



Black Dog Institute

What we know about the Biochemistry of Mood Disorders

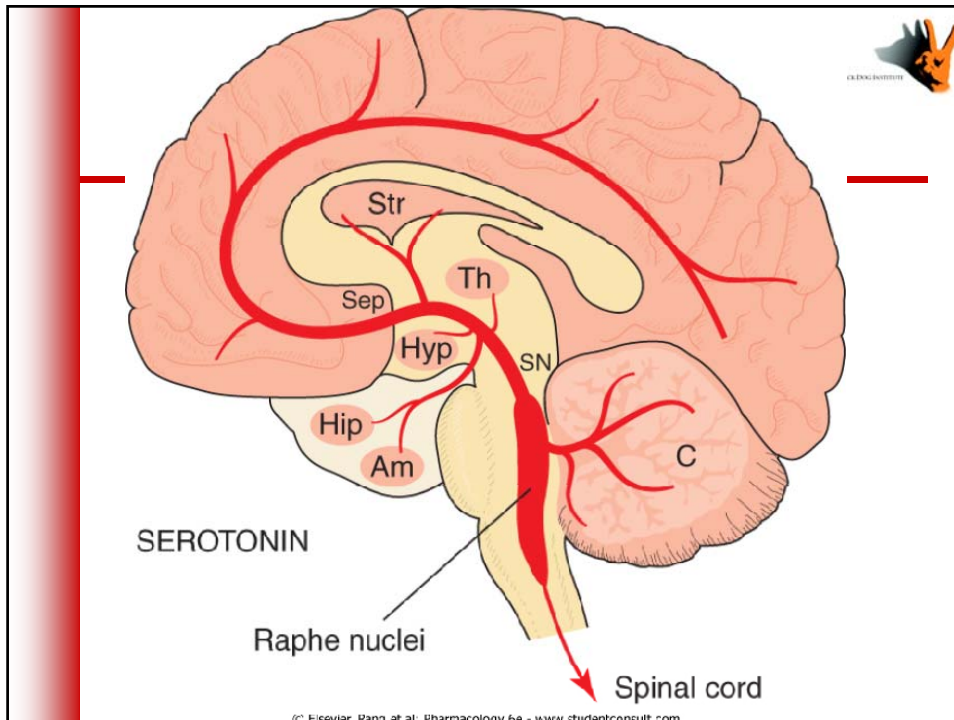
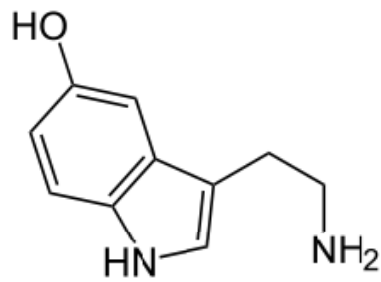
Dr Paul Friend
Clinical Director

Neurotransmitter Pathways in Depression

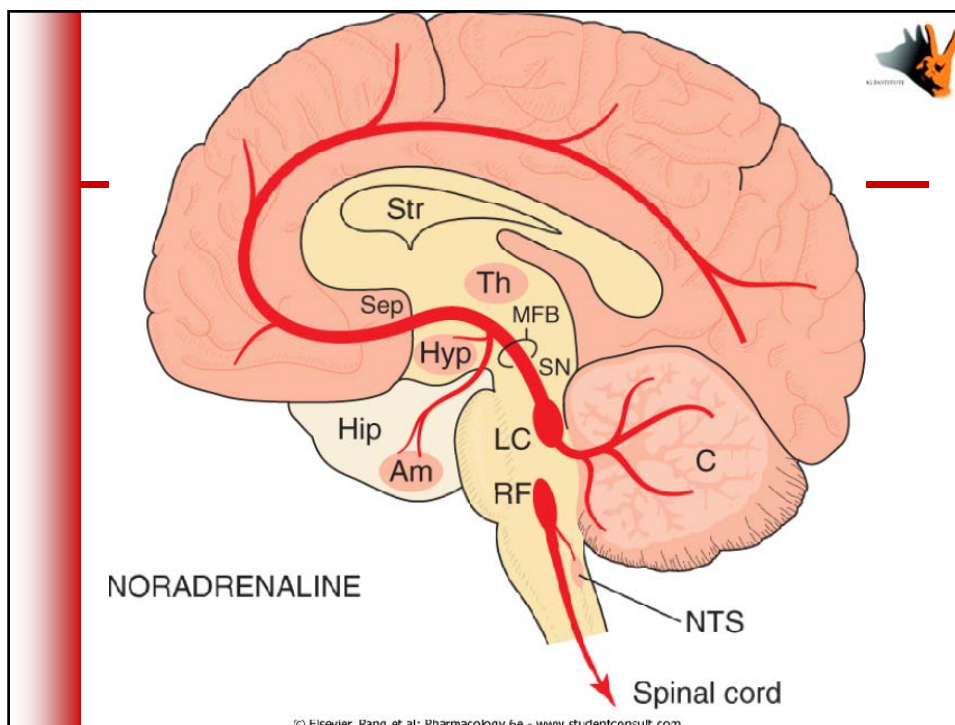
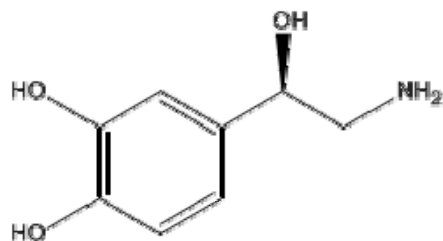


