Mood disorders

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Neurobiology of mood disorders
Mood and affect

• Mood:
  – a pervasive and sustained emotion that colours the person’s perception of the world
  – examples: depression, anxiety

• Affect:
  – external expression of mood
    Affect is variable over time, in response to changing emotional states
  – examples: sadness, anger, euphoria

Affective/mood disorders

• Depressive episode
• Recurrent depressive disorder
• Manic/hypomanic episode
• Bipolar affective disorder
• Persistent mood disorders:
  – dysthymia
  – cyclothymia
• Other and unspecified mood disorders
Epidemiology of depression

• Annual incidence: 1.59%
  – F: 1.89%
  – M: 1.1%

• Lifetime prevalence: 17%
  – F: 9-26%
  – M: 5-12%

• Sex
  F > M (2:1)
  – hormonal differences?
  – effects of childbirth?
  – different social stressors?
  – learned helplessness?
Epidemiology of depression

• Age
  – Mean age: 40 yrs (20-50)

• Marital status
  – most often in person without close interpersonal relationship/ divorced/ separated

Epidemiology of depression

• Socioeconomic & cultural factors
  – no correlation with socioeconomic status
  – more often in rural than urban areas

• No differences between races
Comorbidity

- Increased risk of having more Axis I disorders
  - alcohol abuse/dependency
  - panic disorder/ OCD
  - social phobia
  - eating disorders (F)

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<th>Subst. use</th>
<th>Panic</th>
<th>OCD</th>
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<tr>
<td>MDD</td>
<td>27%</td>
<td>10%</td>
<td>12%</td>
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<tr>
<td>BD</td>
<td>61%</td>
<td>21%</td>
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Etiology of mood disorders

- Biological factors:
  - genetics
  - neurotransmitters
  - structural/ functional changes
  - psychoneuroendocrynological factors
  - photic changes (SAD)

- Psychosocial factors
  - life events
  - personality
Genetics

• Lifetime risk for the development of mood disorders:
  – 1 parent: 10-25%,
  – both parents: 20-50%.

• Twin studies:
  – monozygotic: 50-90%,
  – dizygotic: 16-35%.

• Molecular genetics:
  – causative genes: on chromosomes X, 11, 18q, 22q, 1, 4, 5, 6, 7, 10, 16, 21.

Neurotransmitters and mood

• Monoamine hypothesis:
  – Serotonin (5-HT),
  – Noradrenaline (NA),
  – Dopamine (D).
Monoamine hypothesis

• Antidepressants act as:
  – monoamine reuptake inhibitors (TCA, SSRI)
  – monoamine oxidase inhibitors (RIMA, IMAO)

• Amphetamine
  – lifts mood (structure similar to monoamines)

• CSF level reduction of 5-HT metabolite in depression

Psychoneuroendocrynological factors

• Disturbances of hypothalamus-pituitary-adrenal axis:
  – ↑ corticotrophin (ACTH), ↑ cortisol,
  – ↑ neuropeptides (NPY, SP, TRH, CRH, β-endorphin).

• Changes in thyroid hormones, growth hormone and prolactine

• Association with endocrinopathies (hypo- and hyperthyreosis, Cushing’s, Addison’s disease)
Psychoimmunology

• Interleukines (IL-1→12).
• Tumor Necrosis Factors (TNF).
• Interferons (IFN-α, -β, -γ).
• Other (M-CSF, G-CSF, MG-CSF).

Structural changes

• Decreased volume of:
  – frontal lobes
  – parietal lobes
  – hippocampus
  – subcortical nuclei
• Increased volume of:
  – lateral ventricles
  – third ventricle
**Major depressive disorder**

*DSM-V*

- A patient with major depression will experience at least 5 symptoms. These symptoms must be present for most of the day, nearly every day for at least TWO weeks.

