

World Psychiatric Association (WPA)
Working Group on Medical Students



Clinical Handbook in Psychiatry

**Khalid Bazaid, Kien Crosse, Alexander Simmons,
Jessie Montanaro, Esther Lee, Kelsie Ou**



About This Handbook

This handbook was designed as an educational and reference resource originally for medical trainees at University of Ottawa. It can also be a useful resource for primary care practitioners. It was written by a team of medical students at the University of Ottawa (currently residents in psychiatry and family medicine at the University of Ottawa and the University of Toronto) under the supervision of Dr. Khalid Bazaid, MD, FRCPC, the former Clerkship Rotation Director (Anglophone) and former Director of the Undergraduate Education Program, Department of Psychiatry, College of Medicine, University of Ottawa. During his time as the Director of the Undergraduate Education Program, Dr. Bazaid provided invaluable support and guidance in the development of this handbook. He is also a member of the World Psychiatric Association (WPA) Working Group on Medical Students. Revisions were done by staff psychiatrists affiliated with the University of Ottawa.

The authors appreciate the invaluable help of Alex Sinha and Khadije Sobh, the former and current coordinators, respectively, of the Undergraduate Education Program in the Department of Psychiatry, Faculty of Medicine at the University of Ottawa.



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Foreword

The World Psychiatric Association (WPA) has, over the last few years, made it a priority to advocate for the promotion of psychiatry among medical students and support the medical learners. Capacity building and to promote psychiatry among medical students is one of the major components of World Psychiatric Association (WPA) Triennium Action Plan 2020- 2023. To this end, we have established the WPA Working Group on Medical Students with the primary aims of addressing the mental health and wellbeing of medical students, fighting against ongoing stigma as a barrier to mental health, and promoting the field of psychiatry as an enriching, meaningful career path.

I am pleased to support this excellent work, developed by one of the members of the WPA Working Group on Medical Students, Dr. Khalid Bazaid, MD, FRCPC, the former Clerkship Rotation Director (Anglophone) and former Director of the Undergraduate Education Program, Department of Psychiatry, College of Medicine, University of Ottawa, and a team of accomplished medical students at the University of Ottawa (currently psychiatric residents and family medicine at the University of Ottawa and the University of Toronto).

The idea of writing this handbook was conceived by the medical students, who wanted to create a resource encompassing the breadth of knowledge needed to achieve clinical competence in psychiatry. Their goal was to publish this book for the use of learners and practitioners alike.

WPA is convinced that this book will find its way to a wide readership and serve as a reference for our medical students, young learners and aspiring professional workforce in their future course of education.



Dr. Afzal Javed
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Foreword

Capacity building and promoting psychiatry among medical students is an important pillar of World Psychiatric Association (WPA) Triennium Action Plan 2020-2023. WPA Working Group on Medical Students has played a major role in this regard.

Dr. Khalid Bazaid is an integral member of WPA Working Group on Medical Students and has contributed significantly in success of this group. He and his team of committed medical students including Kien Crosse, Esther Lee, Jessie Montanaro, Alexander Simmons, and Kelsie Ou from University of Ottawa conceived the idea of creating a psychiatry handbook for medical students. Currently, these medical students are psychiatry and family medicine residents at University of Ottawa and University of Toronto.

This psychiatry handbook provides comprehensive introduction to various psychiatric conditions and would be an excellent resource for medical students, not just in Canada but around the globe. I wish this team the very best in their future endeavours.



Prof. Muhammad Waqar Azeem,
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Introduction

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The Psychiatric Interview

1. Identification data

- Basic information which provides key context for the patient's situation
- Patient age, gender, relationship status, children, how do they financially support themselves, do they drive/have a license

2. Reason for referral

- Important to note not only the reason for referral outlined by the referring provider, but also the patient's primary reason for seeking a psychiatric referral

3. History of present illness

- The most important part of the psychiatric interview
- Important to construct a chronological narrative with note of possible precipitating factors for presentation
- Screen for symptoms. Include safety screen and substances
 - **See the [Emergency Psychiatry](#) chapter for a detailed description of a safety screen*

4. Past psychiatric history

- A syndromal history and treatment history are key components
- Syndromal history can include age at onset, premorbid functioning, episodic history
- A thorough treatment history can help to clarify appropriate options for management plans
 - This includes previous diagnoses, admissions, contact with psychiatry/mental health, psychotherapy/counselling, types of psychiatric medications and doses, previous suicide attempts

CLINICAL PEARL

General guidelines for obtaining a good psychiatric history

- Allow sufficient time - consults may take 45-60 minutes (and can be even longer, e.g. when interviewing youth)
- Obtain collateral information from the patient's family/friends.
- Consider a wide differential and do a thorough review of symptoms (depression, mania, anxiety, psychosis, substance use, safety, etc).
- Ensure a thorough chart review is performed
- Take note of the patient's psychiatric history, including any previous consultations, admissions, visits to emergency department
- Also make note of the patient's other health conditions, and whether these may be contributing to their presentation

5. General medical conditions

- Screening for medical illnesses is particularly important as many psychiatric patients have poor medical follow-up, and may have a higher prevalence of undiagnosed medical conditions
- Medical illnesses and medication can also cause or exacerbate psychiatric symptoms
- **Past medical history**
 - Ask about head injuries, seizures, thyroid problems, cardiac, chronic illnesses, surgeries, etc
- **Medications**
 - Ask about current, past, dosages, length of treatment, side effects, reasons for discontinuation
- **Allergies**

6. Substance use history

- **See the [Substance-related and Addictive Disorders chapter](#) for more information on how to take a detailed substance use history.*

7. Family history

- Family history can be important as many psychiatric disorders have evidence of familial transmission
- Ask about psychiatric and medical history, types of psychiatric medications and doses, completed suicides

8. Social history

- The social history allows one to learn about the patient as a person rather than a diagnosis, which is the focus of the HPI
- Social history is also important to the diagnosis of a Personality Disorder
- Ask about childhood adversity, developmental milestones, social support, relationships, education, employment

9. Legal history

- Ask about: Any charges? What type? Violence?

MNEMONIC

Questions around past treatment history

"Go CHaMP"

- **G**eneral questions
- Who is your current **C**aregiver?
- Have you been psychi-
atrically **H**ospitalized?
- Have you taken **M**edications for these symptoms?
- Have you had **P**sycho-therapy?

MNEMONIC

General medical conditions

"MIDAS"

- **M**edications
- Medical **I**llnesses
- Primary care **D**octor (does the patient have one?)
- **A**llergies, reactions, and/or side effects from medications
- **S**urgeries

The Mental Status Examination

The **mental status examination** (MSE) is the psychiatric equivalent of a physical examination (but does not exclude performing a physical exam as well). It should capture the status of the patient at the time of evaluation using a combination of observations made during the interview and information obtained through direct questioning. While a single assessment may be of limited clinical utility, repeated MSEs over time can be helpful to monitor the signs and symptoms of mental illness.

The broad domains of the MSE include the patient's appearance, behaviour, motor activity, speech, mood, affect, thought process, thought content, perceptual disturbances, cognition, insight, and judgement.

MNEMONIC

The Mental Status Exam

"ASEPTIC"

Apppearance/Behaviour
Speech
Emotion
Perceptual disturbances
Thought (form and content)
Insight and judgement
Cognition

Appearance and behaviour	<u>Appearance</u> • Age – appears stated age, younger (e.g. developmental delay) or older (e.g. underlying severe medical illness, substance abuse) • Hygiene – measure of functioning (e.g. poor grooming due to severe depression, neurocognitive disorder, or psychotic disorder) • Dress – type of clothing, appropriate for weather (e.g. wandering outside without proper clothing in winter) • Other features – lacerations or scars (e.g. injury, self harm, IV drug use, suicide attempts), tattoos <u>Behaviour</u> • Attitude – cooperative, guarded, agitated (e.g. in pain or distressed from internal stimuli); difficulty maintaining attention (e.g. attending to auditory or visual hallucinations) • Eye contact – appropriate, fleeting or intermittent, intense, fixed in space (e.g. attending to internal stimuli) • Motor activity – psychomotor changes (e.g. agitation in intoxication or mania, or slowing in depression or neurocognitive disorders), abnormal movements (e.g. tremors, akathisia, tics, mannerisms)
Speech	• Amount – paucity or poverty (e.g. only responding in yes/no; may be seen in depression, anxiety), verbose (e.g. anxiety, mania); presence of spontaneous speech • Fluency – word-finding difficulties (e.g. neurocognitive disorder, altered mental status) • Rate – normal, slowed (e.g. depression, neurocognitive disorders) or pressured (e.g. mania, intoxication) • Latency – delayed response (e.g. neurocognitive disorders, thought blocking in psychotic disorders) • Rhythm – slurring (e.g. intoxication), dysarthria (e.g. motor dysfunction) • Volume – soft (e.g. depression), loud (e.g. agitation, neurocognitive disorder) • Tone – may indicate mood
Emotion	<u>Mood</u> - subjective emotional state of the patient • Use the patient's own words describing how they are feeling • May also use a Likert scale of 0-10 (e.g. 0 being the worst, 10 being the best possible mood) to help quantify and monitor over time <u>Affect</u> - based on observation • Quality – euthymic, dysphoric, irritated, etc. • Range – full > restricted > blunted > flat • Stability – fixed, labile • Congruence – compared to stated mood • Appropriateness – in the context of their thought content

(continued on next page)

Perceptual disturbances	"Hallucination": abnormal auditory, visual, tactile, gustatory, or olfactory perception in the absence of any external stimuli "Illusion": misperception of an existing external stimulus (e.g. thinking their name was called in a crowd) <u>Auditory hallucinations</u> • Voices or sounds/noises • Characterize voices – familiarity, number, apparent gender(s) • Content – commands (especially to hurt self or others), commentary (describing patient's actions), nature (e.g. benevolent vs. antagonistic/threatening) <u>Other (visual, tactile, etc.) hallucinations</u> • Explore further description, content, triggers <u>Disturbance of self and environment</u> • Depersonalization • Derealization
Thought	<u>Thought process/form</u> • Organization - Linear/goal-directed: thought process is logical and easy to follow - Circumstantial: thoughts are connected but circuitous and venture off-topic before returning to the original subject; may be over-inclusive - Tangential: series of thoughts that are connected but derail and do not return to the original topic - Flight of ideas: stream of rapid thoughts with abrupt shifting from one topic to another with no central direction; often associated with mania or psychosis - Loose/disorganized: little connection between thoughts, difficult to follow • Thought blocking: abrupt interruption of stream of thought • Perseveration: persistent repetition of specific words or concepts in the process of speaking • Verbigeration: stereotyped repetition of random words or phrases in response to a stimulus • Echolalia: automatic repetition of words or phrases said by others • Clang associations: the use of words based on sounds, such as rhyming or punning, rather than their meanings • Neologisms: creation of new words that only have meaning to the patient • Word salad: an unintelligible string of random words <u>Thought content</u> • Safety – thoughts of self harm, suicidal ideation, homicidal ideation - Explore frequency and pervasiveness of thoughts, active vs. passive ideation, protective factors • Obsessions: recurrent and persistent thought or image, not stopped by logic or reason and causes marked distress (e.g. themes of contamination/cleanliness, sexual, pathological doubt/worry/guilt) • Delusions: firm, fixed beliefs which are not part of a cultural belief system and persist despite contradicting evidence (e.g. grandiose, paranoid, persecutory, somatic, religious, erotomaniac) • First rank symptoms of schizophrenia – thought withdrawal, thought insertion, thought broadcasting • Ideas of reference • Preoccupations, perseveration • Overvalued ideas

(continued on next page)

Insight and judgement	<u>Insight</u>: a patient's understanding of the nature of their illness and their functionality • Poor, limited, fair, good • Worsening, improving • Ask the patient: Why are you in the hospital? Why are you taking this medication? What would happen if you stopped taking it? <u>Judgement</u>: a patient's ability to make good decisions • Poor, limited, fair, good • Worsening, improving • E.g. Is the patient dressed appropriately? Are they acting appropriately given their current situation? Are they able to take care of themselves (and others)?
Cognition	• Alertness – alert, somnolent, obtunded, in a stupor, comatose • Orientation – person, place, time • Attention/concentration – observe attention throughout interview, serial 7s, WORLD backwards (impairment may be seen in anxiety, depression, poor sleep, or neurocognitive disorder) • Memory – immediate recall (e.g. list of random words/numbers, sentence), delayed recall (e.g. after 1-5 min), short-term memory (e.g. HPI or events earlier in the day), and long-term memory (e.g. childhood, wedding) • Abstract reasoning – ask what two objects have in common or how to interpret a common proverb; concrete thinking and inability to infer abstract meaning may be seen in some intellectual disabilities, neurocognitive and other disorders Do further testing with MoCA or MMSE if indicated.

Table 1. Components of the Mental Status Examination.

Adapted from Toronto Notes 2020 “Mental Status Exam” pg. PS3-PS4.

Biopsychosocial Case Formulation

Biopsychosocial case formulation is an approach that takes biological, psychological and social factors into consideration in order to develop a deeper understanding of patients.

It is a technique used to develop hypotheses about the origins and causes of patients’ symptoms, and can be used to guide management.

A biopsychosocial approach as formatted below is often taken for case formulation:

Factors	Biological	Psychological	Social
Predisposing	Genetic predisposition Toxin/infection exposure in utero Ostetrical complications Traumatic brain injury	Attachment style Personality traits Temperament	Adverse childhood experiences Poverty Trauma
Precipitating	Medication side effect Disrupted sleep Substance use Medication non-compliance	Grief Loss of relationship Life stressor	Divorce Loss of job Loss of home Academic stressor
Perpetuating	Poor response to medication Chronic pain/illness	Personality traits Poor coping mechanisms Pessimistic explanatory model	Stigma surrounding mental illness Financial instability Abusive relationship
Protective	Intelligence Healthy diet Adequate sleep Exercise Resilience Genetic predisposition	Psychological mindedness Insight Healthy coping strategies	Strong community Supportive relationships Financial stability Connection to faith Family physician

Table 2. Examples of common key factors to consider when formulating a biopsychosocial case.
Adapted from Psych DB.

Cultural Psychiatry

Cultural psychiatry is a field that examines the impact that culture has on human behaviour, mental health, psychopathology, and treatment. Culture can be defined as the patterns in behaviour and lifestyle, including a set of beliefs, values, and attitudes, which are shared by a group of people and which distinguish them from another group of people. Culture is learned through “enculturation” and is passed along generations through families and in social environments.

Culture can impact an individual's health and mental health as it determines how we experience illness and distress, how we perceive it, and how we respond to it. It should be noted that the information presented in this chapter is primarily based on English-language literature published in Western nations.

NOTE

Culture differs from race, which is a constructed categorization of groups based on superficial physical traits. Although there is no consistent biological definition, race can have negative effects on mental health as a component of racism and discrimination.

Cultural formulation

Cultural formulation can assist in assessing the impact of culture on an individual's presentation and care. The Outline for Cultural Formulation was introduced in the DSM-IV and has been revised for the DSM-5. Under the revised Outline, the following should be assessed:

- The cultural identity of the individual: Describe the individual's racial, ethnic, or cultural groups that may influence their relationships, access to resources, challenges, conflicts, or predicaments
- Cultural conceptualization of distress: Describe the cultural constructs that influence how the individual experiences, understands, and communicates their symptoms or problems to others
- Psychosocial stressors and cultural features of vulnerability and resilience: Identify the stressors and supports in the individual's social environment, as well as the role of religion, family, and other social networks in providing support.
- Cultural features of the relationship between the individual and the clinician: Identify differences in culture, language, and social status between an individual and clinician that can cause challenges in communication and influence diagnosis and care
- Overall cultural assessment: Summarize the components of the cultural formulation and appropriate management and treatment intervention

Cultural concepts of distress

- Cultural formulation is now understood through the **cultural concepts of distress**, which is a term used to refer to ways that cultural groups experience, understand, and communicate suffering, behavioural problems, or troubling thoughts and emotions
 - This perspective allows many DSM diagnoses to be understood as prototypes which started as cultural syndromes, and later became widely accepted due to clinical and research utility

The three cultural concepts of distress are:

1. **Cultural syndromes** are sets of symptoms that tend to occur among individuals in specific cultural groups or communities
2. **Cultural idioms of distress** are manners of expressing distress which provide common ways to experience and discuss personal and social issues
3. **Cultural explanations** or **perceived causes** are explanatory models which demonstrate a culturally recognized etiology for symptoms or distress

Cultural formulation interview

The Cultural Formulation Interview (CFI) is a new approach to assessment in the DSM-5, consisting of a set of 16 questions in four domains:

1. Cultural Definition of the Problem
2. Cultural Perceptions of Cause, Context, and Support
3. Cultural Factors Affecting Self-Coping and Past Help Seeking
4. Cultural Factors Affecting Current Help Seeking

The CFI can be helpful in situations where there is:

- Difficulty in assessment due to cultural, religious, or socioeconomic backgrounds between the clinician and patient
- Unclear distinction between diagnostic criteria and culturally specific symptoms
- Difficulty in judging illness severity
- Limited engagement in and adherence to treatment, or disagreement between patient and clinician on the course of care

FYI

Cultural formulation was previously understood through the structure of “culture-bound syndromes”.

This has fallen out of favour as the term does not consider that cultural differences in clinical practice are often due to differing explanations or experiences for distress, as opposed to culturally distinct constellations of symptoms.

FYI

The full CFI is available online at: https://www.psychiatry.org/File%20Library/Psychiatrists/Practice/DSM/APA_DSM5_Cultural-Formulation-Interview-Informant.pdf

Indigenous Mental Health

- Indigenous populations in Canada and around the world are affected by a disproportionate burden of mental and physical illness
 - A history of colonialism based in racism, discrimination, and genocide has greatly affected Canada's Indigenous population
 - Determinants of health which stem from a history of colonialism, including racism and poverty, are correlated with higher rates of infant mortality, acute and chronic pain, and injury
 - Colonialism has been implicated as a cause of mental illness through practices such as residential schools
 - Colonialism has also been implicated as a structure which can construct mental illnesses based on a set of norms and definitions which may not be as applicable across populations
 - Further, the colonial structures embedded in the health care system can create barriers of Indigenous individuals seeking care
- In Canada, colonialism is present at the structural, distal, and proximal levels
 - The structural level refers to the broad, institutionalized policies that maintain the colonial structure
 - Colonialism at the distal level causes effects at the societal level, with racism and poverty being examples
 - Colonialism at the proximal level causes individual-level effects such as poor-health and unemployment
 - The effects of colonialism are diverse in their manifestation, and thus can not be generalized across the entire Indigenous population
- Currently there are significant clinical and research efforts to integrate Indigenous methods of healing into the mental health system
 - This is done with the goal of improving the experience of accessing services for Indigenous people, although there is not yet a strong evidence base for these type of interventions

IMPORTANT

Mental health services which are developed by or with input of Indigenous community members tend to be more successful!

Sample Psychiatric Interview Template

Identification:	Name: Age: Marital status: Children: Living situation: Employment: Source of Income: Country/City of Origin: HCPs:
Reason for Referral:	
Chief Complaint	
HPI Time frame Stressors Symptoms/DSM Risk factors Substance use/abuse Current meds Med compliance Psychosocial supports Coping strategies	

Substance Use				
Safety				
Review of Symptoms	MDD (M/I + 5)	GAD A: Excessive worry (6 months)	Mania (E+3, I+4)	Psychosis
More:	M	B: Uncontrollable	G	Hallucinations
OCD	S	C: (3/6, BE SKIM)	S	Paranoia
Dissociative Disorders	I	Blanking out (concentration)	T	Ideas of reference
Trauma/Stressor disorders	G	Easily fatigued	P	Thought Blocking/Thought Withdrawal/Thought Interference
Eating disorders	E	Sleep disturbance	A	
Sleep disorders	C	Keyed up/restless	I	
Somatic disorders	A	Irritability	D	
Borderline traits	P	Muscle tension		
	S			

Past Psych History	Most recent admission: Number of admissions, where: First episode of psychiatric illness: First psychiatric contact: Past treatments Suicide attempts Legal History Substance abuse
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	Affect Thought process Thought content Suicidal/homicidal ideation Perception Cognition Insight Judgement Impulse Control Reliability
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Additional Educational Resources

- Guidelines
 - CANMAT Guidelines for [Depression](#) and [Bipolar](#) disorders
 - [CPA 2017 Schizophrenia Guidelines](#)
 - [CAMESA Guidelines](#)
 - [CADDRA Guidelines](#)
- Study/Clinical Resources
 - Caplan et al. Mnemonics in a Mnutshell: 32 aids to psychiatric diagnosis
 - Stephen Stahl Essential of Psychopharmacology
 - Kaplan & Sadock`s Synopsis
 - DSM-5
 - Toronto Notes
- [Choosing Wisely Canada, recommendations in Psychiatry](#)
- [SwitchRx](#) (tool to guide clinicians in adjusting patients' psychotropic medication regimens)

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Psychotherapy and the Therapeutic Alliance

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Introduction

Psychotherapy (or “talk therapy”) involves treatment of mental illness through a collaborative, therapeutic dialogue, facilitated by individuals with specific training.

- Practitioners may include psychiatrists, psychologists, family physicians, social workers, nurses, counsellors, and registered psychotherapists in the province.
- Numerous modalities of psychotherapy exist, with robust empirical support.
- Psychotherapy is indicated for a wide range of psychiatric disorders, but most commonly indicated for depressive disorders, anxiety disorders, substance use disorders, eating disorders, and personality disorders.
- Psychotherapy can also be used without a psychiatric disorder, to achieve a deeper understanding of one’s psychological make-up, to address challenges in relationships and intimacy, or to navigate losses and transitions in life.
- A **therapeutic alliance** is the fundamental pillar for all psychotherapies, and is often defined as “a collaborative relationship and positive connection between patient and therapist, with mutual agreement upon goals of treatment”.

This chapter includes a brief overview of the following therapies:

- Psychodynamic Therapy
- Cognitive Behavioural Therapy (CBT)
- Interpersonal Therapy (IPT)
- Dialectical Behavioural Therapy (DBT)
- Family Therapy
- Group Therapy

Psychodynamic Therapy

Psychodynamic therapy (“insight oriented therapy”) utilizes psychoanalytic theories and concepts (transference, the unconscious, defense mechanisms, resistance, dream interpretation), with the goal of developing insight into problematic patterns in life.

- Used in the treatment of complex personality disorders, anxiety disorders, depressive disorders, somatic symptoms disorders, and where complications of early life have significant ramifications in adulthood.
- Treatment course is typically once weekly, and may either be brief (12-20 sessions) or long-term (months to years).
- While certain psychoanalytic theories became less relevant in modern times (e.g. psychosexual stages of development), many of these concepts remain fundamental (e.g. unconscious repetitions throughout the lifespan, transference and countertransference), and other have been revised and updated to contemporary practice (e.g. relational and intersubjectivity)

For example, a well-established concept in psychoanalytic theory is **defense mechanisms**.

- Defense mechanisms are unconscious processes (thoughts, feelings, behaviours) which shield us from painful emotions, and protect us from suffering.
- Often categorized into mature, primitive (immature), and neurotic defenses
- E.g. “Splitting” is often encountered in cluster B personality disorders (and the most common defense mechanism in Borderline PD). Splitting allows the individual to experience their surroundings in polarized terms, either idealized (all good) or devalued (all bad), but without middle ground. Different members of the treating team can also be ‘split’ (or pitted against one other, causing rifts between healthcare providers).

FYI

Psychoanalytic theories were developed and popularized by Sigmund Freud in the early 1900's, as the first formally established “talking therapy”.

Psychoanalysis (and its branches into various theoretical schools of thought) was a mainstay of psychotherapy until the 1970's, until various short-term therapies (CBT) began to emerge.

FYI

For further reading on defense mechanisms, visit: <https://www.ncbi.nlm.nih.gov/books/NBK559106/>.

Cognitive Behavioural Therapy

Cognitive behavioural therapy (CBT) is built on the fundamental premise that we can “change the way we feel, by changing the way we think”.

- “Schemas” or “core beliefs” influence how we respond to the world.
- Schemas develop from our early life experiences, and may be adaptive but also may be pathological. This leads to “cognitive distortions” (see sidebar) which misrepresent the situations we face, and negatively influence our mood or anxiety.

In CBT, patients are treated with a combination of cognitive and behavioural techniques.

- **Cognitive techniques** focus on identifying a patient’s cognitive distortions and automatic thoughts, developing strategies to challenge them, to find a more realistic appraisal of the circumstances.
- **Behavioural techniques** can include activity scheduling in depression, or exposure and response prevention in OCD

CBT is indicated across a variety of mental health disorders, including mood disorders, anxiety disorders, obsessive-compulsive disorder, eating disorders, and substance use disorders.

Treatment is time-limited (typically 12-20 weekly sessions), and can be delivered individually or in group therapy, or by workbooks or online programs.

NOTE

Examples of cognitive distortions

- Personalization: Interpreting events as reflecting on the individual when they are unrelated
- Overgeneralization: Making general conclusions on experiences and relationships based on a single instance
- Arbitrary inference: Drawing and erroneous conclusion from an experience
- Catastrophizing: Placing undue weight on the worst possible outcomes or exaggerating the impact of a small problem
- Magnification and minimization: Magnifying another’s positive attributes while minimizing one’s own

Click [here](#) for more examples of cognitive distortions.

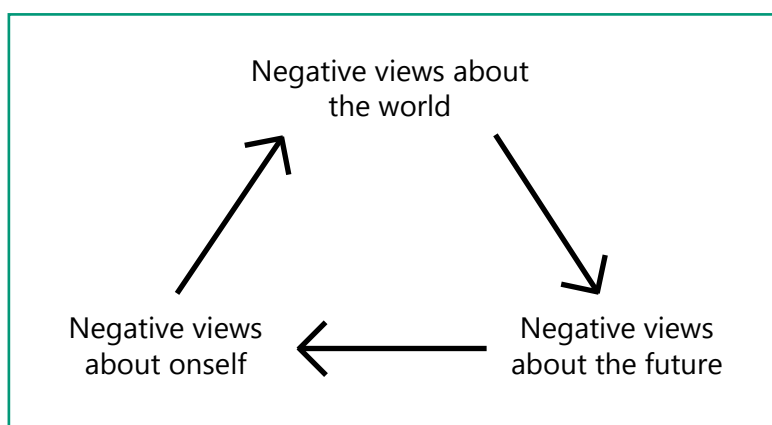


Figure 1. Dr. Aaron Beck’s “Cognitive Triad” (pattern of thinking in depression)

EVIDENCE-BASED PRACTICE

Studies have shown that CBT can be as effective as pharmacotherapy, with a lower rate of relapse, in mild to moderate depression and anxiety disorders.

Interpersonal Therapy

Interpersonal therapy (IPT) is based on the observation that depression is often closely tied to the interpersonal context (and disruptions in relationships).

- Can involve any one of four areas of focus, including: grief, interpersonal disputes, interpersonal deficits, and role transitions
- Short-term, structured, and manualized therapy.
- Typically consists of 12-16 weekly sessions, either individual or group

Dialectical Behavioural Therapy

Dialectical behavioural therapy (DBT) is one type of specialized psychotherapy in the treatment of borderline personality disorder.

- Combines CBT and mindfulness concepts
- Combines individual and group therapy, over a 1 year timeframe.
- 4 core skills include: emotional regulation, distress tolerance, interpersonal effectiveness, and mindfulness
- It balances acceptance and responsibility for change, with the overarching goal of “building a life worth living”

Family Therapy

- Used to help members of families understand and support each other, by improving interactions and strengthening communication.
- Employs CBT, psychoeducation, identifying problems and practical solutions
- Therapies may also meet with family members individually
- Often indicated when the family dynamic is contributing to (or perpetuating) illness

Group Therapy

Group therapy allows for several patients to be in therapy simultaneously, with one or two therapist facilitators. In contrast to individual therapy, group therapy provides a unique scenario for group members to share and learn from one another, towards positive change.

- Groups can be open (new members allowed to join at any time) or closed.
- Can be inpatient or outpatient groups
- Can involve a facilitator (e.g Day Hospital group), or without (e.g. support group)

FYI

Therapeutic mechanisms in group therapy*

- Instilling hope
- Developing socializing skills
- Using imitative behaviour
- Imparting information
- Behaving altruistically through helping others in the group
- Experiencing a corrective recapitulation of the primary family group
- Sense of group cohesion
- Diminishing feelings of isolation
- Learning how one's behaviour affects others
- Sense of universality

*As described by Dr. Irvin Yalom - in chapter reviewed by Dr. Saul's lecture notes.

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Review Questions

1. A 35 year old patient of yours expresses interest in psychotherapy. She has a longstanding history of recurrent depression. There is no history of psychosis or mania. There is no history of suicidality, nor any history of psychiatric hospitalizations. She is psychologically minded and motivated. She has tried several antidepressants over the years, but with mixed results and only partial improvements. Which of the following therapies would be recommended as most evidence based?
 - a) Dialectical Behavioural Therapy (DBT)
 - b) Interpersonal Psychotherapy (IPT)
 - c) Acceptance and Commitment Therapy (ACT)
 - d) Long-term psychodynamic psychotherapy (LTPP)

2. A 22 year old patient is admitted to your surgical service with a self-inflicted abdominal wound. Over the next few days, you notice a series of escalating disagreements erupting between residents and nursing staff caring for this patient. When you meet with this patient, he reports feeling mistreated by the resident, and feeling his needs are neglected by the nursing team. He praises you on your tremendous skills as a clinician, and describes you as “the only doctor who can help me”. Which of the following defense mechanisms is most likely being demonstrated?
 - a) Regression
 - b) Sublimation
 - c) Splitting
 - d) Projection

3. A young patient of yours has struggled with chronic suicidal thoughts, superficial self-harm behaviour, turbulent relationships, and emotional dysregulation. She has a previous diagnosis of Borderline Personality Disorder, and previously completed DBT. She is searching for a new psychotherapist, and asks your opinion on what would best serve her needs. Which of the following factors is most predictive of successful therapy?
 - a) The experience and expertise of the therapist
 - b) The type of therapy, reinforcing DBT principles
 - c) The intensity and frequency of therapy
 - d) The therapeutic alliance

Answers:
1. b)
2. c)
3. d)

Psychotic Disorders

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Definition

As per the DSM-5, schizophrenia spectrum and other psychotic disorders are defined by abnormalities in one of five domains: **delusions, hallucinations, disorganized thinking, grossly disorganized or abnormal motor behavior, and negative symptoms.**

- Positive symptoms:
 - Delusions are fixed beliefs that are not flexible to change despite contradictory evidence.
 - Hallucinations are perception-like experiences that occur in the absence of an external stimulus.
 - Disorganized thinking is most often inferred from an individual's speech, which must be disorganized enough to impair effective communication.
 - Grossly disorganized or abnormal motor behaviour can take a number of forms including catatonia, repetitive movements, staring, and echoing of speech.
- Negative symptoms:
 - Anhedonia, avolition (decrease in self-motivated activities), apathy, affective flattening, and alogia (decrease in speech).

NOTE

Delusions, hallucinations, disorganized thinking, and disorganized/abnormal motor behaviour are grouped together as **positive symptoms.**

Hallucinations and delusions are further grouped as **psychotic symptoms.**

Disorganized thinking and disorganized/abnormal motor behaviour are further grouped as **disorganized symptoms.**

NOTE

Cognitive symptoms are among core features of schizophrenia but are NOT required for diagnosis.

Types of psychotic disorders

- Schizophrenia
- Schizoaffective disorder
- Delusional disorder
- Brief psychotic disorder
- Schizophreniform disorder

**Note: This chapter will focus on schizophrenia. A brief section on the other psychotic disorders is presented at the end of the chapter. Schizotypal disorder is described under both the Schizophrenia Spectrum and Other Psychotic Disorders and Personality Disorders chapters of the DSM-5. It will be described in the [Personality Disorders](#) chapter of this handbook.*

Schizophrenia

DSM-5 Criteria for Schizophrenia

- A. **Two (or more)** of the following, each present for a significant portion of time during a **1-month period** (or less if successfully treated). **At least one** of these must be (1), (2), or (3):
1. Delusions
 2. Hallucinations
 3. Disorganized speech (e.g., frequent derailment or incoherence)
 4. Grossly disorganized or catatonic behavior
 5. Negative symptoms (i.e., diminished emotional expression or avolition)
- B. For a significant portion of the time since the onset of the disturbance, **level of functioning** in one or more major areas, such as work, interpersonal relations, or self-care, is **markedly below the level achieved prior to the onset** (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).
- C. **Continuous signs** of the disturbance persist for **at least 6 months**. This 6-month period must include **at least 1 month** of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).
- D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been **ruled out** because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.
- E. The disturbance is **not attributable** to the physiological effects of a substance (e.g. a drug of abuse, a medication) or another medical condition.
- F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made **only if prominent delusions or hallucinations**, in addition to the other required symptoms of schizophrenia, are also present for **at least 1 month** (or less if successfully treated).

NOTE

Types of delusions

- **Bizarre:** Involving a phenomenon that the individual's culture would regard as impossible.
- **Delusional jealousy:** A delusion that the individual's sexual partner is being unfaithful.
- **Erotomaniac:** A delusion that another person is in love with the individual.
- **Grandiose:** A delusion of inflated worth, knowledge, identity, or power.
- **Somatic:** A delusion focused on the appearance or function of the individual's body.
- **Persecutory:** A delusion that the individual or someone close to them is being attacked, persecuted, harassed, cheated, or conspired against.
- **Thought broadcasting:** A delusion that the individual's thoughts are being broadcast out loud.
- **Thought insertion:** A delusion that the individual's thoughts are not their own and are instead inserted into their mind.

Specifiers:

- First episode, multiple episodes, or continuous
- Currently in acute episode, partial remission, or full remission
- With catatonia
- Current severity (optional)

Epidemiology

- ~1% prevalence in population
- Risk factors:
 - Birthdate in late winter or early spring
 - Being raised in an urban environment
 - Maternal infection during pregnancy and birth complications with hypoxia
 - Advanced paternal age
 - Adverse childhood experiences
 - Substance use

Course and prognosis

- Peak age of onset is 10-25 years for males and 25-35 years for females. Women have a bimodal age distribution with a second peak in middle age.
- “Late onset” (onset >45 years of age): 10% of cases, more women.
- “Very late onset” (onset >60 years of age): Rare, more women. Little negative or cognitive symptoms.
- Onset typically occurs as a gradual development of signs and symptoms.
- Cognitive impairment is common and may persist when other symptoms are in remission.
- Hallucinations and delusions tend to diminish with age. Negative symptoms tend to be the most persistent and closely linked to prognosis.
- Males tend to have lower educational achievement, more significant negative symptoms and cognitive impairment, and generally worse outcomes.
- The pattern of illness during the first 5 years after the diagnosis generally indicates the patient’s course.

- Failure to return to baseline functioning after each relapse is the major distinction between schizophrenia and the mood disorders.
- Prognosis:
 - ~20-30% lead somewhat normal lives.
 - ~20-30% of patients continue to experience moderate symptoms.
 - ~40-60% remain significantly impaired by the disorder.
- Good prognosis: late onset, obvious precipitating factors, acute onset, good premorbid functioning, mood disorder symptoms, married, family history of mood disorders, good support systems, positive symptoms.
- ~5-6% of individuals with schizophrenia die by suicide, 20% attempt suicide at least once.
 - Suicide risk is especially high for younger males with comorbid substance use.
 - Risk factors for suicide include depressive symptoms, feelings of hopelessness, unemployment, and the time period after a psychotic episode or hospital discharge, high premorbid achievement, awareness of loss of function.

