Major Depressive Disorder
Block 15
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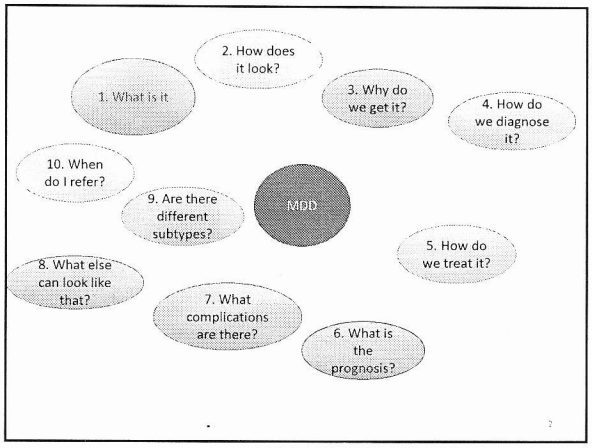
Dr Ilse du Plessis
Psychiatrist
Weskoppies Hospital
University of Pretoria



1. What is it

Mood

- Pervasive and sustained feeling tone that is experienced internally and that, in the extreme, can markedly influence virtually all aspects of a person's behaviour and perception of the world. (Distinguished from affect: the external expression of the internal feeling tone) Kaplan & Sadock
- *Internal emotional state*

Mood episode

1. What is it

- Distinct periods of time in which some abnormal mood is present.
  - They include depression, manic, mixed-state and hypomania

Mood disorders / Affective disorders

1. What is it

- Abnormal range of moods
- Loss of control over them
- Distress present due to severity of moods
- Impairment in social and occupational functioning

DEFINED BY PATTERNS OF MOOD EPISODES

Classification of mood disorders

1. What is it

I. Depressive
   Major depressive disorder - single
   - recurrent
   Dysthymic disorder
   Depressive disorder NOS
II. Bipolar disorders
   Bipolar I disorder (single manic episode, most recent episode hypomania /mania /mixed / depressed / unspecified)
   Bipolar II
   Cyclothymic disorder
   Bipolar disorder NOS
III. Other
   Mood disorder due to GMC
   Substance induced mood disorder
   Mood disorder NOS
IV. Adjustment disorder with depressed mood
V. Related syndromes
   Minor depressive disorder
   Recurrent brief depressive disorder
   Pre—menstrual dysphoric disorder

Symptoms and signs

2. How does it look?

- Depressive mood
- Anhedonia (↓ interest and pleasure)
- ↓/↑ weight
- ↓/↑ appetite
- ↓/↑ sleep
- Psychomotor retardation / agitation
- Fatigue
- ↓ energy
- Worthlessness

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- Excessive / inappropriate guilt
- ↓ Ability to think
- ↓ Concentration
- Indecisiveness
- Recurrent thoughts of thought
- Recurrent suicide ideation
- Suicide attempts
- Distress
- Impaired functioning
- ↓Libido

2. How does it look?

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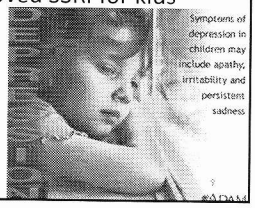
Presentation in children

- Irritability
- Behaviour problems
- Learning problems
- Fluoxetine only FDA-approved SSRI for kids

2. How does it look?



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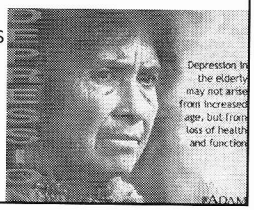
Presentation in the elderly

2. How does it look?

- Pseudodementia
- Somatic complaints
- Anxiety

Remember drug-interactions

Less with Citalopram
Sertraline
Escitalopram



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Major Depressive Episode(MDE) (DSM-IV)

5 / 9 symptoms for 2 weeks, (must include nr 1 and/or 2)

1. Depressed mood
2. Anhedonia (loss of interest in pleasurable activities)
3. Change in appetite or body weight (↑ or ↓)
4. Change in sleep (↑ or ↓)
5. Fatigue or ↓ energy
6. Feelings of worthlessness or excessive guilt
7. ↓ concentration
8. Psychomotor agitation or retardation
9. Recurrent thoughts of death or suicide

2. How does it look?

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MDE

- Bipolar disorder
- Schizoaffective
- Mood disorder due to General medical condition (GMC)
- Substance-induced mood disorder

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Major Depressive Disorder (MDD)

- At least 1 Major depressive episode
- No history of manic or hypomanic episodes
- Not due to GMC / substance
  - Functional impairment

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Epidemiology

Who gets it?

