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 plateau. 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 girlfriend, 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

1. Psychiatric Illnesses
2. Hearing loss
3. Iron deficiency
4. Alcohol use
5. COPD
6. Osteoarthritis
7. Schizophrenia
8. Falls
9. Bipolar affective
10. Asthma
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

• 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.

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

Social and environmental domain

Psychological domain

Biological Domain
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’

Drug induced depression

- Corticosteroids
- 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.

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’

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

- **Yes**
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…”

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?

- 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
What decides poor outcome and efficacy with Anti Depressant Drugs?

- Chronicity
- Severity
- Medical & psychiatric Comorbidity
- 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

Core personality: Ego-Conscious-unconscious

Biological Defenses

Psychological Defenses

Social and Environmental defenses

Spiritual Defenses
Symptom development and influence of ‘events’

Environmental
- Genotype

Psychological Unmasking
- Behavioral Traits-Correlates
- Brain Vulnerability

Social Unmasking
- Life style issue
- Risk factors
- Essential Etiological factors

Understanding the Illness
How the illness of ‘Depression’ is caused: Available Evidence

Psychological event – Loss

Social event – Adverse life situation

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

Reduced disability, Improved Functioning & Social Integration

Good Outcome

Adequate Treatment

Lack of Treatment

Disability, Mortality & morbidity
Social Factors and Social pathology in Mental disorders; WHR, WHO, 2001

Economic Impact:
Increased Health expenditure,
Loss of Job,
reduced Productivity

Poverty:
economic deprivation, Low education, Unemployment

Mental & Behavioral Disorder:
High prevalence,
Lack of care,
More severe Course

Understanding the Illness
Treatment Decisions

Where to treat:
- Treatment setting
  - Outpatient
  - Day Hospital
  - Inpatient

How to treat:
- Treatment modality
  - Medication
  - Psychotherapy
  - Combination
  - ECT

What to treat:
- Symptom, disease, response, remission, comorbidity

How Long to treat:
- Short term and Long term Goals

When to treat:
- Prodrome
- Clinical depression
- Symptoms not fulfilling the criteria
- Subthreshold
- Sub-syndromal

Who should treat:
- Family Physician
- Counselor
- Psychologist
- Psychiatrist
- Social worker
- Nurse Practitioner

The way Forward
Assessment

Is there a preceding ‘life event’ & is it’ disappointment reaction

‘Yes- psychotherapy in the choice, medication are minimally effective

Is the patient at Risk for suicide, or physical impairment- Refer to secondary/tertiary Care

No, Classify Clinical features to determine ‘Biological Sub-type’

First Episode, H/O Previous episode, H/O previous response to drug

Is there a family History, what is the history Treatment, response and outcome

Are there other psychiatric illnesses/comorbidity or chances of personality disorder

Is there a medical illness present

Yes, Investigate

No, Is the patient on any medication that can cause depression? Deal accordingly

No RISK-→ Proceed

Diagnosis

The way Forward

Proceed
Using Diagnostic Criteria: DSM-IV; ICD-10, Nosological or Clinical, RDC.

Complete assessment

Quantify

List Clinical Priorities of the patient

Do essential Blood investigations & Thyroid Function, ECG

Discuss treatment Options, speed of recovery, Nature of illness & Expectations (patients’ expectations are different than Professionals)

Identify barriers to Compliance

Differential Diagnosis: Key to Success

- Transient disappointment
- Organic Depression
- Drug induced depression
- Secondary Depression (to medical or psychiatric Illness)
- Primary ‘Biological Depression
- Depression without Comorbidity of Axis I
- Depression with Comorbid Axis I & Axis II
### Depression Typology

<table>
<thead>
<tr>
<th>Agitated depression</th>
<th>Panic Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retarded Depression</td>
<td>Atypical depression</td>
</tr>
<tr>
<td>Melancholic-Psychotic depression</td>
<td>Cyclic Depression</td>
</tr>
<tr>
<td>Anxio-depressive state</td>
<td>Seasonal depression</td>
</tr>
<tr>
<td>Young-Hostile depression</td>
<td>Characterological depression</td>
</tr>
<tr>
<td>Obsessive-Compulsive Depression</td>
<td>Pre-psychotic Depression</td>
</tr>
<tr>
<td>Phobic Depression</td>
<td>Pre-menstrual</td>
</tr>
</tbody>
</table>
Diagnosing treatment resistance

- Was compliance adequate? **Y**
- Was dosage adequate? **Y**
- Was the duration of Tx adequate? **Y**
- Was the diagnosis correct? **Y**
- Was the assessment comprehensive? **Y**
- Was anything interfering with drug-kinetics? **N**
1. Depressed Mood
2. Suicide ideation or attempt

