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MRCPsych General Adult Module

Bipolar Disorder - I

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Aims and Objectives

- The overall aim is for the trainee to gain an increased understanding of BPAD – this is the first session

- By the end of the session trainees should:
  - Develop an understanding of the clinical presentation of Bipolar disorder.
  - Develop an understanding of aetiological theories and epidemiology of Bipolar disorder.

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Expert Led Session

Bipolar Affective Disorder – Aetiological Theories and Epidemiology

Lecture Overview

- Brief definition
- A bit of history
- Types of episode - ICD10
- Proposed subtypes of BPAD (I-VI)
- Epidemiology
- Aetiology – fragments of theory, neuroanatomy, chemistry

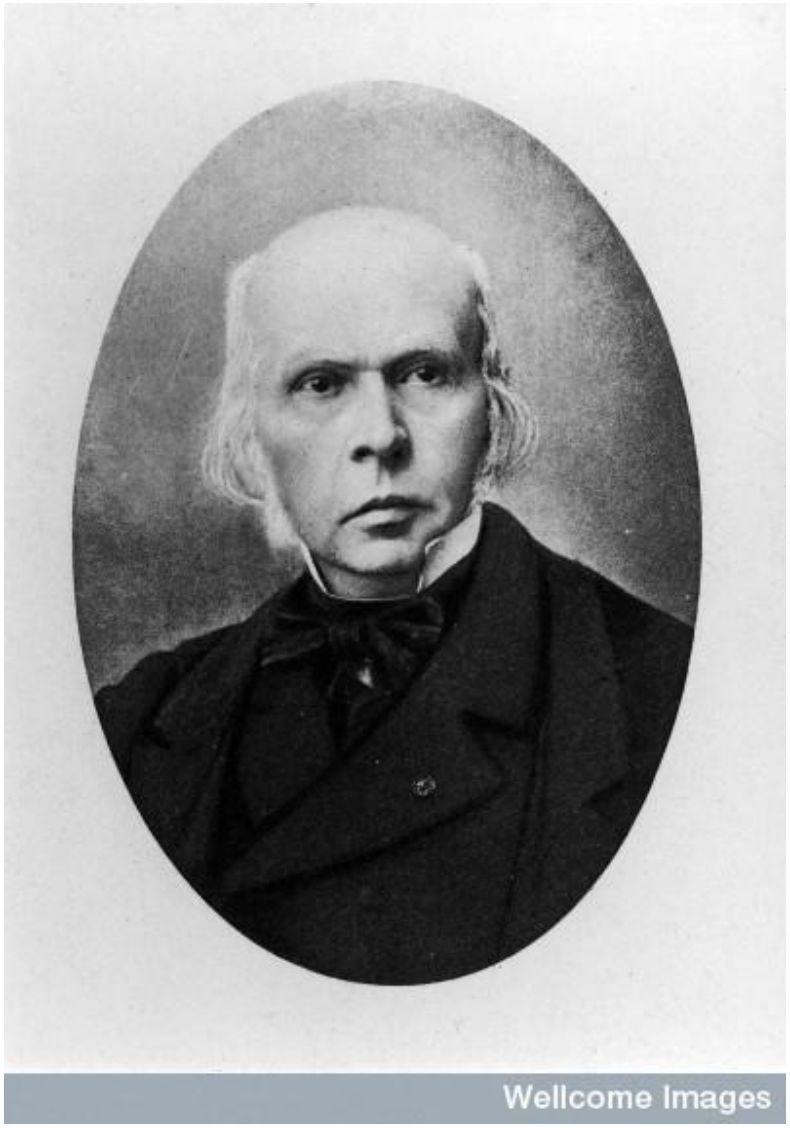
Definition

- A common, severe, enduring mental health condition that follows a relapsing-remitting course.
- It is characterised by recurrent episodes whereby patients meet criteria for depression, (hypo)mania or mixed affective state.
- These episodes may occur with or without psychotic symptoms.

