Mood (s. Affective) Disorders

Last updated: April 24, 2019

MOOD (S. AFFECTIVE) DISORDERS - ***disturbance of mood*** along happy-sad axis.

Two basic mood abnormalities, **depression** and **mania**, occur on *continuum from normal to clearly pathological*. While minor symptoms may be extension of normal sadness or elation, more severe symptoms are associated with discrete syndromes (affective disorders) that differ qualitatively* from normal processes. **Depression** is morbid sadness, dejection, or melancholy, whereas **mania** is disordered mental state of extreme excitement. Both have accompanying ***emotional*** - ***cognitive*** - ***motoric*** features.

*overly intense, continue longer than expected for causative event, occur without cause + impaired function!

ETIOPATHOGENESIS

- interaction of **GENETIC**, **BIOLOGIC** and **PSYCHOSOCIAL** factors determines which individuals will develop mood disorders.

Historical concept - EXOGENOUS-ENDOGENOUS DICHOTOMY - **endogenous** depression (caused by biologic factors) and **exogenous** depression (caused by loss or other environmental stresses)

ETIOLOGY

- over years, experts have debated whether mood disorders represented ***brain disease*** or reflected ***intrapsychic conflicts***; recently, they have returned to belief that conditions represent multifactorial biologic process.

GENETIC FACTORS

- mood disorders ***run in families*** - mood disorders are at least partly genetic.
- no single chromosomal site seems to play dominant role (i.e. multiple different genetic loci, each of small effect).
- ***expanding triplet repeats*** may account for finding that bipolar illness has earlier onset and more severe symptomatology in subsequent generations of some families.

MAJOR DEPRESSIVE disorder

- ≈ 50% patients have 1st-degree relative with mood disorder (more often depression than bipolar);
- concordance for monozygotic twins ≈ 50%, for siblings (including fraternal twins) ≈ 15%.

BIPOLAR disorder (*higher genetic influence* than in major depressive disorder!)

- ≈ 90% patients have 1st-degree relative with mood disorder (either bipolar or depressive);
- concordance for monozygotic twins ≈ 33-90%, for siblings (including fraternal twins) ≈ 5-25%.
- 1st-degree relatives of patient with BP I are 7 times more likely to develop BP I than general population.

Multiple vulnerability genes operate in different families by different mechanisms and through complex interactions with life events

NEUROCHEMICAL FACTORS

All clinically useful antidepressants potentiate, either directly or indirectly, actions of **NOREPINEPHRINE**, **DOPAMINE**, and/or **SEROTONIN** in brain → **BIOGENIC AMINE THEORY**:

depression is due to *deficiency* of biogenic amines at certain key sites in brain; vs. **mania** is caused by *overproduction* of these neurotransmitters

NOREPINEPHRINE is associated with mood disorders:
- some **antidepressants** (e.g. DESIPRAMINE, NORTRIPTYLINE) ***down-regulate β-receptors***.
- NE metabolites are generally diminished in depression.
- increased NE activity has been speculated to be involved in mania.

SEROTONIN
- **selective serotonin reuptake inhibitors** are effective antidepressants.
- 5-HT depletion (e.g. by tryptophan-depleted diet) can worsen depression.

DOPAMINE is less solidly linked to depression.
- BUPROPION is effective antidepressant that is dopaminergic without directly affecting 5-HT or NE transmission.
- *Parkinson disease* (dopaminergic dysfunction) often leads to depressive symptoms.

OTHER BIOLOGIC FACTORS

Neuroendocrine regulation
- overactive *hypothalamic-pituitary-adrenal axis* in depression – in dexamethasone suppression test depressed patients exhibit ***nonsuppression*** (i.e. cortisol remains elevated after administration of dexamethasone).
- *hypothyroidism* may mimic depression, and *hyperthyroidism* may mimic mania.

Sleep and circadian rhythm
- depressed patients experience insomnia or hypersomnia; manic patients typically have decreased need for sleep.
- in polysomnography many depressed patients have **shortened rapid eye movement (REM) latency** (i.e. time from falling asleep to first REM period is about 60 minutes rather than 90 minutes).
- **sleep deprivation** is effective treatment for depression (although depression returns after next night's sleep).

Kindling (repeated, subthreshold stimulation of brain eventually results in seizure activity) – for bipolar illness: some patients have first episode of illness in response to stress (e.g. loss), with subsequent episodes following lower-grade stress, and spontaneous episodes eventually occur.

PSYCHOLOGICAL AND SOCIAL FACTORS

- stress commonly precedes first episode of both major depression and mania (stress precipitates brain changes, which make individual more vulnerable to future mood episodes).
- loss of parent before age of 11 years has been linked to depression in adulthood.
- some psychodynamic theorists have proposed that depression represents **anger turned inward**; that is, person becomes angry at loved one (often one who was lost) but, because such anger is intrapsychically unacceptable, patient experiences depression and self-hatred.
- animal model of depression - **learned helplessness** (animal exposed to inescapable shock will, over time, fail to escape shock even when given opportunity); antidepressant medications reverse this behavior.

DIAGNOSIS

- requires identification of **mood episodes**, which are not actual diagnoses in themselves (rather, they are building blocks clinicians use in making diagnosis of mood disorder):

N.B. if patient has ever had psychotic features (delusions or hallucinations) for at least 2 weeks in absence of mania or major depression, then **psychotic disorder** (rather than **mood disorder with psychotic features**) must be diagnosed.