Differential diagnosis

- Other primary psychotic disorders (described in table at end of chapter)
- Substance/medication-induced psychotic disorder
- Major depressive or bipolar disorder with psychotic or catatonic features
 - Diagnosed if psychotic symptoms only occur during a major depressive or manic episode
- Dementia
- Personality disorders, dissociative disorders
- Autism spectrum disorders
- Delirium
- Mental disorder due to another medical condition
- Obsessive-Compulsive disorder

FYI

The impact of culture on diagnosis

- Cultural and socioeconomic factors are important in diagnosis as ideas that may appear delusional in one culture may not be in another culture.
- Visual or auditory hallucinations with religious content are normal part of religious experience in some cultures.
- Assessing disorganized speech may be difficult due to cultural differences in narrative styles.
- Norms in emotional expression, eye contact, and body language differ across cultures, and should be taken into account when assessing affect.

Etiology

Schizophrenia is a disorder characterized by multiple factors:

- Genetics
 - Concordance of 47% in monozygotic twins, 12% in dizygotic.
 - Probability of developing schizophrenia is 12% if one parent has schizophrenia, 40% if both do.
- Neurobiology
 - The Dopamine Hypothesis suggests that dopamine (DA) plays a significant role in the symptoms of schizophrenia.

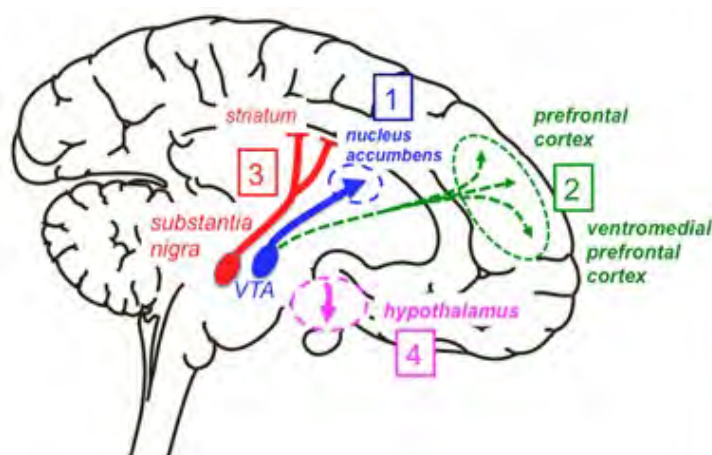


Figure 1. Diagram illustrating the four key dopaminergic pathways in the brain.

From Rogers T's lecture notes on Psychosis.

- Hyperactivity of dopamine in the **mesolimbic pathway** causes positive and disorganized symptoms (delusions, hallucinations, disorganized thinking, disorganized/abnormal behaviour)
 - Antipsychotics work to antagonize D2 receptors here to reduce positive symptoms
- Hypoactivity of dopamine in the **mesocortical pathway** causes negative and cognitive symptoms
 - As antipsychotics antagonize D2 receptors, these symptoms can be difficult to treat pharmacologically
- Hypoactivity of dopamine in the **nigrostriatal pathway** causes extrapyramidal symptoms (EPS)
 - EPS can be induced by antipsychotics
 - As second-generation antipsychotics have lower D2 receptor activity than first-generation antipsychotics, they cause EPS at lower rates
- Hypoactivity of dopamine in the **tuberoinfundibular pathway** causes hyperprolactinemia
 - This can be exacerbated by antipsychotics

- Acetylcholine and glutamate are also thought to be implicated.
 - Acetylcholine:
 - Studies have suggested that patients with schizophrenia have altered brain muscarinic activity.
 - There are high rates of smoking among patients with schizophrenia. Many report that they smoke to reduce negative symptoms and counteract medication side effects.

- Glutamate:
 - Glutamate is an excitatory neurotransmitter that is abundant in the brain and mediated by NMDA-receptors.
 - The cerebrospinal fluid of patients with schizophrenia has been noted to have decreased glutamate levels.
 - Patients who use NMDA-receptor antagonists such as ketamine often display psychotic symptoms.
- Neurodevelopmental influences such as poor maternal nutrition, viral illness in second trimester, and obstetrical complications are associated with higher rates of schizophrenia.

Assessment

**As per the CPA Schizophrenia Guidelines, 2017.*

1. Assessment & care planning

- Full psychiatric history.

2. Assessment of first episode

- 2 weeks appropriate standard wait time for a scheduled non-urgent first episode psychosis referral.

3. Neuropsychological testing

- Neuropsychological testing for patients with a first episode of psychosis and patients with poor response to treatment.
- Neurocognitive testing is a robust predictor of overall level of functioning.
- MATRICS Consensus Cognitive Battery (MCCB) is approved by FDA.
 - MCCB evaluates key cognitive domains relevant to schizophrenia.

4. Brain imaging

- Indications for imaging:
 - Symptoms suggestive of brain pathology: headache, nausea/vomiting, seizure-like activity, later age of onset.
 - Symptoms of autoimmune encephalitis.

5. Genetic testing

- Patients with schizophrenia have an increased genome wide burden of copy number variations (CNV).
- 22q11.2 deletion is a CNV on a long arm of chromosome 22.
- Up to 25% of adults with a deletion have schizophrenia.
- 22q11.2 has a prevalence of 1-2% in patients with schizophrenia.

6. Ongoing assessment of positive and negative symptoms

- Brief Psychiatric Rating Scale (BPRS), Positive and Negative Symptom Scale (PANSS).

7. Assessment of suicide risk

- Lifetime risk of suicide in schizophrenia is 25%.
- Robust risk factors: previous depressive disorder, previous suicide attempt, drug misuse, motor restlessness/agitation, fear of mental disintegration, poor adherence to treatment, and recent loss.
- The Suicide Risk Assessment Guide, The Columbia Suicide Severity rating scale.

8. Assessment of aggression risk

- More detailed assessment when: current aggressive psychotic ideas, impulsivity/anger issues, access to firearms, patients with aggression toward them in the past or present.
- Schizophrenia is associated with violence but most of the risk is associated with comorbid substance use disorder.
- Treatment with antipsychotics decreases the risk.
- Rate of violence at onset is more common in less developed countries.
- Despite high rate of verbal aggression, physical violence is uncommon in first episode psychosis.

9. Substance use

- Urine toxicology need NOT to be carried routinely.

10. Involvement of patient in treatment decision making

Comorbidities

- High rate of comorbidity with substance-related disorders.
 - More than 80% of individuals with schizophrenia smoke, with a 50% lifetime prevalence of other substance use.
- Comorbidity with anxiety disorders, particularly obsessive-compulsive disorder and panic disorder are more common in individuals with schizophrenia.
- Life expectancy in individuals with schizophrenia is reduced due to comorbid medical conditions.
 - Weight gain, diabetes, metabolic syndrome, cardiovascular disease, and pulmonary disease are more common.

Psychosocial management

Family intervention

- 10 sessions over 3 months is the minimal effective dose.
- Should include: communication skills, problem solving, and psychoeducation.
- Strong evidence for reduction of symptom severity and likelihood of hospitalization.
- Some evidence for beneficial effects on functioning, knowledge of disorder, and distress.

Supported Employment Program

- Most effective method in obtaining competitive employment or any employment, but long term benefits are unknown.

Cognitive Behavioural Therapy

- CBT should be offered to all with inadequate response to treatment.
- CBT can be started in acute phase or recovery.
- Minimum of 16 sessions.
- Reduction of symptom severity, hospitalization, and relapse; also beneficial for depression.
- Evidence on comparative efficacy of group vs. individual therapy is unclear.

Cognitive remediation

- May be considered for patients with persisting problems with cognition

Social skills training

- Should be available for those having difficulty/stress related to social interaction.
- Some evidence for effects on social functioning and negative symptoms.

Life skills training

- This can aid patients in their daily functioning.

Patient education

- Psychoeducation helps patients to understand their illness.

Comprehensive Community Treatment

The definition of “**recovery**”:

- Subjective approach: a way of living a satisfying, hopeful, and contributing life. Emphasizes the role of the individual as central.
- Objective/functional approach: combination of symptom remission and vocational functioning, independent living, and peer relationships; has a role on clinical research and outcome measurement.

Community Mental Health Teams

- **CMHA case management**
- Assertive Community Treatment Team (ACTT)
 - Mobile mental health teams that aid patients in the community with an individualized approach to help with medication adherence and social supports among other aids.
- Housing
 - Some housing options such as group homes provide peer support as well as staff supervision.

MNEMONIC

The **5 keys for recovery** with comprehensive treatment:

"CHIME"

Connectedness
Hope
Intity
Meaning
Empowerment

Pharmacological management

- Antipsychotics are the cornerstone of schizophrenia treatment.
- **First generation antipsychotics** exert their actions through blocking D2 receptors.
- **Second generation (atypical) antipsychotics** additionally block 5HT_{2a} receptors.
- Atypical antipsychotics have the same treatment response regarding positive symptoms as first generation antipsychotics. They do however have demonstrated superiority in treating negative symptoms and cognitive impairment, while having lower risk of extrapyramidal symptoms.
- The choice of antipsychotic should be based on:
 - Previous response to antipsychotics.
 - Side effect profile.
 - Medical history.
 - Concerns regarding compliance (for which long-acting injectable may be preferred).

- Response and/or treatment resistance.
- Starting with an atypical antipsychotic is recommended.
- If a patient has failed two adequate trials of antipsychotics, clozapine is recommended.
 - It can also be used for patients with persistent suicidality or persistent violence or aggression.
- “Adequate trial”: initial titration phase over several weeks, followed by **6 weeks** on adequate therapeutic dose (**midpoint or more** of therapeutic range).
- Treatment duration:
 - At least 18 months following first episode.
 - For multiple episodes: following resolution of positive symptoms, maintenance at least 2-5 years.

IMPORTANT

Several years of stabilization does NOT confer immunity to relapse!

	Haloperidol	Chlorpromazine
Dose range	1-40 mg/day Emergency use: 10mg IM q4-6h with lorazepam and cogentin prn. “Start low, go slow.”	25-75 mg BID-TID, up to 200-800 mg/d 25-50 mg IM q4-6h prn

Table 1. First generation antipsychotics (oral unless otherwise indicated).

	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Aripiprazole	Paliperidone
Starting dose	0.5-1 mg/day	5-10 mg/day	50 mg BID (increase by 25-50 BID each day)	40-80mg BID with 500 calories	10-15 mg/day	3-6mg/day
Target dose	2-8 mg/day	10-20 mg/day	600-800 mg/day	40-200 mg/day	15-30 mg/day	6-12mg/day

Table 2. Second generation antipsychotics (oral).

	Risperidone Consta	Paliperidone palmitate (Sustenna)	Paliperidone palmitate (Trinza)	Olanzapine
Dose	25-75mg q2weeks	75-150mg q4weeks	175-525mg q12weeks	10mg, can be repeated in 2 hours. Max 3 doses in 24 hours (short-acting, only used as PRN).

Table 3. Second generation antipsychotics (intramuscular).

Extrapyramidal Symptoms (EPS)

Extrapyramidal symptoms are motor side-effects of antipsychotics.

Duration of Antipsychotic Treatment	EPS	Treatment
Minutes to hours	Acute dystonic reaction - torticollis, laryngospasm, oculogyric crisis.	Benztropine 2mg or other anticholinergic PO/IM
Days	Pseudoparkinsonism - bradykinesia, rigidity, mask-like facies, cogwheel rigidity, perioral tremor.	Benztropine 2mg, Dose reduction, or switch to an atypical with less potential for EPS
Days to weeks	Akathisia - feeling of restlessness, inability to stay still.	Beta blocker - propranolol 30-90mg Benzodiazepine
Long-term	Tardive dyskinesia - choreoathetoid movements, most common around mouth and face. Absent in sleep and exacerbated by stress. Monitor with abnormal involuntary movement scale (AIMS). 5% risk/year with first generation antipsychotics due to long-term D2 blockade.	Switch to quetiapine, clozapine, or olanzapine. Some evidence for electroconvulsive therapy, botox, vitamin B6. Often irreversible.

Table 4. Types of extrapyramidal symptoms and associated treatments.

Common Medication Side Effects

General:

- Reduction of seizure threshold
- QTc prolongation
- Endocrine and sexual side effects
 - Less with quetiapine and clozapine

Low potency typical antipsychotics (e.g. chlorpromazine):

- Less EPS, more anticholinergic side effects (see sidebar)

High potency typical antipsychotics (e.g. haloperidol):

- More EPS, less anticholinergic side effects

NOTE

Anticholinergic side effects

- Sedation
- Postural hypotension
- Elevated heart rate
- Constipation
- Dry mouth
- Cognitive dulling

Atypical antipsychotics:

- Weight gain
 - Significant with olanzapine and clozapine.
- Dyslipidemia
 - Ziprasidone is weight and lipid neutral.
- Metabolic syndrome
- Type 2 diabetes

Clozapine:

- 0.5-1% risk of agranulocytosis, greatest in first 6 months.
 - Heart rate, blood pressure, and temperature must be monitored.
 - White blood cell count must be taken weekly for 6 months, then biweekly for 6 months, and then monthly.
- Myocarditis, cardiomyopathy
- Venous thromboembolism, pulmonary embolism, sudden death
- Risk of seizure is higher than other antipsychotics.

Physical Health and Drug Safety

- Antipsychotic polypharmacy: average prevalence of 20%.
- ~80% of second antipsychotic was discontinued without issue.
- Usual screening:
 - Smoking, BP, HbA1c/glucose, lipids: baseline, 3-months, and annually (at 1 month only if clinically indicated).
 - BMI/weight/waist circumference, EPS: baseline, 1-month, 3-months, annually.
 - Prolactin as clinically indicated.
 - Medical history: baseline and annually.
- First episode patients have significant metabolic abnormalities early in the illness.
- Schizophrenia is an independent risk factor for DM.
- Metformin should be considered for patients with weight gain on antipsychotics (Grade B recommendation).
- Highest weight gain with olanzapine, clozapine, chlorpromazine.

EVIDENCE-BASED PRACTICE

Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study:

- 88% with dyslipidemia, 62% with HTN, 38% with DM received no treatment.
- Rate of antipsychotic discontinuation due to weight gain: 9.2% for olanzapine, 3.6% for seroquel.

EVIDENCE-BASED PRACTICE

A 2016 review in the US revealed that 70% of patients taking antipsychotics remain unscreened and untreated.

Neuroleptic Malignant Syndrome (NMS)

- Neuroleptic malignant syndrome is the most severe complication of antipsychotic use.
- NMS will typically develop within hours to days of exposure to a causative drug.
 - Most will exhibit symptoms within 2 weeks.
- It is characterized by **mental status change, muscle rigidity, fever, and autonomic dysfunction**.
 - Typically muscle rigidity will be followed by fever and mental status change including drowsiness, agitation, confusion, severe delirium, or coma.
 - Autonomic instability due to NMS includes labile blood pressure, tachypnea, tachycardia, sialorrhea, diaphoresis, flushing, pallor, and incontinence.
- Laboratory findings seen in NMS include elevated creatinine phosphokinase due to rhabdomyolysis, and leukocytosis. Metabolic acidosis and iron deficiency are also common.
 - These are not present in all cases and are also not specific for NMS.
 - Rhabdomyolysis can be severe enough to cause renal failure.
- The pathophysiology is believed to be due to a sudden reduction in central dopaminergic activity due to D2 receptor blockade in the nigrostriatal, hypothalamic, and mesolimbic/cortical pathways.
 - It is also suggested that sympathoadrenal hyperactivity may play a role.
- The main risk factors for developing NMS are the initiation or increase in dose of an antipsychotic/neuroleptic medication.
 - High-dose, high-potency, and long-acting forms of these medications are also risk factors.
 - Other risk factors include dehydration, physical exertion, exposure to heat, malnutrition, trauma, alcohol, psychoactive substances, and the presence of a structural or functional brain disorder.
- As NMS is a neurologic emergency, prompt hospitalization and treatment is important.
 - There is no evidence-based treatment approach, but general guidelines have been developed.
 - The first step in treatment is **stopping the presumed causative agent**.
 - If NMS occurs due to withdrawal of a dopaminergic medication, then this medication should be re-started as quickly as possible.
 - Supportive treatment is then initiated:
 - Aggressive hydration is often required, and cooling blankets or ice packs can be used to treat hyperthermia.
 - Metabolic abnormalities if present should be corrected.
 - In severe cases, empiric pharmacologic therapy is typically attempted:
 - Bromocriptine mesylate (a dopamine agonist) can be used to reverse the hypodopaminergic state.
 - Dantrolene sodium is a muscle relaxant which inhibits calcium release from the sarcoplasmic reticulum.
- If recognized and treated early, NMS is typically not fatal with most patients recovering completely within 14 days. Resolution may take longer if diagnosis and treatment are delayed.
- Current mortality rates are around 10%, with arrhythmias, disseminated intravascular coagulation, or cardiovascular, respiratory, or renal failure being the primary causes.

Schizophrenia Spectrum and Other Psychotic Disorders

Schizophreniform disorder

DSM-5 Criteria for Schizophreniform Disorder

- A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):
1. Delusions.
 2. Hallucinations.
 3. Disorganized speech (e.g., frequent derailment or incoherence).
 4. Grossly disorganized or catatonic behavior.
 5. Negative symptoms (i.e., diminished emotional expression or avolition).
- B. An episode of the disorder lasts at least 1 month but less than 6 months. When the diagnosis must be made without waiting for recovery, it should be qualified as “provisional.”
- C. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.
- D. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

Specifiers:

- With or without good prognostic features
- With catatonia
- Current severity (optional)

Schizoaffective disorder

DSM-5 Criteria for Schizoaffective Disorder

- A. An uninterrupted period of illness during which there is a major mood episode (major depressive or manic) concurrent with Criterion A of schizophrenia.
***Note: The major depressive episode must include Criterion A1: Depressed mood.**
- B. Delusions or hallucinations for 2 or more weeks in the absence of a major mood episode (depressive or manic) during the lifetime duration of the illness.
- C. Symptoms that meet criteria for a major mood episode are present for the majority of the total duration of the active and residual portions of the illness.
- D. The disturbance is not attributable to the effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

Specifiers:

- Bipolar type
- Depressive type
- First episode, multiple episodes, or continuous
- Currently in acute episode, partial remission, or full remission
- With catatonia
- Current severity (optional)

Delusional disorder

DSM-5 Criteria for Delusional Disorder

- A. The presence of one (or more) delusions with a duration of 1 month or longer.
- B. Criterion A for schizophrenia has never been met.
***Note: Hallucinations, if present, are not prominent and are related to the delusional theme** (e.g., the sensation of being infested with insects associated with delusions of infestation).
- C. Apart from the impact of the delusion(s) or its ramifications, functioning is not markedly impaired, and behavior is not obviously bizarre or odd.
- D. If manic or major depressive episodes have occurred, these have been brief relative to the duration of the delusional periods.
- E. The disturbance is not attributable to the physiological effects of a substance or an other medical condition and is not better explained by another mental disorder, such as body dysmorphic disorder or obsessive-compulsive disorder.

Specifiers:

- Type of delusion
- With bizarre content
- First episode, multiple episodes, or continuous
- Currently in acute episode, partial remission, or full remission
- With catatonia
- Current severity (optional)

Brief psychotic disorder

DSM-5 Criteria for Brief Psychotic Disorder

- A. Presence of one (or more) of the following symptoms. At least one of these must be (1), (2), or (3):
1. Delusions.
 2. Hallucinations.
 3. Disorganized speech (e.g., frequent derailment or incoherence).
 4. Grossly disorganized or catatonic behavior.
- *Note: Do not include a symptom if it is a culturally sanctioned response.**
- B. Duration of an episode of the disturbance is at least 1 day but less than 1 month, with eventual full return to premorbid level of functioning.
- C. The disturbance is not better explained by major depressive or bipolar disorder with psychotic features or another psychotic disorder such as schizophrenia or catatonia, and is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

Specifiers:

- With or without marked stressors
- With postpartum onset
- With catatonia
- Current severity (optional)

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Review Questions

1. Which of the following is a feature of catatonia?
 - a) Apraxia
 - b) Positivism
 - c) Posturing
 - d) Narcolepsy
 - e) Tremor

2. A 34-year-old man with a diagnosis of schizophrenia was recently started on quetiapine (Quetiapine XR) to manage his hallucinations and delusions. Blockade of which dopamine pathway is thought to be responsible in reducing positive symptoms?
 - a) Nigrostriatal
 - b) Mesolimbic
 - c) Mesocortical
 - d) Tuberoinfundibular
 - e) Amygdala

3. You ask a 24-year-old man with a history of schizophrenia why he came to the hospital. He replies, "The cat is up the tree. Too many people know the code. I am Jesus Christ." This is an example of:
 - a) Loosening of associations
 - b) Circumstantiality
 - c) Tangentiality
 - d) Word salad
 - e) Overinclusiveness

Answers:
1. c)
2. b)
3. a)

Depressive Disorders

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Introduction

- Depressive disorders are characterized by sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly impair capacity to function
- DSM-5 Classification:
 - Disruptive mood dysregulation disorder (DMDD) – see [Pediatric Mood Disorders chapter](#)
 - Major depressive disorder (MDD)
 - Persistent depressive disorder (PDD)
 - Premenstrual dysphoric disorder (PMDD)
 - Other: substance/medication-induced, due to another medical condition, other specified depressive disorder, and unspecified depressive disorder

Diagnostic Criteria

Major Depressive Disorder (MDD)

DSM-5 Criteria for Major Depressive Disorder

- A. ≥ 5 (must include #1 or #2) of the following 9 symptoms for ≥ 2 weeks, nearly everyday:
1. Depressed mood for most of the day, either by subjective report or observation by others
 2. Markedly diminished interest or pleasure in all or almost all activities, either by subjective report or observation by others
 3. Significant unintentional weight loss or weight gain (e.g., $\Delta 5\%$ of body weight in a month), or increased/decreased appetite
 4. Insomnia or hypersomnia
 5. Psychomotor agitation/retardation observable by others
 6. Fatigue or loss of energy

MNEMONIC

Criterion A for MDD

"M-SIG-E-CAPS"

Mood ▼
Sleep ▼/▲
Interest ▼
Guilt ▲
Energy ▼
Concentration ▼
Appetite ▼/▲
Psychomotor ▼/▲
Suicidal ideation ▲

- 7. Feelings of worthlessness or excessive/inappropriate guilt (which may be delusional)
 - 8. Diminished concentration or indecisiveness, either by subjective report or observation by others
 - 9. Recurrent thoughts of death, recurrent suicidal ideation (SI) without a specific plan, or a suicide attempt or specific plan for suicide
- B. Clinically significant distress or impairment in important areas of functioning.
- C. Not attributable to the effects of a substance or to another medical condition.
- D. Not better explained by a schizophrenia spectrum or other psychotic disorder.
- E. No manic or hypomanic episodes, unless the episodes are attributable to substance use or another medical condition.

Note: Criteria A to C represent a **major depressive episode (MDE).*

Specifiers:

The diagnosis should be recorded with the specifiers in the following order:

- Major depressive disorder, (1) single or recurrent episode, (2) severity/psychotic/remission specifiers, and (3) as many of the other specifiers as pertains to current episode - e.g. “Major depressive disorder, recurrent, severe, with anxious distress.”

(1) Episode	(2) Severity/course†		(3) Other Specifiers†
• Single • Recurrent*	• Mild • Moderate • Severe • With psychotic features**	Only use if full criteria for MDE are currently met	• With anxious distress • With mixed features • With melancholic features • With atypical features • With mood-congruent psychotic features • With mood-incongruent psychotic features • With catatonia • With peripartum onset • With seasonal pattern
	• In partial remission • In full remission	Only use if full criteria for MDE are currently met	
	• Unspecified		

* A recurrent episode requires an interval of ≥2 consecutive months between separate episodes during which criteria for MDE are not met.

** If psychotic features are present, this specifier should be used irrespective of episode severity.

† See Appendix A for definitions of severity/course and other specifiers.

NOTE

Responses to significant loss (e.g. bereavement, financial ruin, losses from natural disaster, a serious medical illness or disability) may resemble MDE.

Although these symptoms may be considered appropriate to the loss, **presence of a MDE in addition to the normal response** should also be carefully considered, taking into account individual history and cultural norms for expression of grief.

Persistent Depressive Disorder

DSM-5 Criteria for Persistent Depressive Disorder

- A. Depressed mood for most of the day, for more days than not, for ≥ 2 years (either by subjective report or observed by others).
 - In children or adolescents, mood may be irritable and duration ≥ 1 year.
- B. During the period described in Criterion A, ≥ 2 of the following 6 symptoms are present:
 1. Increased/decreased appetite
 2. Insomnia or hypersomnia
 3. Low energy or fatigue
 4. Low self esteem
 5. Diminished concentration or indecisiveness
 6. Hopelessness
- C. No more than 2 months at a time spent free from symptoms in Criteria A and B.
- D. Criteria for MDD may be continuously present for 2 years.
- E. No manic or hypomanic episodes, and never met criteria for cyclothymic disorder.
- F. Not better explained by a schizophrenia spectrum or other psychotic disorder.
- G. Not attributable to the effects of a substance or to another medical condition.
- H. Clinically significant distress or impairment in important areas of functioning.

MNEMONIC

Criterion B for persistent depressive disorder

"HE'S 2 SAD"

Hopelessness

Energy ▼

Self-esteem ▼

2 or more years (in adults)

Sleep ▼ / ▲

Appetite ▼ / ▲

Decision-making ▼

Specifiers:

	Specifier	Definition
Onset	Early onset	<21 years old
	Late onset	≥21 years old
Presence of MDE	With pure dysthymic syndrome	Full MDE criteria not met in at least last 2 years
	With persistent MDE	Full MDE criteria met throughout last 2 years
	With intermittent MDE, with current episode	Full MDE criteria currently met, but there have been periods of ≥8 weeks in at least the last 2 yrs where full MDE criteria were not met
	With intermittent MDE, without current episode	Full MDE criteria not currently met, but ≥1 MDE in the last 2 years
Current severity	Mild Moderate Severe	See Appendix A
Course	In partial remission In full remission	
Other	With anxious distress With mixed features With melancholic features With atypical features With mood-congruent psychotic features With mood-incongruent psychotic features With peripartum onset	

Premenstrual Dysphoric Disorder (PMDD)

DSM-5 Criteria for Premenstrual Dysphoric Disorder

- A. In the majority of menstrual cycles, ≥ 5 symptoms that are present in the final week before the onset of menses, start to improve within a few days after the onset of menses, and become minimal/absent in the week postmenses.
- B. ≥ 1 of the following symptoms:
 - 1. Marked affective lability or increased sensitivity to rejection
 - 2. Marked irritability/anger or increased interpersonal conflicts
 - 3. Marked depressed mood, hopelessness, or self-deprecating thoughts
 - 4. Marked anxiety, tension and/or feeling on edge
- C. ≥ 1 of the following symptoms in addition to Criterion B to reach a total ≥ 5 :
 - 1. Decreased interest in usual activities
 - 2. Subjective difficulty in concentration
 - 3. Low energy or easy fatigability
 - 4. Marked change in appetite or specific food cravings
 - 5. Hypersomnia or insomnia
 - 6. Sense of being overwhelmed/out of control
 - 7. Physical symptoms (e.g. breast tenderness/swelling, joint/muscle pain, bloating, weight gain)
- D. Clinically significant distress or interference with important areas of functioning.
- E. Not merely an exacerbation of symptoms of another mood/personality disorder, though they may be concurrent.
- F. Criterion A should be confirmed by prospective daily ratings during ≥ 2 symptomatic cycles, though diagnosis may be made provisionally before this confirmation.
- G. Not attributable to the effects of a substance or to another medical condition.

**Note: Criteria A to C must have been met for most menstrual cycles over the past year.*

Other Depressive Disorders

Substance/medication-induced depressive disorder	• Evidence from history, physical examination, or laboratory findings of temporal correlation of symptoms with substance intoxication/withdrawal or exposure to medication. • Substance/medication in question is capable of producing aforementioned symptoms.
Depressive disorder due to another medical condition	• Evidence from history, physical examination, or laboratory findings that the mood disturbance is a direct pathophysiological consequence of another medical condition.
Other specified depressive disorder	• Applicable when clinician chooses to communicate a specific reason that presentation does not meet criteria for other depressive disorders (e.g. recurrent brief depression, short-duration depressive episode, depressive episode with insufficient symptoms).
Unspecified depressive disorder	• Applicable when presentation does not meet full criteria for any other depressive disorder (e.g. insufficient information to make diagnosis).

Table 1. Summary of other depressive disorders.

Epidemiology

- Depressive disorders represent the second leading cause of disability worldwide
 - In Ontario, the disease burden (measured in health-adjusted life years) with MDD was greater than that of breast, lung, colorectal and prostate cancers combined
- In the Canadian general population, annual prevalence of MDE is 4.7% and lifetime prevalence 11.3%
 - Excluding bipolar disorders, annual and lifetime prevalence of MDD are 3.9% and 9.9%, respectively
 - Annual prevalence of MDD is greater in women (4.9%) than men (2.8%)
 - Prevalence has an inverse relationship with age
- Despite increases in mental health services in recent years, annual prevalence of MDE in Canada remains unchanged (4.8% in 2002 vs. 4.7% in 2012)
 - Similar trends are seen in the US and Australia

Screening

- Value of screening remains controversial due to limited evidence on effectiveness
- CANMAT guidelines recommend screening in primary and secondary care settings in individuals with risk factors (see below table) when resources and services for subsequent diagnostic assessment and management are available
- Quick 2-question screen:
 - “In the last month, have you been bothered by little interest or pleasure in doing things?”
 - “In the last month, have you been feeling down, depressed, or hopeless?”
 - ‘Yes’ to either question requires a more detailed assessment.

Clinical factors	Symptom factors
History of depression Family history of depression Psychosocial adversity High use of the medical system Chronic medical conditions (especially cardiovascular disease, diabetes, neurological disorders) Other psychiatric conditions Times of hormonal challenge (e.g. peripartum)	Unexplained physical symptoms Chronic pain Fatigue Insomnia Anxiety Substance abuse

Table 2. Risk factors for depression screening.
Adapted from CANMAT 2016 Clinical Guidelines for MDD.

Development and Prognosis

- MDD may develop at any age, however the likelihood of onset increases markedly with puberty
- The course of MDD can be highly variable
 - Population-based surveys have shown that ~50% MDEs are brief, resolving within 3 months
 - The presence of chronic depressive symptoms substantially increases the likelihood of underlying personality, anxiety, and substance use disorders, and decreases the likelihood that treatment will result in full symptom resolution
 - MDE in the setting of other major non-mood disorders (e.g. substance use, anxiety, borderline personality disorder) or chronic medical conditions (e.g. diabetes, morbid obesity, cardiovascular

disease) are more likely to be refractory to treatment

- PDD often has an early and insidious onset; the course, by definition, is chronic
 - Early onset (age <21 years) is associated with higher likelihood of comorbid personality disorders and substance use disorders
- In those with MDD, recovery typically begins within 3 months of onset for 40% of individuals and within 1 year for 80% of individuals
 - Favourable prognostic factors: recent onset
 - Poor prognostic factors: longer episode duration, psychotic features, prominent anxiety, personality disorders, and more severe symptoms
- Risk of recurrence diminishes over time as duration of remission increases
 - A US-based study (Hasin and Grant, 2015) showed that in individuals with MDE at baseline and subsequent episode remission, 35% experienced a recurrent MDE in the next 3 years
 - Risk factors for recurrence: preceding MDE was severe, young age, history of multiple MDEs, persistence of depressive symptoms (even mild) during remission
- MDD, especially with psychotic features, may transition into schizophrenia

IMPORTANT

A depressive episode may be the beginning of bipolar illness.

Risk factors include:

- Adolescent onset
- Psychotic features
- Family history of bipolar illness
- “With mixed features” specifier also increases risk for future manic/hypomanic episodes

Children	Adolescents	Adults	Elderly
• Somatic complaints • Anxiety • Agitation • Phobias • Hallucinations (especially <12 years old)	• Irritability • Mood lability • Social isolation • Restlessness • Truancy & school difficulty • Substance abuse • Increased suicidality • Antisocial behaviour • Promiscuity • Rejection hypersensitivity • Poor hygiene	• Somatic complaints (especially cardiovascular, GI, GU, low back pain, other orthopedic symptoms) • Low or depressed mood	• May not complain of depressed mood • Somatic complaints • Anxiety • Cognitive deficits • Pseudodementia • Psychosis

Table 3. Manifestations of depression across various age groups.

Adapted from Suntharalingam, 2020.

Risk Factors

Temperamental

- Neuroticism (negative affectivity) – for both development of MDD and poorer long-term outcomes
- Presence of anxiety disorders or conduct disorder also associated with poorer long-term outcomes
 - MDD and anxiety disorders are highly comorbid - an estimated 60% of individuals with one disorder also meet criteria for the other

Environmental

- Adverse childhood experiences, especially the presence of multiple types
- Parental loss or separation in childhood
- Psychosocial stressors (e.g. health, finances, academic, relationships)

Genetic and physiological

- First degree family member with MDD is associated with a 2- to 4-fold higher risk of developing MDD than general population
- Individuals with PDD are more likely (vs. those with MDD) to have a higher proportion of first degree relatives with PDD
- PDD maybe associated with changes in some brain regions (e.g. prefrontal cortex, anterior cingulate, amygdala, hippocampus) and polysomnographic abnormalities

Etiology

Biological

- Genetic: twin studies suggest a heritability of 40-50%
- Neurotransmitter (NT) dysfunction: insufficient synaptic amount/activity of serotonin (5HT), norepinephrine (NE), and dopamine (DA), with possible compensatory upregulation of postsynaptic receptors; changes in GABA and glutamate activity
- Neuroendocrine dysfunction: abnormal hypothalamic-pituitary-adrenal (HPA) axis activity, stress-induced changes in NT signal transduction cascade

- Neuroanatomy and neurophysiology: decreased hippocampal volume, larger ventricles; decreased REM latency and slow-wave sleep; increased REM length
- Immunology: increased pro-inflammatory cytokines (e.g. IL-6, TNF)

Symptoms	5HT	NE	DA
Psychomotor	√	√	√
Depressed mood	√	√	√
Sleep disturbances	√	√	√
Apathy/anhedonia		√	√
Fatigue		√	√
Weight/appetite	√		
Suicide	√		
Guilt/worthlessness	√		

Table 4. Neurotransmitters implicated in depressive symptoms.

