Diseases of the Brain

Brain Bee is on Monday!

- Sherry's temp number: 902-914-6761
- Erin's temp number: 902-914-6941
- Feedback on a question
- Final prep to do?

Perception of psychiatric diseases

- Historical
- Impact of neuroscience
- https://pmc.ncbi.nlm.nih.gov/articles/PMC9842491/
- https://twin-cities.umn.edu/news-events/do-images-brain-make-us-more-likely-believe-what-we-read
- https://pmc.ncbi.nlm.nih.gov/articles/PMC6870243

Psychiatric disease

Figure 16.2 The DSM-5 is the manual that is used by psychiatrists to diagnose various psychiatric conditions.

- Depends on both genes and environment
- What are "risk factors"?

- Typically diagnosed based on guidelines in the DSM-5-TR (2022) in North America
  - Lots of overlap between different diagnoses
- International Classification of Diseases (ICD) from the World Health Organization is used more in Europe and other parts of the world
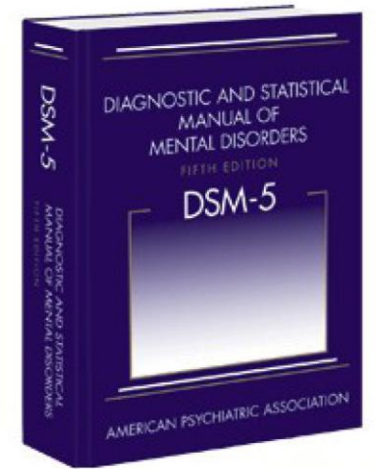
Treatment for psychiatric diseases

- Sometimes VERY effective! But,
- Not always effective
- Hard to develop effective treatments when we don't fully understand the disease

Studying psychiatric diseases with animal models

- Face validity
  - Does it look similar?
  - E.g., symptoms
- Construct validity
  - Does it have a similar mechanism?
  - E.g., causes
- Predictive validity
  - Is it good at predicting human outcomes?
  - E.g., treatment response

Schizophrenia

- Often confounded with dissociative identity disorder (multiple personality disorder) – although perhaps less so now

- Incidence: just under 1%, affects men slightly more often than women

- Strongly associated with low socioeconomic status

- Neonatal nutritional deficiency or food insecurity may be risk factors

- Prenatal drug exposure, heavy drug use during early adolescence, and childhood adversity are risk factors

- Typically diagnosed between late adolescence and 30s (while brain is still maturing)

- The later symptoms appear, the better the outcomes are

- Typical intelligence

Dr. John Forbes Nash
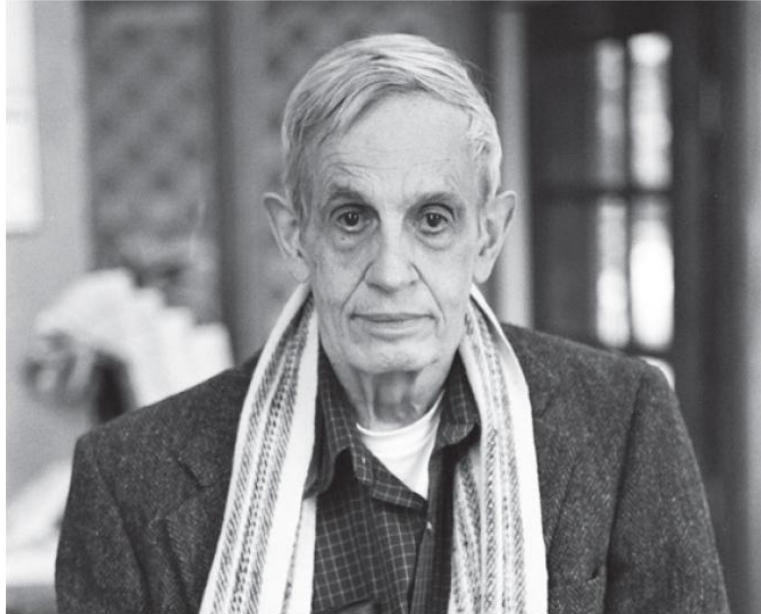
Figure 16.4 Dr. John Forbes Nash was diagnosed with schizophrenia before receiving the Nobel Prize in Economics in 1994.

