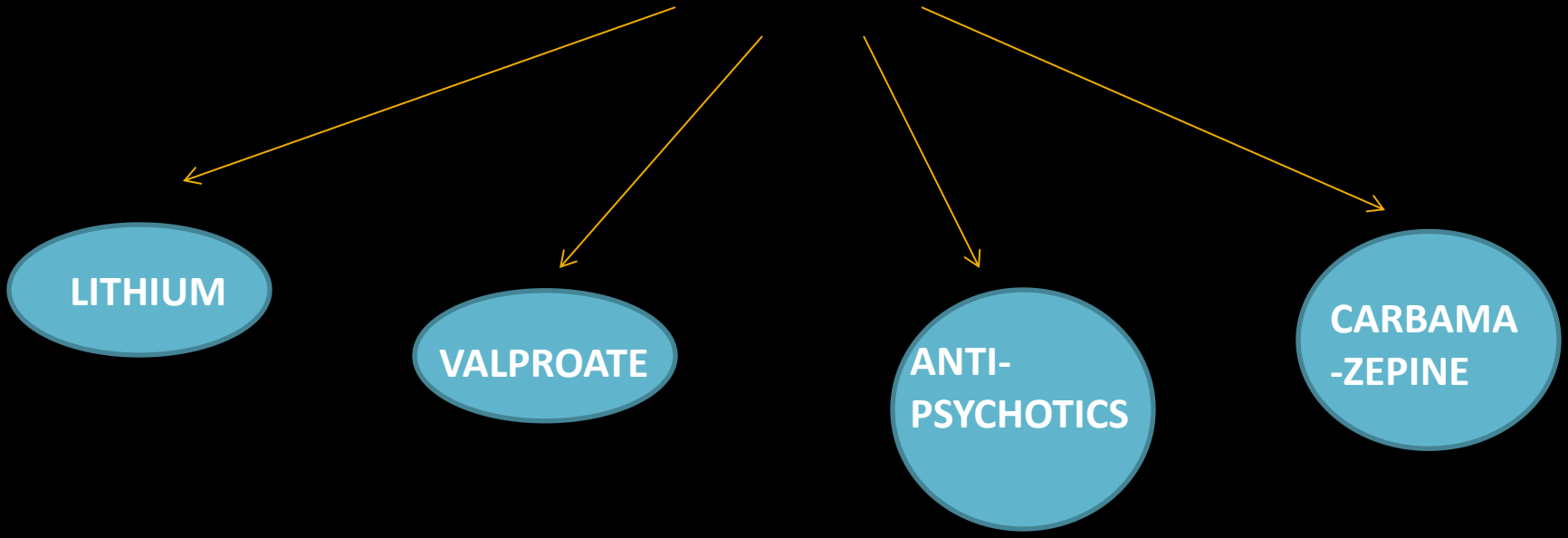
*Clozapine an exception

ACUTE MANIA



ACUTE MANIA

On anti -manic medications



ACUTE MANIA

LITHIUM or VALPROATE

- Check plasma levels
- Increase the dose to give levels 1.0–1.2 meq/L and 125 mg/L respectively
- And/or add an antipsychotic

