Medical Pharmacology

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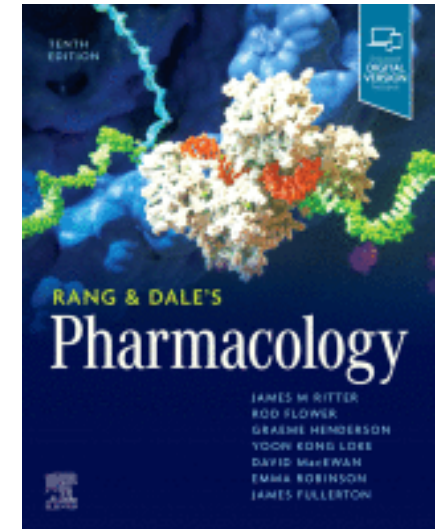
Celebrating 50 YEARS 1970 - 2020

CNS
Psychotropic drugs 1 - Antidepressants
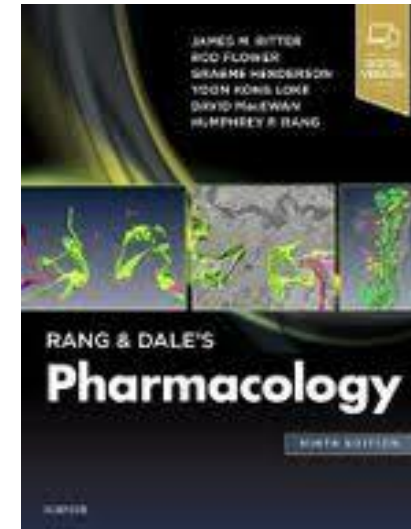
Rang & Dale's Pharmacology
9th edn 2019
Chap 45, 48

Rang & Dale's Pharmacology
10th edn 2023
Chap 45, 48

Psychotropics - drug treatment of psychiatric disorders

Focus on the main classes of drugs used in the treatment of the following disorders:

- depression
  - major depression
- anxiety

Week 9

- schizophrenia
- bipolar disorder
- sleep disorders
  - insomnia

Week 11

- 45% of Australians will experience a mental illness in lifetime

MP week 9 drug classes

THERAPEUTIC CLASS	SUB CLASS	EXEMPLAR	SCRIPT 1000's
Antidepressants	Selective serotonin reuptake inhibitors (SSRIs)	escitalopram sertraline	12,000
	Serotonin and norepinephrine reuptake inhibitors (SNRIs)	venlafaxine duloxetine	6400
	Selective NE reuptake inhibitors	reboxetine	50
	Tricyclic antidepressants	amitriptyline	3000
	Monoamine oxidase inhibitors (MAOIs)	phenelzine	25
	reversible inhibitors of monoamine oxidase (RIMAs)	moclobemide	120
	Monoamine receptor antagonists	mirtazepine	2200
	Melatonin receptor agonists	agomelatine	
Anxiolytics	Benzodiazepines	Diazepam	

Rank	Drug Name	Total Prescription Volume 2021
6	ESCITALOPRAM	5,386,263
8	SERTRALINE	5,036,782
18	VENLAFAXINE	3,336,350
21	MIRTAZAPINE	3,040,248
26	AMITRIPTYLINE	2,680,384
29	FLUOXETINE	2,457,227
32	DESVENLAFAXINE	2,351,648
40	DULOXETINE	2,023,112
49	CITALOPRAM	1,775,981

Ten leading causes of burden of disease, world, 2004 and 2030

2004 Disease or injury	As % of total DALYs	Rank		Rank	As % of total DALYs	2030 Disease or injury
Lower respiratory infections	6.2	1		1	6.2	Unipolar depressive disorders
Diarrhoeal diseases	4.8	2		2	5.5	Ischaemic heart disease
Unipolar depressive disorders	4.3	3		3	4.9	Road traffic accidents
Ischaemic heart disease	4.1	4		4	4.3	Cerebrovascular disease
HIV/AIDS	3.8	5		5	3.8	COPD
Cerebrovascular disease	3.1	6		6	3.2	Lower respiratory infections
Prematurity and low birth weight	2.9	7		7	2.9	Hearing loss, adult onset
Birth asphyxia and birth trauma	2.7	8		8	2.7	Refractive errors
Road traffic accidents	2.7	9		9	2.5	HIV/AIDS
Neonatal infections and other[a]	2.7	10		10	2.3	Diabetes mellitus
COPD	2.0	13		11	1.9	Neonatal infections and other[a]
Refractive errors	1.8	14		12	1.9	Prematurity and low birth weight
Hearing loss, adult onset	1.8	15		15	1.9	Birth asphyxia and birth trauma
Diabetes mellitus	1.3	19		18	1.6	Diarrhoeal diseases

World Health Organization

Depression

Introduction

- Depression is a mental disorder characterised with negative mental status

  - Depress mood vs. clinical depression

    - Depress mood is part of the range of normal expression in human in response to emotional stress (e.g. Losing of love one)

    - Depression/clinical depression is referred to continuous depress status (over weeks or months) and/or severe-extreme negative mental status (e.g. Suicidal thought)

- The aetiology of clinical depression is multi-factorial and not fully understood – genetic, stressors, Neuro-endocrine abnormalities & neurodegenerative diseases, Childhood experience & Parent-child relationship, Vascular

