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Selecting Antidepressant Drugs for Management of Depression in Primary Care (Part 1)

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Selecting Antidepressant Drugs for management of depression in Primary Care

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Declaration

- Janssen Group
- Eli Lilly
- Astra Zeneca
- Nicholas Piramal-Rosch
- Sun Pharma- India

- Consultant
- Advisor
- Drug trial coordinator
- Research Investigator
- Reviewer
- Speaker
- Educational Groups

Examples

Case scenario.1

- 42/M, single, Known case of Bipolar affective disorder was treated for number of years.
- Recovery reached a platue. Psychiatrist transferred the case into care of family physician and a CMHA case manager.
- After 4-5 years of remission, since last two weeks he became nervous, feeling lo, variability of his mood, loss of concentration.
- He was taking: Epival 500 mg BID PO, & Effexor XR 150 mg OD PO.
- He case to crisis service and crisis worker wants to review the medication.

Q1. how would you assess?
Q2. what investigations you would like to have?
Q3. What medications you would prescribe?

Case.2

- A 46 years , male , separated, working in health case industry, was transferred from general hospital after successful treatment of an overdose.
- He has no past history, no psychiatric treatment, never felt depressed, no previous attempt, no substance abuse.
- Started feeling depressed 4 weeks back because of pressure of girl friend, who refused to live with him is he remains connected with his ex -wife regarding any matter.
- Examination shows mild to moderate depression with disturbance of sleep, appetite, sadness of mood, no hypo manic or psychotic features.

Q1. What information you would gather?
Q2. What medication you would select?

Case.3

- 20 years female, delivered a baby 6 weeks back, she is in a group home. started feeling stressed, low, showing mood variability, irritability. Gets angry.
- Has a past H/O bipolar affective episode, ADHD, Conduct disorder, violence, substance abuse, was charged for violence, Court assessment suggested alcohol fetal syndrome with lower limits of intelligence.
- Had stopped medication 3 years back, was on Epival 500 mg BID and Quetiapine 300 mg HS
- She has been hospitalized for stabilization of mood.

Q1. what medication you will choose?

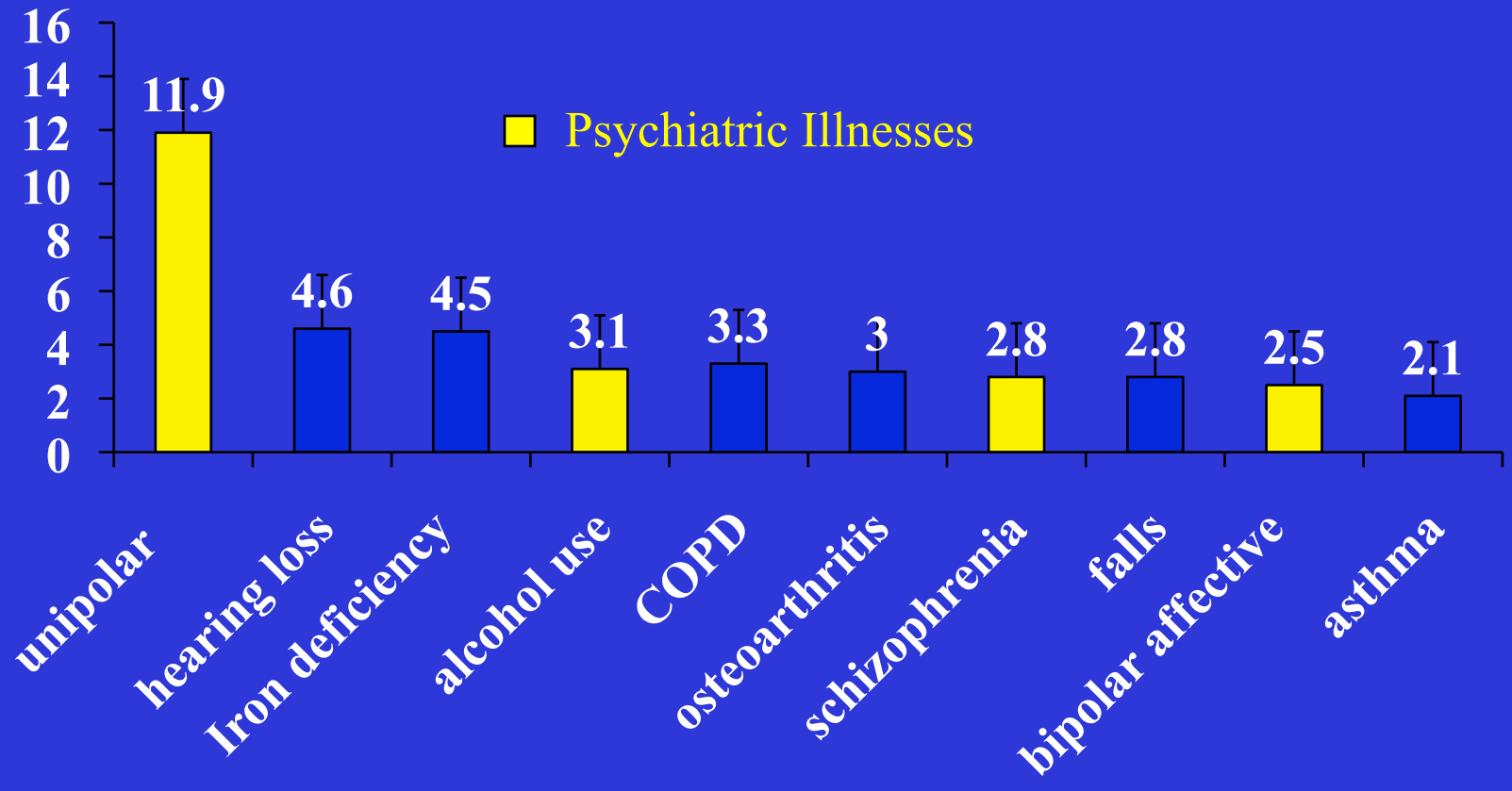
Case.4

- 30 year female , obese, came in the crisis services for feeling low and depressed.
- She has no previous episode, uses cannabis occasionally and drinks occasionally, depressive feeling is persisting since 1 year, which started soon after her move to a new city.
- She is in a relationship since 2 years and has moved with him, No family history of mental illness, alcoholism or suicide,
- She needs medication besides therapy

Q1. what medication you will choose?

Depressive disorder

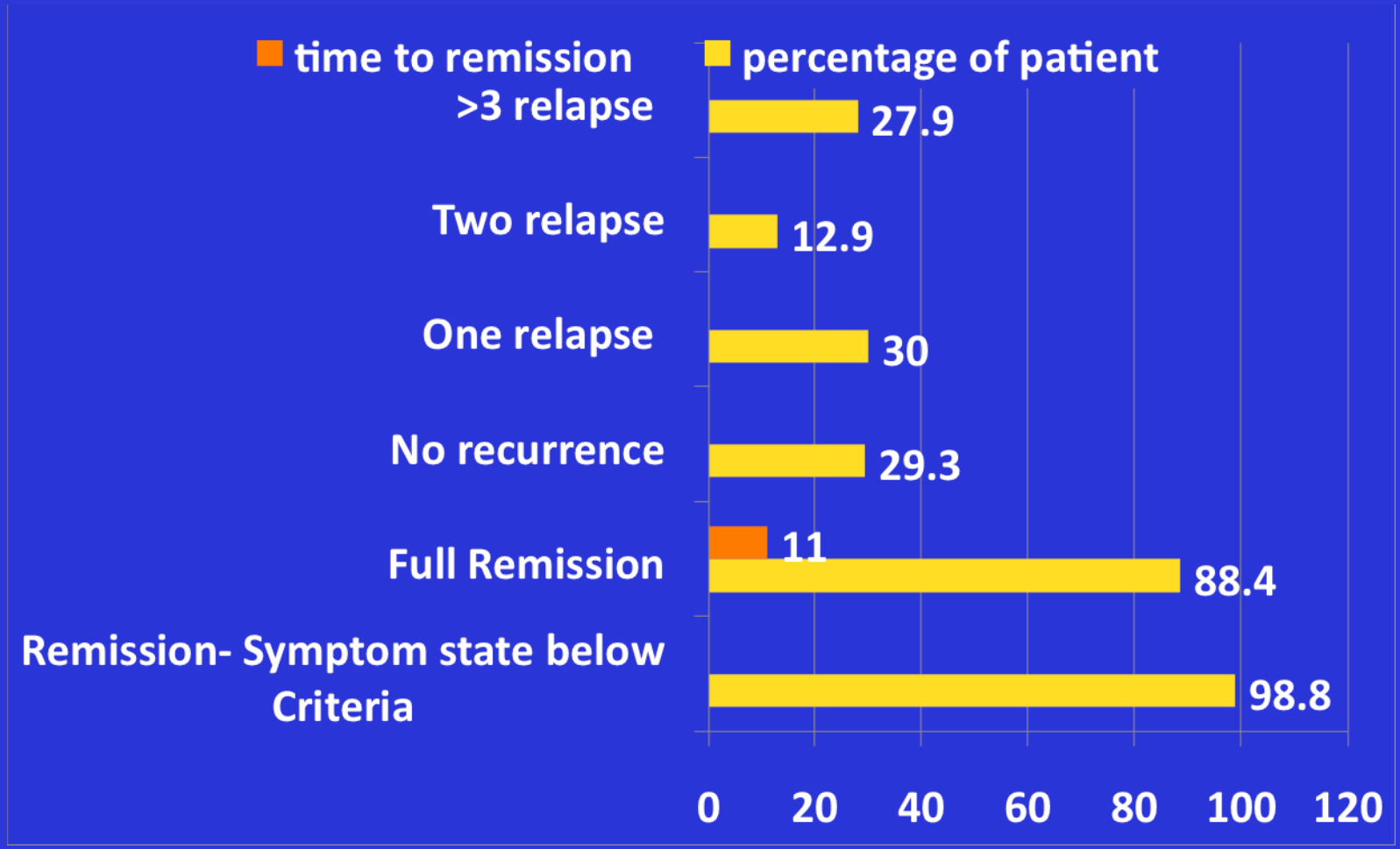
Years of life lived with disability (YLD)
Total ; Male + female TOP TEN CAUSES



Depressive Disorders: Some hard facts…

- Widely prevalent: 17% in general Population
- 10% Unipolar and 35% depression related- in General practice
- Leading cause of disability and YLD
- Projected as second leading cause of death, 2020, & 1 in 4 women will have depression
- Closely linked with suicide
- 1 million people die due to suicide and at least 6 million attempt world wide every year
- Occurs across all age spectrum
- Economic Burden in 83 Billion , about 40% from loss of productivity
- A major public health issue
- A major risk factor for cardio vascular illness
- Highest prevalence is in productive years of life
- A Recurrent, Chronic, relapsing illness
- A poorly identified, undertreated and Under-diagnosed condition
- Valuable advancement in understanding, causation and treatment has been made

Long-term outcome of major depressive disorder in psychiatric patients is variable. Current Status



Holma KM, J Clin Psychiatry. 2008 Feb;69(2):196-205.

Current comorbidity of psychiatric disorders among DSM-IV major depressive disorder

- **269 patients with a new episode of MDD were enrolled, Axis I and II comorbidity was assessed**
- **majority (79%) of patients with MDD suffered from 1 or more current comorbid mental disorders,**
- **anxiety disorder (57%),**
- **alcohol use disorder (25%),**
- **personality disorder (44%).**
- **Comorbid disorders are associated with sociodemographic factors,**
- **inpatient versus outpatient status,**
- **lifetime number of depressive episodes.**

Melartin TK, et al J Clin Psychiatry. 2002 Feb;63(2):126-34

Challenges and barriers in Treatment of Depression in Primary care

- Is the diagnosis in correct
- Is there any ‘Risk’
- Is the medication selection Correct
- Is the progress unsatisfactory
- Are there side effects
- Are there barriers to compliance
- Is there a need for non-pharmacological therapy
- Is the outcome satisfactory

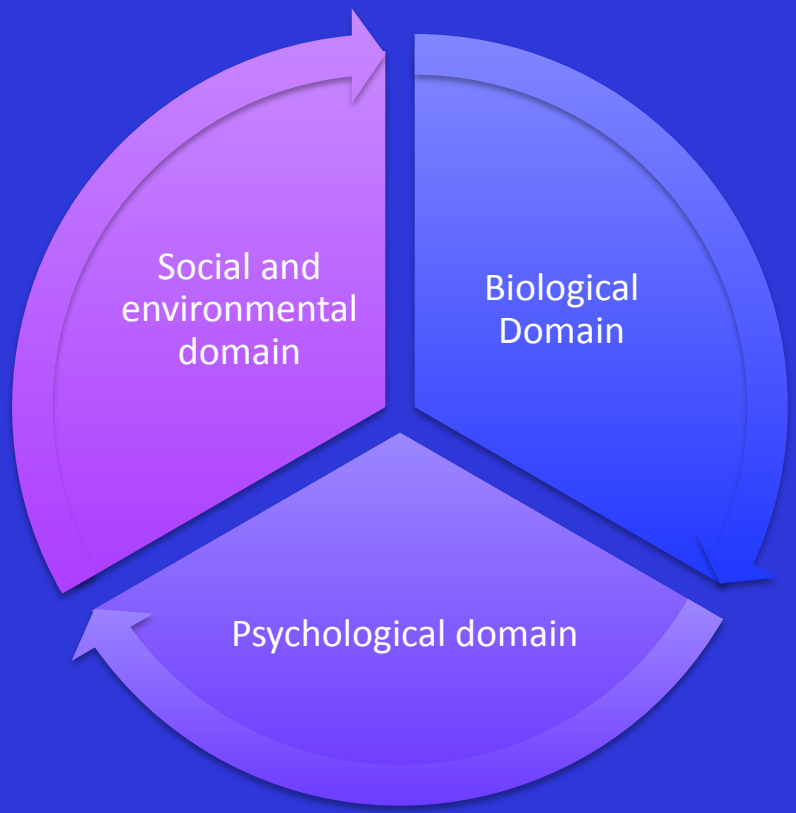
General principles

- Treatment needs to be targeted from where the disease originates.
- There are situations where medication is least effective.
- As far as possible treatment needs to be integrated.
- Continuity of Care
- Patient's education

Drug-Drug Interaction

High risk patients

Origin of depressive disorder



Dilemma of decisions in treatment of Depression in Clinical Practice

- **When to reduce the dose**
- **How long to treat**
- **Persisting symptoms?**
- **Limited functioning**
- **Dealing with disability**
- **Enhancing quality of life**
- **Treatment of side effects**
- **Appearance of medical complications**
- **'Break-through' Depression**
- **Recognizing 'depressive spectrum disorder'**

1.Bipolar spectrum, 2. Serotonin Spectrum, 3. OCD Spectrum, 4. ADHD Spectrum

Drug induced depression

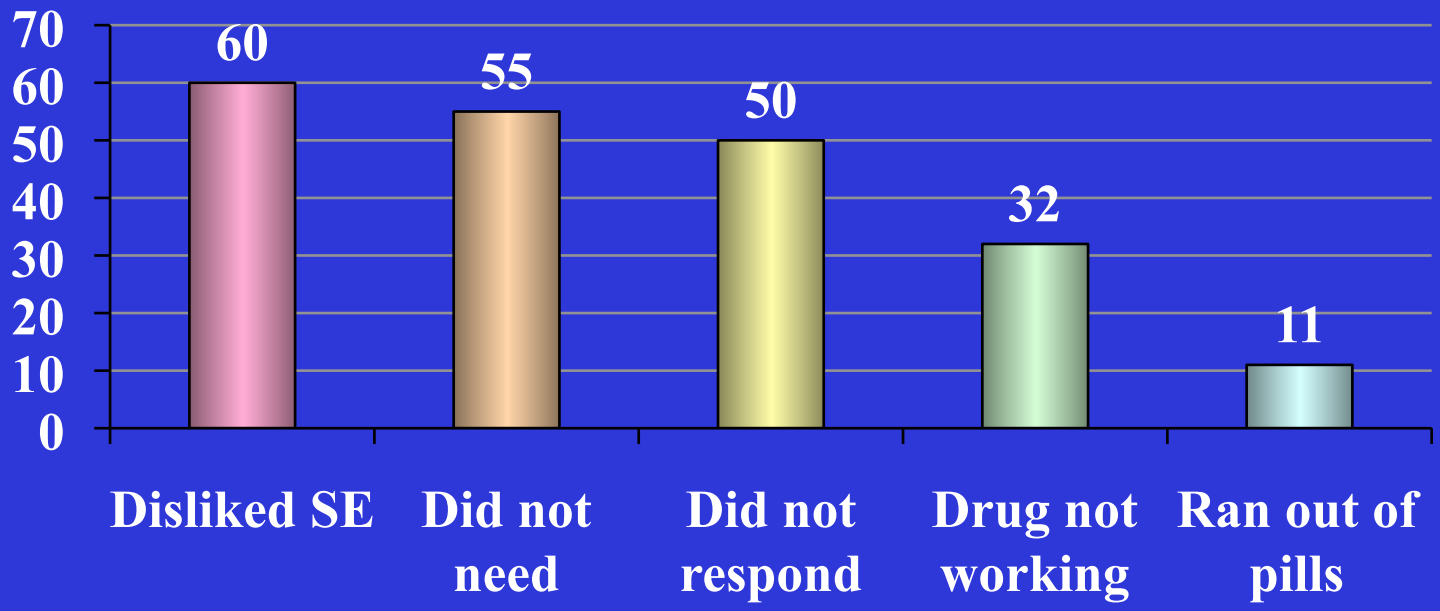
- **Costicosteroids**
- **Oral contraceptives**
- **Hormone therapy**
- **Cancer Chemotherapy**
- **Antipsychotics**
- **Levodopa / carbidopa**
- **Chloroquine**
- **Stimulants**

Drugs mostly precipitate depression in vulnerable candidates

Manifestation of depression in CNS disorders : reported incidence

- Parkinson’s : 40%
- Huntington's : 40%
- CVA : 30-50%
- MS : 10-50%
- Alzheimer’s : 15-55%

Common reason for discontinuation



Lin , Med Care 1995

All Anti Depressant Drugs have equal efficacy.