CARBAMAZEPINE

- Add antipsychotic

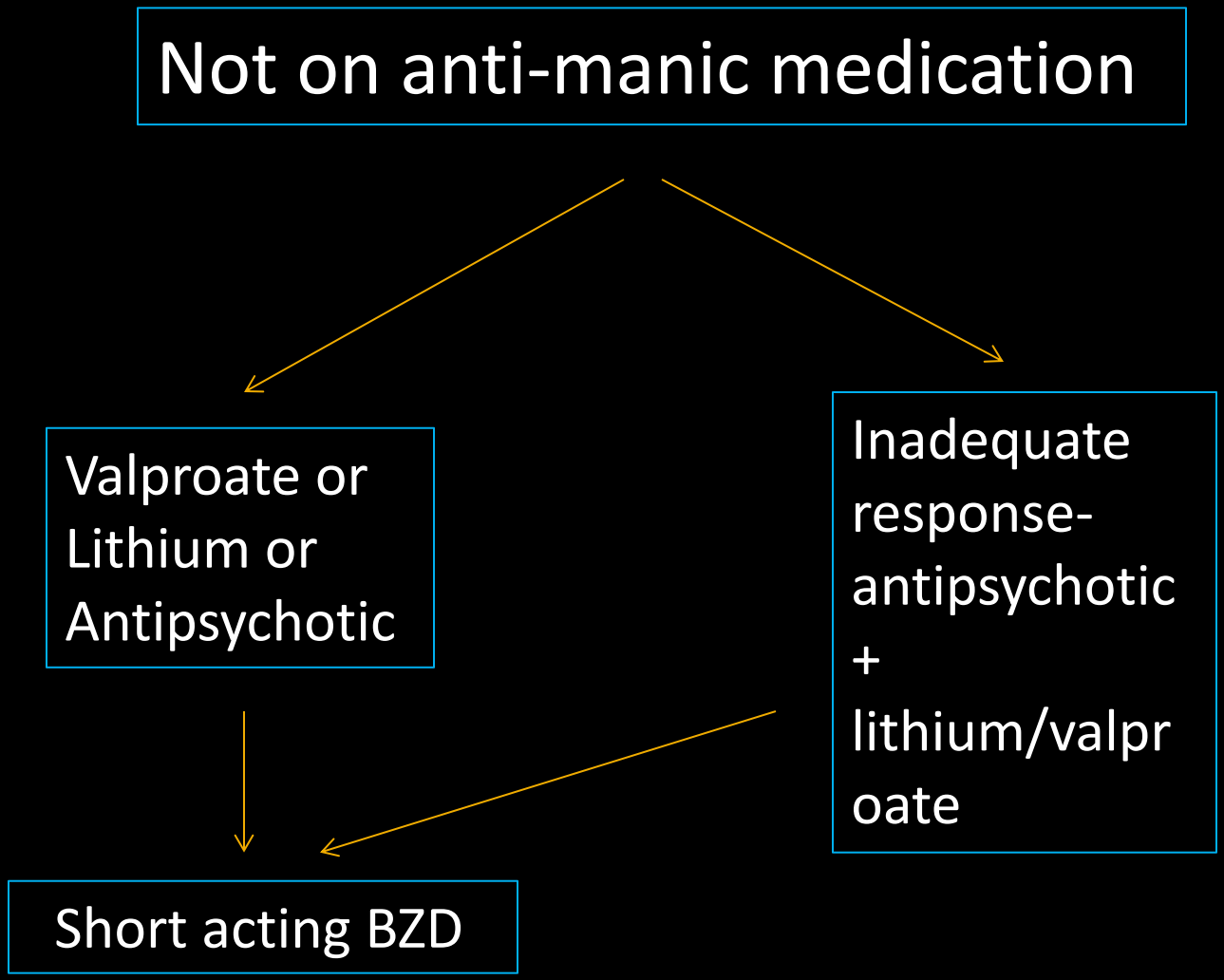
ACUTE MANIA

ANTIPSYCHOTICS

- Olanzapine, risperidone, quetiapine, aripiprazole, asenapine, ziprasidone, haloperidol(SGA>FGA)
- Check compliance and dose.
- Increase if necessary.
- Consider adding lithium or valproate.

➢ All patients- short acting benzodiazepines

ACUTE MANIA


Not on anti-manic medication
Valproate or Lithium or Antipsychotic
Inadequate response- antipsychotic + lithium/valproate
Short acting BZD

CHOICE OF DRUG

1. Clinical presentation

- Antipsychotics

➢ Acute agitation and aggressive behavior

➢ Equally effective in classical mania as well as those with mixed episodes.

➢ Continual exhibition of psychotic symptoms

ANTIPSYCHOTICS

Drug	Dose (mg)	Acute mania	Acute bipolar depression	Prophylaxis
Olanzapine	5-20	Yes	Yes	Yes
Risperidone	1-6	Yes	No data	Yes
Quetiapine	300-800	Yes	Yes	Yes
Ziprasidone	80-160	Yes	No	Yes
Aripiprazole	15-30	Yes	No	Yes
Paliperidone	6-12	Yes	No data	Yes
Asenapine	10-20	Yes	No data	Yes
Lurasidone	40-120	No data	Yes	Studies underway
Cariprazine	3-12	Yes	Yes	No data

CHOICE OF DRUG

- Valproate
  - Dysphoric/irritable mania,
  - Mixed features
  - Comorbid alcohol or substance abuse
  - Brain trauma
  - Multiple episodes
  - Avoid in women of child-bearing age

VALPROATE

Indications	Mania, hypomania, bipolar depression and prophylaxis of bipolar affective disorder May reduce aggression in a range of psychiatric disorders (data weak) Note that sodium valproate is licensed only for epilepsy and semi-sodium valproate only for acute mania
Pre-valproate work up	FBC and LFTs. Baseline measure of weight desirable
Prescribing	Titrate dose upwards against response and side-effects. Loading doses can be used and are generally well tolerated Note that controlled release sodium valproate (Epilim Chrono) can be given once daily. All other formulations must be administered at least twice daily Plasma levels can be used to ensure adequate dosing and treatment compliance. Blood should be taken immediately before the next dose
Monitoring	FBC and LFTs if clinically indicated Weight (or BMI)
Stopping	Reduce slowly over at least 1 month

CHOICE OF DRUG

- Lithium-

➢ Classical grandiose euphoric mania
➢ Family history of positive response
➢ No history of prior episodes
➢ Suicidality
➢ Likely to continue
➢ Difficulties- rapid response, titration and monitoring

LITHIUM

Indications	**Mania, hypomania, prophylaxis of bipolar affective disorder and recurrent depression. Reduces aggression and suicidality**
Pre-lithium work up	e-GRF and TFTs. ECG recommended in patients who have risk factors for, or existing cardiovascular disease. Baseline measure of weight desirable
Prescribing	Start at 400 mg at night (200 mg in the elderly). Plasma level after 7 days, then 7 days after every dose change until the desired level is reached (0.4 mmol/L may be effective in unipolar depression, 0.6–1.0 mmol/L in bipolar illness, slightly higher levels in difficult to treat mania). Blood should be taken 12 hours after the last dose. Take care when prescribing liquid preparations to clearly specify the strength required
Monitoring	Plasma lithium every 6 months (more frequent monitoring is necessary in those prescribed interacting drugs, the elderly and those with established renal impairment or other relevant physical illness). e-GFR and TFTs every 6 months. Weight (or BMI) should also be monitored
Stopping	Reduce slowly over at least 1 month. Avoid incremental reductions in plasma levels of >0.2 mmol/L