Clinical presentation/symptoms

- The clinical depression can be presented with a wide range of symptoms
  - Patient with depression may present with combination of the symptoms, but not all of the symptoms
  - The symptoms usually divided into categories
    - Emotional
    - Physical
    - Cognitive
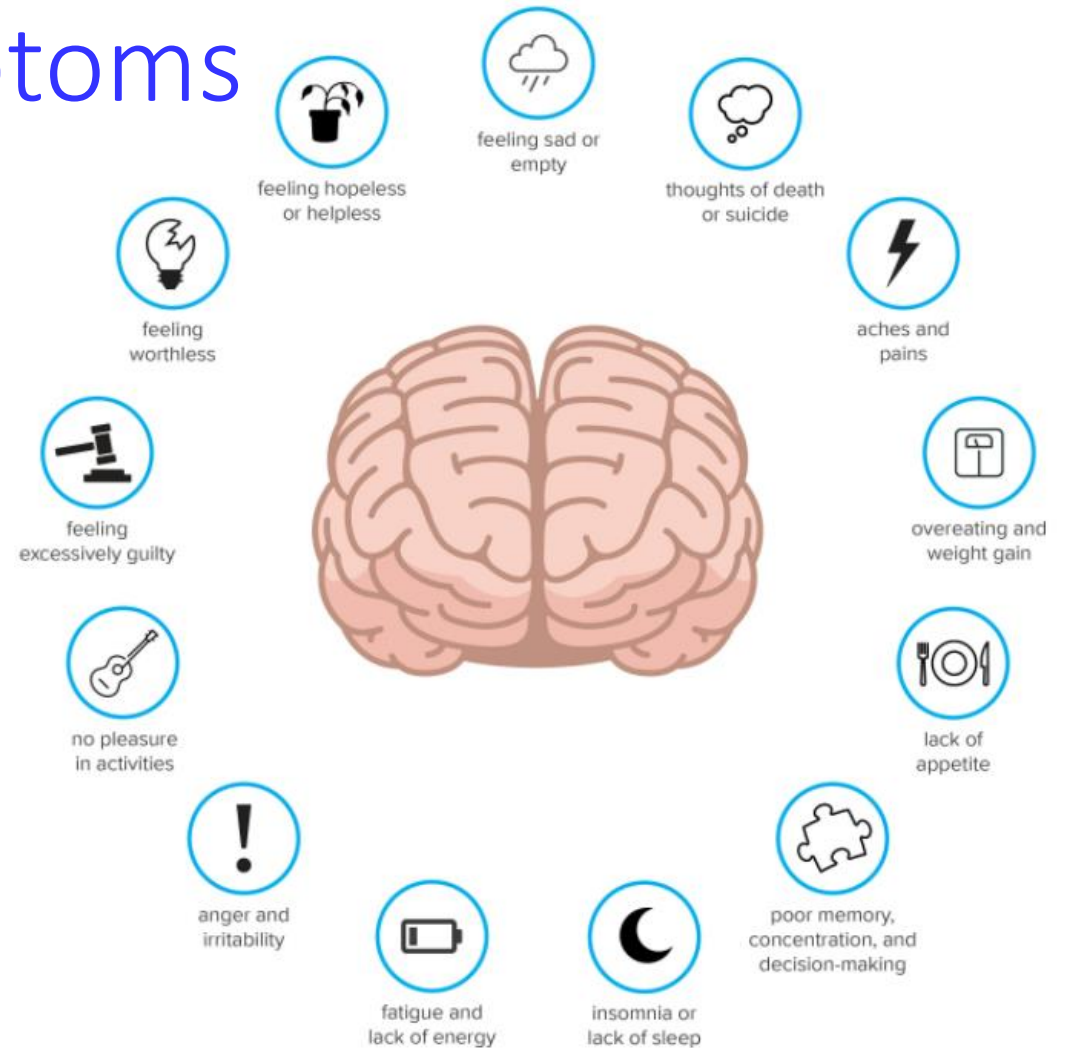   - Psychiatric symptoms
    - Atypical symptoms
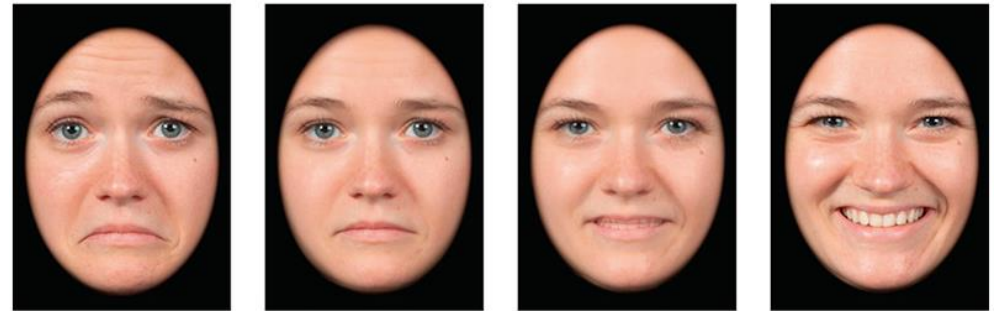
Reprinted from the P1vital Oxford Emotional Test Battery, P1vital Products Ltd.

Source: Rang & Dale Pharmacology; 10th ed; Ch 48.

- The symptoms are non-specific and can be observed in individuals with no clinical depression
  - i.e. Presence of symptom(s) ≠ presence of clinical depression

Clinical presentation/symptoms

- Emotional symptoms
  - Depressed mood nearly every day for most of the day for 2 weeks or longer
  - Anhedonia (Markedly decreased interest in most/all activities)
    - Unable to experience pleasure
  - Sadness
  - Pessimism
    - Focus on the negative aspect of events
  - Feeling of emptiness
  - Irritability
  - Anxiety
  - Worthlessness
  - Suicidal ideation

feeling hopeless or helpless

feeling sad or empty

thoughts of death or suicide

feeling worthless

aches and pains

feeling excessively guilty

overeating and weight gain

no pleasure in activities

lack of appetite

anger and irritability

fatigue and lack of energy

insomnia or lack of sleep

poor memory, concentration, and decision-making

Source: https://www.medicalnewstoday.com/articles/326769#13-symptoms-of-depression

Clinical presentation/symptoms

- **Physical symptoms**
  - Disturbed sleep
  - Change in appetite/weight
  - Psychomotor changes
  - Decreased energy
  - Fatigue
  - Body aches & pains

- Cognitive
  - Impaired concentration
  - Indecisiveness
  - Poor memory

- Psychotic symptoms
  - Hallucinations
  - Delusions

- Atypical features
  - Reactive mood
  - Significant increase in appetite/weight gain
  - Hypersomnia/excessive sleepiness
  - Heavy feeling in arms or legs
  - Sensitivity to interpersonal rejection

Major depression (Major depressive disorder)

Diagnosis

- diagnosis when symptoms reported for longer than a 2 week period of time, and disrupt normal social and occupational functioning (DSM-V criteria)

Prevalence

- One of the most common chronic disorders in Australian community
  - Estimated 100,000 people affected each year
    - 1 in 6 experience depression sometime in their life
      - 1 in 5 of female; 1 in 8 males
- 4.6% 12-month prevalence of depressive episode in the Australian community in 2020/2021 (1.5 million)

Affective disorders

6.2   8.5

Males   Females
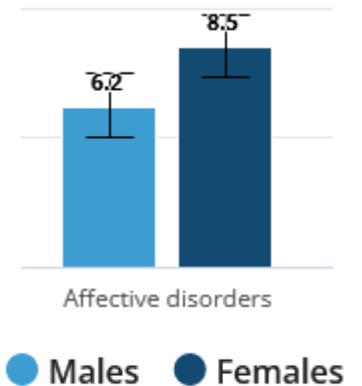
Main brain regions involved in depression

<u>Limbic system</u>

- hippocampus, amygdala, cingulate gyrus

<u>Midbrain</u>

- nucleus accumbens, ventral tegmental area, locus coeruleus,

<u>Prefrontal cortex</u>

<u>Hypothalamus</u>

- sleep disturbances
- appetite and energy
- HPA axis/stress

- various studies show alterations in blood flow, volume, neuron / receptor densities etc in these areas

To PFC
From PFC
VTA
DR
NAc
Hypo-thalamus
Amygdala Hippocampus
LC

© Scott Bodell '02
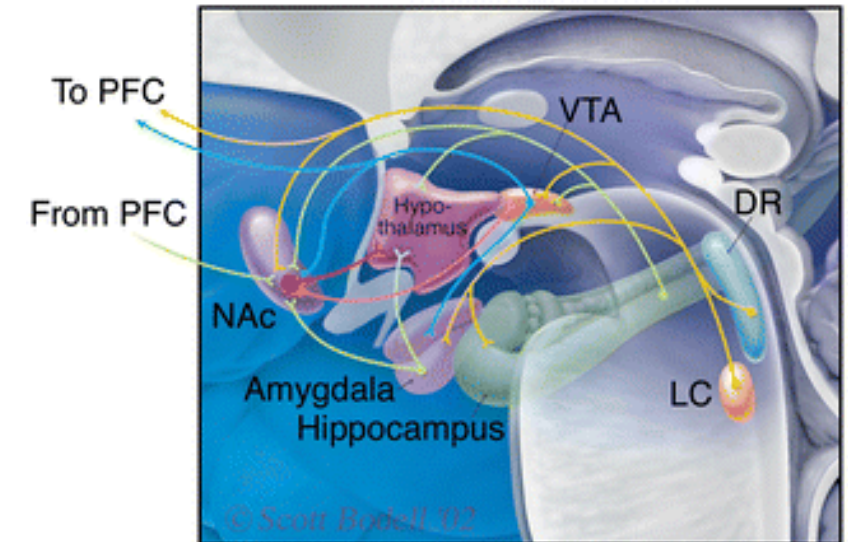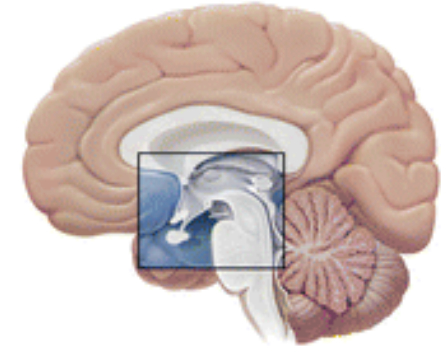
— GABAergic
— Glutamatergic
— Dopaminergic
— Peptidergic
— NEergic/5HTergic