- Serotonin
- Noradrenaline (norepinephrine)
- Dopamine

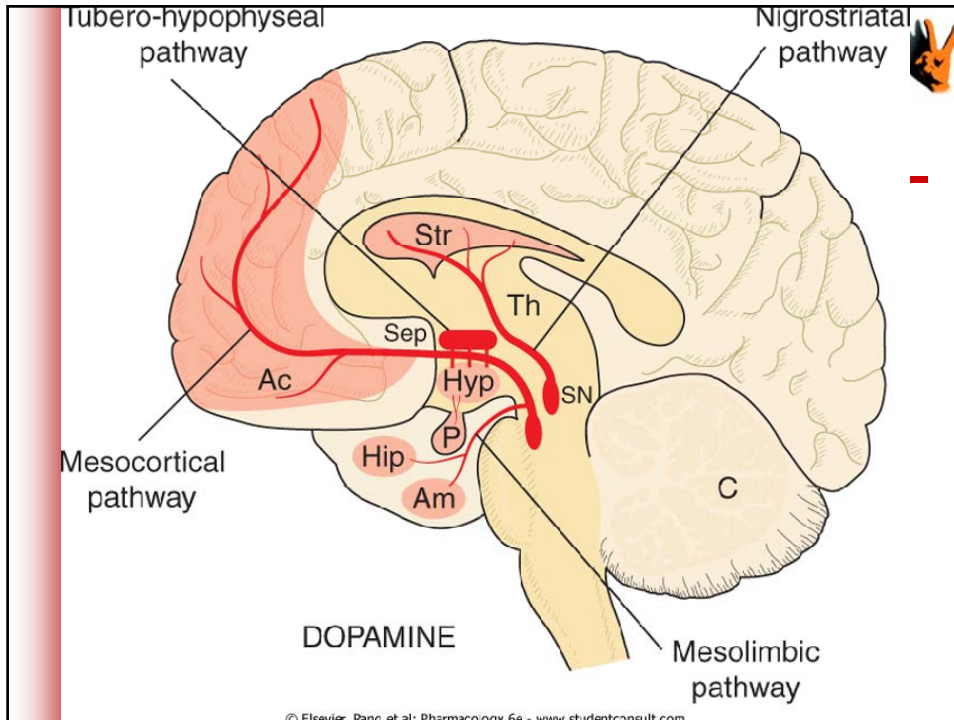
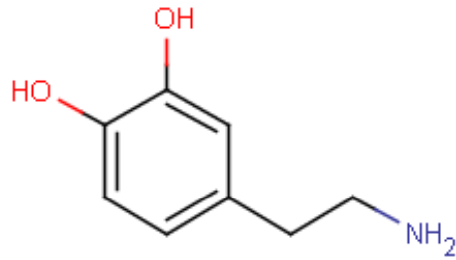
Serotonin



Noradrenalin (Norepinephrine)



Dopamine





The location of the main groups of cell bodies and fibre tracts is in solid colour. Light-shaded areas show the location of neurotransmitter terminals. Am, amygdaloid nucleus; C, cerebellum; Hip, hippocampus; Hyp, hypothalamus; LC, locus coeruleus; MFB, medial forebrain bundle; NTS, nucleus of the tractus solitarius (vagal sensory nucleus); RF, brain stem reticular formation; Sep, septum; SN, substantia nigra; Str, corpus striatum; Th, thalamus.

