Biological Treatments in Psychiatry

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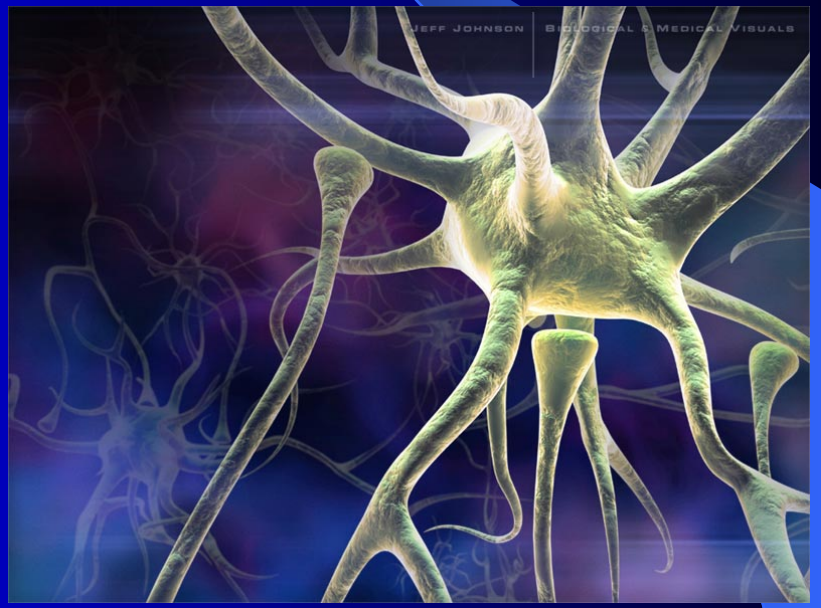
From Jeff Johnson, Hybrid Medical Animation



Take Home Points

- Placebo!!

Take Home Points

- Placebo
- Neurotransmitters=provide clues to how medications work and side effects!!

Take Home Points

- Placebo
- Neurotransmitters

Take Home Points

- Placebo
- Neurotransmitters
- Medications: What class are you!?!

Previous Treatments

- Convulsive treatments using camphor in the 16th century for psychosis and mania
- spa treatments
- Fever and shock treatments
- Lobotomies

Overview of Neurobiology of Mood Disorders

- **Genetic and Epigenetic findings**
- **Neuroanatomic/ Imaging Findings**
- **Biochemical explanations**
- **Neuroendocrine pathology**
- **Immune System Dysregulation**
-

Current Biological Treatments

- Psychopharmacology*
- Electroconvulsive treatment (ECT)*
- Transcranial Magnetic Stimulation
- Vagal Nerve Stimulation
- Light Treatment*
- Psychosurgery

* Routinely used currently

Before you Prescribe

- Discussion with patient and family
  - Working diagnosis
  - Various treatment options, risks/benefits
  - Rationale for specific medication
  - Side effects, course (timeline) of treatment

After you prescribe

- Document in the file:
  - What was done and why
  - When was it done
  - Who was involved in the decision making

Guiding the selection of a medication:

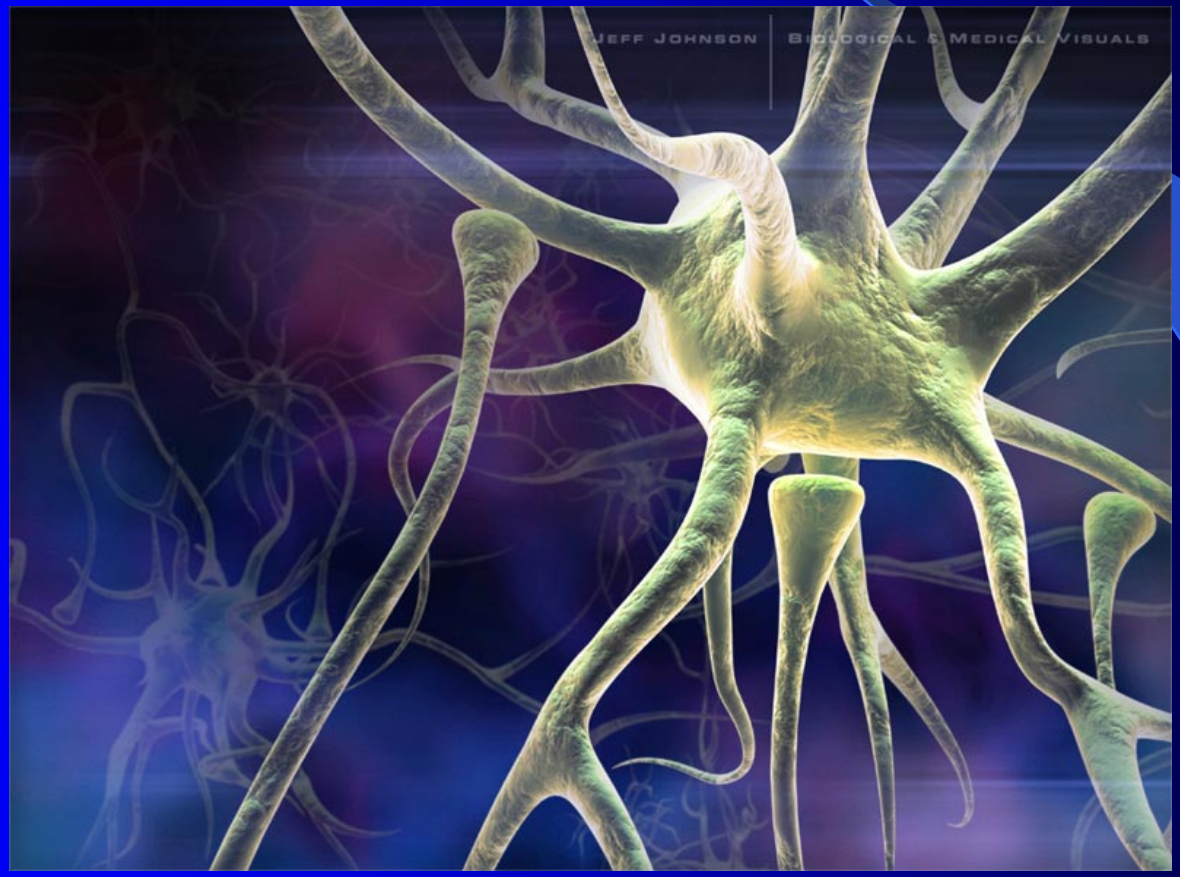
Psychopharmacology

- Antidepressants
- Anti-anxiety medications
- Mood Stabilisers
- Antipsychotics
- Anticholinergics
- Miscellaneous agents

Antidepressants

- Classes
  - Tricyclic AD's
  - MAOI's
  - Serotonergic AD's
  - "Atypical" AD's