Pathophysiology/Theories of depression

- There is very limited understanding of the pathophysiology of depressive disorders
  - Most information are surrounding the **neurotransmitter** and **receptors**
  - Current understandings mainly based on various hypothesis with some supporting data
    - Monoamine hypothesis
    - Neurotransmitter receptor hypothesis
    - Other hypothesis(es)

Original monoamine theory

- thought that depression was due to functional decrease in 5-HT and NA in certain brain regions ?
  - based largely on pharmacological observations that antidepressant drugs all <mark>increase</mark> levels of 5-HT, NA
  - drugs that block these effects abolish antidepressant actions, and drugs that decrease monoamines worsen mood
- but not always supported by studies investigating direct changes in these systems in depressed patients
- activation of post-synaptic 5-HT1a appears important, while inhibition of other subtypes may also play a role
- HOWEVER, while antidepressant drugs produce their actions on monoamine levels in hours....
- clinical effects of antidepressants require at least 2 weeks of treatment
- clearly suggests that effects are due to secondary adaptive changes in these pathways – receptor desensitisation/expression, neuroplasticity

Theories of depression – stress / neuroendocrine

- depressive illness is clearly associated with stressful life events
- Stress has been associated with the development of and relapse to depression in humans

- Abnormalities of the hypothalamic-pituitary-adrenal axis in major depression
- Stress can lead to depression-like behavioural and neuroendocrine states in pre-clinical animal models
- Effects of stress can be mimicked by chronic CRH or glucocorticoid administration
- Antidepressants normalise stress-induced behavioural and structural brain alterations in pre-clinical models
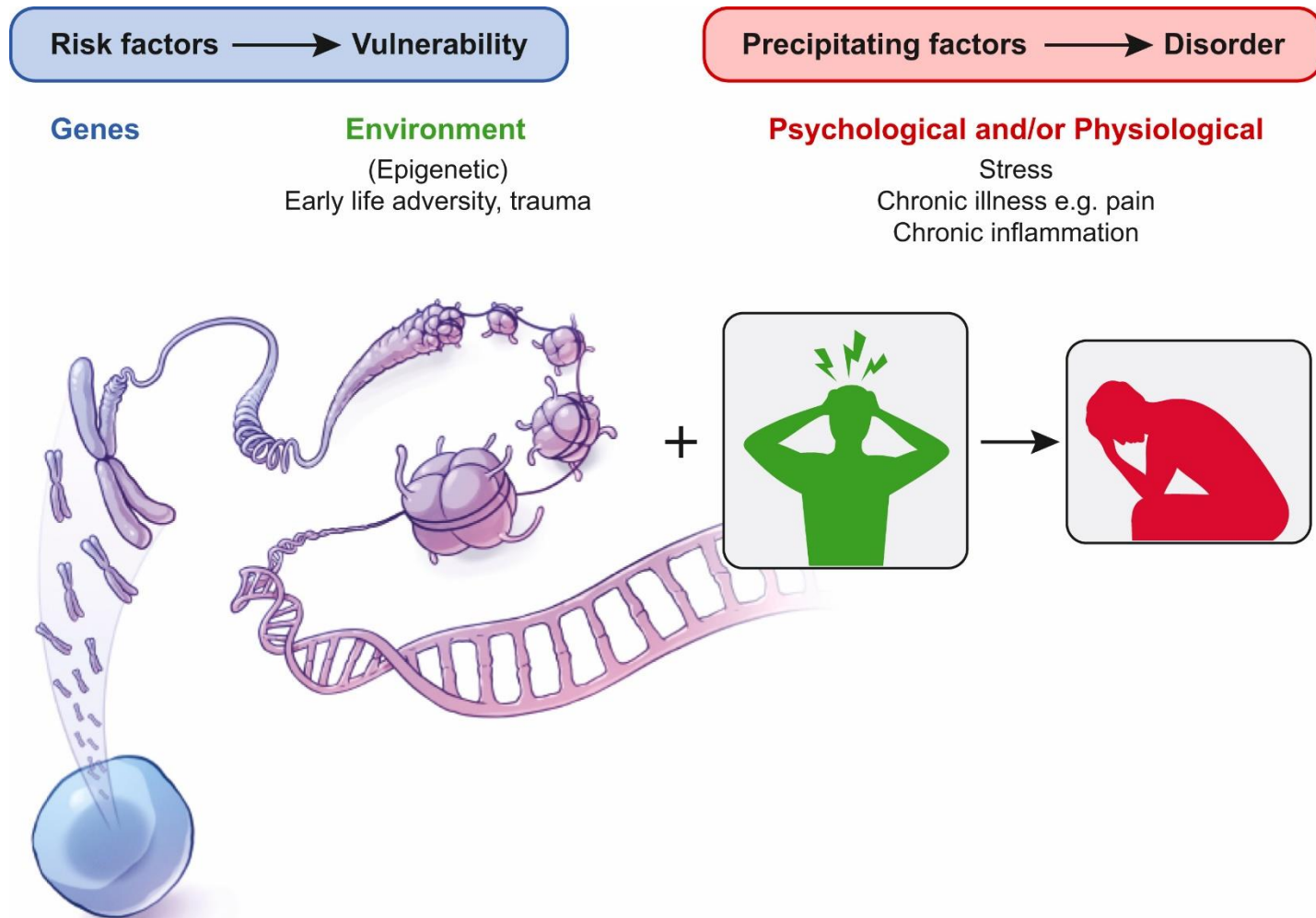
Fig. 48.1 Genetic and environmental factors which contribute to the risks of developing depression.