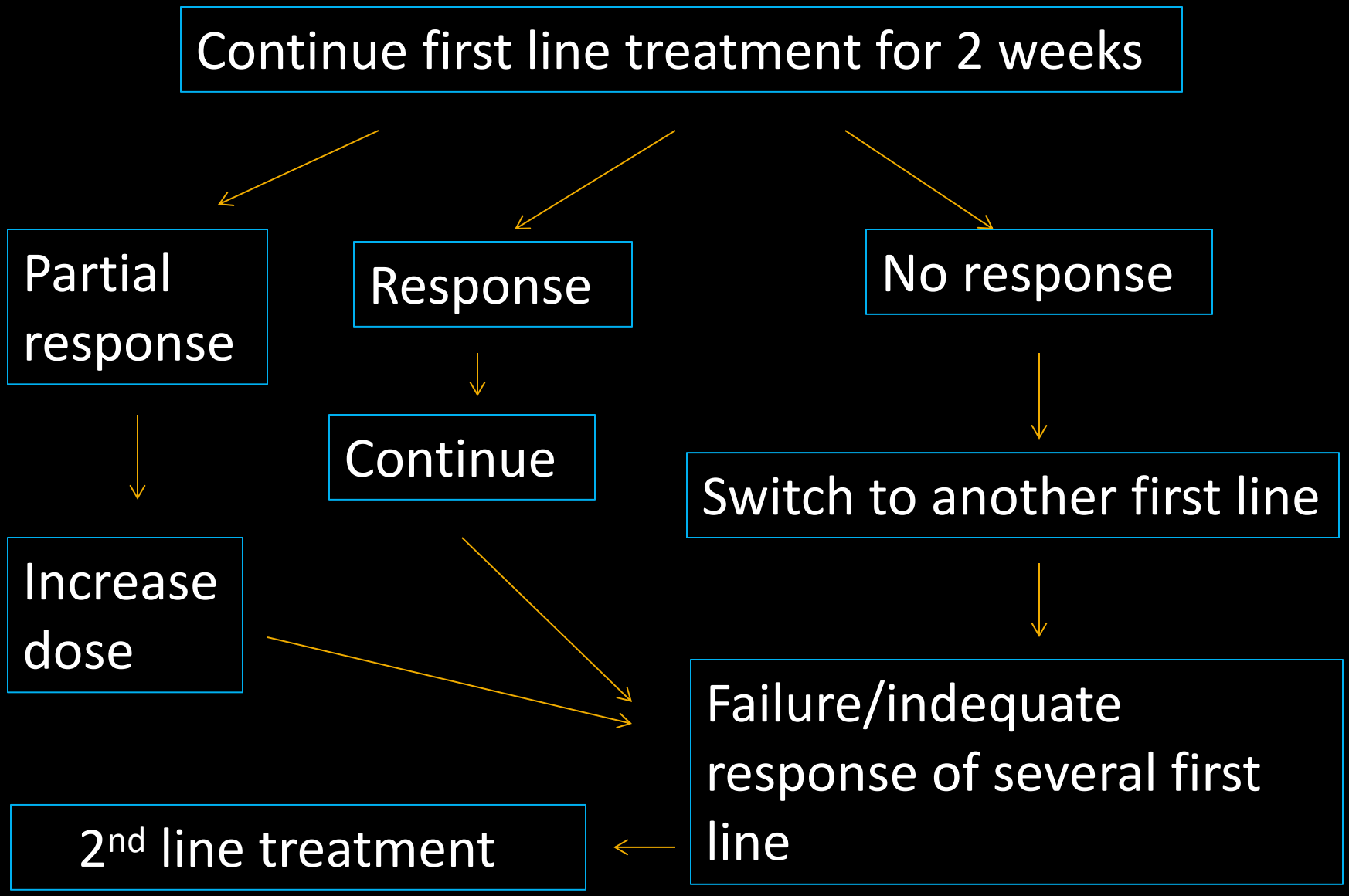
LITHIUM

- CANMAT- start at 900 mg/day and measure serum levels at 5 days

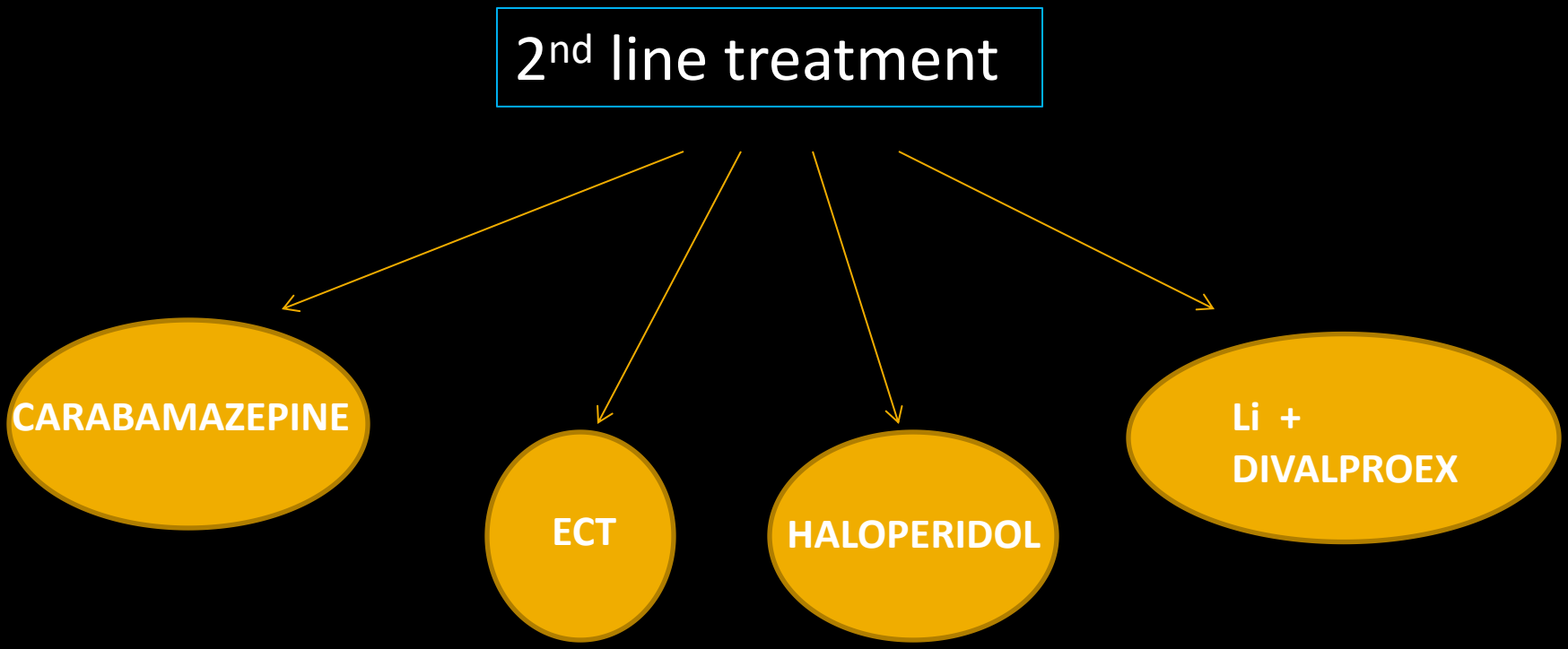
CHOICE OF DRUG

2. Previous history of response
3. Adverse drug profile
4. Patient choice

ACUTE MANIA


Continue first line treatment for 2 weeks
Partial response
Response
No response
Continue
Switch to another first line
Increase dose
Failure/indequate response of several first line
2nd line treatment

ACUTE MANIA


2nd line treatment
CARABAMAZEPINE
ECT
HALOPERIDOL
Li +
DIVALPROEX

ACUTE MANIA

- CARBAMAZEPINE
- Not well tolerated
- Induces its own metabolism
- TDM not required