- Rule out psychological antecedents
- MD due to general medical condition
- Substance intoxication/withdrawal
- Substance-induced mood disorder
- > 2 weeks, with manic symptoms for >1 week; Mixed episode
- Organic Depression
- Polarity

TRD - Common Diagnosis
Focus on ‘symptoms constellation’
exclusion of physical & psychiatric conditions

- Depression within personality disorder
  - No manic or hypomanic feature
  - Major depressive episode
  - Has ever had manic/mixed episode & psychotic symptoms occur Schizoaffective type
  - No psychotic symptom, only manic episode: **BIPOLAR I disorder**
  - H/O hypomanic episode & at least one major depressive episode. **BIPOLAR II Disorder**
Differentiate treatment resistance from features of chronicity.

H/o Hypo manic >2 Yrs. & periods of depressed mood, CYCLOTHYMIA

BIPOLAR DIS. NOS, no H/o hypomania, depressed mood or 2 years.

Major depressive Disorder.

Hysteroid-dysphoric, Characterological, Young-hostile

DYSTHYMIA

Co morbidities: OCD, GAD, Psychosis, Impulse dyscontrol, sleep disorders.

DEPRESSIVE DIS. NOS ADJUSTMENT DIS
Towards a Comprehensive assessment of Depressive disorder.

Outcome

Low functioning
Life event & Stressors
HT, DM, CVD, Collagen Dis, cancer
Personality Dis, LD
Comorbidity, anxiety, SUD, eating Dis, PTSD

Axis V
Axis IV
Axis III
Axis II
Axis I
Classification of Mood Disorders

- **Unipolar**
  - Single episode
  - Recurrent
  - Dysthymia

- **Bipolar**
  - Bipolar I
  - Bipolar II
  - Cyclothymia
  - Unipolar-Hyperthymic

- **Depression**
  - With history of mania/hypomania
  - Without history of depression/mania

- **With history of depression**
  - With history of mania/hypomania
Bipolar Disorder is a Multidimensional Illness

Mania  Subsyndromal mania (hypomania)

Subsyndromal depression

Depression

Remission

Mania

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

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.
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
Dysthymic 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
Dysthymic 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
Dysthymic 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 suicidal 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               |
|                                 |
| episodic--chronic                |
|                                 |
| DEPRESSIVE DISORDERS            |
|                                 |
| episodic--chronic                |
|                                 |
| MAJOR DEPRESSION                |
|                                 |
| CYCLOTHYMIA                     |
|                                 |
| BIPOLAR                         |
|                                 |
| CYCLOTHYMIA                     |
|                                 |
| psychotic/ melanochlia/         |
| nonpsychotic  no melancholia    |
|                                 |
| psychotic/ nonpsychotic         |
| seasonal/ not seasonal           |
| mood congruent/ incongruent      |
|                                 |
Bipolar disorder
Classification of Mood Disorders

Unipolar
- Unipolar single episode
- Unipolar recurrent
- Dysthymia

Bipolar
- Bipolar I
- Bipolar II
- Cyclothymia
- Unipolar-Hyperthymic
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/hypomaniac 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

American Psychiatric Association 2000; Judd et al 2002; Tondo et al 2003;
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

- 53% Asymptomatic
- 32% Depressed
- 6% Manic/hypomanic
- 9% Cycling/mixed

86 bipolar II patients followed 13.4 years

- 50% Depressed
- 46% Asymptomatic
- 1% Manic/hypomanic
- 2% Cycling/mixed

*%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

146 Bipolar I Patients Followed 12.8 y

% wks

50
40
30
20
10

Subsyndromal, minor depressive, hypomanic symptoms
Major depression, mania

Judd LL et al. Arch Gen Psychiatry. 2002;59:530-537.

86 Bipolar II Patients Followed 13.4 y

% wks

50
40
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10

Subsyndromal, minor depressive, hypomanic symptoms
Major depression, mania

Judd LL et al. Arch Gen Psychiatry. 2003;60:261-269.
Psychosocial Outcome in Bipolar Disorder

- 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

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

Aspects of Daily Life Often Impacted by Bipolar Disorder

MDQ positive
MDQ negative

MDQ = Mood Disorder Questionnaire

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

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.

- Healthy life: Reduced by 12 years
- Working life: Reduced by 14 years
- Life expectancy: Reduced by 9 years
- Employment problems: Twice as common
- Divorce / separation: Twice as common

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

Coryell et al 1993; Scott 1995
Addressing Diagnostic Issues
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]
The prevalence and epidemiology of psychiatric comorbidities in bipolar disorder is high.