N.B. if mood change is due to **general medical condition** or **substance use** other mood disorder diagnoses (e.g. major depressive disorder) are not made!

e.g. 69-year-old man recently suffered left anterior stroke and now has major depressive symptoms = mood disorder due to cerebrovascular accident, with major depressive-like episode;
32-year-old woman presents to ED with manic behavior with traces of amphetamine in her urine = amphetamine-induced mood disorder with manic features, with onset during intoxication.

1. MAJOR DEPRESSIVE EPISODE (MDE)

A. ≥ 5 of following symptoms have been present during same 2-week period and represent change from previous functioning (baseline); at least one of symptoms is either (1) depressed mood or (2) loss of interest / pleasure.
1. **Depressed mood** most of day, nearly every day, as indicated by either subjective report (e.g. feels intense sadness, hopelessness, despair) or observation made by others (e.g. appears tearful); in children and adolescents, irritable mood suffices.
2. Markedly **diminished interest*** **/ pleasure** (anhedonia) in all, or almost all, activities most of day, nearly every day (as indicated either by subjective account or observation made by others). *commonly extends to *loss of libido*.
3. Significant weight loss / weight gain when not dieting (> 5% of body weight in 1 month), or decrease / increase in appetite nearly every day; in children, consider failure to make expected weight gains.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation* / retardation** nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
   *pacing, hand wringing (N.B. agitated patients do not apply this energy in useful, purposeful activities, vs. manic patients)
   **soft speech, lack of eye contact, immobility, loss of spontaneous movement + flattening or loss of reactivity in patient's affect
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive / inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
   Negative thinking (often with ruminative features) predominates!
8. Diminished ability to think / concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others) – i.e. affected cognition!
9. Recurrent thoughts of death (not just fear of dying); recurrent suicidal ideation (with or without specific plan; or suicide attempt).

B. Symptoms cause ***clinically significant distress*** or ***impairment in functioning*** (social, occupational or other important areas).

C. Symptoms are **not due to** direct effects of **substance** (e.g. drugs of abuse, medication) or **general medical condition** (e.g. hypothyroidism).

D. Symptoms are not better accounted for by **bereavement** (i.e. after loss of loved one, symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation).

- major life stresses (esp. separations and losses) commonly precede MDE.
- attack gradually builds over period of week to month, and if untreated may last 3-8 months.
- in *primary care setting*, presenting complaints often can be somatic (fatigue, headache, abdominal distress, change in weight).

- some patients demonstrate *mood congruent* **psychotic features** (i.e. content of delusion or hallucination reflects depression):
  e.g. mood-congruent delusion might be belief that one has committed terrible crimes or sins; mood-congruent hallucination might be voice that tells one to die or says that one is loser.
  - psychotic features should prompt evaluation to rule out bipolar disorder, schizophrenia or schizoaffective disorder, substance abuse, or organic brain syndrome!
- depression can produce measurable **cognitive deficits / worsening of preexisting dementia** (appears to arise from impaired concentration or motivation) - dementia of depression (s. pseudodementia) - remits with successful treatment of MDE.
- decline in **grooming** and **hygiene** can be observed; **nutrition** may be severely impaired, requiring immediate intervention.
- typical **neurovegetative symptoms** are insomnia (initial insomnia [trouble falling asleep], or middle insomnia [awakening during night], or terminal insomnia [early morning awakening]), decreased appetite.
  in **ATYPICAL depression** - oversleeping, increased appetite (with weight gain), rejection sensitivity.
- *elderly persons* experience more somatic - cognitive symptoms (confusion with general decline in functioning) and fewer complaints of sad or dysphoric mood; of particular importance is increasing risk of suicide among elderly men.
- *children* may present with misleading symptoms – marked irritability (!!!), decline in school performance, social withdrawal, somatic complaints (headaches, chest, abdominal, or back pains);
  - **children 7-30 months** may demonstrate ***ANACLITIC DEPRESSION***; cause is lengthy separation (> 1 week) from caregivers with whom child has established attachment relationship; symptoms - listlessness, anorexia, psychomotor retardation, sad facial expressions; treatment - restitution of relationship.
  - **preschool children** often demonstrate behavioral difficulties (hyperactivity, aggression) - often called ***DEPRESSIVE EQUIVALENTS***.
  - **schoolchildren** already manifest usual signs and symptoms of depression.

Differential diagnosis of MDE:

(1) **Other psychiatric disorders** with high incidence of affective symptoms - anxiety disorders, eating disorders, personality disorders (can be difficult to determine in setting of acute affective symptoms!)

(2) **Substance-induced** mood disorder:
a) intoxication with depressant drugs (e.g. alcohol, opiates, barbiturates)
b) withdrawal from stimulants (e.g. cocaine, amphetamines)
c) steroids
d) antihypertensives (reserpine, propranolol, methyldopa, Ca-channel blockers)
e) medications that affect sex hormones (estrogen, progesterone, testosterone, GnRH antagonists).
f) H_2 blockers
g) chemotherapy agents
h) sedatives; muscle relaxants; appetite suppressants.

(3) Mood disorders due to **general medical condition**:
a) ***neurologic disorders*** - stroke (particularly of left frontal lobe), seizure disorders, MS, Huntington disease, Parkinson disease (!!!), sleep apnea (!), encephalitis, HIV, neurosyphilis, tuberculosis, brain tumors (diencephalic, temporal region).
b) disorders involving ***hypothalamic-pituitary-adrenal axis*** or ***thyroid*** (Cushing disease, hypothyroidism).
c) ***other*** - pernicious anemia, pancreatic cancer, renal failure.