CARBAMAZEPINE

Indications	Mania (not first line), bipolar depression (evidence weak), unipolar depression (evidence weak), and prophylaxis of bipolar disorder (third line after antipsychotics and valproate). Alcohol withdrawal (may be poorly tolerated) Carbamazepine is licensed for the treatment of bipolar illness in patients who do not respond to lithium
Pre-carbamazepine work up	U&Es, FBC and LFTs. Baseline measure of weight desirable
Prescribing	Titrate dose upwards against response and side effects; start with 100–200 mg bd and aim for 400 mg bd (some patients will require higher doses) Note that the modified release formulation (Tegretol Retard) can be given once to twice daily, is associated with less severe fluctuations in serum levels, and is generally better tolerated Plasma levels can be used to assure adequate dosing and treatment compliance. Blood should be taken immediately before the next dose. Carbamazepine induces its own metabolism; serum levels (if used) should be re-checked a month after an increase in dose
Monitoring	U&Es, FBC and LFTs if clinically indicated Weight (or BMI)
Stopping	Reduce slowly over at least 1 month

ACUTE MANIA

- ECT
- Believed to be highly effective
- Cognitive adverse event profile
- Only after failure of first-line
- First- line in:

1. Delirious mania
2. First trimester of pregnancy

ACUTE MANIA

- HALOPERIDOL
- Effective
- Switch to depression
- Drug induced extra-pyramidal symptoms
- Second line

ACUTE MANIA

- LITHIUM + VALPROATE
- Untested
- Refractive to monotherapy

ACUTE MANIA

- 3RD LINE TREATMENT
- Non-responder to 1st and 2 nd line
- FGA
- Clozapine

ACUTE MANIA

	Monotherapy	Combination Therapy
First Line	Lithium, Divalproex, Olanzapine, Risperidone, Quetiapine, Aripiprazole, Ziprasidone, Asenapine, Paliperidone, Cariprazine	Lithium/Divalproex + Risperidone/Quetiapine/ Olanzapine/Aripiprazole/ Asenapine
Second Line	Carbamazepine, ECT, Haloperidol	Lithium + Divalproex
Third Line	Chlorpromazine, Clozapine, Tamoxifen	Lithium/Divalproex + Haloperidol Lithium + Carbamzepine Adj. Tamoxifen
Not Recommended	Gabapentin, Topiramate, Lamotrigine, Verapamil, Tiagabine	Carbamazepine + Olanzapine/Risperidone

ACUTE MANIA

DRUG	START DOSE	UPTO
lithium	400 mg/day (900 mg/day)	Till plasma level- 08 to 1.2 meq/L
valproate	Semi-sodium – 250 mg tds Sodium valproate slow release- 500 mg/day Loading- 20-30 mg/kg/day	Titrate upwards to Plasma level more than 94 mg/L Regular- 20 mg/kg
aripiprazole	15 mg/day	30 mg/day
asenapine	5 mg bd	10 mg bd
olanzapine	10 mg/day	15-20 mg/day
risperidone	2 to 3 mg/day	6 mg/day
quetiapine	IR- 100 mg/day ER- 300 mg/day	IR- 800 mg/day ER- 600 mg/day on day 2
haloperidol	5-10 mg/day	15 mg/day
lorazepam		4 mg/day
clonazepam		8 mg/day

ACUTE MANIA

- OTHER POSSIBLE TREATMENTS

1. Allopurinol- effective on addition to lithium in one rct
2. Gabapentin, lamotrigine, levetiracetam, topiramate- not recommended
3. Tamoxifen- 80 mg/day when added to lithium proved effective in studies

ACUTE MANIA

4. Verapamil- mixed results n trials
5. Nimodipine- effective in small trials
6. Ritanserin, tryptophan depletion- supported by single RCT
7. Calcitonin- initially thought to be effective but recent trial proved otherwise

BPAD- DEPRESSION

ACUTE DEPRESSION

- Goals-

1. Achieve full remission of current episode
2. Avoiding switch
3. Preventing relapse

- Assess suicidal risk
- Adjunctive psychosocial interventions

ACUTE DEPRESSION

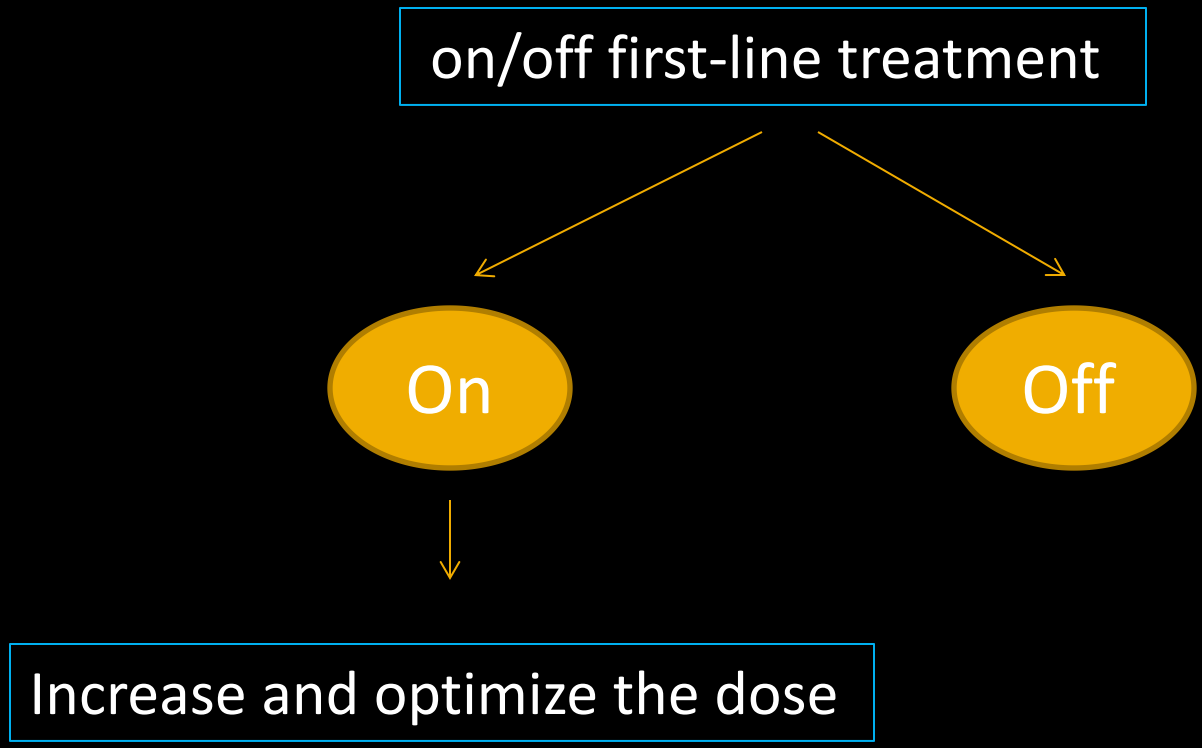
- Controversies in selection of treatment options:

1. lack of well-conducted trials and proven drug efficacy
2. long-term considerations.