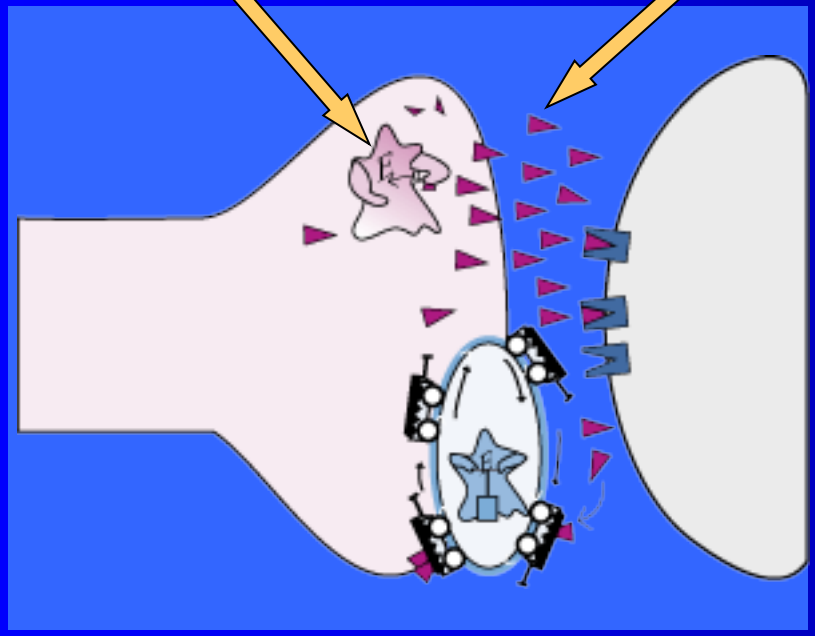
Why do they work?

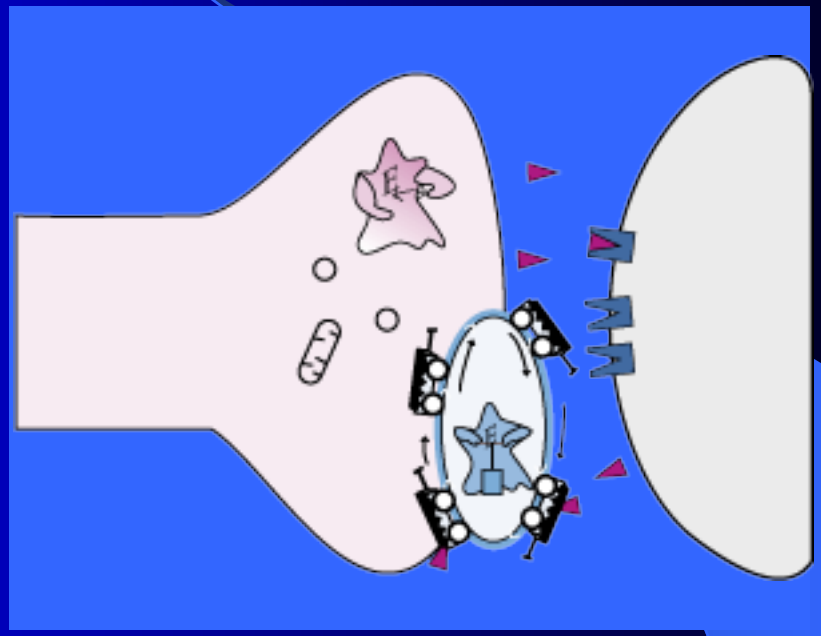


MONOAMINE HYPOTHESIS

MAO enzyme destroying neurotransmitter

monoamine neurotransmitter



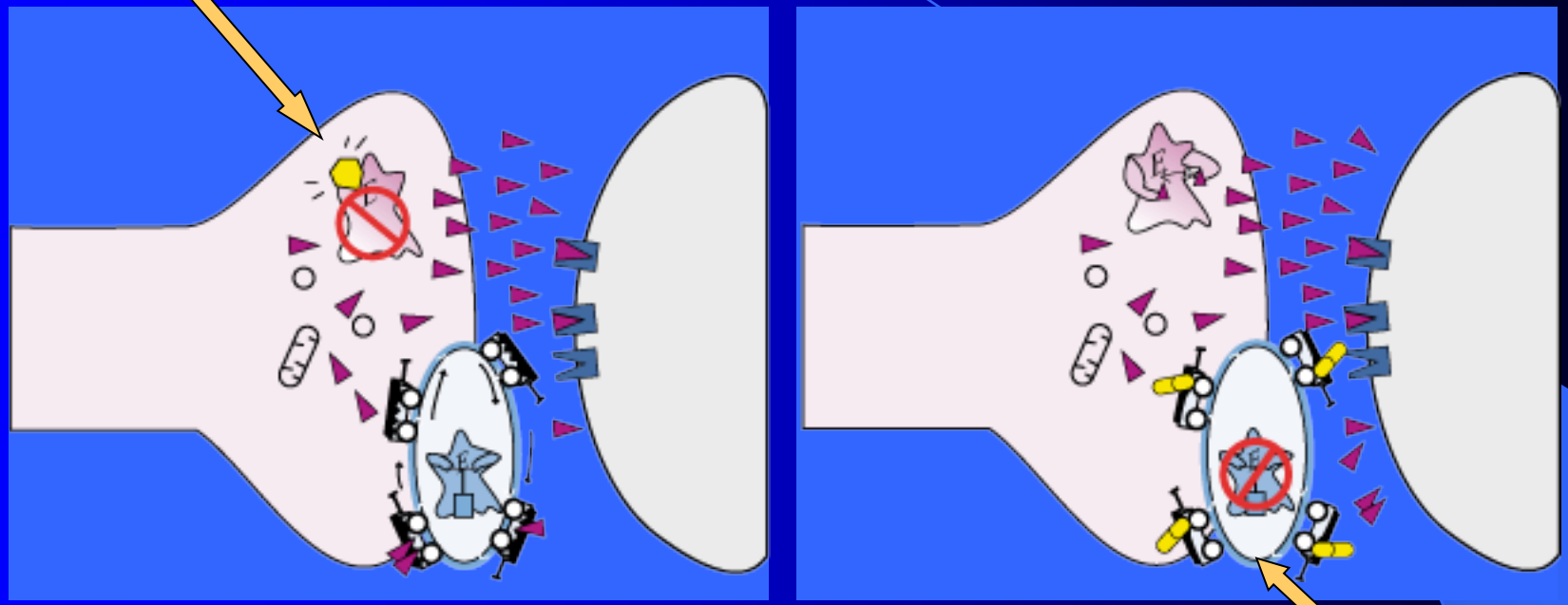


NORMAL STATE -- no depression

DEPRESSION -- caused by neurotransmitter deficiency

Stahl S M, Essential Psychopharmacology (2000)