(4) **Normal forms of sadness** - **grief** (normal emotional response to loss), **bereavement** (normal emotional response to death of loved one).
N.B. diagnosis of major depressive disorder is not usually made unless MDE criteria are still met 2 months after loss (symptoms and duration of "normal" bereavement vary among cultures!); also some symptoms are atypical of normal bereavement (e.g. hallucinations unrelated to loss, prolonged functional impairment).
Normal forms of sadness do not respond favorably to psychotherapy or antidepressants.

2. MANIC EPISODE

A. Distinct period of abnormally and persistently **elevated, expansive, or irritable mood** lasts at least 1 week (or any duration if hospitalization is necessary).
B. *During period of mood disturbance*, at least three of following symptoms have persisted (four if mood is only irritable) and have been present to significant degree:
   1. Inflated self-esteem or grandiosity (up to grandiose delusions).
      i.e. extreme self-confidence with impaired judgment.
   2. Decreased need for sleep (e.g. feels rested after only 2-3 hours of sleep) .
   3. More talkative than usual or pressure to keep talking (***pressured speech***).
   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) – demonstrated by vigilance tests (part of mental status exam).
   6. Increase in goal-directed activity (e.g. socially, at work or school, or sexually) or psychomotor agitation.
   7. Excessive involvement in pleasurable activities that have high potential for painful consequences (e.g. gambling, sexual promiscuity, reckless driving, unrestrained buying sprees, foolish business investments).
C. Mood disturbance is sufficiently severe to cause ***marked impairment*** in occupational functioning or in usual social activities or relationships with others or to ***necessitate hospitalization*** to prevent harm to self or others, or there are ***psychotic features****.
   *psychotic features (delusions [75% patients], hallucinations, and disorganization) are most often *mood congruent*; severity can be similar to schizophrenia.
D. Symptoms are not due to direct effects of **substance** (e.g. drugs of abuse, medication) or **general medical condition** (e.g. hyperthyroidism).

Note: manic episodes that are clearly precipitated by somatic antidepressant treatment (e.g. medication, electroconvulsive therapy, light therapy) should not count toward diagnosis of bipolar I disorder.

- manic episode usually develops over few days.
- garments often are too bright, colorful, or garish – patients stand out in crowd because their dress frequently attracts attention.
  N.B. public nakedness is nearly always pathognomonic for mania!
- patient can be openly combative and aggressive, highly demanding with no patience or tolerance for others + grandiose belief that others must obey their commands, wishes, and directives → risk of **homicide**!!! (vs. MDE – suicide).
- at times it is difficult to distinguish excited schizophrenic patient from manic one (one must examine longitudinal course of illness).

Differential diagnosis of manic episode:

1. **Substance-induced mood disorder** - intoxication (cocaine, amphetamine, corticosteroids, dopamine agonists, anticholinergics, cimetidine), antidepressant drugs (can "switch" patients from depression to mania).
2. **Mood disorder due to general medical condition** (AIDS, Cushing disease, hyperthyroidism, lupus, temporal lobe epilepsy, MS, Wilson disease, neurosyphilis).

3. MIXED EPISODE

– satisfied criteria for both **manic episode** and **MDE** over 1-week period.

4. HYPOMANIC EPISODE

– similar but **less severe than manic episode**:

a. episode lasts ≥ 4 days.
b. episode must not lead to hospitalization, must not include psychotic features (e.g. delusions), and must not cause severe social / occupational impairment.

- for some people, hypomanic states contribute to success in business, leadership, achievement, and artistic creativity; however, they more often have serious detrimental interpersonal and social results (e.g. interpersonal relationships are often stormy).

CLASSIFICATION

Disorder	Major Depressive Episode	Milder Depression	Manic or Mixed Episode	Hypomania
Major depressive	+	±	–	–
Dysthymia	– [1]	+	–	–
Bipolar I	±	±	+	±
Bipolar II	+	±	–	+
Cyclothymia	–	+	– [2]	+

\+ = syndrome must be present to make diagnosis;
– = syndrome must be absent to make diagnosis;
± = this syndrome may be present or absent.

[1]major depressive episode must not occur during first 2 years of illness.
[2]manic episode must not occur during first 2 years of illness.

Bipolar I = mania ± other.
Bipolar II = depression + hypomania.

DSM-IV provides **SPECIFIERS** that better describe current (or most recent) mood episode:

1. **Severity/remission status** - mood episodes can be: mild / moderate / severe* and in partial / full remission.
   *presence / absence of ***psychotic features*** should be noted (psychotic features should be described as *mood-congruent* or *mood-incongruent*).
2. **Catatonic features** - when mood episode features two of following:
   a) immobility
   b) excess purposeless activity
   c) negativism or mutism
   d) posturing, mannerisms or stereotypic behaviors
   e) echolalia or echopraxia.

TREATMENT

- patients with mood disorders are most often treated in **outpatient settings** by clinicians other than mental health professionals.
- indications for **voluntary or involuntary HOSPITALIZATION**:
  1) dangerous / disorganized patients
     All treating physicians must assess risk of suicide at each visit!
  2) failed outpatient treatment – in hospital, doses can be advanced more rapidly + side effects can be rapidly identified and alleviated

N.B. mood disorders are often recurrent! - good follow-up care after acute episode is key to successful treatment!

MAJOR DEPRESSIVE DISORDER (MDD)

- presence of ≥ 1 major depressive episode(s) + absence of any manic, hypomanic, or mixed episodes.

- patients are at risk for other psychiatric conditions (e.g. alcohol or other substance abuse, anxiety disorders).