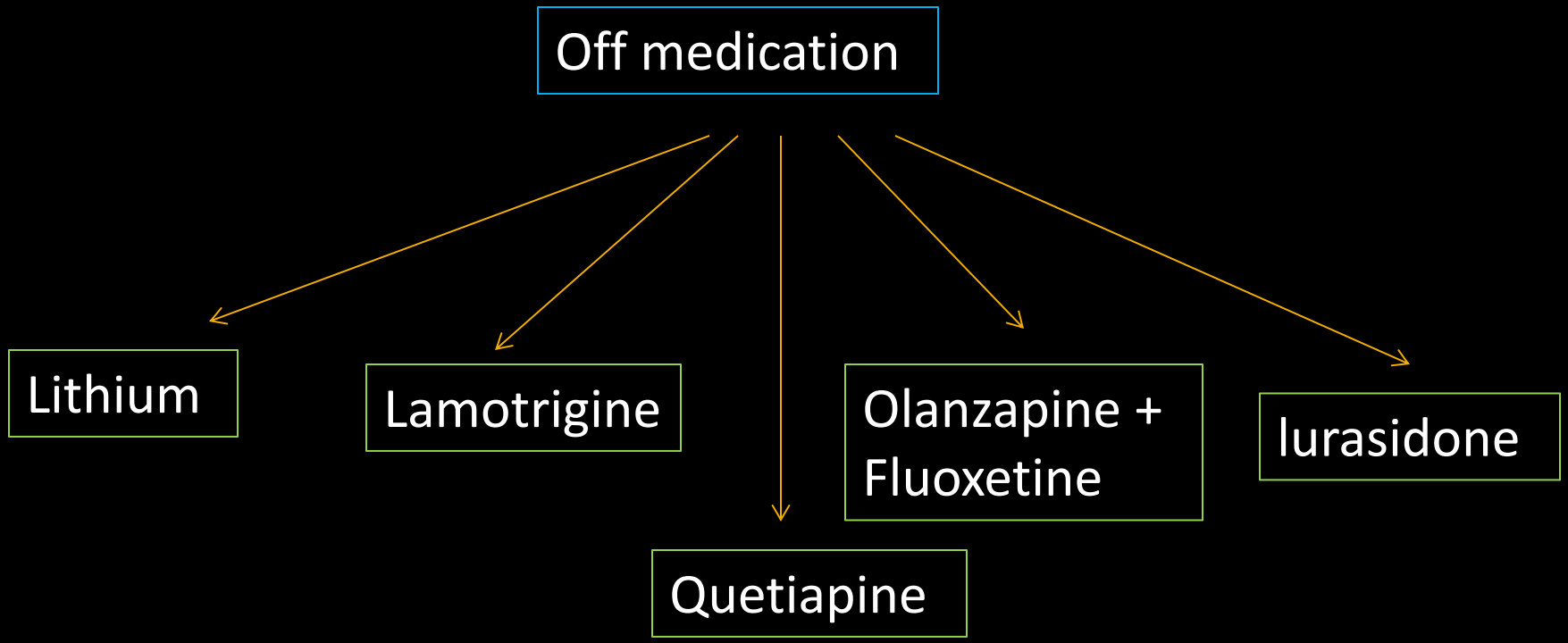
ACUTE DEPRESSION

	APA	NICE	CANMAAT
1st line	• Lithium • Lamotrigine • Lithium+ anti-depressant	• Olanzapine + fluoxetine • Alternative first-line - quetiapine, olanzapine, lurasidone, lamotrigine valproate.	• Quetiapine • Lithium • Lurasidone • Lamotrigine • Lurasidone+ lithium/valproate • Adjunctive lamotrigine