MAO inhibitor blocks the enzyme from destroying monoamine neurotransmitter

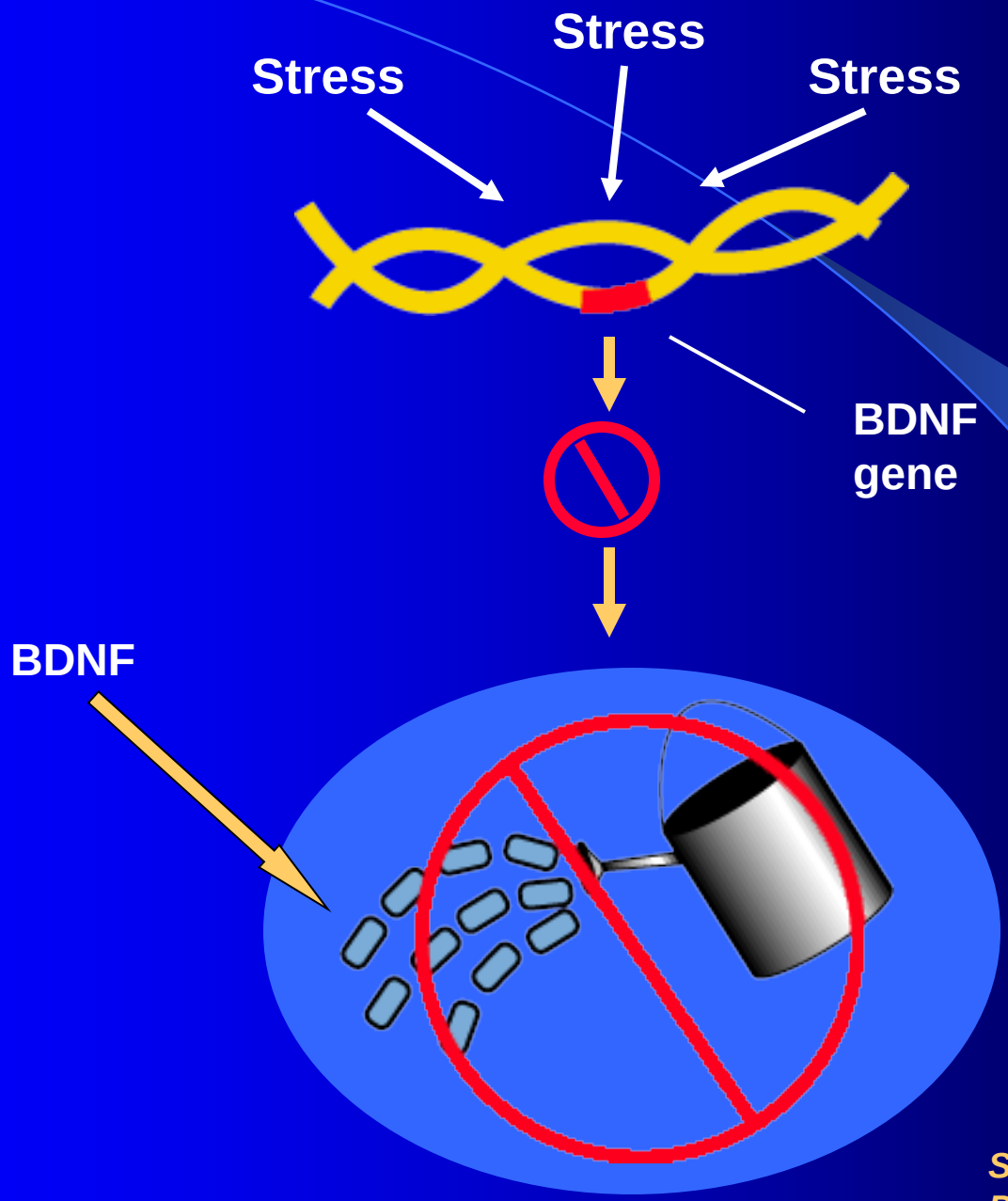


reuptake pump blocked by antidepressant

Increase in neurotransmitters causes return to normal state

5-15
5-16

Stahl S M, Essential Psychopharmacology (2000)



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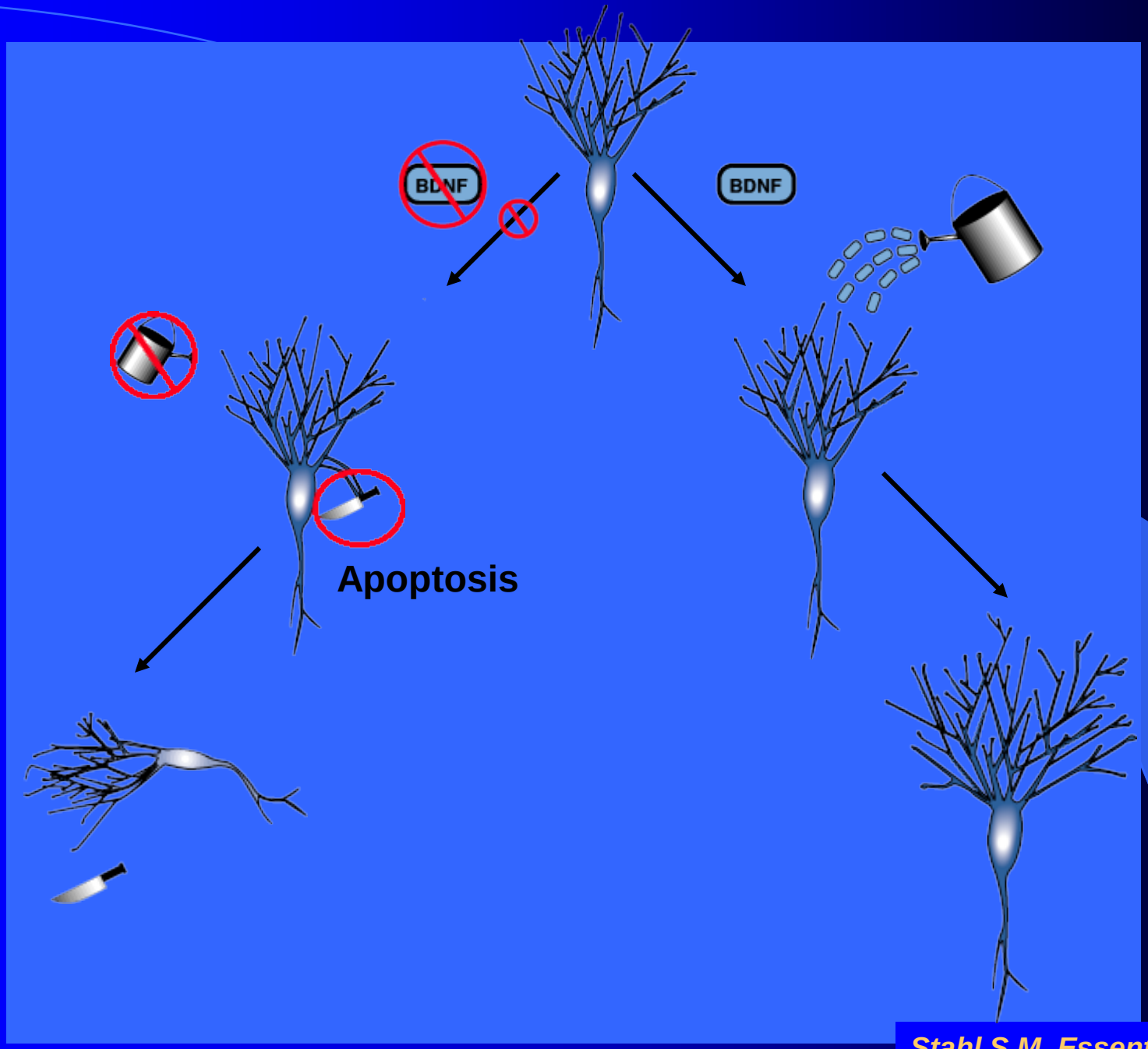

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Antidepressants

- Classes
  - Tricyclics
    - Imipramine, amitryptiline, nortriptiline, desipramine, doxepin, clomipramine
    - Mechanism of action

      Affects 5 Neurotransmitter systems
      - Norepinephrine reuptake blockade- ↑ NE ***
      - Serotonin reuptake inhibition (mild)
      - Anticholinergic
      - Alpha adrenergic antagonist
      - Antihistamine

Antidepressants

- Classes
  - Tricyclics
    - Adverse Effects
      - Anticholinergic signs
        - Dry mouth, blurred vision, urinary retention, constipation, memory disturbances
      - Antihistaminic effects
        - Sedation and weight gain
      - Alpha adrenergic blockade
        - Dizziness and hypotension
      - Potential lethality in OD !!!!!!