MELANCHOLIA (*more severe subtype* of major depression) = profound anhedonia + three of following:

a. distinct quality to sad mood (e.g. it does not resemble normal grief or sadness)
b. symptoms worse in morning
c. early morning awakening
d. marked psychomotor changes
e. marked anorexia / weight loss
f. excessive guilt

EPIDEMIOLOGY

- lifetime risk 20% for women, 12% for men (i.e. ≈ 15 times more common than bipolar disorder).
  Primary care providers should strongly consider presence of depression in their patients!
  Major depression is most common psychiatric disorder!!!
- risk factors:
  1) 1st-degree relatives with mood disorders. *see above >>*
  2) chronic medical illnesses, alcoholism, panic disorder, psychosocial stress* – these can play role in both initiation and maintenance of MDD.
     *significant losses in early life predispose to MDD over lifespan of individual!
- point prevalence: 2-4% for men, 4-6% for women.
- women : men = 2 : 1
- mean age of onset - **mid 20s** (range from preschool childhood to old age); rates are highest in 25-44 years.
  – of teenagers diagnosed with MDD, bipolar disorder is diagnosed in 50% of them as they grow into adulthood.

DIAGNOSIS

Diagnosis lies in **history** and **mental status examination**!

Results of **dexamethasone suppression test (DST)** are positive if patient fails to suppress plasma cortisol levels to < 5 μg/dL between 8 and 24 hours after oral dose of 1 mg dexamethasone given at 11:00 P.M. night before.

- DST is not useful for diagnosis - false-negative rate ≈ 50%.
- DST can be useful for monitoring treatment of patients who have abnormal DST response.

EEG - relative absence of slow-wave sleep (stages 3 and 4), shortened period between sleep onset and first dreaming period (REM latency), lengthened first REM episode & shortened first NREM episode

- these disturbances of sleep improve when mood disturbance improves.

TREATMENT

Thought content always should be assessed for suicidal/homicidal/violent ideation!

- ***physical activity & exercise*** contribute to recovery from MDD.
- **REMISSION** - minimal or no symptoms; **RESPONSE** - 50% reduction in symptoms.

PSYCHOTHERAPY

a) **psychodynamic** (psychoanalytically oriented) **psychotherapy** - most commonly used with depressed patients.
b) effective intensive brief forms of time-limited therapy - **cognitive psychotherapy** and **interpersonal psychotherapy**.

- patients are usually relieved when their suffering is recognized and they are permitted to discuss it.
- psychotherapy is most effective once somatic and melancholic symptoms have improved with medication.
- long-term psychotherapy is unnecessary.
- **support** is important - ***family & friends, day hospitalization, supportive living arrangements*** (group homes).

MEDICATIONS

1. **Antidepressants** see p. Psy15 >>
   SSRIs are first-line drugs for depression!
2. **Psychostimulants** (DEXTROAMPHETAMINE, PEMOLINE, METHYLPHENIDATE) - augmenting agents in ***resistant depression*** (esp. patients who are medically ill).
3. **Antipsychotic medications** – for depression with ***psychotic features***.
4. **Thyroid hormones** (LIOTHYRONINE) - may convert nonresponders (to antidepressants) to responders by increasing receptor sensitivity and enhancing effects of TCAs.

- it is standard of care to initiate antidepressant at time of diagnosis.
- always ask how patient's relatives with depression fared on different antidepressant drugs, because new patient will likely fare similarly.
- ***follow-up ambulatory visits*** should be scheduled on regular basis and more frequently than for other medical treatments; if improvement has not begun in 4-8 weeks → psychiatric consultation.
  N.B. treatment failures often are caused not by clinical resistance, but by noncompliance / inadequate duration of therapy / inadequate dosing!
- treatment duration:
  – once episode is resolved successfully, treatment should be continued for 6 months ÷ 1 year (to reduce risk of relapse);
  – most antidepressants (esp. SSRIs) should be tapered off (by decreasing dose by ≈ 25%/week) rather than discontinued abruptly.
  – most experts now agree that children who have experienced ≥ 2 major depression episodes should be treated indefinitely.

ELECTROCONVULSIVE THERAPY (ECT)

- safe and effective treatment. see p. Psy5 >>

- extremely effective in severe depression!!!
- more rapid onset of action than drug treatments.
- reserved for:
  a) those who have ***failed trials of antidepressants***.
  b) depression with ***psychotic features***
  c) severe ***suicidal*** depression
  d) depression during ***pregnancy***
  e) patients who have ***stopped eating***.
- relapse after ECT is common, and drug therapy is often maintained after ECT.
- side effect – cognitive deterioration.

TRANSCRANIAL MAGNETIC STIMULATION

Less effective but substantially safer than ECT

NEUROSTAR TMS brain-stimulating device - FDA cleared for depressed adults for whom one antidepressant has failed to work (but who had not yet tried second antidepressant).

- uses magnetic field to induce small electric current in specific part of brain without causing seizure or loss of consciousness (vs. ECT).
- does not require sedation - administered on outpatient basis (vs. ECT).
- 4-5 times a week for 4 weeks; during this time, patient is started on new antidepressant and weans from TMS.
- target – dorsal prefrontal cortex.

BROAD-SPECTRUM LIGHT THERAPY

- may have some efficacy as augmenting agent with antidepressant medication.

VAGUS NERVE STIMULATION

- investigational; some long-term efficacy in treatment-resistant depression.

DBS

- up to 20% patients are refractory to standard therapies – niche for DBS.
- DBS for depression remains in research phase.