Symptoms of schizophrenia

- Positive symptoms (excess of function)
- Negative symptoms (deficit of function)
- Not all individuals with schizophrenia experience all symptoms

Positive symptoms

- Hallucinations
- Delusions

Negative symptoms

- Flat affect

- Alogia (decrease in language use, use of vague language, language that is lacking in content, or repetitive language)

- Deficits in motivation or interest

- Anhedonia (inability to experience pleasure)

- Avolition (decrease in goal-directed activity)

- Decreased episodic memory

- Reduced performance on attention tasks

- Motor disturbances including catatonia and stereotypy (repetitive, purposeless behaviours)

Catatonia

Figure 16.7 After being moved gently into an unusual body position, a person with catatonia may stay in that position for a prolonged time.

Odds ratio for developing schizophrenia
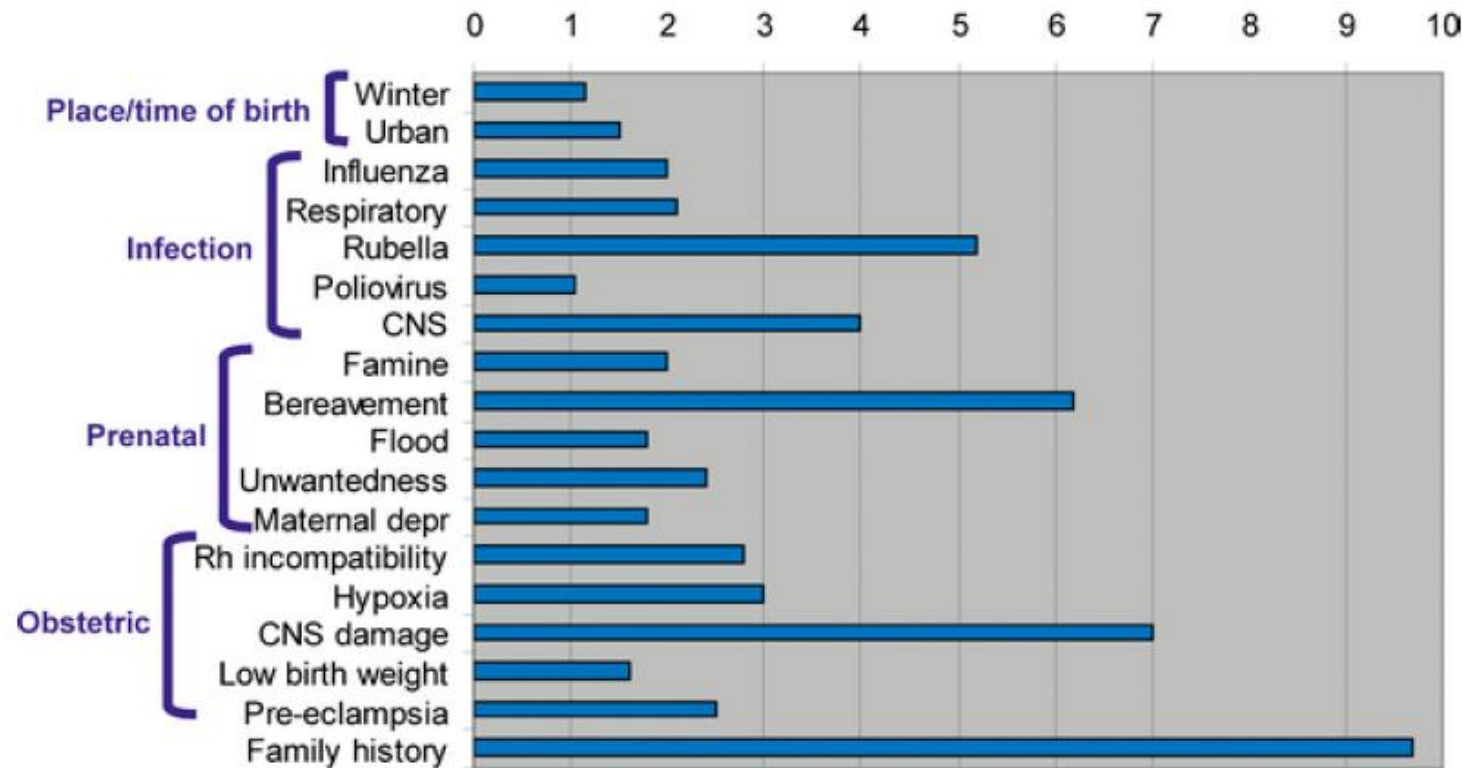
Figure 16.8 Many environmental factors contribute to the risk of developing SZ.