- Stress sensitive medical disorder prevalent
- Cardiometabolic disorders most common specific cause

Comorbid Conditions Complicate Diagnosis and Management of Bipolar Disorder

- Impaired psychosocial functioning
- Decreased QoL
- More severe disease course
- Possible earlier age of onset
- Complicates diagnosis and treatment
- Greater risk of depressive and mixed episodes and suicidal behaviour
- Poorer treatment adherence

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)
# Diagnostic Overview (DSM-IV-TR)

<table>
<thead>
<tr>
<th>Bipolar I</th>
<th>Bipolar II</th>
<th>Bipolar NOS</th>
<th>Cyclothymia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manic or mixed episode</td>
<td>Hypomania ≥ 4 days</td>
<td>Do not meet specific criteria for bipolar I or II disorder, e.g., hypomania for &lt;4 days</td>
<td>≥ 2 years</td>
</tr>
<tr>
<td>Obvious symptoms and functional impairment</td>
<td>Never a manic or mixed episode</td>
<td>Usually with recurrent depression</td>
<td>Mood states do not meet full criteria for depressive, manic, or mixed episode</td>
</tr>
<tr>
<td>Usually with recurrent depression</td>
<td>Recurrent depression</td>
<td>Usually with recurrent depression</td>
<td>Dysthymia</td>
</tr>
</tbody>
</table>
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.

Features of Hypomania

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

<table>
<thead>
<tr>
<th>Hypomania</th>
<th>Mania</th>
</tr>
</thead>
<tbody>
<tr>
<td>Little to mild dysfunction</td>
<td>Severe dysfunction</td>
</tr>
<tr>
<td>Little to mild, lapses of judgment</td>
<td>Major lapses of judgment</td>
</tr>
<tr>
<td>Commonly responds to outpatient management</td>
<td>Often requires inpatient treatment</td>
</tr>
<tr>
<td>Non-psychotic symptoms</td>
<td>Psychotic symptoms</td>
</tr>
</tbody>
</table>

- Patients with hypomania have a distinct period of persistently elevated, expansive, or irritable mood, lasting for $\geq 4$ days, that is different from usual non-depressed mood
Features of Bipolar Depression

**Affective**
- Sadness
- Poor self-esteem
- Apathy
- Poor concentration
- Anhedonia
- Irritability
- Suicidal ideas
- Anxiety
- Self-blame

**Cognitive**
- Change in sleep
- Change in appetite
- Indecisiveness
- Decreased activity
- Low energy
- Change in weight

**Physical**
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

Choosing a Treatment Regimen
Therapeutic Objectives

Phase of Treatment
- Acute Mania
- Acute Depression

Objective
- Symptom Remission
- Full Psychosocial Functioning
- Maintain Functioning & Prevent Relapses
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
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

# Treatment Options for Bipolar Disorder

<table>
<thead>
<tr>
<th>Lithium</th>
<th>Atypical antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Divalproex</td>
<td>- Clozapine</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>- Olanzapine</td>
</tr>
<tr>
<td>Carbamazepine and other anticonvulsants</td>
<td>- Quetiapine</td>
</tr>
<tr>
<td></td>
<td>- Quetiapine XR</td>
</tr>
<tr>
<td></td>
<td>- Risperidone</td>
</tr>
<tr>
<td></td>
<td>- Ziprasidone</td>
</tr>
<tr>
<td></td>
<td>- Paliperidone</td>
</tr>
<tr>
<td>Typical antipsychotics</td>
<td>- Aripiprazole*</td>
</tr>
<tr>
<td></td>
<td>Antidepressants</td>
</tr>
</tbody>
</table>

* 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
• Texas (Department 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

<table>
<thead>
<tr>
<th>Agents</th>
<th>Acute Bipolar Depression</th>
<th>Acute Mania</th>
<th>Maintenance Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATYPICALS</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Clozapine (Clozaril®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine (Zyprexa®)</td>
<td></td>
<td>√</td>
<td>√*</td>
</tr>
<tr>
<td>Quetiapine (SEROQUEL XR®)</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Risperidone (Risperdal®)</td>
<td></td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Paliperidone (Invega ®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ziprasidone (Zeldox®)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>OTHER</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
<td>√</td>
<td>√+</td>
</tr>
<tr>
<td>Divalproex</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lamotrigine</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td></td>
<td>√</td>
<td></td>
</tr>
</tbody>
</table>

+ 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.*

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