History

- Useful to see how diagnostic frameworks and treatment rationales have evolved

Falret
Folie circulaire 1851

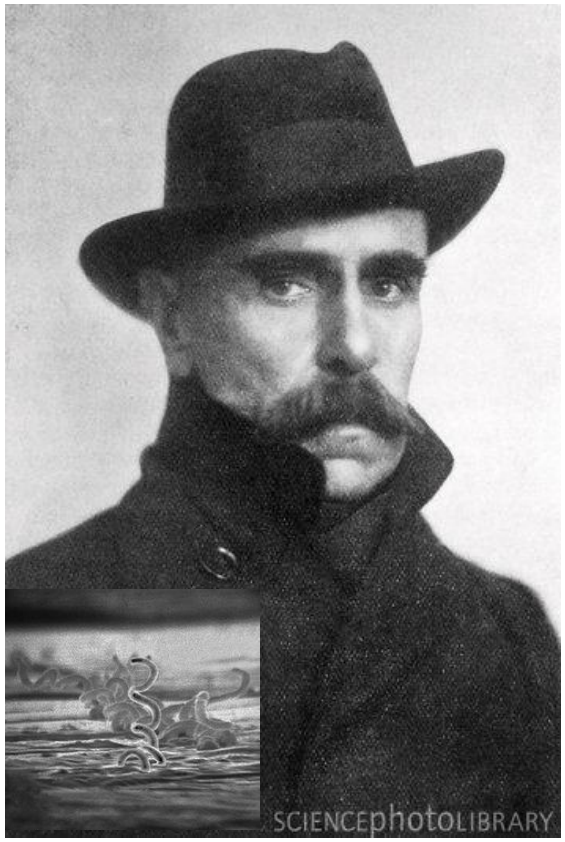


Baillarger
La Folie a Double forme 1854

Kraepelin 1899

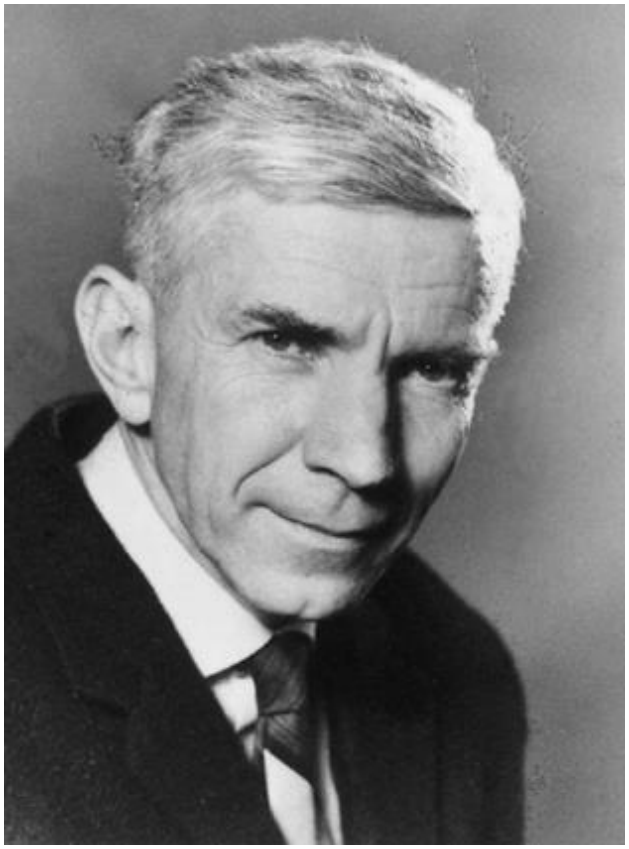
Manic depressive insanity

“the assertions of the patients that they are Messiah, the pearl of the world, the Bride of Christ, Queen of Heaven, Emperor of Russia, Almighty God, that they have ten thousand children.”



Wagner Jauregg - Malaria cure for General paralysis of the insane. Netted him the Nobel Prize for Medicine 1927

John Cade discovered mood stabilising properties of Lithium in 1949



Ronald Kuhn discovered the feel good properties of Imipramine in 1958. Also discovered its propensity for switching depression to mania

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ICD-10 Bipolar (Affective) Disorder

- Requires at least **2** episodes, one of which must be mania/hypomania/mixed, with remission between episodes:
  - Hypomania
  - Mania without psychosis
  - Mania with psychosis
  - Mild/moderate depression
  - Severe depression without psychosis
  - Severe depression with psychosis
  - Mixed affective episode

Bipolar subtypes (DSM)

- I - Bipolar affective disorder (mania and depression)
- II - bipolar depression (hypomania and depression)

Controversial alternatives:

- Klerman lists 4 further subtypes
  - III : Cyclothymia
  - IV: Antidepressant induced hypo/mania
  - V: Depression with family history of Bipolar I or II
  - VI: Unipolar Mania