Antidepressant Therapies in Historical Order



- Asylums
- Blood letting – leeches
- Purgatives
- The Retreat at York - William Tuke, Hannah Mills

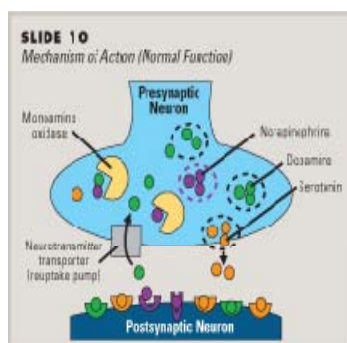


Antidepressant Therapies

- Psychiatric medications/treatments like many things in medicine were developed from a chance finding or intuitive thought
- The mechanism of action and factors influencing effectiveness of antidepressant medication was often determined after clinical trials, especially for the earlier antidepressants



Release of Neurotransmitters





Convulsive Therapies

- Induced convulsions release all types of neurotransmitters
- 1934 Meduna used camphor and later metrazol
- 1937 Cerletti and Bini used electrical current.
- ECT - repetitive narrow width pulsed direct current 0.25-1.5 msec, 10-70 Hz (140), 0.9A



Non selective Monoamine Oxidase Inhibitor antidepressant medications – MAOIs 1950s

- MAOIs were developed from the anti-tuberculosis medication, iproniazid, (MAOI properties) which was noted to cause euphoria in some patients being treated for tuberculosis.

Non selective Monoamine Oxidase Inhibitor antidepressant medications – MAOIs 1950s



- Irreversibly inhibit Type A and Type B monoamine oxidase enzymes in the presynaptic neuron increasing the cytoplasmic stores of stores of serotonin, noradrenaline and dopamine and increased leakage of these monoamines from presynaptic neurone.
- Also causes increased release of indirectly acting monoamines adrenalin and tyramine.

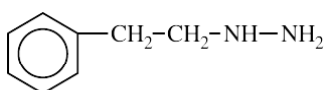
Non selective Monoamine Oxidase Inhibitor antidepressant medications



- Ingestion of tyramine containing substances most commonly aged or preserved foods strong cheeses, gamey meat, salted or pickled meat, fish, vegetables, dried fruit whilst taking MAOIs can cause hypertensive crisis and death (rare).
- tranylcypromine, phenelzine – most potent standalone antidepressant medications.



Phenelzine



PHENELZINE



Tricyclic antidepressant medications – TCAs late 1950's

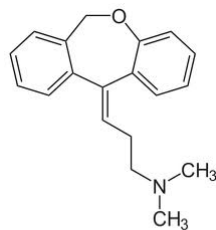
- non-selective inhibition of the reuptake of serotonin and noradrenaline into the presynaptic neuron, some dopaminergic activity
- Also inhibit muscarinic acetylcholine, histamine and serotonin receptors which cause side effects: dry mouth, blurred vision, constipation, postural hypotension, sedation, increased appetite

Tricyclic antidepressant medications - TCAs



- amitriptyline, doxepin, imipramine, nortriptyline, dothepin, clomipramine, trimipramine

Doxepin Hydrochloride



Selective Serotonin Reuptake Inhibitors – SSRIs - 1987



- Inhibit the reuptake of serotonin into the presynaptic neuron
- fluoxetine, paroxetine, citalopram, escitalopram, sertraline, fluvoxamine

Selective Type A Monoamine Oxidase Inhibitor antidepressant medications – RIMA –early 1990's



- Reversibly inhibit Type A monoamine oxidase enzymes in the presynaptic neuron reportedly only increasing the cytoplasmic stores of stores of serotonin.
- In recommended therapeutic doses have weak antidepressant activity and in higher doses seem to have similar risks and side effects as MAOIs.
- moclobemide