- Prevalence (lifetime): ± 15% (25 in females)
- Gender: M:F = 1:2
- Age: Can start in childhood, onset 20-50 y
- Race: No difference
- Marital status:
  - No close interpersonal relationships > divorced/separated > married
- Socio-economic: No correlation

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Etiology

3. Why do we get it?

Unknown, probably not a homogenous group

- Biological
- Genetic
- Psychosocial

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What causes depression?

3. Why do we get it?

- ↓ mono-amines
- ↓ excitatory neurotransmitters
- ↓ neurotrophin synthesis (BDNF / NGF / VEGF) / ↓ neuroplasticity
- ↓ support from neuroglia
- ↓ capacity to recycle neurotoxins from chronic inflammation

?All / any /none

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This leads to.....

- Changes in neural networks (connectivity)
  - Cortico-limbal
- Structural changes due to endocrine and immune induced apoptosis:
  - Hippocampus atrophy
  - Frontal cortex atrophy /asymmetry

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Etiology

3. Why do we get it?

1. Biological
   - A. Biogenic amines
     1. Serotonin
     2. Noradrenalin
     3. (Dopamine + acetylcholine+ glutamate)
   - B. Neuro-endocrine regulation
     1. Abnormalities in LHPA axis (limbic-hypothalamic—pituitary-adrenal)
   - C. Sleep abnormalities (EEG)
   - D. Summary: Pathology in
     - Limbic system
     - Basal Ganglia
     - Hypothalamus

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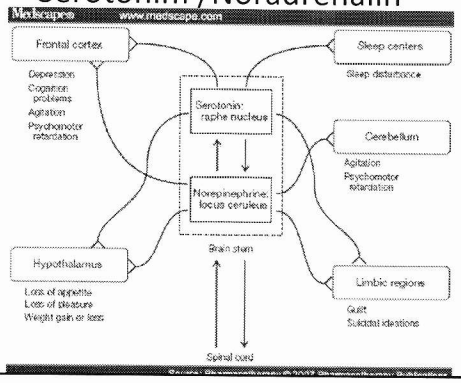
Serotonim /Noradrenalin



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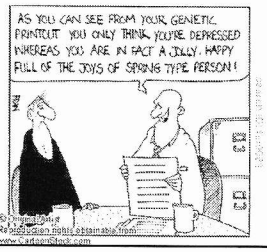
2. Genetic

- Runs in families

3. Why do we get it?



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3. Psychosocial:

A. Life events and environmental stress
- Stress often precedes the 1st episode, more so often in subsequent ones
- Losses:
  - Parent before 11 years of age
  - Life partner

B. Premorbid personality
- Dependant
- Obsessive-compulsive
- Histrionic
- Narcissistic

C. Cognitive
- Misinterpretations lead to negative distortions, negative self-image, pessimism and hopelessness

3. Why do we get it?

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Major Depressive episode: Criteria (DSM-IV-TR)

4. How do we diagnose it?

- A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Note: do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations
- Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful) Note: In children and adolescents can be irritable mood
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
- Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month), or decreased appetite nearly every day
- Insomnia, or hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
- Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan or a suicide attempt or a specific plan for committing suicide

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4. How do we diagnose it?

- B. The symptoms do not meet criteria for a Mixed episode
- C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
- D. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism)
- E. The symptoms are not better accounted for by bereavement, i.e. after the loss of a loved one, the symptoms may persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation

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Scales to use in depression

- HAM-D (Hamilton Depression Rating Scale)
- MADRS (Montgomery Aberg Depression Rating Scale)
- Zung self-rating scale

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SPECIFIERS OF DEPRESSIVE DISORDERS
MDD, single episode

- Mild, moderate, severe
- With / without Psychotic features. Delusions: mood congruent. Hallucinations: usually transient
- With Catatonic features
- With Melancholic features
- With Atypical features
- With Postpartum onset
- Chronic
- Longitudinal: with or without interepisodic recovery
- With seasonal pattern
- Full remission- 2 months or more- no symptoms
- Partial remission- some symptoms present, but not full criteria

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Subtypes of Depression

9. Are there different subtypes?

- Melancholic
  - Anhedonia
  - Early morning awakening
  - Psychomotor disturbance
  - Excessive guilt
- Atypical
  - Hypersomnia
  - Hyperphagia
  - Reactive mood
  - Leaden paralysis
  - Hypersensitivity to interpersonal rejection

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9. Are there different subtypes?