- Persistent depressed mood
- Pervasive anhedonia (loss of interest/pleasure)
- Change in weight (+/- 5%) or appetite
- Sleep disorder (insomnia/hypersomnia)
- Psychomotor retardation/agitation
- Fatigue/loss of energy
- Guilt/low self-esteem
- Difficulty concentrating/indecisiveness
- Recurrent thoughts of death or suicide
Special types of Depression

• Melancholic
  – Anhedonia, severely depressed mood
  – Somatic symptoms (worse in the morning, early morning awakening, weight loss, loss of libido, excessive guilt)
  – More common in elderly
• Atypical
  – Overeating, oversleeping, anxiety
• Catatonic (extremely rare)
  – Catalepsy, motoric immobility/negativism, echolalia, echopraxia

Special types of Depression (2)

• Seasonal Affective Disorder
  – Excessive sleep, weight gain, carbohydrate craving
  – Melatonin produced only in dark (winter blues, cabin fever)
  – Morning phototherapy
• Postpartum onset
  – maximum 5%, onset within 4 weeks postpartum
  – 50-80% blues within 1-5 days postpartum
  – 1/1000 psychotic depression or mania within 1-3 days postpartum
  – More severe reactions predict similar in future births
Psychotic Symptoms

- Hallucinations & delusions in depression or mania
- mood congruent:
  - in depression (inadequacy, guilt, disease, death, nihilism, punishment)
  - in mania (inflated worth, power, knowledge, identity, special relationship to deity or famous person)
- mood incongruent:
  - in depression and mania (eg. paranoid)
- Poorer prognosis

Physical Symptoms

- Headache
- Vague
- Sleep disturbances
- Fatigue
- Aches and pains
- Back pain
- Significant change in appetite resulting in weight loss or gain
- Constipation
Mood disorders: Special Populations

• Elderly
  – Late onset common & chronic, marked by sleep difficulties, hypochondriasis, agitation.
  – Complicated by dementia.
  – Equal prevalence for men and women.

• Children
  – Very young manifest changes in facial expression, eating, sleeping & play.
  – Older children's mimic adults.
  – Depression & Bipolar peak in adolescence.
  – Bipolar adolescents impulsive, accident-prone.
  – Conduct disorder for boys.
  – Dangerous due to skyrocketing suicide attempts during adolescence.

Dysthymia

• Dysthymia, milder but persistent (2 years for diagnosis).
• Median Duration: 5 years, with little improvement across lifespan (can last 20-30 years).
• Early vs. Late Onset Dysthymia
  – Early Onset (before 21 years): 1) greater chronicity, 2) poorer prognosis, and 3) greater likelihood of familial transmission.

• Double Depression (40% of those with major depressive disorder), dysthymia & major depressive episodes (61% do not recover within 2 years), severe psychopathology, pessimistic prognosis.
Dysthymia

- Chronic (>2 years) depression of mood.
- Does not fulfill the criteria for recurrent depressive disorder
- 5-6% of population

Minor depressive disorder

- Episodes of slightly depressive mood
- Does not fulfill the criteria for recurrent depressive disorder
Recurrent Brief Depressive Disorder

- Brief (<2 weeks) episodes of depression
- Does fulfill other criteria for recurrent depressive disorder

Premenstrual dysphoric disorder

- Depression, anxiety, affective lability, decreased interest in activity in most menstrual cycles in past year
- Symptoms only during last week of the luteal phase
- Symptoms severe enough to markedly interfere with work, school, or unusual activities
- Absent for at least 1 week postmenstrually
Secondary mood disorders

1. Caused by a general medical condition
   • hormonal changes, neurologic (eg. stroke, SM), oncologic, cardiologic conditions…

2. Substance-induced mood disorder

Treatment of depression

• TCA’s
• MAOI’s
• SSRI’s
• SNRI’s
• NaSSA’s
• 5-HT₁ agonists
• Atypical antipsychotics
• Psychostimulants
• Herbals
• Experimentals
Treatment of depression (2)

- cognitive-behaviour therapy
- psychoanalytic psychotherapy
- interpersonal therapy
- family and group therapy
- electroconvulsive therapy (ECT)

Treatment of depression - Efficacy

- SSRI’s  63%
- TCA’s  60%
- Placebo  35%

- TCA’s > MAOI’s in severe depression
- MAOI’s > TCA’s in atypical depression
Treatment of depression - Efficacy

(2)

- High-dose TCA's 70-80% effective in severely depressed inpatients
- Venlafaxine (2nd gen. SNRI)
  - Approaches this efficacy in high doses (>150 mg)
  - at lower doses equivalent to fluoxetine, paroxetine
Mood disorders (2)
Bipolar disorder

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Epidemiology of bipolar disorder

• Annual incidence: <1%
  M=F
• M: more common manic episodes
• F: more common depressive, mixed episodes, more often rapid cycling
Genetics of BD

- **Genetics (susceptibility):**
  - polygenic (many genes)

- **Environment (triggers):**
  - rough times/stress
  - alcohol and drugs
  - big changes
  - poor nutrition