Serotonin Noradrenaline Reuptake Inhibitors – SNRI mid 1990's



- Inhibit the reuptake of serotonin and noradrenaline into the presynaptic neurone
- venlafaxine, desvenlafaxine, duloxetine

Noradrenalin Reuptake Inhibitors – NRI – late 1990's



- Inhibit the reuptake of noradrenaline into the presynaptic neuron
- Reboxetine

Neurotransmitter release antidepressant – early 2000's



- **Mirtazepine** increases the presynaptic release of serotonin and noradrenaline by inhibiting central α_2 -auto and hetero adrenoceptors
- blocks serotonin type 2 and 3 post synaptic receptors

What we don't know



- The brain at its core level of functioning is signalling with neurotransmitters of many types
- We do not know the neurophysiological /chemical process of depression
- We do not understand neurophysiological /chemical differences between normal mood swings, melancholic and non-melancholic depression

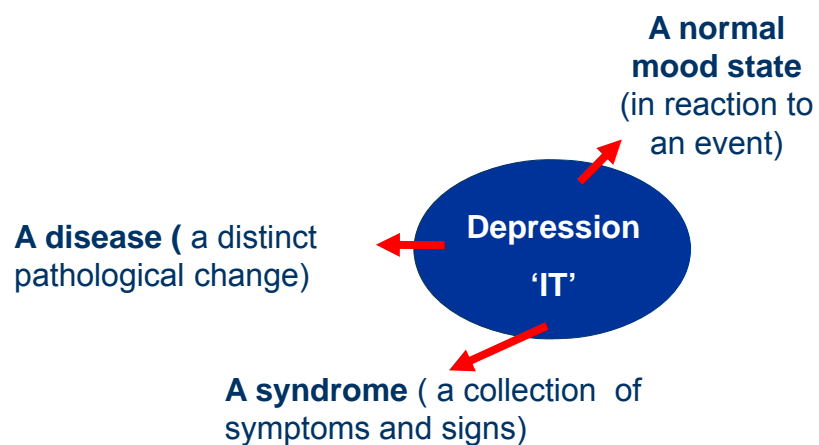


What we don't know

- We do not know how antidepressant medications actually treat depression
- It has been suggested that they act through the Hypothalamic adrenal axis resetting the amount of cortisol secreted by the adrenal glands



What is clinical depression and why can it be can be confusing





Normal Mood Swings



- 'Depressed moods' are normal
- Most people 'bounce' back
- People with clinical depression lack the capacity for spontaneous remission

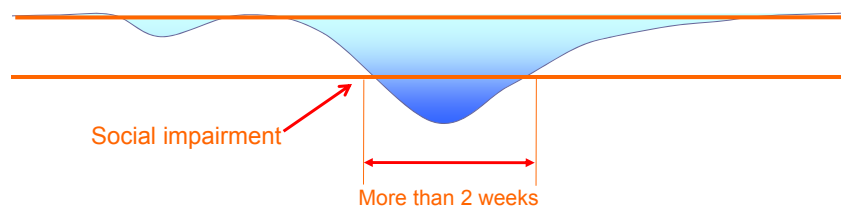


Clinical Depression- Features

- **Key features**
 - Decline in self-esteem
 - Self-criticism
 - Depressed mood
- **Associated features**
 - Anhedonia
 - Non-reactive mood
 - Hopelessness and helplessness
 - Amotivation
 - Suicidality
- **Non-specific features**
 - Insomnia
 - Libido changes
 - Fatigue
 - Appetite and weight changes



Non-melancholic Depression



Key features

- Decline in self-esteem
- Self-criticism
- Depressed mood
- Usually identifiable triggers



Non-melancholic Depression 'Aetiology'