Targets:

1) **subcallosal cingulate gyrus (s. subgenual cingulate gyrus, area Cg25)** – the midpoint between the genu of corpus callosum and the anterior commissure – hypermetabolic in depression (and even in normally sad mood) and normalizes with successful treatment with antidepressants; only specific area is responsive to DBS (need DTI to find the confluence of bundles) – see studies below >>
2) **nucleus accumbens** – promising target (old studies were targeting too high)
3) rostral cingulate cortex (area 24a)
4) ventral capsule/ventral striatum
5) inferior thalamic peduncle
6) lateral habenula
7) anterior limb of internal capsule

Studies:

Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial.
Dr Paul E Holtzheimer, Prof Mustafa M Husain, MD, Sarah H Lisanby, MD, Prof Stephan F Taylor, MD, Prof Louis A Whitworth, MD, Shawn McClintock, PhD, Prof Konstantin V Slavin, MD, Joshua Berman, MD, Guy M McKhann, MD, Parag G Patil, MD, Barry R Rittberg, MD, Prof Aviva Abosch, MD, Prof Ananda K Pandurangi, MD, Prof Kathryn L Holloway, MD, Prof Raymond W Lam, MD, Prof Christopher R Honey, DPhil, Prof Joseph S Neimat, MD, Prof Jaimie M Henderson, MD, Prof Charles DeBattista, MD, Prof Anthony J Rothschild, MD, Prof Julie G Pilitsis, MD, Prof Randall T Espinoza, MD, Georgios Petrides, MD, Alon Y Mogilner, MD, Prof Keith Matthews, MD, DeLea Peichel, BS, Prof Robert E Gross, MD, Clement Hamani, MD, Prof Andres M Lozano, MD, Prof Helen S Mayberg, MD
*The Lancet Psychiatry Volume 4, No. 11, p839–849, November **2017***

– multisite, prospective, randomised, sham-controlled trial.

- all patients had been unresponsive to a minimum of four antidepressant medications from at least three drug classes.
- average duration of depression prior to receiving DBS in the current study was 12 years.
- DBS targeting **bilateral subcallosal cingulate white matter**.
- Libra XP Deep Brain Stimulation System (St. Jude Medical).
- randomised to 6 months of active or sham DBS, followed by 6 months of open-label subcallosal cingulate DBS; at the conclusion of the 12-month study, a subset of patients were followed up for up to 24 months.
- *primary outcome* was **frequency of response** (defined as ≥ 40% reduction in depression severity from baseline on Montgomery-Åsberg Depression Rating Scale) averaged over months 4–6 of the double-blind phase.
- *futility analysis* was performed when **90 patients** (approximately half of the proposed sample) received DBS implantation and completed the double-blind phase.
- *finding*:
  1) both groups showed improvement, but there was no statistically significant difference in response during the double-blind, sham-controlled phase (12 out of 60 [20%] patients in the stimulation group *vs* 5 out of 30 [17%] patients in the control group).
  2) 28 patients experienced 40 serious adverse events; 8 of these (in 7 patients) were deemed to be related to the study device or surgery.
  3) not all patients reached the follow-up endpoint; at 30-month follow-up, the antidepressant responses improved in 29% of patients at 12 months, 53% at 18 months, and 49% at 24 months; remission rates also improved, from 14% of patients at 12 months to 18% at 18 months and 26% at 24 months.
- *interpretation*:
  1) study confirmed the safety and feasibility of subcallosal cingulate DBS as a treatment for treatment-resistant depression
  2) study did not show statistically significant antidepressant efficacy in a 6-month double-blind, sham-controlled trial; 6 additional months of DBS did not increase the proportion of patients who responded to DBS or who achieved remission.
  3) long-term outcomes are clinically meaningful and greater than would be expected with treatment as usual in this highly treatment-refractory patient population," → authors conclude that "the negative outcome of this trial should not be interpreted simply as a failure of subcallosal cingulate DBS for treatment-resistant depression."

Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH: Deep brain stimulation for treatment-resistant depression. Neuron 45(5):651-60, ***2005****.*

- pilot study to evaluate **Cg25WM** as a target for DBS in treatment-resistant depression
- 5 out of 6 patients showed a clinical response (≥ 50% reduction in Hamilton Depression Rating Scale) at 2 months.
- clinical response was maintained in 4 out of these 5 patients at 6 months

Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH: Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. Biol Psychiatry 15;64(6):461-7, ***2008****.*

Kennedy SH, Giacobbe P, Rizvi SJ, Placenza FM, Nishikawa Y, Mayberg HS, Lozano AM: (in press). Deep brain stimulation for treatment resistant depression: follow-up after 3 to 6 years. Am J Psychiatry 168(5):502-10, ***2011****.*

SPECIAL SITUATIONS

TREATMENT-RESISTANT DEPRESSION

- assuming that (1) diagnosis is correct, (2) there are no significant complicating diagnoses, and (3) current treatment has been at therapeutic dose for sufficient amount of time, possible interventions for persistent symptoms can include following:

1. Increase medication dose to maximum tolerated
2. Change to different antidepressant
3. Adding psychotherapy
4. DBS to subcallosal cingulate gyrus region (64.3% response rate 3-6 years later).
5. Electroconvulsive therapy (ECT) - highly effective treatment for depression
6. Transcranial magnetic stimulation - long-term efficacy for resistant depression
7. Vagus nerve stimulation (VNS) - FDA approved for adults who have failed to respond to at least 4 adequate medication and/or ECT treatment regimens.
8. Augmenting current medication:
   a) LITHIUM plus any antidepressant
   b) BUSPIRONE plus TCA or SSRI
   c) TRIIODOTHYRONINE plus any antidepressant
   d) **TCA** added to **SSRI**
   e) METHYLPHENIDATE or DEXTROAMPHETAMINE added to any antidepressant (other than MAOI)
   f) addition of bright-light therapy to any antidepressant

DEPRESSION DURING PREGNANCY

- MDD can have significant negative impact on woman's experience of pregnancy and parenting.
- benefits of prompt medical treatment often outweigh risks of exposure of fetus to antidepressant (no clear evidence that available antidepressants are teratogenic).
- in severe cases, ECT can be safest and quickest treatment option.