Current controversies.

They differ on pharmacology, mechanism of action, side effects and drug - drug interactions

Anti Depressant Drugs alone are not efficacious in treatment of moderate to severe depression

Do Drugs working on Different NT systems Differ in Outcome and efficacy?

- No
- N. Freemantle et al BJP 2000"
- 'Predictive value of Pharmacological activity for relative efficacy of ADD'

Current controversies.

Do ECT and Anti Depressant Drugs together, in maintenance treatment, prevent relapse?

- Yes
- Gerard G Gagne, BJP, 2000; 157, 1960-1965

Is there a risk of suicide with ADD?

- Yes,…Bridge JA, JAMA, 297, 2007 April……. but
- " Benefit of Anti Depressant Drugs appear to be much greater than risk from suicidal ideation/suicide attempts across indications…"

Current controversies.

Are Anti Depressant Drugs Beneficial ?

Data from FDA submitted trials?

- NO, …Kirch,I, PLoS Medicine Feb 2008
- Not in severe depression,& in short term trials,

What is efficacious in treatment of depression?

Current controversies.

- **Medication alone ----NO**
- **CBT , Psychotherapy alone----NO**
- **ECT alone—Yes, short term only**
- **Combination of ADD and CBT &/ psychotherapy-Yes**
- **Combination of ADD & ECT--Yes**

What decides good efficacy and outcome with Anti Depressant Drugs?

- Early intervention
- Patient selection – mild to moderate depression
- Pure depressions
- Dose selection
- Adequate duration
- Maintenance treatment
- Combining with CBT and Psychotherapy

Need for Action

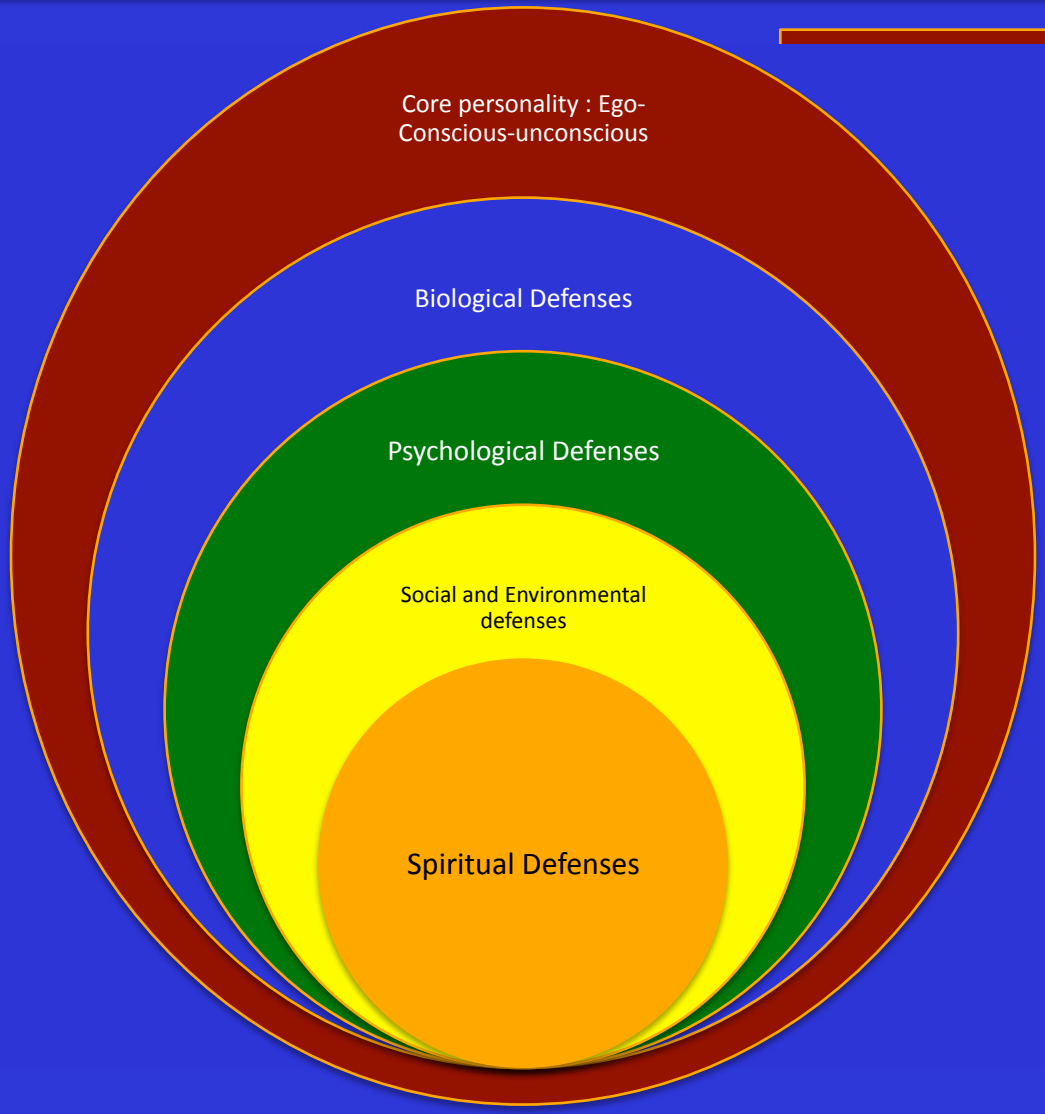
What decides poor outcome and efficacy with Anti Depressant Drugs?

- Chronicity
- Severity
- Medical & psychiatric Comobi
- Substance abuse
- Drug sensitivity
- Acceptance
- Compliance
- Early discontinuation
- Personality disorder
- Presence of psychosis

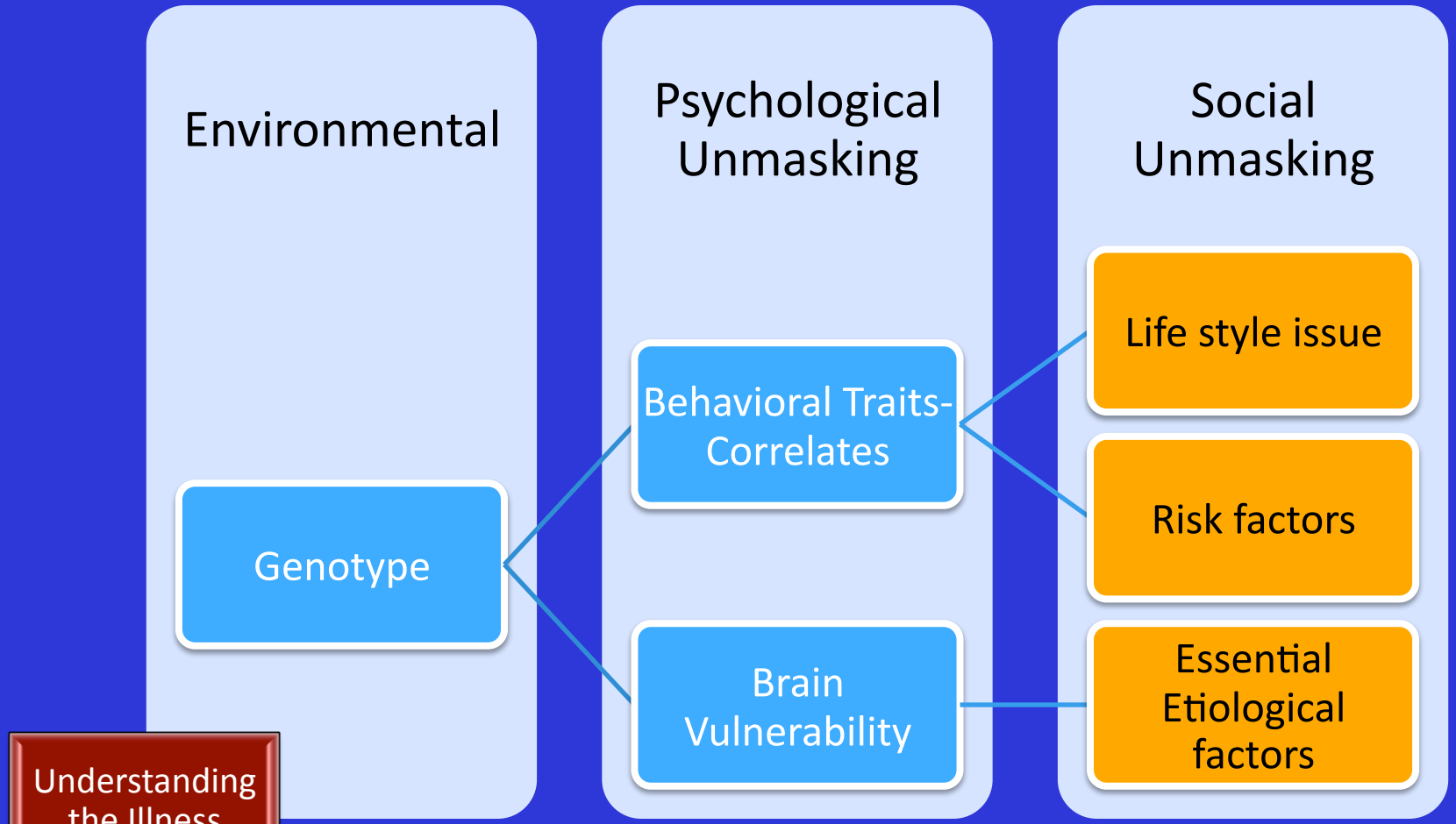
- Nature of illness- Cyclic , rapid cycling
- Family History- genetic Loading
- Tolerability
- Side effects
- Wrong diagnosis
- Inappropriate optimization

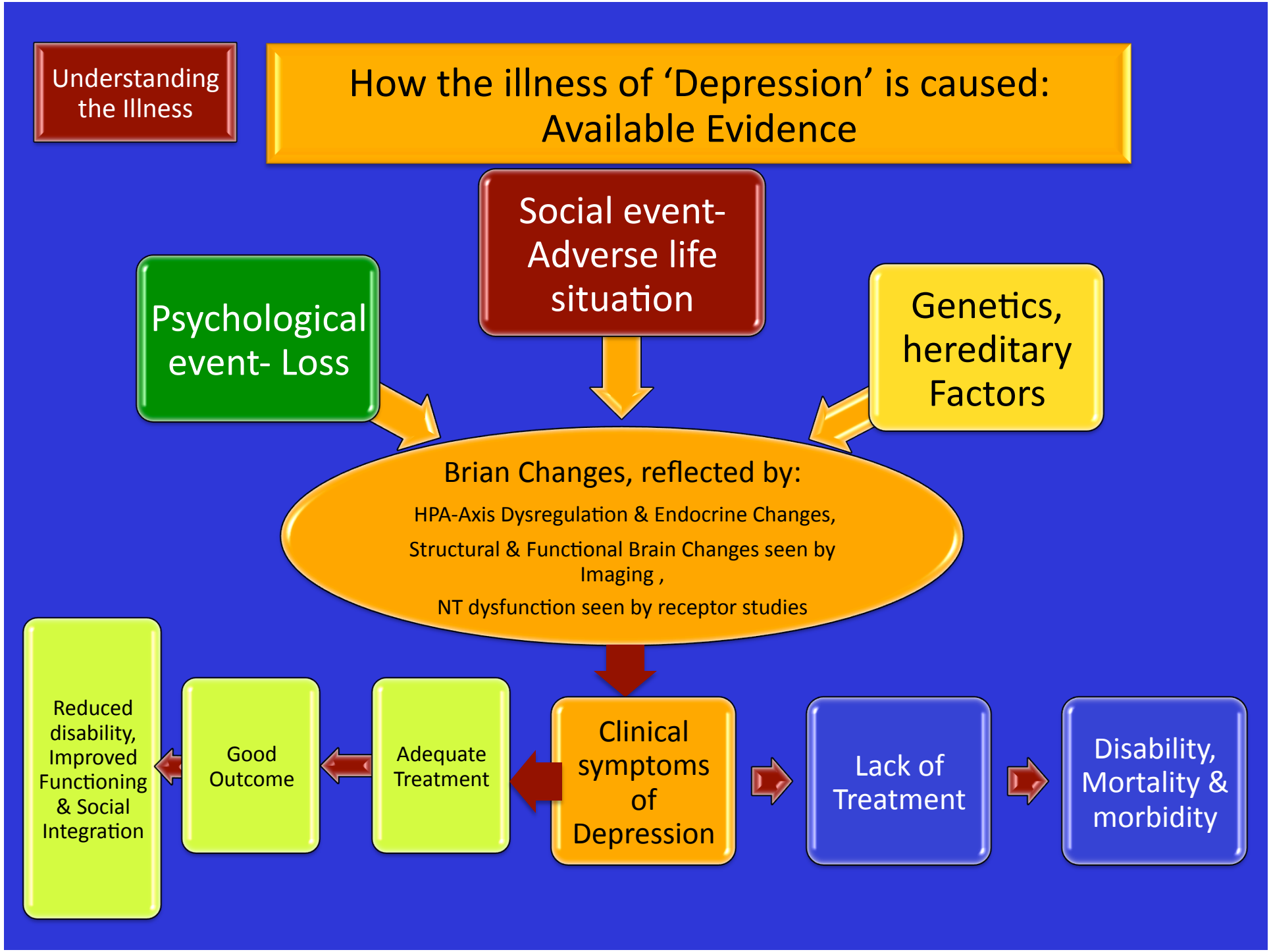
Need for Action

Understanding Personality, Defense mechanisms & Development of symptoms

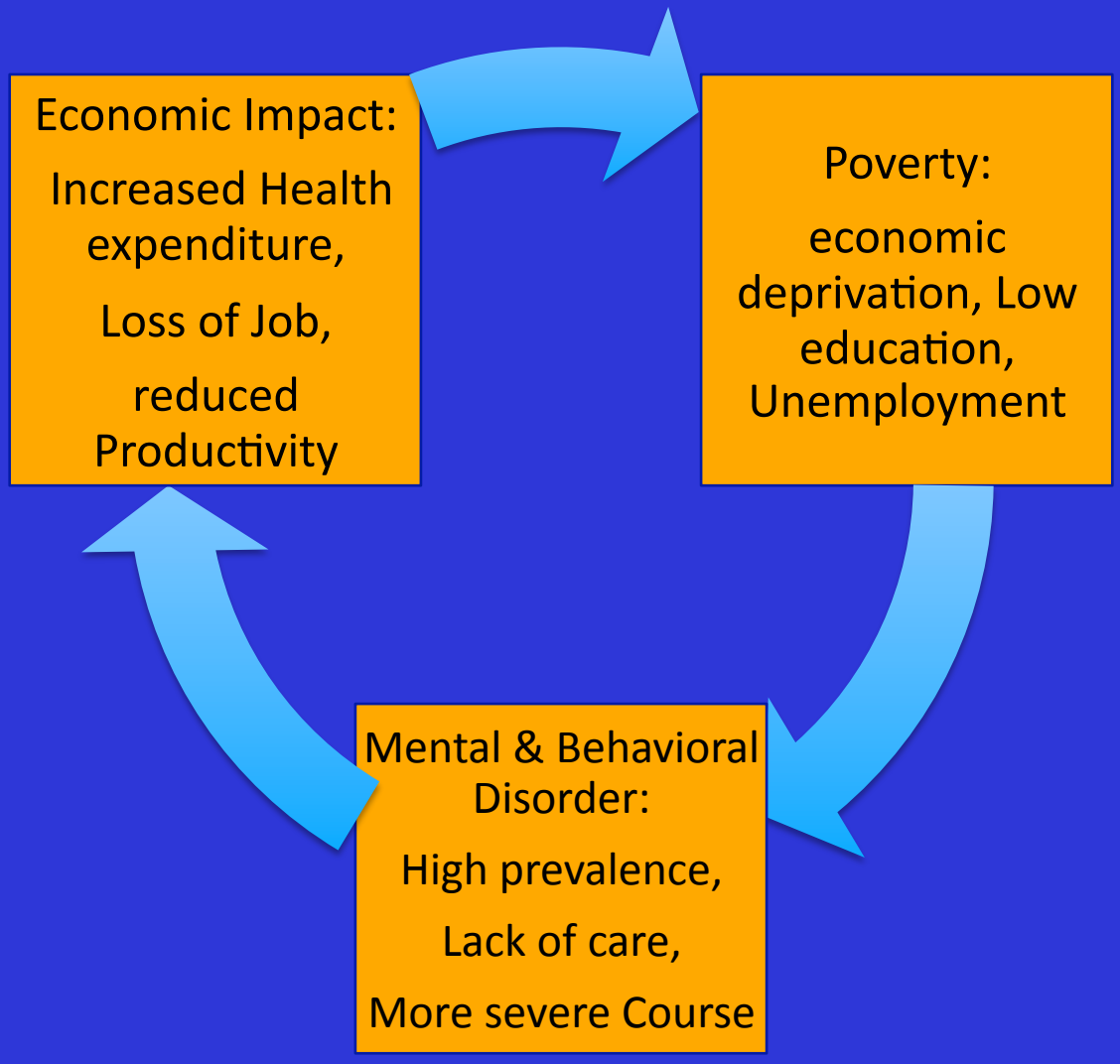


Symptom development and influence of ‘events’