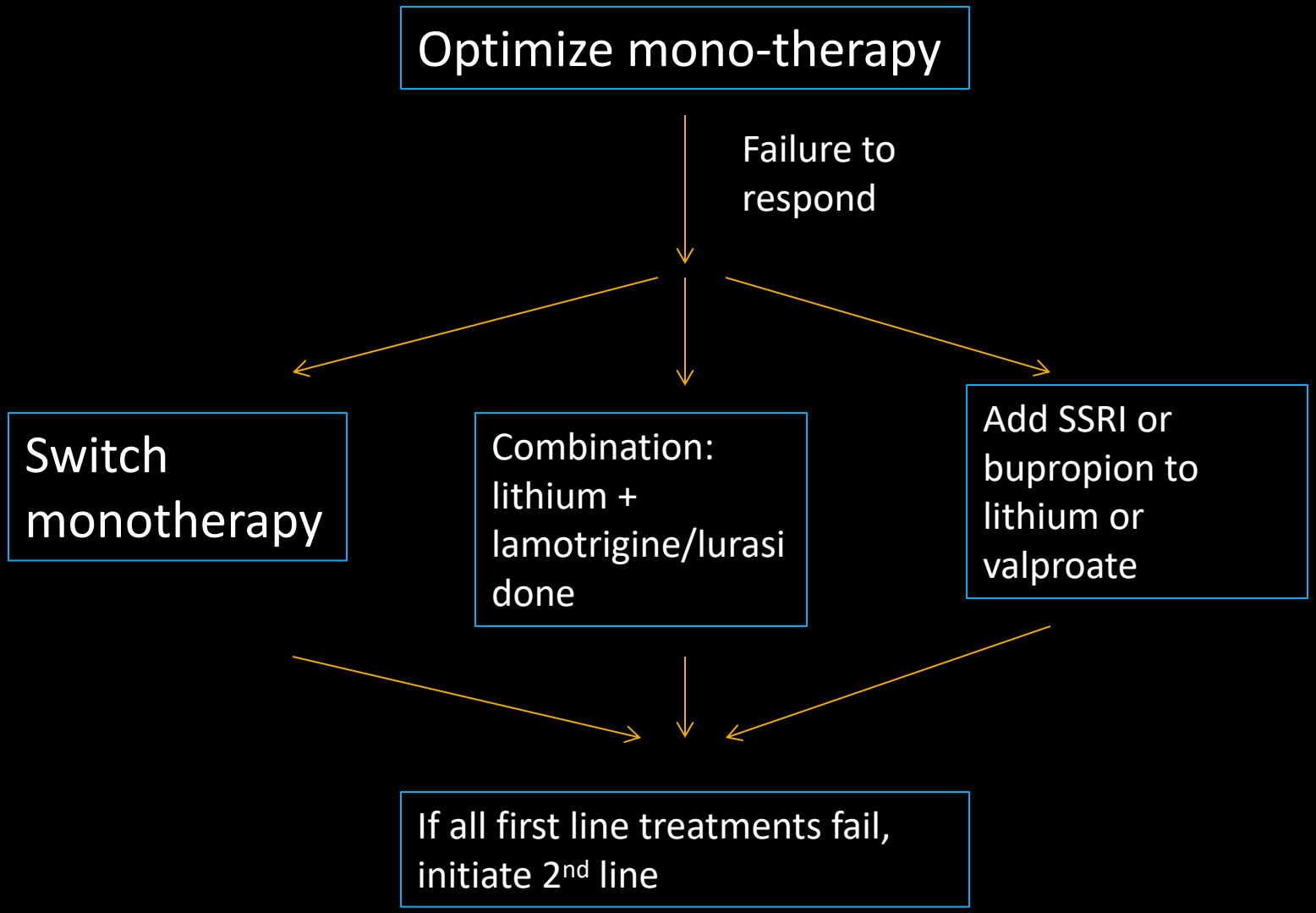
ACUTE DEPRESSION



ACUTE DEPRESSION



ACUTE DEPRESSION



ACUTE DEPRESSION

CHOICE OF DRUGS

1. LITHIUM

- History of classical manic episodes
- Course of mania, depression, and euthymia pattern
- Family history of bipolar disorder

- Serum levels- >= 0.8 meq/L

ACUTE DEPRESSION

2. LAMOTRIGINE

- Frequent depressions and infrequent mild manias
- Treatment + prophylaxis
- No switching/ rapid cycling
- Skin rash- slow upward titration
- Dose-50-200 mg/day. In USA mean dose of 250 mg/day with highest of 1200 mmg/day
- Not appropriate for severely depressed patients

ACUTE DEPRESSION

3. QUETIAPINE

- Frequent depressions as well as manic episodes
- Relapse prevention
- Reverse vegetative symptoms- worsen hypersomnia and hyperphagia
- Dose- 300-600 mg/day

ACUTE DEPRESSION

4. OLANZAPINE + FLUOXETINE

- Depression with psychotic features
- Dose- 5/20- 10/40 mg/day
- First-line and most effective according to NICE

5. LURASIDONE

- Weight neutral
- Prefer in combination

ACUTE DEPRESSION

6. ANTI- DEPRESSANTS

- Widely used by clinicians
- Avoid monotherapy
- Avoid TCA, MAOI, SNRI
- Avoid in history of rapid cycling /mixed features.
- Adjunctive to lithium/valproate

ACUTE DEPRESSION

- STEP BD- continuation of antidepressant therapy was associated with a trend toward less depressive symptom burden without increasing manic/hypomanic symptoms.
- Recent meta-analysis- manic switch higher with anti-depressants
- Anti-depressants can be tapered and discontinued 8 weeks after remission
- Weigh pros and cons of continuation

ACUTE DEPRESSION

2ND AND 3RD LINE TREATMENT

- **ECT**- suicidality, treatment failure, psychotic symptoms, elderly, poor oral intake
- **Valproate**- mixed features, better tolerability
- **Cariprazine** (1.5 mg/day) and carbamazepine monotherapy

ACUTE DEPRESSION

- **Modafinil /armodafinil/ pramipexole** –
- Dose- 100mg/day, 150 mg/day and 1.7 mg/day respectively
- adjunctive in anergia, anhedonia, and hypersomnia.

- **Adjunctive EPA**(1-4 gm/day)- refractory cases

ACUTE DEPRESSION

- **NAC**- glutathione precursor, protects against oxidative stress
- 2g/day- improves depressive symptoms
- No tolerability issues

- **rTMS**- extensive literature supporting its efficacy

ACUTE DEPRESSION

	Monotherapy	Combination Therapy
First Line	Lithium, Lamotrigine, Quetiapine, Quetiapine XR, Lurasidone	Lithium/Divalproex + Lurasidone, SSRI, Bupropion Olanzapine + SSRI Lithium + Lamotrigine
Second Line	Divalproex, Cariprazone, Carbamazepine, Olanzapine, ECT	Adjunctive SSRI to Atypical AP Adj. modafinil/Pramipexole/EPA
Third Line		Lithium + Carbamazepine, Adjunctive NAC/rTMS
Not Recommended	**Gabapentin, Aripiprazole, Ziprasidone**	**Adj. Ziprasidone/Levetiracetam**

ACUTE DEPRESSION

- Other treatments

1. Ketamine-A single IV dose of 0.5 mg/kg is effective in refractory bipolar depression.

- Anti-suicidal, rapid improvement

2. Riluzole
3. Magnetic seizure therapy
5. Thyroxine
6. Inositol

BPAD - PROPHYLAXIS

PROPHYLAXIS

NEED FOR PROPHYLAXIS

- Recurrent illness
- 90 %of patients have recurrence of a mood episode within 5 years
- Syndromal or subsyndromal symptoms 50 percent of the time with predominance of depressive symptoms

PROPHYLAXIS

GOALS

- Prevention of mood episodes
- Prevention of/improvement in subsyndromal symptoms,
- Prevention of suicidal behavior
- Improvement in treatment adherence, quality of life, cognitive, social, and work function.