Potential causes of schizophrenia

- Dopamine hypothesis:
  - Motor and motivation symptoms
  - Genetic differences (polymorphisms) in the dopamine D2 receptors
- Cortical network hypothesis:
  - 40 Hz activity (gamma oscillations) normally result from a combination of excitatory and inhibitory neuron signaling
  - In schizophrenia, there is a decrease in the density of dendritic spines on the excitatory neurons, with a simultaneous decrease in GABA-ergic signaling. Result: unpredictable gamma oscillations.

Animal models of schizophrenia

- Schizophrenia-like state can be induced in non-human animals by administering amphetamine (dopaminergic) or ketamine or phenylcyclohexyl piperidine (PCP) (NMDA glutamate receptor antagonists)

- Methylazoxymethanol acetate (MAM) administration to or inducing a strong immune response in pregnant rat results in pups displaying schizophrenia-like state

- Impossible to detect delusions and difficult to detect hallucinations in animal models

- Overall, models have helped test efficacy of anti-schizophrenia drugs

Treatments for schizophrenia

- Dopamine antagonists decrease hallucinations and delusions in some patients
  - Effectiveness of a given D2 antagonist is correlated with its ability to block D2 receptors
  - E.g., haloperidol
- Clozapine: Atypical anti-psychotic
  - D2 antagonism plus 5-HT2A receptor antagonism
- Effectiveness
  - 1/3 of patients discontinue treatment
  - 1/5 report adverse side effects such as extrapyramidal motor symptoms (similar to PD), sedation, and weight gain

TMS for schizophrenia

- Targeted activation may decrease severity of auditory hallucinations

- May also improve negative symptoms

Major depressive disorder (MDD)

- Lifetime risk of depression: 18%
- 5% of women and 2.5% of men
- How do we feel about these numbers?

Prevalence versus incidence

- Prevalence includes all cases, both new and preexisting, over a specified time period
  - Point prevalence: prevalence measured at a specific point in team

- Incidence is limited to new cases only (also measured over a specified time period)

- What's missing from the number? What could make them make sense?
  - Lifetime risk of depression: 18%
  - 5% of women and 2.5% of men

- Also consider:
  - Prevalence similar across high and low income countries, *indicating that biological factors contribute significantly to the disease*
    - What is the reasoning here?

Comorbidity

- Presence of more than one diagnosis
- E.g., terminal illness is comorbid with depression

Symptoms of MDD

- Of sufficient severity and duration (daily for two weeks or longer):

- Depressed mood

- Low self-esteem

- Low energy

- Anhedonia

- Feelings of worthlessness

- Changes in sleep

- Changes in appetite

- Difficulty concentrating

- Suicidal ideation

To date, there is no biomarker for depression

- How is this possible?

Treatments for MDD

- No completely effective treatment for MDD that reliable works for everyone

- Accepted (evidence-backed) strategies can be divided into behaviour and chemical treatments

# Cognitive behavioural therapy (CBT)

- Also effective for anxiety, obsessive-compulsive disorder, insomnia, substance use disorders, behavioural addictions
- Example:
  - Teach a patient to identify moments when they dwell on something negative
  - Learn to tell themselves "That thought does not make my day better. Let's start the day by getting out of bed and see what happens next"