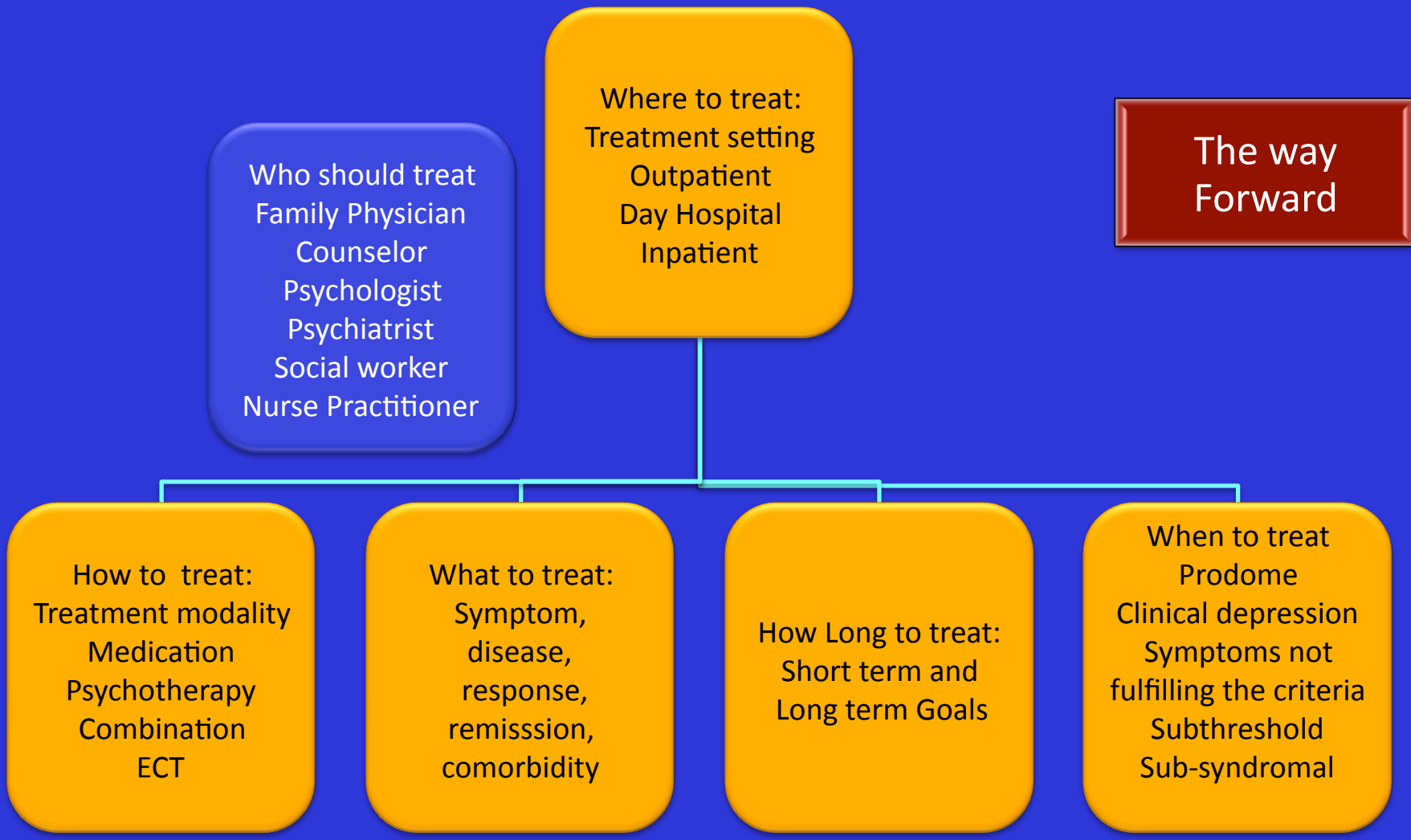

Understanding the Illness
How the illness of 'Depression' is caused: Available Evidence
Social event- Adverse life situation
Psychological event- Loss
Genetics, hereditary Factors
Brian Changes, reflected by:
HPA-Axis Dysregulation & Endocrine Changes,
Structural & Functional Brain Changes seen by Imaging ,
NT dysfunction seen by receptor studies
Clinical symptoms of Depression
Lack of Treatment
Disability, Mortality & morbidity
Adequate Treatment
Good Outcome
Reduced disability, Improved Functioning & Social Integration

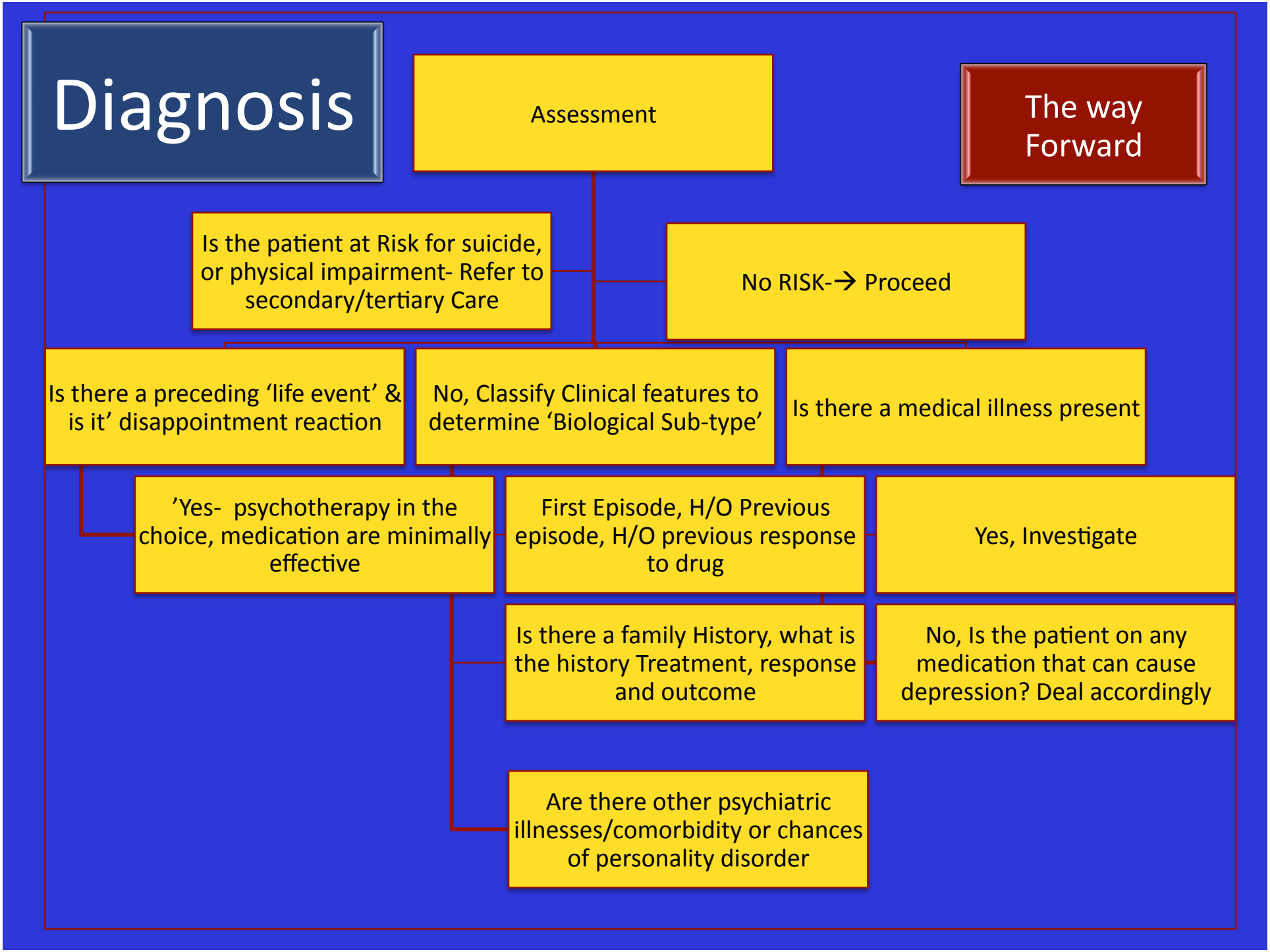
Social Factors and Social pathology in Mental disorders; WHR , WHO , 2001



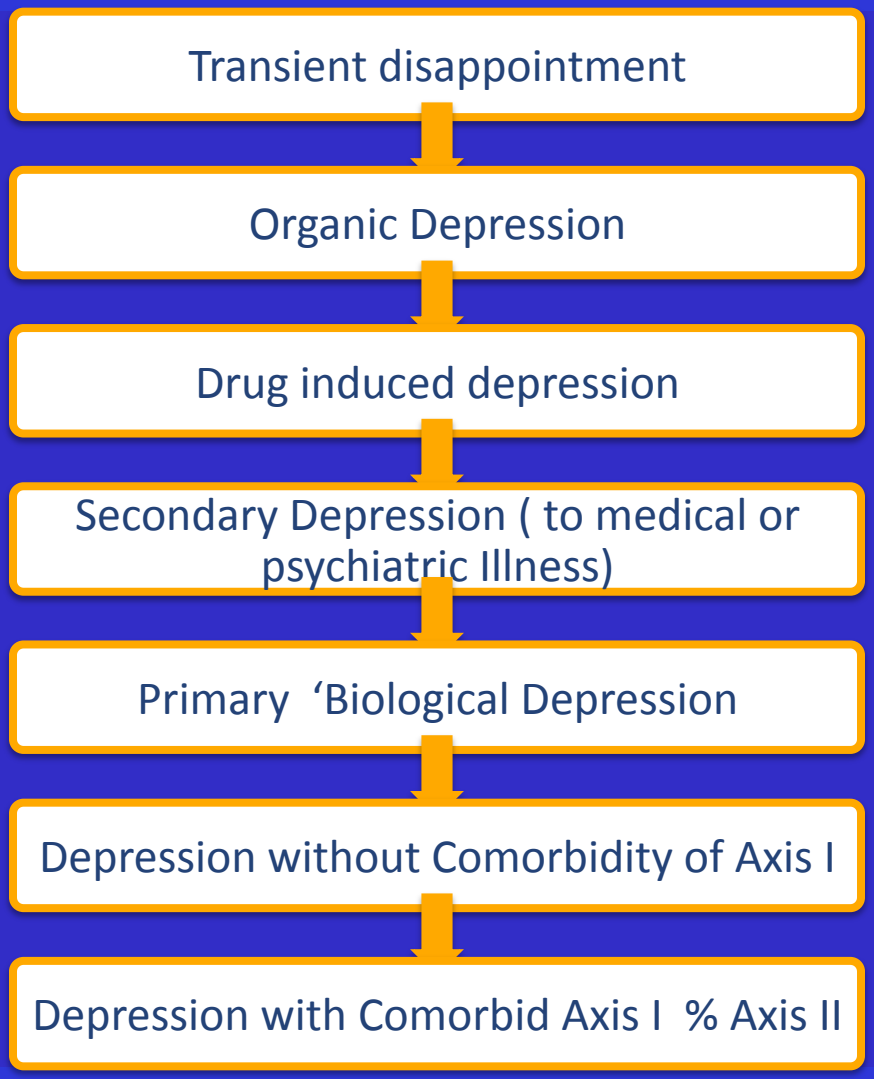
Understanding the Illness

Treatment Decisions




Diagnosis
Assessment
The way Forward
Is the patient at Risk for suicide, or physical impairment- Refer to secondary/tertiary Care
No RISK-→ Proceed
Is there a preceding 'life event' & is it' disappointment reaction
No, Classify Clinical features to determine 'Biological Sub-type'
Is there a medical illness present
'Yes- psychotherapy in the choice, medication are minimally effective
First Episode, H/O Previous episode, H/O previous response to drug
Yes, Investigate
Is there a family History, what is the history Treatment, response and outcome
No, Is the patient on any medication that can cause depression? Deal accordingly
Are there other psychiatric illnesses/comorbidity or chances of personality disorder