Antidepressants

- MAOI's (monoamine oxidase inhibitors)
  - Tranylcypramine
  - Monoamine oxidase breaks down norepinephrine and serotonin in the presynaptic neuron
  - Inhibition of MAO results in more NE and 5HT for release into the synapse

Antidepressants

- MAOI's
  - Underutilized despite its high efficacy
  - Should always be an option
  - Adverse effects
    - **Hypertensive crisis** when tyramine restricted diet (MAOI diet) is not adhered to
      - Tyramine is a pressor agent found in certain foods (red wine, yeast, broad beans, marmite, vegemite, smoked preserved meats, aged cheeses), meperidine, dextrometorphan, cocaine, other antidepressants

Antidepressants

- SSRI's (Selective Serotonin Reuptake Inhibitors)
  - Examples
    - fluoxetine (prozac), paroxetine (aropax), citalopram (cipramil), sertraline (zoloft)
  - Mode of action
    - Serotonin (5HT) reuptake inhibition resulting in more serotonin in the synapse

Antidepressants

- SSRI's
  - Safety in overdose
  - Adverse effects
    - GI, headache, sexual dysfunction, agitation, sleep disturbance
    - Beware of P450 interactions
    - Serotonin syndrome

Antidepressants

- Atypical/Novel (in NZ)
  - SNRI (venlafaxine/mirtazapine)
    - 5HT and Noradrenergic reuptake inhibition
    - For treatment resistant depression
  - NDRI (bupropion)
    - Noradrenergic and dopamine reuptake inhibition
    - No weight gain, no sexual dysfunction
    - Also for anti-smoking

Antidepressants

- Indications/ uses (R. Baldessarini 1997)

Effective or probably effective

- Acute MDE, prevention of early relapse and later relapse
- Panic component of panic-agoraphobia syndrome (not bupropion)
- Enuresis (TCA)
- ADHD (TCA's, SRI)
- Bulimia (not anorexia)
- OCD and impulse syndromes
- Mild geriatric pseudodementia
- Chronic or neuropathic pain (tertiary amine TCA's)
- Tic disorders (possibly including Tourette's)

Less Certain but reported

- Aggression, dyscontrol, agitation (inc. brain damaged)
- Alcohol abuse
- Neurological disorders (migraine, narcolepsy)
- Medical disorders (ulcer, colitis, myositis, dermatitis)
- Premature ejaculation (SSRI's)

Antidepressants

- SSRI's first line treatment
  - Why?
- Each medication trial should be of proper dose and duration (at least 4-8 weeks, if patient can tolerate it) before moving on to next medication trial

Antidepressants

- Duration of treatment
  - Standard practice is 6-12 months past full clinical recovery to avoid relapse; strong evidence for this
  - For maintenance, 1-5 years to prevent unipolar recurrences- evidence not as strong as above
  - For 3 or more episodes, chronic course of treatment is suggested
  - Optimal dosing long term not established yet

Mood Stabilisers

- Lithium, Valproic acid (2 main mood stabilisers)
- Carbamazepine
- Newer generation antipsychotics
- Lamotrigine (for depression)

Mood Stabilisers

- Lithium
  - Indications
    - “gold” standard for bipolar disorder
    - Treatment of choice for classic/ euphoric mania
    - May need to be augmented with second or third (?) mood stabiliser for people with rapid cycling, mixed mania, or treatment resistance.

Mood Stabilisers

- Lithium
  - Mode of action
    - Still not clear; probably involves sites beyond the receptor- in the 2nd messenger system
    - ? Inhibition of inositol monophosphatase ? G protein modulator
  - Adverse Events
    - GI, renal, thyroid, skin, CNS toxicity
    - Need to monitor serum levels, renal and thyroid function

Mood Stabilisers

- Valproic Acid
  - Mode of action
    - Unknown for bipolar disorder
    - Reduces Na influx
    - Changes in the metabolism of the GABA system
      - Inhibits breakdown, decreases turnover, increases GABAb receptor density
      - Enhances neuronal responsiveness to GABA
  - Adverse events
    - CNS toxicity, GI, hepatotoxicity, hematologic effects, hair loss, teratogenic.

Mood Stabilisers

- Carbamazepine
  - Mode of action
    - Reduction of high frequency neuronal discharge through binding to and inactivating voltage-sensitive sodium channels and decreasing sodium influx
  - Adverse events
    - CNS toxicity, GI and hepatic toxicity, hematologic (aplastic anemia, thrombocytopenia, agranulocytosis), teratogenic.
    - Potential P450 interaction (self induced metabolism)

Mood Stabilisers

- Olanzapine, Risperidone, Quetiapine, Clozapine, Aripiprazole, Ziprasidone Amisulpride
  - Good antimanic effects
  - Some with evidence for treating depression
  - Olanzapine has good long term relapse prevention for mania
  - Main side effect: sedation and weight gain

Mood Stabilisers

- Issue of combined medications
- Treating from above (mania) and below (depression)
- Dealing with phase changes of the illness (depressed phase*, manic phase, mixed state, rapid cycling) as well as maintenance treatment.