POSTPARTUM DEPRESSION

- very serious problem.

- > 80% women develop mood disturbances in postpartum period:
  - most often - transient syndrome called **BABY BLUES** - tearfulness and mood changes that resolve spontaneously in few days to 2 weeks).
  - > 10% meet criteria for MDD during first year following delivery.
- principles of treatment for postpartum MDD are same as during any other time of life.

PROGNOSIS

- 50% patients experience **recurrence** (after two episodes, recurrence rate is ≈ 70%, and after three episodes ≈ 90%).
  - some have relapses of sufficient frequency to warrant long-term preventive use of antidepressants (other patients can discontinue treatment after resolution of episode).
- in addition to high risk of suicide (*see below >>*), patients have higher risk of illness / death due to medical causes (impaired food intake, alcoholism, drug abuse, own health neglect, etc).
  - depression increases risk of MI and stroke.
  - some patients may perform homicide!

    e.g. mother with severe depression believed world was so bleak that she planned to kill her children to spare them from world's misery

SUICIDE

- suicide is uniquely human behavior.
- 11th cause of death in USA.

- represents 10-30% deaths in those aged 20-35 years (2nd or 3rd leading cause of death in adolescents).
- death rate: men : women = 4 : 1 (but women attempt suicide 3-4 times as often).

ETIOLOGIC FACTORS

Psychiatric illness is present in almost all people who commit suicide!

  - comorbidity (i.e. multiple psychiatric illnesses) is common.
- major risk factor – **MDD** (lifetime risk of suicide 2-15%)
  - MDD plays role in > 50% of all suicide attempts.
  - suicide risk is highest *initially after hospital discharge* (when treatment has been initiated and psychomotor activity is returning to normal but mood is still dark); risk remains high for 1 yr after discharge.
- other factors that increase risk of suicide:
  1) alcohol use (plays role in > 25% suicides), substance use
     Alcohol / drugs of abuse increase disinhibition and impulsivity + worsen mood!
     Alcoholics are suicide-prone even when sober!
  2) schizophrenia (5% suicides)
     N.B. schizophrenia has ≈ same risk for suicide as major depression!!! (i.e. ≈ 10% schizophrenics attempt suicide)
  3) delirium, dementia, and other cognitive disorders (4% suicides)
  4) borderline and antisocial personality disorders
  5) panic disorders
  6) history of suicide attempts
  7) family history of suicide (suicides run in families!)
  8) agitation or delusional ideas, command hallucinations
  9) premenstrual state
  10) personally significant anniversaries
  11) social isolation (e.g. divorced, widowed, unemployed)
  12) chronic painful medical illness or acute disabling change in physical health.
  13) men > 55-69 yrs (elderly account for 10% American population and 25% suicides).
  14) white race, some Native American groups
  15) access to firearms
- there appears to be ***genetic risk of suicide*** that is independent of risk of psychiatric illness (e.g. suicides occur only among monozygotic twins, not among dizygotic pairs).
- suicide is less common among practicing members of most religious groups (particularly **Roman Catholics**).
- **power of suggestion** - rise in suicides is seen after well-publicized suicide (e.g. of rock star) and among self-identified populations (e.g. high school, college dormitory).

METHODS

- method choice is determined by **cultural factors**, **availability**, **seriousness** of intent.
- some methods (e.g. jumping from heights) make survival virtually impossible, whereas others (e.g. drug ingestion) make rescue possible.
  N.B. using method that proves not to be fatal does not necessarily imply that intent was less serious.
- ***bizarre method*** suggests underlying psychosis.
- most frequent methods:
  in *suicide attempts* - drug ingestion.
  for *completed suicides* - firearms (74% men, 31% women), hanging (men), drug ingestion (women).

CLINICAL PRESENTATION

Suicidal behavior includes:

I. Self-destructive acts:

a) completed suicide - results in death.

b) attempted suicide - act intended to be self-lethal, but one that does not result in death (frequently, suicide attempts involve at least some ambivalence about wishing to die and may be cry for help).

> 25÷200 attempts are made for every death; rate of attempts is disproportionately high among adolescent girls

c) suicide gestures - attempts that involve action with very low lethal potential (e.g. inflicting superficial scratches on wrist, overdosing on vitamins).

II. Suicidal ideation - thoughts and plans about suicide.

- suicide gestures and suicide ideation are most often pleas for help from people who still wish to live.
- *GROUP SUICIDES* (such as lovers or spouses) represent extreme form of personal identification with others; in rare instances, former lovers or estranged spouses are involved in *MURDER-SUICIDES* (one person murders another, then commits suicide).
- ***suicide notes*** are left by about 1 in 6 people who complete suicide (content may indicate mental disorder that led to suicidal act).

A. Overt

Suicidal behavior - patient may ingest drugs, slash wrists, take overdose, jump out window → patient often requires medical / surgical intervention (gastric lavage, suturing, etc) before psychiatric assessment; *patient is considered acutely suicidal* until proven otherwise → careful observation to prevent patient from leaving ED (→ another suicide attempt).
Suicidal ideation - patient may be obviously depressed, expressing concerns with little prompting and experiencing considerable pain and distress; she may ask for help in control of suicidal impulses and for relief from depression.

B. Covert

Suicidal behavior - although ***patient denies*** implications of her behavior, she may have accidents that range from suspiciously to obviously suicidal; special type - patient appears homicidal or assaultive but his behavior is primarily attempt to provoke others (such as police) to kill him.
Suicidal ideation - patient seeks medical evaluation for somatic symptom; patient may show distress out of proportion to objective findings or may visit ED many times over short period; patient may take medication given for somatic symptom in suicide attempt!