Psychosocial

- Cognitive factors: distorted schemata, Beck’s cognitive triad (views about self, world, and future)
- Comorbid psychiatric diagnoses (e.g. anxiety, substance use, developmental disability, dementia, eating disorder)
- Life stressors (e.g. job loss, bereavement, childhood adversity) may precipitate

Differential Diagnosis

- Other medical disorders
 - CNS – e.g. Parkinson’s, dementia, multiple sclerosis (MS), neoplastic lesions
 - Endocrine – e.g., hyper- or hypothyroidism
 - Drug-related – e.g., CNS depressants, cocaine abuse
 - Infectious – e.g., mononucleosis
 - Other – anemia, sleep-related disorders
- MDD vs. PDD
- Substance/medication-induced
 - Substances: EtOH, cannabis, amphetamine, PCP, cocaine

- Medications: steroids, antihypertensives, oral contraceptives, Accutane, antiepileptics, benzodiazepines
- Bipolar disorder - depressive episode
- Psychotic disorders - schizoaffective disorder, schizophrenia negative symptoms
- Adjustment disorder
- Bereavement

Investigations

- CBC with differential, extended electrolytes, thyroid function, renal and liver function, vitamin B12, folate, vitamin D, cortisol level, glucose, iron studies, drug screen, medications review, ECG

Suicide Risk

- Assess risk at every clinical encounter
- History of previous suicide attempt is the strongest risk factor

Non-modifiable	Modifiable
• Older male • Past suicide attempt • History of self-harm behaviour • Being a sexual minority • Family history of suicide • History of legal problems	<u>Symptoms and life events</u> • Active suicidal ideation • Hopelessness • Psychotic symptoms • Anxiety • Impulsivity • Stressful life events (e.g. bankruptcy) and victimization <u>Comorbid conditions</u> • Substance use disorders (especially alcohol) • PTSD • Comorbid personality disorders (especially cluster B disorders) • Chronic painful medical conditions • Cancer

Table 5. Modifiable and non-modifiable risk factors of suicide.

Adapted from CANMAT 2016 Clinical Guidelines for MDD.

Management

Depression rating scales

- Using rating scales for measurement-based care of depression can improve outcomes such as symptom remission and adherence
- Routine monitoring of patient outcomes should also include evaluation of functional impairment (in various domains, e.g. occupational, social, educational) and quality of life
- Patient-rated questionnaires are highly correlated with clinician-rated scales but may be simpler to use and more efficient
- Use of measurement tools should supplement, not replace, clinical judgment

Outcome	Clinician-rated	Patient-rated
Symptoms	• Hamilton Depression Rating Scale (HAM-D, HAM-7) • Montgomery-Asberg Depression Rating Scale (MADRS) • Inventory for Depressive Symptomatology (IDS)	• Patient Health Questionnaire (PHQ-9) • Quick Inventory for Depressive Symptomatology, Self-Rated (QIDS-SR)
Functioning	• Multidimensional Scale of Independent Functioning (MSIF) • WHO Disability Assessment Scale (WHO-DAS) • Social and Occupational Functioning Assessment Scale (SOFAS)	• Sheehan Disability Scale (SDS) • WHO-DAS, self-rated • Lam Employment Absence and Productivity Scale (LEAPS)
Tolerability	• UKU Side Effect Rating Scale	• Frequency, Intensity and Burden of Side Effects Rating (FIBSER)
Quality of life	• Quality of Life Interview (QOLI)	• Quality of Life, Enjoyment and Satisfaction Questionnaire (QLESQ) • EuroQoL-5D (EQ-5D)

Table 6. Examples of validated outcome scales for depressive disorders.

Adapted from the CANMAT 2016 Guidelines.

Pharmacological therapy

Antidepressant therapy

- See [Table 7](#) for summary chart
- There are multiple classes of antidepressants with varying mechanisms of action:
 - Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), serotonin antagonist and reuptake inhibitors (SARIs), and tricyclic antidepressants (TCAs): block reuptake of monoamine NTs into the presynaptic neurons
 - Noradrenergic and specific serotonergic antidepressants (NaSSAs): block presynaptic α_2 adrenergic receptor (which mediate feedback inhibition of NE release) $\Rightarrow$ increased release of NE $\Rightarrow$ secondary increase of 5HT into synaptic cleft
 - Monoamine oxidase inhibitors (MAOIs) and reversible inhibitors of monoamine oxidase-A (RIMAs): inhibit monoamine oxidase $\Rightarrow$ reduced destruction of monoamine NTs

Antidepressant therapy response and duration

- See [Figure 1](#) for a summary flow chart on the approach to pharmacological treatment
- Early improvement (defined as a >20-30% reduction from baseline in a depression rating scale after 2-4 weeks) is correlated with response and remission at 6-12 weeks
 - If no improvement at 2-4 weeks: increase dose if tolerated, or switch drug if tolerability is an issue
- MDD treatment has two phases: acute phase (getting to symptomatic remission) and maintenance phase (preventing relapse and recurrence)
 - Maintain antidepressant treatment for 6-9 months after achieving symptomatic remission
 - Extend treatment to 2 yrs or more if there are risk factors for recurrence, which include:
 - Frequent, recurrent episodes
 - Severe episodes (psychosis, severe impairment, suicidality)
 - Chronic episodes
 - Presence of comorbid psychiatric or other medical conditions
 - Presence of residual symptoms
 - Difficult-to-treat episodes

CLINICAL PEARL

Factors to consider when selecting antidepressant agent(s)

Patient factors:

- Clinical features and symptom profile
- Comorbidities
- Response and side effects to previous trials of antidepressants
- Patient preference

Medication factors:

- Comparative efficacy
- Side effect profile
- Potential drug-drug interactions
- Lowest risk of drug-drug interactions: citalopram, escitalopram, venlafaxine, desvenlafaxine, mirtazapine
- Highest risk of drug-drug interactions: paroxetine, fluoxetine, fluvoxamine, sertraline, manerix
- Cost

Class	Drug	Starting dose (mg)	Daily dose range (mg)
First-line treatments			
SSRI (selective serotonin re-uptake inhibitor)	Escitalopram (Cipralex)	10	10-20
	Citalopram (Celexa)	20	20-40
	Fluoxetine (Prozac)	20	20-80
	Paroxetine (Paxil)	20	20-60
	Sertraline (Zoloft)	50	50-200
	Fluvoxamine (Luvox)	50	100-300
SNRI (serotonin norepinephrine reuptake inhibitor)	Venlafaxine (Effexor)	75	75-375
	Desvenlafaxine (Pristiq)	50	50-100
	Duloxetine (Cymbalta)	60	60-120
	Levomilnacipran (Fetzima) ¹	20	40-120
NDRI (norepinephrine and dopamine reuptake inhibitor)	Bupropion SR or XL (Wellbutrin)	150	150-300
NaSSA (noradrenergic and specific serotonergic antidepressant)	Mirtazapine (Remeron)	30	30-60
Serotonin modulator	Vortioxetine (Trintellix) ²	5-10	10-20
	Vilazodone (Viibryd) ³	10	20-40
Second-line treatments			
SARI (serotonin 2A reuptake inhibitor)	Trazodone (Desyrel)	150-200	150-300
TCA (tricyclic antidepressant)	Desipramine (Norpramin)	25	100-200
	Nortriptyline (Aventyl)	10-25	75-150
	Clomipramine (Anafranil)	25	100-200
	Imipramine (Tofranil)	25	50-150
	Amitriptyline (Elavil)	25	5-150
	Doxepin (Sinequan)	254	75-150
Antipsychotic	Quetiapine XR (Seroquel)	50	150-300
RIMA (reversible inhibitor of monoamine oxidase A)	Moclobemide (Manerix)	300	300-600
Third-line treatments			
MAOI (monoamine oxidase inhibitor)	Phenelzine (Nardil)	45	45-90
	Tranylcypromine (Parnate)	20	30-60

Table 7. Pharmacological agents used in the treatment of depressive disorders.

Adapted from CANMAT 2016 Clinical Guidelines for Antidepressant Therapy.

¹ Levomilnacipran: newly approved; greater selectivity for NE than 5HT

² Vortioxetine: newly approved; evidence for positive effects on neuropsychological performance in multiple cognitive domains in MDD patients

³ Vilazodone: newly approved; take with food to ensure adequate absorption and minimize GI effects

⁴ Doxepin starting dose for insomnia is 3-6 mg

***Note:** Common and important side effects of antidepressants are covered extensively in the [Psychopharmacology](#) chapter.

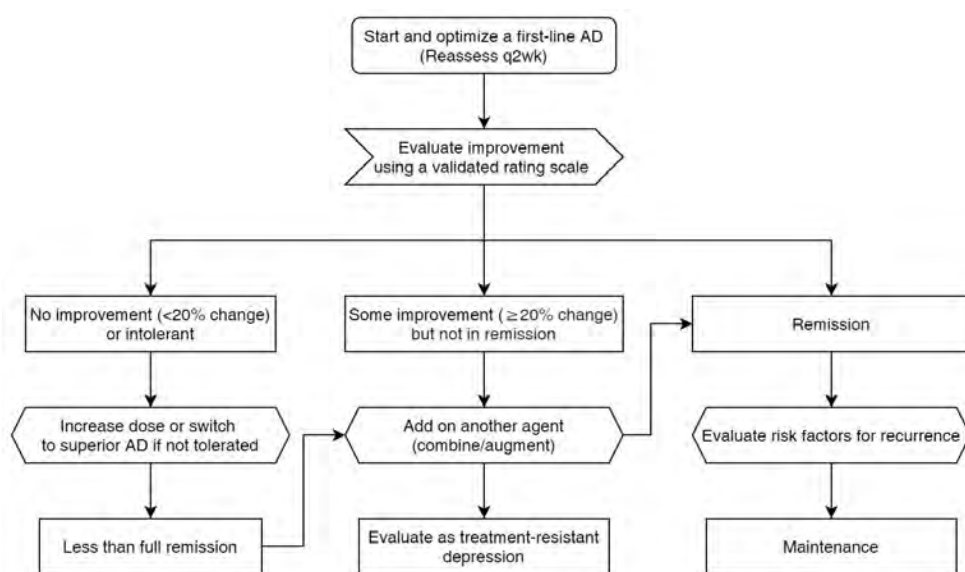


Figure 1. Approach to the pharmacological management of depressive disorders.

NOTE

Terminology used when describing response to antidepressants

Partial response = 25-50% decrease from baseline depression scale scores

Response = At least a 50% improvement in symptoms; may have residual symptoms

Remission = Minimal residual symptoms, subthreshold scores for scales (e.g., <5 in PHQ9)

Recovery = Remission of symptoms and improvement of functioning

First-line recommendations for switch strategies

- Escitalopram, sertraline, venlafaxine, mirtazapine, citalopram (from paroxetine)

Recommendations for adjunctive medications for non- or partial response

- First-line:
 - Aripiprazole 2-15 mg
 - Quetiapine 150-300 mg
 - Risperidone 1-3 mg
- Second-line:
 - Brexpiprazole 1-3 mg
 - Olanzapine 2.5-10 mg
 - Bupropion 150-300 mg
 - Lithium 600-1200 mg to therapeutic serum level
 - Mirtazapine 30-60 mg
 - Modafinil 100-400 mg
 - Triiodothyronine 25-50 mcg
- Third-line:
 - Other antidepressants
 - Other stimulants (e.g. methylphenidate, lisdexamfetamine)
 - TCAs
 - Ziprasidone 20-80 mg bid

Serotonin Syndrome

Characteristic features

- Neurological: tremor, myoclonus, rigidity, hypertonicity, hyperreflexia, ataxia
- Mental: restless, impaired consciousness, confusion, delirium
- Autonomic instability: fever, sweating, tachycardia, dyspnea, diarrhea

Diagnosis

- Various diagnostic criteria exist (e.g. Sternbach criteria, Hunter criteria)
- Hunter criteria (more sensitive and specific):
 1. Presence of serotonergic agent (recent addition, increased dose/overdose, interaction); AND
 2. Any 1 of:
 - Spontaneous clonus
 - Inducible clonus with agitation or diaphoresis
 - Ocular clonus with agitation or diaphoresis
 - Tremor and hyperreflexia
 - Hypertonia, hyperthermia (>38oC), and ocular/inducible clonus

	Serotonin syndrome	Neuroleptic malignant syndrome (NMS)
Associated medications	Serotonergic agents	Dopaminergic agents
Proposed mechanism	Excessive stimulation of central and peripheral 5HT receptors	Dopamine receptor antagonism, resulting in hypodopaminergic states in the striatum and hypothalamus
	Dose-dependent	Not dose-dependent - may occur after a single dose, a dose adjustment, or years of treatment
Timeline	Onset variable, generally <24 hrs Resolve within a few days of treatment	Onset variable, days to weeks Resolve within 9-14 days of treatment
Distinct features	Hyperreflexia Clonus (unless masked by increased muscle tone) Mydriasis Hyperactive bowel sounds	Hyporeflexia Normal pupillary dilation Normal or hypoactive bowel sounds
Identical features	Hypertension, tachycardia, tachypnea, hyperthermia (>40°C), hypersalivation	
Overlapping features	Diaphoretic Variable mental status; agitation, coma Increased tone, especially in lower extremities	Diaphoretic, pale Variable mental status; stupor, coma, alert 'Lead-pipe' rigidity in all muscle groups
Investigations	More commonly no lab findings	Elevated CK, leukocytosis, low serum Fe
Management	• Discontinue serotonergic agents • Supportive care (O2, IV fluids, cooling, cardiac monitoring) • Benzodiazepines, antihypertensives • If severe, serotonergic antagonist (e.g. cyproheptadine)	• Discontinue causative agents • Supportive care (O2, IV fluids, cooling, cardiac monitoring); ICU if necessary • Benzodiazepines, antihypertensives • Medical therapy (e.g. dantrolene, bromocriptine, amantadine)

Table 9. Comparison between serotonin syndrome and neuroleptic malignant syndrome.

Adapted from Turner et al., 2019; Kateon, 2013; and Bienvenu et al., 2012

SSRI Discontinuation Syndrome

- May occur in up to 40% of patients when antidepressant stopped abruptly
- Occurs within 1-3 days of abrupt cessation, subsides within several days after last dose
- Symptoms: flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances (“electric shock” sensations), hyperarousal
- Most frequently seen with paroxetine and venlafaxine
- Less likely in agents with long half-life (e.g. fluoxetine, vortioxetine)
- To minimize symptoms, slowly taper dose over several weeks when discontinuing antidepressant

MAOI and Hypertensive Crisis

- Tyramine: an amine found in high amounts in aged foods (e.g. cheeses, wine) which causes release of NE
- With MAOI, tyramine deamination in gut does not occur → tyramine is taken up by neurons and released as NE → excess NE cannot be broken down due to presence of MAOI → hypertensive crisis
- Early signs: headache, stiff neck, nausea/vomiting, sweating

Neurostimulation

Electroconvulsive therapy (ECT)

- A treatment which consists of inducing a generalized tonic-clonic seizure by running a small electrical current through the brain.
- Exact mechanism of action is still unclear
- Seizure-induced changes in NTs, neuroplasticity, and functional connectivity
 - ECT may increase levels of brain-derived neurotrophic factor (BDNF) → antidepressant effect
- Delivered in a controlled clinical setting after induction of general anesthesia and application of a muscle relaxant
- Response rates can reach 70-80% with remission rates approximately 40-50%

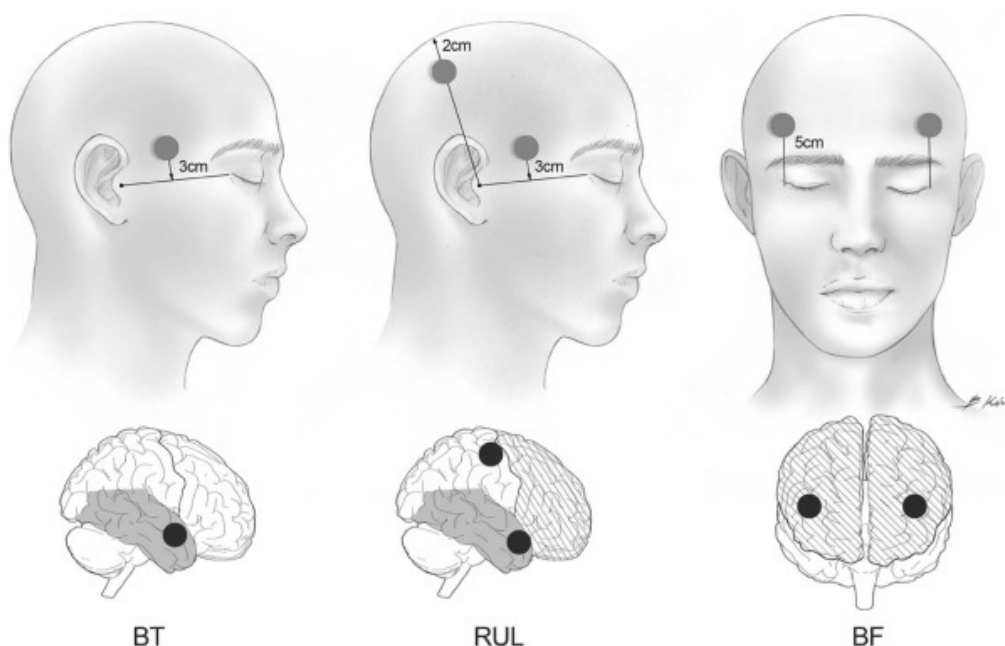


Figure 2. Electrode placement in ECT.

Image taken from McDonald, 2016.

Treatment parameters

- Electrode position
 - Bitemporal (BT), right unilateral (RUL), and bifrontal (BF) have similar efficacy but may adversely affect specific cognitive domains differently
 - BF and RUL are first-line recommendations, while BT is second-line due to higher rates of short-term cognitive adverse effects
- Electrical intensity - based on the minimum intensity to produced a generalized seizure (i.e. seizure threshold [ST])
 - Bilateral treatments (BT and BF) often use 1.5 to 2.0 times ST
 - RUL may use 5 to 8 times ST
- Pulse width
 - Usually uses brief pulse (BP) width
 - Ultrabrief pulse (UBP) - pulse width <0.5 ms
 - May be associated with less short-term cognitive impairment, specifically loss of autobiographical memory
 - May have slower speed of improvement and require more treatments than BP
 - UBP RUL is recommended as second-line ECT, especially to minimize cognitive impairment
- Number and frequency of sessions

NOTE

ECT is generally recommended as second-line treatment for MDD due to adverse effects.

Clinical indications for ECT as a first-line treatment for MDD:

- Acute suicidal ideation*
- Psychotic features*
- Treatment-resistant depression*
- Repeated medication intolerance
- Catatonic features
- Prior favourable response to ECT
- Rapidly deteriorating physical status
- During pregnancy, for any of the above indications
- Patient preference

*Level 1 (highest level) evidence

- Index course: number of ECT treatments required to achieve response and/or remission (usually ranges between 6 and 16)
- Sessions are usually 2-3 treatments per week during index course

IMPORTANT

>3 treatments in a week is generally not recommended as it is associated with a higher frequency of cognitive side effects.

Contraindications

- There are no absolute contraindications to ECT
- Relative contraindications (medical conditions that increase risk):
 - Space-occupying cerebral lesion
 - Increased intracranial pressure
 - Recent MI
 - Recent cerebral hemorrhage
 - Unstable vascular aneurysm or malformation
 - Pheochromocytoma
 - Class 4 or 5 anesthesia risk

Adverse effects

- Common:
 - Headache
 - Muscle ache
 - Nausea
 - Memory impairment (highest risk in first 6 months)
 - Significant variability between individuals
 - Retrograde amnesia
 - ▶ Worst shortly after treatment
 - ▶ Gradual improvement after ECT discontinued
 - ▶ Patchy memory loss extending for several months prior to ECT; some may return with time while others may be permanent
 - Anterograde amnesia
 - ▶ Temporary, usually disappears within few weeks after ECT discontinued
- Rare:
 - Mortality – approximately 1/10,000 patients or 2/100,000 to 1/80,000 treatments
 - Cardiovascular
 - Secondary initial vagal stimulation (10-15 sec) → bradycardia, asystole, ectopic activity

- Secondary sympathetic stimulation (1-5 min) → tachycardia, hypertension, arrhythmia, MI
- Prolonged apnea – pseudocholinesterase deficiency
- Prolonged seizure – manage with IV benzodiazepine

Repetitive transcranial magnetic stimulation (rTMS)

- Powerful focused magnetic field pulses (1.0 to 2.5 Tesla) to induce electrical currents in neural tissue noninvasively using an inductor coil placed against the scalp
- Therapeutic mechanism of action still under investigation
- No anesthesia required
- rTMS is recommended as a first-line neurostimulation treatment for patients who have failed at least 1 antidepressant.

EVIDENCE-BASED PRACTICE

Multiple studies show that rTMS is less effective than ECT, particularly in patients with psychosis.

However rTMS should be considered prior to ECT as rTMS response rates are poor in patients where ECT has failed.

Treatment parameters

- Stimulation intensity - based on individually determined resting motor threshold (RMT; minimum intensity to elicit muscle twitches in relaxed upper or lower extremities, by visual inspection or electromyography)
 - Most commonly 110% RMT or 120% RMT
 - Newer theta-burst stimulation (TBS) protocols are more commonly delivered at lower intensities (e.g. 70-80% RMT)
- Frequency
 - High-frequency (5-20 Hz) - considered excitatory
 - Low-frequency (1-5 Hz) - considered inhibitory
- Pattern
 - Conventional: 2- to 10-second trains at 10- to 60-second intervals, in 15- to 45-min sessions
 - TBS: only 1-3 min of stimulation required
 - Intermittent TBS (iTBS) - considered excitatory
 - Continuous TBS (cTBS) - considered inhibitory
- Site
 - Dorsolateral prefrontal cortex (DLPFC) - left, right, or bilateral
 - Dorsomedial prefrontal cortex (DMPFC) - bilateral

Adverse effects

- Common:
 - Scalp pain during stimulation (~40%)
 - Transient headache after stimulation (~30%)
 - Both diminish steadily over treatment, typically respond to over-the-counter analgesics, and result in low rates of discontinuation.
- Rare:
 - Induction of seizures
 - <25 cases of rTMS-induced seizures have been reported worldwide

Contraindications

- Absolute:
 - History of seizures (currently considered an absolute contraindication by most rTMS practitioners)
 - Metallic hardware (e.g. cochlear implants, aneurysm clips) anywhere in the head except the mouth
- Relative:
 - Cardiac pacemaker
 - Implantable defibrillator
 - History of epilepsy
 - Brain lesion (vascular, traumatic, neoplastic, infectious, or metabolic)

Phototherapy

- Daily exposure to bright light
- Typically administered at home with a fluorescent light box
- Proposed mechanisms of action: alteration of circadian rhythm, modulation of serotonin/catecholamine systems
- Recommended as a first-line monotherapy for seasonal depression, or a second-line monotherapy or adjunct for mild to moderate non-seasonal depression

Treatment parameters

- Intensity (measured in lux)
- Spectrum (soft white to “blue enhanced” light)
- Exposure

- Duration
- Time of day
- Standard protocol: 10,000 lux for 30 min per day during early morning for up to 6 weeks

Adverse effects

- Eye strain, headache, agitation, nausea, sedation

Psychosocial

- Lifestyle: increase aerobic exercise, mindfulness-based stress reduction
- Social: social skills training, vocational rehabilitation

Psychotherapy

- First-line recommendations for psychotherapies to manage acute MDD:
- Cognitive-behavioural therapy (CBT)
 - Short-term (12-16 weekly sessions)
 - Focus on symptoms
 - Premise: distorted beliefs about self, world, and future (negative cognitive triad) maintain depressive affect
 - Key concepts: cognitive distortions, automatic thoughts
- Interpersonal therapy (IPT)
 - Short-term (12-16 weekly sessions)
 - Focus on problematic functioning including:
 - Role transitions
 - Interpersonal role dispute
 - Interpersonal deficits (i.e., social isolation)
 - Unresolved grief

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Review Questions

1. A 36-year-old male is admitted to the psychiatry unit due to severe low mood. He has been experiencing imagery of suicide as well as feelings of hopelessness and guilt. He believes that he has committed a sin and deserves to be punished. The resident physician thinks that he is suffering from OCD with thoughts of guilt and suspects that patient has a primary obsessional disorder. The attending psychiatrist explains that patient is not obsessional but severely depressed because:
 - a) The patient has suicidal ideation.
 - b) The patient has indeed committed a sin.
 - c) The patient is not distressed by the guilty feelings which are ego-syntonic.
 - d) The psychiatrist thinks so.
 - e) Antidepressants alone were not effective.

2. A 35-year-old man has a 3-year history of major depression that is managed with sertraline. Multiple attempts to discontinue therapy led to severe relapses with major depressive symptoms and strong suicidal ideation. He reports problems with his marriage because of sexual dysfunction, i.e., lack of libido. He discloses the presence of nocturnal erections but a lack of interest in sexual intimacy with his wife. They have a good relationship otherwise. Which of the following medications is your first choice for relieving his symptoms of sexual dysfunction?
 - a) Amitriptyline
 - b) Bupropion
 - c) Fluoxetine
 - d) Citalopram
 - e) Sildenafil

3. A 40-year-old married man presents to his family physician one month after a recent hospitalization for a car accident which left him with limited use of his arm and hand. He works as a general contractor, but after the accident he was instructed to avoid any work with his hand. He continues to monitor his workers on the job but now complains that he feels anxious and has low mood at times, with episodes of irritability and tearfulness, and a decreased interest in his work. He still enjoys coaching his son's baseball team, and he has had no sleep or appetite changes. He also feels that his sexual desire has diminished. The patient has no prior personal or familial history of a mood disorder or psychiatric disorder. Which of the following is the most likely diagnosis?
 - a) Adjustment disorder with depressed mood
 - b) Bipolar disorder, most recent episode depressed
 - c) Conversion disorder
 - d) Dysthymic disorder
 - e) Major depressive disorder

Review Questions (continued)

Answers:
1. c)
2. b)
3. a)

Appendix A - Specifiers for Depressive Disorders

Current Severity

(Based on number of criterion symptoms, their severity, and degree of resulting functional impairment.)

Mild	• No more or only a few more symptoms than those required to make the diagnosis. • Symptoms are distressing but manageable. • Minor impairment in social/occupational functioning.
Moderate	• Number of symptoms, severity of symptoms, and/or functional impairment are between "mild" and "severe".
Severe	• Significant number of symptoms in addition to those required to make the diagnosis. • Symptoms are seriously distressing and unmanageable. • Marked impairment in social/occupational functioning.

Course

In partial remission	• Symptoms of MDE still present but full criteria not met, or; • <2 months without significant MDE symptoms following the end of a MDE.
In full remission	• No significant signs or symptoms during the past 2 months.

Other

With anxious distress High levels of anxiety have been associated with higher suicide risk, longer illness duration, and decreased likelihood of treatment response.	Presence of ≥ 2 of the following during the majority of days of MDE or PDD: 1. Feeling keyed up/tense. 2. Feeling unusually restless. 3. Difficulty concentrating due to worry. 4. Fear that something awful may happen. 5. Feeling of losing control. Current severity: • Mild: 2 symptoms • Moderate: 3 symptoms • Moderate-severe: 4 or 5 symptoms • Severe: 4 or 5 symptoms + motor agitation
With mixed features Significant risk factor for development of bipolar I or II.	A. ≥ 3 of the following manic/hypomanic symptoms during majority of days of MDE: 1. Elevated mood 2. Grandiosity 3. Pressured speech or more talkative 4. Flight of ideas or racing thoughts 5. Increased energy or goal-directed activity 6. Increased engagement in activities with high potential for painful consequences (e.g. spending sprees, gambling, sexual indiscretion) 7. Decreased need for sleep (feeling rested despite little sleep) B. Mixed symptoms observable by others and are a change from usual behaviour. C. If symptoms meet full criteria for mania or hypomania, diagnosis should be bipolar disorder type I or II, respectively. D. Symptoms are not attributable to the effects of a substance.
With melancholic features Only somewhat likely to repeat across episodes. More frequent in inpatients, more severe MDEs, and those with psychotic features.	A. ≥ 1 of the following during the most severe period of the current episode: 1. Loss of pleasure in all (or almost all) activities. 2. Lack of reactivity to usually pleasurable stimuli. B. ≥ 3 of the following: 1. Distinctly depressed mood, characterized by profound despondency, despair, and/or moroseness. 2. Depression that is regularly worse in the morning. 3. Early-morning awakening (≥ 2 hours before usual awakening). 4. Marked psychomotor agitation or retardation observable by others. 5. Significant anorexia or weight loss. 6. Excessive or inappropriate guilt.
With atypical features "Atypical" has historical significance and does not connote an uncommon or unusual presentation.	A. Mood brightens in response to actual or potential positive events. B. ≥ 2 of the following: 1. Significant weight gain or increase in appetite. 2. Hypersomnia – extended nighttime sleep or daytime naps totalling ≥ 10 hrs (or ≥ 2 hrs more than when not depressed). 3. Lead paralysis in arms or legs. 4. Long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) resulting in significant social/occupational impairment. C. Criteria not met for "with melancholic features" or "with catatonia" during the same episode.
With psychotic features	Presence of delusions and/or hallucinations: • With mood-congruent psychotic features: Content of all delusions/hallucinations is consistent with typical depressive themes (inadequacy, guilt, disease, death, nihilism, deserved punishment). • With mood-incongruent psychotic features: Content of delusions/hallucinations does not involve typical depressive themes or is a mix of mood-incongruent and -congruent themes.
With catatonia	Presence of catatonic features during most of a manic episode or MDE.
With peripartum onset	Applied to current MDE (or if full MDE criteria currently not met, the most recent MDE) if onset of mood symptoms occurs during pregnancy or within 4 weeks following delivery.

With seasonal pattern In bipolar disorders, seasonal pattern more likely in bipolar II vs. I. Prevalence of winter-type pattern increases with higher latitude and younger age.	*Applies to recurrent MDD. A. Regular temporal relationship between MDE onset and particular time of year, without seasonally related psychosocial stressors (e.g. regularly being unemployed every winter). B. Full remissions (or change from MDE to mania/hypomania) also occur at a particular time of year. C. In the last 2 years, there have been 2 MDEs demonstrating temporal seasonal relationships with no nonseasonal MDEs during that same period. D. Seasonal MDEs substantially outnumber the nonseasonal MDEs that may have occurred over a person's lifetime.
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Bipolar Disorders

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Introduction

- Bipolar disorders are a spectrum of diagnoses characterized by periods of depression and periods of mania
- A bridge between schizophrenia spectrum and depressive disorders in terms of symptomatology, family history, and genetics
- DSM-5 classification:
 - Bipolar I disorder (BDI) and bipolar II disorder (BDII)
 - Cyclothymic disorder
 - Substance/medication-induced bipolar and related disorder
 - Bipolar and related disorder due to another medical condition
 - Other specified bipolar and related disorder
 - Unspecified bipolar and related disorder

Manic and Hypomanic Episodes

DSM-5 Criteria for Manic and Hypomanic Episodes

Manic Episode

- A. A distinct period of ≥ 1 week (or any duration if hospitalization is necessary) in which both of the following are present for most of the day, nearly every day:
1. Abnormally and persistently elevated, expansive, or irritable mood;
- AND
2. Abnormally and persistently increased goal-directed activity or energy
- B. During the period described in Criterion A, ≥ 3 (if mood is elevated, or ≥ 4 if mood is irritable) of the following are present and are a noticeable change from usual behaviour:
1. Inflated self-esteem or grandiosity
 2. Decreased need for sleep (e.g., feeling rested after only 3 hours of sleep)
 3. More talkative than usual, or pressure to keep talking

MNEMONIC

Criterion B for mania "GST PAID"

Grandiosity
Sleeplessness
Talkative
Pleasurable activities with painful consequences
Activity increased
Ideas (flight of)
Distractible

4. Flight of ideas or subjective experience that thoughts are racing
 5. Distractibility (attention drawn too easily to unimportant or irrelevant things), as reported or observed
 6. Increase in goal-directed activity (e.g. socially, at school, at work, sexually) or non-goal-directed activity (i.e. psychomotor agitation)
 7. Excessive involvement in activities with a high potential for painful consequences (e.g. unrestrained buying sprees, sexual indiscretions, foolish business investments, etc.)
- C. The mood disturbance is severe enough to cause ≥ 1 of:
1. Marked impairment in functioning
 2. Hospitalization to prevent harm to self or others
 3. Psychotic features
- D. Not attributable to the effects of a substance or to another medical condition

Hypomanic Episode

- A. A distinct period of ≥ 4 consecutive days in which both of the following are present for most of the day, nearly every day:
1. Abnormally and persistently elevated, expansive, or irritable mood
- AND
2. Abnormally and persistently increased goal-directed activity or energy
- B. During the period described in Criterion A, ≥ 3 (if mood is elevated, or ≥ 4 if mood is irritable) of the following are present and are a noticeable change from usual behaviour:
1. Inflated self-esteem or grandiosity
 2. Decreased need for sleep (e.g., feeling rested after only 3 hours of sleep)
 3. More talkative than usual, or pressure to keep talking
 4. Flight of ideas or subjective experience that thoughts are racing
 5. Distractibility (attention drawn too easily to unimportant or irrelevant things), as reported or observed
 6. Increase in goal-directed activity (e.g. socially, at school, at work, sexually) or non-goal-directed activity (i.e. psychomotor agitation)
 7. Excessive involvement in activities with a high potential for painful consequences (e.g. unrestrained buying sprees, sexual indiscretions, foolish business investments, etc.)
- C. Marked change in functioning that is uncharacteristic of the person

- when not symptomatic.
- D. Mood disturbance and change in functioning are observable by others.
 - E. Not severe enough to cause marked impairment in functioning or to necessitate hospitalization. No presence of psychotic features (if any are present, the episode is manic).
 - F. Not attributable to the effects of a substance.

Bipolar I Disorder (BDI)

DSM-5 Criteria for Bipolar I Disorder

- A. Criteria have been met for ≥1 manic episode.
- B. Occurrence of manic episode(s) and major depressive episode(s) (MDE) is not better explained by a schizophrenia spectrum or other psychotic disorder.

Specifiers:

The diagnosis should be recorded with the specifiers in the following order:

- Bipolar I disorder, the type of current/most recent episode (1), severity/psychotic/remission specifiers (2), and as many of the other specifiers as pertains to current or most recent episode (3).
- (E.g. “Bipolar I disorder, most recent episode manic, in partial remission”)

(1) Type*	(2) Severity/Course†		(3) Other‡
• Manic • Hypomanic • Depressed • Unspecified**	• Mild • Moderate • Severe • With psychotic features‡	Only indicated if full criteria for a mood episode <u>are</u> currently met	• With anxious distress • With mixed features • With rapid cycling • With melancholic features • With atypical features • With mood-congruent psychotic features • With mood-incongruent psychotic features • With catatonia • With peripartum onset • With seasonal pattern
	• In partial remission • In full remission	Only indicated if full criteria for a mood episode <u>are not</u> currently met	
	Unspecified		

Table 1. Bipolar disorder specifiers.

* For the current or most recent episode.

** Severity, psychotic, and remission specifiers do not apply.

‡ If psychotic features are present, this specifier should be used irrespective of episode severity.

† See Appendix A for definitions of severity/course and other specifiers.

NOTE

Hypomanic episodes are common in bipolar I disorder but are NOT required for the diagnosis.

Bipolar II Disorder (BDII)

DSM-5 Criteria for Bipolar II Disorder

- A. Criteria have been met for ≥ 1 hypomanic episode and ≥ 1 MDE.
- B. No manic episodes.
- C. Occurrence of hypomanic episode(s) and MDE(s) is not better explained by a schizophrenia spectrum or other psychotic disorder.
- D. The symptoms of depression or the frequent alternation between depression and hypomania causes clinically significant distress or interference with important areas of functioning.

Specifiers:

- Specifiers for bipolar II disorder are the same as bipolar I disorder, with the exception that there is no manic type.

CLINICAL PEARL

Although bipolar II disorder only has one diagnostic code, the type of current/most recent episode, severity, presence of psychotic features, course, and other specifiers should still be indicated in writing.