1. Response to Stress



Acute Stress

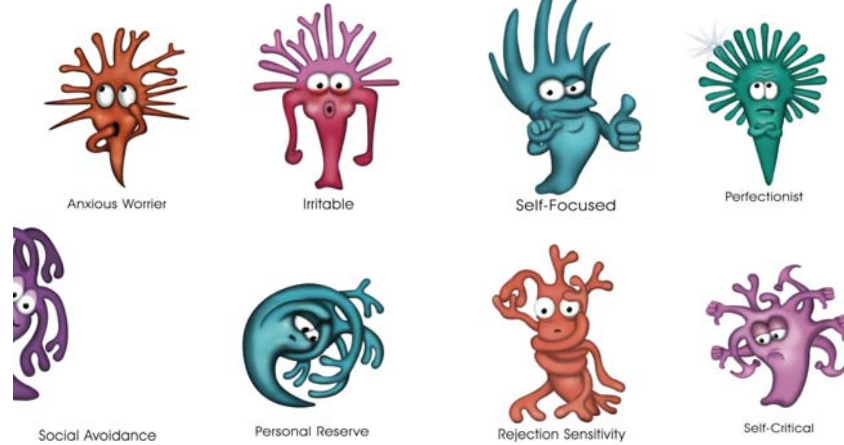


Chronic Stress

Non-melancholic Depression 'Aetiology'

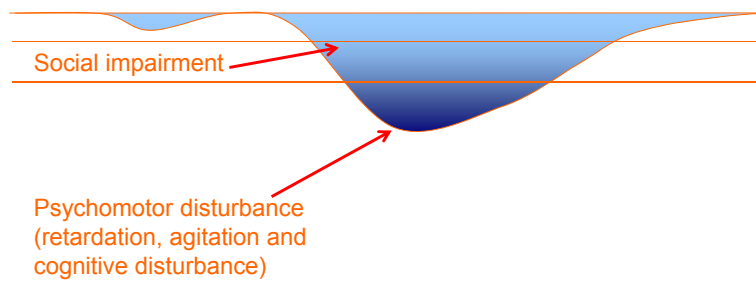


2. Vulnerable personality styles



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Melancholic Depression



Symptoms of Melancholic Depression - 1



Key features of depression as discussed previously *plus*

- Anhedonia – loss of pleasure
- Non-reactive mood (cannot be cheered up)
- Profound and uncharacteristic anergia (lack of energy)
- Mood and energy worse in the morning or evening (diurnal mood variation)

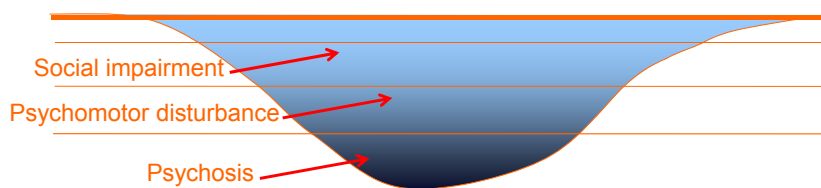
Symptoms of Melancholic Depression - 2



- Repeated disturbed sleep pattern, early morning wakening
- Family History across generations
- Episodic pattern
- Absence of precipitants or triggering events for every episode



Psychotic Depression

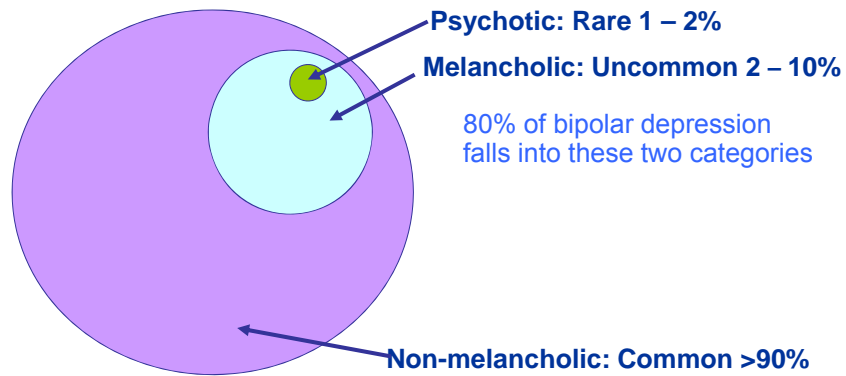


Diagnosis of Psychotic Depression

Observable severe depressed mood and severe social impairment with...