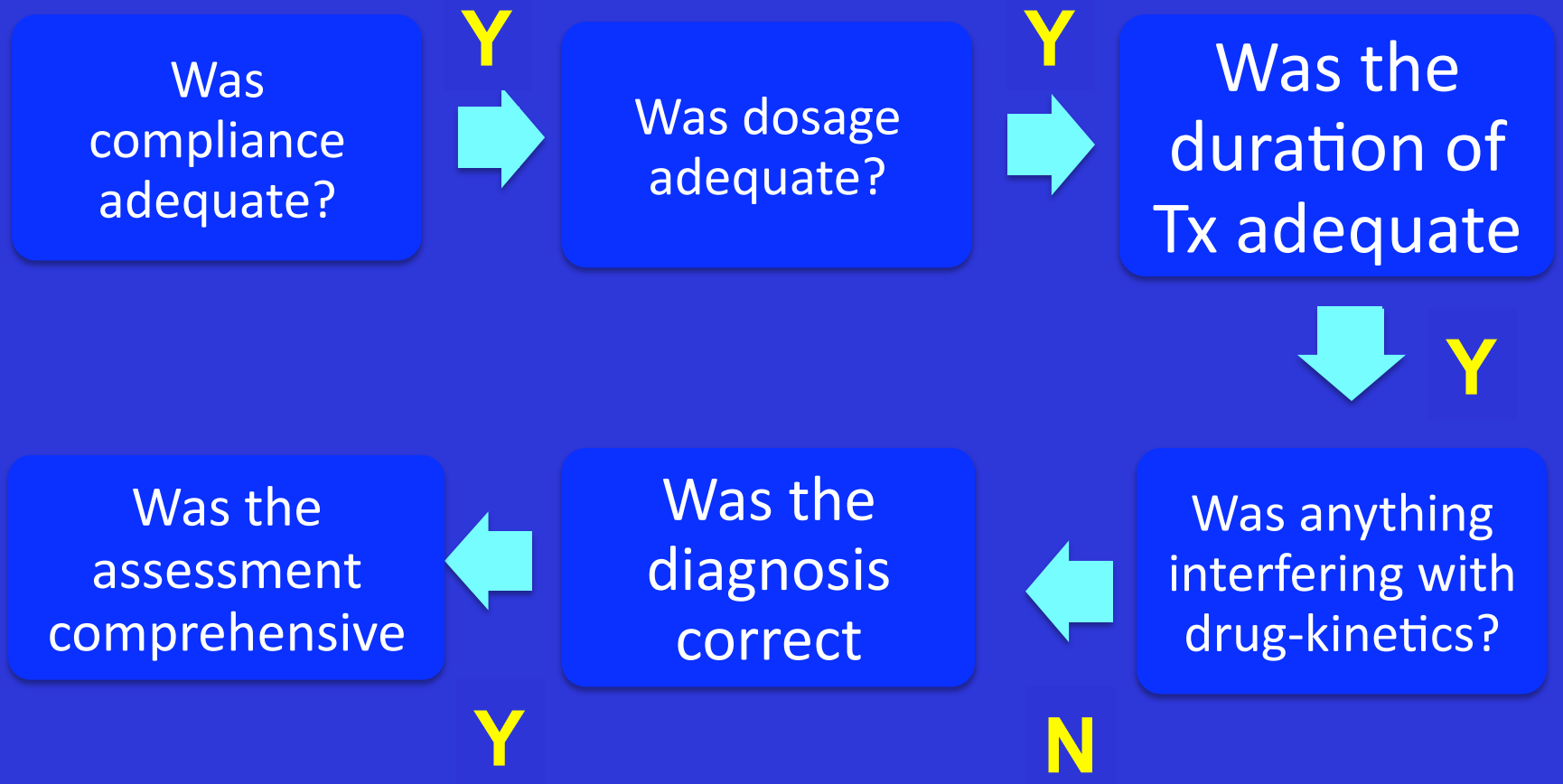
Differential Diagnosis: Key to Success



Depression Typology

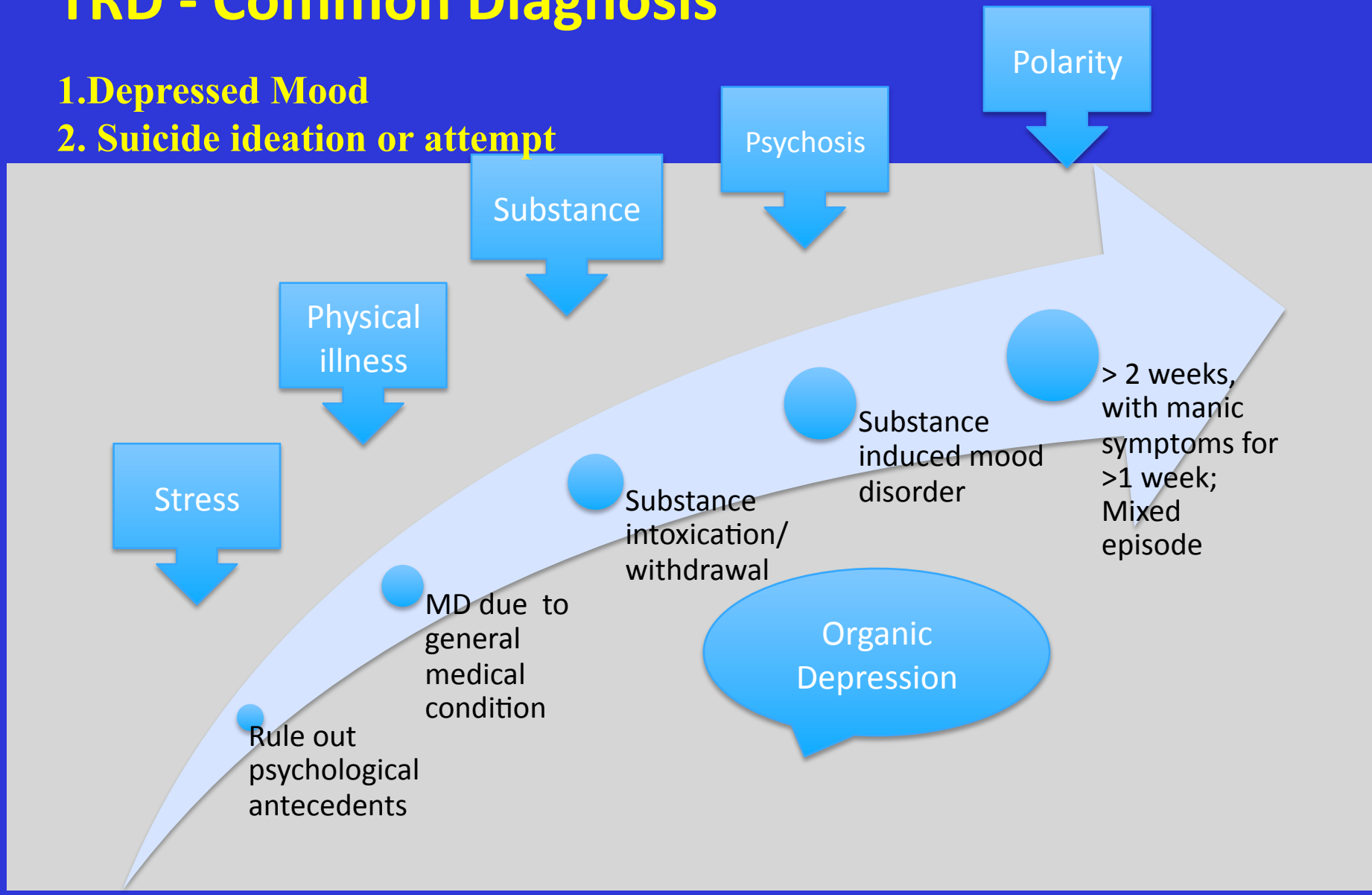
- Agitated depression
- Retarded Depression
- Melancholic-Psychotic depression
- Anxio-depressive state
- Young-Hostile depression
- Obsessive-Compulsive Depression
- Phobic Depression
- Panic Disorder
- Atypical depression
- Cyclic Depression
- Seasonal depression
- Characterological depression
- Pre-psychotic Depression
- Pre-menstrual

Diagnosing treatment resistance

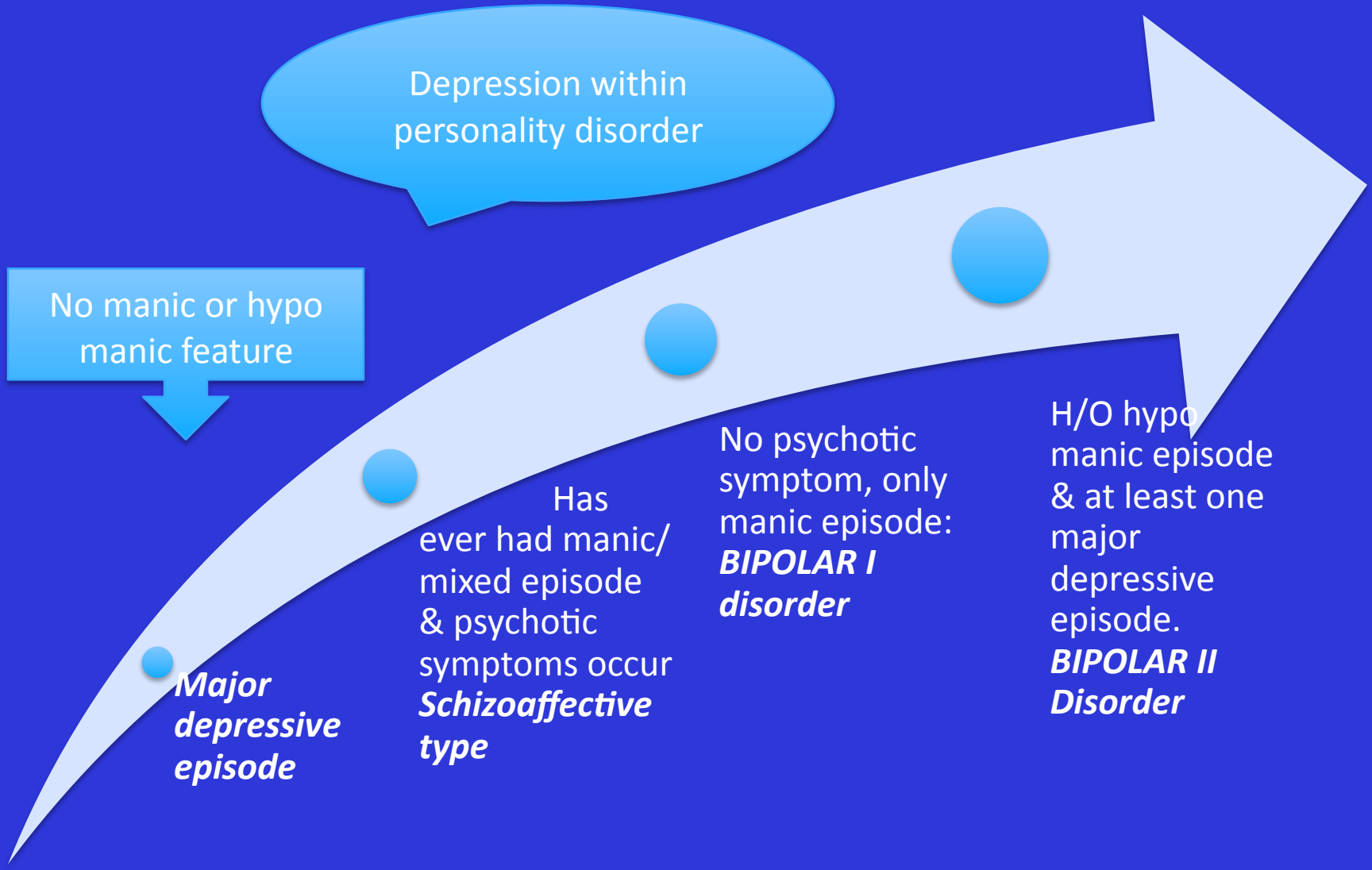


TRD - Common Diagnosis

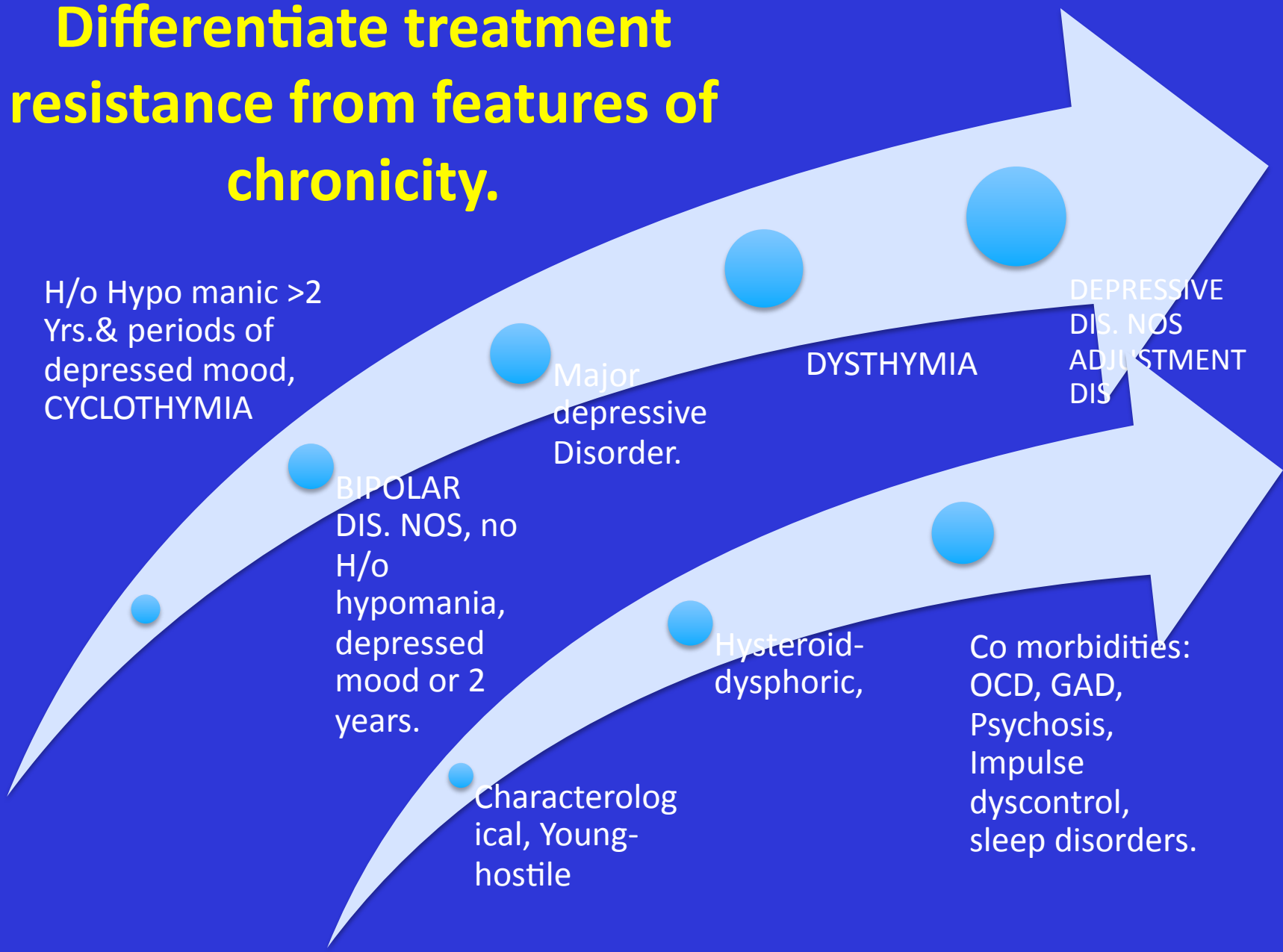
1.Depressed Mood
2. Suicide ideation or attempt



Focus on 'symptoms constellation '
exclusion of physical & psychiatric conditions

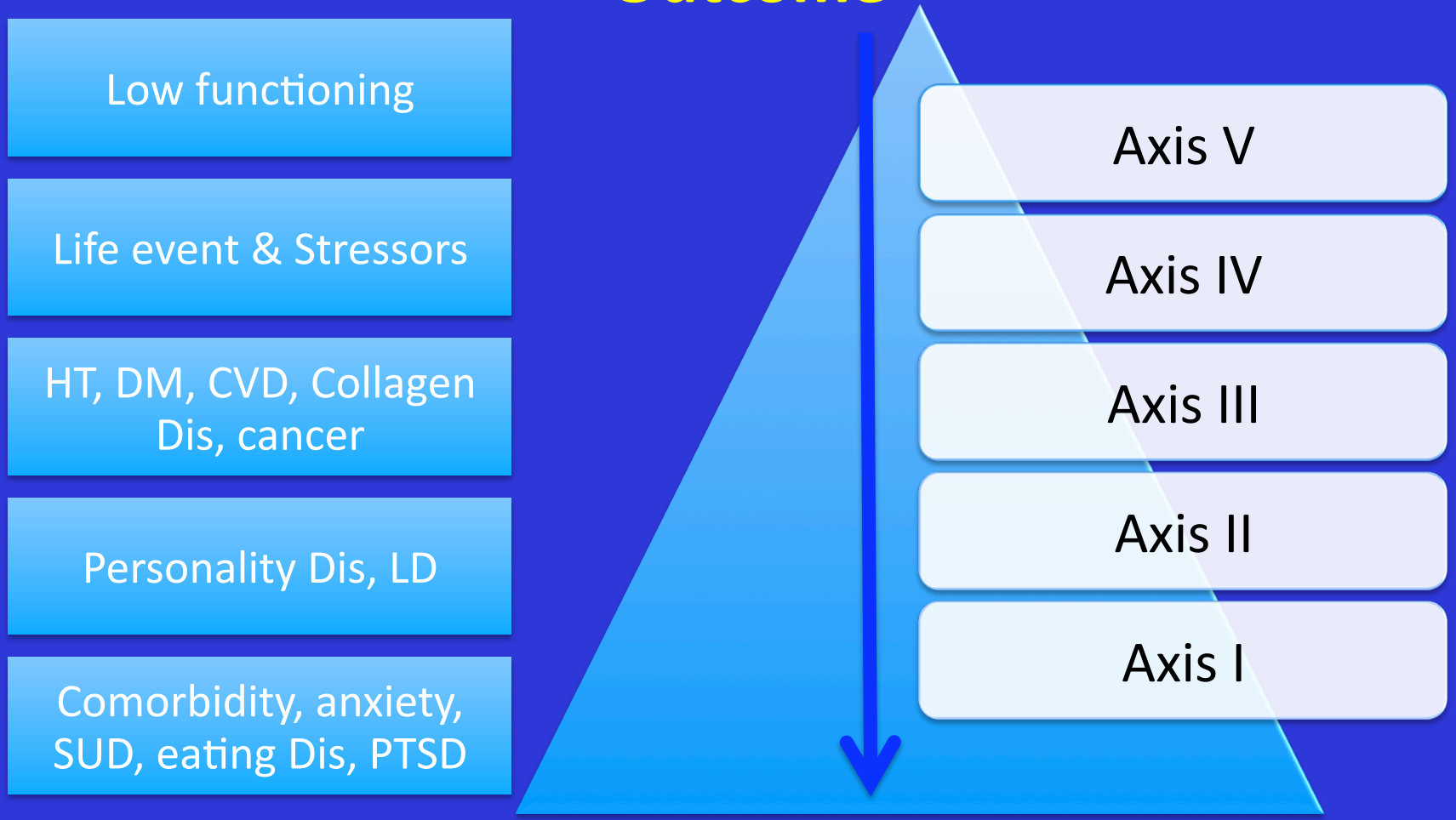


Differentiate treatment resistance from features of chronicity.