Bipolar subtypes

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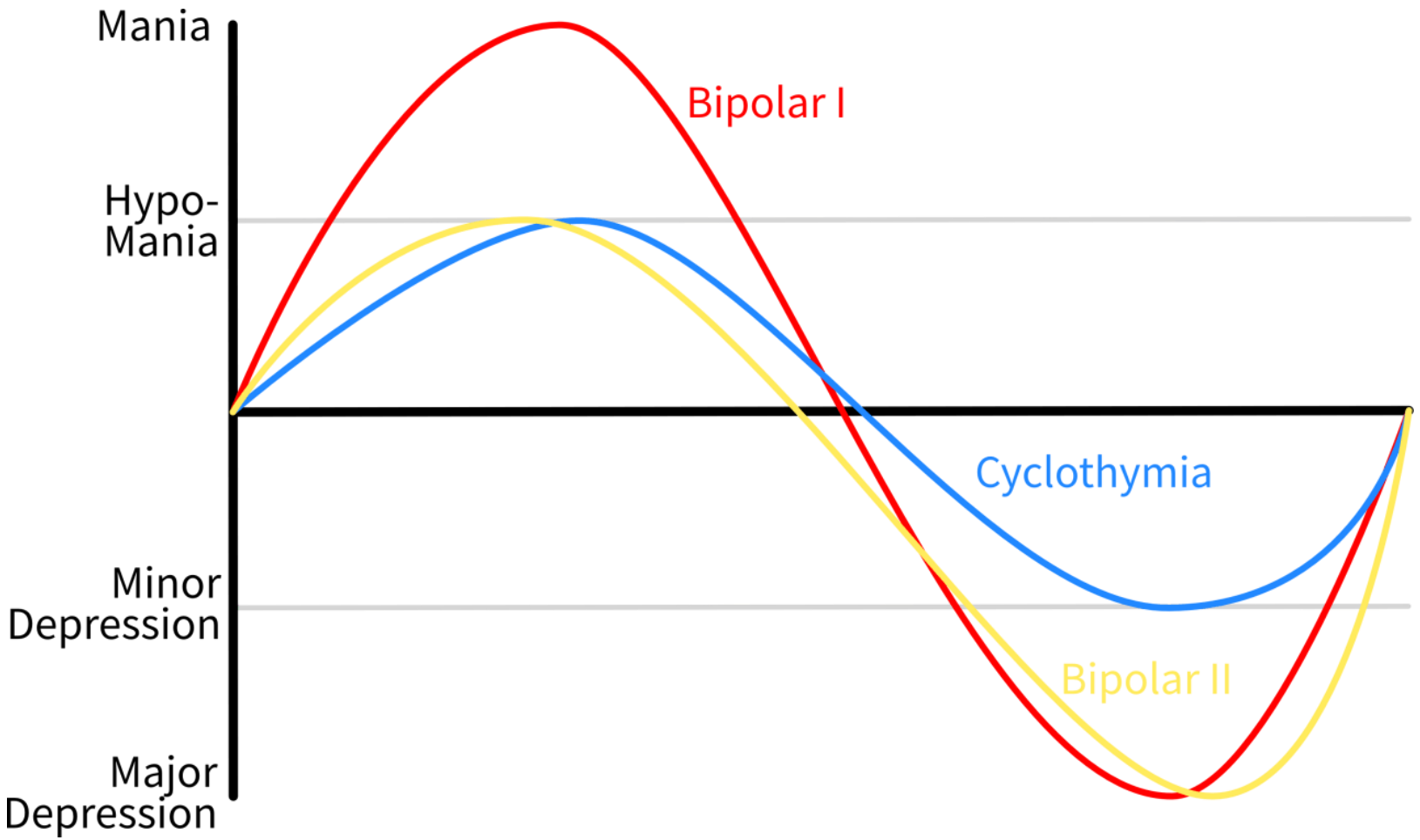

Epidemiology

- Lifetime prevalence – estimates vary between 0.3% - 1.5%
- Six month prevalance rates are similar to lifetime prevalence rates – reflects chronicity/recurrence
- Incidence = 4 per 100 000. AESOP study suggests geographic and ethnic group variation (higher rates in London and in Black and Minority ethnic (BME) groups)

The AESOP data at a glance

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- Three cities - London, Bristol, Nottingham
- Population at risk (16-64 years) = 1,631,462

	Whole sample	White	BME
All 3 centres	75	34	41
London	44	14	30
Nottingham	26	17	9
Bristol	5	3	2
Male, n (%)	36 (48)	17 (50)	19 (46)
Age at onset, years, Mean (SD)	29.2 (9.1)	32 (10.7)	26.8 (6.8)
Age range (yr)	17-56	17-56	17-50

*BME=Black and Minority Ethnic groups

Epidemiology

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- Mean age at onset = 15-27 years
  - Non normal distribution so mean is misleading. Mean often early twenties but commonest age of onset in late teens.
- Sex ratio = 1:1
- Comorbidity - anxiety disorders, alcohol (binge drinking) and substance misuse (stimlants)

Risk factors for mania - aetiology?