* Most predominant phase

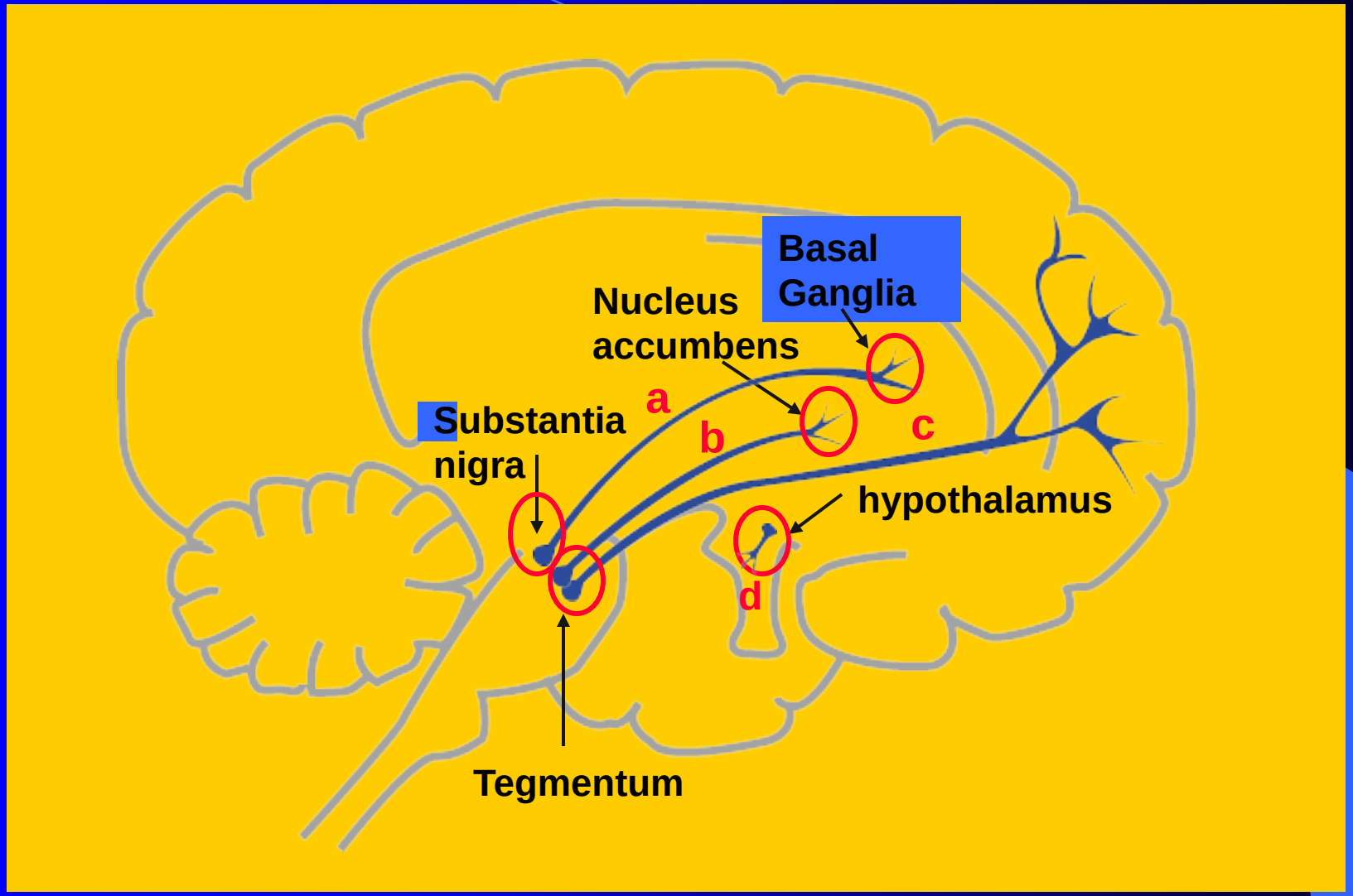
Antipsychotics

- What is psychosis
  - Positive symptoms
    - Hallucinations, delusions, disorganised speech, disorganised thinking
  - Negative symptoms
    - Social withdrawal, apathy, avolition, anhedonia
- Overview of neurobiology of psychosis
  - Overactivity in the mesolimbic dopamine pathway → positive symptoms

Antipsychotics

- Mechanism of action
  - Blockade of post synaptic dopamine receptors → less dopaminergic activity
  - What's dopamine by the way???
  - 4 dopamine tracts affected
    - Mesolimbic → reversal of psychosis
    - Mesocortical → cognitive deficits
    - Nigrostriatal → extrapyramidal symptoms
    - Tuberoinfundibular → hyperprolactinemia

DOPAMINE PATHWAYS



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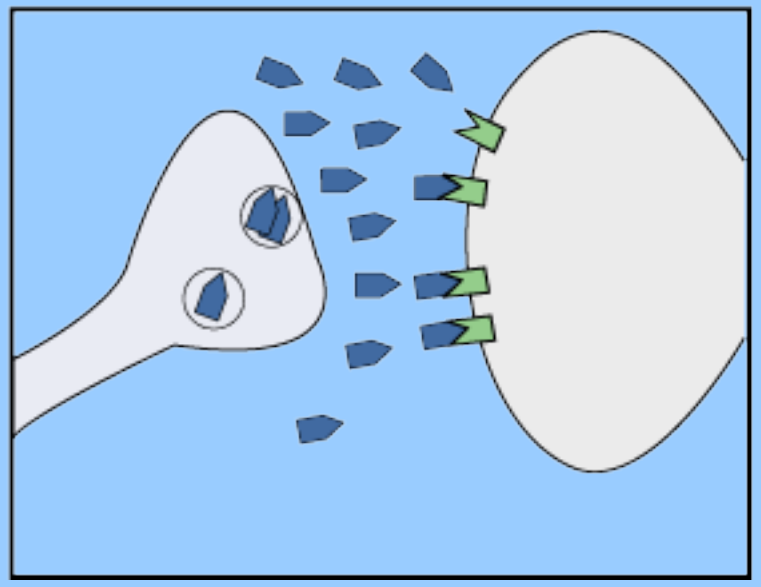

mesolimbic overactivity =
positive symptoms of psychosis

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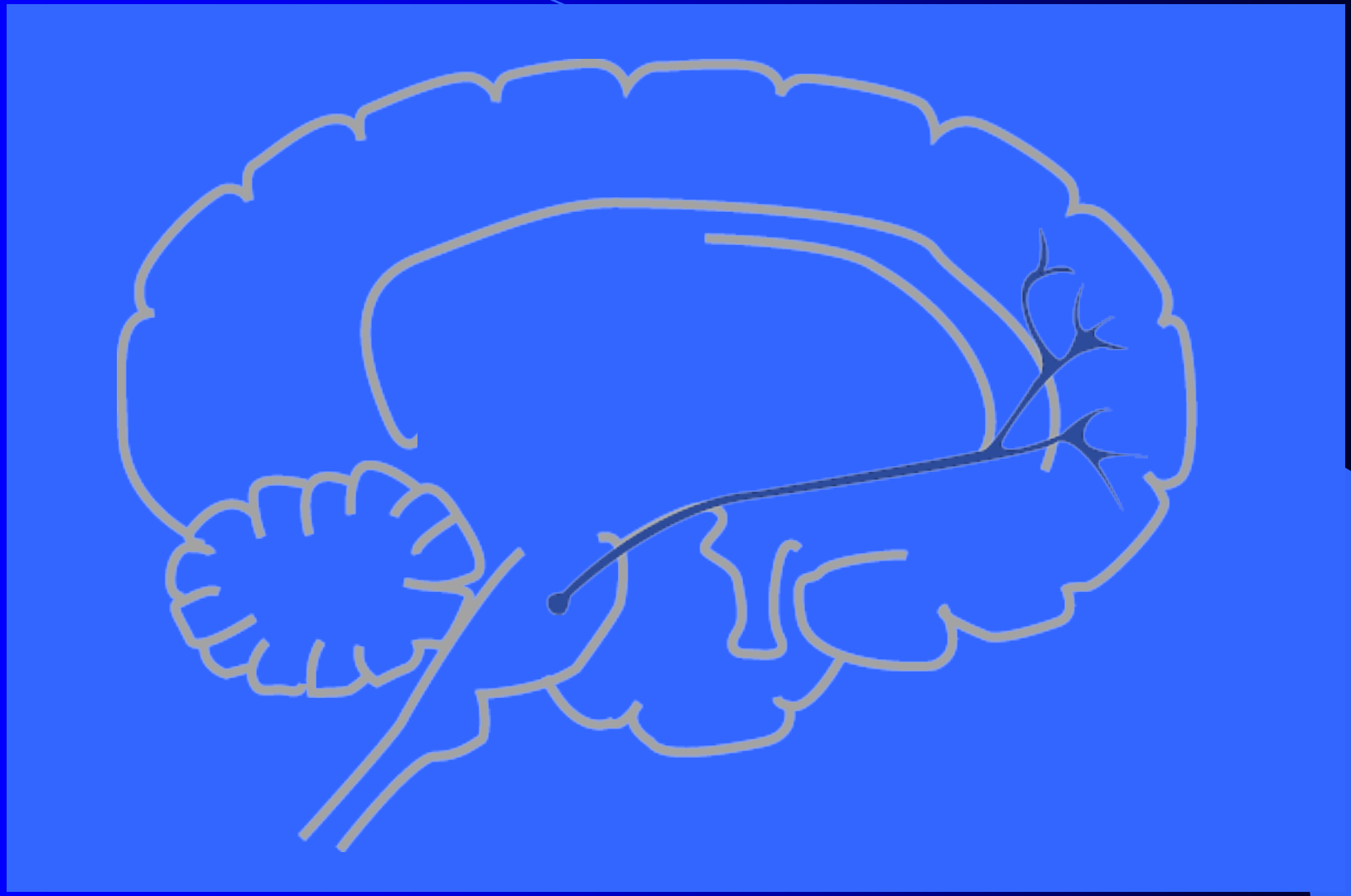
meso-cortical pathway