The causes of depression are complex and poorly understood but this diagram illustrates the different risk factors which have been linked to the development of mood disorders. Genetic factors and early life events, e.g. childhood abuse, neglect or trauma, lead to increased vulnerability possibly due to a sensitisation of the stress system. Precipitating factors in adolescence and adulthood then lead to the development of depression. Stress, particularly uncontrollable stress and social stress, as well as other chronic illnesses and chronic inflammatory disorders have all been linked to precipitating an episode of depression. More vulnerable individuals may develop depression more readily when exposed to chronic stress but even those who have low vulnerability may experience events in adulthood which can lead to the development of depression. Decades of research have failed to find a specific biological impairment or biomarker which can be attributed to causing depression.
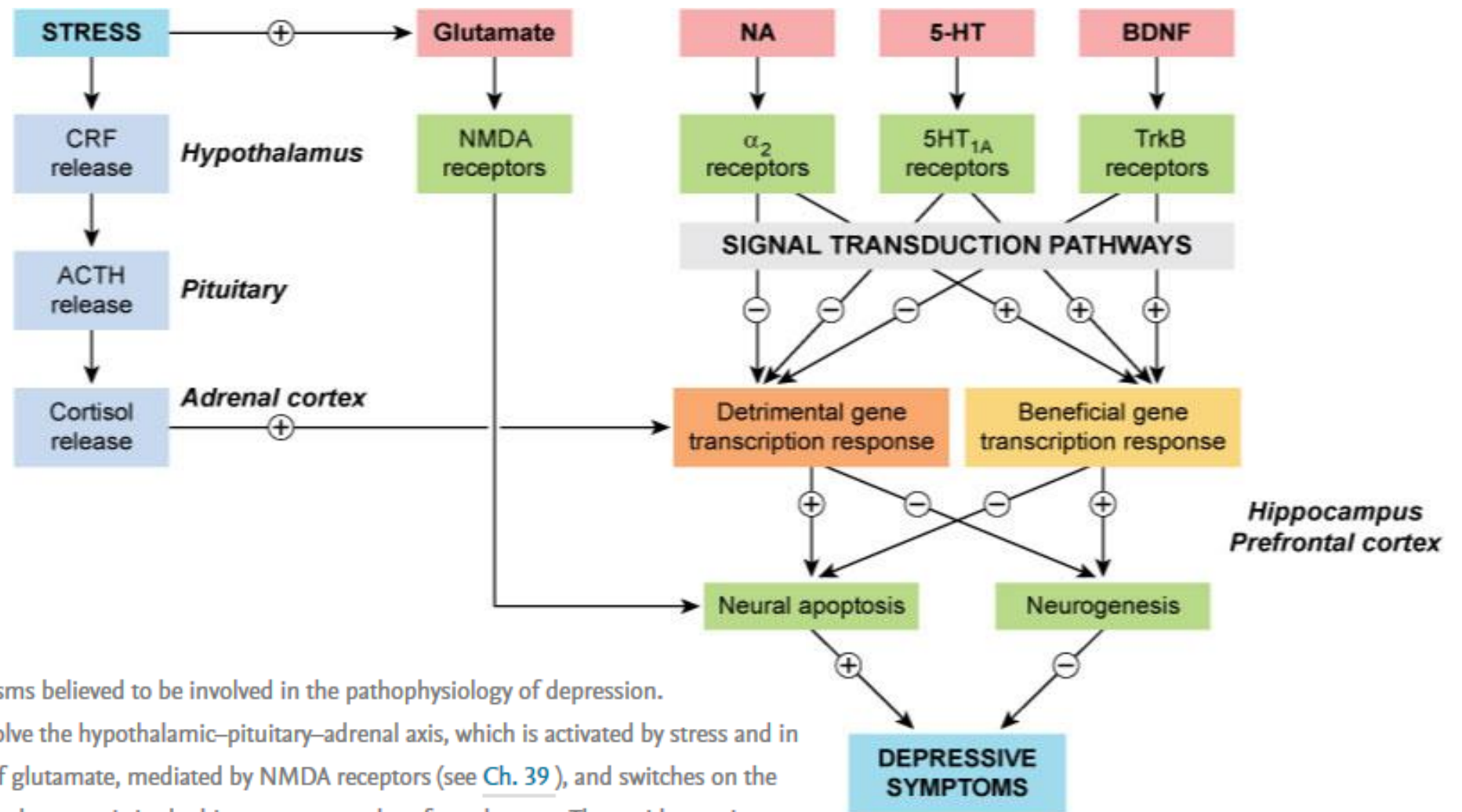
Fig. 48.2

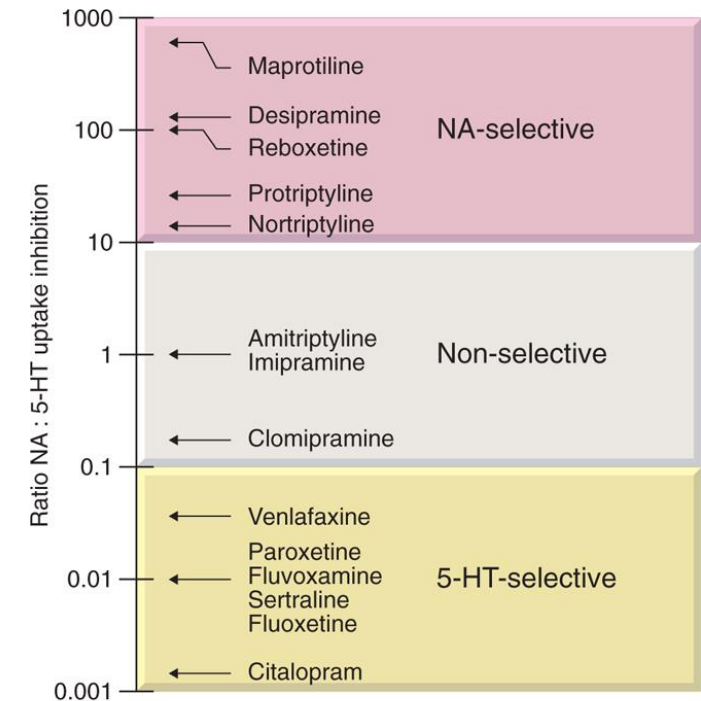Simplified diagram showing mechanisms believed to be involved in the pathophysiology of depression. The main prodepressive pathways involve the hypothalamic–pituitary–adrenal axis, which is activated by stress and in turn enhances the excitotoxic action of glutamate, mediated by NMDA receptors (see Ch. 39), and switches on the expression of genes that promote neural apoptosis in the hippocampus and prefrontal cortex. The antidepressive pathways involve the monoamines noradrenaline (NA) and 5-hydroxytryptamine (5-HT), which act on G protein–coupled receptors, and the brain-derived neurotrophic factor (BDNF), which acts on a kinase-linked receptor (TrkB), switching on genes that protect neurons against apoptosis and also promote neurogenesis. *ACTH,* adrenocorticotrophic hormone; *CRF,* corticotrophin-releasing factor.

Theories of depression – neuroplasticity and depression

- low levels of BDNF associated with depression

- other neurotransmitter systems including glutamate

  - newer rapidly-acting antidepressants (eg ketamine, psilocybin)

- evidence for loss of neurons in critical CNS regions eg prefrontal cortex, hippocampus) in human and animal models of stress / depression

- some evidence that this can be reversed by antidepressants

Summary

- some drugs in clinical trials
  interact with other proposed mechanisms

- drugs that increase monoamine
  transmission systems are still
  the main treatments for depression

- most antidepressants have multiple
  monoamine transmission effects

Ratio NA : 5-HT uptake inhibition		
1000		
100	Maprotiline	
	Desipramine	NA-selective
	Reboxetine	
	Protriptyline	
10	Nortriptyline	
1	Amitriptyline	Non-selective
	Imipramine	
0.1	Clomipramine	
	Venlafaxine	
0.01	Paroxetine	5-HT-selective
	Fluvoxamine	
	Sertraline	
	Fluoxetine	
0.001	Citalopram	

Theories of depression – neuropsychological hypothesis

- patients with depression show negative affective biases, i.e. tend to prioritise emotionally negative or unfavourable information or outcomes