Cyclothymia

DSM-5 Criteria for Cyclothymia

- A. ≥ 2 years (≥ 1 year in children and adolescents) with numerous periods of hypomanic symptoms and numerous periods of depressive symptoms, never meeting full criteria for a mood episode.
- B. During the above 2-year (or 1-year in children and adolescents) period, the hypomanic and depressive periods have been present for $\geq 50\%$ of the time with no more than 2 months at a time spent free from symptoms.
- C. Criteria for MDE, mania, or hypomania have never been met.
- D. Not better explained by a schizophrenia spectrum or other psychotic disorder.
- E. Not attributable to the effects of a substance or to another medical condition.
- F. Clinically significant distress or impairment in important areas of functioning.

Specifiers:

- With or without anxious distress (See [Appendix B - Specifiers for Bipolar Disorders](#)).

Other Bipolar and Related Disorders

Substance/medication-induced bipolar and related disorder	- Evidence from history, physical examination, or laboratory findings of temporal correlation of symptoms with substance intoxication/withdrawal or exposure to medication. - Substance/medication in question is capable of producing aforementioned symptoms.
Bipolar and related disorder due to another medical condition	Evidence from history, physical examination, or laboratory findings that the mood disturbance is a direct pathophysiological consequence of another medical condition.
Other specified bipolar and related disorder	Applicable when clinician chooses to communicate a specific reason that the presentation does not meet criteria for other bipolar and related disorders (e.g. short-duration hypomanic episodes and MDEs, hypomanic episodes with insufficient symptoms and MDEs, hypomanic episode without prior MDE, short-duration cyclothymia).
Unspecified bipolar and related disorder	Applicable when the presentation does not meet full criteria for any other bipolar and related disorder (e.g. insufficient information to make the diagnosis).

Table 2. Summary chart of other bipolar related disorders.

Epidemiology

- From the World Mental Health Survey Initiative (Merikangas et al., 2011): across BDI, BDII, and subthreshold BD subtypes, total lifetime prevalence ~2.4% and 12-month prevalence ~1.5%
 - Subthreshold BD most common: lifetime prevalence 1.4% and 12-month prevalence 0.8%
- The Canadian Community Health Survey-Mental Health (McDonald et al., 2015)
 - Lifetime prevalence of BDI ~0.87%
 - Lifetime prevalence of BDII ~0.67%

Development and Course

- Average onset is at age 25 years
 - From Bauer et al., 2015:
 - Early-onset – age 17 (largest group, 42%)
 - Middle-onset – age 24 (25%)
 - Late-onset – age 32 (33%)
 - May differ based on geographical location – e.g., average onset age was 20 for a US sample but 29 for a European sample

- Earlier age of onset is associated with:
 - Longer delay to treatment
 - Greater depressive symptom severity
 - Higher levels of comorbid anxiety and substance use
- Course is heterogeneous but on average, number of previous episodes is associated with:
 - Increased risk of recurrence
 - Increased duration and symptomatic severity of subsequent episodes
 - Decreased threshold for developing further episodes
 - Increased risk of dementia in the long term

Risk and Prognostic Factors

Genetic and physiologic

- Family history of BD is one of the strongest and most consistent risk factors for BD
 - Average 10-fold increased risk among adult relatives of individuals with BDI and BDII
 - Magnitude of risk increases with degree of kinship
- Schizophrenia and BD likely share a genetic origin, reflected in the familial co-aggregation seen in both

Environmental

- More common in high-income vs. low-income countries (1.4 vs. 0.7%)
- Separated, divorced, or widowed individuals have higher rates of BDI than people who are married or have never been married

Course modifiers

- A manic episode with psychotic features increases risk of psychotic features in subsequent manic episodes
- Incomplete inter-episode recovery is more common when the current episode is accompanied by mood-incongruent psychotic features

Suicide Risk

- Suicide is one of the leading causes of death in BD
 - Approximately 6-7% of identified BD patients die by suicide
 - BD may account for 25% of all completed suicides
 - Risk is substantially higher in BD (10.7 per 100 000 per year) compared to general population
 - Fatality of suicide attempts is also higher in BD compared to general populations
 - Men are at higher risk (0.366 per 100 person years) compared to women (0.217)
- Factors associated with suicide attempts:
 - Female sex
 - Younger age of illness onset
 - Depressive polarity of first illness episode
 - Depressive polarity of current/most recent episode
 - Comorbid anxiety disorder, substance use, or cluster B/ borderline personality disorder
 - First-degree family history of suicide
 - Previous suicide attempts
 - Current or recent (<6 weeks) hospitalization
- Factors associated with suicide deaths:
 - Male sex
 - First-degree family history of suicide
 - Lithium and anticonvulsants may contribute to preventing suicide attempts and deaths

FYI

Suicide Prevention Infographic

<http://www.isbd.org/Files/Admin/Knowledge-Center-Documents/Suicide-Prevention-Tip-Sheet.pdf>

Screening and Diagnosis

- Diagnosis of BD is made based on clinical assessment
- Difficult to diagnose due to frequent depressive onset, variable help-seeking for hypomanic or manic periods, temporal instability of symptoms, and high rates of comorbidity
- Many individuals are not accurately diagnosed until up to 10 years after symptom onset

- Most frequent misdiagnosis is MDD
 - Patients are more likely to present for treatment of depressive symptoms
 - Patients may not recall periods of hypomania or mania, or may not think they are pathological
 - Acute depression is often associated with impaired recall and insight, difficulties with memory or concentration
- Second most common misdiagnosis is schizophrenia
- Bipolar symptoms can also overlap significantly with ADHD, borderline personality disorder, and substance use disorder
 - Other comorbidities include impulse control disorders, anxiety disorders, and other cluster B disorders
- Rating scales:
 - Screening tools are available, but sensitivity and specificity are variable and therefore should not replace clinical judgment in diagnosis or treatment planning
 - Examples of tools:
 - [Mood Disorders Questionnaire](#) (MDQ): patient-rated
 - [Young Mania Rating Scale](#) (YMRS): 11-item scale based on patient's subjective report of their condition over the last 48 hours, as well as clinical observations made during interview
 - [Altman Self-Rating Mania Scale](#) (ASRM): 5-item self-reported scale

CLINICAL PEARL**Features of depression that should increase your suspicion of bipolar disorder**

- Earlier age of onset
- Highly recurrent depressive episodes
- Family history of BD
- Psychotic features
- Psychomotor agitation
- Atypical depressive symptoms – hypersomnia, hyperphagia, leaden paralysis
- Postpartum depression and psychosis
- Past suicide attempts
- Antidepressant-induced manic symptoms
- Rapid cycling

Differential Diagnosis

**For manic episode*

- Bipolar disorder – manic or mixed episode
- ADHD
- Substance-induced – e.g., EtOH, PCP, sedatives, anxiolytics, amphetamines, cocaine
- Medication-induced – e.g., steroids, immunosuppressants, levodopa
- MDE with irritable mood
- Schizophrenia spectrum disorder
- Other psychotic disorder
- Personality disorders
- Organic medical disorders – e.g., hyperthyroidism, malignancy, renal failure
- Neurological conditions – e.g., infarcts, multiple sclerosis, neoplasms

Investigations

- CBC
- Thyroid studies (e.g., TSH, free T4)
- Vitamin B12, folate
- Electrolytes and extended electrolytes
- Urea, Cr
- Liver enzymes
- Drug screen

Management

Biological

	Acute mania	Maintenance	Acute depression
First-line	Lithium Quetiapine DVP Asenapine Aripiprazole Paliperidone (>6 mg) Risperidone Cariprazine Quetiapine + Li/DVP Aripiprazole + Li/DVP Risperidone + Li/DVP Asenapine + Li/DVP	Lithium Quetiapine DVP Lamotrigine Asenapine Quetiapine + Li/DVP Aripiprazole + Li/DVP Aripiprazole Aripiprazole qMonthly	Quetiapine Lurasidone + Li/DVP Lithium Lamotrigine Lurasidone Lamotrigine (adj)
Second-line	Olanzapine Carbamazepine Olanzapine + Li/DVP Lithium + DVP Ziprasidone Haloperidol	Olanzapine Risperidone LAI Risperidone LAI (adj) Carbamazepine Paliperidone (>6 mg) Lurasidone + Li/DVP Ziprasidone + Li/DVP	DVP SSRIs/bupropion (adj) Cariprazine Olanzapine-fluoxetine

Table 3. Hierarchical rankings of first- and second-line medications by phase.

adj: adjunctive; DVP: divalproex (including valproate, valpromide, valproic acid, divalproex sodium); LAI: long-acting injectable; Li: lithium

Adapted from the CANMAT and ISBD 2018 guidelines.

	Lithium	Valproic acid (Epival)	Lamotrigine (Lamictal)
Indications	Acute mania, depression, maintenance	Acute mania, maintenance	Depression, maintenance
Initial workup and ongoing monitoring	- CBC - Electrolytes, urea, creatinine - TSH - ECG - Serum level q5d until steady state, then at 3-6mos or with signs of dehydration or toxicity - Kidney function, TSH, and ECG q6-12mos	- CBC - Liver enzymes - Serum level weekly until steady state - Repeat tests q1mo x 6 mos, then q6mos or if symptoms	
Dosing	- Adults: 600-1500 mg/day; serum level 0.5-1.2 - Geriatric: 150-600 mg/day; serum level 0.4-0.8 Serum level is ▲ by: - NSAIDs - Thiazides - ACEi - Tetracyclines - Anticonvulsants Serum level is ▼ by: - Osmotic diuretics (mannitol) - Carbonic anhydrase inhibitors - Caffeine - High salt	Starting dose: 250 mg qhs (geriatrics) 250 mg bid-tid (adults) Dose range: 750-3000 mg/day, split into bid dosing Serum levels: 350-700 umol/L	Start at 25 mg/day, increase q2wks by 25-50 mg Usual maintenance dose: 100-200 mg, up to 500 mg, split into bid dosing
Side effects (drug levels within normal range)	- Lethargy - Insipidus (diabetes) - Tremor/Teratogen (increased risk of Ebstein's anomaly in 1st trimester, 0.1% vs. 0.005%) - Hypothyroid (5%) - Increased weight, increased WBC (transient) - Vomiting, GI upset - Miscellaneous: ECG changes (bradycardia, T-wave flattening or inversion; contraindicated in sick sinus syndrome), acne, rashes, alopecia	Acute: - Sedation (31%) - Tremor (10-30%) - Unsteadiness - Nausea, GI upset (20%) Longer term: - Appearance - Acne - Alopecia - Rashes (incl. SJS*) - Weight gain - Systemic - Blood dyscrasias – thrombocytopenia, anemia, agranulocytosis, coagulopathies - Liver dysfunction +/- elevated ammonia - Reproductive – menstrual irregularities, PCOS, teratogenicity	- Rash (incl. SJS) - Activation (3-8%) - Ataxia - Sedation and cognitive slowing - Sleep disturbances - Headache - Hypersensitivity reaction
Toxicity (drug levels exceeding normal range)	(Lithium >1.2 mEq/L) - Early: GI distress, hand tremor, fatigue, thirst, headache, impaired concentration - Late: ataxia, stupor, myoclonic jerks, hyperreflexia, seizure - Can lead to irreversible neurotoxicity including cognitive impairment, cerebellar dysfunction, peripheral neuropathy - Hospitalize for levels >2.0 or based on clinical symptoms		

Table 4. Summary table for commonly used mood stabilizers in bipolar disorder.

PCOS: polycystic ovarian syndrome; SJS: Stevens-Johnson Syndrome

Other agents

- First- and second-generation antipsychotics
 - Please see the [Psychopharmacology](#) and [Psychotic Disorders](#) chapters for further information about dosing for first- and second-generation antipsychotics.

Psychosocial

- **Psychoeducation** for the patient and family, especially at illness onset, can help prevent relapse
 - Provide information about the nature of BD, treatments, and key coping strategies
 - Psychoeducational models for BD include:
 - Detecting and managing prodromes of depression and mania
 - Ongoing stress management
 - Problem solving
 - Diminishing effects of stigma and denial of illness
 - Enhancing medication adherence
 - Developing healthy lifestyles (e.g., increase exercise, minimize substance use, regular sleep-wake)
 - May occur in individual or in group settings
 - Empirical models involve face-to-face interaction with the therapist; newer strategies being studied include online tools, smartphone apps, workbooks
- **Adjunctive psychosocial interventions** can be useful for acute depressive episodes, maintenance to prevent relapse, and to restore quality of life
 - Positive evidence for maintenance therapy:
 - Cognitive behavioural therapy (CBT)
 - Family-focused therapy (FFT)
 - Interpersonal and social-rhythm therapy (IPSRT)
 - Peer support
 - Other strategies being studied:
 - Family/caregiver interventions
 - Dialectical behavioural therapy (DBT)
 - Mindfulness-based cognitive therapy (MBCT)
 - Cognitive and functional remediation
 - Online interventions

NOTE

There are no current recommendations for specific psychosocial interventions for acute manic episodes.

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Review Questions

1. A 29 year old female presents to hospital with a 2 week history of elated mood. She has not been sleeping during this time period, stating that she has a lot of energy. In addition she presents as sexually provocative. She is speaking very quickly and jumping from one topic to the next. She reported to the nurses that she is “chosen by God to be ‘the second virgin Mary.’” Blood urea nitrogen (BUN), creatinine, electrolytes, TSH and an ECG are all within normal limits. A pregnancy test is also completed which is negative. Given her above presentation, which would be the best first line treatment option?
 - a) Paliperidone
 - b) Olanzapine
 - c) Lithium
 - d) Abilify
 - e) Divalproex

2. A 32 year old female presents to the ED today as her family have reported a change in her behaviour. Currently, she presents with a 5 day history of elevated mood. In addition, she reports increased energy, despite not sleeping as much. Collateral from her family indicate that she is more talkative than usual. They also find that she is easily distractible. She has still been able to go to work during this time, and is functioning fairly well. She has never had an episode similar to this in the past. She reports a history of depressive episodes dating back to when she was 18 years of age. She has never taken an antidepressant for her depression. She has never been hospitalized for mental health reasons. Given the above information, which diagnosis is most accurate for this patient?
 - a) Bipolar I disorder
 - b) Bipolar II disorder
 - c) Borderline personality disorder
 - d) Cyclothymic disorder
 - e) Major depressive disorder

3. A 29 year old male was brought to the hospital after he was found running around the streets with no shoes in the middle of winter. He was noted to be screaming at people that he is going to be the next prime minister. He has not slept for the past 3 to 4 weeks. He also been spending money on new computers and video games which he cannot afford. He is noted to be irritable and explosive at times. On mental status examination, the patient is noted to be irritable and elated. He is wearing bright coloured clothing and is not dressed appropriately for the weather. He is noted to be pacing the room and not sitting down despite requests to do so. His speech is increased in volume and rate and he is difficult to interrupt. He reports his mood as “great”. He reports that “people are jealous of him because he is going to the prime minister”. He reported being destined for greatness. His thought process is tangential. No hallucination or delusions. No suicidal or homicidal ideation. Based on the above presentation and diagnosis, which of the following is not true:
 - a) The patient is experiencing a manic episode.
 - b) The patient is experiencing a mixed episode.
 - c) The patient is experiencing a depressive episode.
 - d) The patient is experiencing a psychotic episode.
 - e) The patient is experiencing a bipolar disorder.

Review Questions (continued)

- a) Family history is the strongest and most consistent risk factor
- b) Male sex is associated with an increased risk of death by suicide compared to female sex
- c) It is more common in low income versus high income countries
- d) Earlier age of onset is associated with higher levels of comorbid anxiety and substance use
- e) Number of previous episodes is associated with increased risk of dementia in the long term

Answers:

1. c) Lithium - Listed in the Bipolar Guidelines 2018 as the first line treatment for an acute mania. Paliperidone, Abilify and Divalproex are also listed as first line, but lower on the hierarchy.

2. b

3. c

Appendix B - Specifiers for Bipolar Disorders

Current Severity

(Based on number of criterion symptoms, their severity, and degree of resulting functional impairment.)

Mild	• No more or only a few more symptoms than those required to make the diagnosis. • Symptoms are distressing but manageable. • Minor impairment in social/occupational functioning.
Moderate	• Number of symptoms, severity of symptoms, and/or functional impairment are between "mild" and "severe".
Severe	• Significant number of symptoms in addition to those required to make the diagnosis. • Symptoms are seriously distressing and unmanageable. • Marked impairment in social/occupational functioning.

Course

In partial remission	• Symptoms of immediately previous mood episode are still present but do not meet full criteria, or; • <2 months without significant symptoms following the end of an episode.
In full remission	• No significant signs or symptoms during the past 2 months.

Other

With anxious distress High levels of anxiety have been associated with higher suicide risk, longer illness duration, and decreased likelihood of treatment response.	Presence of ≥ 2 of the following during the majority of days of the current or most recent mood episode: 1. Feeling keyed up/tense. 2. Feeling unusually restless. 3. Difficulty concentrating due to worry. 4. Fear that something awful may happen. 5. Feeling of losing control. Current severity: • Mild: 2 symptoms • Moderate: 3 symptoms • Moderate-severe: 4 or 5 symptoms • Severe: 4 or 5 symptoms + motor agitation
With mixed features Significant risk factor for development of bipolar I or II.	*Applies to the current mood episode (hypomanic/manic/major depressive [MDE]) in bipolar I or II. Manic/hypomanic episode, with mixed features A. Full manic/hypomanic criteria plus ≥ 3 of the following manic/hypomanic symptoms during majority of days of episode: 1. Prominent dysphoria or depressed mood – either by subjective report or observation by others. 2. Diminished interest/pleasure in all (or almost all) activities – either by subjective report or observation by others. 3. Psychomotor retardation observable by others. 4. Fatigue/loss of energy. 5. Worthlessness or excessive/inappropriate guilt. 6. Recurrent thoughts of death, passive or active suicidal ideation (SI). B. Symptoms are observable by others and are a noticeable change from usual behaviour. C. If both manic and MDE criteria are fully met, diagnosis should be “manic episode, with mixed features”. D. Not attributable to effects of a substance. Depressive episode, with mixed features A. Full MDE criteria plus ≥ 3 of following manic/hypomanic symptoms during the majority of days of the MDE: 1. Elevated mood 2. Grandiosity 3. Pressured speech or more talkative 4. Flight of ideas or racing thoughts 5. Increased energy or goal-directed activity 6. Increased engagement in activities with high potential for painful consequences (e.g. spending sprees, gambling, sexual indiscretion) 7. Decreased need for sleep (feeling rested despite little sleep) B. Mixed symptoms are observable by others and are a change from usual behaviour. C. If symptoms meet full criteria for mania or hypomania, diagnosis should be bipolar disorder type I or II, respectively. D. Symptoms are not attributable to the effects of a substance.
With rapid cycling	*Applies to bipolar I or II. • ≥ 4 mood episodes in the past 12 months that meet criteria for mania, hypomania, or MDE, in any combination and order. • Episodes are demarcated by either: • Partial/full remission of ≥ 2 months; or • Switch to episode of opposite polarity (mania/hypomania $\leftrightarrow$ MDE).
With melancholic features Only somewhat likely to repeat across episodes. More frequent in inpatients, more severe MDEs, and those with psychotic features.	A. ≥ 1 of the following during the most severe period of the current episode: 1. Loss of pleasure in all (or almost all) activities. 2. Lack of reactivity to usually pleasurable stimuli. B. ≥ 3 of the following: 1. Distinctly depressed mood, characterized by profound despondency, despair, and/or moroseness. 2. Depression that is regularly worse in the morning. 3. Early-morning awakening (≥ 2 hours before usual awakening). 4. Marked psychomotor agitation or retardation observable by others. 5. Significant anorexia or weight loss. 6. Excessive or inappropriate guilt.

With atypical features “Atypical” has historical significance and does not connote an uncommon or unusual presentation.	*Applied when these features predominate during the majority of the current/most recent MDE. A. Mood brightens in response to actual or potential positive events. B. ≥ 2 of the following: 1. Significant weight gain or increase in appetite. 2. Hypersomnia – extended nighttime sleep or daytime naps totalling ≥ 10 hrs (or ≥ 2 hrs more than when not depressed). 3. Lead paralysis in arms or legs. 4. Long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) resulting in significant social/occupational impairment. C. Criteria not met for “with melancholic features” or “with catatonia” during the same episode.
With psychotic features	• Presence of delusions and/or hallucinations. • With mood-congruent psychotic features: Content of all delusions/hallucinations is consistent with typical depressive themes (inadequacy, guilt, disease, death, nihilism, deserved punishment). • With mood-incongruent psychotic features: Content of delusions/hallucinations does not involve typical depressive themes or is a mix of mood-incongruent and -congruent themes.
With catatonia	Presence of catatonic features during most of a manic episode or MDE.
With peripartum onset	Applied to current MDE (or if full MDE criteria currently not met, the most recent MDE) if onset of mood symptoms occurs during pregnancy or within 4 weeks following delivery.
With seasonal pattern In bipolar disorders, seasonal pattern more likely in bipolar II vs. I. Prevalence of winter-type pattern increases with higher latitude and younger age.	*Applies to the lifetime pattern of mood episodes (mania/hypomania/MDE). A. Regular temporal relationship between onset of at least 1 type of mood episode and a particular time of year, without seasonally related psychosocial stressors (e.g. regularly being unemployed every winter). The other types may not follow a seasonal pattern. B. Full remissions (or change from MDE to mania/hypomania or vice versa) also occur at a particular time of year. C. In the last 2 years, mood episodes of at least 1 type have demonstrated temporal seasonal relationships with no nonseasonal episodes of that polarity during that same period. D. Seasonal episodes substantially outnumber the nonseasonal episodes that may have occurred over a person’s lifetime.

Pediatric Depressive Disorders

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General Features

- Depressive disorders in children and adolescents are common but often difficult to identify and distinguish from normal experience.
- Untreated depression can lead to impaired development of emotional, cognitive, and social skills, as well as poor school or work functioning, impaired family relationships, substance abuse, legal problems, and suicidal ideation or behaviour.
- DSM-5 classification of depressive disorders:
 - Disruptive mood dysregulation disorder (DMDD)
 - Major depressive disorder (MDD)
 - Persistent depressive disorder (PDD)
 - Premenstrual dysphoric disorder (PMDD) – please see [Depressive Disorders chapter](#)
 - Other: substance/medication-induced, due to another medical condition, other specified depressive disorder, and unspecified depressive disorder – please see [Depressive Disorders chapter](#)

Diagnostic Criteria

Disruptive mood dysregulation disorder

DSM-5 Criteria for Disruptive Mood Dysregulation Disorder

- A. Severe recurrent verbal and/or behavioural temper outbursts grossly out of proportion in intensity or duration to the situation.
- B. Outbursts are inconsistent with developmental level.
- C. Outbursts occur ≥ 3 times per week on average.
- D. Mood between outbursts is persistently irritable/angry most of the day, nearly every day, and is observable by others.
- E. Criteria A to D are present for ≥ 12 months with no period of ≥ 3 consecutive months spent free from all symptoms.

- F. Criteria A and D are present in ≥ 2 of and are severe in ≥ 1 of: home, school, or with peers.
- G. Diagnosis should not be made for the first time before age 6 or after age 18.
- H. Onset of Criteria A to E occurs before age 10, by history or observation.
- I. No distinct period of ≥ 1 day during which full criteria for manic or hypomanic episodes have been met.
- J. Behaviours do not occur exclusively during major depressive episodes (MDEs) and are not better explained by another mental disorder.
- K. Not attributable to the effects of a substance or to another medical or neurological condition.

**Note: Developmentally appropriate mood elevation (e.g. a positive event or anticipation for the event) should not be considered as a symptom of mania or hypomania.*

NOTE**A diagnosis of DMDD CANNOT coexist with:**

- Oppositional defiant disorder (if criteria for both DMDD and oppositional defiant disorder (ODD) are met, only a diagnosis of DMDD should be given).
- Intermittent explosive disorder
- Bipolar disorder

A diagnosis of DMDD CAN coexist with:

- MDD
- Attention deficit hyperactivity disorder (ADHD)
- Conduct disorder
- Substance use disorder(s)

Major depressive disorder in pediatric populations

DSM-5 Criteria for MDD in Pediatric Populations

- A. ≥ 5 (must include #1 or #2) of the following 9 symptoms for ≥ 2 weeks, nearly everyday:
 1. Depressed mood for most of the day, either by subjective report or observation by others
 2. Markedly diminished interest or pleasure in all or almost all activities, either by subjective report or observation by others
 3. Significant unintentional weight loss or weight gain (e.g. $\Delta 5\%$ of body weight in a month), or increased/decreased appetite
 4. Insomnia or hypersomnia
 5. Psychomotor agitation/retardation observable by others
 6. Fatigue or loss of energy
 7. Feelings of worthlessness or excessive/inappropriate guilt (which may be delusional)
 8. Diminished concentration or indecisiveness, either by subjective report or observation by others

CLINICAL PEARL**Key pointers regarding criterion A in pediatric populations**

Mood - in children and adolescents, irritability may be more common.

Weight change - adolescents typically report fewer appetite and weight changes than children; young children may fail to make expected weight gain.

Sleep - adolescents typically report more hypersomnia than children.

- 9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for suicide
- B. Clinically significant distress or impairment in important areas of functioning.
- C. Not attributable to the effects of a substance or to another medical condition.
- D. Not better explained by a schizophrenia spectrum or other psychotic disorder.
- E. No manic or hypomanic episodes, unless the episodes are attributable to substance use or another medical condition.

Note: Criteria A to C represent a **major depressive episode (MDE).*

NOTE

Responses to significant loss (e.g. bereavement, financial ruin, losses from natural disaster, a serious medical illness or disability) may resemble MDE.

Although these symptoms may be considered appropriate to the loss, **presence of a MDE in addition to the normal response** should also be carefully considered, taking into account individual history and cultural norms for expression of grief.

Persistent depressive disorder (dysthymia) in pediatric populations

DSM-5 Criteria for PDD in Pediatric Populations

- A. Depressed or irritable mood for most of the day, for more days than not, for ≥ 1 year (as opposed to ≥ 2 years in adults) either by subjective report or observed by others.
- B. During the period of time described in Criterion A, presence of ≥ 2 of the following 6 symptoms:
 - 1. Increased/decreased appetite
 - 2. Insomnia or hypersomnia
 - 3. Low energy or fatigue
 - 4. Low self esteem
 - 5. Diminished concentration or indecisiveness
 - 6. Hopelessness
- C. No more than 2 months at a time spent free from symptoms described in Criteria A and B.
- D. Criteria for MDD may be continuously present for 1 year.
- E. No history of a manic or hypomanic episode, and criteria for cyclothymic disorder have never been met.
- F. Not better explained by a schizophrenia spectrum or other psychotic disorder.

- G. Not attributable to the effects of a substance or to another medical condition.
- H. Presence of clinically significant distress or impairment in important areas of functioning.

Other depressive disorders

**Please see the [Depressive Disorders chapter](#) for details.*

- Premenstrual dysphoric disorder
- Substance/medication-induced depressive disorder
- Depressive disorder due to another medical condition
- Other specified depressive disorder
- Unspecified depressive disorder

Epidemiology

- Lifetime prevalence of MDE in Canadian youth (age 12 to 19) is estimated to be approximately 5% in males and 12% in females.
 - Other studies estimate MDE prevalence rates of approximately 2% in children and 4-8% in adolescents.
 - In childhood, the M:F ratio is approximately 1:1; in adolescence, up to twice as many girls may be affected.
- Up to 60% of adolescents with depression may have recurrences throughout adulthood.
- Suicide is the second leading cause of death among Canadians aged 15-24, accounting for almost 25% of all deaths in this age group (second only to MVAs).
 - Females attempt suicide more often but males are more often successful.
 - Adults with a history of adolescent depression have a higher rate of suicide than those without.

Screening

- Screening tools alone are not a substitute for a complete interview and clinical judgement in making the diagnosis of a depressive disorder.
- These tools may also be useful in monitoring response to treatment.
- Use of standardized depression screening tools is recommended for children and youth. Some tools include:
 - Children's Depression Inventory (CDI)
 - Beck Depression Inventory (BDI)
 - Center for Epidemiologic Studies – Depression Scale (CES-D)
 - Reynolds Adolescent Depression Scale (RADs)
- When possible, a semi-structured interview should be employed (e.g. Kiddie Schedule for Affective Disorders [K-SADS])

Risk Factors

Biological

- Female sex
- Older adolescent age
- Parent/family history of depression
- Comorbid chronic illness (e.g. diabetes, ADHD)
- Past history of depression
- Comorbid learning disorders
- Genetics (e.g. serotonin-transporter gene variants)
- Medications (e.g. steroids, Accutane)
- Substance use

Psychosocial

- Family or peer conflict (e.g. bullying)
- Adverse childhood experiences (neglect or abuse, whether physical, emotional, or sexual)
- Reactive attachment disorder
- Low SES
- Recent loss (e.g. death of a loved one, end of a romantic relationship)
- Academic difficulties or school failure

- Parents with less education
- Discrimination, social exclusion
- Poor home-school relationships (e.g. presence of conflict)
- Migration (e.g. refugee status)

Clinical Features

- Mood is often more angry than sad, compared to adult population
 - Temper tantrums, mood lability, irritability, low frustration tolerance
 - Anger may be a more acceptable/comfortable emotion than sadness in some households
- Problems with sleep, appetite, energy and concentration
- Decreased enjoyment of life, school, or activities
- Trouble coping at home, school, or work
- Children may become more anxious/clingy with caregivers
- Socially withdrawn, yet may still feel good while with their friends
- Somatic complaints are more common as children/adolescents may still be developing their ability to verbalize their feelings
- Behavioural changes may be mistaken for “teenage behaviour” and brushed aside

NOTE

For a comparison of manifestations of depression across different age groups, please see [Table 3 in the Depressive Disorders chapter](#).

Differential Diagnosis

- Other medical disorders - e.g. hypothyroidism, mononucleosis, anemia, autoimmune diseases, neoplasms
- Substance-induced depressive disorder - e.g. EtOH, cannabis, amphetamines, cocaine
- Medication-induced depressive disorder - e.g. stimulants, corticosteroids, oral contraceptives, Accutane, antihypertensives
- Adjustment disorder with depression
- Bipolar disorder
- Bereavement
- Autism spectrum disorder
- Reactive attachment disorder

- Parent-child relational disorder
- ADHD

Assessment

Safety and risk assessment

- Danger to self (suicide, self-harm)
- Danger to others (homicide, aggression)
- Abuse/trauma
- Impairment of reality

Self-harm (non-suicidal self-injury)

- A coping strategy used to deal with intense emotions or difficult situations
 - Injuries can range from minor to more serious, but are generally not life-threatening
- Usually starts in adolescence and can carry on into adulthood
 - In early adolescence, girls are more likely than boys to engage in self-harm behaviors
 - As age increases, males and females are at similar risk
- Includes cutting, scratching, burning, biting, skin picking, hair pulling, overdosing or poisoning (but not to lethal levels), head banging

Suicide Risk

- Assess risk at every clinical encounter
- History of previous suicide attempt is the strongest risk factor

Risk factors	Protective factors
• Previous suicide attempt(s) • Feelings of hopelessness or worthlessness • Family history of suicide • Exposure to others who have died by suicide • Mental health disorders including substance use disorder • Physical illness • History of abuse or mistreatment • Impulsive or aggressive tendencies • Financial loss • Relationship loss • Isolation or lack of social support • Easy access to methods/means of suicide	• Psychological and clinical care for physical, mental, and substance use disorders • Secure attachments to family and other nurturing adults • Developing problem-solving and conflict-resolution skills • Family and community support • Religious and cultural belief systems that discourage suicide • Limited access to methods/means of suicide

Table 2. Risk factors for and protective factors against suicide.

Adapted from Suntharalingam, 2020.

Investigations

- CBC with differential
- Extended electrolytes
- Thyroid function
- Renal & liver function
- Vitamin B12, folate
- Vitamin D
- Glucose
- Iron studies
- Drug screen
- Medications review
- ECG

Psychiatric comorbidities

- Anxiety disorders
- ADHD
- Disruptive behavioural disorders
- Substance use disorder
- Eating disorders
- Learning disabilities

Psychosocial assessment

- Parent-child relationship – supportive/critical/stressed
- Social stresses - school, bullying, social pressures
- Friendships, romantic relationships – supportive/destructive/mixed
- Other stressors
- Other support systems

Management

Psychosocial

- Psychoeducation for patient and family, and family therapy, if indicated.
- Lifestyle changes: good sleep hygiene, healthy eating habits, exercise.

Psychotherapy

- Psychotherapy should be considered first-line in mild to moderate presentations.
- CBT confers modest antidepressant effects in depressed children/adolescents relative to comparison conditions (e.g. waitlist, minimally-treated, active placebo), with more evidence for use in adolescents.
- Interpersonal therapy (IPT) has shown benefit over comparison conditions in both short and long term contexts
- Internet-based interventions may reduce symptoms, especially in adolescents

EVIDENCE-BASED PRACTICE

As there is no clear comparative advantage for pharmacotherapy or psychotherapy in treating children/youth with non-treatment-resistant MDD, **psychotherapy should be the first line of treatment in mild to moderate MDD.**

Recommendation	Treatment	Level of evidence
First line	CBT or IPT	Level 1
	Internet-based psychotherapy (for mild cases, if in-person is not possible)	Level 1
Second line	Fluoxetine	Level 1
	Escitalopram, sertraline, citalopram ^a	Level 2
Third line	Venlafaxine ^b , TCA ^b	Level 2
Minimal/nonresponse		
First line	Add SSRI to psychotherapy	Level 1
Second line	Switch to another SSRI (if unresponsive to fluoxetine)	Level 2
Third line	Venlafaxine ^b	Level 2
	TCA ^b	Level 3
Treatment-resistant		
First line	SSRI + psychotherapy	Level 2
Second line	Switch to another SSRI (if unresponsive to fluoxetine)	Level 2
Third line	Venlafaxine ^b	Level 2
	TCA ^b	Level 3
	Neurostimulation (ECT ^b or rTMS ^b)	Level 3

Table 2. Recommended treatments for MDD in children and adolescents.

Adapted from the CANMAT 2016 Guidelines.

CBT: cognitive behavioural therapy; ECT: electroconvulsive therapy; IPT: interpersonal therapy; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; rTMS: repetitive transcranial magnetic stimulation.

^aNot recommended in congenital long QT syndrome, congenital heart disease, or hepatic impairment.

^bOnly recommended for adolescents (>12 years old).

Pharmacological

Antidepressant therapy

- Pharmacotherapy may be initiated early in youth with moderate to severe MDE, with SSRIs as first-line agents
 - Health Canada has not approved any antidepressants for use in age <18 years
 - Fluoxetine, escitalopram, sertraline, and citalopram are the most commonly used
 - Fluoxetine is the only SSRI that is FDA-approved for preadolescents (age ≥8 years) and is also available in liquid formulation
 - Both fluoxetine and escitalopram are FDA-approved for age ≥12 years
 - The FDA issued a black-box warning in 2003 on SSRI use in individuals <24 years of age due to concern for increased risk of

suicidal ideation.