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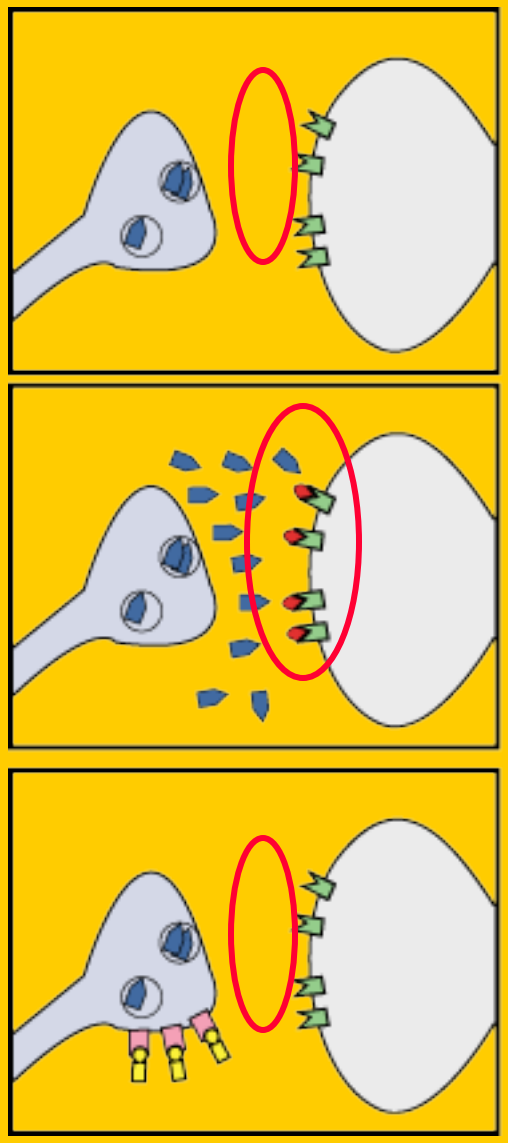


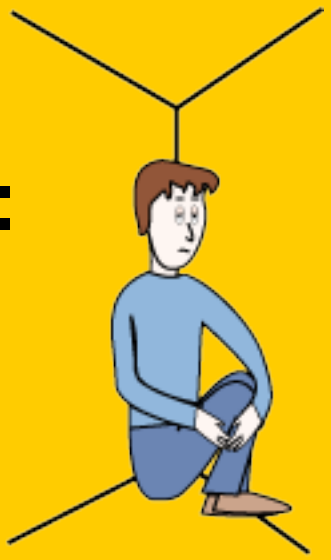
primary dopamine deficiency

D2 receptor blockade

secondary dopamine deficiency

mesocorticalpathway

=



increase in negative symptoms

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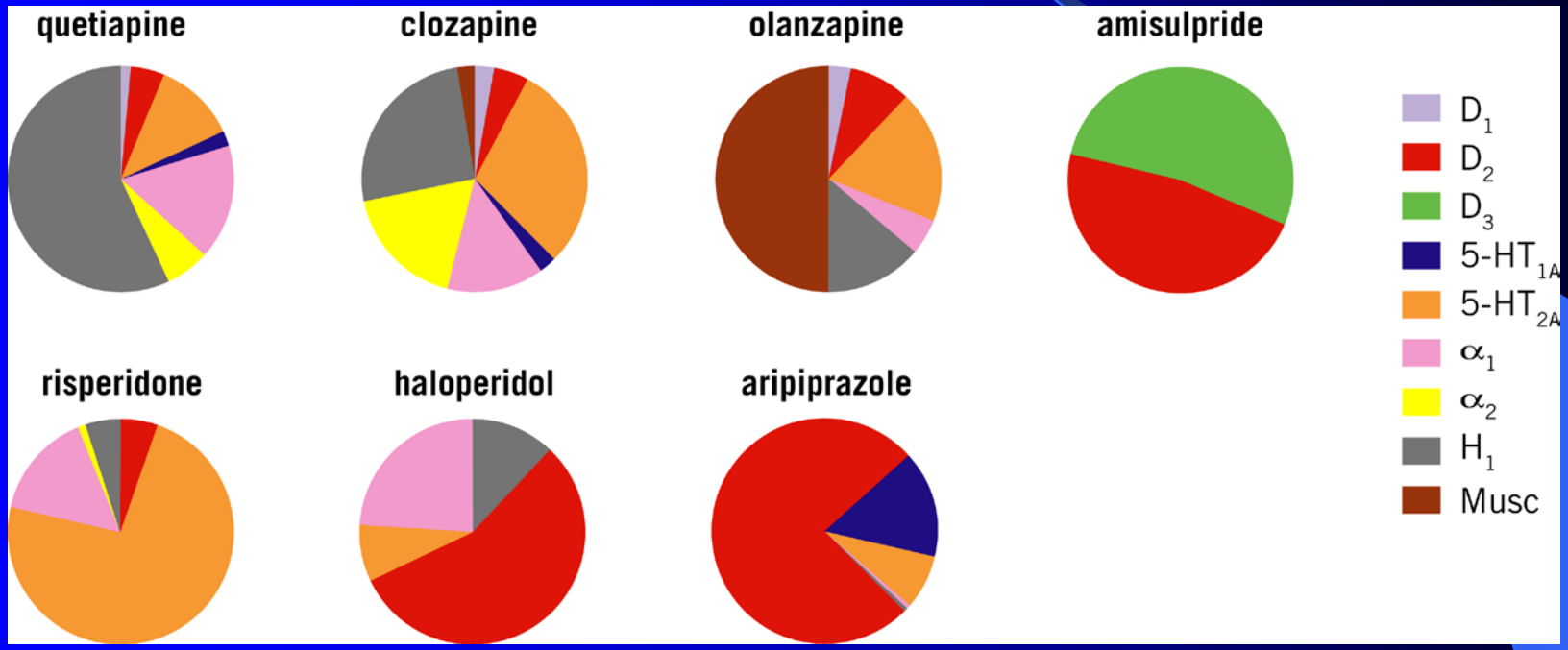
Antipsychotics