Chemical treatments

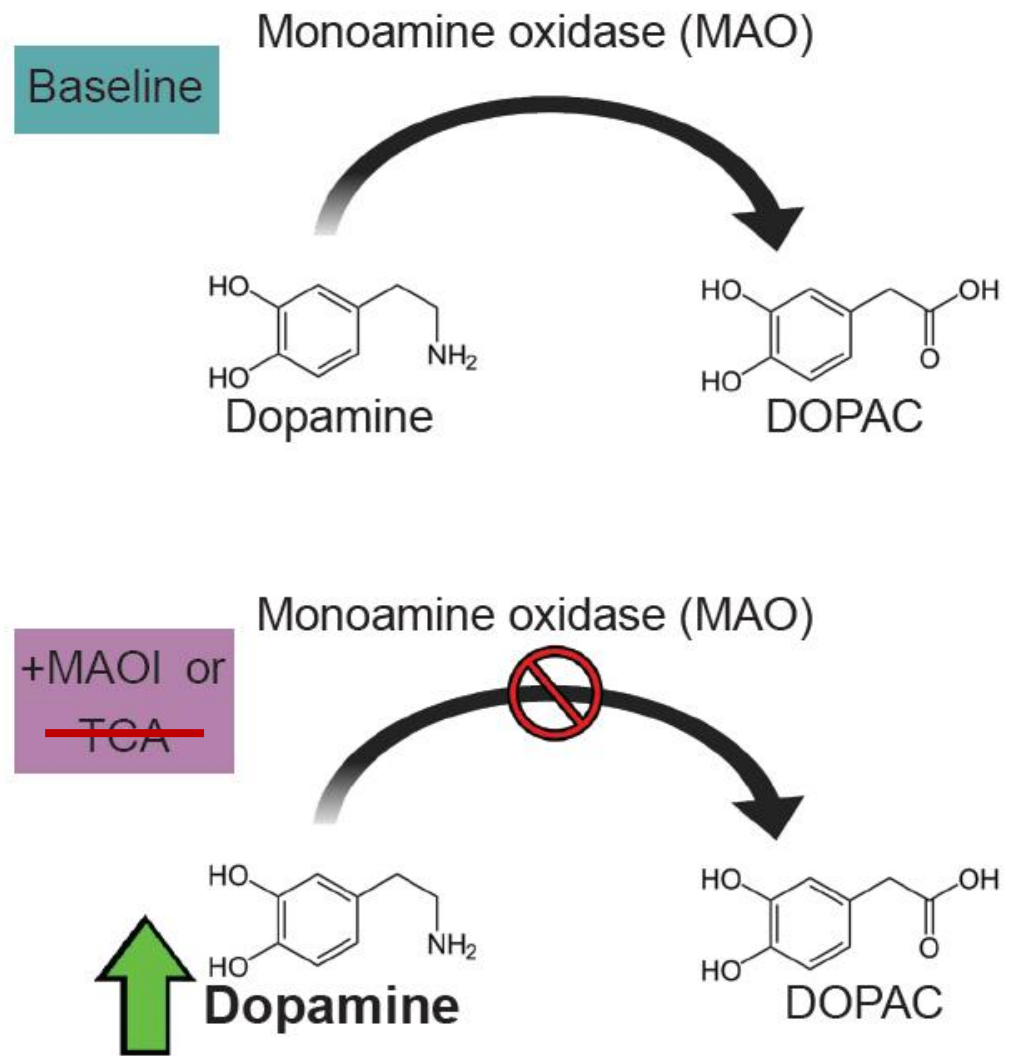# 1st generation antidepressants: monoamine oxidase inhibitors (MAOIs)

- Monoamines: class of neurotransmitters including serotonin, norepinephrine, dopamine