Towards a Comprehensive assessment of Depressive disorder.

Outcome

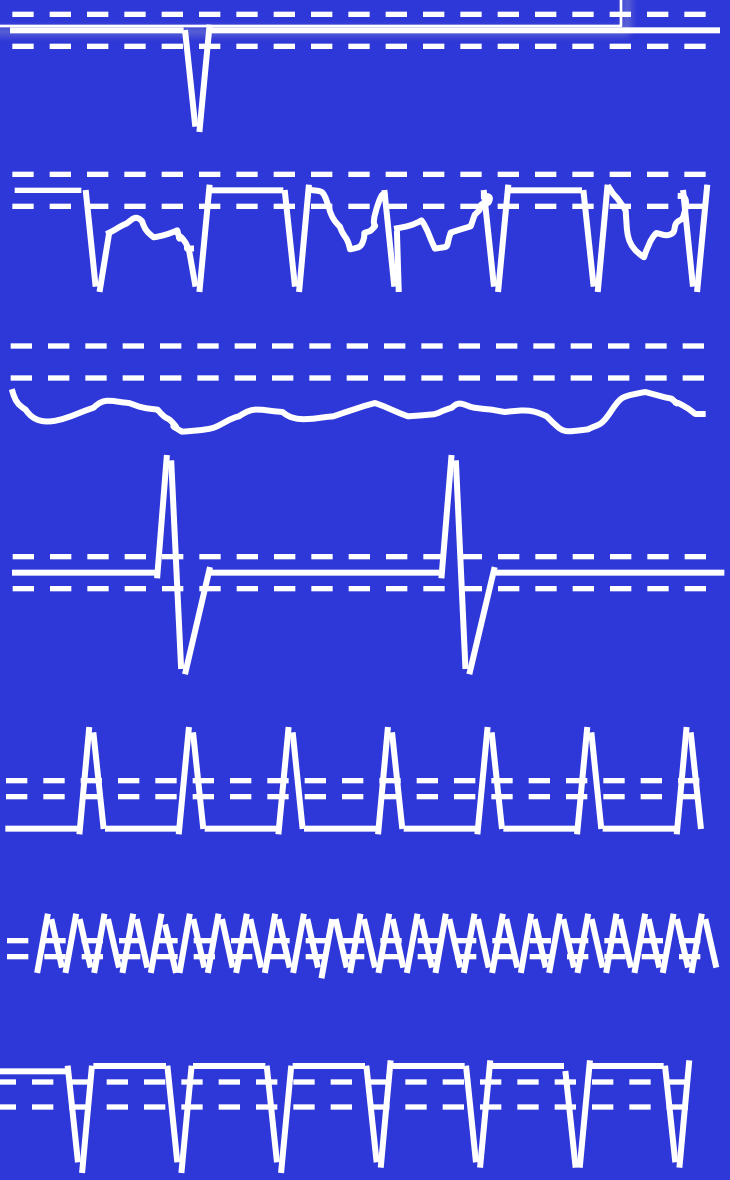


Classification of Mood Disorders

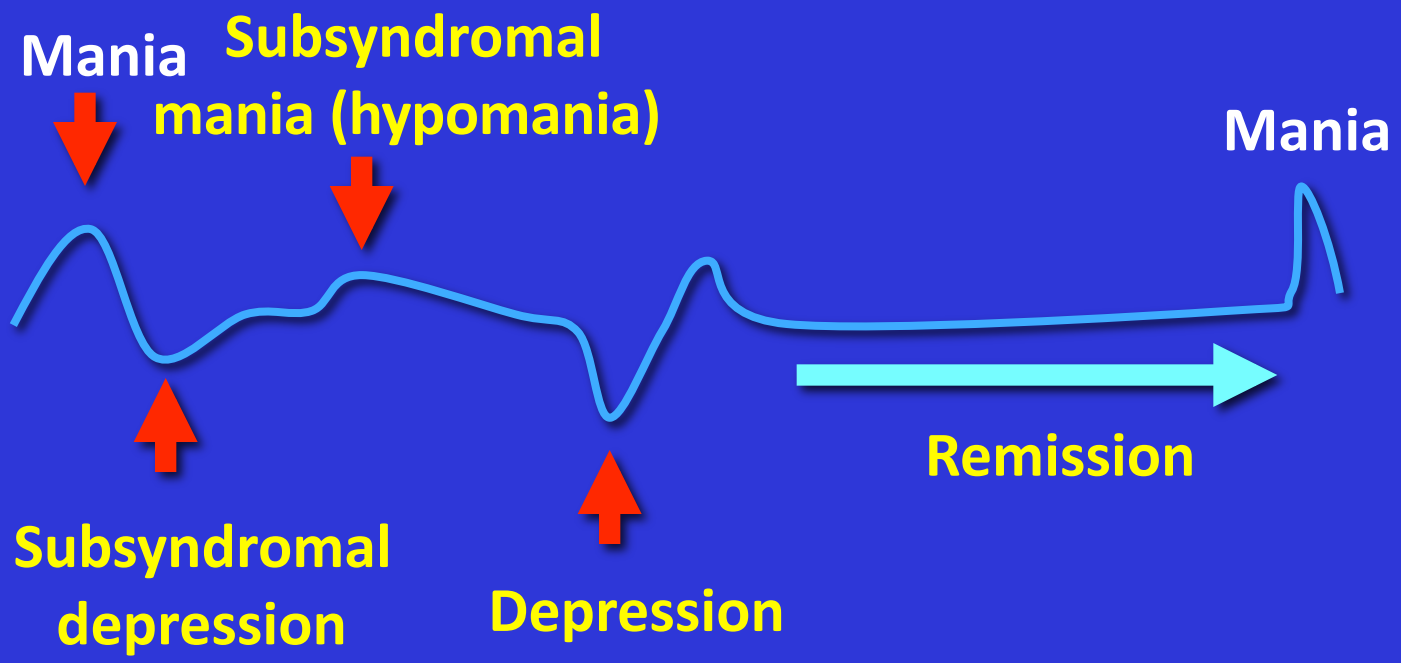
- **Unipolar**
  - Unipolar single episode
  - Unipolar recurrent
  - Dysthymia
- **Bipolar**
  - Bipolar I
  - Bipolar II
  - Cyclothymia
  - Unipolar-Hyperthymic

Depression: With history of mania/ hypomania

depression: Without history of mania



Bipolar Disorder is a Multidimensional Illness



Lifelong management of this lifelong illness involves targeting all phases of the disorder – atypical antipsychotics can play a major role

Vieta E, et al. Bipolar Disord 2005; 7 Suppl 4:21-33.

Bipolar II Depression

- Bipolar II disorder is a common disorder,
- prevalence of approximately 3-5%.
- Distinct clinical features
- The key to diagnosis - recognition of past hypomania,
- This is responsible for a significant rate of missed diagnosis,
- It is unclear if bipolar II disorder is over-represented in TRD

Bipolar II disorder: a review.
Berk M, Dodd S.
Bipolar Disord. 2005 Feb;7(1):11-21.

Why should I care?

- Major depression affects:
  - 12 million people in the US
  - 17% of the population at some point in their lifetime.
  - Prevalence in primary care settings 5-10%
- Major depression results in:
  - 5.6 lost productive hours per week in the US.
  - $44 billion in lost productivity in annual wages alone
- Patients present at PMD > Psychiatrist

Depressive Disorders

- Major Depression
- Dysthymic Disorder
- Characterologic Depression
- Adjustment Disorder with depressed mood
- Bereavement
- Depression NOS
- Depressive Disorder due to…

Secondary Depression / Comorbidity

- Mood Disorder due to …
  - Medical - hypothyroidism, anemia, medications
  - Substance Abuse/Dependence – esp alcohol, stimulants
  - Symptoms should resolve with treatment of underlying condition but can take weeks, months
- Comorbidity
  - Any of the above
  - Psychiatric – esp anxiety disorders, bipolar disorder

Management differs by diagnosis

- Major Depression
  - Antidepressants, psychotherapy
- Dysthymia, Characterologic Depression
  - Psychotherapy, possibly antidepressants
- Bereavement, Adjustment Disorder
  - Supportive psychotherapy, anxiolytics

Who to screen

- Patients who ask
- Certain medical conditions:
  - DM, obesity, cancer, history of MI, chronic pain, pregnant/postpartum
- Social
  - Financial strain, isolated, the elderly
- Loss of interest in sexual activity
- Multiple unexplained physical symptoms
- Patient “looks depressed.”

Initial Screening

Two questions:

- (1) "Over the past two weeks, have you ever felt down, depressed, or hopeless?“
- (2) "Have you felt little interest or pleasure in doing things?“

- Positive response to either question should prompt further evaluation.

Major Depressive Episode

- **At least 5 symptoms** for at least 2 weeks
- Daily or near daily and significant change from baseline.
- Must include depressed mood or loss of interest.
  - Depressed mood.
  - Loss of interest or pleasure in most or all activities.
  - A considerable loss or gain of weight (5% or more)
  - Difficulty falling or staying asleep, or sleeping more than usual.
  - Behavior that is agitated or slowed down.
  - Feeling fatigued, or diminished energy.
  - Thoughts of worthlessness or extreme guilt
  - Ability to think, concentrate, or make decisions is reduced.
  - Frequent thoughts of death or suicide or attempt of suicide.

SIG E CAPS + Mood

5 or more positive responses for > 2 weeks makes the diagnosis

- Sleep (insomnia or hypersomnia)
- Interests (diminished interest or pleasure in activities)
- Guilt (excessive or inappropriate, feeling worthless)
- Energy (loss of energy or fatigue)
- Concentration (diminished or indecisive)
- Appetite (decreased or increased, weight gain or loss)
- Psychomotor (retardation or agitation)
- Suicide (recurrent thoughts, suicidal ideation or attempt)
- Mood

SIG E CAPS + Mood

- Performed during appt
- 5 or more suggestive of Major Depression
- 2-4 suggestive of Dysthymia or other “Minor Depression”

- Not enough time?
  - Rating scales

Rating Scales

- Done by patient in waiting room prior to encounter
- Beck Depression Inventory (BDI)
  - 21 items covering most dimensions of major depression, including suicidal ideation and plans.
- Patient Health Outcomes-9 Symptom Checklist (PHQ-9)
  - Part 1 consists of 9 separate questions, Part 2 is a single question that assesses the functional health

Rating Scales- still need to interview

- Scales do not address duration of symptoms, degree of impairment, and co-morbid psychiatric disorders.
- Does not address secondary causes
- Clinical judgment needed to consider clinical manifestations of depression that vary by age, gender, or cultural background.

Major Depression

- Impairment seen in all spheres:
  - Mood: depressed and/or anhedonic
  - Psychomotor activity: posture, speech, mentation
  - Cognition: self-esteem, guilt, helplessness
  - Vegetative symptoms: weight, sleep
- Melancholic Features
  - Represents severe cases where vegetative symptoms predominate.

Major Depression

- Don’t be a bean counter.
  - Consider secondary depressions
  - MDD has an onset (episodic)
  - MDD is experienced as qualitatively different
- Disability
  - No disability = No disorder
  - MDD is Incapacitating
  - Helps determine severity
  - Markers of response to treatment

Dsythymic Disorder

- Long-standing, low-grade depression, part of habitual self.
- Represents an intensification of temperamental instability, not a sequel to well-defined major depressive episodes.
- Onset usually before 21: "I've always been depressed."
- Symptoms often outnumber signs: emphasizes cognitive symptoms

Dsythymic Disorder Criteria

- Depressed mood, most days, at least 2 years.
- Presence, while depressed, of two (or more):
  - poor appetite or overeating
  - insomnia or hypersomnia
  - low energy or fatigue
  - low self-esteem
  - poor concentration or difficulty making decisions
  - Feelings of hopelessness

Dsythymic Disorder Criteria

- No Major Depressive Episode has been present during the first 2 years of the disturbance

- After the initial 2 years of Dysthymic Disorder, there may be superimposed episodes of Major Depressive Disorder: Double Depression.

Implications of Dysthymia

- History may find:
  - stable albeit unremarkable employment history
  - multiple medication trials with little benefit
- Treatment plan should emphasize psychotherapy to address cognitive symptoms rather than antidepressants as outcomes are less robust for dysthymia vs MDD

Characterological Depression

- Similar to dysthymia in chronicity of symptoms but qualitatively different.
- Seen in patients with borderline personality disorders
- A feeling of pervasive and chronic loneliness, emptiness and boredom yet lack the vegetative signs of major depression.
  - Suicidal gestures
  - Rage
  - Demanding and concern with loss

Characterological Depression

- Tends to have more dramatic exacerbations compared to dysthymia
- More chaotic with relationships and jobs

- Management also emphasizes psychotherapy rather than medications
- Medications often used symptomatically, not to cure

Bereavement

- The reaction to the death of a loved one.
- Present with symptoms similar to Major Depression
- Should start to improve after two months (but can vary by culture)

- No role for antidepressants

NOT typical of bereavement

- Generalized guilt
- Active suidicial ideation (versus passive)
- Morbid preoccupation with worthlessness
- Hallucinations (beyond brief thoughts of hearing or seeing the deceased)
- Prolonged and marked functional impairment

- Above suggests Major Depression

Adjustment Disorder with Depressed Mood

- Subsyndromal depressive symptoms AND identifiable stressor within three months of onset of the stressor.
- Sometimes diagnosis is provisional or made later with resolution of symptoms.
- Danger of suicide still present
- Caution with “due to general medical condition” and “I’d be depressed too if…”

Adjustment Disorder

- Management includes emphasis on immediate safety (may consider hospitalization) and supportive psychotherapy.

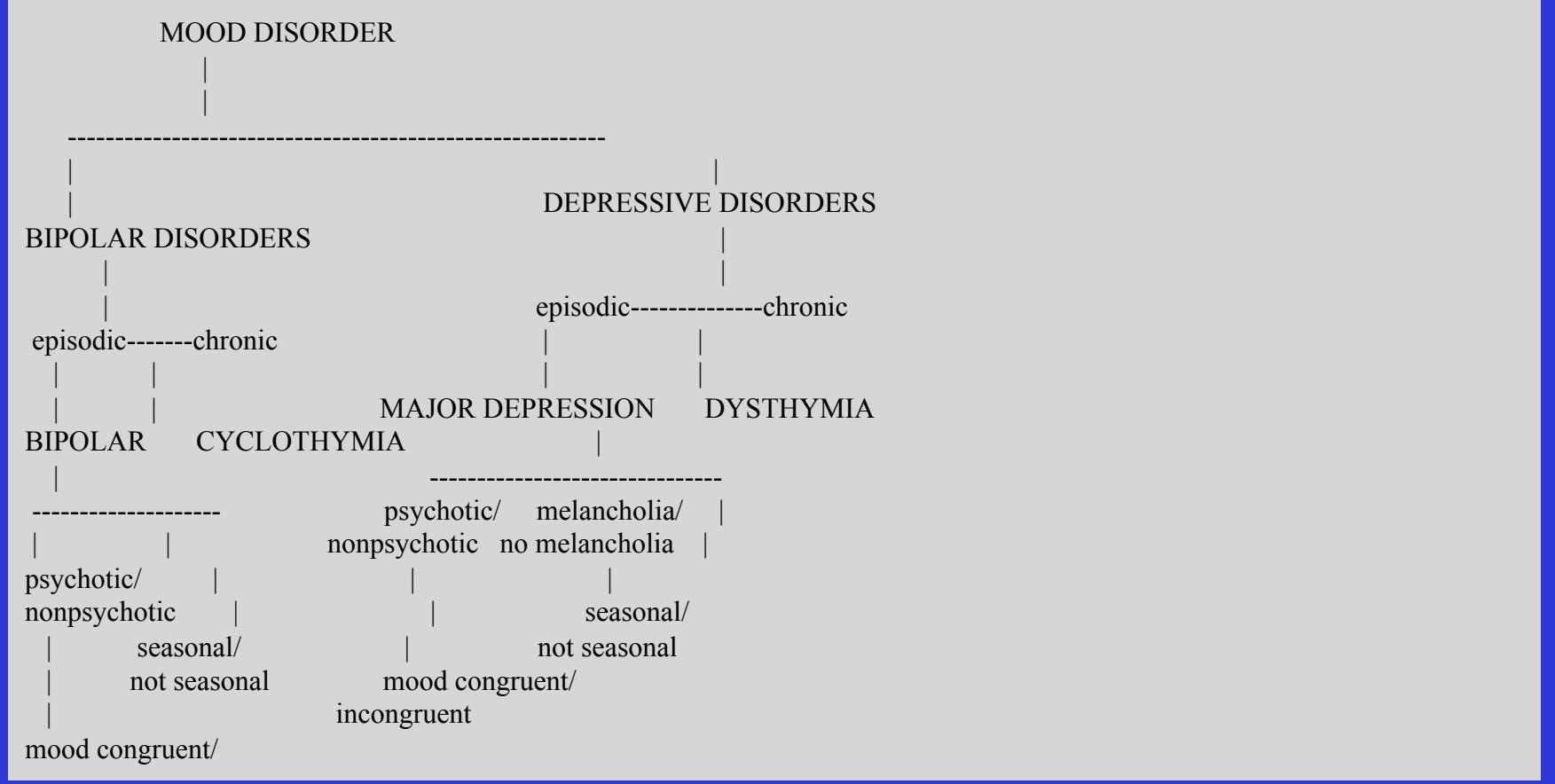
- Antidepressants have no role in adjustment disorder
- May consider a benzodiazepine cautiously in selected cases