	First Generation	Second/Third Generation
Positive symptoms	+++	+++
Negative symptoms	0	+?
Mood stabilisation	+	++
Tardive dyskinesia	++	+/0
Weight gain	+	+++/+
Depot IM (long acting)	+	Risperidone/Olanzapine
Cost	$	$$$$$
Patient preference	+	++

Receptor binding profiles of antipsychotic agents



Data are derived from different, non-comparative *in vitro* studies
Abilify Product Information, 2005; Lawler *et al.*, 1999; Tandon *et al.*, 1999; Scatton *et al.*, 1997

Antipsychotics

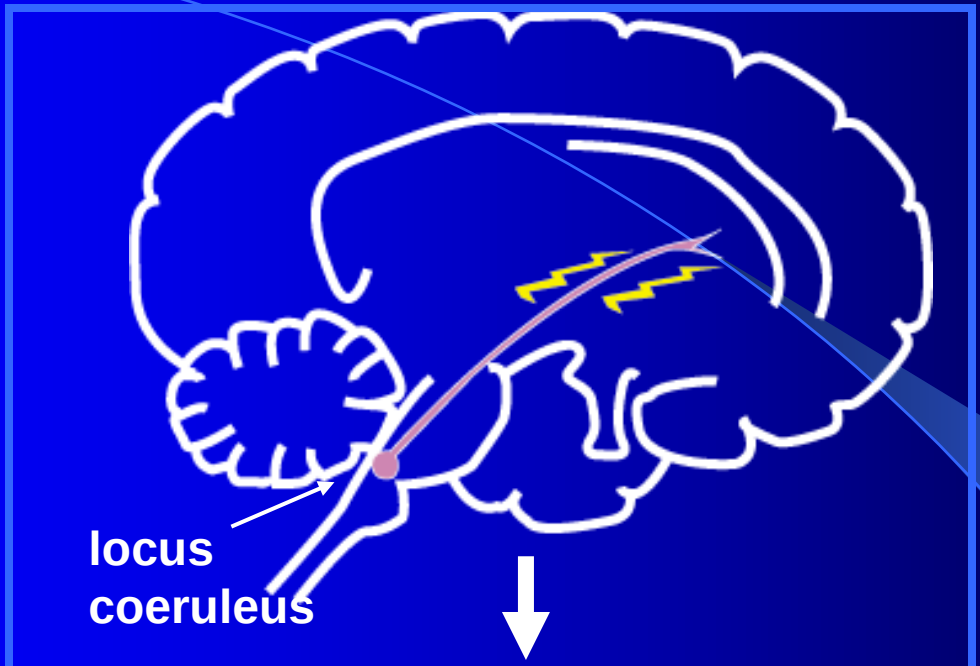
- Extrapyramidal symptoms
  - Dystonia, akathisia, parkinsonism
- Tardive Dyskinesia
- Neuroleptic Malignant Syndrome
  - Autonomic instability, acute confusion/ delirium, leukocytosis, ↑CPK

Antipsychotics

- Second/Third Generation AP's
  - Clozapine, risperidone, olanzapine, quetiapine, ziprasidone, amisulpride, aripiprazole
- As a class
  - less D2 receptor blockade, less EPS, TD (?)
  - More specific with mesolimbic Dopamine block, sparing the nigrostriatal tract
  - Perhaps better efficacy on negative symptoms
  - Patient preference

Anticholinergics

- Benztropine mesylate, trihexylphenidyl, diphenhydramine
- Counteracts dystonia and EPS
- Can cause anticholinergic signs/ toxicity
  - “dry syndrome” and cognitive side effects



anxiety

dilated pupils

tremor

sweating

tachycardia

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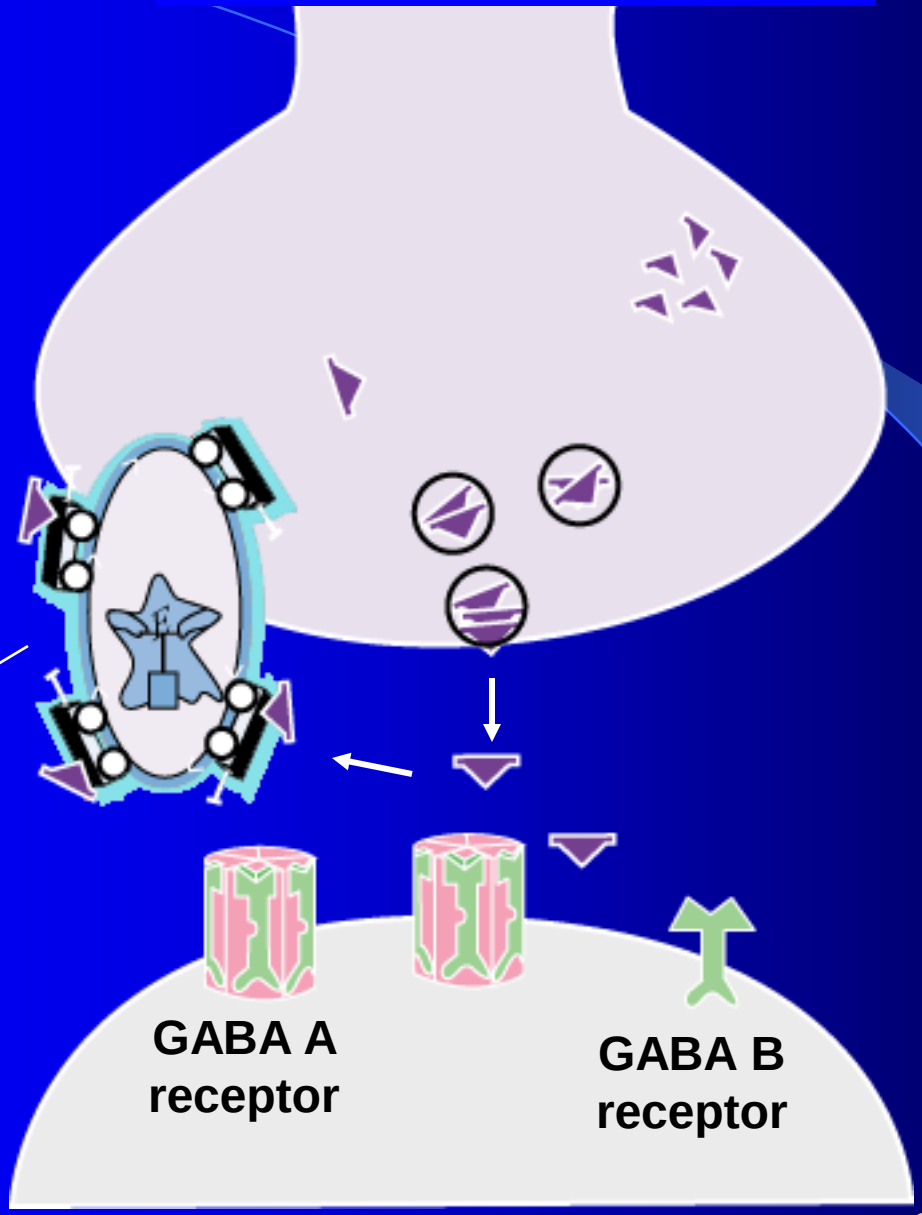
Anti-anxiety agents

- Overview of Neurobiology of anxiety
  - GABA-Benzo system dysfunction
    - GABA as major inhibitory neurotransmitter in the brain
  - Locus Coeruleus –Noradrenergic system dysfunction
    - Excessive NE activity resulting in peripheral signs of anxiety
  - 5HT excess?