PROPHYLAXIS

- Begin prophylaxis after first manic episode
- Treatment selection:

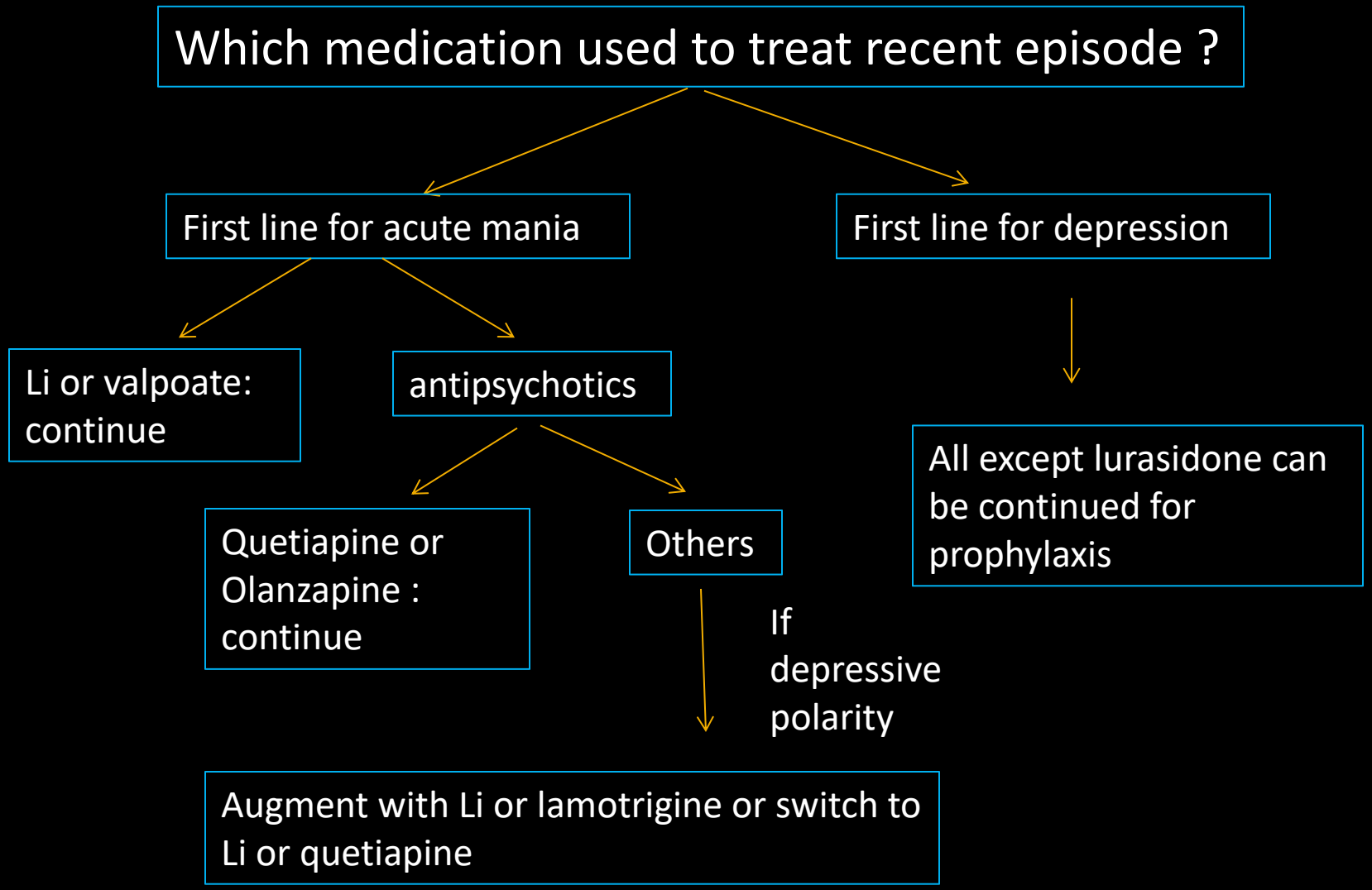
1. Course of the illness
2. Response and tolerability to previous treatments
3. Predominant polarity of the illness
4. Co-morbidity
5. Family history of response