Depressive Disorder NOS

- Depressive disorders not meeting criteria for major depression, dysthymic disorder, adjustment disorder
  - Premenstrual Dysphoric Disorder
  - Minor Depressive Disorder
  - Recurrent brief depressive disorder
    - Characterologic Depression
  - Postpsychotic Depressive Disorder of Schizophrenia

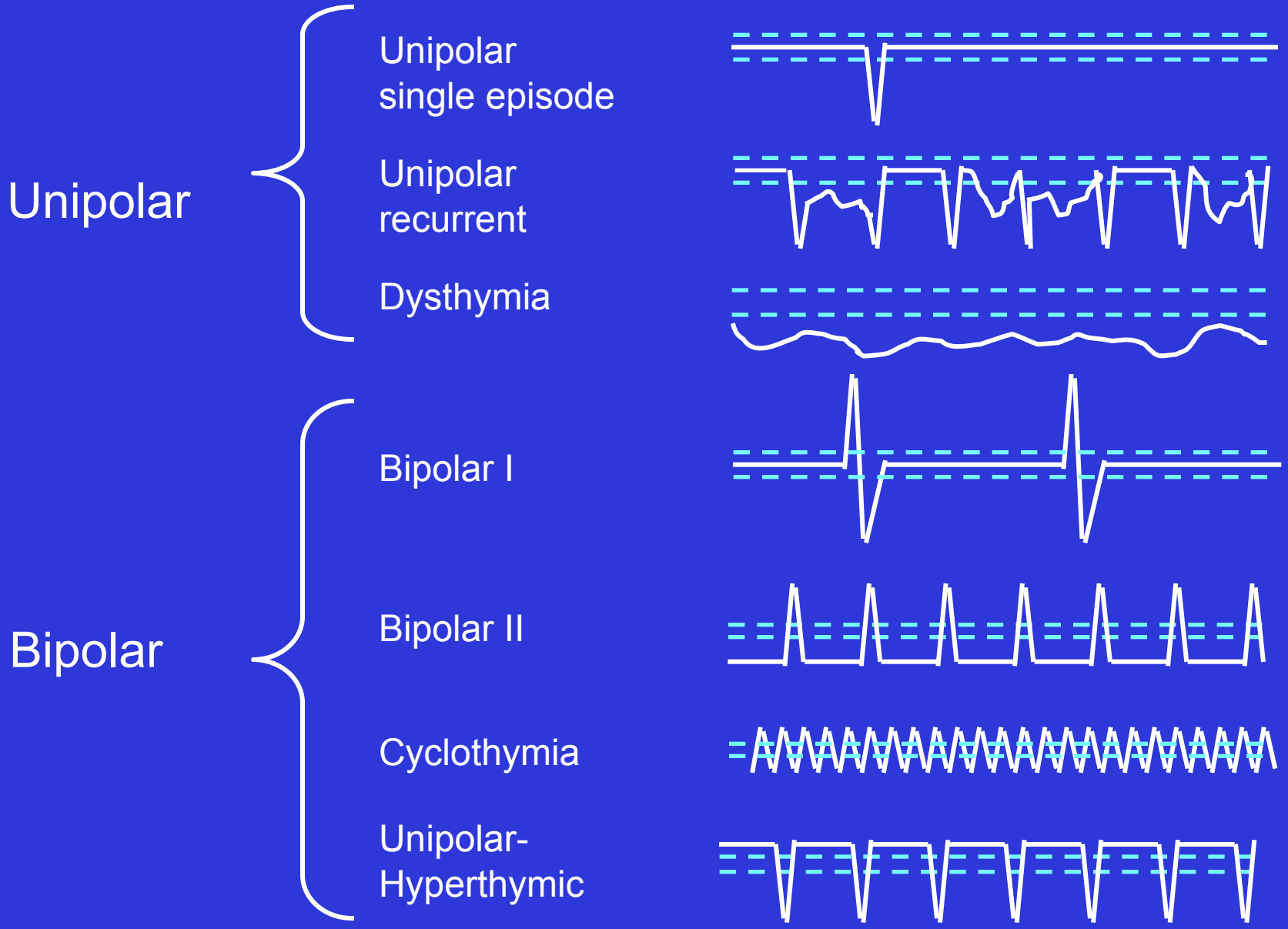
Points to Ponder

- Feeling depressed ≠ Major Depression
- Feeling depressed ≠ Antidepressants
- SIGECAPS + Mood
- Treatment varies by diagnosis
- Major depression is disabling


MOOD DISORDER
BIPOLAR DISORDERS
DEPRESSIVE DISORDERS
episodic-------chronic
episodic----------chronic
BIPOLAR
CYCLOTHYMIA
MAJOR DEPRESSION
DYSTHYMIA
psychotic/ nonpsychotic
melancholia/ no melancholia
seasonal/ not seasonal
mood congruent/ incongruent

Bipolar disorder

Classification of Mood Disorders



Bipolar Disorder

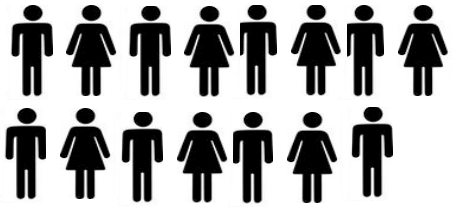
A lifelong, chronic and devastating affective disorder, characterised by recurrent episodes of major disturbance at the two ‘poles’ of mood disturbance: mania and depression

Bipolar Disorder - The Big Picture

- A serious public health problem with significant morbidity and mortality
- Typically recurrent with lifelong vulnerability
- Subsyndromal symptoms are common, along with full-blown episodes of mania or depression of varying frequency and severity
- Increased risk of suicide
- Increased risk of alcohol and substance use disorders
- High personal, economic, and social burden

People Living with Bipolar Disorder

Major Depressive Disorder



Bipolar Disorder

Alzheimer's Disease

Schizophrenia

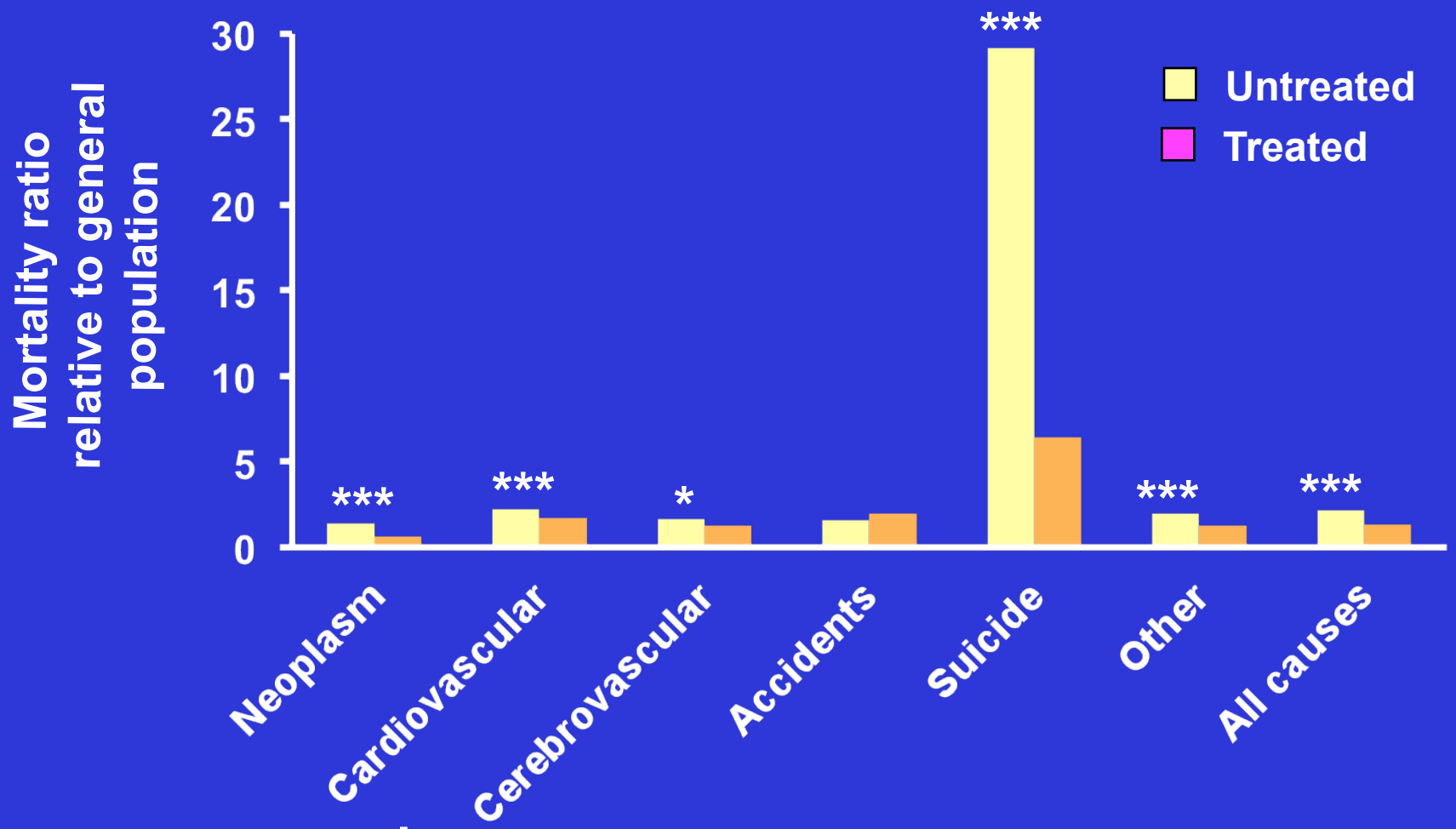
www.nimh.nih.gov

Impact of Bipolar Disorder

- Prevalence of bipolar disorder:
  - bipolar I disorder: 0.5 - 2.4%
  - bipolar II disorder: 0.2 - 5.0%
- Patients experience more depressive episodes than manic/hypomanic episodes
  - bipolar I disorder: 3:1 ratio
  - bipolar II disorder: 37:1 ratio
- Disease onset occurs in late adolescence or early adulthood
- Negative impact on patient's quality of life, physical and social well being
- 25–50% of patients with bipolar disorder attempt suicide at least once during their lifetime

CANMAT Guidelines for Bipolar Disorder. Bipolar Disord 2005: 7 (Suppl. 3): 5–69.
American Psychiatric Association 2000; Judd et al 2002; Tondo et al 2003;
Pini et al 2005; Shastry et al 2005; Moussavi et al 2007

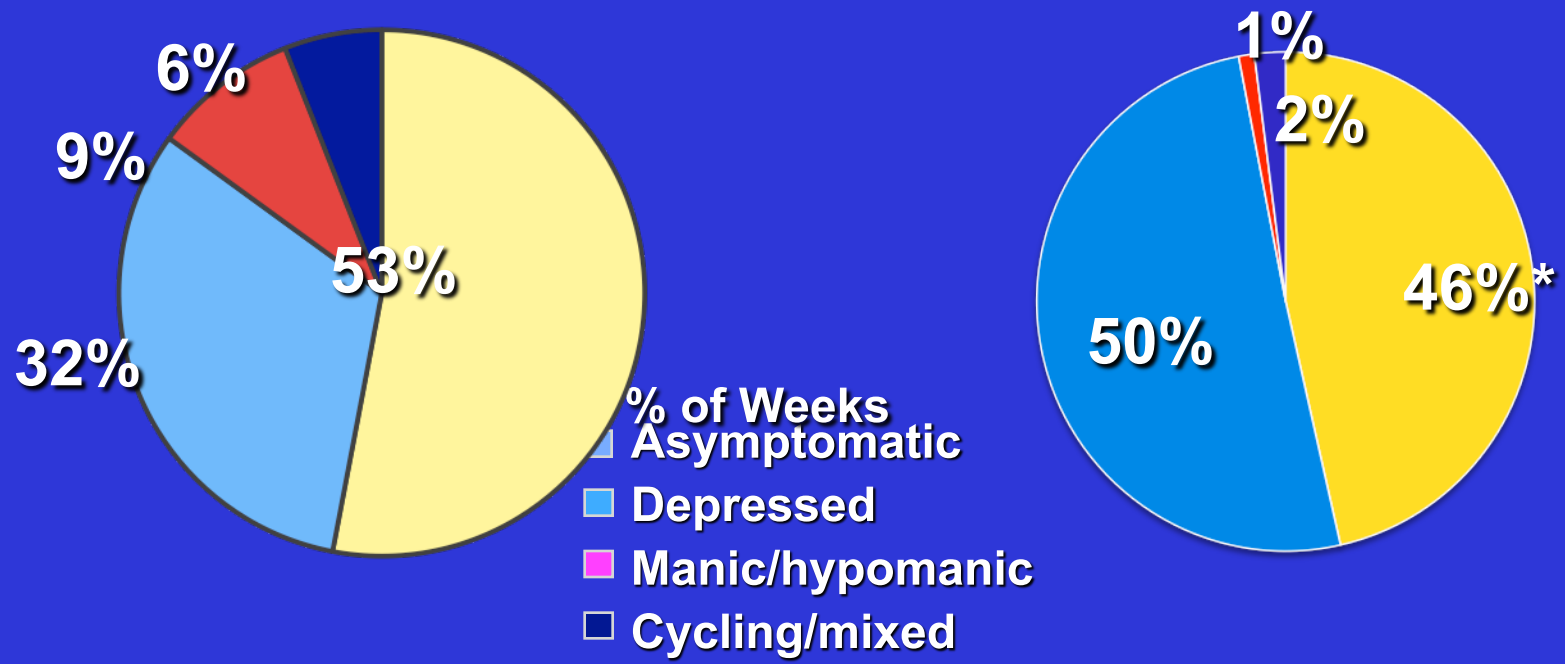
Mortality Rates: Untreated & Treated Bipolar Disorder



*p<0.05; ***p<0.001 vs treated patients n=220

Angst et al 2002

Time Spent in Specific Bipolar Disorder Affective Symptoms



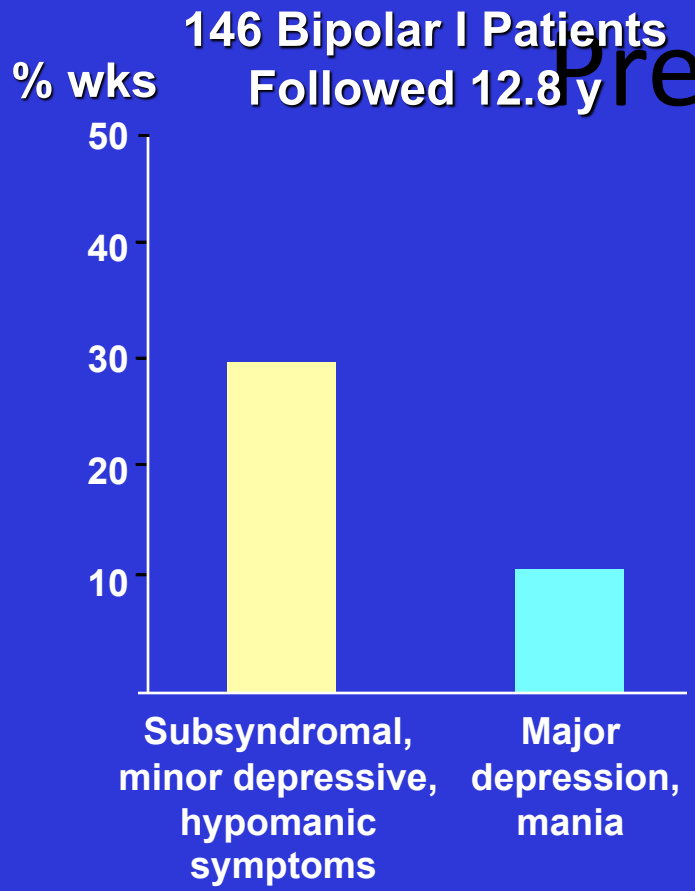
146 bipolar I patients followed 12.8 years