- E.g., phenelzine, isocarboxazid

- Side effects: cardiovascular events (interaction with cheese!), psychosis, nausea
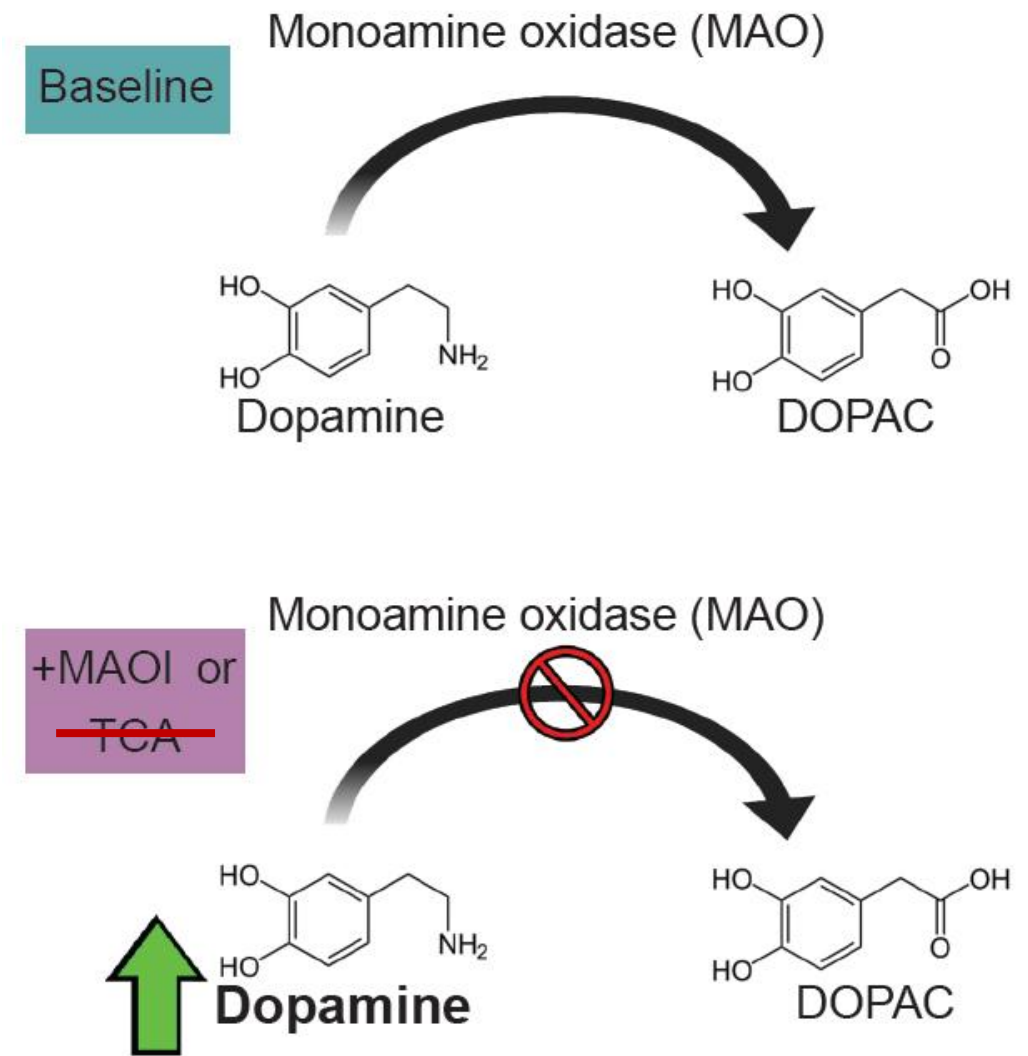
Figure 16.12 MAOIs and TCAs both increase neuronal signaling by decreasing the metabolic degradation of neurotransmitters, such as dopamine.

Tricyclic antidepressants

- Monoamine reuptake inhibitors
- (Figure wrong in textbook)
- Side effects: Seizures, tachycardia, heart attacks

Figure 16.12 MAOIs and TCAs both increase neuronal signaling by decreasing the metabolic degradation of neurotransmitters, such as dopamine.