- One possible explanation is that the adolescents with SSRI exposure were more severely depressed and at higher risk of suicidality.
 - As untreated depression is more likely to result in harm, SSRI treatment may still be appropriate with careful monitoring and follow-up.
- TCAs have little utility in treating depression in children, and there is only minimal evidence to support their use on adolescents.
- MAOIs are not recommended in children and youth due to:
 - Lack of studies of effectiveness in this population
 - Significant side effect profile
 - Potential difficulty maintaining a tyramine-free diet
- **Please see the [Depressive Disorders chapter - Pharmacological Therapy section](#) and the [Pharmacology chapter - Antidepressants section](#) for more information including mechanisms of action, side effects, discontinuation syndrome, and serotonin syndrome.*

Timepoint	Fluoxetine (Prozac)	Sertraline (Zoloft)	Notes
Start	10 mg	25 mg	Follow-up: weekly for first 4 weeks of treatment, then every 2 weeks for a month, and then at 12 weeks of treatment • Monitor for increased suicidal ideation and other adverse events • Augment with another medication (e.g. bupropion) if some symptoms remain after maximum dose is reached • If after 12 weeks only partial response is reached despite adequate dosing, consider switching
1st week	20 mg (target dose) for 4 weeks	50 mg	
2nd week		75 mg (target dose) for 4 weeks	
Further dose titration	30 mg for 4 weeks 40 mg for 4 weeks 50 mg for 4 weeks 60 mg for 4 weeks	100 mg for 4 weeks 125 mg for 4 weeks 150 mg for 4 weeks 175 mg for 4 weeks 200 mg for 4 weeks	Stop increasing dose at any time patient is back to fully functioning Maintenance therapy: 1 year or more if history of ≥ 2 MDEs or 1 severe/chronic MDE; 6-12 months if no MDD history To discontinue, taper slowly during a relatively stress-free time

Table 3. Example dose titration for fluoxetine and sertraline.

EVIDENCE-BASED PRACTICE

- Cochrane review of newer generation antidepressants showed that median baseline risk of suicide-related outcomes (ideation and behaviour) rose from 25/1000 to 40/1000 (Hetrick et al., 2012).
- FDA meta-analysis showed a ~1.5- to 2-fold risk of increased suicidal thoughts/behaviour (no deaths reported) for newer antidepressants (Bridge et al., 2007).
- Although epidemiological data did not demonstrate a relationship between prescriptions of antidepressants and suicide deaths (Kisicki et al., 2012), a systematic review of observational studies show higher risk for suicidal acts with SSRI exposure in adolescents, but a reduced risk in older age groups (Barbui et al., 2009).

CLINICAL PEARL

Start at the low end of the therapeutic range and continue dose for 4 weeks before considering an increase.

Neurostimulation

- Please see the [Depressive Disorders chapter – Neurostimulation section](#).

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Review Questions

1. A diagnosis of DMDD can co exist with the following psychiatric disorders except:
 - a) MDD
 - b) ADHD
 - c) Substance use disorder
 - d) Oppositional defiant disorder
 - e) Conduct disorder

2. An adolescent has an adequate trial of fluoxetine but is still feeling significantly depressed and has suicidal ideation. The clinician should:
 - a) Add CBT and continue fluoxetine
 - b) Add CBT and stop fluoxetine
 - c) Add CBT and switch to another SSRI
 - d) Augment fluoxetine with an antipsychotic
 - e) Switch to sertraline only

3. A 13 year old male is referred to you with a history of severe depression. You want to treat him with an antidepressant. What are the antidepressants that are approved by FDA for the treatment of adolescent depression?
 - a) Bupropion and escitalopram
 - b) Escitalopram and fluoxetine
 - c) Fluoxetine and sertraline
 - d) Fluoxetine and venlafaxine
 - e) Paroxetine and sertraline

Answers:
 1. (d)
 2. (c)
 3. (b)

Anxiety Disorders

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Faculty Reviewer: **Dr. Rebecca Gomez**, MB, BAO, BCh, FRCPC; Psychiatrist, Operational Stress Injury Clinic and Program psychiatrique francophone du nord de l'Ontario; Lecturer, Department of Psychiatry, University of Ottawa.

Introduction

Definitions

- Anxiety: response to anticipated threat (in the future).
- Fear: response to imminent threat (in the present).
- Main brain structure involved is the amygdala.

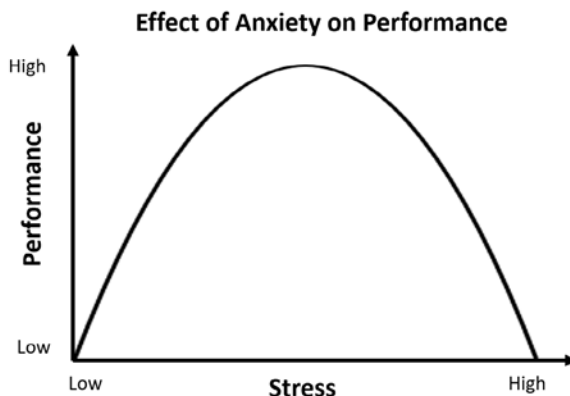


Figure 1. Stress-diathesis model of anxiety.

Based on Monroe SM, Simons AD. Diathesis-stress theories in the context of life stress research: Implications for the depressive disorders. *Psychological Bulletin*. 1991;110 (3): 406–425

NOTE

Effect of anxiety on performance

Functional anxiety is adaptive, tolerable, mobilizing, and motivating.

Dysfunctional anxiety is disproportional, uncontrolled, distressing, and impairing.

Types of anxiety disorders

- Chapter on “Anxiety Disorders” in the DSM-5 includes the following:
 - Separation anxiety disorder*, Selective mutism*, Social anxiety disorder, Specific phobia, Panic disorder, Agoraphobia, Generalized anxiety disorder, substance or drug induced anxiety disorder, anxiety disorder due to a medical condition

*Covered in the [Childhood Anxiety Disorders chapter](#).
- The following psychiatric disorders were classified in the “Anxiety Disorders” chapter in the DSM-4, but were given their own distinct chapters in the DSM-5:
 - Obsessive-compulsive and related disorders
 - Trauma-and stressor related disorders

Risk Factors

**Note: These risk factors apply to all anxiety disorders.*

- Temperamental:
 - Negative affectivity (neuroticism): proneness to experiencing negative emotions
 - Anxiety sensitivity: disposition to believe that symptoms of anxiety are harmful.
- Environmental:
 - Adverse childhood experiences.
- Genetic:
 - Heritability varies depending on type of anxiety disorder ([Table 3](#)).
 - Temperamental traits predisposing individuals to anxiety disorders are genetically influenced.

Epidemiology

- For most anxiety disorders, F:M = 2:1
- In general, anxiety disorders begin in early life (childhood to young adulthood)
- Prevalence rates decrease in 50 and older age groups.

Clinical Features

- Acute: panic attacks, sympathetic nervous system arousal.
- Chronic: tension, exhaustion, indigestion or GERD, unexplained somatic symptoms

	Childhood and adolescence	Adulthood	Old age
Presenting complaints	Irritability Poor sleep Somatic symptoms Behavioural symptoms	Fatigue Poor sleep Irritability Somatic symptoms	Cognitive and somatic symptoms Fatigue Insomnia
Contexts	School	Work/social life	ADLs, healthcare
Burden	School refusal Burden on family	Disability Interpersonal dysfunction	Caregiver burden Physical health Premature death
Comorbidities	Depression ADHD	Depression Substance abuse	Depression Dementia

Table 1. Varying features of anxiety disorders associated with age.

FYI

Cultural aspects of anxiety disorders

Culture shapes the experience and expressions of anxiety symptoms, signs, and behaviors.

Anxiety manifestations may or may not be recognized as an illness within the culture (i.e. cultural idioms of anxiety or distress, cultural explanations or perceived cause).

Examples of cultural syndromes with anxiety:

- “Susto” in Latinos
 - Frightening event causes the soul to leave the body and results in unhappiness and sickness
- “Ataque de nervios” in Latinos - Acute agitation usually in reaction to stressful events
- “Taijin kyofusho” in Japan and “taein kong po” in Korea - Concern about offending or embarrassing others
- “Koro” in India, China, Japan - Fear that the penis is shrinking or retracting
- “Khyal cap” in Southeast Asia - “Wind” attacks = panic-like episodes

FYI

Contrary to popular belief, the prevalence rate of anxiety disorders appear to be stable over time in the last few decades.

	DSM-5 criteria*
Social anxiety disorder	A. Marked fear/anxiety about social situation(s) of possible scrutiny B. Fear of negative evaluation C. Social situations almost always provoke fear/anxiety D. Situations are avoided or endured with intense fear/anxiety E. Fear/anxiety out of proportion to the actual threat F. Duration >6 months G. Significant distress or functional impairment H. Not explained by substance or another medical condition I. Unrelated or excessive to a present medical condition
Panic disorder	A. Recurrent unexpected panic attacks. • Abrupt surge of intense fear or discomfort with at least 4 out of 13 fast-peaking symptoms** B. >1 of the attacks has been followed by 1 month or more of one or both of the following • Concern or worry about additional attacks or their consequences • A significant maladaptive change in behaviour to avoid panic attacks C. Not caused by substance or another medical condition D. Not better explained by another mental disorder.
Agoraphobia	A. Marked fear or anxiety about >2 of the following 5 situations: public transportation, open spaces, enclosed spaces, standing in line or being in crowd, being outside home alone. B. Fear or avoidance due to perceived difficulty to escape or get help in case of panic-like or other symptoms C. Agoraphobic situations almost always provoke anxiety D. Agoraphobic situations are actively avoided, require a companion or endured w/ fear or anxiety E. Fear or anxiety are out of proportion to the actual danger F. Duration >6 months G. Causing significant distress/impairment H. Clearly excessive in relation to medical condition, if present
Generalized anxiety disorder	A. Excessive anxiety and worry most days for at least 6 months about a number of events or activities B. Worry is difficult to control C. Anxiety/worry associated with at least 3 of the following 6 symptoms: restlessness, fatigue, difficulty concentrating, irritability, muscle tension, insomnia D. Significant distress or functional impairment E. Not caused by the effects of substance or another medical condition
Specific phobia	A. Marked fear or anxiety about a specific object or situation B. Exposure provokes fear or anxiety C. Phobic object or situation is actively avoided or endured with fear or anxiety D. The fear or anxiety is out of proportion to the actual danger E. Lasting for 6 months or more F. Causes significant distress or functional impairment
Separation anxiety	A. Developmentally inappropriate and excessive fear/anxiety about separation from major attachment figures (MAF); shown by >3 of the following: 1. Distress when anticipating/experiencing separation from home or from MAFs 2. Worry about losing MAFs or about possible harm to them 3. Worry about an untoward event that causes separation from a MAF 4. Reluctance/refusal to leave a MAF because of the fear of separation 5. Fear/ reluctance about being alone or without MAFs at home or in other settings 6. Reluctance or refusal to sleep away from home or go to sleep without being near MAF 7. Repeated nightmares about separation 8. Repeated complaints of physical symptoms when separation from MAFs occurs or is anticipated B. >4 weeks in childhood and 6 months in adults C. Disturbance leads to distress in important areas of functioning

Table 2. DSM-5 criteria for anxiety disorders.

* The DSM-5 criteria for all the above anxiety disorders necessarily include: “**Not better explained by another mental disorder**” (but was left out of the table for conciseness). Additionally, the table does not include selective mutism, which is covered in the [Childhood Anxiety Disorders chapter](#).

** Fast-peaking symptoms: Palpitations, sweating, trembling, shortness of breath, feelings of choking, chest pain/discomfort, nausea/abdominal distress, dizziness, chills/heat sensations, paresthesias, derealization, fear of losing control or “going crazy”, fear of dying.

	Social anxiety disorder (SAD)	Panic disorder (PD)	Agoraphobia	Generalized anxiety disorder (GAD)	Specific phobia	Separation anxiety
Epidemiology	F>M in general population; M>F in clinical settings	F>M of 2:1	F>M of 2:1	F>M of 2:1	F>M of 2:1 but F=M for blood injection injury phobia	
12-month prevalence (in the U.S.)	7%	2-3%	1.7%	Adolescents: 0.9% Adults: 2.9%	7%-9%	Adults: 0.9-1.9% Children: 4% Most prevalent anxiety disorder in children <12 years
Age of onset	Median age at onset: 13	Median age of onset: 20-24	Overall mean age at onset: 17 years Agoraphobia without preceding panic attacks or panic disorder mean age of onset: 25-29 years	Median age of onset: 30	Median age at onset: 7-11 Mean age of onset: 10	
Specific risk factors (in addition to general risk factors mentioned previously)	<u>Genetic/physiological:</u> First-degree relatives have a 2 to 6 times greater chance of having social anxiety disorder.	<u>Environmental:</u> Smoking Interpersonal stressors <u>Genetic/physiological:</u> Increased risk among offspring of parents with anxiety, depressive, and bipolar disorders. <u>Other:</u> Respiratory disturbance, such as asthma, is associated with panic disorder.	<u>Environmental:</u> Stressful events (i.e. being attacked/mugged) Reduced warmth in family climate Parental overprotection <u>Genetic/physiological:</u> Heritability is 6.1%. Of the various phobias, agoraphobia has the strongest and most specific association with the genetic factor that represents proneness to phobias.	<u>Environmental:</u> Parental overprotection <u>Genetic/physiological:</u> One-third of the risk of experiencing generalized anxiety disorder is genetic, and these genetic factors overlap with the risk of neuroticism and are shared with other anxiety and mood disorders, particularly major depressive disorder.	<u>Environmental:</u> Parental overprotection Parental loss and separation Negative or traumatic encounters with the feared object or situation <u>Genetic/physiological:</u> Genetic susceptibility to a certain category of specific phobia For blood-injection-injury phobia: propensity to vasovagal syncope (fainting) in the presence of the phobic stimulus.	<u>Environmental:</u> Often develops after life stress, especially a loss, change of schools, parental divorce, more, etc. Parental overprotection or intrusiveness. <u>Genetic/physiological:</u> Heritability estimated at 73%. Children with separation anxiety disorder display enhanced sensitivity to respiratory stimulation using CO ₂ -enriched air.

Table 3. Summary table of the DSM-5 anxiety disorders.

Baseline Assessment and Monitoring

- Review of systems, prescribed and OTC medications, substance use (including caffeine) and safety risks
- Laboratory tests: CBC, electrolytes, fasting glucose and lipid profile, liver enzymes, BUN and creatinine, TSH, urine drug screen; ECG
- Medication: monitor initially every week, then every 4 weeks for effect, adverse effects and adherence
- Monitor closely in young children, older or medically ill, those with metabolic risks or taking multiple medications

Differential Diagnosis

- Cardiac conditions (panic attack can mimic myocardial infarction; valvular insufficiencies can present as panic attacks)
- Pulmonary conditions
- Hyperthyroidism
- Pheochromocytoma
- Vestibular dysfunctions
- Seizure disorders

Management

Condition	Recommendation
At-risk or mild anxiety	Psychoeducation Guided self-help (bibliotherapy) Internet-based CBT
Moderate anxiety	CBT or pharmacotherapy, or both
Severe or resistant anxiety	Both CBT and pharmacotherapy

Table 4. Approach to selection of treatment modality for anxiety disorders.

Psychological

- Cognitive behavioural therapy (CBT) - first-line treatment
 - CBT protocols for anxiety disorders include:
 - Education (especially important in panic attacks/ disorder)
 - Examining perception of danger/fear/threat

FYI

Effective components of CBT for anxiety

Exposure:

- Encourage patient to face fears: gradual, repetitive exposure, corrective experiences

Reduction of overt/covert safety behaviours:

- Encourage patient to restrict anxiety-reducing behaviours (i.e. avoidance)

Cognitive strategies:

- Cognitive restructuring, behavioural experiments, challenging dysfunctional beliefs.

- Linking thoughts, behaviours, emotions, and bodily sensations
 - Confronting feared trigger in a safe and graduated manner
 - Increasing stress reduction techniques (deep breathing, progressive muscle relaxation)
 - Reducing safety behaviours (especially avoidance)
 - Relapse prevention
- Supportive psychotherapy for anxiety:
 - Teach coping skills and problem solving
 - Teach anxiety reduction skills (i.e. using breath)
 - Boost self-confidence and sense of self control
 - Promote emotional growth and self-expression
 - Practice goal directed behavior; redirect energy and creativity
 - Identify a new source of fulfillment

Biological

- See [Table 5](#) for summary chart and [Table 6](#) for dosing
- SSRI or SNRI antidepressants:
 - Long-term, remission oriented use (however remission unlikely with medications alone)
 - Allow 6-8 weeks for response evaluation
 - Attention to worsening on discontinuation
- Benzodiazepines and anxiolytics:
 - Short-term, symptom relief oriented use (2-6 weeks)
 - Facilitation of treatment with antidepressant (while titrating to targeted dose)
 - Minimal effective dose - be mindful of risk of addiction (especially tolerance)
 - Discontinuation worsening - slow taper
- Alternate and adjunct medications:
 - Serotonergic
 - Buspirone
 - Noradrenergic
 - Desipramine, nortriptyline, bupropion, mirtazapine
 - GABA/ion channels - anticonvulsants
 - **Pregabalin**, gabapentin, valproate, topiramate
 - Multi-receptor - atypical antipsychotics
 - E.g. Quetiapine, olanzapine, risperidone, aripiprazole

CLINICAL PEARL

When starting SSRIs, remember “start low, go slow, and aim high”.

	1st-Line	2nd-Line	3rd-Line	Adjunct
Panic disorder	SSRI Venlafaxine	Benzodiazepine TCA Other antidepressant (AD)	MAOI Other AD Anticonvulsants Atypical antipsychotics (AP)	Benzodiazepine Anticonvulsant Atypical AP
Social anxiety disorder	SSRI Venlafaxine Pregabalin	Benzodiazepine Gabapentin Phenelzine	Other AD Anticonvulsants	Buspirone Atypical AP
General anxiety disorder	SSRI Venlafaxine Pregabalin	Benzodiazepine Buspirone Quetiapine Other AD	Other AD Anticonvulsants	Pregabalin Atypical AP

Table 5. Recommended pharmacotherapy treatment for different anxiety disorders.

Tips When Prescribing Medications for Anxiety

- Consider patient's preference and past results (ideas, concerns, expectations).
- Patients with anxiety hesitate to start, change, stop, or take multiple medications.
- Consider starting at lower doses of SSRIs (compared to patients with MDD) and titrate up slowly. Patients with anxiety are more sensitive to side effects, but often require high or maximal doses of medications.
- Discuss adverse effects and black box warnings.
- Monitor adherence and doses.
- In patients with moderate to severe anxiety, a 4-week course of clonazepam twice daily might be necessary to manage symptoms while 1st line medication is titrated up. Be cognizant of risk of addiction when prescribing benzodiazepines, and always taper when discontinuing.

Drug	Starting dose (mg)	Increments (mg)	Usual dose (mg)	Max dose (mg)
Citalopram (Celexa)	10	10	20	40
Escitalopram (Lexapro)*	5-10	5-10	10-20	20
Fluoxetine (Prozac)*	5-20	5-20	20-40	60
Fluvoxamine (Luvox)	25-50	25-50	100-300	300
Paroxetine (Paxil)	10	10	20	60
Sertraline (Zoloft)*	25	25-50	50-150	200
Pregabalin (Lyrica)	100-150	150	300	600
Venlafaxine (Effexor)	37.5-75	75	75-225	225

Table 6. Dosing chart for first-line medication in the treatment of anxiety disorders.

* Best tolerability and effectiveness.

Anxiety During Pregnancy

- Sex hormones have anxiolytic effects, but anxiety may be precipitated or exacerbated by pregnancy
- Maternal anxiety poses the fetus to risks of neurodevelopmental problems, preterm labor, low birth weight, and lower Apgar scores
- Perinatal OCD and GAD are more prevalent
- Anxiety symptoms and disorders may develop in women with fertility problems and those who experience a pregnancy loss

	Specific perinatal presentation
Panic disorder	General pattern of improvement during pregnancy, followed by worsening during the postpartum.
OCD	Fears of intentionally or accidentally harming the fetus or child (insight intact, preventive efforts).
GAD	Worries about the health of the fetus or anticipation of a painful delivery are common.
PTSD	Childbirth as a trauma; reactivation of past trauma, esp. childhood and adult sexual assault.

Treatment of antenatal anxiety

- CBT as first-line treatment for mild/moderate anxiety and as an adjunct to medication whenever possible
- Weigh risks of anxiety against risks of treatment, to both mother and fetus, throughout the pregnancy
- Choose well-studied agents with few active metabolites, low placental transfer, and minimal drug-drug interactions
- Favor monotherapy
- Avoid agents with adverse effects that complicate pregnancy
- Dosage requirements may change during the pregnancy (increased dose in third trimester)
- Avoid high doses (especially benzodiazepines)
- Avoid abrupt discontinuation whenever possible

Use of antidepressants in pregnancy

- Side-effects of antidepressants may be challenging (nausea in first trimester)
- Some women may need dose increases as pregnancy progresses
- A partial dose taper may be considered toward the end of pregnancy in women with relatively low relapse risk
- If breastfeeding is planned, sertraline may be a treatment of choice because the average breast milk sertraline level is low (an estimated 0.5% of the maternal weight-adjusted dose)

IMPORTANT

Use of benzodiazepines in pregnancy

- Caution is warranted in the first trimester, although data about teratogenicity are controversial.
- A gradual taper may be considered toward the end of pregnancy to prevent neonatal withdrawal.
- Lorazepam does not accumulate in fetal tissue and may therefore decrease the risks associated with antenatal benzodiazepine use.

EVIDENCE-BASED PRACTICE

The antidepressants with the most evidence in pregnancy are **fluoxetine** and **sertraline**.

IMPORTANT

Paroxetine should be avoided in the first trimester.

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Review Questions

1. A 29-year-old female patient books a visit with you to request medication for insomnia. She does not take any medications, and has no significant medical history nor allergies. Her insomnia began 6 months ago when her father was admitted to hospital after a myocardial infarction. Since then, she has been having panic attacks several times per week, her neck and shoulders are stiff and sore, she feels exhausted all day, and she has used up all of her sick days at work. Upon further questioning, you learn that she has “always been a worrier.” After providing her with a detailed handout on sleep hygiene and psychoeducation on anxiety and panic attacks, as well as an extension of her sick leave, you recommend:
 - a) CBT + 1st line SSRI for panic disorder, and follow-up in 2 weeks
 - b) Trazodone for initial insomnia, and follow-up in 2 weeks
 - c) CBT + low dose Clonazepam PO BID + 1st line SSRI for generalized anxiety disorder, and follow-up in 2 weeks
 - d) CBT + 1st line pharmacotherapy treatment for Illness anxiety disorder, and follow-up in 2 weeks
 - e) Reassure, and follow-up in 4 weeks to review handouts

2. You are seeing a 26-year-old male who came to see you at the urging of his girlfriend. He reports she has been bothering him to cut down on his use of cannabis, which has increased since starting his new job in marketing. He smokes about 1g daily, which includes taking 1-2 puffs before important client presentations. Without it, he feels like his heart is going to jump out of his chest, his hands cannot stop shaking, and he sweats profusely during those times. He has smoked recreationally with friends since his mid-teens. He is generally well, and does not take any medications. When you ask about his schooling, you find out he has always hated standing up in front of the class, because he was worried others would make fun of him, and sometimes feigned illness to avoid giving an oral presentation. Having smoked cannabis has always made it easier to attend parties and socialize in university. What is the correct diagnosis?
 - a) Panic disorder
 - b) Agoraphobia
 - c) Cannabis use disorder
 - d) Social anxiety disorder
 - e) Specific phobia

Review Questions (continued)

3. A 32-year-old male comes to see you at the advice of the emergency room physician, who thinks he has anxiety. Your patient has been to the emergency room 3 times in the past 6 weeks due to what feels like a heart attack, with shortness of breath, chest pain, nausea, sweating, and dizziness. He has a history of well-controlled asthma, but reports that he has been using his inhaler more often in the past 3 months due to the above symptoms. He has also stopped playing hockey twice a week, because when he feels short of breath, he feels he is going to have an asthma attack. His symptoms are not always precipitated by physical activity—they sometimes occur spontaneously during the day. He lives at home with his wife and 10-month old baby, as well as his mother, whose home is undergoing renovations. He does not want to take medications. What is his diagnosis and best treatment option?
- a) Panic disorder; start 1st line SSRI.
 - b) Panic disorder; recommend CBT.
 - c) Generalized anxiety disorder with panic attacks; recommend CBT and 1st line SSRI.
 - d) Panic disorder; recommend CBT and start 1st line SSRI.
 - e) Generalized anxiety disorder with panic attacks; recommend CBT.

Answers:

1. c) Diagnosis is GAD with panic attacks. This question highlights the common presentation of insomnia for underlying anxiety, and assesses knowledge of GAD symptoms and treatment, including the higher severity of illness prompting the use of clonazepam BID initially.
2. d) Diagnosis is SAD. This question highlights the common presentation of substance use for underlying anxiety, and assesses knowledge of SAD symptoms, distinguishing SAD from specific phobia. Although he may have cannabis use disorder, there is insufficient information in the stem to make that diagnosis.
3. b) Diagnosis is Panic disorder. This question highlights the common presentation of emergency visits for MI, and assesses knowledge of PD symptoms and risk factors (asthma, psychosocial stressors). It also emphasizes the importance of listening to patient preference, in this case, not wanting to try medications.

Pediatric Anxiety Disorders

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Introduction

- Anxiety is a normal part of childhood, but excessive or irrational worries can be disabling. Features of anxiety disorders (vs. developmentally normative anxiety) include:
 - Excessive or persistent beyond developmentally appropriate periods
 - Long in duration (typically >6 months) or are recurrent
 - Cause distress, resulting in impaired functioning
 - A greater number and intensity of symptoms
- Anxiety and related disorders can have significant long-term impact on a child's life.
 - May increase risk of major depressive disorder (MDD), other anxiety disorders, and substance use disorder in adulthood.
- Anxiety and related disorders among younger patients are associated with higher rates of comorbid psychiatric conditions, substance use disorder, sleep problems, somatic symptoms, and suicidality.
 - Can also be detrimental to a child's development and functioning by causing problems with cognition and attention, academic performance, and peer relationships.

Anxiety Disorders in the DSM-5

- | | |
|---|---|
| <ul style="list-style-type: none">• Separation anxiety disorder*• Selective mutism*• Specific phobia**<ul style="list-style-type: none">- Animal- Natural environment- Blood-injection-injury (fear of blood, injections/transfusions, other medical care, and/or injury)- Situational- Other | <ul style="list-style-type: none">• Social anxiety disorder (social phobia)**• Panic disorder• Agoraphobia• Generalized anxiety disorder (GAD)**• Substance/medication-induced anxiety disorder• Anxiety disorder due to another medical condition• Other specified anxiety disorder• Unspecified anxiety disorder |
|---|---|

*Common anxiety disorders in childhood.

**Diagnoses with modified criteria for children.

This chapter focuses on the diagnoses marked with * or ** above. For more information on the other anxiety disorders, please see the [Anxiety Disorders chapter](#).

Common Anxiety Disorders in Children

Separation Anxiety Disorder

DSM-5 Criteria for Separation Anxiety Disorder

- A. Developmentally inappropriate and excessive fear or anxiety about separation from major attachment figure(s) as shown by ≥ 3 of following:
 - 1. Recurrent excessive distress with anticipated or real separation from home or major attachment figure(s).
 - 2. Persistent and excessive worry about harm to or loss of major attachment figure(s).
 - 3. Persistent and excessive worry about adverse event that causes separation from major attachment figure(s).
 - 4. Persistent reluctance to go away from home due to fear of separation.
 - 5. Persistent and excessive fear about being alone or without major attachment figure(s) at home or in other settings.
 - 6. Persistent reluctance to sleep away from home or go to sleep without being near major attachment figure(s).
 - 7. Repeated nightmares involving the theme of separation.
 - 8. Repeated physical symptoms with anticipated or real separation from major attachment figure(s).
- B. Fear or anxiety lasts ≥ 4 wks in children/adolescents and ≥ 6 mos in adults.
- C. Clinically significant distress or impairment in important areas of functioning.
- D. Not better explained by another mental disorder.

Selective Mutism

DSM-5 Criteria for Selective Mutism

- A. Consistent failure to speak in specific social situations in which there is an expectation for speaking (e.g. at school) despite speaking in other situations.
- B. The disturbance interferes with educational or occupational achievement or with social communication.
- C. Duration of disturbance is ≥ 1 month (not limited to the first month of school).
- D. Failure to speak is not attributable to a lack of knowledge of, or comfort with, the spoken language required in the social situation.
- E. Disturbance not better explained by a communication disorder (e.g. childhood-onset fluency disorder) and does not occur exclusively during the course of autism spectrum disorder, schizophrenia, or another psychotic disorder.

Diagnoses with Modified Criteria for Children

**NOTE: Only the modifications are discussed in this section. For the full diagnostic criteria please see the [Anxiety Disorders chapter](#).*

Specific Phobia

- In children, the fear or anxiety may be expressed by crying, tantrums, freezing, or clinging.
- **Specifiers:** “Other” for children may include loud sounds or costumed characters.

Social Anxiety Disorder (Social Phobia)

- In children, the anxiety must occur in peer settings and not just during interactions with adults.
- In children, the fear or anxiety may be expressed by crying, tantrums, freezing, clinging, shrinking, or failing to speak in social situations.

Generalized Anxiety Disorder

- Criterion C lists 6 symptoms (restlessness, being easily fatigued, difficulty concentrating, irritability, muscle tension, and sleep disturbance) of which 3 must be present for adults – in children, **only 1 of these is required.**

Epidemiology

- Anxiety and related disorders were the most common psychiatric disorders noted in the American National Comorbidity Survey-Adolescent supplement (NCS-A; age 13-18), with a lifetime prevalence of 31.9%.
 - In adolescents, anxiety and related disorders were found to have the earliest median age of onset (age 6) compared to other psychiatric disorders (age 11-15).
 - The same trend was seen in adults, where the median age of onset for anxiety and related disorders was 11 vs. age 20-30 for other psychiatric disorders.
- In 2009, 4% of youth (age 12-19) and 5.8% of young adults (age 20-29) in Canada were diagnosed with an anxiety disorder. These rates were higher in young women and in Aboriginal populations.
- Individuals may have multiple comorbid anxiety disorders (e.g. “anxiety triad” – GAD, separation anxiety, and social anxiety often co-occur together).
- Separation anxiety is a significant cause of school refusal - may account for 50-80% of cases.

Risk Factors

Genetic and physiological

- Parental anxiety disorder has been associated with increased risk of anxiety disorder in children.
- Heightened physiologic arousal to stress or anxiety-provoking situations.

Temperamental

- Early temperamental traits of passivity and shyness between ages 3 to 5.
- Behavioural inhibition (a tendency to show fear and withdrawal in new or unfamiliar situations).

Environmental

- Anxious parents may model fear and anxiety, reinforce anxious coping behaviour, and/or unwittingly maintain avoidance.
- Overprotective, overcontrolling, or overly critical parenting styles can limit the development of autonomy in children and may also increase risk of anxiety disorders in children with temperamental vulnerability.
- Insecure attachment relationships with caregivers, especially anxious/resistant attachment, can contribute to the development of childhood anxiety disorders.
- Maternal depression and anxiety may have significant detrimental effect on attachment, emotion regulation and stress responses
- Family accommodation – facilitates avoidance; failure to accommodate may result in the child becoming angry or abusive with worsening anxiety symptoms.
- Abuse and trauma
- Academic or social stressors
- Loss

Differential Diagnosis

- Anxiety disorder due to a medical condition – e.g. for panic attacks: hyperthyroidism, hyperparathyroidism, pheochromocytoma, vestibular dysfunction, seizure disorders, cardiac dysrhythmias, asthma
- Substance-induced anxiety disorder – e.g. EtOH, cannabis, caffeine
- Medication-induced anxiety disorder – e.g. corticosteroids, stimulants for ADHD
- Mood disorder – especially with irritable mood
- Obsessive compulsive disorder (OCD; vs. GAD – content of GAD worries is usually “normal”, while obsessions tend to be irrational or unrealistic)
- Attention deficit hyperactivity disorder (ADHD; vs. GAD – both can exhibit restlessness or inattention, however in GAD this is driven by

intrusive worries and hypervigilance to threat cues, while in ADHD these symptoms are caused by preoccupation with external activities or stimuli)

- Autism spectrum disorder (ASD; vs. social anxiety – ASD is also associated with repetitive patterns of behaviour or interests, such as echolalia, hyper- or hyporeactivity to sensory input, and inflexible adherence to routines; children with ASD also do not demonstrate fear of social interactions)
- Psychotic disorders (vs. anxiety-driven hallucinations – the latter tend to be tactile or visual hallucinations that present at night, such as a child who sees a man in his room when the lights are off)

Comorbidities

- More than 50% of patients with an anxiety disorder have multiple anxiety disorders.
 - Almost 30% will have ≥ 3 comorbid anxiety or related disorders.
- Common comorbidities:
 - Mood disorders – may significantly increase risk of suicidal behaviour
 - MDD – 60% of MDD patients may also have an anxiety disorder
 - Bipolar disorder
 - Substance use disorders
 - Psychotic disorders
 - ADHD
 - Other medical disorders – e.g. pain syndromes, cardiovascular disease, diabetes, other metabolic syndromes

Screening Tools

- Diagnosis of anxiety is primarily clinical.
- Tools that may be of use:
 - Multidimensional Anxiety Scale for Children (MASC) – self-report screen for children and adolescents

- Screen for Child Anxiety Related Emotional Disorders (SCARED) – both parent- and self-report versions
- Spence Children's Anxiety Scale (SCAS) – both parent- and self-report versions

Investigations

- Postural vitals – postural orthostatic tachycardia syndrome (POTS)
- CBC, differential – anemia, leukocytosis/infection
- Monospot – infectious mononucleosis
- TSH – hyperthyroidism
- Liver function, electrolytes, urea, Cr
- bhCG
- Vitamin B12, folate, vitamin D
- ECG if indicated

Management

Psychosocial

- Psychoeducation for patient and family
- Lifestyle modifications
 - Sleep hygiene
 - Balanced diet
 - Regular exercise
 - Minimize substance use
- School interventions
 - Address bullying, teasing, violence, abuse
 - Appropriate remediation and placement
 - School psychoeducation
- Psychotherapies
 - Cognitive behavioural therapy (CBT)
 - e.g. Coping Cat program for separation anxiety, GAD, and social phobia
 - Presence of comorbidities may reduce efficacy of CBT;

EVIDENCE-BASED PRACTICE

CBT is well regarded as an effective evidence-based treatment.

Meta-analyses and RCTs have demonstrated efficacy of CBT in children with SAD, panic disorder, OCD, PTSD, school refusal, and separation anxiety disorder.

however, integrated protocols that are designed to target both conditions have shown benefits in children with anxiety/related disorder with comorbid ADHD, aggression, or substance use disorder.

- Other strategies:
 - Attention bias modification (ABM)
 - Mindfulness-based therapies (e.g. mindfulness-based stress reduction [MBSR] and mindfulness-based cognitive behavioural therapy [MBCT])
 - Psychodynamic psychotherapy
- Approaches that include the involvement of parents or family may provide additional advantages over those that involve children only, especially if the parents suffer from an anxiety or related disorder.

Biological

- There is good evidence for the efficacy of selective serotonin reuptake inhibitors (SSRIs) in anxiety disorders in the pediatric population. Psychological treatments are generally preferred, however SSRIs may be considered for severe anxiety or if the child is unable to benefit from psychotherapy.