- antidepressant drugs may produce immediate psychological effects

- but patients receiving the drugs need time for these to bias new learning before they become aware of the improvements in their mood
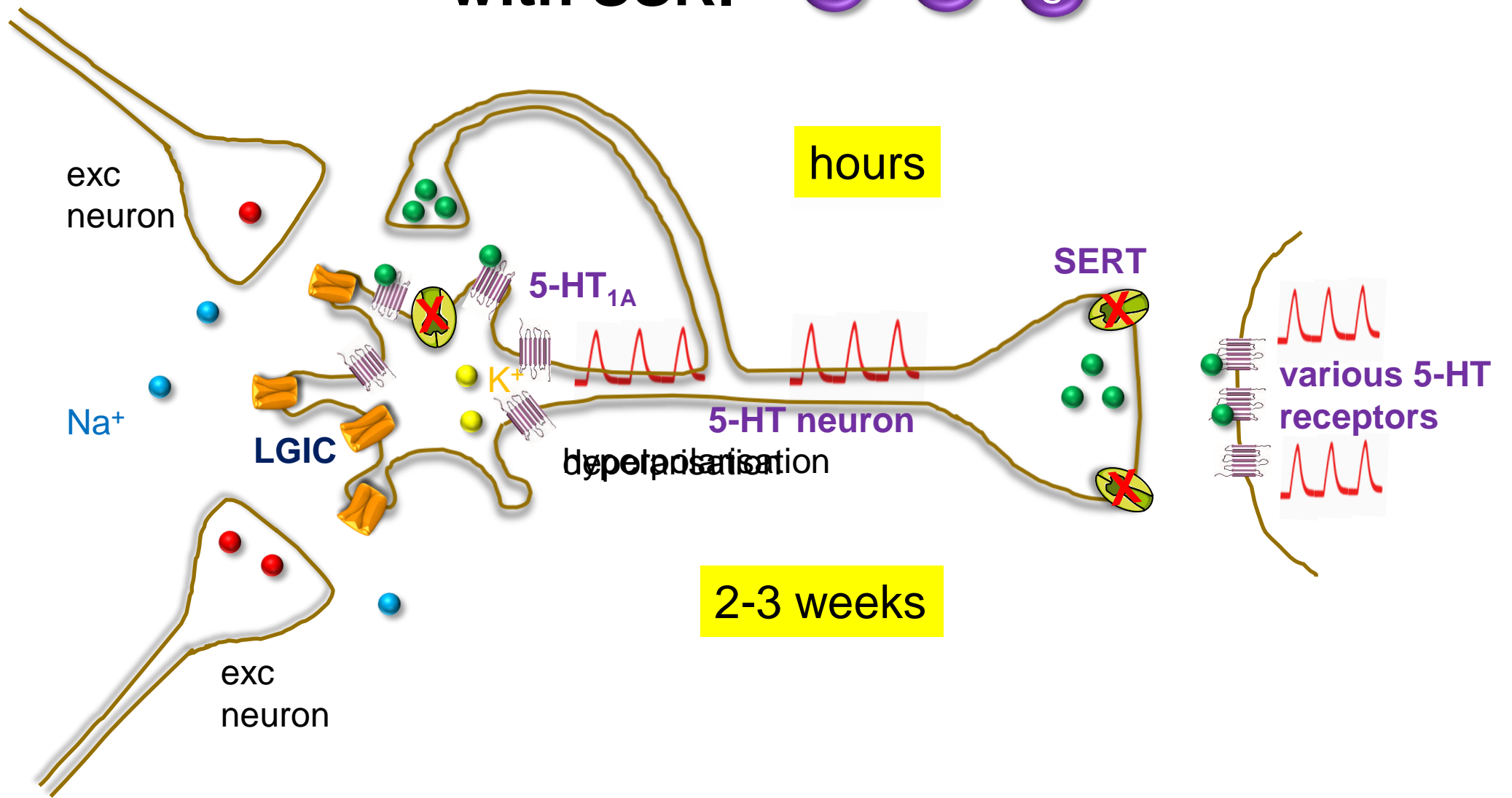
Delayed effects of antidepressants - proposed 5-HT MoA

- numerous mechanisms have been proposed to explain the delayed chronic adaptive changes, eg receptor downregulation and neuroplastic changes

- normally, neuronal 5-HT release is inhibited via autoinhibitory somatodendritic 5-HT1A receptors

- initially, acute administration of drugs which inhibit 5-HT uptake (e.g. by SSRIs) will increase synaptic levels of 5-HT, but this may actually increase the inhibitory effect at 5-HT1A receptors

- with chronic administration, autoinhibitory 5-HT1A receptors desensitise, and thus 5-HT signalling increases

- postsynaptic 5-HT1A receptors do not appear to desentitise and appear to be important in mediating antidepressant effects of increased 5-HT

Acute v chronic effects of blocking 5-HT reuptake

Ⓐ

Absence

other

5-HT

5-HT

5-HT

5-HT

Postsynaptic
5-HT receptors

Acute 5-HT reuptake inhibition

other

5-HT

5-HT

5-HT

5-HT

5-HT

Chronic 5-HT reuptake inhibition

other

5-HT

5-HT

5-HT

5-HT

5-HT

● 5-HT$_{1A}$ receptor
○ desensitised 5-HT$_{1A}$ receptor
● 5-HT$_{1B/D}$ receptor

exc
neuron

exc
neuron

somatodendritic
inhibitory

LGIC

5-HT$_{1A}$

5-HT neuron

SERT

various 5-HT
receptors

exc
neuron

somatodendritic
inhibitory

5-HT$_{1A}$

SERT

Na$^+$

K$^+$

LGIC

various 5-HT
receptors

5-HT neuron

depolarisation

hyperpolarisation

exc
neuron

Effects of antidepressants - additional MoA

- 5-HT release is also regulated by NE acting at

    - somatodendritic alpha-1 receptors (excitatory)

    - presynaptic alpha-2 receptors on nerve terminals (inhibitory)

thus:
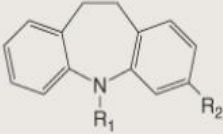
- alpha-2 antagonism removes presynaptic inhibition and increases 5-HT release

- alpha-2 antagonism can also reduce effects of NE at inhibitory autoreceptors on NA nerve terminals, increasing NE release onto postsynaptic alpha-1 receptors on 5-HT neurons

    - also increases 5-HT release
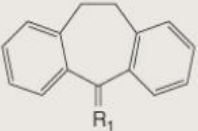
Additional effect of alpha-2 blockade on 5-HT release

B

Absence

NA

NA

NA

NA

NA

5-HT

In presence of α_2-adrenoceptor antagonist

NA

↑NA

NA

+

NA

↑5-HT

Postsynaptic 5-HT receptors

○ α_1-adrenoceptor

● presynaptic α_2-adrenoceptor

⦿ antagonist bound α_2-adrenoceptor
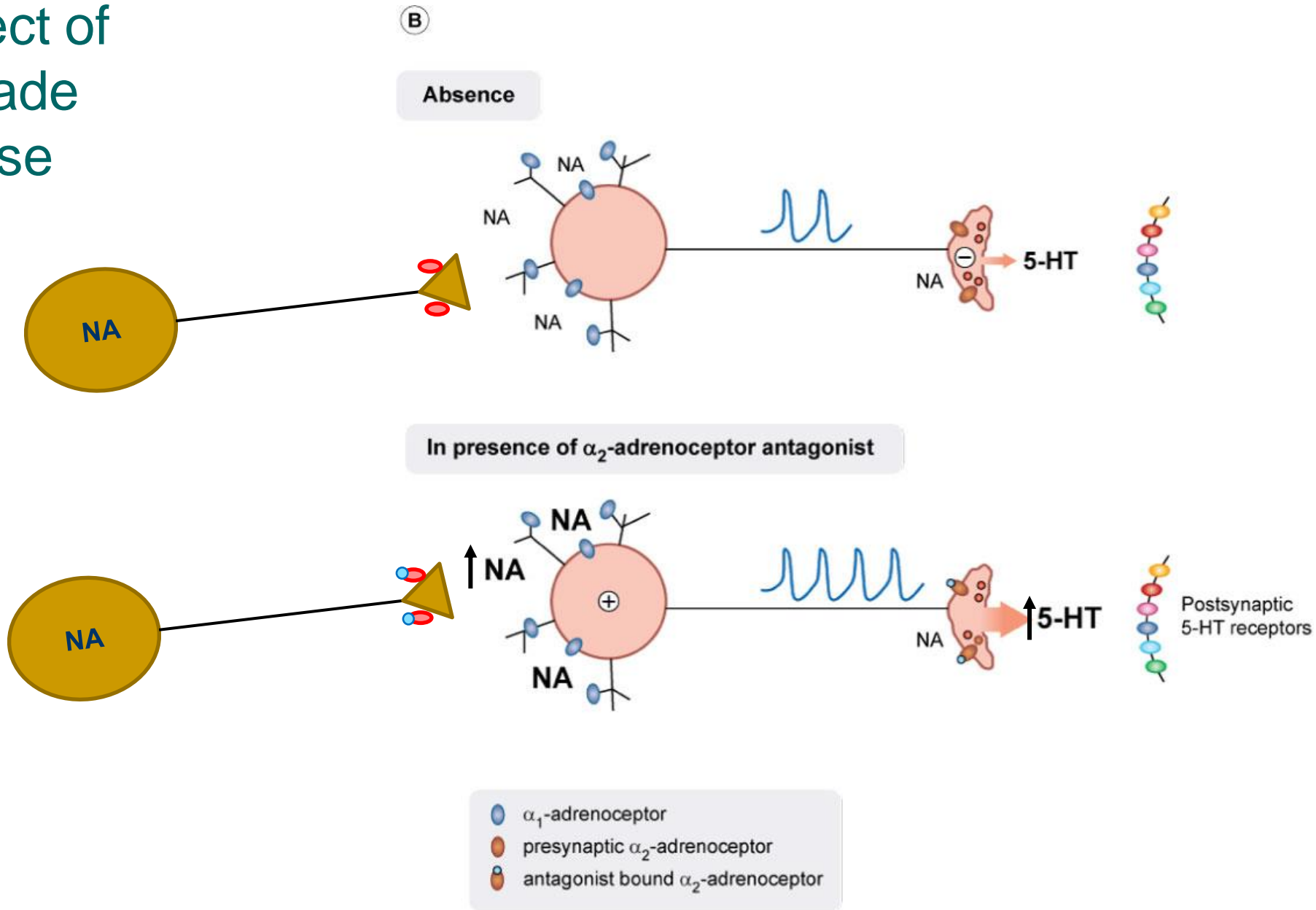
Overview of antidepressant drug classes