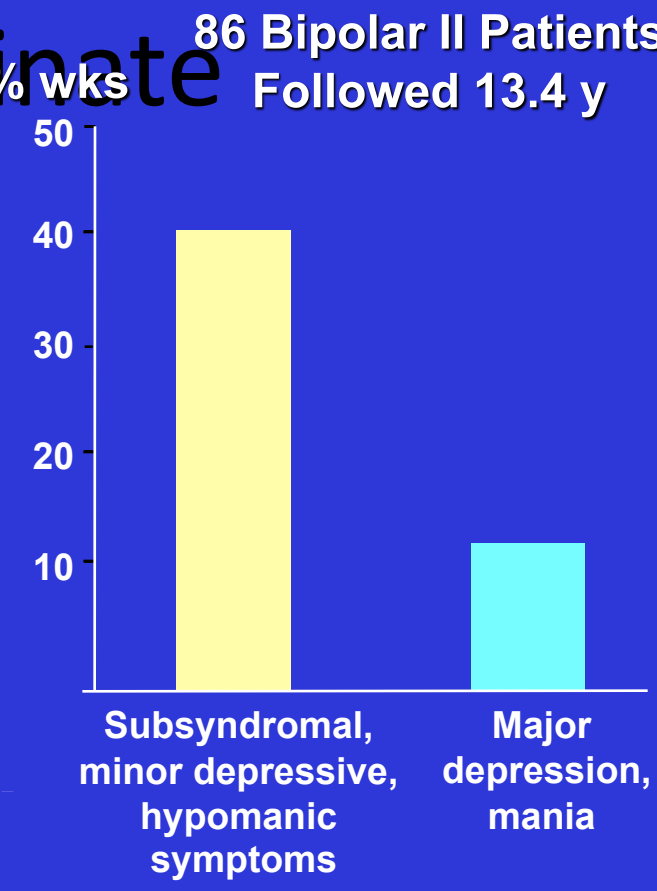
86 bipolar II patients followed 13.4 years

*%s do not add to 100 due to rounding

Judd LL et al. Arch Gen Psychiatry. 2002;59:530-537.
Judd LL et al. Arch Gen Psychiatry. 2003;60:261-269.

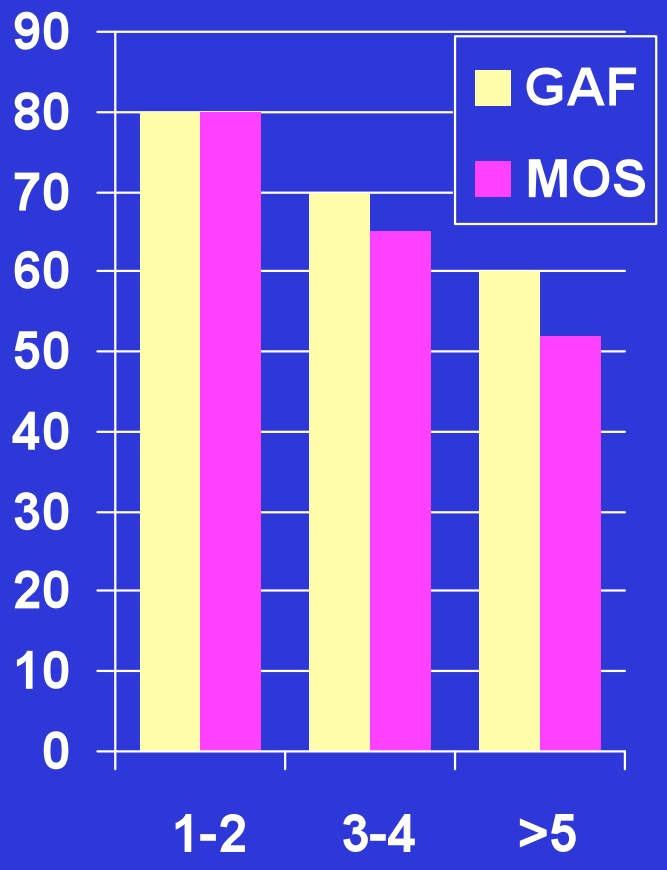
Subsyndromal, Minor Depressive, and Hypomanic Symptoms Predominate





Judd LL et al. Arch Gen Psychiatry. 2002;59:530-537.
Judd LL et al. Arch Gen Psychiatry. 2003;60:261-269.

Psychosocial Outcome in Bipolar Disorder

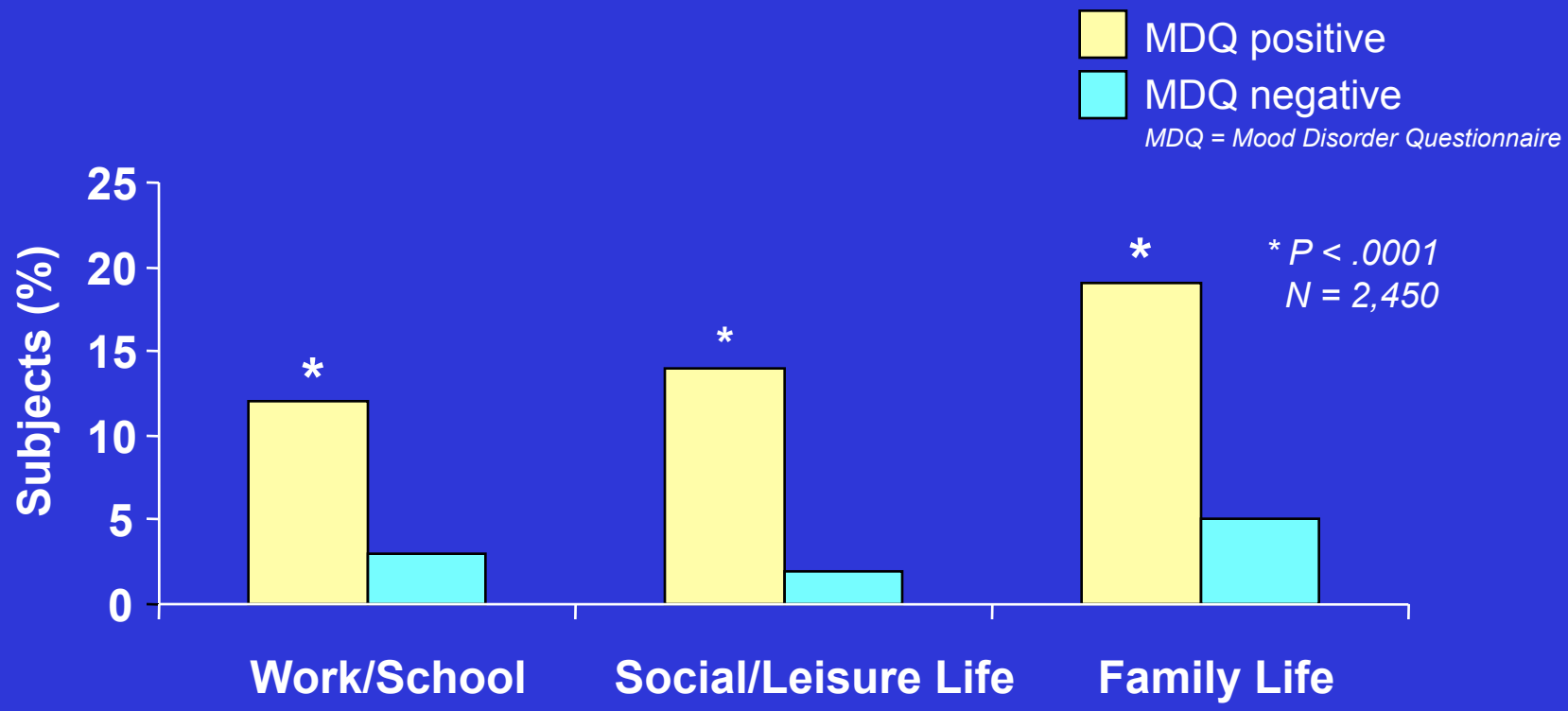


GAF=Global Assessment of Functioning
MOS=Medical Outcomes questionnaire Short form

- Avg 14.1 years of illness
  - 5.2 depressions
  - 3.6 manias
- Increasing number of depressions associated with decreased function
- Number of manias not a strong predictor of function

MacQueen GM, Young LT, Robb J, et al. Acta Psychiatrica Scandinavica 2000;101:374-381.

Aspects of Daily Life Often Impacted by Bipolar Disorder

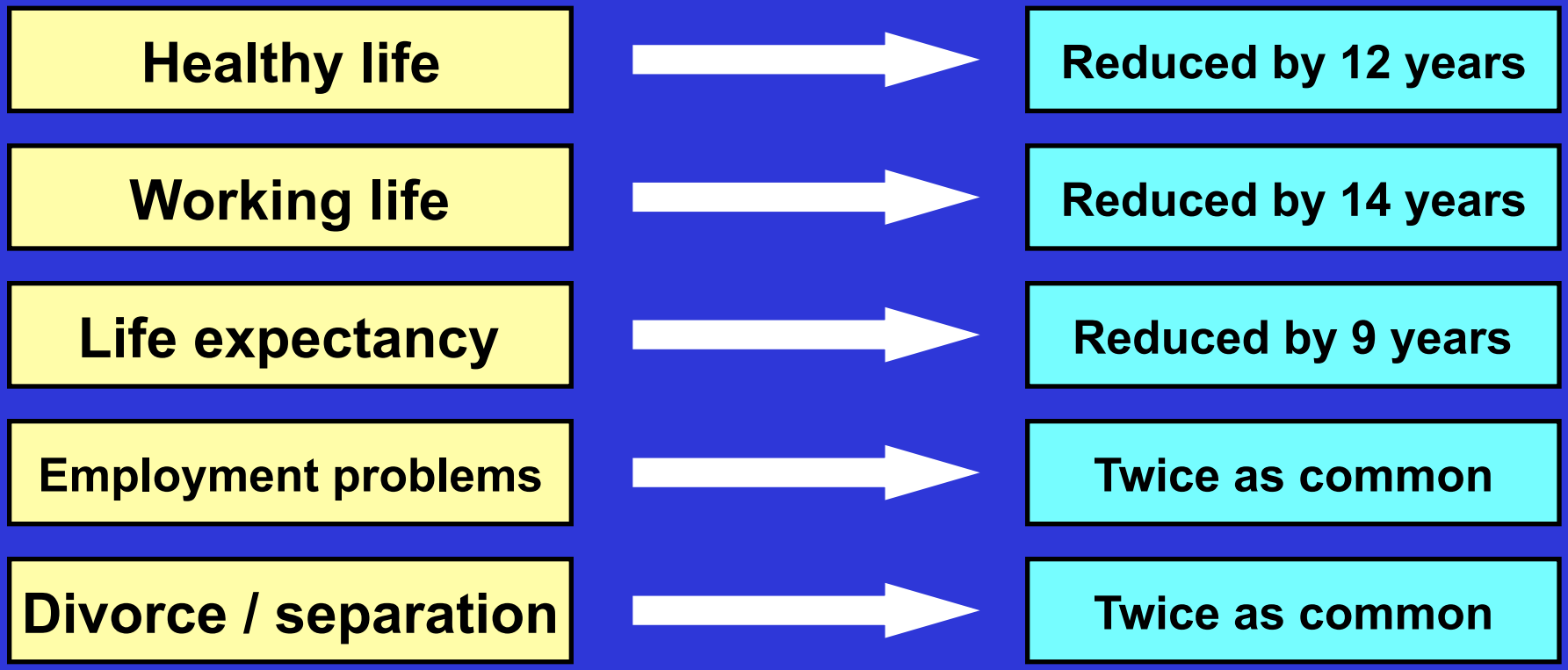


Subjects with impact ratings of 8, 9, or 10 as assessed by the Sheehan Disability Scale

Calabrese JR et al. J Clin Psychiatry. 2003;64:425-432.

Impact of Bipolar Disorder on Patients' Lives

Onset is usually during late adolescence and early adulthood, a time at which individuals are establishing their careers and building long-term relationships



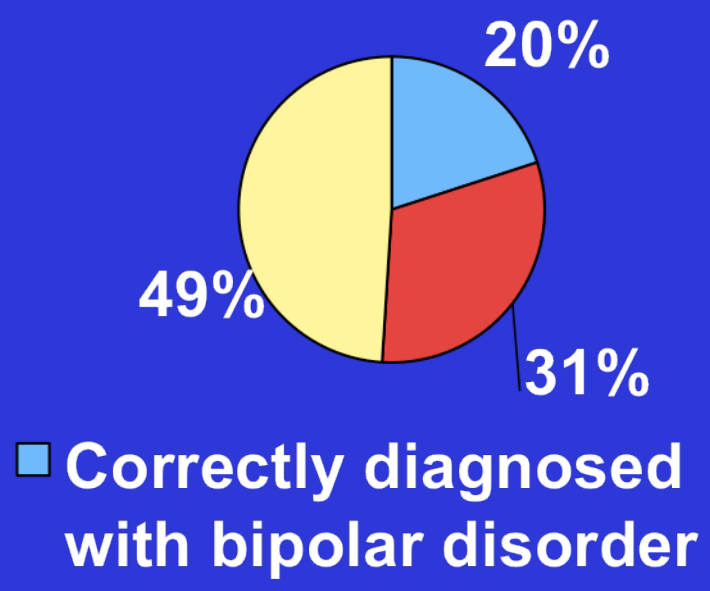
Results for patients developing bipolar disorder in their mid-20s

Coryell et al 1993; Scott 1995

Addressing Diagnostic Issues

Bipolar Disorder: Unrecognized and Underdiagnosed

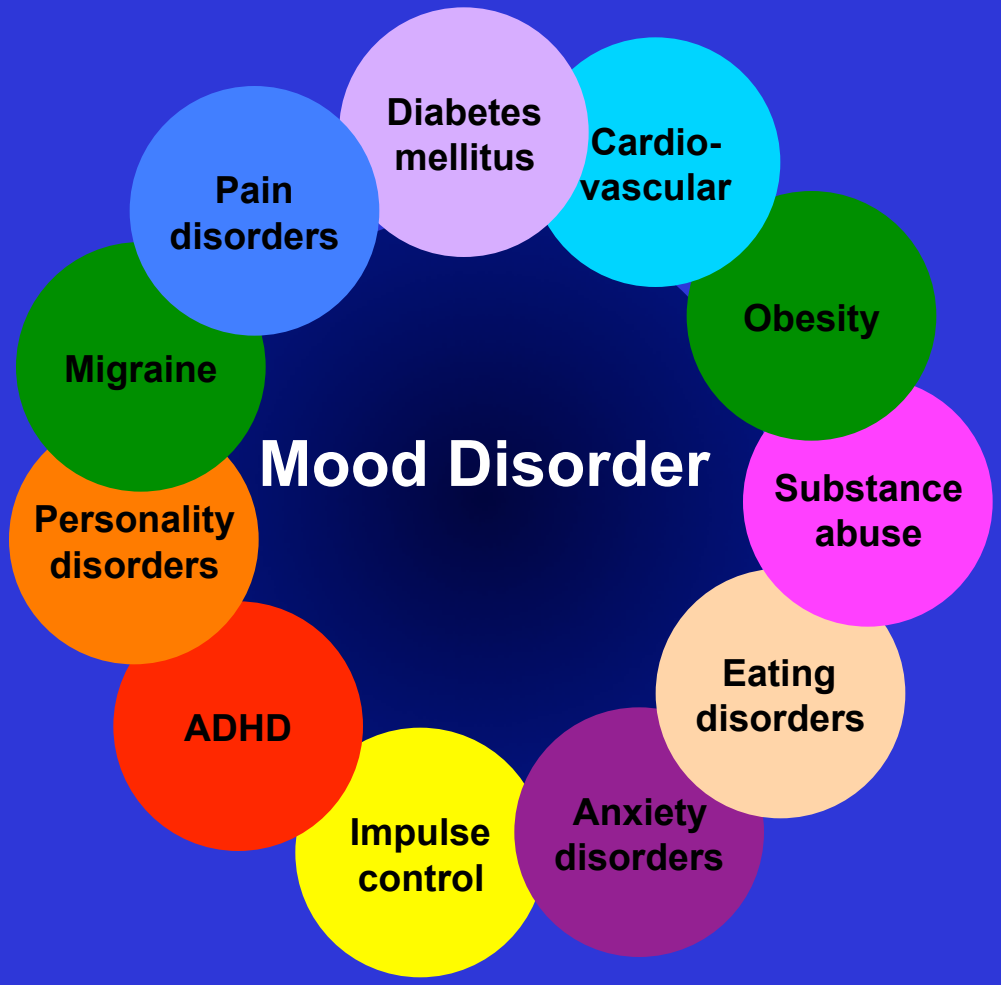
Mood Disorder Questionnaire Positive Rates (US Population)



- Prevalence of bipolar spectrum disorder 3.7% [Hirschfeld et al, 2003a]
- Findings consistent with patient survey that found 69% are misdiagnosed, most frequently with unipolar depression [Hirschfeld et al, 2003b]
- 35% of patients are symptomatic at least 10 years before being accurately diagnosed [Hirschfeld et al, 2003b]

Hirschfeld RM et al. J Clin Psychiatry. 2003a:64:53-59.