FYI

Components of CBT for pediatric anxiety disorders

- Psychoeducation
- Managing somatic reactions – e.g. relaxation training, diaphragmatic breathing
- Cognitive restructuring
- Problem solving for coping with challenges
- Systematic exposure to feared stimuli or situations with a focus on desensitization, eliminating safety behaviours
- Relapse prevention

Disorder	Antidepressants	Benzodiazepines (*see sidebar)
Panic disorder		Clonazepam (Level 4) Alprazolam (Level 4)
Social anxiety disorder	Fluoxetine (Level 1) Fluvoxamine (Level 2) Paroxetine (Level 2) Venlafaxine XR (Level 2) Escitalopram (Level 3) Sertraline (Level 3) Mirtazapine (Level 3)	
Separation anxiety disorder	Fluoxetine (Level 2) Fluvoxamine (Level 2)	
Generalized anxiety disorder	Fluoxetine (Level 2) Fluvoxamine (Level 2) Sertraline (Level 2)	
School refusal	Citalopram (Level 4) Adjunctive imipramine (Level 2)	

Table 1. Pharmacological therapies for common childhood anxiety disorders.
Information in this table was adapted from Katzman et al., 2014.

IMPORTANT

Benzodiazepines have little evidence supporting efficacy in anxiety and related disorders in children and adolescents.

To minimize risk of addiction, they may be used for short-term therapy in specific situations requiring rapid reduction in severe anxiety symptoms to allow exposure-related psychotherapy.

- Prior to initiation of SSRIs:
 - Document the patient's somatic symptoms of anxiety to prevent misattribution to side effects of medication
 - Screen for bipolar disorder and family history of bipolar disorder
- Monitor for increased risk of suicidality:
 - Fluoxetine is the only SSRI that is FDA-approved for preadolescents (≥ 8 years old), and both fluoxetine and escitalopram are FDA-approved for ≥ 12 years old. Health Canada has not approved any antidepressants for use in < 18 years old.
 - The FDA issued a black-box warning in 2003 on SSRI use in individuals < 24 years of age due to concern for increased risk of suicidal ideation.
 - Please see the [Pediatric Depressive Disorders chapter](#) for further information on the evidence regarding suicide-related outcomes and SSRI use.
 - The potential risks of SSRI use must be weighed carefully against the harms associated with untreated anxiety - as such, SSRI treatment may be appropriate with careful monitoring and follow-up.
- SSRIs are generally well-tolerated in children and adolescents. It is important to start at a low dose and titrate slowly to therapeutic dosages.
 - Most common side effects in children:
 - Activation (e.g., insomnia, agitation, tremor, anxiety)
 - Vomiting and other GI symptoms
 - More common in adolescents:
 - Somnolence
- Benzodiazepines should be avoided where possible
 - Paradoxical reaction to benzodiazepines (disinhibition, increased excitement, confusion) – risk increased in pediatric and geriatric populations
 - Risk of dependence and abuse
- Combination psycho- and pharmacotherapy is also an option if indicated (see sidebar).

EVIDENCE-BASED PRACTICE

Combination psycho- and pharmacotherapy

A randomized controlled trial of 488 children with separation anxiety disorder, GAD, or social anxiety disorder showed that a combination of sertraline and CBT was significantly superior to both monotherapies in (Walkup et al., 2008).

In OCD, the addition of CBT in those with partial response to SSRIs resulted in significantly greater response rates compared to SSRI alone (Franklin et al., 2011).

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Review Questions

1. John is a 9 year old boy who presents with symptoms of generalized anxiety disorder. Which treatment option(s) may be appropriate for patients aged 6 to 18 years with anxiety disorders?
 - a) CBT
 - b) SSRIs
 - c) SNRIs
 - d) Any of the above
 - e) None of the above

2. Which of the following combination therapies could be offered preferentially over either modality alone to treat anxiety disorders in children?
 - a) SSRIs and SNRIs
 - b) SNRIs and CBT
 - c) SSRIs and CBT
 - d) Any of the above
 - e) None of the above

3. Antidepressants that are approved by Health Canada for use in the pediatric population include:
 - a) Fluoxetine
 - b) Sertraline
 - c) Escitalopram
 - d) All of the above
 - e) None of the above.

Answers:
 1. d)
 2. c)
 3. e)

Obsessive-Compulsive Disorder (OCD)

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Definition

- Presence of both obsessions (recurrent intrusive thoughts, images, or urges) and compulsions (repetitive mental or behavioural acts) that are time-consuming or cause significant distress and/or functional impairment.

Types and classification

- DSM-5 chapter on “obsessive-compulsive and related disorders” includes the following: obsessive-compulsive disorder (OCD), body dysmorphic disorder, hoarding disorder, trichotillomania (hair-pulling disorder), excoriation (skin-picking) disorder, substance/medication-induced obsessive-compulsive and related disorder, obsessive-compulsive and related disorder due to another medical condition, and other specified obsessive-compulsive and related disorder and unspecified obsessive-compulsive and related disorder.
- Guided by uOttawa learning objectives, this handbook chapter will focus exclusively on OCD.

FYI

Obsessive-compulsive and related disorders were previously classified in the DSM-4 chapter under “Anxiety disorders”, but was made into its own chapter in the DSM-5.

DSM-5 Criteria for Obsessive-Compulsive Disorder

A. Presence of obsessions, compulsions, or both.

Obsessions defined by both 1 & 2:

1. Intrusive unwanted thoughts/urges/images
2. Attempts to ignore, suppress or neutralize

Compulsions are defined by both 1 & 2:

1. Repetitive behaviours in response to obsessions or rigid rules
2. Behaviours/mental acts aimed at preventing dreaded event
Note: Young children may not be able to articulate the aims of these behaviors or mental acts.

B. The obsessions or compulsions are time consuming or cause significant distress/functional impairment.

C. Not caused by substance or medical condition.

D. Not better explained by another medical condition.

Specifiers:

- Insight: e.g. good, fair, poor, absent, delusional
- Tic-related

Epidemiology

Age of onset

- Mean age of onset in the US: 19.5 years.
- 25% of cases start by 14 years.
- Onset ≥ 35 years is rare.
- Onset of symptoms is usually gradual.

Prevalence

- 12-month prevalence of 1.2% in the US.

Gender differences

- Slightly more common in females than in males, but more common in males during childhood.
- Males have an earlier age of onset and are more likely to have comorbid tic disorders.
- Females: more likely to have symptoms in cleaning dimension.
- Males: more likely to have symptoms in the forbidden thoughts and symmetry dimensions.

Comorbidity

- About 60-90% of patients with OCD also have a comorbid disorder.
- 76% of individuals develop an anxiety disorder in their lifetime.
- 63% develop a mood disorder in their lifetime.
- Comorbid OCPD is common (23-32% of patients with OCD).
- Up to 30% of OCD patients also have lifetime tic disorder.
 - Most common in males with childhood onset of OCD.
 - Triad of OCD, tic disorder, attention-deficit/hyperactivity disorder (ADHD) can be seen in children.

CLINICAL PEARL

Common **symptom dimensions** in OCD include the following:

- Cleaning: contamination obsessions and cleaning compulsions.
- Harm: e.g., fears of harm to oneself or others and related checking compulsions.
- Forbidden or taboo thoughts: e.g., aggressive, sexual, and religious obsessions and related compulsions.
- Symmetry: symmetry obsessions and repeating, ordering, and counting compulsions.

Risk Factors and Pathogenesis

Temperamental risk factors

- Greater internalizing symptoms.
- Higher negative emotionality.
- Behavioral inhibition in childhood.

Environmental risk factors

- Adverse-childhood events.
- Post-infectious autoimmune syndrome, especially for sudden onset OCD.

Genetic and physiological risk factors

- 2x increase in OCD among first-degree relatives of adults with OCD; 10x increase among first degree relatives of children/adolescent onset of OCD.
- Evidence of genetic factors due to a concordance rate of 0.57 for monozygotic vs. 0.22 for dizygotic twins.
- Dysfunction in the orbitofrontal cortex, anterior cingulate cortex, and striatum have been most strongly implicated.

Differential Diagnosis

- Anxiety disorders
- Major depressive disorder
- Other obsessive-compulsive and related disorders
- Eating disorders
- Tic disorder and stereotypes movements
- Psychotic disorders
- Other compulsive-like behaviours
- Obsessive compulsive personality disorder

Management

Psychosocial: Cognitive behavioural therapy

- First-line treatment
- Cognitive behavioural therapy (CBT) protocols for OCD include:
 - Exposure with response prevention (ERP), which involves exposure to feared situation and prevention of compulsive behaviours.
 - Cognitive strategies such as challenging underlying beliefs.
 - Exposure to feared situations.
 - Relapse prevention.

Biological: Pharmacotherapy

- FDA approved agents include selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), and clomipramine (though generally less well-tolerated than SSRIs/SNRIs).
- Adjunctive antipsychotics may be used in refractory cases.
- SSRIs/SNRIs may require higher therapeutic doses than those used for depression.
- **See Table 1 for list of common agents prescribed in the treatment of OCD and dosing guidelines.*

Drug	Starting dose (mg)	Increments (mg)	Usual target dose (mg)	Max dose (mg)	Occasionally prescribed max dose (mg)
Citalopram (Celexa)	20	10-20	40	80	120
Clomipramine (Anafranil)	25	25	100-250	250	N/A
Escitalopram (Lexapro)	10	10	20	40	60
Fluoxetine (Prozac)	20	20	40-60	80	120
Fluvoxamine (Luvox)	50	50	200	300	450
Paroxetine (Paxil)	20	10	40-60	60	100
Sertraline (Zoloft)	50	25-50	200	200	400

Table 1. Common pharmacotherapeutic drugs used in treating OCD.

Adapted from Lambert M. APA Releases Guidelines on Treating Obsessive-Compulsive Disorder. Am Fam Physician. 2008 Jul 1;78(1):131-135.

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Review Questions

1. A 28-year-old man with obsessions about contamination and illness asks that you repeat an HIV screening test, because he has used a public washroom. Which of the following is the most appropriate plan?
 - a) You repeat the test, telling him it is the last time.
 - b) You prescribe the test once every 3 months to reassure the patient.
 - c) You refer the patient to a microbiologist.
 - d) You refuse, telling him that it is impossible to catch HIV by using the washroom.
 - e) You refuse, explaining that repeating the test would become a part of his compulsion.

2. A 22-year-old student presents to your office with a depressed mood. She has been an A+ student, but just started dental school, and comments that now she does not have the time to rewrite all her notes the way she likes. She is still doing well in school, but her classmates tell her she is too “perfectionist”. She makes lists frequently, and feels good when these things are done, but since dental school started, these lists are more difficult to complete.
 - a) Obsessive-compulsive disorder
 - b) Obsessive-compulsive personality disorder
 - c) Adjustment disorder
 - d) Histrionic personality disorder
 - e) Major depressive disorder

3. TCAs are not generally prescribed for treatment of OCD symptoms. There is one specific TCA however that is supported through clinical trials to help with OCD. Which one?
 - a) Amitriptyline
 - b) Nortriptyline
 - c) Desipramine
 - d) Clomipramine
 - e) Imipramine

Answers:
1. e)
2. b)
3. d)

Somatic Symptom and Related Disorders

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Somatization

- Somatization is the manifestation or amplification of physical symptoms in response to emotional stress.
- This is a normal and common experience, however it becomes a problem when individuals are unable to identify the process and seek medical attention for unexplained physical symptoms.
- Also referred to as “medically unexplained physical symptoms” (MUPS).
- Results in increased disability and health care burden, and may account for up to 25-50% of primary care visits.

NOTE

Somatization as defined by Lipowski (1988):

≥ 1 somatic symptom(s) that:

- Lack an adequate medical explanation or are disproportionate to the pathology.
- Cause significant distress or impairment.
- Prompt healthcare-seeking behaviour.

Somatic Symptom and Related Disorders

DSM-5 classification

- Somatic symptom disorder
- Illness anxiety disorder
- Conversion disorder
- Psychological factors affecting other medical conditions
- Factitious disorder
- Other specified somatic symptom and related disorder
- Unspecified somatic symptom and related disorder

Time course

- Acute: usually associated with a stressor
- Subacute: often associated with mood or anxiety disorder
- Chronic: pervasive and enduring pattern of somatization

NOTE

The diagnosis of somatic disorder is based on **the presence of distressing somatic symptoms and associated abnormal thoughts, feelings, and behaviours**, rather than absence of a medical explanation for the symptoms.

- Somatic symptoms and related disorders can co-occur with organic medical disorders.
- Lack of medical explanation still remains a key feature of conversion disorder and pseudocyesis (false pregnancy).

General etiology

- Biological - e.g. increased pain sensitivity, sensitive hypothalamic-pituitary-adrenal (HPA) axis
- Psychological - e.g. early trauma, social learning/sick role
- Psychodynamic - e.g. symbolic of an unconscious inner conflict, self-inflicted punishment

Diagnostic Criteria and Related Information

Somatic symptom disorder

DSM-5 Criteria for Somatic Symptom Disorder

- ≥1 somatic symptom(s) causing significant distress or disruption of daily life.
- Excessive thoughts, feelings or behaviours related to the somatic symptoms or associated medical concerns, manifested by ≥1 of:
 - Disproportionate and persistent thoughts about the seriousness of the symptoms.
 - Persistently high anxiety about health or the symptoms.
 - Excessive time/energy devoted to health concerns or symptoms.
- Although any 1 symptom may not be continuously present, the state of being symptomatic is persistent (typically >6 months).

Specifiers:

- With predominant pain: somatic symptoms predominantly involve pain.
- Persistent: severe symptoms, marked impairment and long duration (>6 months).
- Severity
 - Mild: 1 symptom in Criterion B
 - Moderate: ≥2 symptoms in Criterion B
 - Severe: ≥2 symptoms in Criterion B + multiple somatic complaints or one very severe symptom

Epidemiology and course

- Prevalence is estimated at 5-7%, up to 15%
- Usually occurs between 20-30 years old but can occur at any age
- Likely female > male, as females tend to report more somatic symptoms
- 1/3 to 1/2 of cases eventually improve

Risk factors

- Temperament - negative affectivity (neuroticism), comorbid anxiety/ depression
- Social - fewer years of education, low socioeconomic status
- Psychological - recent stressful life events/ trauma

Diagnostic and clinical features

- Symptoms may or may not be associated with another medical condition.
- May be underdiagnosed in older adults - certain somatic symptoms (e.g. fatigue, chronic pain) and illness worry are sometimes considered “normal” aging.
- In children, most common symptoms include recurrent abdominal pain, headache, fatigue, nausea. The parents’ response to the symptom is crucial as this may determine the level of associated distress.
- Often associated with a high level of medical care utilization which rarely alleviates the individual’s concerns:
 - May seek care from multiple doctors for the same symptoms.
 - Reassurance from a doctor is usually short-lived and may be experienced as not being taken seriously.

Illness anxiety disorder

DSM-5 Criteria for Illness Anxiety Disorder

- A. Preoccupation with having or acquiring a serious illness.
- B. Somatic symptoms are absent or mild in intensity. If another medical condition (or high risk for one) is present, the preoccupation is clearly excessive/disproportionate.
- C. High anxiety about health.
- D. Exhibits excessive health-related behaviours or maladaptive healthcare avoidance.
- E. Illness preoccupation for ≥ 6 months, but the specific feared illness may vary.
- F. Illness-related preoccupation is not better explained by any other mental disorder.

Specifiers:

- Care-seeking type
- Care-avoidant type

Epidemiology

- Prevalence is estimated at 1-10% in the community
- No specific age of onset but usually in early/middle adulthood
- Males $\approx$ females
- $\frac{1}{3}$ to $\frac{1}{2}$ of cases are transient

Risk factors

- Psychological – childhood adversity/ abuse, serious childhood illness, major life stress, serious but ultimately benign threat to health

Conversion disorder

FYI

Conversion disorder is also known as **functional neurological symptom disorder**.

DSM-5 Criteria for Conversion Disorder

- A. ≥ 1 symptom(s) of altered voluntary motor or sensory function.
- B. Clinical evidence of incompatibility between symptom(s) and recognized neurological/medical conditions.
- C. Not better explained by another medical/mental disorder.
- D. Clinically significant distress or impairment in important areas of functioning.

Specifiers:

Symptom type	• With weakness or paralysis • With abnormal movement (e.g. tremor, dystonia, myoclonus, gait disorder) • With swallowing symptoms • With speech symptoms • With attacks or seizures • With anesthesia or sensory loss • With special sensory symptom (e.g. visual, olfactory, or hearing disturbance) • With mixed symptoms
Duration	• Acute episode (<6 months) • Persistent (≥ 6 months)
Stressor	• With psychological stressor (specify) • Without psychological stressor

Epidemiology

- Presents mostly in secondary care settings
- Prevalence is ~5% in neurology clinics
- Onset has been reported throughout life course - e.g. onset of non-epileptic attacks peaks in the third decade; onset of motor symptoms peaks in the fourth decade
- May be associated with antisocial personality disorder (ASPD)
- 2-3 times more common in females vs. males

Risk factors

- Temperament - maladaptive personality traits
- Psychological - childhood abuse and neglect, and stressful life events
- Genetic and physiological - comorbid neurological disease (e.g. non-epileptic seizures are more common in patients who also have epilepsy)

Diagnostic and clinical features

- May have a history of multiple similar somatic symptoms
- Onset may be associated with stress/trauma of physical/psychological nature
- Often associated with dissociative symptoms (e.g. depersonalization, derealization, dissociative amnesia)
- Diagnosis requires clear evidence of incompatibility with neurological disease; for example:
 - EEG obtained during an attack showing normal tracings
 - Hoover's sign: in a healthy individual who is supine, flexion of a leg against resistance results in involuntary extension of the other leg.
 - To perform the manoeuvre, start with the patient supine and place one hand under the heel of the unaffected leg. Ask the patient to flex the affected hip against resistance while keeping the leg straight.
 - If the examiner feels the unaffected limb pushing down onto their hand while the patient attempts to raise the affected limb, the patient is making an honest effort and this supports an organic cause for the paresis.
 - If the examiner does not feel the unaffected limb pushing down onto their hand while the patient attempts to raise the affected limb, effort is not being transmitted to the other leg and the weakness is functional.



Figure 1a: Patient is asked to press the weak right leg down forcefully - no downward pressure felt under the right heel



Figure 1b: Patient is asked to raise the normal left leg against resistance – downward pressure felt under the right heel

Figure 1a-b. Demonstration of Hoover's sign.

Image from Mehndiratta et al., 2014.

- Tunnel vision: the normal visual field is a funnel, not a tunnel - i.e. the visual field should expand as the target moves farther from the eye.
 - If the patient reports constricted visual fields during testing by confrontation, increase the distance between patient and the target.
 - If the visual field defect follows the normal (funnel) shape, the cause is more likely organic.
 - If the visual field defect remains the same or constricts further with increased distance, the cause is more likely functional.

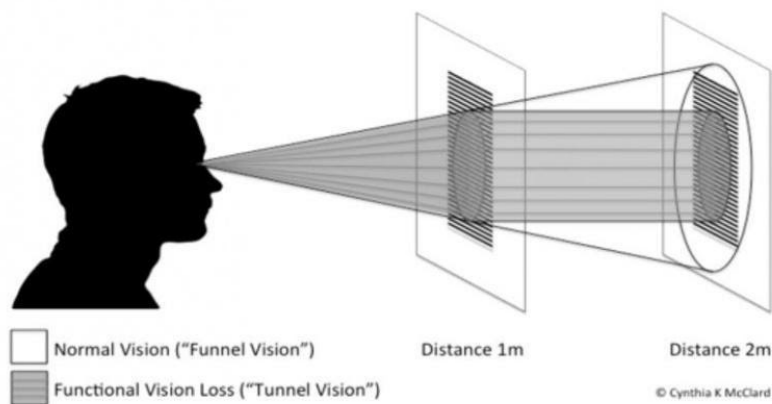


Figure 2. Tunnel vision.

Image from Chacko and McClard, 2020.

Psychological factors affecting other medical conditions

DSM-5 Criteria for Psychological Factors Affecting Other Medical Conditions

- A. A medical symptom or condition (other than a mental disorder) is present.
- B. Psychological/behavioural factors affect this medical condition in ≥ 1 of the following way(s):
 1. Close temporal association between the factors and development, exacerbation, or delayed recovery from the medical condition.
 2. Factors interfere with treatment of the medical condition.
 3. Factors constitute additional well-established health risks.
 4. Factors precipitate/exacerbate symptoms or necessitate medical attention.
- C. Not better explained by another mental disorder.

Specifiers:

- Mild: increases medical risk (e.g. inconsistent adherence to antihypertensive medications)
- Moderate: aggravates underlying medical condition (e.g. anxiety aggravating asthma)
- Severe: results in hospitalization or Emergency Department visit
- Extreme: results in life-threatening risk (e.g. ignoring heart attack symptoms)

Epidemiology

- Unclear
- May be more common than somatic symptom disorder
- Occurs across the lifespan

Diagnostic and clinical features

- Adverse effects may be acute with immediate medical consequences (e.g. Takotsubo cardiomyopathy) or chronic (e.g. chronic occupational stress increasing risk for hypertension)

- Affected medical conditions can be:
 - Clear in pathophysiology (e.g. diabetes, cancer, coronary artery disease)
 - Functional syndromes (e.g. migraine, irritable bowel syndrome, fibromyalgia)
 - Idiopathic (e.g. pain, fatigue, dizziness)

Factitious disorder

DSM-5 Criteria for Factitious Disorder

Factitious disorder imposed on **self**:

- A. Falsification of physical or psychological signs or symptoms, or induction of injury or disease, associated with deception.
- B. The individual presents themselves to others as ill, impaired, or injured.
- C. Deceptive behaviour is evident even in absence of external rewards.
- D. Not better explained by another mental disorder.

Factitious disorder imposed on **another**:

- A. Falsification of physical or psychological signs or symptoms, or induction of injury or disease, in another person, associated with deception.
- B. The individual presents another person (victim) to others as ill, impaired, or injured.
- C. Deceptive behaviour evident even in absence of external rewards.
- D. Not better explained by another mental disorder.

**Note: The diagnosis applies to the perpetrator, not the victim.*

Specifiers:

- Single episode
- Recurrent episode: ≥ 2 events of falsification of illness and/or induction of injury.

Epidemiology

- ~1% in hospital settings; <1/3000 for factitious disorder imposed on another
- May have higher education, show cognitive astuteness and/or have a history of medical jobs
- Usually manifests as intermittent episodes
- Onset usually in age 20s or 30s

Risk factors

- Social: Medical paraprofessional
- Psychological: True physical disorder in childhood leading to extensive medical treatment or recent hospitalization for a medical condition or psychiatric disorder

Diagnostic and clinical features

- Deceptive reporting of symptoms
- Manipulating a laboratory test (e.g. adding blood to a urine sample)
- Falsifying medical records
- Ingesting substance/medication to induce illness or abnormal laboratory results
- Physically injuring self or another (e.g. injecting fecal material to induce sepsis)

	Symptoms produced intentionally	Conscious awareness of reasons for symptoms
Somatoform disorder	-	-
Factitious disorder	+	-
Malingering	+	+

Table 1. Comparison between somatoform disorder, factitious disorder, and malingering.

Other specified somatic symptom and related disorder

- Applies to presentations that do not meet full criteria for other disorders:
 - **Brief somatic symptom disorder:** symptoms <6 months
 - **Brief illness anxiety disorder:** symptoms <6 months
 - **Illness anxiety disorder without excessive health-related behaviour**
 - **Pseudocyesis:** a false belief of being pregnant with objective signs and reported symptoms of pregnancy

Unspecified somatic symptom and related disorder

- Applicable in situations with insufficient information to make a specific diagnosis.

Differential Diagnoses

Differential diagnosis	Details
Other medical conditions	• For somatic symptom disorder – e.g. IBS, fibromyalgia • For illness anxiety disorder – e.g. neurological or endocrine disorders, occult malignancies • For conversion disorder – e.g. organic neurological disease (the two may coexist)
Adjustment disorder	• Worry is in response to a medical condition and is time-limited
Anxiety disorders	• Panic disorder – somatic symptoms occur in acute episodes with characteristic cardiorespiratory symptoms • Generalized anxiety disorder (GAD) – anxiety about health may not be the main focus and be only one of many worries
Obsessive-compulsive disorder (OCD)	• More intrusive thoughts about somatic symptoms or illness, as well as the associated repetitive behaviours aimed at reducing anxiety • Usually focused on fears of contracting a disease in the future, whereas in illness anxiety the preoccupations are focused on having a disease currently
Depressive disorders	• Somatic symptoms are common but the clinical picture is predominated by dysphoric mood and anhedonia • Health anxiety may be present, but a separate diagnosis of illness anxiety should not be made if these concerns only occur during major depressive episodes (MDEs)
Psychotic disorders	• In delusional disorder, somatic subtype, the somatic symptom beliefs and behaviour are stronger than those found in somatic symptom disorder • True somatic delusions are generally more bizarre (e.g. an organ is rotting), whereas the concerns in illness anxiety may not be founded in reality but are plausible • Patients with psychotic disorders are less likely to be able to acknowledge the possibility that the feared disease is not present
Dissociative disorder	• Dissociative symptoms may be present and, if criteria are met for a disorder, both disorders are diagnosed
Body dysmorphic disorder	• Health concerns are limited to physical appearance only, which is viewed as defective or flawed

Table 2. *Differential diagnoses for somatic symptom and related disorders.*

Management

The therapeutic relationship

Management of acute somatization

- Inquire about fears about illness.
- Patient may respond to:
 - Information about symptoms
 - Reassurance
 - Problem-solving regarding underlying stressors
 - Strengthening existing support systems

Management of chronic somatization

- Patient should have one primary care physician
- Schedule appointments at regular time-contingent intervals
- Brief physical exam at each visit to address new health concerns
- Judicious use of diagnostic studies based on new symptoms or new physical findings; avoid over-referring and over-investigating
- Once rapport is established, shift the focus to current functioning, stressors, and support systems
- Integrate family and other supports into care plan to corroborate history, level of functional impairment, substance use and healthcare use, as well as support treatment adherence

CLINICAL PEARL

Tips for building the therapeutic relationship:

- Focus on CARING, not curing.
- Maintain an empathetic attitude and validate the patient's discomfort and distress
- Rule out and treat coexisting depressive, anxiety, or substance abuse disorders, as well as general medical conditions (e.g. hyperthyroidism, new-onset diabetes).

Biological

- No good evidence for use of antidepressants or antipsychotics to treat somatic symptoms and related disorders
- Pharmacotherapy, however, may have a role in treating comorbid psychiatric conditions
 - Start with low doses and go slowly to minimize risk of side effects as patients may be hypersensitive to changes in bodily sensations
 - Consider SNRI (duloxetine, venlafaxine) in patients with pain
 - Literature suggests antidepressants prescribed for medically unexplained physical symptoms improved the symptoms considerably (NNT of 4; Price et al., 2000)
 - Caution with narcotics in patients with chronic pain. Narcotics may be providing psychological relief instead/in addition to physical pain relief. Tolerance to this psychological effect develops easily, resulting in requests for escalating doses

Psychosocial

- Psychoeducational and supportive techniques predominate management
 - Insight-oriented therapy may be indicated in some patients
 - CBT may be useful in many somatic symptom and related disorders
- Maintain good sleep hygiene
- Relaxation training (e.g. diaphragmatic breathing, progressive muscle relaxation) may provide some benefit through:
 - Interruption of the muscle tension-pain cycle
 - Reduction of generalized physiologic arousal/reactivity
 - Empowerment of the patient to feel more in control of their body
- Behavioural activation by focusing on 3 categories:
 - Meaningful activities (e.g. volunteering, employment, household projects, education)
 - Pleasurable activities (e.g. hobbies, social activities)
 - Exercise
 - Evidence from RCTs supports advising activity rather than rest for back pain, fatigue, and fibromyalgia.
 - Ask the patient to chart activity, then gradually increase the amount of activity with the goal of cardiovascular training of approximately 30 min daily for 5 days/week (unless medically contraindicated)

IMPORTANT

If using pharmacological aids for sleep, **they should only be used in the short-term.**

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Review Questions

1. Which of the following is the least common symptom of somatic symptom disorder in children?
 - a) Headache
 - b) Abdominal pain
 - c) Nausea
 - d) Fatigue
 - e) Dizziness

2. Which of the following statements regarding the etiology of somatic symptom disorder is TRUE?
 - a) Patients consciously amplify normal physiological function
 - b) Patients misinterpret normal physiological function
 - c) Somatic symptom disorder is associated with increased amygdala volume
 - d) All of the above
 - e) None of the above

3. A 25 year old third year medical school student presents with several medical complaints interfering with class attendance. She has unexplained GI symptoms for the last 2 years. These symptoms include bloating, pain and nausea with occasional vague light-headedness. Her medical work-up is negative. All of the following are clinical features of somatic symptom disorder, EXCEPT:
 - a) Patient is focused on physical symptoms and on the significance of these
 - b) Patient fears harm from any physical activity
 - c) Patient feels better when symptoms are assessed and treated
 - d) Patient performs repetitive body checks for abnormalities
 - e) Symptoms often involve normal bodily functions

4. A 45 year old male is afraid of having a myocardial infarction (MI) since a 50 year old co-worker suffered one at work several months ago. He thinks he is having an MI several times a day. He checks his BP three times each day and asks his primary care provider to check routine ECGs every 3 months. He has no symptoms of chest pain or dyspnea on exertion. His BMI is normal. His lipids are normal except his LDL was higher this year than last, which alarmed him. He denies feeling anxious except for worry about his cardiovascular health. With which diagnosis is this presentation most consistent?
 - a) Adjustment disorder
 - b) Somatic symptoms disorder
 - c) Factitious disorder
 - d) Generalized anxiety disorder
 - e) Illness anxiety disorder

Review Questions (continued)

5. Which is not a clinical feature of factitious disorder?
 - a) Illness does not get better despite treatment
 - b) Reluctance to go for tests
 - c) Feels comfortable in the hospital
 - d) Levels of distress fluctuate
 - e) None of the above

6. You have a virtual appointment with a young woman with chronic headaches, a normal medical work-up and no improvement on pharmacotherapy. She refuses to leave her house to attend school or her part-time job because “the pain is too severe”. Which would not be on your differential?
 - a) Pain disorder
 - b) Malingering
 - c) Hypochondriasis
 - d) Somatic symptom disorder
 - e) All of these would be on my differential

7. In treating patients with somatoform disorders, what is the most appropriate approach?
 - a) Discuss the possible causes of the symptoms
 - b) Minimize the advantages of illness and maximize the advantages of health
 - c) Explore the symbolic meaning of the symptoms
 - d) Investigate all symptoms with repeated physical examinations and investigations
 - e) All of the above

8. Which pharmacological agent could you consider for the treatment of somatic symptom disorder?
 - a) Analgesic
 - b) Sedative
 - c) Antidepressant
 - d) Anxiolytic
 - e) All of the above

Answers:

1. e)
2. b)
3. c)
4. e)
5. b)
6. c)
7. c)
8. c)

Eating Disorders

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Definition

- Eating disorders are characterized by a persistent disturbance in eating that impairs psychosocial functioning or health.
- Consist of thoughts/preoccupation with weight, body image and nutrition as well as unhealthy behaviors including food restriction, over-exercise, bingeing, purging/vomiting and laxative misuse.
- The eating disorders that will be discussed in this chapter are:
 - Anorexia nervosa
 - Bulimia nervosa
 - Binge-eating disorder
 - Other specified feeding and eating disorder (OSFED)
 - Pica
 - Rumination
 - Avoidant/restrictive food intake disorder (ARFID)

Epidemiology

Eating disorder	Long-term prevalence	Male: Female	Age of onset	Mortality
Anorexia nervosa	0.5-1%	10:1	13-20	5-10% (20% suicide, 80% medical)
Bulimia nervosa	2-4%	10:1	16-18	2% per decade
Binge-eating disorder	3.5% female 2% male	2:1	Late adolescence to early 20s	-

Table 1. Comparison chart of epidemiological characteristics of anorexia nervosa, bulimia nervosa, and binge-eating disorder.

FYI

Eating disorders are over-represented in occupations that require rigorous control of body shape (e.g. modelling, ballet).

Etiology

- The development of eating disorders can be understood through the biopsychosocial model:

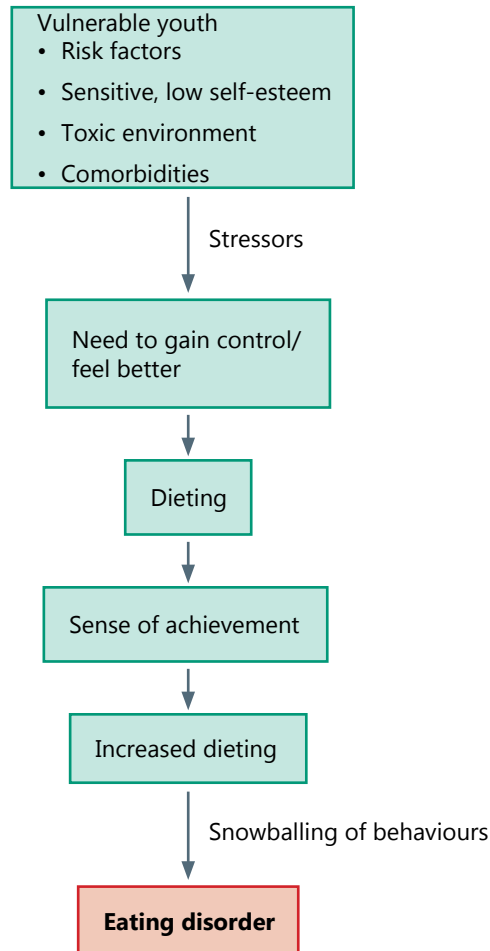


Figure 1. Diagram illustrating a biopsychosocial model for the etiology of eating disorders.

Adapted from Eating Disorders bootcamp lecture.

CLINICAL PEARL

Screening for eating disorders

- Extreme concern regarding weight/shape: Do you worry a lot about your weight or appearance? If yes, how much of the day are these thoughts in your head?
- Restriction: Are you dieting or have you made changes in how you eat? If yes, how so?
- If positive for either question 1 or 2, ask about:
 - Weight loss (quantify)
 - Missed periods (if applicable)
 - Binge-eating
 - Vomiting
 - Exercise
 - Laxative use

Anorexia Nervosa (AN)

Clinical features

- Restriction of energy intake sufficient to cause significantly low body weight, and occurring in the presence of an intense fear of gaining weight or becoming fat and a disturbance in the perception of his or her body weight.
- The **discrepancy between weight and perceived body image** is key to the diagnosis of AN (e.g. fear of gaining weight despite being significantly underweight).
- Loss of 15% of baseline body weight is often used as clinical cutoff for concerning weight loss.
- Amenorrhea is another sign that may indicate anorexia nervosa. It precedes the onset of obvious weight loss in one fifth of female patients.

NOTE

BMI is a useful measure in adults only!

Weight percentiles are used for children and adolescents.

DSM-5 Criteria for Anorexia Nervosa

- Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.
- Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.
- Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

Specifiers:

- Partial remission vs. full remission
- Severity based on BMI
 - Mild: BMI ≥ 17 kg/m²
 - Moderate: BMI 16–16.99 kg/m²
 - Severe: BMI 15–15.99 kg/m²
 - Extreme: BMI < 15 kg/m²
- Binge-eating/purging type vs. restricting type

NOTE

Binge-eating/purging type: recurrent episodes of binge-eating/purging in the last 3 months.