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin and norepinephrine reuptake inhibitors (SNRIs)
- Selective NE reuptake inhibitors (NRIs)
- Tricyclic antidepressants (TCAs)
- Monoamine oxidase inhibitors (MAOIs)
- Reversible inhibitors of monoamine oxidase (RIMAs)
- Monoamine receptor antagonists
- Melatonin receptor agonists
- and more!

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Revise some examples of each class, M/A, indications, adverse effects and important points.

Selective serotonin reuptake inhibitors (SSRIs)

Exemplar

- Escitalopram, sertraline, fluoxetine

Mechanism of action

- selectively inhibit presynaptic reuptake of 5-HT
- some also have 5-HT receptor antagonist actions
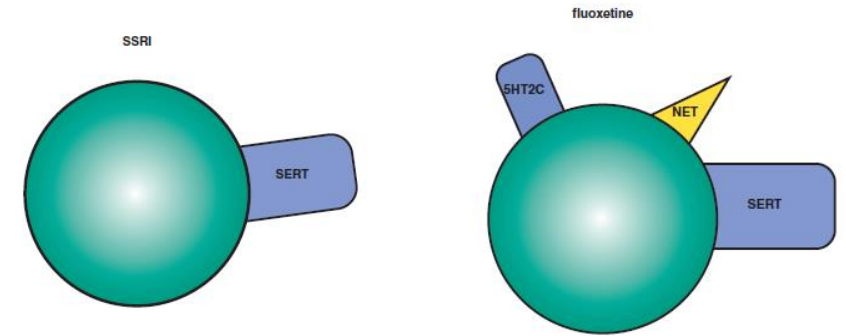
Adverse effects

- nausea, diarrhoea, insomnia, drowsiness, dry mouth, sexual dysfunction

Precautions

- antidepressants may provoke a manic episode when used in bipolar disorder
- potential for increased suicidal thoughts
- patients with risk of bleeding
- reduced seizure threshold

Selective serotonin reuptake inhibitors (SSRIs)

Interactions / pharmacokinetics

- inhibition of metabolism of other drugs
- decrease dose in hepatic impairment

- warfarin – increase anticoagulant effect

- serotonin toxicity with other drugs that increase serotonin (eg MOA-I)

- when stopping SSRI treatment taper over several days-weeks to avoid withdrawal symptoms

Serotonin and norepinephrine reuptake inhibitors (SNRIs)

Exemplar

- venlafaxine, desvenlafaxine, duloxetine

Mechanism of action

- inhibit reuptake of NA and 5-HT
- similar to TCA, less selective for 5-HT than SSRIs
- Less adverse effects than TCAs

Precautions

- bipolar disorder, history of seizures, high risk of bleeding

Adverse effects

- headache, insomnia, dry mouth, dizziness, sexual dysfunction
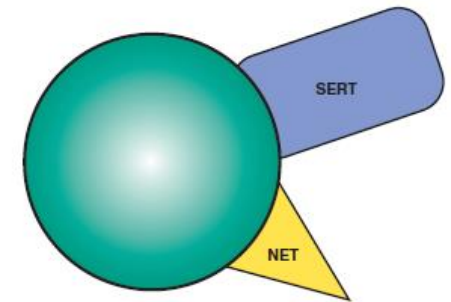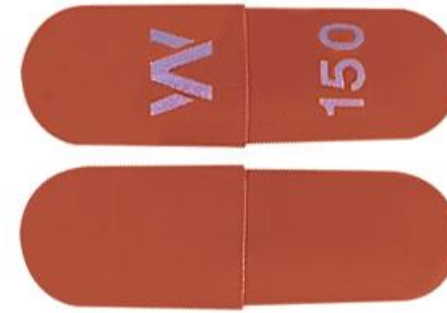
Selective norepinephrine reuptake inhibitors (NRI)

Exemplar

- reboxetine

Mechanism of action

- inhibit reuptake of NE

Precautions

- bipolar disorder, history of seizures, CV disease

Adverse effects

- urinary retention, dysuria, urinary frequency, headache, insomnia, dry mouth, dizziness, orthostatic hypotension
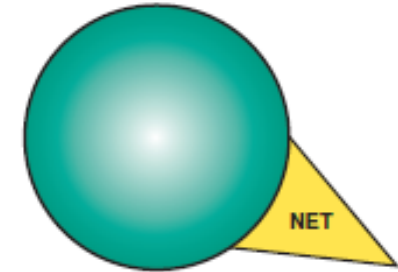
Tricyclic antidepressants (TCAs)

Exemplar

- amitriptyline, doxepine

Mechanism of action

- inhibit reuptake of NE and 5-HT
- also inhibit cholinergic, histamine, alpha1 and 5-HT receptors

Adverse effects

- sedation (H1)
- dry mouth, blurred vision, mydriasis, decreased lacrimation, constipation, sinus tachycardia, urinary hesitancy or retention, reduced GI motility (muscarinic)
- orthostatic hypotension (alpha-1)
- weight gain, impotence, tremor, dizziness, sweating, agitation, insomnia, anxiety, confusion
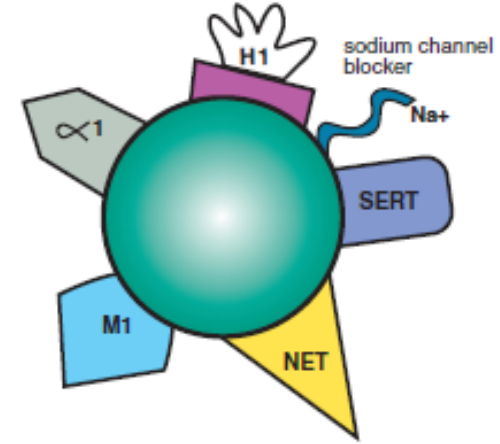
Tricyclic antidepressants

Precautions

- hyperthyroidism - enhanced response to TCAs
- reduced seizure threshold
- tachycardia may precipitate or exacerbate angina
- may prolong the QT interval
- can be fatal in overdose

Indications

- major depression refractory to other treatments
- also used in neuropathic pain

Monoamine oxidase inhibitors (MAO-Is)