- Catatonic
  - Purposeless motor activity
  - Extreme negativism or mutism
  - Bizarre postures and echolalia
- Psychotic
  - Hallucinations or delusions
    - Mood congruent mostly (paranoia / nihilism / guilt)

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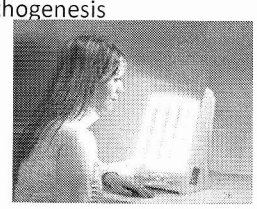
Seasonal affective disorder

9. Are there different subtypes?

- Subtype depression
- Only in winter months
- Respond to light treatment
- Melatonin implied in pathogenesis



Course and prognosis

6. What is the prognosis?

- If left untreated, self-limiting – last 6-13 months
- If treated: last 3 months
- Generally episodes occur more frequently as disorder progresses.
- Risk for subsequent episode 50% within 2 years
- Lifetime risk after single episode: 50-85%
- Lifetime risk after second episode: 80-90%
- **15 % commit suicide**
- 50-60% respond to antidepressants
- Combined treatment of both antidepressant and psychotherapy produce a significantly ↑ response rate

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Effect of MDD on GMC

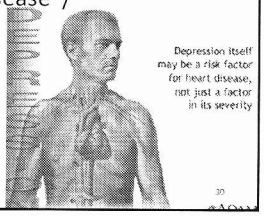
Worsens outcome of Cerebrovascular disease / cardiovascular disease

7. What complications are there?

Risk for Cerebrovascular disease / Cardiovascular disease

Association with DM type II

(reciprocal)



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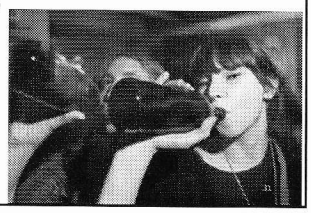
Co-morbidities

- Substance abuse / dependence
- Anxiety disorders
- Eating disorders
- Personality disorders
- Dysthymic disorder



Approach

5. How do we treat it?

- Biopsychosocial
  - Biological
    - Special investigations
    - Pharmacological
    - Physical: ECT / DBS /TMS
  - Psychological
    - Psychotherapy
  - Social
    - Psycho-education of family

Treatment

5. How do we treat it?

- Hospitalization
- Pharmacotherapy
- Psychotherapy
- Electroconvulsive Therapy (ECT)
- Deep brain stimulation (DBS)
- Transcranial magnetic stimulation(TMS)
- Light therapy
- Alternative therapy

Hospitalization

- Indicated if pt risk
  - suicide
  - homicide
  - unable to take care of self

5. How do we treat it?

Pharmacotherapy

- All antidepressants are equally effective but differ in side-effect profiles
- Medication usually takes 4-8 weeks to work
- Antidepressants should be used for 9-12 months before a taper is initiated (6-9 months after recovery)
  - NB: monitor for relapses
  - Indefinitely on Rx if several episodes / strong family history

5. How do we treat it?

Types of Antidepressants

- Selective serotonin reuptake inhibitors
  - Fluoxetine / citalopram / paroxetine / setraline / escitalopram
- Serotonin-noradrenalin reuptake inhibitors
  - Venlafaxine / duloxetine
- Noradrenalin-dopamine reuptake inhibitors
  - Buproprion
- Tricyclic antidepressants
  - Amitrepteline / clomipramine
- Mono-amine oxidase inhibitors
  - moclobemide
- Melatonin agonist
  - Agomelatine

OTHERS: Trasodone /Mirtasepine

5. How do we treat it?

Basic principles of prescribing in depression

5. How do we treat it?

- Discuss with pt choice of drug / other non-pharmacological treatments
- Discuss with pt likely outcomes such as gradual relief from symptoms over weeks
- Prescribe an effective dosage (lowest possible dosage)
- For first episode: treat 6-9 months after resolution of symptoms
- Withdraw gradually, always inform pt about risk and nature of discontinuation symptoms
- Monitor closely in early stages for restlessness, agitation and suicidality (especially young pts)