C. Chronic suicidal ideation and behavior - patient repeatedly calls or visits ED for suicidal ideation and attempts.

- by self-destructive behavior patient attempts to manipulate environment or relieve internal discomfort ***rather than attempt to die*** → patient evokes hostility in caregivers → risk to be ignored or actively rejected.
- patient may evoke so much hostility that physician may wish that patient were dead (others in patient's environment may feel similarly!!!).
- *risk for suicide is great* by design, miscalculation, or impulsiveness.

Situations that must arise suspicion:

1. Unemployed, divorced white men > 45 years.
2. Patient reports hopelessness, helplessness, loneliness, exhaustion.

3. Unexpected change in behavior (e.g. giving away possessions, suddenly writing or changing will) or unexpected change in attitude (e.g. calm or resignation in midst of distressing situation).

- 77% of people who commit suicide were seen by physician within one year before killing themselves.
- primary care physicians encounter ≥ 6 potentially suicidal people in their practice each year.
- when there is any suspicion about suicide potential, it is important to ask patients directly (fear that such inquiry may implant idea of self-destruction is baseless!).

TREATMENT

- patient should not be left alone until he is in secure environment - 10% people who make attempt will eventually die by suicide! (due to reattempt).
- **psychiatric assessment** ASAP for all patients!
- ***transportation*** to psychiatric facility should be accompanied by ***trained professionals*** (e.g. ambulance, police), never by family members or friends!
- ***availability and support of family and friends*** are crucial (they need to be interviewed away from patient to feel comfortable stating their concerns).
- patient should be *hospitalized if lethality of ideation / behavior is high* (e.g. persistence of patient's wish to die, severity of concurrent psychopathology, absence of reliable sources of support in social environment, persistence of causative crisis in patient environment).
- features of high risk attempted suicide:
  1) hanging or gunshot (vs. overdose with OTC drugs, superficial cuts on wrists).
  2) attempt in isolated area (vs. highly visible location).
  3) failure to call (or leave notes) to family members / friends.
- patient's perception of lethality of unsuccessful attempt, expectations of rescue, and relief or disappointment at being alive are often more important than objective dangerousness of attempt.
- severely suicidal patient who resists treatment may require ***one-on-one observation*** to prevent escape or self-injury.
- criteria for outpatient treatment:
  1) no psychosis
  2) no active suicidal ideation
  3) good social support
  4) low-risk suicide attempt
- communication with individual threatening imminent suicide (e.g. patient who calls and declares that he is going to take lethal dose of drug):
  - remind him of his identity (i.e. use his name repeatedly);
  - help sort out problem that has caused crisis;
  - offer constructive help with problem;
  - encourage to take positive action;
  - remind him that family and friends care for him and want to help.

DYSTHYMIC DISORDER

- **chronic depression** (at least 2 years in duration) **not severe enough** to meet criteria for MDE + absence of any manic, hypomanic, or mixed episodes.

N.B. it is chronic (not episodic!) illness

- instead of five symptoms required of MDE, patients must have two of following:
  1) increased or decreased appetite
  2) increased or decreased sleep
  3) low energy or fatigue
  4) low self-esteem
  5) poor concentration or decision-making ability
  6) feelings of hopelessness.
- during 2-year period, person has never been without symptoms for > 2 months at time.
- symptoms typically begin insidiously during adolescence and follow low-grade course over many years or decades.
- associated with social impairment, health problems, alcohol and other drug abuse, and major depressive disorder.
- no MDE has been present during first 2 years of disturbance; if patients experience MDE after 2 years of dysthymia, **DOUBLE DEPRESSION** diagnosis is made (dysthymic disorder and major depressive disorder).

EPIDEMIOLOGY

- lifetime risk ≈ 5%
- women : men = 2 : 1
- patients who develop dysthymia before age 21 are more likely to develop major depressive disorder later.

TREATMENT

- traditionally, dysthymia is treated with **psychotherapy** (cognitive therapy and behavioral therapy).
- condition also is responsive to **antidepressants** (SSRI or MAOI better than TCA).

BIPOLAR I DISORDER (s. CLASSIC MANIC-DEPRESSION)

- at least one **manic** or **mixed episode**.

Bipolar is misnomer - single **manic episode** is sufficient for diagnosis!

- one of most common, severe, and persistent mental illnesses!
- PATHOPHYSIOLOGY is similar to major depressive disorder; genetic predisposition. *see above >>*
- most patients experience both **manic** and **depressive** symptoms, and first episode may be manic, hypomanic, depressed, or mixed (if first episode is hypomanic or depressed, proper diagnosis will not be made until later emergence of mania).
- each episode of illness (whether manic or depressive) lasts 4-13 months (1% go on to chronicity, and some cease much sooner).
- associated psychiatric comorbidity:
  - eating disorders, anxiety disorders, ADHD.
  - alcohol, drug abuse frequently complicate manic episodes (and can carry into other phases of disorder).
- because BP I is lifelong disease, brain **MRI** may be advisable (at least, to establish baseline).

EPIDEMIOLOGY

- lifetime risk < 1%
- men = women (the only mood disorder with equal sex distribution); rapid-cycling (≥ 4 episodes / year) is more common in women.
- mean age of onset - **21 years** (onset of mania in people > 50 years should lead to investigation for medical or neurological disorders).

TREATMENT

- directly related to phase of episode.

- historically, treatment was attempted with **psychosurgery** (such as *prefrontal lobotomy*).
- **ECT** is highly effective for both phases of illness (esp. in treatment-resistant cases).