Exemplar

- phenelzine

Mechanism of action

- long lasting non-competitive inhibition of both MAO-A and MAO-B
- 5-HT, NE mainly broken down by MAO-A
- dopamine mainly broken down by MAO-B
- regulates neuronal stores of neurotransmitter, so control how much is released
- thus MAO-I increase synaptic levels of norepinephrine, dopamine and 5-HT (main target)
- also increase amine levels in periphery

Monoamine oxidase inhibitors (MAO-Is)

Adverse effects / precautions

- postural hypotension, tachycardia, weight gain, insomnia, tremors

- some anticholinergic effects

- reduced seizure threshold, precautions in CV disease

Interactions

- cheese reaction

  - due to MAO-I inhibition of dietary tyramine metabolism

  - tyramine is absorbed – sympathomimetic

  - hypertensive crisis

- indirectly acting sympathomimetics will interact in similar fashion

Reversible inhibitors of monoamine oxidase (RIMAs)

Exemplar

- moclobemide

Mechanism of action

- short-acting reversible (competitive) inhibitors of MAO-A

Adverse effects / precautions

- less significant than MAO-A and MAO-B inhibitors
- dry mouth, GI (nausea, constipation, diarrhoea), anxiety, restlessness, insomnia, dizziness, headache

- does not cause cheese reaction

Monoamine receptor antagonists

Exemplar

- mirtazapine (aka tetracyclic antidepressant)
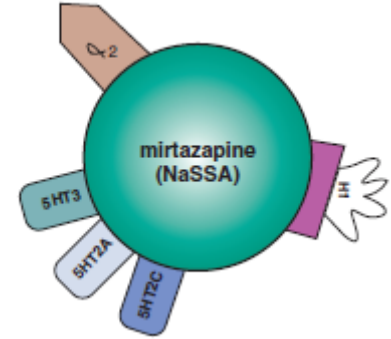
Mechanism of action

- antagonist at alpha-2 / 5-HT2c and 5-HT3 receptors
- main effect is blockade of presynaptic inhibitory alpha-2 adrenoceptors which is believed to lead to increase in release of both NA and 5-HT
- increased 5-HT results in increased activation of 5-HT1A receptors which are not inhibited (same as SSRIs)
- inhibition of 5-HT2c receptors (on inhibitory GABA neurons) may also contribute to antidepressant effects

Adverse effects

- sedation, increased appetite, weight gain, weakness, peripheral oedema
- less sexual dysfunction, nausea than SSRIs (due to 5-HT receptor antagonism?)
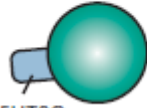
Role of 5-HT2C receptors

Serotonin Normally Inhibits DA and NE Release via 5HT2C Receptors
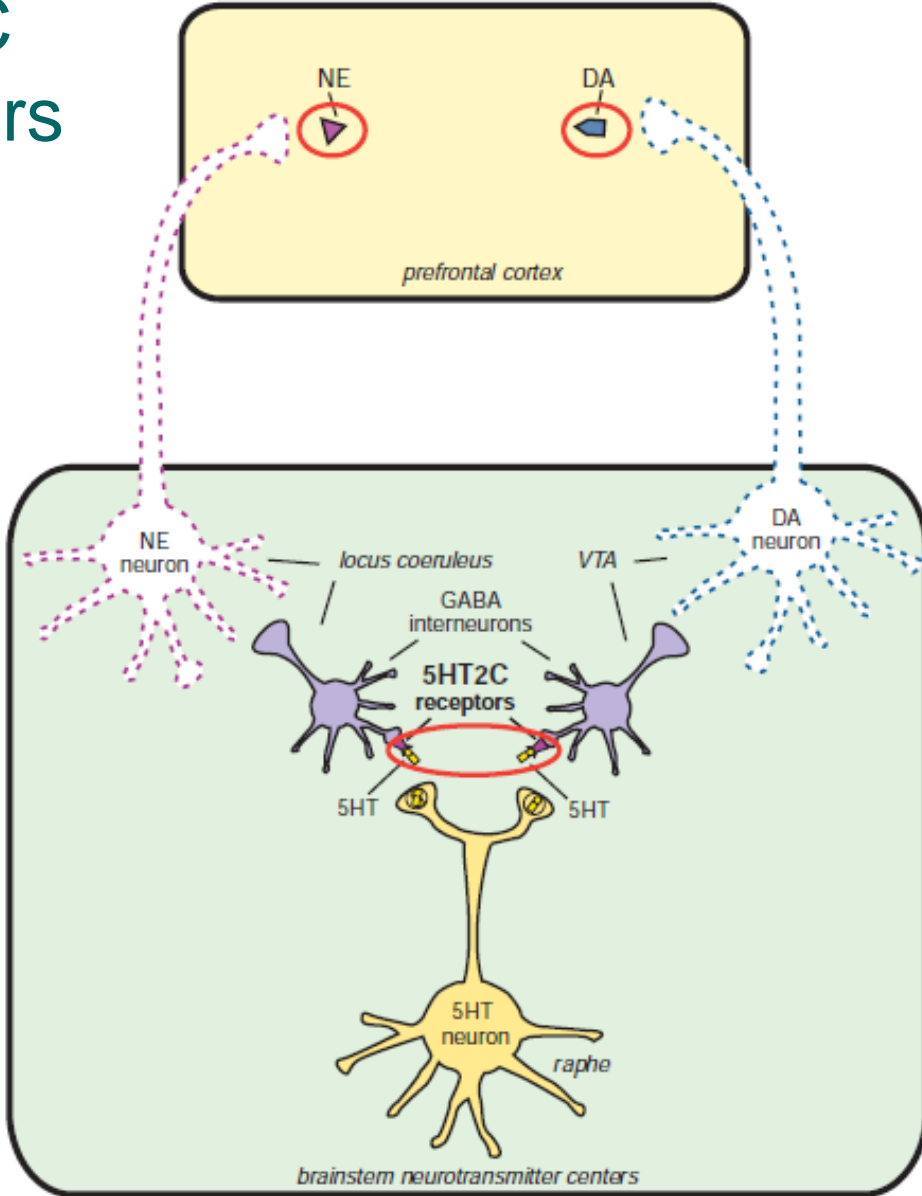
Mechanism of 5HT2C Antagonists as Norepinephrine and Dopamine Disinhibitors in Prefrontal Cortex