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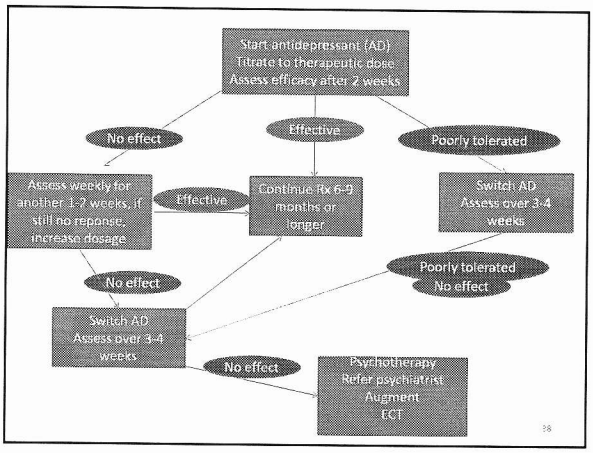

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Augmentation: Adjunct medication

- Liothyronine (T3) or Levothyroxine (T4)
- Lithium
- Atypical antipsychotics
- Buproprion to SSRI
- Others:
  - L-tryptophane
  - Buspirone
  - Stimulants

5. How do we treat it?

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Psychotherapy

- Can be used as monotherapy in mild to moderate depression
- Strongly considered if
  - Psychosocial stressors significant
  - Interpersonal difficulties
  - Personality disorders
  - Pregnancy
- Clinical evidence for:
  - Cognitive behavioural therapy (CBT)
  - Interpersonal therapy
  - Psychodynamic therapy
  - Problem solving and group therapy

5. How do we treat it?

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ECT in MDD

- Unresponsive to pharmacotherapy
- Contraindications to antidepressants / cannot tolerate antidepressants (pregnancy /elderly)
- Immediate risk suicide
- History good response to ECT
- Depression with psychotic features
- > 75% response rate

5. How do we treat it?

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Other physical treatments for MDD

- Deep brain stimulation:
  - Surgical treatment involving the implantation of a medical device called a brain pacemaker which sends impulses to specific parts of the brain
- Vagus nerve stimulation:
  - Type of DBS
  - Access via thorax or neck
- Transcranial magnetic stimulation:
  - A procedure that uses magnetic fields to stimulate nerve cells in the brain to improve symptoms of depression
  - Uses a handheld coil
  - Also used in OCD, parkinson`s and huntington`s disease

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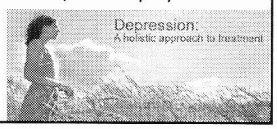
Alternative therapy: Evidence limited

- St Johns Wort (Hypericum Perforatum)
  - Cyp P450+++
- Omega-3 supplementation
- Yoga
- Exercise
- Tryptophan supplementation (eosinophylic-myalgia syndrome)
- Acupuncture

5. How do we treat it?



Prophylaxis /secondary prevention

- Pharmacotherapy: same dose as treatments dose ("what gets you well, keeps you well")
- After ECT: pharmacotherapy prophylaxis / maintenance ECT
- Lithium – maintenance protects against suicide
- Psychotherapy
- Lifestyle modification

5. How do we treat it?

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DDx: depressive features

- Bipolar disorder
- Cyclothymic disorder / Dysthymic disorder
- Adjustment disorder with depressed mood
- Schizoaffective disorder
- Bereavement
- Due to GMC
- Substance-induced
- (Anxiety disorders)
- (Eating disorders)
- (Personality disorders)

8. What else can look like that?

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Differential diagnosis ....due to General Medical Condition

- Endocrinopathies:
  - Hyper- / hypothyroidism
  - Cushings syndrome/ Addisons disease
  - Hyper- / hypocalcemia
- Neurological disease:
  - Parkinsonism
  - Epilepsy
  - Dementia
  - Cerebrovascular disease
- Viral diseases (eg. HIV, Mononucleosis)
- Malignancies
  - Carcinoid syndrome
  - Cancer (Lymphoma , pancreatic CA)
- Collagen disease (SLE)

8. What else can look like that?

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DDx ...due to medication / substance induced

8. What else can look like that?

- **EtOH**
- Antihypertensives / diuretics
- Analgesics (opioids)
- **Corticosteroids**
- Levodopa
- **Sedative-hypnotics**
- Anticonvulsants
- Antipsychotics
- Chemotherapy
- Sulfonamides /quinolones
- Withdrawal of psychostimulants (cocaine, amphetamines)

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Indications for referral to a psychiatrist

- Suicide risk
- Psychosis
- Need for hospitalization
- Complicated medical or psychiatric comorbidity
- Suspected need for combined medication and psychotherapy
- Failure of an adequate antidepressant trial
- Unsure about diagnosis and treatment

10. When do I refer?

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