GABA RECEPTORS



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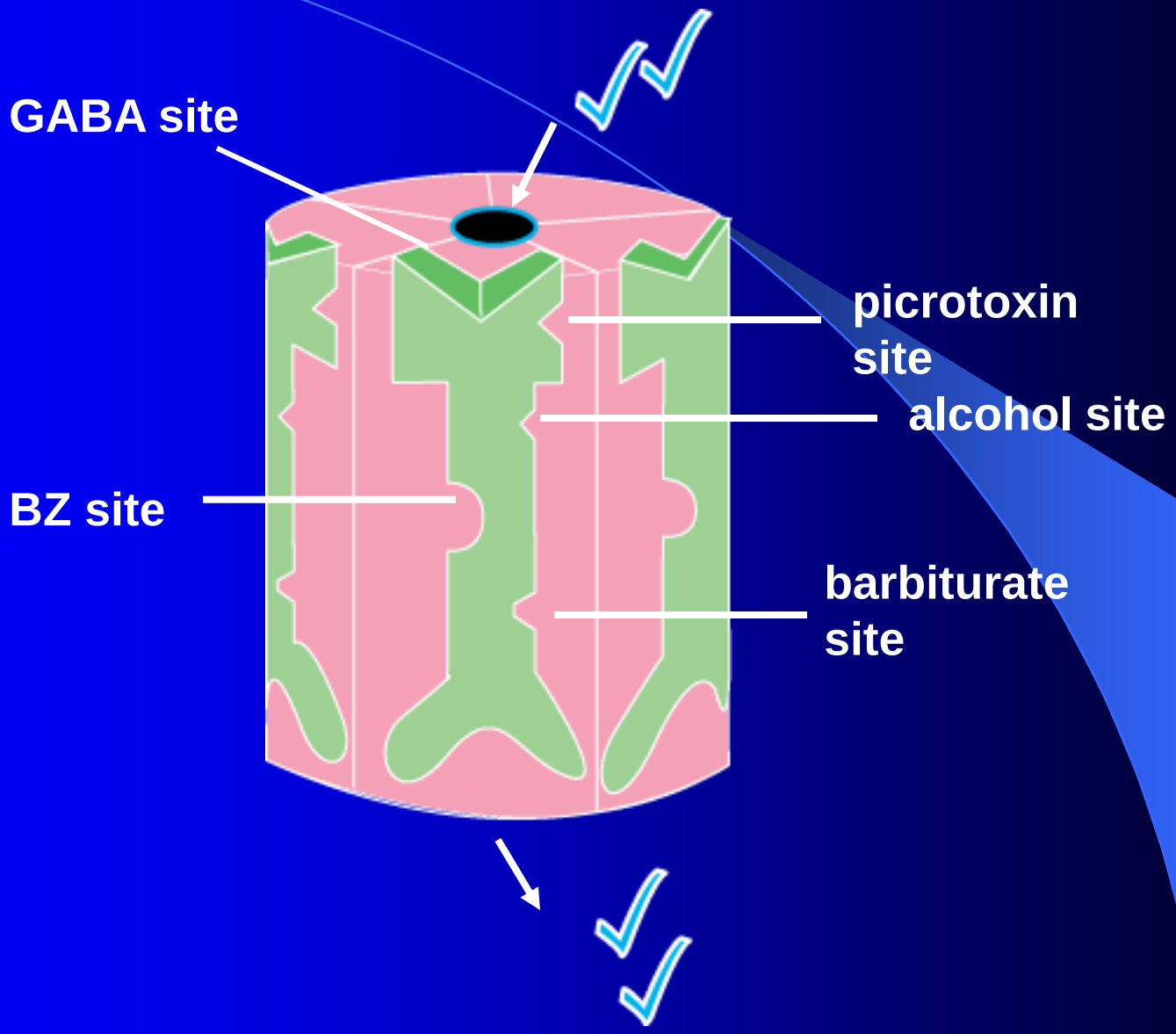

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Anti-Anxiety Medications

- Anxiety disorders
  - Generalised Anxiety Disorder
  - Panic Disorder
  - Social Phobia
  - OCD
  - Post Traumatic Stress Disorder

Anti-anxiety agents

- Types
  - Benzodiazepines and analogues
    - Diazepam, clonazepam, alprazolam, triazolam, zopiclone
  - Antidepressants (still main medication treatment for most anxiety disorders)
    - SSRI's , Venlafaxine, TCA's and MAOI's

Anti-anxiety agents
Benzodiazepines (BZ)

- Mode of action
  - Increase in GABA (primarily an inhibitory NT)
- Indications
  - Anxiolytic, sedative-hypnotic, alcohol withdrawal, anticonvulsant, muscle relaxant
  - In psychiatry, benzodiazepines are used as adjuncts (not main treatment for anxiety)
- Adverse effects
  - Sedation, abuse/dependence, CNS depression, withdrawal syndrome

Anti-anxiety agents
Benzodiazepines

- Choice depends on
  - T ½ (half-life)
  - +/- active metabolites
  - Speed of action (PO, IM, SL)
  - Dependence potential

Anti-anxiety agents
Benzodiazepine representatives

drug	Half-life	Half life of metabolites
triazolam	1.5-5hrs	none
clonazepam	18-50 hrs	none
diazepam	20-50 hrs	50-100 hrs

Miscellaneous Agents

- Herbs – kava, valerian, SJW, gingko
- Vitamin E
- Melatonin
- Omega fatty acids/ fish oils

Electroconvulsive Treatment

- Myths
- Mechanism of action
  - Seizure is necessary
  - Electrical equilibrium
  - Stabilizes dysregulated intracellular signaling linked to multiple transmitter systems
- Indications
  - Severe depressive d/o, immediate suicide risk, major depressive d/o with psychosis, severe mania, treatment resistant schizophrenia, parkinson's, catatonic stupor

Electroconvulsive Treatment

- Efficacy
  - 30-50 percent chance of response in truly medication resistant depression
- Adverse events
  - Mortality rate of 0.002% per treatment and 0.01% per patient (Kaplan and Sadock 6th ed)
  - Dysrhythmias
  - Confusion
  - Cognitive dysfunction

Light Treatments

- Indications
  - Depressive disorders with seasonal patterns
  - Shift work
- Mechanism of action
  - Light phase advances the delayed circadian rhythm associated with seasonal depression
- Efficacy
- Adverse events
  - Headache, eyestrain, irritability

Transcranial Magnetic Stimulation

- Use of high powered magnets to treat mood and anxiety conditions
- No anesthetics, no seizures
- 20-30 minute outpatient sessions
- Efficacy and role still being studied

Psychosurgery

- History- 1890's to 1930's
- Newer techniques
  - Imaging guided cingulotomies and capsulotomies
- Indications
  - Treatment/ medication resistant depression and OCD
- Efficacy
  - 50-70 % of carefully selected patients w/ significant clinical improvement and minimal SE's
- Adverse events
  - Less than 3% are worse after treatment
  - Hemiplegia in less than 0.3%
  - Epilepsy in less than 1%

Take Home Points

- Placebo: Make it work!
- Neurotransmitters=provide clues to how medications work and side effects!!
- Medications: What class are you!?!