reduces depression?
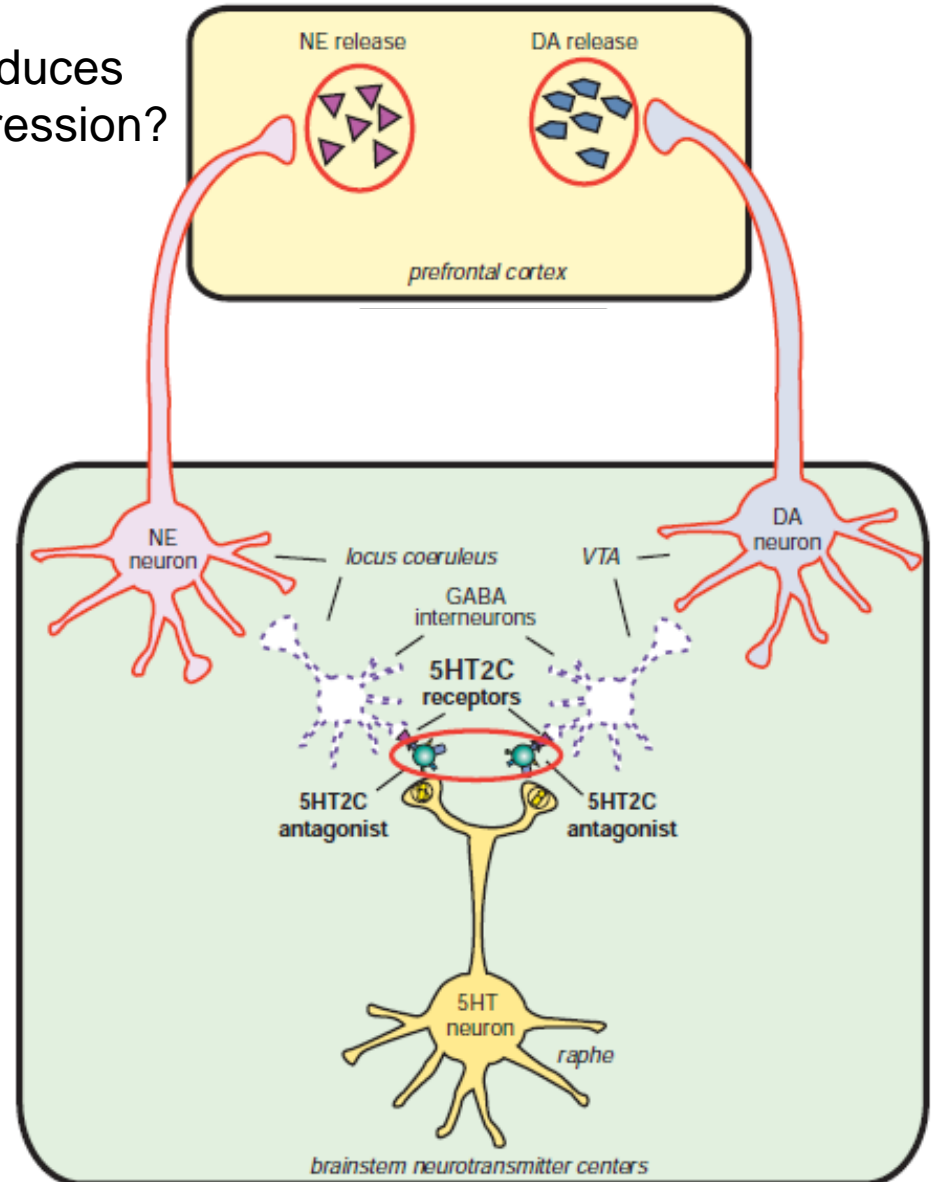
Melatonin receptor agonists

Exemplar

- agomelatine

Mechanism of action

- selective agonist at MT1 & MT2 receptors, antagonist at 5-HT2C receptors
- mechanisms responsible for antidepressant effects have not been elucidated
- believed to involve a synergy between melatonin receptor activation and 5-HT2C receptor inhibition
- also increases production of BDNF, which may promote neurogenesis and protect against neuronal cell death
- may protect neurons against stress-evoked insults

Adverse effects/ Precautions

- dizziness, abdominal pain, rare hepatotoxicity
- not use in combination with CYP1A2 inhibitors
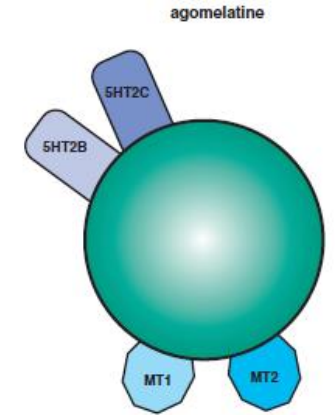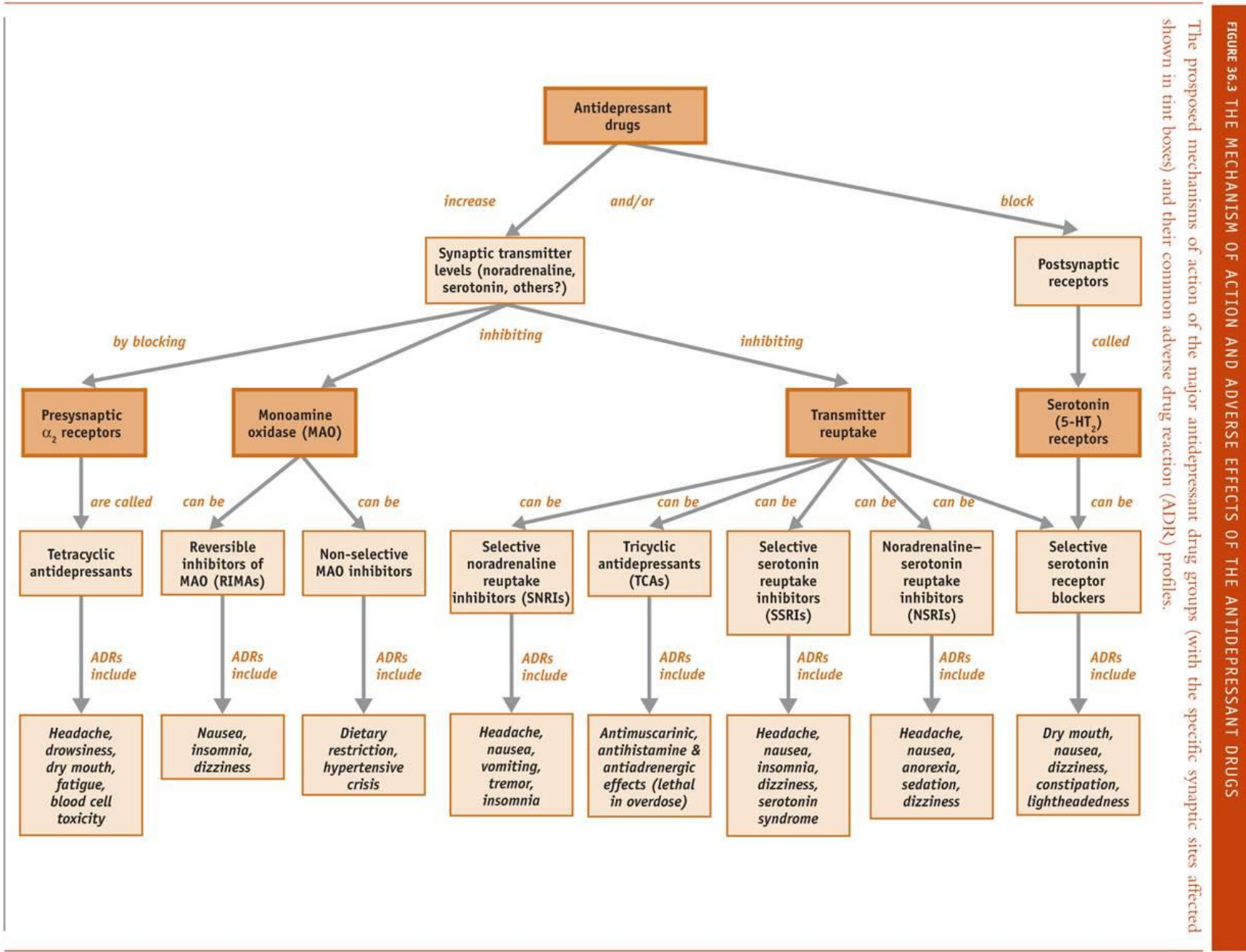
Bullock & Manias

Major depression - therapeutic principles

- mild depression - psychological therapies more effective than antidepressants
- moderate depression - psychological therapies and antidepressants equally effective
- severe depression - antidepressants more effective than psychological therapies

- all antidepressants are of similar efficacy for major depression
- large variation in individual patient responses
- individual drugs differ in adverse effects, drug interactions and safety in overdose
- 1st line = SSRIs, mirtazapine; 2nd line = SNRI, agomelatine
- 3rd line = RIMA, NRI
- TCAs & non-selective MAOIs are less well tolerated and have a narrower safety margin
- combinations not recommended for first-line treatment

MP week 9 Antidepressants

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