For MANIA (hospitalization may be necessary; e.g. patient's behaviors destroys his career and is harmful to those around them)

Manic excitement is medical emergency - patient can die of exhaustion!

A. Psychotherapy (accumulated stresses can propel person into mania or depression).

B. Medications (**compliance** is large problem – impaired judgement* + many patients prefer hypomania to euthymia):

*once mania begins, patients believe that they know better than their physicians

1. LITHIUM - effective for acute mania and for maintenance (relapse rates reduced 50%); dosage and blood level need to be higher during acute treatment than during maintenance prophylaxis. see p. Psy15 >>
2. **Anticonvulsants** (CARBAMAZEPINE, VALPROATE, LAMOTRIGINE) - used if lithium is ineffective or poorly tolerated;
   - effective alone or as adjunct to LITHIUM in acute treatment and / or maintenance (maintenance doses are similar to those used in seizure disorders).
   - especially effective in prevention of rapid mood swings.
   - VALPROATE is as effective as LITHIUM in acute mania (even more effective in mixed episodes).
   - mechanism of action - suppression of subseizure threshold electrical kindling activity in limbic system.
3. **Antipsychotic drugs** - symptomatic relief in acute mania while mood stabilizers are taking effect; long-acting antipsychotics (esp. atypical) may help in maintenance phase.
4. Alternatives for treatment-resistant cases: CLONAZEPAM, VERAPAMIL.

Current consensus: most effective treatment for acute mania is combination **atypical antipsychotic** + **mood-stabilizer**

FDA-approved bipolar treatment regimens (marked as "+"):

Drug	Manic	Mixed	Maintenance	Depression
LITHIUM	+		+	effective
CARBAMAZEPINE extended release	+	+		
VALPROATE	+	effective	effective	
LAMOTRIGINE			+	effective
RISPERIDONE or ZIPRASIDONE	+	+		
OLANZAPINE or ARIPIPRAZOLE	+	+	+	
CHLORPROMAZINE	+			
QUETIAPINE	+			+
OLANZAPINE + FLUOXETINE				+

- in acute mania, VALPROATE can be titrated up to effective level more quickly than LITHIUM (i.e. lithium does not work immediately but should nonetheless be started early in anticipation of maintenance use!);
  - **antipsychotics** or **benzodiazepines** are often coadministered to control behavior and psychosis.
- LITHIUM is first-line agent for long-term prophylaxis;
  - continue (after acute episode) mood stabilizer for at least 6 mo, then taper and stop.
  - mood stabilizer is restarted for recurrent episodes and maintained if episodes are < 3 yr apart.
  - maintenance with LITHIUM is initiated after 2 classic manic episodes < 3 yr apart.

N.B. **mood stabilizers** must be stopped during pregnancy (at least 1st trimester); for severe relapse electroconvulsive therapy is safer!

Treatment for DEPRESSIVE episode → *see above >>*

- **mood stabilizers** (LITHIUM, LAMOTRIGINE) ± **antidepressants** are preferred (antidepressants alone may propel patient into manic episode!)

PROGNOSIS

Prognosis is worse than of major depression!

- > 90% patients after first manic episode have additional episodes of mania or major depression.
  - often, cycling between depression and mania accelerates with age.
- unlike schizophrenics, many patients are socially and occupationally functional when medication is maintained (i.e. free of symptoms between episodes).
- significant morbidity and mortality rates (mortality averages 2-2.5 times expected rate for that age)
  - attempted (25-50%) / completed (11%) suicide are both common during depressive phase.
  - homicide is also danger!

    e.g. delusional manic patient believed everyone was against him; he searched for rifle in order to defend himself and to get them before they got him
  - patients are at risk for drug addiction.
  - comorbid medical problems can deteriorate (poor compliance, generally impaired judgment, reckless behavior).

BIPOLAR II DISORDER

- at least one **MDE** + one **hypomanic episode** + absence of any manic or mixed episodes.

- disorder officially recognized for first time in DSM-IV.
- often, switch follows circadian factors (e.g. going to bed depressed and waking early in morning in hypomanic state).

EPIDEMIOLOGY

- lifetime risk ≈ 0.5%
- men < women.

CYCLOTHYMIC DISORDER

- **dysthymia** with **intermittent hypomanic periods** + no MDE, manic, or mixed episodes* during first 2 years.

*if such episodes occur after 2 years, more than one diagnosis may be made (e.g. cyclothymia and bipolar I disorder).

EPIDEMIOLOGY

- lifetime risk ≈ 1%
- men ≤ women.
- age of onset - **teens ÷ early adulthood**.

TREATMENT

- primarily of **education**.
- some patients with functional impairment require **mood stabilizer** therapy (e.g. DIVALPROEX).
  Antidepressants frequently precipitate manic symptoms!
- patients with artistic inclinations should be encouraged to *pursue careers in arts* (because excesses and fragility of cyclothymia may be better tolerated there).

PROGNOSIS

- 50% patients ultimately develop bipolar II disorder.

SEASONAL AFFECTIVE DISORDER (SAD)

- form of MDD with seasonal pattern of exacerbation and remission (arises during autumn ÷ winter and resolves during spring ÷ summer).

- SAD is common in climates with long or severe winters.
- SAD appears to be triggered by alterations in circadian rhythm and sunlight exposure.
- more likely to report atypical symptoms (hypersomnia, increased appetite).
- treated with **bright light therapy (BLT)*** ± antidepressant medication.

*10,000 lux for 30-90 minutes daily, usually within hour of arising in morning.

BIBLIOGRAPHY for ch. "Psychiatry" → follow this LINK >>