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Etiology - genetics

- **Twin study**–
  Concordance rates of 67% for MZ twins, 20% for DZ for bipolar disorder

- **Neurotransmitter deficiencies** –
  catecholamines (NE and serotonin)

- **Monoamine hypothesis** – shortage of NE, D, 5-HT
Patterns of inheritance

Sample pedigree chart:

If you have…

- identical twin with bipolar:
  - 50-60% chance of bipolar
  - 75% chance of depression

- 1st degree relative (child, parent, sibling) with bipolar:
  - ~8% chance of bipolar
  - ~10% chance for depression

- two parents with bipolar:
  - 30-75% chance of bipolar

- 2nd degree relative (aunt, uncle, cousin, grandparent) with bipolar:
  - 1% chance of bipolar
  - 5% chance for depression

- no affected relatives with bipolar (gen. population):
  - 1% chance of bipolar
  - 5% chance of depression

Types of Bipolar Disorder

- Bipolar I (Mania & Depression).
- Bipolar II (Hypomania & Depression).
- Bipolar III (Treatment induced Mania or Hypomania).
- Bipolar IV (Relative with BPD, presents with only depression).
Manic Episode:

DSM-V

- Elevated, expansive or irritable mood for at least 1 week
- At least three of the following symptoms must be present with the “elevated, expansive, or irritable” mood; if the mood is only irritable, four symptoms must be present.

- 1 inflated self-esteem or grandiosity
  2 decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
  3 more talkative than usual or pressure to keep talking
  4 flight of ideas or subjective experience that thoughts are racing
  5 distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
  6 increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
  7 excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

Hypomania/Manic episode

- Elevation of mood (elation or irritability).
- High energy, overactivity, pressure of speech, loss of social and sexual inhibition.
- Lack of sleep.
Depressive episode

- Depressed mood, anhedonia, pessimism, worthlessness, suicidal thoughts, diurnal variation of mood.
- Psychomotor retardation, reduced energy and activity, tiredness, low attention and memory.
- Biological symptoms, sleep disturbance, reduced appetite, libido and weight, constipation.
- Anxiety (free-floating).

Mixed affective state

- The criteria are met for both a manic and major depressive episode nearly every day for at least a week
- Causes marked impairment in social, occupational or interpersonal functioning
- May be psychotic features
- May require hospitalization
Mixed states

- DSM V-meet criteria for depressive and manic episodes every day for at least 1 week
- Severe stage of mania, intermediate stage between mania and depression, a distinct state
- Turbulent course, increased suicidal risk, poorer response to lithium, better to valproate/CBZ
- 30-40% of all manic episodes
- Dysphoric mania (McElray et al, 1992) mania + depressed mood, anhedonia, hypersomnia, fatigue, weight gain, feelings of hopelessness, worthlessness, suicidal ideation

Cyclothymia

- Chronic instability of mood.
- Numerous periods of mild depression and elation.
Rapid cycling

- At least 4 episodes of a mood disturbance in the previous 12 months that meet criteria for a major depressive, manic, mixed or hypomanic episode
- 2 months interval between similar episodes or switch to an episode of opposite polarity

Lithium

- Efficacy: 49-70%
- Onset of action: 5-21 days
- Predictors of response: classic mania; few episodes; manic-depressive illness episode sequence
- Tolerability: weight gain, neurocognitive, renal, gastrointestinal, endocrine side effects
Divalproex

- Efficacy: 49-65%
- Onset of action: 3-10 days
- Predictors of response: comparable efficacy in classic, mixed and rapid cycling
- Tolerability: gastrointestinal, neurocognitive, hematopoietic side effects; weight gain

Carbamazepine

- Efficacy: 27-63%
- Onset of action: 7-14 days
- Predictors of response: not consistently established
- Tolerability: neurocognitive, dermatologic, hematopoietic side effects
Other Anticonvulsants

- Gabapentin: open trials suggest mood-stabilizing effects as add-on; not confirmed in double-blind, controlled trials
- Lamotrigine: open trial suggest mood-stabilizing effects as add-on or monotherapy; antidepressant effect confirmed in placebo-controlled trial
- Topiramate: open trials suggest mood-stabilizing effects as add-on; no data from controlled trials; anorexia may be a positive side effect

Antipsychotics in Mania

- Use is nearly universal in mania, especially hospitalized patients
- 60-70% of patients in two studies were still on antipsychotics after 6 months, regardless of clinical status
- Atypical antipsychotics as mood stabilizers