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- Genetics (high heritability)
- Circadian rhythm disruption
- Childbirth
- Previous treatment for depression
- Adverse life events
  - Possibly sleep disruption rather than psychological distress associated with the event
- The approach of late spring/early summer

Genetics

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- Heritability = 80-85%
- First degree relatives x7-8 risk (10%)
- MZ twins 60-70%, DZ twins 20%
- Unipolar depression more common in relatives of BPAD probands

Genetics

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- Linkage and association analyses are commonly employed methods to locate and define susceptibility genes for diseases
- Marker allele frequency in probands
  - What does the association actually mean?
  - Spurious false positive?
  - Causal?
  - Susceptibility factor?

Candidate gene loci

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- Dariers disease (12q23-24.1) cosegregates with BPAD
- X linkage – factor IX and G6P deficiency association with BPAD
- 22q11 – COMT gene. Low activity variant associated with rapid cycling
- Locations from meta analyses : 1p35-36, 4p, 4q31, 6p, 6q24, 8q, 10q, 12q, 13q, 14q, 17p, 18p, 21q, 22q

Genes and repeats

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- Genetic polymorphisms associated with BPAD
    - Serotonin
        - TPH1 and 2 (Tryptophan Hydroxylase)
    - ARNTL (circadian rhythm gene)
    - DISC1 (1q-cell proliferation/differentiation) and G72 (13q - D-serine amino acid oxidase activator) – associated with both SCZ and BPAD
- CAG trinucleotide repeats- more common in BPAD and anticipation phenomena (increased severity in offspring)

Pathophysiology - theories

- Kindling (Post 1989)
  - Genetically susceptible individual experiences cumulative minor brain insults, which eventually trigger a manic episode. Neural damage sustained during this episode renders the brain vulnerable to recurrence with smaller triggers. Further injury precipitated by subsequent episodes
  - ?Explains progressively shorter remissions and utility of anticonvulsants as prophylaxis
  - Oxidative stress and inflammatory markers raised in BPAD

Pathophysiology - theories

- Abnormal apoptosis levels in frontal cortex and hippocampus disrupts neural networks involved in emotional regulation (Manji 2003)

- Lithium and Sodium Valproate have neurotrophic properties
  - combat the above process?

Mapping BPAD to structure

- Limbic, striatal, hypothalamic and prefrontal circuits

- Regulation of biological drives and emotion

Early observations

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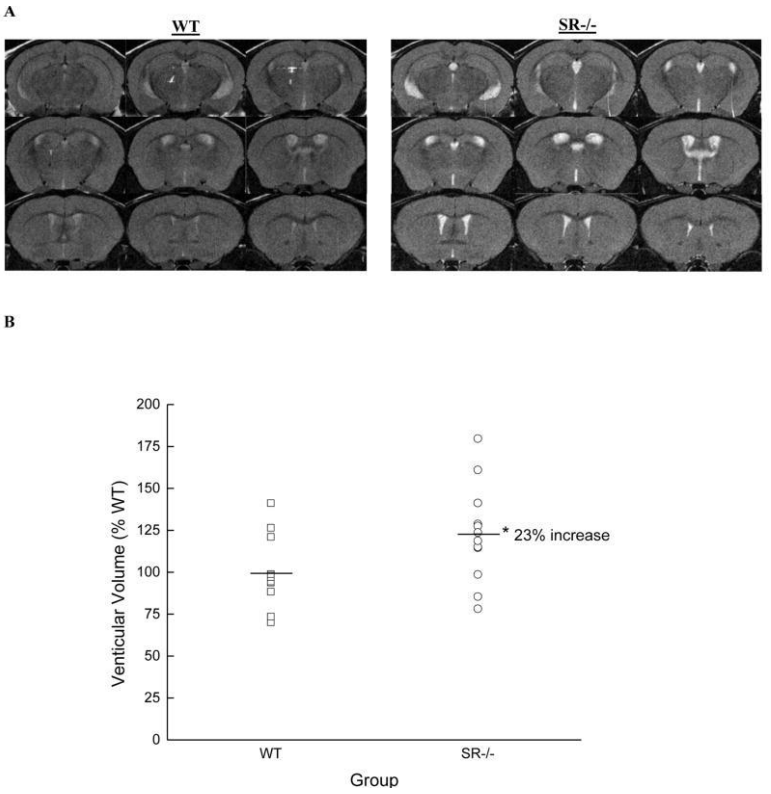
- Ventromedial PFC – motivational relevance of sensory information, behavioural adaptation
- Lesions – avolition, depression, euphoria, irritability, distractibility, hypersexuality, grandiosity, paranoia
- Connected to limbic and hypothalamic centres (emotion and biological drives)
- R mesial temporal lesions – manic/depressive fluctuations