Restricting type: no episodes of binge-eating/purging in the last 3 months.

Risk factors

- Individual
 - Female
 - Preterm birth
 - Puberty and adolescence
- Family
 - Highly genetic (>70%)
 - Family history of anxiety, mood disorder, OCPD
 - Early life “high concern parenting”
- Cultural
 - Internalization of the “thin ideal” and dieting
 - White race
 - Occupations/ activities that require rigorous control of body shape (e.g modelling)

Comorbidities

- 50-65% depression (most common comorbidity)
- >50% anxiety disorders (especially obsessive compulsive, generalized anxiety and social anxiety disorders)
- Cluster C personality traits or disorder (e.g rigidity, restraint, obsessiveness, perfectionism)

Medical evaluation

Subjective symptoms	Signs on physical exam
Amenorrhea	Low BMI (<17.5 kg/m2)
Exertional fatigue	Emaciation (<85% of ideal body weight)
Weakness	Hypothermia
Cold intolerance	Bradycardia
Palpitations	Hypotension
Dizziness	Orthostatic HR and BP changes
Abdominal pain and bloating	Hypoactive bowel sounds
Early satiety	Xerosis (dry, scaly skin)
Constipation	Brittle hair and hair loss
Foot edema	Lanugo hair growth
	Abdominal distension

Table 2. Common signs and symptoms of anorexia nervosa.

Laboratory investigations

- Blood work
 - CBC with differential
 - Serum electrolytes, including extended electrolytes (Ca, PO4, Mg)
 - Renal function (serum Cr and BUN)
 - Serum glucose
 - Liver enzymes
 - Amylase
 - Liver function (albumin, INR)
 - TSH
 - LH, FSH
 - Testosterone (in males)
 - 25-hydroxyvitamin D
 - B-hCG
- Cardiac work-up
 - ECG
- Evaluate for medical illnesses that can present with weight loss, malabsorption and/or secondary amenorrhea, including:
 - Neoplasm
 - Chronic infections (e.g., tuberculosis or acquired immunodeficiency syndrome)
 - Uncontrolled diabetes mellitus
 - Hyperthyroidism
 - Malabsorption syndromes (e.g., celiac disease)
 - Inflammatory bowel disease (e.g, Crohn disease)

Management

Disposition

	Children and adolescents	Adults
Weight	<75% of IBW or ongoing weight loss despite intensive management	<80-85% IDW >1kg/week weight loss
Heart rate	<50 in the day or <45 in the night	<40
Orthostatic Δ	>20bpm or >10 mmHg	>20bpm or >20 mmHg
Temperature	<36°C	<36°C
Safety	Acute suicidality	Acute suicidality

Table 3. Summary chart of admission indications in children/adolescents and adults with AN.

- Goals of admission include symptom interruption, weight restoration (associated with resumption of menses), and treatment of any medical complications.
- Agree on target goal weight (TGW) at the time of admission and reassure that this will not be surpassed.
 - Aim for weight gain of 2-3 lbs/week for inpatients and 0.5-1 lbs/week in outpatient setting.
- Provide psychoeducation regarding the side effects associated with refeeding including delayed gastric emptying, constipation, resurgence of mood and anxiety symptoms, acne, hot-flashes, body image distortion etc.
- Monitor for **refeeding syndrome** (see sidebar)

Pharmacological therapy

- Medications are of little value except for treating comorbidities.
 - SSRIs do not work in context of malnourishment, though they can be used to treat underlying comorbidities following weight restoration.
 - Atypical antipsychotics have limited evidence but may help with obsessionality.
 - Olanzapine is most often used clinically due to associated weight gain but need to monitor for side effects.
 - Benzodiazepines: when administered approximately 30min before meal, may help with anxiety pre-meal.

Psychosocial therapy

- Psychotherapy with malnourished patients is generally ineffective.
- Family-based therapy is the gold-standard for children and adolescents:
 - Blame-free atmosphere
 - Raise parental anxiety
 - Parents take on responsibility as coaches to refeed their child
- Other approaches include CBT, IPT and motivational therapy.
- Psychotherapy should be maintained for at least a year following weight restoration, with a focus on food and body perception, coping mechanisms and health effects.

IMPORTANT

Refeeding syndrome

is a potentially life-threatening metabolic response to refeeding in severely malnourished patients resulting in severe shifts in fluid and electrolyte levels.

Prevention of refeeding syndrome involves:

- Slow refeeding
- Gradual increase in nutrition
- Supplemental phosphorus
- Close monitoring of electrolytes and cardiac status

Prognosis

- Early intervention is much more effective (adolescent onset has much better prognosis than adult onset).
- 1 in 10 adolescents continue to have AN as adults.
- 50% of AN-restrictive type develop bulimic symptoms within 5 years of weight recovery.
- Long-term mortality: 10-20% of hospitalized patients will die in the next 10-30 years (20% suicide, 80% medical complications).
- Poor prognostic factors (associated with mortality):
 - Very low weight
 - Bradycardia
 - No medical follow-up
 - Longer duration of illness
 - Multiple purging methods
 - Chronic self-harm or suicide attempts
 - Amphetamine or cocaine use
 - Severe alcohol abuse

Bulimia Nervosa (BN)

Clinical features

- Recurrent episodes of binge-eating and inappropriate compensatory behaviors to prevent weight gain, with persistent concern regarding weight and body shape.

DSM-5 Criteria for Bulimia Nervosa

- A. Recurrent episodes of binge-eating. An episode of binge-eating is characterized by both of the following:
 1. Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than what most individuals would eat in a similar period of time under similar circumstances.
 2. A sense of lack of control over eating during the episode (e.g. a feeling that one cannot stop eating or control what or how much one is eating).
- B. Recurrent inappropriate compensatory behaviors in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise.
- C. The binge-eating and inappropriate compensatory behaviors both occur, on average, at least once a week for 3 months.
- D. Self-evaluation is unduly influenced by body shape and weight.
- E. The disturbance does not occur exclusively during episodes of anorexia nervosa.

Specifiers:

- Partial remission vs. full remission
- Severity: measured in number of inappropriate compensatory behaviours per week
 - Mild: 1-3
 - Moderate: 4-7
 - Severe: 8-13
 - Extreme: 14+

CLINICAL PEARL

A distinguishing feature between AN and BN is body weight. Individuals with AN have significantly low body weight whereas individuals with BN have normal or elevated body weights.

The Cycle of Bulimia

- A binge is almost always the result of dieting and food restriction.
- Purging/compensatory behavior is due to - shame caused by the loss of control over eating, fear of weight gain and/or the perception of stomach discomfort.

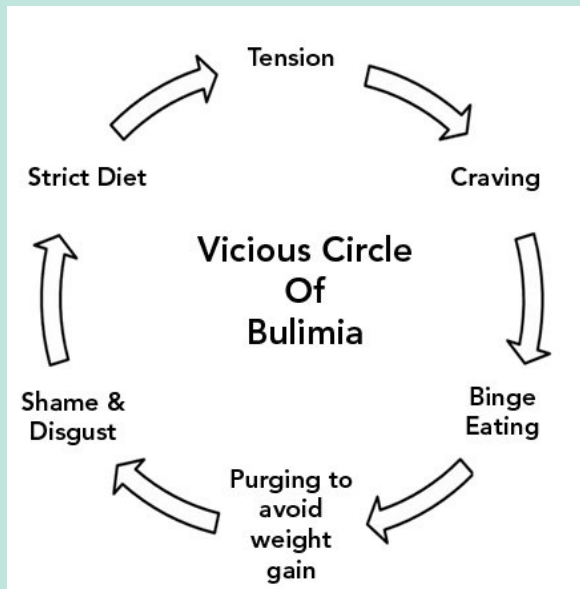


Figure 2. Model of the bulimia cycle.

Figure taken from Columbus Park website.

Risk factors

- Individual
 - Female
 - Low self-esteem/ sense of ineffectiveness
- Family
 - Highly genetic
 - Family history of mood/ anxiety/ substance abuse/ cluster B PD
 - History of sexual abuse
 - Volatile, conflicted family environment
- Cultural
 - Internalization of the “thin ideal” and dieting

Comorbidities

- >50% depression (most common comorbidity)
- >50% anxiety disorders (especially generalized and social anxiety disorders)
- Substance abuse
- Borderline personality traits (e.g. impulsivity, risk-taking behaviours)
- PTSD
- Bipolar spectrum disorders

Medical evaluation

Subjective symptoms	Signs on physical exam
Lethargy Irregular menses Abdominal pain Bloating Constipation	Normal/elevated body weight Hypotension, tachycardia Xerosis Parotid gland enlargement Erosion of dental enamel (from vomiting) *Don't forget to do an abdominal and neurologic examination to look for other causes of weight loss or vomiting.

Table 2. Common signs and symptoms of bulimia nervosa.

Laboratory investigations

- Blood work:
 - CBC with differential
 - Serum electrolytes, including extended electrolytes (Ca, PO4, Mg)
 - Renal function (serum Cr and BUN)
 - Liver enzymes
 - Amylase
 - Liver function (albumin, INR)
 - B-hCG
- Cardiac work-up
 - ECG
- Urine
 - Urinalysis

Management

Disposition

- Admission only if significant electrolyte abnormalities.
- Use of hospital environment to provide external patterning of normal eating behaviour.

Pharmacological therapy

- Structured meal plan to prevent binges and purges.
- In adults, healthy weight is determined based on pre-morbid weight, height/ BMI and resumption of menses. In the pediatric population, growth curves are used to determine treatment goal weight.
- SSRI: **fluoxetine** has best evidence
 - Reduces binge-eating, purging and psychological features of BN.
 - Higher doses than required for major depression (e.g. 60-80 mg).
 - Recommend continuing for 9 months to one year after symptom-free.
- Topiramate has some evidence but side effect profile often limits use.
- Bupropion is contraindicated because of seizure risk.

CLINICAL PEARL

When treating bulimia nervosa, make sure to assess nutritional intake for all patients (even those with normal BMI), as normal weight does not necessarily mean that patient has appropriate intake or body composition!

Psychosocial therapy

- CBT both individual and group (strong support), IPT (some support) and DBT (growing evidence).
- Family-based therapy for children and adolescents (little evidence).
- Psychotherapy focuses on personal etiology of illness and triggers.
- Important to challenge destructive societal views of women

Prognosis

- Relapsing/remitting illness.
- Good prognostic factors include onset before age 15 and achieving healthy weight within 2 years of treatment.
- Poor prognostic factors include onset after age 15, previous hospitalizations, personal and familial disturbances.
- 60-70% good treatment outcome, 15-20% intermediate outcome, 10% poor outcome.

Binge-Eating Disorder (BED)

Clinical Features

- Recurrent binge-eating without compensatory behaviours.
- The distinction between BED and BN is sometimes unclear
 - Compared with BN, people with BED are generally older, more likely to be male and have an older age of onset
 - Nearly two thirds of individuals with BED have a history of inappropriate compensatory behaviours (suggesting a history of BN)

NOTE

Preoccupation with weight and shape are not required for the diagnosis of BED, however, they are commonly part of the presentation.

DSM-5 Criteria for Binge-Eating Disorder

- A. Recurrent episodes of binge-eating. An episode of binge-eating is characterized by both of the following:
 1. Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than what most people would eat in a similar period of time under similar circumstances.
 2. A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).
- B. The binge-eating episodes are associated with three (or more) of the following:
 1. Eating much more rapidly than normal.
 2. Eating until feeling uncomfortably full.
 3. Eating large amounts of food when not feeling physically hungry.
 4. Eating alone because of feeling embarrassed by how much one is eating.
 5. Feeling disgusted with oneself, depressed, or very guilty afterward.

Specifiers:

- Partial remission vs. full remission
- Severity: measured in number of inappropriate compensatory behaviours per week
 - Mild: 1-3
 - Moderate: 4-7
 - Severe: 8-13
 - Extreme: 14+

Management

Pharmacological therapy

- SSRI, topiramate, and lisdexamfetamine (moderate support/low quality of evidence)

Psychosocial

- CBT and CBT-guided self-help (moderate support/moderate quality of evidence)
- IPT (modest support)

Other Specified Feeding or Eating Disorder (OSFED)

- This category applies to presentation in which symptoms of a feeding or eating disorder are present but do not meet full criteria for any specific disorder.
- Examples include:
 - Atypical anorexia nervosa: all of the criteria for anorexia nervosa are met, except that despite significant weight loss, the individual's weight is above or within the normal range.
 - Purging disorder: recurrent purging to influence weight or shape in the absence of binge eating.

Pica, Rumination Disorder, and Avoidant/Restrictive Food Intake Disorder (ARFID)

	Pica	Rumination disorder	ARFID
Criteria	A. Persistent eating of non-nutritive, non-food items >1m B. Inappropriate developmental level C. Not culturally supposed D. If concurrent, warrants individual clinical attention.	A. Recurrent regurgitation >1m. B. Not due to GMC C. Does not occur during AN, BN, BED D. If concurrent, warrants individual clinical attention.	A. Persistent failure to meet nutritional/energy needs as evidenced by: • Weight loss • Nutritional deficiency • Dependence
Epidemiology	• Rare • Up to 15% of ID • Usually remits by adolescence	• Rare • Onset between 3 and 12 months of age	• Can arise at any age • Equally common in M and F in infancy and early childhood • If comorbid ASD, M predominance
Associations	• Iron/ zinc deficiency • Parental neglect • Deprivation • ASD, ID	• ID and ASD • Self-stimulation • Environments of neglect	• Parent-child interactions • Innate temperament • OCD
Treatment	• Correct neglect and maltreatment • Education and behavior modification	• Behavior modification • Aversive conditioning • Diaphragmatic breathing • Gum chewing	• SSRI • CBT • Family therapy and psychoeducation

Table 3. Summary table of characteristics of pica, rumination disorder, and ARFID.

GMC = general medical condition, AN = anorexia nervosa, BN = bulimia nervosa, BED = binge-eating disorder, ID = intellectual disability, ASD = autism spectrum disorder, OCD = obsessive-compulsive disorder, SSRI = selective serotonin reuptake inhibitors, CBT = cognitive behavioural therapy.

Medical Complications of Eating Disorders

System	Starvation/restriction	Purging
Cardiovascular	Low BP, low HR Orthostatic BP and HR Small heart Prolonged QTc and cardiac arrest	Arrhythmias (potassium abnormalities) Cardiac arrest
Metabolic/ Hematologic	Hypothermia Anemia and leukopenia (bone marrow suppression) Poor immunity Vitamin deficiencies Hypothyroidism	Metabolic alkalosis Hypokalemia
Reproductive	Amenorrhea Infertility Pregnancy complications	Amenorrhea Infertility
Dermatological	Dry skin and hair Lanugo hair Yellow skin from high carotene	Russell's sign Parotid gland enlargement Perioral dermatitis Petechiae
GI	Constipation	GI bleed Hematemesis Esophagitis Reflux Poor colon muscle tone
MSK	Muscle wasting Osteoporosis Short stature	Dental erosion and caries Muscle cramps
Renal	Pre-renal failure due to dehydration	Pre-renal failure due to dehydration
CNS	Poor concentration Severe mood swings Decreased white and gray matter	Poor concentration Severe mood swings
Laboratory values	Starvation: - Decreased RBCs, WBCs - Decreased LH, FSH - Decreased estrogen, testosterone - Increased growth hormone - Increased cholesterol Dehydration: - Increased BUN	Vomiting: - Decreased Na⁺, K⁺, H⁺, Cl⁻ - Increased amylase - Hypokalemia with metabolic alkalosis Laxatives: - Decreased Na⁺, K⁺, Cl⁻ - Increased H⁺ - Metabolic acidosis

Table 4. Various medical complications of both starvation/restriction and purging disorders.

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Review Questions

1. You review the blood work of a young female patient on the pediatric inpatient unit. Which result may you expect to see in a patient with anorexia nervosa?
 - a) High cholesterol
 - b) Low beta-carotene
 - c) Low TSH
 - d) High FSH
 - e) None of these options

2. You see a male lawyer, with a BMI of 15.9, in consultation. He is obsessed with staying slim and exercises multiple times each day. He binges 1-2 times per year and induces vomiting once per month. Based on this information, what is your preferred diagnosis?
 - a) Atypical anorexia nervosa
 - b) Anorexia nervosa binge-eating/purging subtype
 - c) Anorexia nervosa restricting type
 - d) Avoidant/restrictive food intake disorder
 - e) Bulimia nervosa

3. Which would not be a criteria for admission of an adult patient with anorexia nervosa?
 - a) Temperature of 35.7°C
 - b) Heart rate of 55
 - c) Orthostatic drop in blood pressure of 25mmHg
 - d) Self-harming behaviors
 - e) All of these options

Answers:
1. a)
2. b)
3. b)

Sleep Disorders

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Sleep

- While the exact function of sleep is still being investigated, studies examining the consequences of sleep disruption have demonstrated that sleep is necessary for healthy functioning
- Individuals deprived of sleep display poorer cognitive function including working memory, performance, cognitive speed, and accuracy
 - When sleep deprived, individuals will tend to select and remember negative memories more frequently
 - They will also display similar emotional responses to low stressors that individuals without sleep deprivation display in response to high stressors
- Sleep is affected in a number of mental illnesses including bipolar disorder, major depressive disorder, schizophrenia, anxiety disorders, trauma disorders, and ADHD and many others.
- Throughout this chapter, definitions of sleep disorders will be used from both the DSM-5 and the International Classification of Sleep Disorders - Third Edition (ICSD-3)

Measuring sleep

- Sleep is measured in a sleep laboratory through use of polysomnography, which consists of:
 - Electroencephalography (EEG) measuring brainwaves
 - Electrooculography (EOG) measuring eye movements
 - Electromyography (EMG) measuring muscle tone
 - Electrocardiogram (ECG)
 - Nasal pressure transducer and/or oronasal thermistor measuring airflow
 - Respiratory Inductance Plethysmography (RIP) belts measuring thoracic and abdominal respiratory efforts
 - Pulse oximeter measuring SpO2
 - Microphone to detect snoring
 - Digital audiovisual recording

FYI

Polysomnography is also known as a **sleep study**.

Stages of Sleep

- Non-rapid eye movement (NREM) and rapid eye movement (REM)
- NREM consists of three stages: N1, N2, N3
 - During NREM, breathing is regular and heart rate decreases

Sleep stage	Features
N1	Hypnic jerks/sleep starts and dozing occur during N1.
N2	Sleep spindle and K complexes occur during this phase.
N3	This is the deepest and most restorative stage of sleep. Length of N3 sleep decreases with age.

- The onset of the first REM period typically occurs 90 minutes after the onset of sleep
 - REM duration increases throughout the night
 - Rapid eye movements are the classic feature of REM sleep
 - During this stage of sleep muscle atonia (paralysis) should be present
 - EEG during REM sleep looks similar to EEG when awake
 - Breathing is irregular with heart rate fluctuations during this stage

Sleep disorders

- There are several categories of sleep disorders in the DSM-5. Those which are bolded will be expanded upon in this chapter:
 - **Insomnia disorder**
 - Hypersomnolence disorder, including narcolepsy
 - **Breathing-related sleep disorders**
 - Circadian rhythm sleep-wake disorders
 - **Non-rapid eye movement sleep arousal disorders**
 - Nightmare disorder
 - **Rapid eye movement sleep behaviour disorder**
 - **Restless legs syndrome**
 - Substance/medication-induced sleep disorder

Breathing-Related Sleep Disorders

- These disorders are characterized by the presence of disturbances in breathing that last longer than 10 seconds.
 - >5 disturbances in an hour is considered clinically significant.
- There are two main categories of breathing-related sleep disorders: **obstructive** and **central**.
- Symptoms of breathing-related sleep disorders include:
 - Excessive daytime sleepiness
 - Morning headaches
 - Snoring
 - Pauses in breathing
 - Waking with a dry mouth
 - Nocturnal
 - Gastroesophageal reflux disease

Obstructive sleep apnea/hypopnea

- Obstructive sleep apnea/hypopnea is a disorder characterized by repetitive episodes of hypopneas (reduced air flow) or apneas (absent air flow) due to upper airway collapse while sleeping.

DSM-5 Criteria for Obstructive Sleep Apnea/Hypopnea

- A. Either (1) or (2):
1. Evidence by polysomnography of at least five obstructive apneas or hypopneas per hour of sleep and either of the following sleep symptoms:
 - a. Nocturnal breathing disturbances: snoring, snorting/gasping, or breathing pauses during sleep.
 - b. Daytime sleepiness, fatigue, or unrefreshing sleep despite sufficient opportunities to sleep that is not better explained by another mental disorder (including a sleep disorder) and is not attributable to another medical condition.
 2. Evidence by polysomnography of 15 or more obstructive apneas and/or hypopneas per hour of sleep regardless of accompanying symptoms.

Specifiers:

- Mild: Apnea hypopnea index is less than 15.
- Moderate: Apnea hypopnea Index is 15-30.
- Severe: Apnea hypopnea index is greater than 30.

Causes

- Narrow upper airway or large tongue
- Elevated BMI

Exacerbating Factors

- Medications/substances
- Supine sleep position
- REM sleep

NOTE

Muscle relaxants, alcohol, and benzodiazepines are some of the most common exacerbating medications/substances.

Associated Conditions

- Hypertension
- Atherosclerosis
- Atrial fibrillation
- Heart failure
- Stroke
- Impaired glucose control
- Gastroesophageal reflux disease
- Major depressive disorder
- Neurocognitive dysfunction
- Elevated risk of motor vehicle accidents

Management

- Continuous Positive Airway Pressure (CPAP), see Figure 1.
- Weight loss
- Avoidance of alcohol and/or sedative medications
- Positional therapy
 - E.g. A ball placed on the back during sleep to prevent supine sleep
- Oral appliances
 - Mandibular repositioning devices to reduce retrognathia

- Provent
 - Nasal device with a valve that closes during exhalation, providing expiratory positive airway pressure (EPAP)
- Upper airway surgery
 - Tonsillectomy in pediatric population
 - Uvulopalatopharyngoplasty
 - Maxillomandibular advancement
 - Tracheostomy

Narcolepsy

- Narcolepsy is a sleep disorder with features including excessive daytime sleepiness, cataplexy, sleep paralysis, and hallucinations.

DSM-5 Criteria for Narcolepsy

- A. Recurrent periods of an irrepressible need to sleep, lapsing into sleep, or napping occurring within the same day. These must have been occurring at least three times per week over the past 3 months.
- B. The presence of at least one of the following:
 1. Episodes of cataplexy, defined as either (a) or (b), occurring at least a few times per month:
 - a. In individuals with long-standing disease, brief (seconds to minutes) episodes of sudden bilateral loss of muscle tone with maintained consciousness that are precipitated by laughter or joking.
 - b. In children or in individuals within 6 months of onset, spontaneous grimaces or jaw-opening episodes with tongue thrusting or a global hypotonia, without any obvious emotional triggers.
 2. Hypocretin deficiency, as measured using cerebrospinal fluid (CSF) hypocretin-1 immunoreactivity values (less than or equal to one-third of values obtained in healthy subjects tested using the same assay, or less than or equal to 110 pg/mL). Low CSF levels of hypocretin-1 must not be observed in the context of acute brain injury, inflammation, or infection.
 3. Nocturnal sleep polysomnography showing rapid eye movement (REM) sleep latency less than or equal to 15 minutes, or a multiple sleep latency test showing a mean sleep latency less than or equal to 8 minutes and two or more sleep-onset REM periods.

- Individuals with narcolepsy will display rapid sleep onset and enter into REM sleep rapidly.
- The narcoleptic tetrad consists of:
 - **Excessive daytime sleepiness**
 - This is measured using the Multiple Sleep Latency Test following a Nocturnal Polysomnogram.
 - MSLT consists of 4-5 opportunities to sleep separated at 2 hour intervals during normal wake times, with sleep-onset measured, as well as REM latency if sleep occurs.
 - An MSLT is considered positive if the patient falls asleep with a mean sleep latency equal to or below 8 minutes and reached REM sleep during 2 or more of the naps.
 - **Cataplexy**
 - Cataplexy is the sudden onset of loss of muscle tone preceded by heightened emotion.
 - These episodes last from seconds to minutes and are attributed to abnormalities in the REM sleep system intruding into wakefulness.
 - **Sleep paralysis**
 - Sleep paralysis is a transient inability to talk or move when waking up. This is thought to be the paralysis of REM sleep intruding upon wakefulness.
 - **Hypnagogic/Hypnopompic hallucinations**
 - Hypnagogic hallucinations are vivid dreamlike experiences that occur while dozing or falling asleep (gogic) or upon awakening (pompic).
- Other features of the disorder include:
 - Difficulty maintaining sleep
 - Although patients fall asleep rapidly, they have frequent awakenings during the night (wakefulness intruding upon sleep).
 - Automatic behaviour
 - Patients may continue to function and talk while asleep and wake with no recollection of these behaviours
 - Obesity
 - Inactivity and sleepiness may predispose to weight gain in patients with narcolepsy. Patients with this disorder have a higher risk of binge eating. The exact mechanisms behind increased weight in a significant portion of patients with narcolepsy is unclear.

- Nighttime eating is also common among patients with narcolepsy

Etiology

- Antigen HLA DQB1*0602 is found in 20% of the general population but 90% of patients with narcolepsy with cataplexy, raising the possibility of an autoimmune etiology.
- Orexin/hypocretin deficiency is found in 90% of individuals with narcolepsy with cataplexy.

Management

- Education – it is important to counsel patients that this is a medical disorder, and that they are not lazy or unintelligent, as the public may perceive them to be, since they can have uncontrollable periods of excessive daytime sleepiness.
- Therapeutic napping
- Stimulants
 - Modafinil
 - Methylphenidate
 - Dextroamphetamine
- REM suppressant medications can treat cataplexy
 - SSRIs or SNRIs
- Sodium oxybate (Na-Gamma hydroxybutyrate) for treating daytime sleepiness and cataplexy (see sidebar for precautions).

IMPORTANT

Sodium oxybate is the most effective treatment for daytime sleepiness and cataplexy.

However, it is a powerful soporific and amnestic drug so it has significant abuse potential as a date rape drug.

Additionally, it is a powerful CNS depressant so it should **NOT** be combined with other CNS depressants such as opioids, alcohol or similar drugs, as such combinations could have fatal consequences.

Parasomnias

- Parasomnias are disorders of arousal, a category of sleep disorders in the ICSD-3 wherein individuals manifest unusual behaviours during or around sleep.
 - These disorders are categorized according to their stage of occurrence, either in **NREM** sleep or **REM** sleep.

NREM disorders

Sleepwalking (somnambulism)

- Sleepwalking occurs during the N3 stage of sleep.
- Individuals experiencing sleepwalking frequently have no recall of a dream or their actions during sleep, and sometimes are able to perform

complex behaviours with a heightened pain threshold.

- Sleepwalking is exacerbated by sleep deprivation, stress, and alcohol.
- It is common in children and individuals with a positive family history.
- It is generally not recommended to wake a sleepwalking individual, but instead escort them back to bed and ensure that the environment is safe.

Sleep terrors (night terrors)

- Sleep terrors emerge from N3 sleep.
- Individuals experiencing night terrors will wake with a scream or uncontrollable crying but usually have no recall of a dream or the experience.
- Sleep terrors are common in children.
- It is generally not recommended to wake someone experiencing a night terror, but rather soothe them back to sleep.

REM disorders

REM Behaviour Disorder (RBD)

- REM behaviour disorder is when the expected muscle atonia during REM sleep does not occur, causing individuals to act out behaviours in the dream.
 - Often the bed partner is the victim of the individual's movements.
 - Unlike with sleepwalking, individuals with REM behaviour disorder can recall their dreams and are easily awakened.
- Individuals with this disorder are overwhelmingly male (90%) with a typical age of onset in the 50s and 60s.
- Causes
 - RBD is strongly associated with the subsequent development alpha synucleinopathies such as Parkinson's disease and Lewy body dementia.
- Diagnostic workup
 - EEG monitoring during polysomnogram.
 - CT Scan and MRI to rule out intracranial lesions.
- Management
 - Ensure a safe environment through keeping the mattress on the floor or using bed rails or restraints.
 - Sleep in a separate room from bed partner.
 - Clonazepam, melatonin, if symptoms persist and/or are causing clinical concerns.

NOTE

RBD can precede the diagnosis of Parkinson's and/or Lewy body dementia, sometimes by decades.

Restless Legs Syndrome

- Restless legs syndrome (RLS) is a neurological disorder leading individuals to have an unpleasant sensation in part of their body at rest and an urge to move.
- It is frequently (80%) accompanied by periodic limb movements in sleep (see Periodic limb movement disorder) and treatment for both of these conditions is identical as they are thought to share the same pathology.

FYI

Restless legs syndrome is also known as **Willis Ekbom disease** or **nocturnal myoclonus**.

DSM-5 Criteria for Restless Legs Syndrome

- An urge to move the legs, usually accompanied by or in response to uncomfortable and unpleasant sensations in the legs, characterized by all of the following:
 - The urge to move the legs begins or worsens during periods of rest or inactivity.
 - The urge to move the legs is partially or totally relieved by movement.
 - The urge to move the legs is worse in the evening or at night than during the day, or occurs only in the evening or at night.
- The symptoms in Criterion A occur at least three times per week and have persisted for at least 3 months.
- The symptoms in Criterion A are accompanied by significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.
- The symptoms in Criterion A are not attributable to another mental disorder or medical condition (e.g., arthritis, leg edema, peripheral ischemia, leg cramps) and are not better explained by a behavioral condition (e.g., positional discomfort, habitual foot tapping).
- The symptoms are not attributable to the physiological effects of a drug of abuse or medication (e.g., akathisia).

- RLS is believed to be caused by dopamine dysfunction in the brain.
 - Some hypothesize that circadian fluctuations in dopamine may play a role, as well as deficiencies in other substances including iron.
 - Risk factors for RLS include iron deficiency (e.g. pregnancy, blood donations, dietary restrictions – veganism etc.), kidney disease.

MNEMONIC

Diagnostic criteria of RLS

"URGE"

Urge to move legs
Rest worsens symptoms
Gets better with movement
Evening is when symptoms are the worst

CLINICAL PEARL

While awake, patients with RLS may describe a variety of sensations in their legs, including:

- Tingling
- Aching
- "Like I have to move"
- Burning
- Itching
- Electricity in veins
- "Creepy crawly" feeling

Associated Comorbidities

- Depression
- Headache
- Hypertension
- Cardiovascular and cerebrovascular disease

Management

- Reducing exacerbating factors
 - Caffeine
 - Tobacco
 - Alcohol
 - Dopamine blocking medications (e.g. serotonin dopamine antagonists)
 - SSRIs
 - Mirtazapine
- Addressing possible nutritional deficiencies
 - Bloodwork for iron, ferritin, Vitamin B12, folate
- Pharmacotherapy
 - First line: Dopamine agonists (e.g. pramipexole, ropinirole, L-dopa)
 - Second line: Gabapentin and pregabalin
 - Third line: Benzodiazepines
 - Fourth line: Opiates

Periodic limb movement disorder

- Periodic limb movement disorder (PLM-D) is characterized by repetitive leg movements during sleep.
- These movements typically occur in intervals of 20-40 seconds and cause awakening and sleep fragmentation, leading to daytime fatigue and/or sleepiness.
- The patient is often not aware of the leg movements, and their bed partner may report being kicked by the patient.
- 5-10% of the population with a widely varied age of onset.
- It is up to 2.5x as common in women.

Insomnia Disorder

- Insomnia is a sleep disorder wherein individuals have difficulty initiating or maintaining sleep.

DSM-5 Criteria for Insomnia Disorder

- A. A predominant complaint of dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms:
 1. Difficulty initiating sleep. (In children, this may manifest as difficulty initiating sleep without caregiver intervention.)
 2. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings. (In children, this may manifest as difficulty returning to sleep without caregiver intervention.)
 3. Early-morning awakening with inability to return to sleep.
- B. The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.
- C. The sleep difficulty occurs at least 3 nights per week.
- D. The sleep difficulty is present for at least 3 months.
- E. The sleep difficulty occurs despite adequate opportunity for sleep.
- F. The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g., narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia).
- G. The insomnia is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication).
- H. Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.

Specifiers:

- With non-sleep disorder mental comorbidity, including substance use disorders
- With other medical comorbidity
- With other sleep disorder
- Episodic: Symptoms last at least 1 month but less than 3 months.
- Persistent: Symptoms last 3 months or longer.
- Recurrent: Two (or more) episodes within the space of 1 year.

MNEMONIC

"Tired but wired"

Patients with insomnia are in a state of hyperarousal which leads to increased metabolism, increased body temperature, anxiety, and agitation.

(This is in contrast to sleep deprivation which is a state of hypoarousal with decreased metabolism, decreased body temperature, lethargy, and short sleep onset times.)

NOTE

Acute and short-term insomnia (i.e. symptoms lasting <3 months but otherwise meeting all criteria with regard to frequency, intensity, distress, and/or impairment) should be coded as **other specified insomnia disorder**.

Causes

- Stress
- Circadian factors
 - Shift work
 - Travel
 - Circadian rhythm sleep wake disorder
- Medical factors
 - Medications
 - Caffeine
 - Medical conditions
- Psychiatric factors
 - Mood disorders
 - Anxiety disorders

Management

- Sleep hygiene
 - Maintain a regular wake/sleep schedule
 - Avoid naps during the day
 - Avoid caffeine in the later afternoon
 - Avoid alcohol late at night
 - Exercise during the day, but not within 3 hours of bedtime
 - Develop a relaxing routine before bedtime
 - Use the bedroom only for sleep/intimacy activities
 - Avoid clock watching
 - Create a comfortable environment for sleep including light, noise, and temperature levels
 - Avoid computers and other backlit screens 2 hours before bed
- Cognitive behavioural therapy
- Sleep restriction therapy
 - This involves initially restricting the amount of time spent in bed to decrease awake time during the night and consolidate sleep
 - Once time awake in the middle of the night is minimized, the amount of time allowed in bed is extended until sufficient sleep is achieved
- Relaxation techniques

- Pharmacotherapy
 - Zopiclone and benzodiazepines
 - Have the most evidence for efficacy, but this does not mean these drugs are the most effective or best choices.
 - These medications can have significant side effects including possible effects on cognition, fall risk, dependence, therefore, caution is warranted if considering these medications for use.
 - Trazodone is used frequently clinically, but the evidence is weak.
 - Mirtazapine can be reasonable to consider for individuals with comorbid depression.
 - Serotonin dopamine antagonists are not recommended as first line medications for insomnia unless there is a significant psychiatric comorbidity, due to the paucity of evidence of efficacy and significant potential side effect profile.

EVIDENCE-BASED PRACTICE

In general, there are many medications available to try and use for insomnia, but the evidence of use of such medications, as reviewed by the American Academy of Sleep Medicine, for treating insomnia disorders (in the absence of other conditions) is weak.