- CBT, FFT, IPSRT

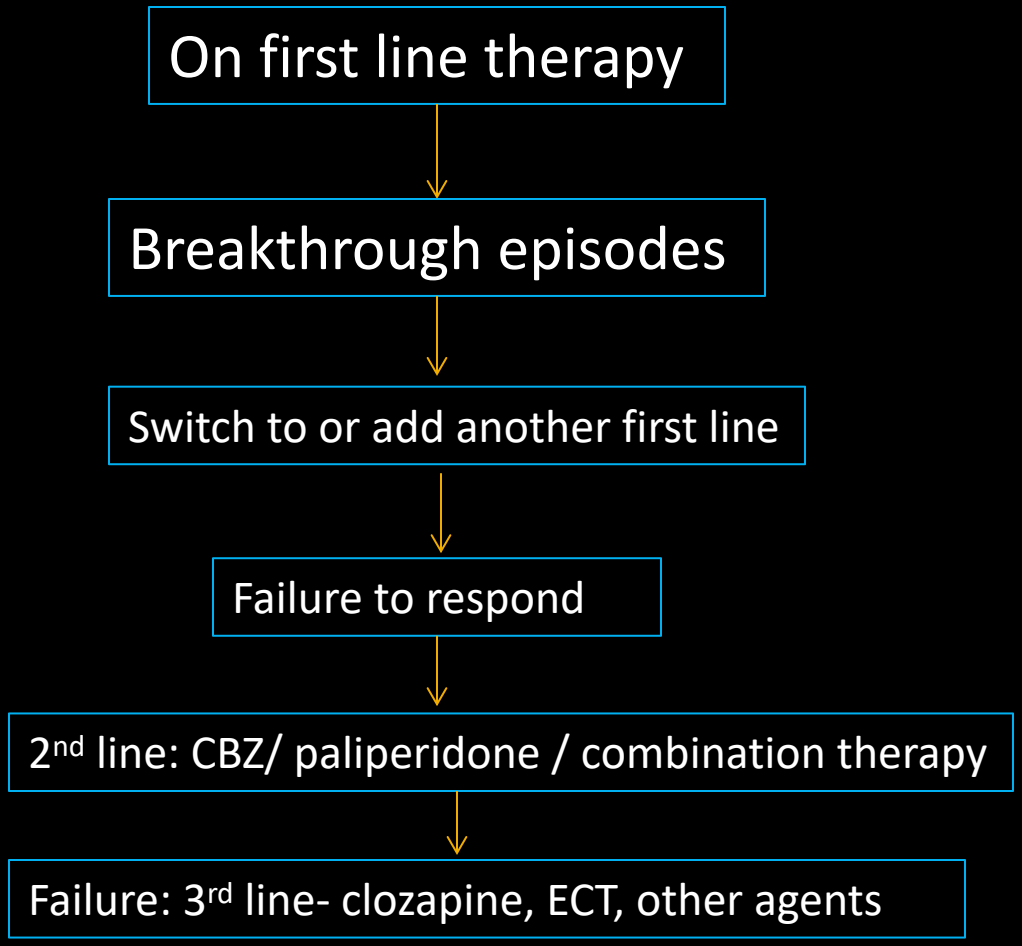
PROPHYLAXIS

	Monotherapy	Combination Therapy
First Line	Lithium, Lamotrigine (Limited Efficacy), Divalproex, Olanzapine, Quetiapine, Risperidone LAI (Prevention), Asenapine	Lithium/Divalproex + Quetiapine, Risperidone LAI, Aripiprazole, Ziprasidone
Second Line	Carbamazepine, Paliperidone	Lithium + Divalproex/Carbamazepine /Risperidone/ Lamotrigine Lithium/Divalproex + Olanzapine
Third Line	Ziprasidone, Risperidone	Clozapine, ECT, Omega 3-FA, Oxcarbazepine, Gabapentin
Not Recommended	**Gabapentin, Topiramate, Antidepressants**	**Flupenthixol**

PROPHYLAXIS



PROPHYLAXIS



PROPHYLAXIS

- **Lithium**- gold standard, 0.6-1.2 meq/L
- **Valproate**- initial doubts about its efficacy but recent studies show it is beneficial, same dose as for mania
- **Antipsychotics**- all atypical antipsychotics except olanzapine and quetiapine only prophylactic for mania.
- **Lamotrigine**- FDA approved, skin rash and SJ syndrome

PROPHYLAXIS

- NICE guidelines- lithium and lamotrigine as first choice with option for continuation of previous treatment at patient preference

BPAD II

- HYPOMANIA- discontinue antidepressants, if persistent symptoms treat with anti-manic agents
- DEPRESSION- quetiapine proven efficacy, others- lithium, lamotrigine, valproate, lurasidone.
- Adjunctive antidepressant use finds favour
- PROPHYLAXIS- lithium, lamotrigine, quetiapine, anti-depressants

RAPID CYCLERS

Step	Suggested treatment
1	**Withdraw antidepressants** in all patients[12–17] (some controversial evidence supports continuation of SSRIs[18,19])
2	**Evaluate possible precipitants** (e.g. alcohol, thyroid dysfunction, external stressors)[2]
3	**Optimise mood stabiliser treatment**[20–23] (using plasma levels), and **Consider combining mood stabilisers**, e.g. lithium + valproate; lithium + lamotrigine, or go to Step 4
4	**Consider other (usually adjunct) treatment options**: (alphabetical order; preferred treatment options in bold) **Aripiprazole**[24,25] (15–30 mg/day) Clozapine[26] (usual doses) Lamotrigine[27–29] (up to 225 mg/day) Levetiracetam[30] (up to 2000 mg/day) Nimodipine[31,32] (180 mg/day) **Olanzapine**[20] (usual doses) **Quetiapine**[33–36] (300–600 mg/day) Risperidone[37–39] (up to 6 mg/day) Thyroxine[40,41] (150–400 µg/day) Topiramate[42] (up to 300 mg/day)

BPAD AND PREGNANCY

- Warn about terarotogenic effects and encourage contraception
- Do not offer valproate in woman of reproductive age
- Genetic counselling

BPAD AND PREGNANCY

USA FDA SAFETY RATING FOR TERATOGENIC RISK

D	C	B
Lithium, CBZ, valproate	Risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, asenapine	Clozapine, lurasidone, lamotrigine

BPAD AND PREGNANCY

- Acute mania- haloperidol, lithium, ECT
- Acute depression- lamotrigine, quetiapine, olanzapine + fluoxetine, lithium
- Prophylaxis- Individual tailoring, Offer options and weigh risk and benefits

BPAD IN CHILDREN AND ADOLESCENTS

GUIDELINES	YEAR	FIRST-LINE	SECOND-LINE
CABF	2005	Lithium/CBZ/valproate/olanzapine/risperidone	Alternative drug class/combination
NICE	2006	Atypical antipsychotic	Lithium+/-valproate
AACAP	2007	Lithium/valproate +/- atypical antipsychotics	Lamotrigine/olanzapine

SUMMARY

- Aim – complete remission of symptoms, prevent further episodes and intermorbid wellness
- Consensus on treatment of acute mania- lithium, divalproex and atypical anti-psychotics

SUMMARY

- Depressive episodes more common but few well established drugs and recommendations differ- lithium, lamotrigine, lurasidone, quetiapine, olanzapine, divalproex
- Lithium has stood test of time- gold standard for prophylaxis
- Choice of drugs- therapy tailored to individual patients

REFERENCES

- Sadock, Benjamin J.; Sadock, Virginia A.; Ruiz, Pedro Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 10th Edition 2017 Wolters Kluwer

- David M. Taylor, Thomas R. E. Barnes, Allan H. Young. The Maudsley prescribing guidelines in psychiatry. 13th edition 2018 John Wiley & Sons

- National Institute for Health and Care Excellence. Bipolar disorder: assessment and management. Clinical Guideline 185, 2014; last updated February 2016.
  https://www.nice.org.uk/guidance/cg185.

REFERENCES

- Healy D. Mania: A short history of bipolar disorder. JHU Press; 2008 May 22.
- American Psychiatric Association. American Psychiatric Association Practice Guidelines for the treatment of psychiatric disorders: compendium 2006. American Psychiatric Pub; 2006.
- Cox JH, Seri S, Cavanna AE. Clinical Guidelines on Long-Term Pharmacotherapy for Bipolar Disorder in Children and Adolescents. Journal of clinical medicine. 2014 Jan 21;3(1):135-43.
- Epstein RA, Moore KM, Bobo WV. Treatment of bipolar disorders during pregnancy: maternal and fetal safety and challenges. Drug, healthcare and patient safety. 2015;7:7.

THANK YOU