3rd generation antidepressants

- Selective serotonin reuptake inhibitors (SSRIs)
- E.g., fluoxetine (Prozac)
- Takes 2-4 weeks before clinically meaningful change in symptoms appears
  - Despite molecular-level effects being evident within a few hours
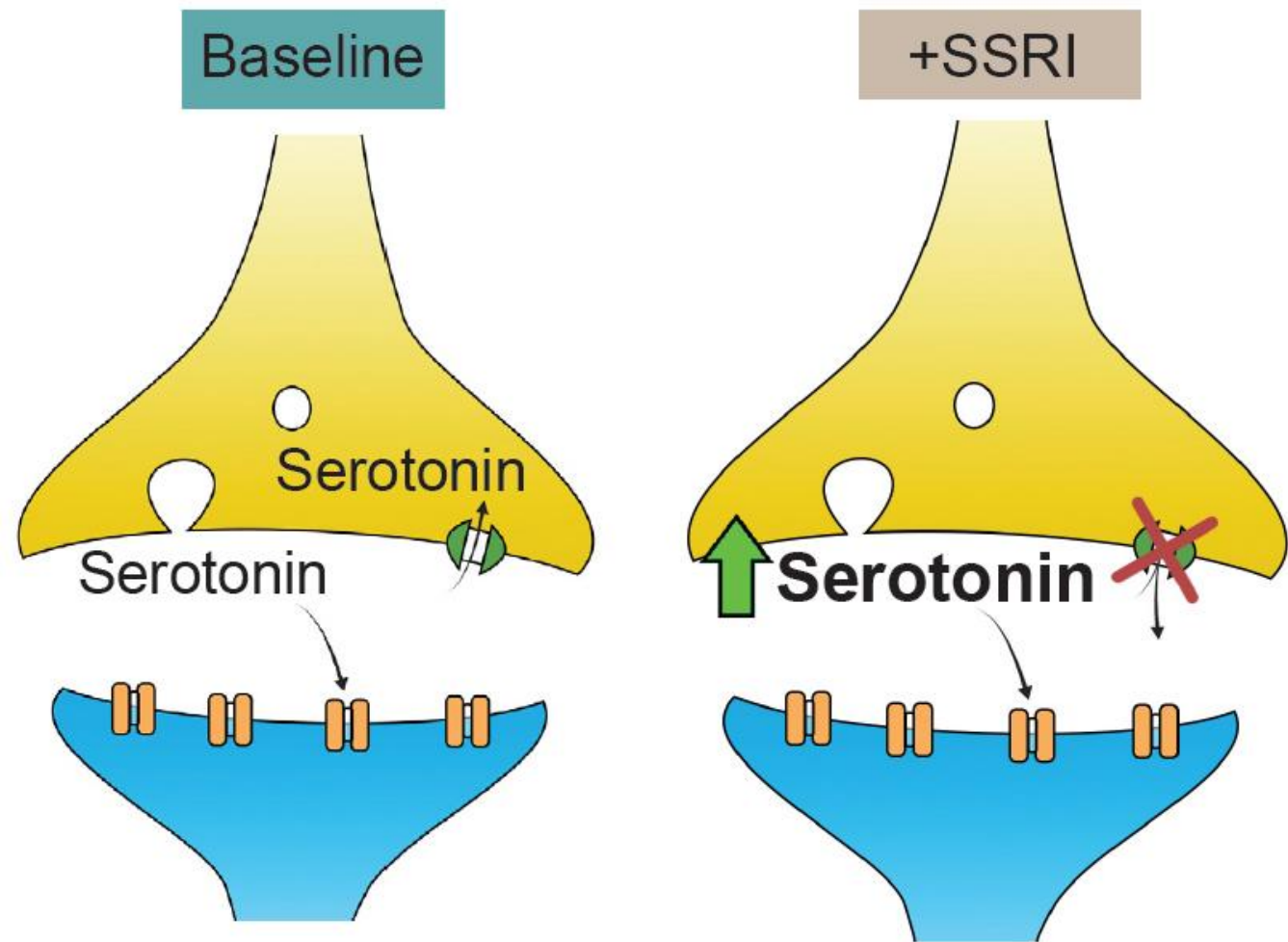
Figure 16.13 Third-generation antidepressants act to increase neurotransmission at the synapse by inhibiting reuptake.

Serotonin syndrome

- Mild: Elevated body temperature, excessive sweating, rapid heart rate, elevated blood pressure

- Severe: Fevers, seizures

- Can occur due to overdose of SSRI; or interactions with MAOIs, MDMA, amphetamines, or cocaine

Ketamine

- Newest treatment for MDD
- Dissociative anesthetic, veterinary tranquilizer, recreational drug
- Nasal spray administration; reduced symptoms within hours

Brain stimulation

- Started with electroconvulsive therapy (ECT)
- Transcranial magnetic stimulation
  - Generally over the left prefrontal cortex for depression
  - Canada is a leader: https://www.camh.ca/en/science-and-research/discoveries/camh-research-impact-report-2019/brain-stimulation#:~:text=In%202002%2C%20Health%20Canada%20approves,Administration%20follows%20suit%20in%202008.
  - Clinic in Halifax: https://www.nshealth.ca/patient-education-resources/1975

Animal behavioural tests of depression: Despair-based

Figure 16.14 The tail suspension test (left) and the forced swim test (right) are despair-based tests that assess depression-like behaviors in non-humans.