Neuroimaging data

- Increased volumes of the lateral ventricles and the third ventricle and decreased cross-sectional area of the corpus callosum
- Decrease in the volume of the anterior cingulate cortex
- Reduced GM volume in PFC, ventral striatum and mesial temporal cotex
- Prefrontal and callosal WM abnormalities
- Asymmetry in Uncinate fasciculi



Shizukuishi et al. Magn Reson Med Sci, Vol. 12, No. 3, pp. 153–159, 2013
Gama et al. Rev Bras Psiquiatr. 2013;35:070-074

Cognition

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- Deficits in:
    - Executive function (shifting, planning, prioritizing/updating information within working memory, decision making, response inhibition)
    - Abstraction
    - Sustained attention
    - Verbal memory

- Prefrontal and medial temporal cortices Implicated.

Neuroanatomy

- Lesion, neuroimaging and neuropsychological data suggest that structural and functional changes in prefrontal-limbic circuitry may be associated with BPAD.

- Consensus model - failure of ventral prefrontal-limbic modulation may predispose to mania.

- Strakowski et al. Bipolar Disord. 2012 Jun;14(4):313-25.

Risk factors revisited – links to anatomy?

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- Candidate genes?
- Circadian rhythm disruption?
- Childbirth?
- Adverse life events?
  - Possibly sleep disruption rather than psychological distress associated with the event
- The approach of late spring/early summer?

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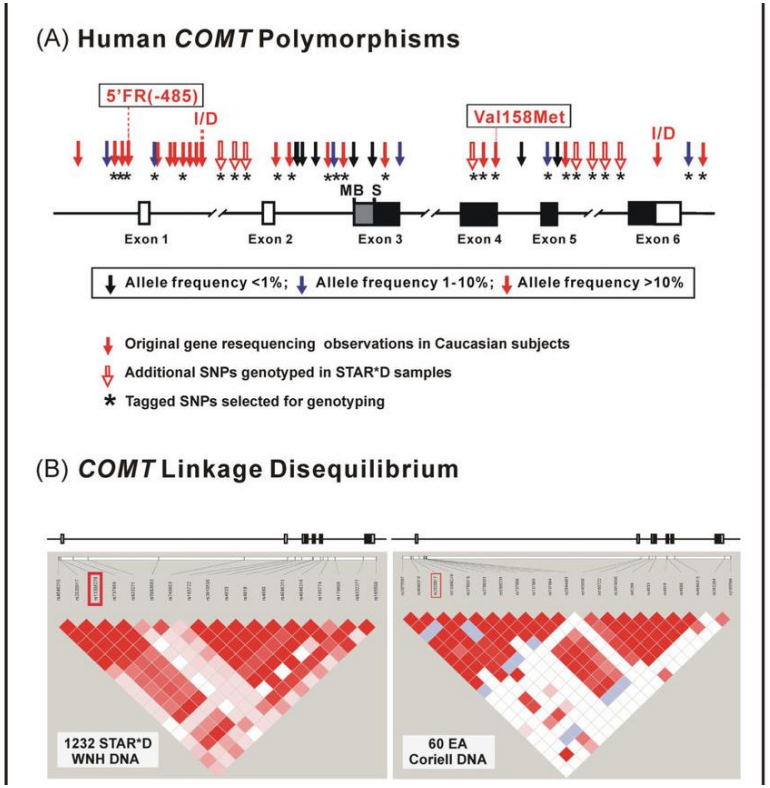
Mapping BPAD to chemistry

Monoamine signalling

Endocrine axis disruption

Noradrenaline (NA)

- 3-Methoxy-4-hydroxyphenylglycol (major metabolite of NA) levels raised in mania
- Polymorphisms in tyrosine hydroxylase and COMT genes in BPAD may affect amine metabolism



Serotonin

- In a nutshell, unimpressive and inconclusive data. Appears more robustly associated with depression
- However – antidepressants can induce manic switch…evidence for dysregulated signalling (exaggerated response)?