Psychotic features	➔	Generally consistent with mood Delusions more common than hallucinations – 90% vs 10%
Pathological guilt	➔	Common in psychotic depression - often with guilty ruminations
Psychomotor disturbance	➔	Profound
Cognitive function	➔	Mild cognitive processing problems through to pseudo-dementia

Depression Types in General Practice

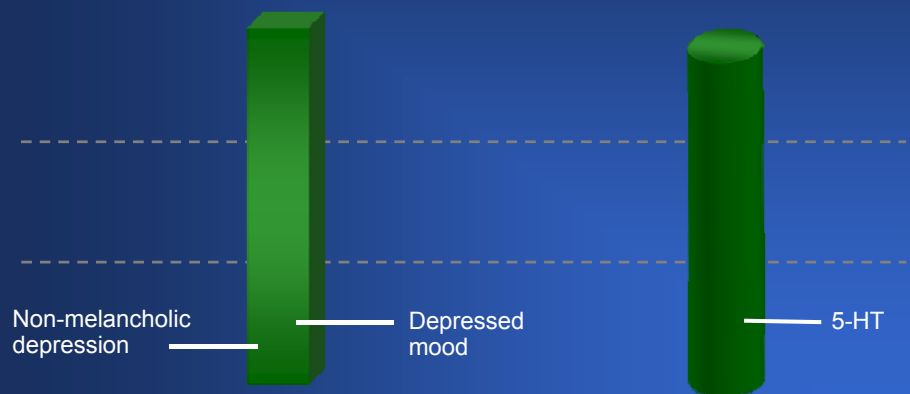


Hierarchical Model of Depressive Disorders The model - part 1

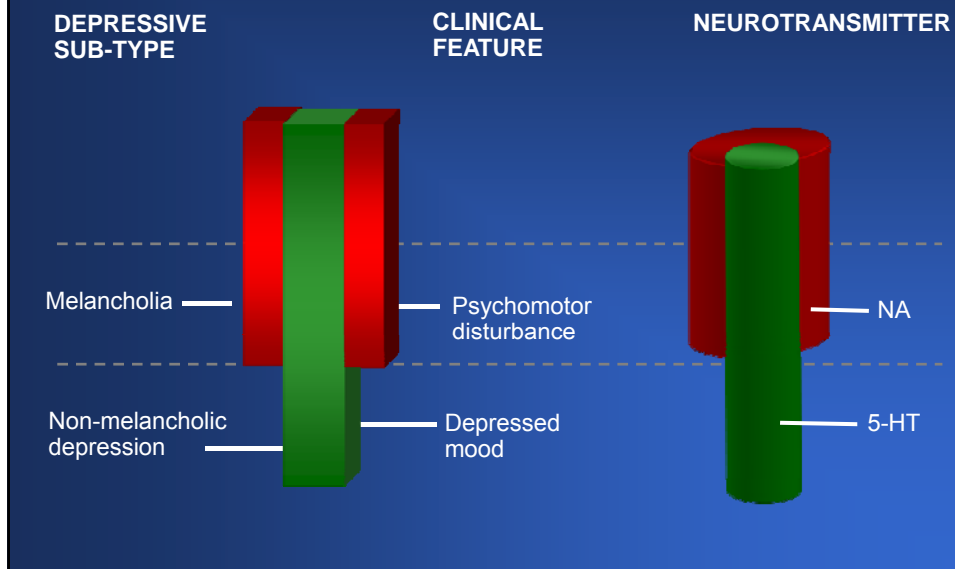
DEPRESSIVE
SUB-TYPE

CLINICAL
FEATURE

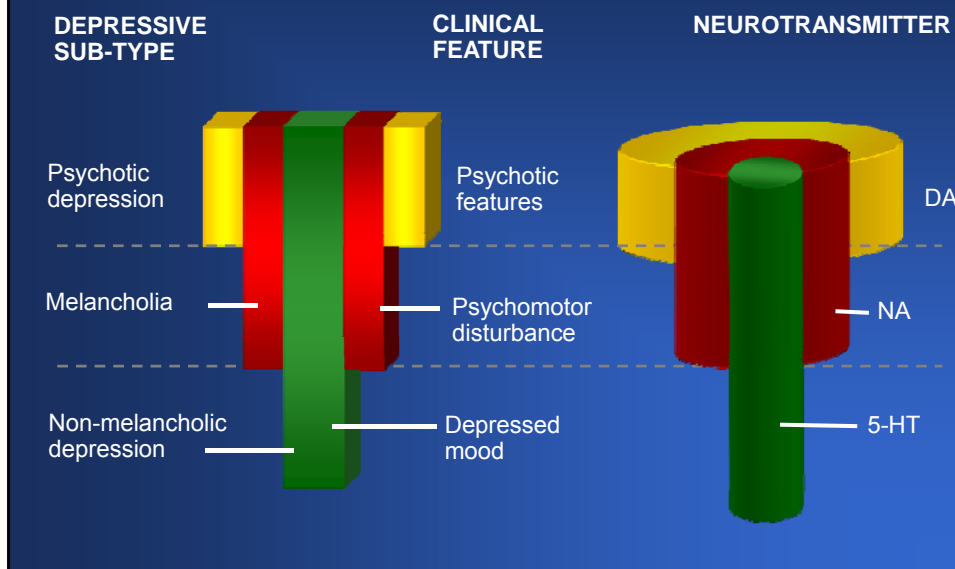
NEUROTRANSMITTER



Hierarchical Model of Depressive Disorders The model - part 2



Hierarchical Model of Depressive Disorders The model - part 3





Antidepressant Classes

	Serotonergic	Noradrenergic	Dopaminergic
Selective			
SSRIs	✓		
Reboxetine		✓	
Dual Action			
SNRIs	✓	✓	
Mirtazapine	✓	✓	
TCAs	✓	✓	✓
MAOIs	✓	✓	✓



Antidepressant Strategy

- Single action SSRI antidepressant medication
- Dual Action SNRI antidepressant medication
- Tricyclic antidepressant medication
- MAOI antidepressant medication
- Partial response augment with lithium carbonate, atypical antipsychotic or methylphenidate (not with MAOIs).
- ECT if not responsive, especially if psychotic depression



Bipolar Disorder - 1

- We know very little about Bipolar Disorder
- Lithium Carbonate interfere with ions such as Na^+ , Mg^{++} or Ca^{++} , and apparently thereby lithium influences the release of neurotransmitters and affects the metabolism of monoamines as well as synaptic transmission.
