THE BIPOLAR SPECTRUM

Bipolar I disorder (mixed mania) ---------- Bipolar II disorder (mixed hypomania) ---------- MDD with mixed features (subsyndromal hypomania) ---------- MDD (non-mixed)

GENETICS VS. EPIGENETICS

GENETICS – "LOADING THE GUN"

- 7-fold risk of developing bipolar if person has a 1st degree relative with the illness
- Family & Genome wide association studies (GWAS) suggest bipolar I and II are in part genetically different
- SNP's (single nucleotide polymorphisms) linked to bipolar disorder (many candidates)
  - CACNA1C (calcium channel voltage-dependant L-type subunit)

EPIGENETICS – "PULLING THE TRIGGER"

- Heritable alterations in gene expression without a change in DNA sequencing
- Alterations occur throughout the lifetime
- Explains why some twin studies have reported lower concordance rates
- Medications can cause epigenetic changes
  - Valproic acid has histone deacetylase properties

BRAIN STRUCTURES INVOLVED:

INCREASED	DECREASED
• Ventricular dimension • Amygdala volume	• Cortical volume • Grey matter in PFC regions

- Too much activity in emotional centres, and too little in frontal lobes (supposed to be able to inhibit action)
- Medications may make a difference (increased frontal lobe activity when on treatment)

NEUROCHEMICAL THEORIES:

- Monoaminergic systems involving DA, NE & 5-HT are widely distributed throughout key regions of brain thought to be involved with symptoms of bipolar disorder
  - Limbic, striatal, and prefrontal cortex regions
- GABA deficiencies or excessive glutamate cause changes in DA and NE activity that may lead to bipolar symptoms
  - BZDs & Mood Stabilizers modulate GABA & glutamate
  - Clozapine, quetiapine, olanzapine & VPA are suggested to activate DNA-demethylation of GABAergic gene promoters to correct downregulation

NEUROENDOCRINE DYSFUNCTION:

- Alterations in the HPA axis function & elevations in cortisol
- Chronic exposure to elevated cortisol levels reduces hippocampal size and promotes neuronal vulnerability to insults → glutamate neurotoxicity

IMMUNE MEDIATED DYSFUNCTION:

- Bipolar disorder is a pro-inflammatory illness with peripheral inflammatory markers elevated compared with healthy controls
  - Inflammatory cytokines: TNF-alpha, IL-4, IL-6, CRP
- These cytokines are implicated in excessive glutamate production, suppression of BDNF synthesis, and disruption of monoamine neurotransmission
- Immune-mediated dysfunction also contributes to HPA-axis dysfunction

CIRCADIAN DYSFUNCTION:

- Disruptions in sleep-wake cycles occur during manic and depressive episodes
- Circadian rhythm alteration can precipitate mood episodes
- Hypothalamic suprachiasmatic nucleus is responsible for circadian rhythms and controlled by the expression of CLOCK & BMAL1 t hat are linked to bipolar disorder

NEUROPLASTICITY & SIGNALLING:

- Neuroplasticity mechanisms (such as intracellular signalling cascades, gene regulation, synapse modifications) have demonstrated influence on the long-term course and treatment response
- Agents used to treat bipolar disorder have been shown to alter extracellular stimuli that have direct effects on intracellular signalling cascades

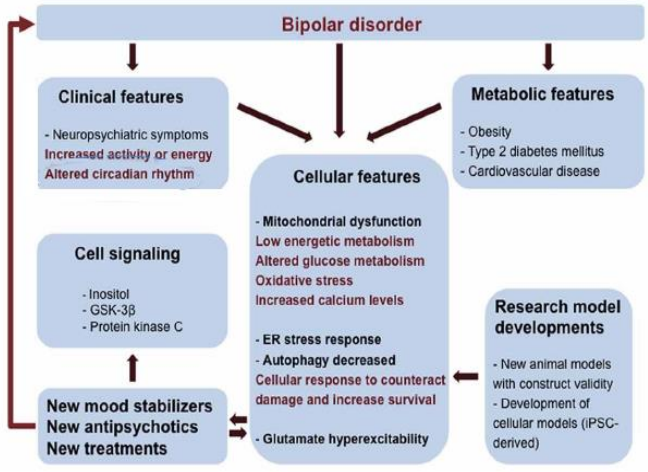
MITOCHONDRIAL DYSFUNCTION:

- Numerous genes implicated in the etiology of bipolar disorder code for mitochondrial proteins
- Mitochondrial dysfunction NEGATIVELY impacts neuro-plasticity & promotes apoptosis

CALCIUM SIGNALLING:

- Plays a crucial role in the modulation of neurotransmitters, neuron excitation and long-term neuroplastic changes

PATHOPHYSIOLOGY OF BIPOLAR DISORDER SUMMARY:



CLNICAL COURSE:

- 69% of pts who seek treatment during the first year of onset are misdiagnosed
- Pts spend one-third of life in a depressvive state
- Chronic life-long illness with frequent recurrences
- 80% of pts experience > 4 episodes in a lifetime

AGE OF ONSET:

- Bipolar I: mean age of first mood episode is 18 years old
  - Mania = 60% of all first episodes
- Bipolar II: mean age of onset is mid 20s

NOTE: Bipolar I and II are genetically different

- Bipolar II = greater chronicity of illness, more lifetime episodes, more time spent with depressive symptoms than Bipolar I

SUICIDALITY IN BIPOLAR DISORDER:

- 20 times higher suicide rate than general population
- Up to 50% of pts will attempt suicide, with 8-20% of pts completing suicide
- Bipolar pt most at risk of attempting suicide when finishing manic stage and entering depressive stage (usually dealing with repercussions of actions in manic stage)
  - Other risk factors: female, diagnosis of bipolar II, comorbid substance use, eating disorder, personality disorder

COMORBIDITIES:

ANXIETY:
- 56% suffer from anxiety disorder
  - HPA-axis dysfunction
- More time spent ill, increased risk of relapse, treatment non-response, suicidality

SUBSTANCE USE DISORDER:
- 60.7% lifetime prevalence risk in pts with bipolar I
- Alcohol is most commonly abused substance
  - Increased risk of rapid cycling and greater severity of symptomology

ADHD:
- 20% have comorbid ADHD
- Children with ADHD have 10-fold increased risk of being diagnosed with bipolar disorder later in life
- Worse prognosis, earlier onset, more depressive episodes
- Stimulant-induced mood destabilization
  - Bupropion as first-line therapy
  - Stimulants when risk of manic switch is low

MEDICAL COMORBIDITIES:
- Reduced life expectancy is approximately 10 years less compared with general population
- Diabetes, dyslipidemia, obesity occur more frequently & present earlier in pts with bipolar disorder
  - General metabolic disorders may “metastasize” to the brain
- Biological mechanisms, lifestyle, pharmacotherapy