Dopamine

- DA agonists can function as antidepressants and precipitate mania

- Catecholamine depletion studies -rebound hypomania in BPAD patients (compensatory overshoot)

Hormones and light

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- Puerperal psychosis
    - Precipitous fall in Oestrogen post partum
    - Increased dopamine receptor sensitivity
    - Precipitous fall in CRH post partum, with subsequent ACTH and cortisol rebound

- Circadian rhythm disturbance
    - Clock gene polymorphisms and manic behaviour
    - Sleep deprivation affects PFC function
    - SSRI’s affect circadian rhythms – switch?

Summary

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- Defined
- History noted
- Episode types outlined
- Subtypes outlined
- Epidemiology overviewed
- Aetiology discussed - fragments of theory, neuroanatomy, chemistry

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Any further questions?

MCQs are next…

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MCQs

1. The following statements about bipolar disorder are true except :

A. The lifetime risk of bipolar disorder lies between 0.3% and 1.5%.
B. The prevalence in men and woman is the same.
C. Majority of bipolar patients, particularly women, begin with a manic episode.
D. The age of onset is earlier in bipolar disorder than in major depressive disorder.
E. An onset over the age of 60 is more likely to be associated with organic brain disease.

Answer: C

Majority of bipolar patients, particularly women, begin with a manic episode.

Explanation: It is known that majority of bipolar patients, particularly women, begin with depressive episodes. Community surveys have estimated life time risk of bipolar disorder between 0.3% and 1.5%.Bipolar has equal sex ratio and an earlier age of onset compared with unipolar depression. The mean age of onset is about 17 years for bipolar compared with unipolar major depression, which is about 27 years. An onset over the age of 60 is more likely to be associated with organic brain disease.

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MCQs

2. Which of the following most closely reflects the risk of Bipolar Disorder in a first degree relative of an affected proband?

A. 0.3-1.0%
B. 1-2%
C. 5-10%
D. 15%
E. 20%

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Answer: C

- 5-10%

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MCQs

3. 48 year old woman is stable on Lithium Carbonate. She has developed hypertension. Which of the following antihypertensives has the least potential for interaction with Lithium?

A. Losartan
B. Furosemide
C. Ramipril
D. Atenolol
E. Bendroflumethiazide

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Answer: D

Atenolol

Explanation: Thiazide diuretics (e.g**.** Bendroflumethiazide), lo& op diuretics (Furosemide), ACE inhibitors (Ramipril), angiotensin ii receptors antagonists (Losartan) may affects serum levels. Beta-blockers such as Atenolol are least likely to interact with Lithium.

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MCQs

4. Factors associated with a change of polarity from unipolar to bipolar include all except:

A. Hypersomnia and psychomotor retardation.
B. Absence of psychotic features.
C. Younger age of onset.
D. Family history of bipolar disorder.
E. Antidepressant induced hypomania

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Answer: B

- Absence of psychotic features

- One in 10 of those who begin with depressive episode go on to develop an episode of mania. The likelihood of such a switch drops markedly after the third episode of depression, by which time more than two thirds of those who will show bipolar disorder have already done so. The two main predictors are family history of bipolar disorder and an early age of onset. Others include male sex, psychotic depression, antidepressant induced hypomania, occurrence in the year after child birth (post-partum episode), hypersomnia and psychomotor retardation

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MCQs

5. Select one incorrect statement regarding bipolar depression in comparison with unipolar depression

A. Slower in onset
B. More frequent
C. More severe and shorter.
D. Cause greater socio-economic burden
E. More likely to be associated with psychotic symptoms

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MCQs

- Which of the following statements about bipolar disorder is TRUE?

A. Lifetime risk is between 0.3-1.5 %
B. Prevalence in women is twice that in men
C. Mean age of onset is 30 years of age
D. 6-month prevalence is far more than lifetime prevalence
E. Substance misuse is not usually a comorbid condition

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Answer: A

- Slower in onset

- Explanation: Episodes of bipolar depression are, compared with unipolar depression, more rapid in onset, more frequent, more severe, shorter, and more likely to involve psychotic symptoms, hypersomnia and hyperphagia.

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Any Questions?

Thank you