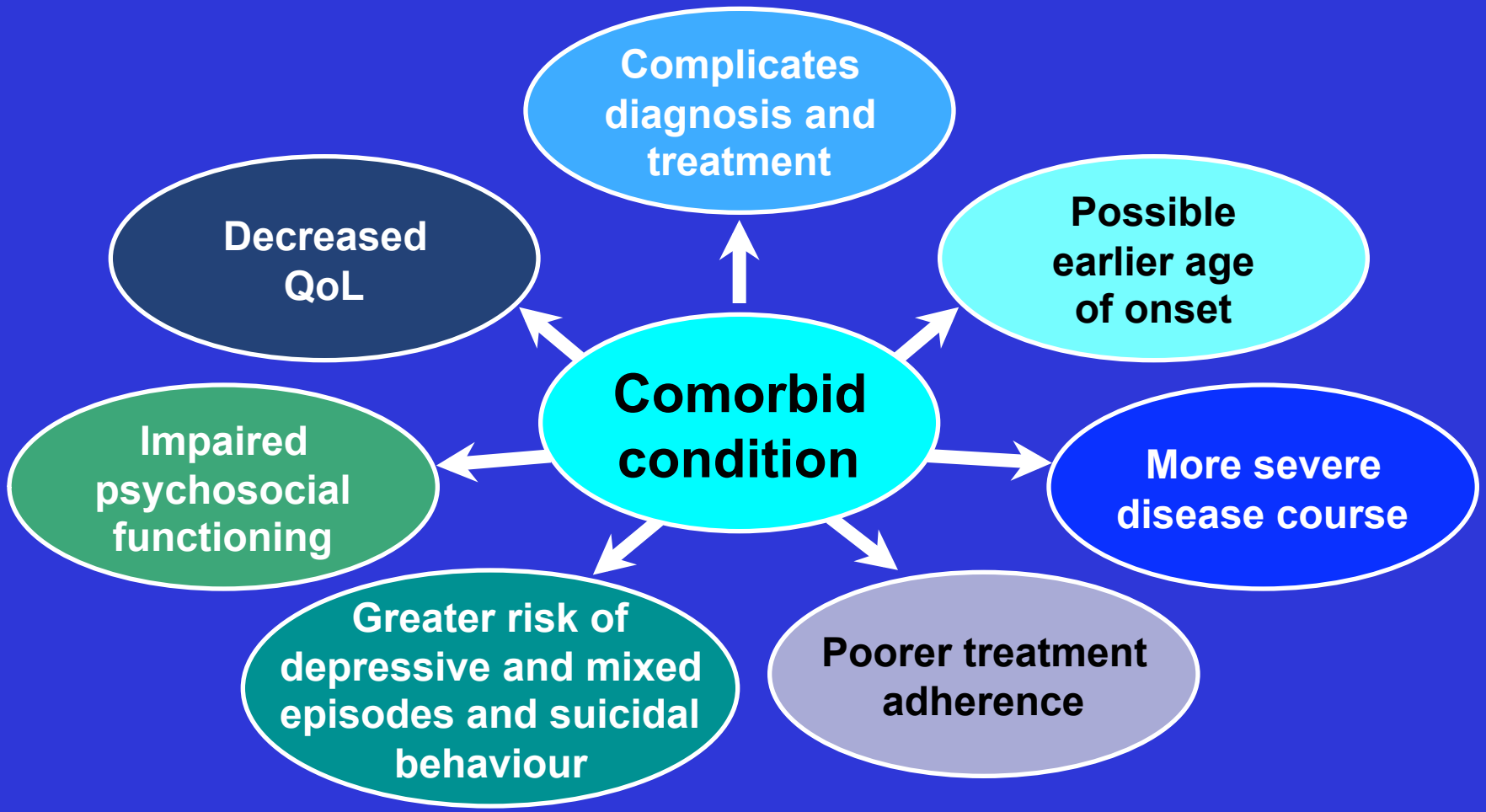
Multidimensionality of Mood Disorders



- The prevalence and epidemiology of psychiatric comorbidities in bipolar disorder is high
- Stress sensitive medical disorder prevalent
- Cardiometabolic disorders most common specific cause

McIntyre RS, et al. Hum Psychopharmacol. 2004;19:369-386.

Comorbid Conditions Complicate Diagnosis and Management of Bipolar Disorder



Colom et al 2000; Pollack et al 2000; Vieta et al 2001; Keller 2006.

Diagnostic Challenges of Bipolar Disorder

- Diagnosis may take up to 10 years
- Symptom overlap with other disorders leads to misdiagnosis
  - 1 out of 3 patients are misdiagnosed
  - some patients see ≥4 physicians before receiving a correct diagnosis
- Patient denial of diagnosis
- Comorbid conditions (eg, anxiety disorders, eating disorders, substance abuse)
- Children / adolescents (misdiagnosis, stigma)

Evans 2000; Hirschfeld 2002, 2003; Citrome 2005

Diagnostic Overview (DSM-IV-TR)

Bipolar I	Bipolar II	Bipolar NOS	Cyclothymia
Manic or mixed episode	Hypomania ≥ 4 days	Do not meet specific criteria for bipolar I or II disorder, eg hypomania for <4 days	≥ 2 years
Obvious symptoms and functional impairment	Never a manic or mixed episode		Mood states do not meet full criteria for depressive, manic, or mixed episode
Usually with recurrent depression	Recurrent depression	Usually with recurrent depression	Dysthymia

Features of Manic and Mixed Manic Episodes

Affective

Pure Mania

Elevated, euphoric, or irritable mood

Grandiosity

Agitated, aggressive, or hostile behavior

Impulsiveness

Dysphoric/Mixed

Depression

Anxiety

Irritability

Hostility

Violence or suicide

Cognitive

Racing thoughts

Distractibility

Poor insight

Disorganization

Impaired attention

Impaired comprehension

Psychotic

Delusions

Hallucinations

Sensory hyperactivity

Physical

Rapid or pressured speech

Increased energy

Decreased need for sleep

Increased libido

Overly active, hostile behavior

Recklessness, destruction of property

Patients With Depression:

Do They Have a History of (Hypo)mania?

- Depression is the initial symptom reported by the majority of patients with bipolar disorder
- It is therefore important to establish whether there is a history of mania and hypomania in a patient with depression and/or a family history of bipolar disorder
- Involve family and significant others in the evaluation process
- Use a screening instrument for bipolar disorder, eg, the Mood Disorder Questionnaire

Hirschfeld RM et al. Am J Psychiatry. 2000;157:1873-1875.

Features of Hypomania

- Hypomania can be described as a less severe form of mania and is distinct from mania in several characteristics

Hypomania	Mania
Little to mild dysfunction	Severe dysfunction
Little to mild, lapses of judgment	Major lapses of judgment
Commonly responds to outpatient management	Often requires inpatient treatment
Non-psychotic symptoms	Psychotic symptoms

- Patients with hypomania have a distinct period of persistently elevated, expansive, or irritable mood, lasting for ≥4 days, that is different from usual non-depressed mood

American Psychiatric Association 2000.

Features of Bipolar Depression

Affective	Cognitive	Physical
Sadness	Poor self-esteem	Change in sleep
Apathy	Poor concentration	Change in appetite
Anhedonia	Indecisiveness	Decreased activity
Irritability	Suicidal ideas	Low energy
Anxiety	Self-blame	Change in weight

Features of Rapid Cycling

- Rapid cycling denotes a high frequency of bipolar episodes
- Diagnostic criteria define rapid cycling as 4 or more separate episodes per year
  - However 4 episodes per year may not be a clinically meaningful threshold
- Overall morbidity and impairment increases with the number of episodes
- Rapid cycling bipolar disorder may be less responsive to medication, particularly treatment with lithium

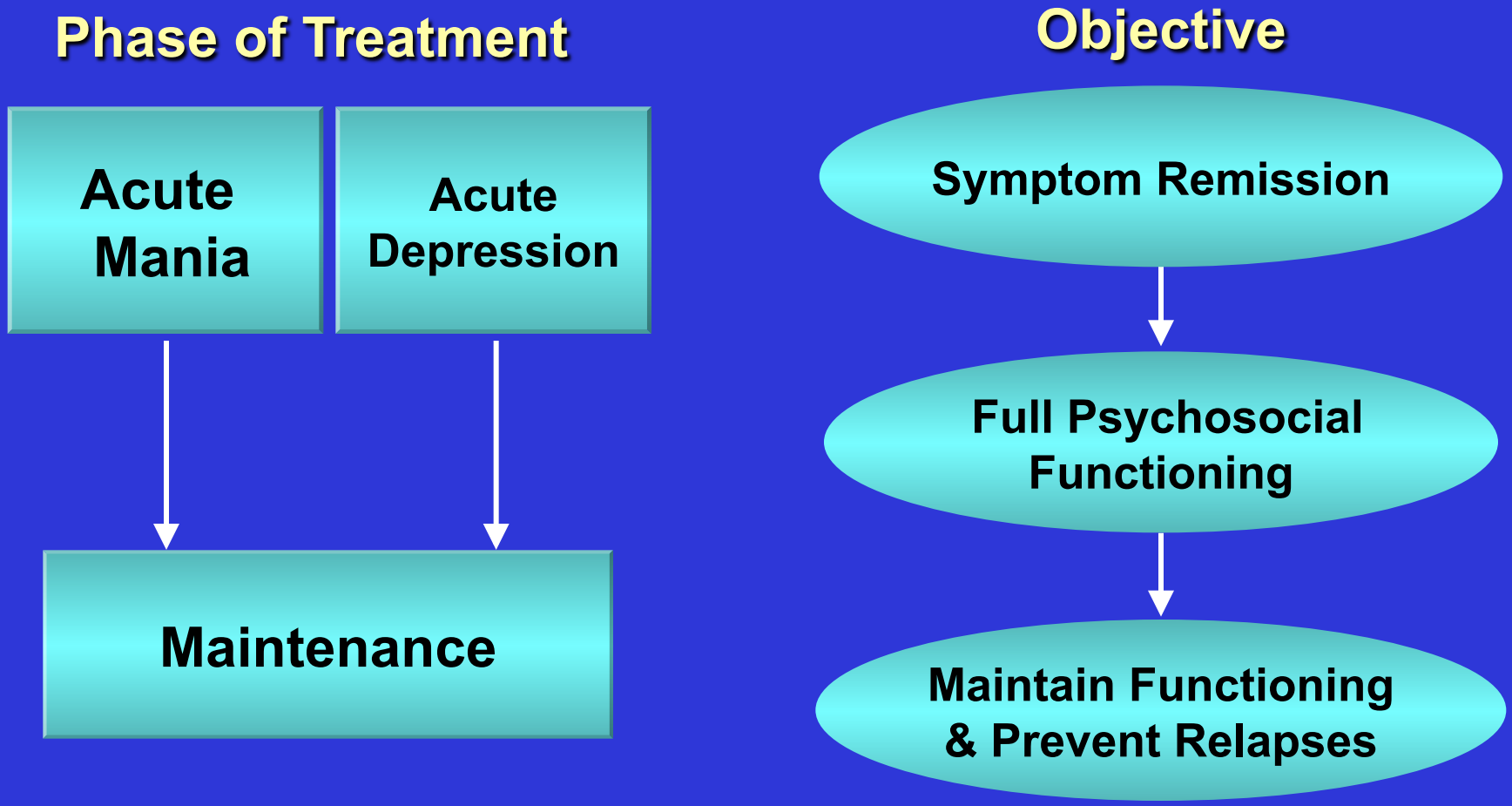
Index Mood Episode Predicts Polarity of Relapse

- Polarity of index episode tends to predict polarity of relapse
  - 2:1 to 3:1 ratio
- Polarity of the index episode has important implications for the development of mood stabilizing agents
  - Both manic and depressive index episodes must be studied

Calabrese JR et al. Biol Psychiatry. 2004;56:957-963.

Choosing a Treatment Regimen

Therapeutic Objectives

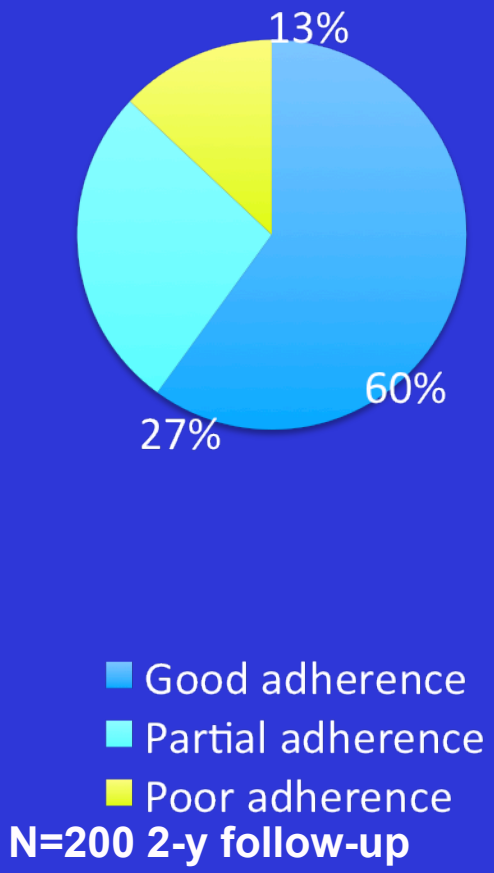


Treatment Challenges

- No cure for bipolar disorder
- Non-adherence rate is high
- Symptom overlap among diagnoses
- Efficacy: acute and long term
  - all symptom domains
  - all phases of disorder (mood stabilisation)
  - patients with bipolar I and II disorder
  - rapid cyclers
  - suicidality
- Safety and tolerability
- Comorbidity

Brady 2000; McIntyre 2004

Treatment Adherence



Factors influencing adherence:

- A strong therapeutic alliance
- Psychoeducation about disease and its treatment
- Choosing treatments that are well accepted
- Discussing possible side effects with patients and how to manage them

Colom F et al. J Clin Psychiatry. 2000;61:549-555.

Treatment Options for Bipolar Disorder

Lithium

Divalproex

Lamotrigine

Carbamazepine and other anticonvulsants

Typical antipsychotics

- **Haloperidol**
- **Chlorpromazine**

Atypical antipsychotics

- **Clozapine**
- **Olanzapine**
- **Quetiapine**
- **Quetiapine XR**
- **Risperidone**
- **Ziprasidone**
- **Paliperidone**
- **Aripiprazole***

Antidepressants

* Not available in Canada

Treatment Guidelines for Bipolar Disorder

- Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: Update 2007. Yatham et al, 2006
- American Psychiatric Association (APA) Practice Guidelines. Hirschfeld et al, 2002
- World Federation of Societies for Biological Psychiatry (WFSBP) Guidelines. Grunze et al, 2002
- British Association for Psychopharmacology Consensus Group. Evidence-based guidelines. Goodwin, 2003
- Texas (Deptartment of Mental Health) Implementation of Medication Algorithms (TIMA). Suppes et al, 2002
- The Royal Australian and New Zealand College of Psychiatrists (RANZCP) Practice Guidelines. Mitchell et al, 2003

Health Canada Approved Indications for Agents Used in the Treatment of Bipolar Disorder

	Acute Bipolar Depression	Acute Mania	Maintenance Treatment
Agents			
ATYPICALS			
Clozapine (Clozaril®)			
Olanzapine (Zyprexa®)		√	√*
Quetiapine (SEROQUEL XR®)	√	√	
Risperidone (Risperdal®)		√	
Paliperidone (Invega ®)			
Ziprasidone (Zeldox®)			
OTHER			
Carbamazepine		√	√+
Divalproex		√	
Lamotrigine			
Lithium		√	√

+ for use after treatment failure on traditional mood stabilizer

*See PM. Evaluation from 2 “time to relapse” trials with manic or mixed index episode

This chart does not imply comparable efficacy or safety profiles.