- Lithium affects the generation of intracellular messengers, which are formed when membrane receptors are stimulated by neurotransmitters.



Bipolar Disorder - 2

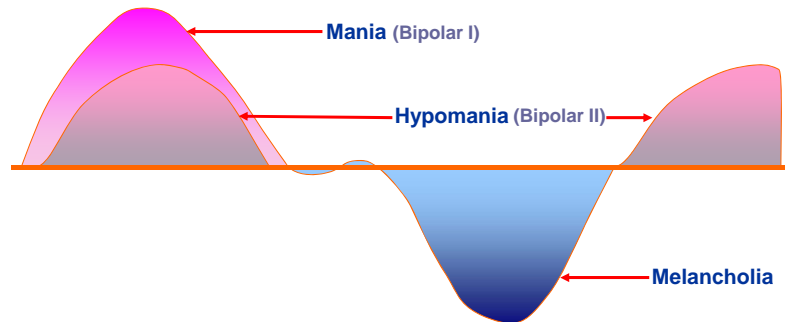
- lithium, valproic acid and carbamazepine seem to act on the same enzyme, prolid oligopeptidase, which regulates the activity of the phosphoinositide cycle



Bipolar Disorder



Always screen for bipolar disorder in a depressed patient.
Of the depressed patients referred by GPs to a psychiatrist,
some 30% have a bipolar course.



About 80% of these depressive episodes are psychotic or melancholic in type.



Diagnosis of Bipolar Disorder – Key Features of ‘Highs’

- Energised and wired
- Talk more and over people
- Spend more money
- Are indiscrete
- Require less sleep and do not feel tired
- Increased libido
- Creative and grandiose plans
- *And* can be irritable, argumentative or aggressive.

Medication Management of Bipolar Depression



- Bipolar depression is usually psychotic or melancholic and will require appropriate antidepressants
(if psychotic add antipsychotic)
- Be aware of risk of possible manic switch with use of antidepressants
- Consider long term mood stabiliser

Non-melancholic Depression Treatment principles



- Serotonergic dysfunction probably underpins depressed mood features, and (commonly) drives anxiety – SSRI is treatment of choice if medication indicated
- Psychological treatments play key role to address – personality vulnerabilities
 - current stressors
 - patient priorities