Animal behavioural tests of depression: Reward-based

- Two-bottle choice task

- Intracranial self-stimulation paradigm (recall Chapter 11)

Bipolar disorder (previously called manic depression)

- Phases of clinical depression interleaved with periods of mania

- Mania
  - Very little sleep
  - Difficulty concentrating
  - "Pressure of speech": Perceived need to speak very rapidly to get their thoughts out
  - Poor decisions

- No good animal models

Bipolar disorder prevalence

- 2.5% (over what time period?)
- Often misdiagnosed as MDD
- Some genetic factors involved (family history is a risk factor)

Bipolar disorder diagnosis

- Mood cycle has to last for a week or more

- Rapid-cycling bipolar disorder: at least 4 mood transitions annually

- Usually diagnosed in adolescence and early adulthood

- Two categories (but really a spectrum)
  - Bipolar 1 disorder: More severe
  - Bipolar 2 disorder: Less severe

Treatments for bipolar disorder

- Mood stabilizers (lithium drugs)
- Mechanism unknown
- Very toxic
- Requires therapeutic drug monitoring
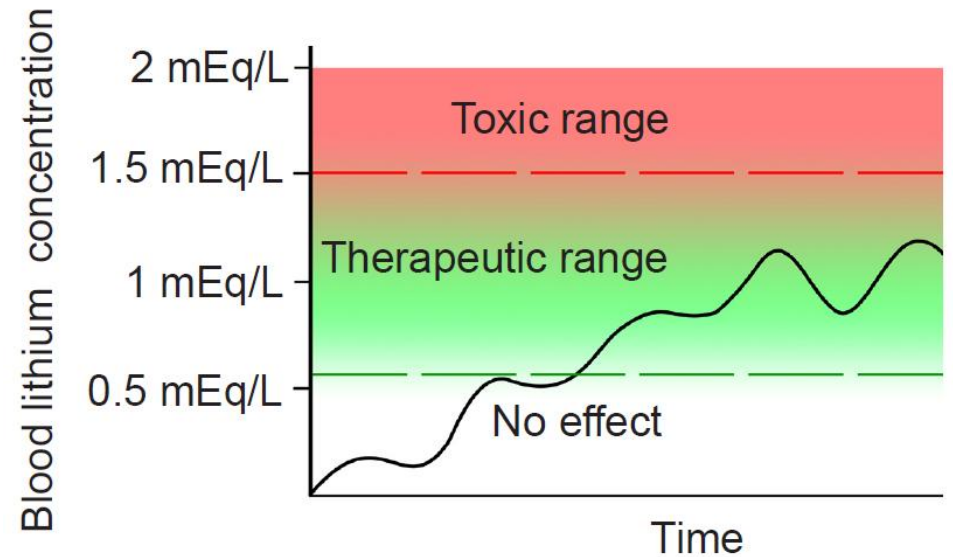
Figure 16.16 Therapeutic drug monitoring is important for people taking lithium for BPD since the medication is ineffective at low doses, but toxic at high doses.

Anxiety disorder

- Everyone experiences anxiety
- Not everyone has a clinical diagnosis, but very common (29% lifetime prevalence)
- Symptoms:
  - Elevation of blood pressure and heart rate
  - Sweating
  - Shortness of breath
  - State of panic

Generalized anxiety disorder (GAD)

- Constant sensation of being overwhelmed accompanied by fear and worry

- Must happen on most days for 6 months or longer for a diagnosis

Specific phobias

- Perception that a specific stimulus (e.g., snakes, open spaces) are a major threat
- Lifetime prevalence 7%

Panic disorder

- Frequent panic attacks
  - Sudden increases in heart rate, shortness of breath, dizziness, numbness or tingling
- May occur independently of external influences

Treatments: CBT or Anxiolytics

- SSRIs
- Positive allosteric modulators of GABA (e.g., the benzodiazepine clonazepam)
  - Addictive
- Opioids
  - Addictive
- Norepinephrine reuptake inhibitors

Animal models of anxiety

- Elevated plus maze
- Open field test
- Predator exposure paradigm
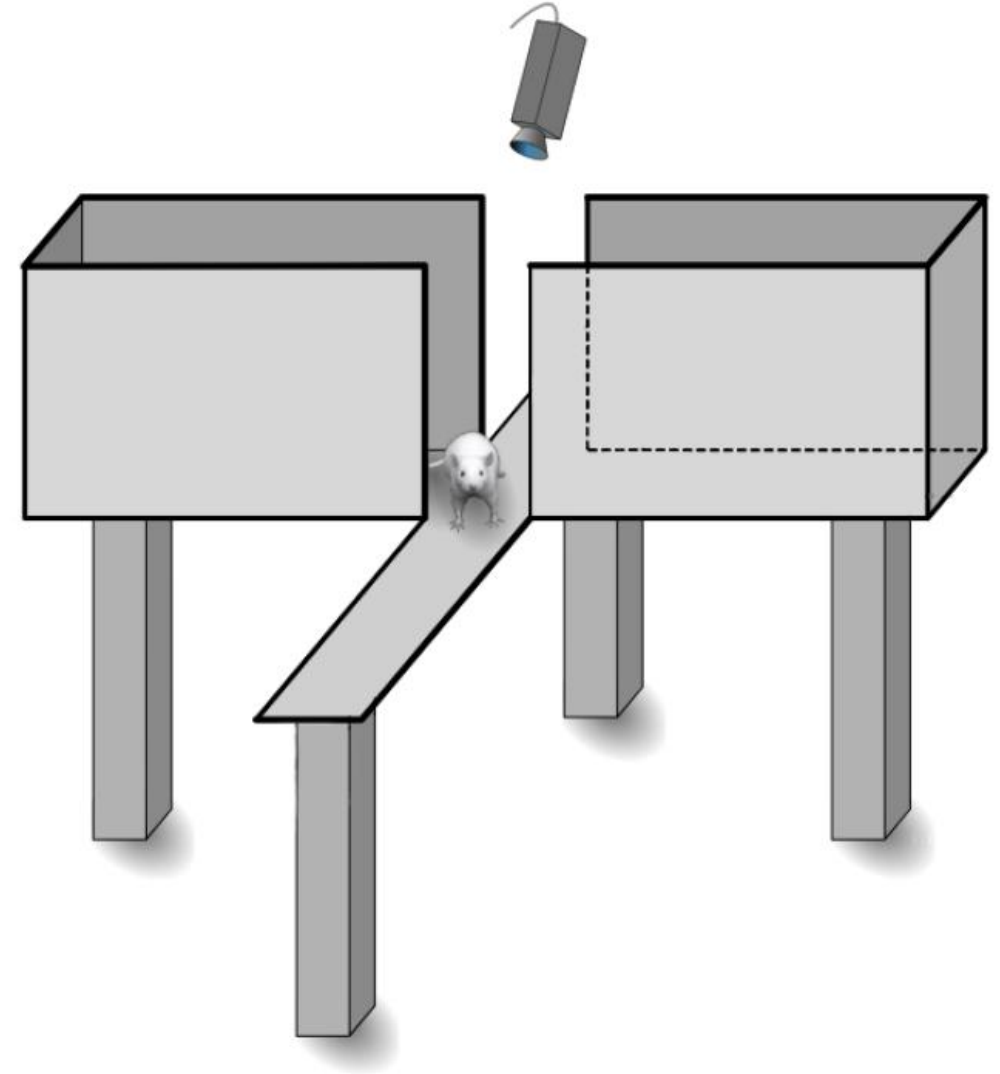
Figure 16.18 An elevated plus maze is one behavioral test for measuring anxiety behaviors in non-human animals.

OER survey

- Complete the online survey to provide your feedback on the OER we are using in this class