Sleep and Mental Illness

Depression

- Greater than 90% of patients with Major Depressive Disorder report sleep disturbances that appear on polysomnogram
 - This is most common in melancholic and atypical subtypes
- Short REM latency, increased time in REM sleep, and decreased slow wave (deep) sleep are common in major depressive disorder

ADHD

- Initially restless and disturbed sleep were part of the diagnostic criteria for ADHD, but has been removed due to being non-specific
- Sleep problems are estimated to be present in 25-50% of children and adolescents with ADHD.
 - Most common are difficulty initiating and maintaining sleep

Schizophrenia

- Sleep-onset and maintenance insomnia are very common in schizophrenia
- Studies indicate that the latency of deep sleep and REM are reduced in individuals with schizophrenia, with REM duration unchanged

Bipolar Disorder

- Sleep disturbances are present in both manic and depressive phases of bipolar disorder
- During depressive episodes, patients display reduced REM latency, increased REM density, heightened fragmentation of REM sleep, and more awakenings
- During manic episodes, patients display reduced REM latency, increased REM density, heightened percentage of stage I sleep, and shortened total sleep time

Obstructive Sleep Apnea (OSA)

- OSA can exacerbate mental illness
 - Aggression in schizophrenia
 - Depression
 - Nightmares in post-traumatic stress disorder
 - Cognitive dysfunction of dementia
 - Relapses in substance use

Restless Legs Syndrome (RLS)

- RLS is highly comorbid with panic disorder and anxiety disorders
- RLS is exacerbated by serotonin and dopamine antagonists and serotonergic drugs, affecting compliance with these medications

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Review Questions

1. A 20-year-old male presents complaining of feeling excessively tired all day. He does not report feeling down or sad, and has no past psychiatric history. He tells you that he has strange spells of weakness in his neck when he tells a joke, or if he gets startled. He also reports that he does not sleep well, and sometime when he wakes up from sleep, he sees spiders on his arms and legs. Which of the following tests would most likely clarify the diagnosis?
 - a) Sleep deprived electroencephalogram (EEG)
 - b) Magnetic resonance imaging (MRI) of the head
 - c) Minnesota multiphasic personality inventory (MMPI)
 - d) Multiple sleep latency test (MSLT)
 - e) Complete blood count (CBC)

2. A 5-year-old boy presents with a history of “waking up at night with a horrifying scream” numerous times in the last 2 weeks. His parents say he looks scared, sometimes says he sees “spiders and snakes everywhere”, seems confused, and then does not remember the episode the next day. On several occasions, he has gotten out of bed and ran around screaming “nonsense”. What is the most likely diagnosis?
 - a) Sleep terrors
 - b) Acute stress disorder
 - c) Nightmare disorder
 - d) Brief psychotic disorder
 - e) REM sleep behaviour disorder

Answers:
 1. d)
 2. a)

Sexual Disorders

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Sexual Function

Normal sexual response

The human sexual response is divided into three stages:

- Libido
- Arousal
- Orgasm

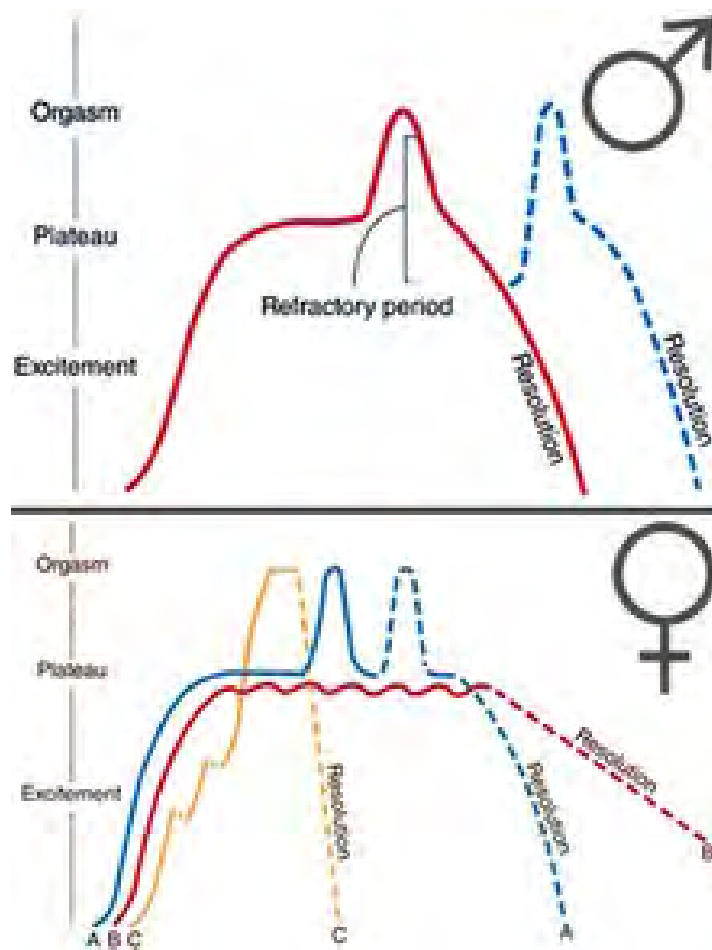


Figure 1. Diagram illustrating the normal human sexual response in both males and females.

Figure taken from Sexual Disorders Bootcamp Lecture.

Aging and sexual function

	Male	Female
Desire	▼	▼
Excitement	▼ full erection	▼ estrogen effects
Plateau	Pre-ejaculation state prolonged (plateau)	
Orgasm	Shorter, less urgent, less force and volume	Shorter, less vigorous, capable of multiple orgasms
Resolution	Shorter, prolonged refractory period	More rapid

Table 1. Table demonstrating the effects of aging on sexual function in both males and females.

Table taken from Sexual Disorders Bootcamp Lecture.

Health and sexual function

Libido ▼	Depression, endocrine problems, relationship problems, medical illness, menopause
Arousal ▼	Diabetes, hypertension, alcohol/drug use, obesity, smoking, major depressive , relationship problems, aging
Orgasm ▼	Diabetes, major depressive episode, neuropathy, relationship problems

Table 2. Table demonstrating the effects of various medical conditions on sexual function.

Table taken from Sexual Disorders Bootcamp Lecture.

Drugs and sexual function

Libido ▲	Bupropion, amphetamine, methyphenidate, cocaine, apomorphine
Libido ▼	SSRIs, antipsychotics (AAP, CAP)
Arousal ▲	Sildenafil, bupropion, prostaglandin, apomorphine
Arousal ▼	SSRI, anticholinergic medications, antipsychotics, alcohol
Orgasm ▲	Apomorphine, sildenafil
Orgasm ▼	SSRI, beta-blockers, antipsychotics

Table 3. Table demonstrating the effects of various medications on sexual function.

Table taken from Sexual Disorders Bootcamp Lecture.

CLINICAL PEARL

Bupropion has the least sexual side effects of all the antidepressants due to its lack of serotonergic activity (it can actually increase sexual desire).

Sexual Dysfunction

DSM-5 diagnoses

- **Sexual desire disorders**
 - Female sexual interest/arousal disorder
 - Male hypoactive sexual desire disorder
- **Sexual arousal disorders**
 - Female sexual interest/arousal disorder
 - Male erectile disorder
- **Orgasmic disorders**
 - Female orgasmic disorder
 - Delayed ejaculation
 - Premature ejaculation
- **Sexual pain disorders**
 - Genito-pelvic pain/penetration disorder
- **Substance/medication-induced sexual dysfunction**
 - Specify if: onset during intoxication, onset during withdrawal or onset after medication use

CLINICAL PEARL

When screening for sexual dysfunction, try asking: **“Do you have any concerns about your sexual function? If so, how often?”**

Concerns regarding sexual function with 75% or more of sexual encounters is considered clinically significant.

Specifiers for all the sexual dysfunction disorders include:

- Lifelong vs. acquired
- Generalized vs. situational
- Mild, moderate or severe

Etiology

- Performance anxiety: fear of negative evaluation during sex
- Spectatoring: critically monitoring one's own sexual performance
- Inadequate communication with partner regarding sex
- Fantasy:
 - Absence of fantasy
 - Distracting thoughts
 - Fantasies incompatible with sexual arousal
- Psychological issues:
 - Early conditioning, sexual trauma
 - Depression, anxiety, guilt, fear of intimacy or separation

- Relationship issues:
 - Lack of trust, power and control issues, anger at partner
- Sociocultural factors:
 - Attitudes and values, religious beliefs
- Educational & cognitive:
 - Sexual myths (gender roles, age and appearance, sexual expectations), sexual ignorance

Treatment

- Take a biopsychosocial approach regarding causes and management plan.
- Consult other specialties if necessary (e.g. obs/gyn, urology).
- Treat comorbid psychiatric illnesses first (e.g. anxiety, depression).

Pharmacological	Psychological
PDE-5 inhibitors Bupropion Lorazepam or propranolol (for anticipatory anxiety) Cyproheptadine (periactin) 4-8mg for women or 2h pre-coitus for men	Dual-sex therapy CBT Insight-oriented therapy Assertiveness training Group therapy

Table 4. Table demonstrating both the pharmacological and psychological treatment modalities for sexual dysfunction.

Table taken from Sexual Disorders Bootcamp Lecture.

CLINICAL PEARL

SSRIs are a first line treatment option for premature ejaculation.

Gender Dysphoria

DSM-5 Criteria for Gender Dysphoria

In children:

- A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least six of the following (one of which must be Criterion A1):
 1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender).
 2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.
 3. A strong preference for cross-gender roles in make-believe play or fantasy play.
 4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender.
 5. A strong preference for playmates of the other gender.
 6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities.
 7. A strong dislike of one's sexual anatomy.
 8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.
- B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

Specifiers:

- Specify if with a disorder of sexual development
 - E.g. a congenital adrenogenital disorder such as congenital adrenal hyperplasia or androgen insensitivity syndrome.

In adolescents and adults:

- A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least two of the following:
1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).
 2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
 3. A strong desire for the primary and/or secondary sex characteristics of the other gender.
 4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
 5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).
 6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).
- B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

Specifiers:

- Specify if with or without a disorder of sexual development
- Specify if post-transition (see sidebar)

FYI**"Post-transition"**

describes an individual who has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen - namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female).

Epidemiology

- Unknown prevalence but 1/30,000 (M) and 1/100,000 (F) present for gender affirming surgery
- 2-3:1 (M:F) present in clinic as adults

EVIDENCE-BASED PRACTICE

Recent studies suggest that the prevalence of a self-reported transgender identity in children, adolescents and adults ranges from 0.5 to 1.3%. This is significantly higher than prevalence rates based on clinic-referred samples of adults (Zucker, 2017).

Clinical course

- Boys may begin to experience gender dysphoria before the age of 4
 - Cross-dressing may also occur (75% will start before the age of 4)
- Trajectory:
 - Review of the evidence from prospective and retrospective follow-up studies suggests that gender dysphoria in prepubertal children continues into adolescence/adulthood in a minority of children
 - However, children with consistent, persistent and insistent gender-diverse behaviours are more likely to maintain diverse gender identities in the long term
 - In contrast to prepubertal gender diversity, gender dysphoria that intensifies with the onset of puberty rarely subsides
- Desire for gender affirming surgery occurs in less than 10% of gender dysphoria patients

Management

- Watchful waiting approach in children
- Psychotherapy
- Hormonal therapy
- Gender affirming surgery
- Treatment of any comorbidities

Paraphilias

Definitions

- **Paraphilia:** intense and persistent sexual interest that is not sexual interest in genital stimulation or preparatory fondling with phenotypically normal, physically mature, consenting human partners
- **Paraphilic disorder:** paraphilia that causes distress or functional impairment to the individual, or a paraphilia whose realization entails personal harm, or risk of harm to others; occurring for greater than 6 months

Subtypes of paraphilias include: voyeuristic, exhibitionistic, frotteuristic, sexual masochism, sexual sadism, pedophilic, fetishistic, transvestic, other specified paraphilic disorder, and unspecified paraphilic disorder.

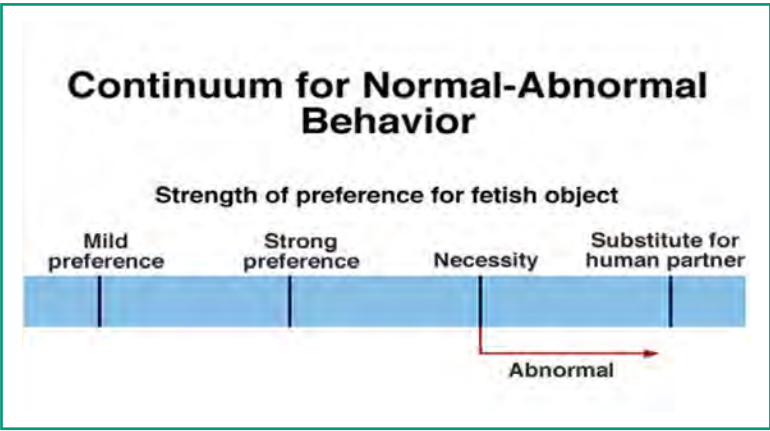


Figure 2. The continuum for normal-abnormal sexual behaviour.
Figure taken from Understanding Human Sexuality.

CLINICAL PEARL

Strategies for obtaining a complete sexual behaviour history

- Detailed self-report questionnaire regarding patient’s history of sexual behaviours, completed prior to initial evaluation
- Collateral source interview of prior relationship and/ or sexual partners or family members
- Collateral documentation from police reports or prior treatment

Paraphilic disorders

Disorder	Atypical sexual interest
Voyeuristic disorder	Observing an unsuspecting person who is naked, disrobing, or engaging in sexual activity.
Exhibitionistic disorder	Exposure of one’s genitals to an unsuspecting person.
Frotteuristic disorder	Touching or rubbing against a nonconsenting person.
Sexual masochism disorder	Being humiliated, beaten, bound, or otherwise made to suffer.
Sexual sadism disorder	Physical or psychological suffering of another person.
Pedophilic disorder	Prepubescent children.
Fetishistic disorder	Nonliving objects or nongenital body parts.
Transvestic disorder	Cross-dressing

Table 5. The major DSM-5 specified paraphilic disorders.
Information taken from Paraphilias: From Diagnosis to Treatment, Brian Holoyda.

Epidemiology and clinical course

- Rarely self-referred; often come to medical attention through interpersonal or legal conflict
- Person usually has more than one paraphilia; 5% of paraphilias attributed to women
- Amongst those with a convicted sex offence, 74% had an identified paraphilia (37% with pedophilia; other majority fall under the not-otherwise-specified category)
- Typical presentation: begins in childhood or early adolescence, increasing in complexity and stability with age
- Chronic, decreasing with advancing age but may increase with stress
- Most paraphilias do not come to medical attention

IMPORTANT

Not all sex offenders have a paraphilia and not all those with paraphilias are sex offenders!

EVIDENCE-BASED PRACTICE

GnRH analogs have the highest efficacy among the pharmacological treatments for paraphilias/paraphilic disorders (comparable to that of physical castration).

Management

Level	Description	Recommendation
1	Paraphilias that do not affect conventional sexual activity	Psychotherapy (e.g. CBT)
2	Mild cases of hands-off paraphilic disorders with low risk of sexual violence	SSRI
3	Hands-on paraphilic disorders with fondling, but without penetration; paraphilic sexual fantasies without sexual sadism	SSRI with low-dose antiandrogen
4	Moderate and high risk of sexual violence without sexual sadism	Full dosage synthetic steroidal analog
5	High risk of sexual violence and severe paraphilic disorders	Long-acting GnRH analog
6	Catastrophic cases	GnRH analog with synthetic steroidal analog; may consider SSRI

Table 6. The paraphilia/paraphilic disorder treatment algorithm from the World Federation of Societies of Biological Psychiatry.
Table taken from Paraphilias: From Diagnosis to Treatment, Brian Holoyda.

The Sexual Behaviours Clinic

The Sexual Behaviours Clinic (SBC) is an outpatient clinic at The Royal in Ottawa. The SBC treats men and women with problematic sexual interests and behaviours. Many of the clinic's clients are receiving treatment because they have a sexual interest in children, some have been charged with sexual offences and others have never acted on their sexual interest in children.

- Treatment goals: eliminate problematic sexual interests and behaviours and promote healthy sexual interests and legal sexual behaviours.
- Treatment model: based on the belief that pedophilia is a sexual interest (not a sexual orientation) and that sexual interests can be changed. The clinic's treatment model includes aspects of CBT as well as the Good Lives Model of treatment.
- Success rate: in the past 14 years, ZERO clients actively receiving treatment in the SBC have gone on to commit a known hand-on sexual re-offence against a child.

**For more information on the SBC, please visit: <https://www.sexualbehavioursclinic.ca/who-we-are/>.*

Pedophilic disorder

DSM-5 Criteria for Pedophilic Disorder

- Over a period of at least 6 months, recurrent, intense sexually arousing fantasies, sexual urges, or behaviors involving sexual activity with a prepubescent child or children (generally age 13 years or younger; not to be mistaken with attraction to adolescents).
- The individual has acted on these sexual urges, or the sexual urges or fantasies cause marked distress or interpersonal difficulty.
- The individual is at least age 16 years and at least 5 years older than the child or children in Criterion A.

**Note: Do not include an individual in late adolescence involved in an ongoing sexual relationship with a 12- or 13-year-old.*

Specifiers:

- Exclusive type (*only* attracted to children) vs. non-exclusive type
- If sexually attracted to males, females, or both
- If limited to incest

Epidemiology

- Less than 3% of the population
- 95% identify as heterosexual
- 50% have consumed alcohol at time of offence, >90% are men
- Many have also done exhibitionism, voyeurism & rape
- Often feel more accepted by kids, have low self-esteem, or body image problems
- Common comorbidities include: anxiety, depression, substance abuse, personality problems, intellectual delay, other paraphilias (i.e. exhibitionism, voyeurism)

Etiology

- Learning theory: a child who is the victim or observer of inappropriate sexual behaviours may learn to imitate that behaviour
- Masturbatory conditioning: non-sexual objects become sexually arousing if repeatedly associated with pleasurable sexual activity
- Cycle of sexual abuse: leads to cognitive distortions supportive of child molestation
- Neurodevelopmental disorder

Management

- External control
 - Incarceration: can include indeterminate sentencing; option of long-term or dangerous offender
 - Release conditions: sex offender registry, community notification and castration
- Pharmacological management
 - Partial sex drive reduction with SSRIs (only for hands-off offences)
 - Complete sex drive reduction with ablation of testosterone
 - Testosterone antagonist: Cyproterone (Androcur)
 - Negative feedback to LH and FSH: Medroxyprogesterone (Provera)
 - Indirect GnRH agonists: Leuprolide (Lupron), Goserelin (Zoladex)
 - Inhibit peripheral conversion of testosterone (adjunct): Finasteride

- Medical workup prior to and during treatment of pedophilia is necessary
 - Pre-medication:
 - LH, FSH, serum f-testosterone
 - LFTs, CBC, glucose, renal function
 - ECG, bone density, weight, BP
 - Endocrinology consult
 - During treatment:
 - Monthly testosterone for 4 months, then once every 6 months
 - BUN, creatinine, LH, prolactin every 6 months
 - Bone density yearly if on Leuprolide or Goserelin
- Treat comorbidities
 - Anxiety, depression
 - Substance abuse
 - Relational problems
- Psychosocial management
 - CBT: correct cognitive distortions
 - Covert sensitization: imagine negative social consequences of actions
 - Masturbatory reconditioning (satiation): learning to associate pleasurable sexual activity with appropriate stimuli (consenting adults)
 - Olfactory aversion: ammonia paired with deviant stimuli
 - Relapse prevention group: teach triggers and precursors leading up to deviant behaviour
 - Social skills group
 - Self-regulation group

Prognosis

- Those with pedophilic disorder have a very low recidivism rate when compared to other offenders.
- Overall 5-yr recidivism = 13.4%, 12.7% for child molesters, 18.9% for rapists
- Incest offenders the lowest at 4-10%
- 53% for extrafamilial child molesters

Poor prognosis	Better prognosis
Early onset High frequency of paraphilic activity Lack of guilt/shame about acts Comorbid substances *The above are true for ALL paraphilias!	History of normal coitus in addition to paraphilia Self-referral for treatment (vs. legal involvement) Absence of multiple paraphilias Normal IQ Lack of substances No ASPD/traits Successful adult attachments

Table 7. Prognostic factors relating to all paraphilias.

Table taken from *Sexual Disorders Bootcamp Lecture*.

Age of Consent

The definition of pedophilic disorder specifies that it is an interest in prepubescent children. Nevertheless, sexual activity with adolescents has legal implications despite not meeting the criteria of pedophilic disorder (can sometimes apply the unspecified paraphilic disorder).

According to the Child, Youth and Family Services Act – CYFSA (in Ontario):

- Age 12+ can consent to:
 - Sexual activity with a person no more than 2 years older, and who is not in a position of authority or trust
 - A temporary care arrangement
 - A child protection proceeding
 - Can apply for a review of status of being in care (society supervision, society or Crown wardship)
- Age 14+ can consent to:
 - Can consent to sexual activity with a person no more than 5 years older, and who is not in a position of authority or trust
- Age 16+ can consent to:
 - A picture or video of a youth under 18 years old who is naked or semi-naked, or engaging in a sex act is considered child pornography
 - Can withdraw from parental control under
 - Allowed to assert and defend individual privacy rights and access to information (FIPPA and MFIPPA)
 - CYFSA still applies until age 18 except duty to report a child in need of protection ends (unless in care)
 - Can name an attorney for personal care (SDA)
 - Can act as someone's Substitute Decision Maker (Health Care Consent Act; HCCA)
 - Prior capable wishes must be respected under HCCA

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Review Questions

1. Of the following, the individual who should be diagnosed with gender dysphoria is:
 - a) Joe, who gets sexually aroused by wearing women's bras
 - b) Lisa, who is gay and has traditional masculine traits
 - c) Mark, who feels like a woman trapped in a man's body
 - d) Sid, who can only become sexually aroused while dressed like a woman
 - e) All of them should be diagnosed with gender dysphoria

2. Which psychotropic medication has been shown to preserve sexual function, and it can be used to improve libido and arousal?
 - a) Escitalopram
 - b) Mirtazepine
 - c) Risperidone
 - d) Bupropion
 - e) Sertraline

3. Billy gets very sexually excited by women's shoes. While he used to fantasize about women wearing particular shoes, he now focuses almost exclusively on the shoes themselves. Billy has a(n):
 - a) Sexual dysfunction
 - b) Unusual interest but does not have a diagnosable disorder
 - c) Transvestic disorder
 - d) Fetishistic disorder
 - e) Frotteuristic disorder

Answers:
 1. c)
 2. d)
 3. d)

Forensic Psychiatry

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Adverse Childhood Experiences

Definition

- **Adverse childhood experiences (ACEs)** are traumatic events that occur during childhood (0-17 years) that can have negative, lasting effects on health and wellbeing.
 - ACEs include not only overt abuse/trauma but also household dysfunction such as divorce, incarcerated relatives and mental illness and/or substance abuse in the household.
- ACEs are linked to chronic health problems, mental illness and substance misuse in adulthood → ACEs can also negatively impact education and job opportunities → however, ACEs can be prevented.
- The ACE score is the total sum of the different categories of ACEs reported by participants → study findings show a graded dose-response relationship between ACEs and negative health and well-being outcomes.

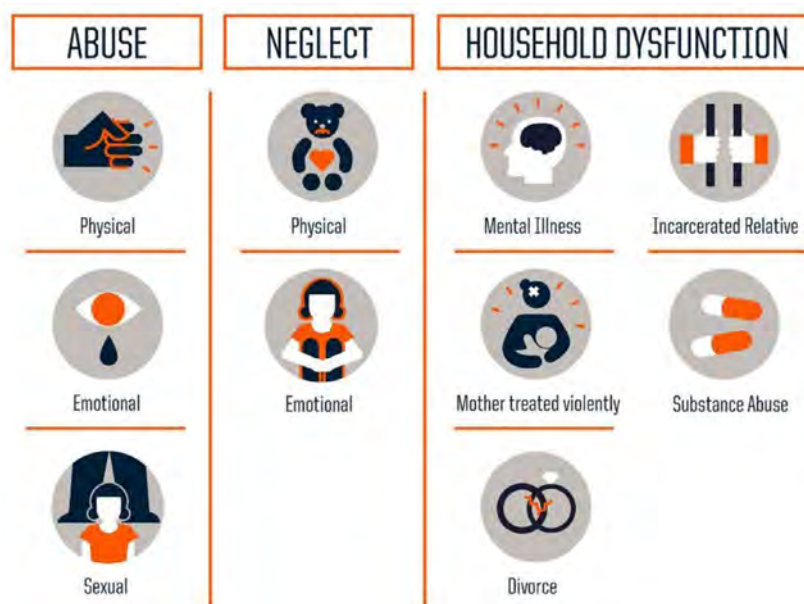


Figure 1. Major categories of ACEs.

Figure taken from the Robert Wood Johnson Foundation.

Prevalence and societal consequences

- About 61% of adults surveyed across 25 states reported that they had experienced at least one type of ACE, and nearly 1 in 6 reported they had experienced four or more types of ACEs.
- Preventing ACEs could potentially help reduce a large number of chronic health conditions → up to 1.9 million cases of heart disease and 21 million cases of depression could have potentially been avoided by preventing ACEs.
- Some children are at greater risk than others → women and several ethnic/racial minority groups were at greater risk for having experienced 4 or more types of ACEs.
- The economic and social costs to families, communities and society totals hundreds of billions of dollars each year.

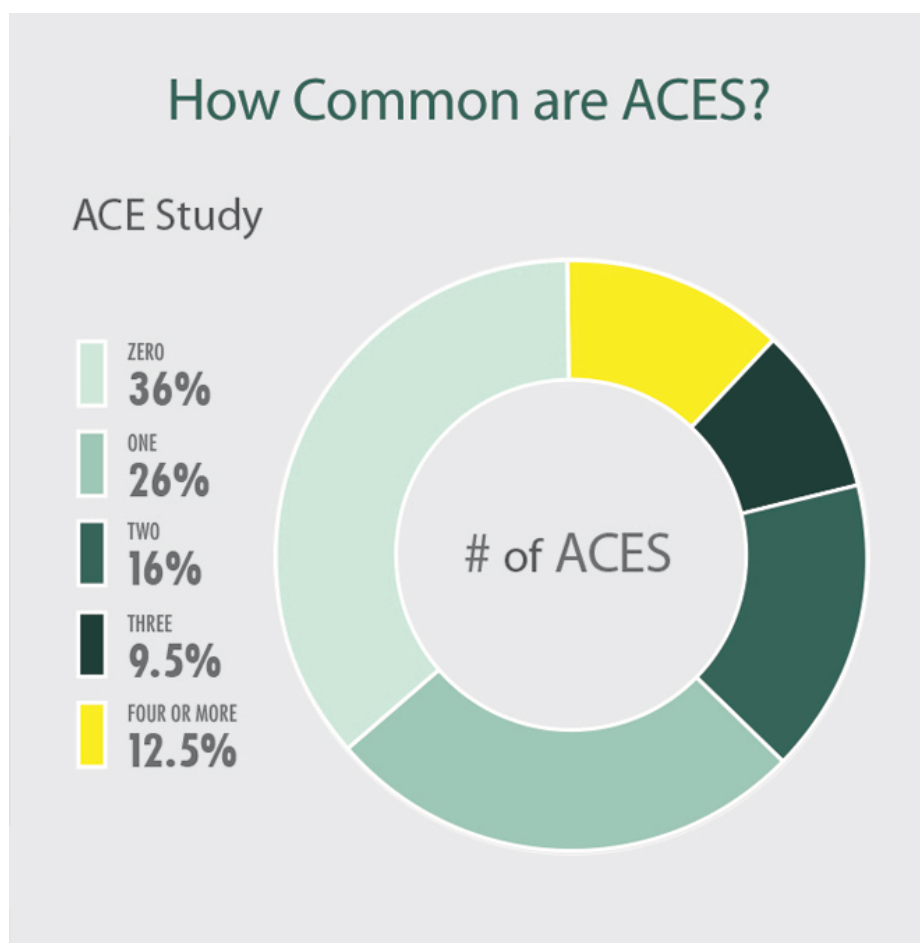


Figure 2. ACE score prevalence among the CDC-Kaiser ACE study participants, Waves 1 and 2.

Figure taken from Center for Disease Control and Prevention, Kaiser Permanente.

ACEs and toxic stress

- ACEs and associated conditions, such as living in under-resourced and racially segregated communities, frequently moving and experiencing food insecurity, can cause toxic stress (extended or prolonged stress).
- Toxic stress from ACEs can affect brain development and disrupt things like attention, decision-making, learning and response to stress.
 - Children growing up with toxic stress may have difficulty forming healthy and stable relationships (i.e. reactive attachment disorder) → may struggle with jobs, finances and depression throughout life.
 - Children may also turn to substances and/or other maladaptive coping strategies (i.e. risky sexual behavior, overeating etc.) to cope with the toxic stress they are experiencing.
- These effects can be passed on to their own children → some children may experience further exposure to toxic stress from historical or ongoing traumas due to systemic racism or the impacts of poverty.

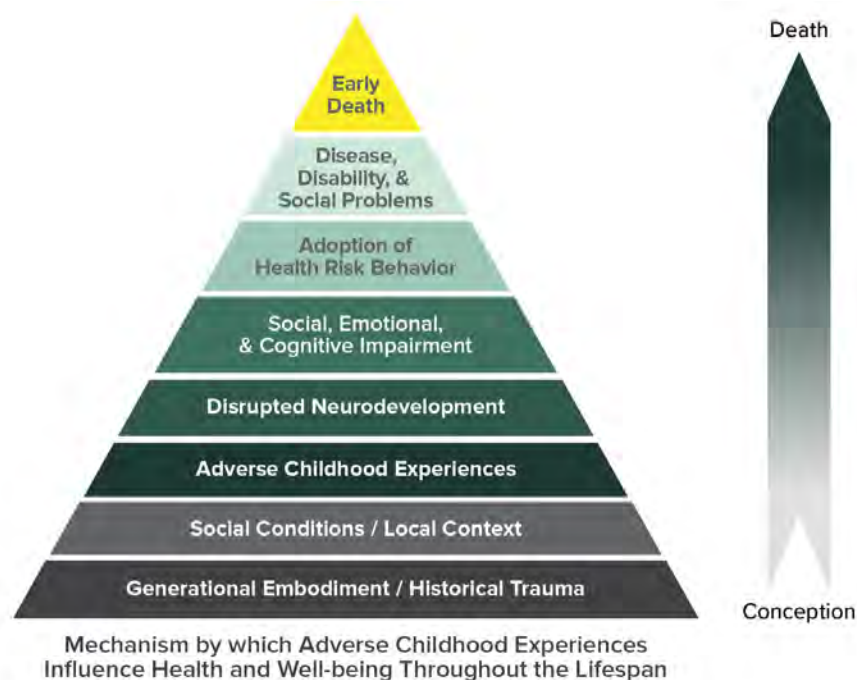


Figure 3. The ACE Pyramid, a model which demonstrates the mechanism by which ACEs influence health and well-being throughout the lifespan.

Figure taken from Center for Disease Control and Prevention.

Health outcomes

- ACEs can increase the risk of injury, STIs, maternal and child health problems, teen pregnancy, involvement in sex trafficking and a wide range of chronic health conditions and leading causes of death including cancer, diabetes, heart disease and suicide.
- Chronic stress is associated with suppression of both cellular and humoral immune responses.



Figure 4. Negative health outcomes associated with ACEs.
Figure taken from Center for Disease Control and Prevention.

4-12x increase	2-4x increase	1.4-1.6x increase
Alcohol abuse	Smoking	Physical inactivity
Drug abuse	Poor self-rated health	Severe obesity (BMI >35)
Depression	>50 sexual partners	
Suicide attempt	STIs	

Table 1. Increased risk for various negative health outcomes associated with having 4 or more ACEs.
Table adapted from ACEs Handout for MS3.

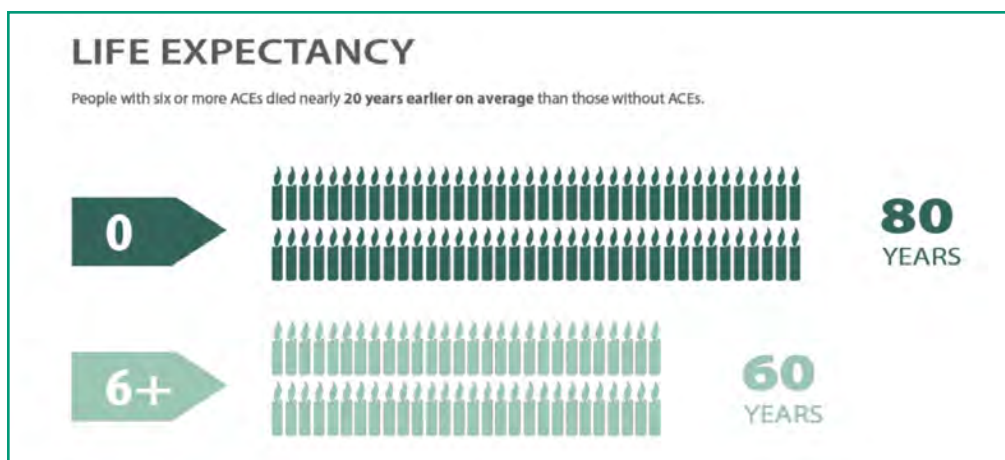


Figure 5. There is a 20-year decrease in life expectancy associated with having 6 or more ACEs.
Figure taken from Center for Disease Control and Prevention.

Screening for ACEs

Considerations for screening for ACEs and trauma

1. Treatment setting and patient population should guide screening.
2. Screening should benefit the patient.
3. Care coordination should be employed to avoid unnecessary rescreening.
4. Ample training should precede screening.

Responding to ACEs

- Prior to screening for ACEs, providers should have referral processes in place to ensure that patients identified with behavioral, social or trauma-specific service needs can be connected with trained professionals.
- Some organizations have integrated services and are able to hand-over patients to these referral partners.
- Others must build referral networks outside of the clinical setting and develop the ability to effectively track and follow-up with patients to ensure they have connected to needed supports.

CLINICAL PEARL

A variety of tools exist for the screening and assessment of ACEs:

- [ACE Questionnaire](#)
- [Centre for Youth Wellness' ACE Questionnaire](#)

These screening tools can be administered face-to-face with a staff member or independently by the patient.

A universal screening approach is most commonly used, as it provides a better understanding of the entire patient population and reduces the risk of racial/ethnic bias.

IMPORTANT

It is NOT necessary to discuss the details of the specific adversities or traumas experienced at the time of ACE screening.

Preventing ACEs

- ACEs are preventable by creating and sustaining safe, stable, nurturing environments for children and families.
- Preventing ACEs requires addressing factors at all levels of society: the individual, relational, community, and societal levels.
- Raising awareness about ACEs can help shift the focus from individual responsibility to community solutions and reduce stigma around seeking help for parental challenges and for substance misuse, depression, or suicidal thoughts.
- Screening for ACEs in children can allow for targeted family interventions in children who screen positive.



Figure 6. Various strategies that can be implemented to help reduce ACEs.

Figure taken from Center for Disease Control and Prevention.

Health in Corrections

Trans-institutionalization

- **Trans-institutionalization** is defined as “the movement of those with mental illness out of state hospitals and into the criminal justice system”.
- With the deinstitutionalization movement in the second half of the twentieth century, an increasing number of individuals with mental illness have become involved with the criminal justice system.
- This is in large part due to a scarcity of mental health resources in the community, and has been referred to as the “criminalization of mental illness”.

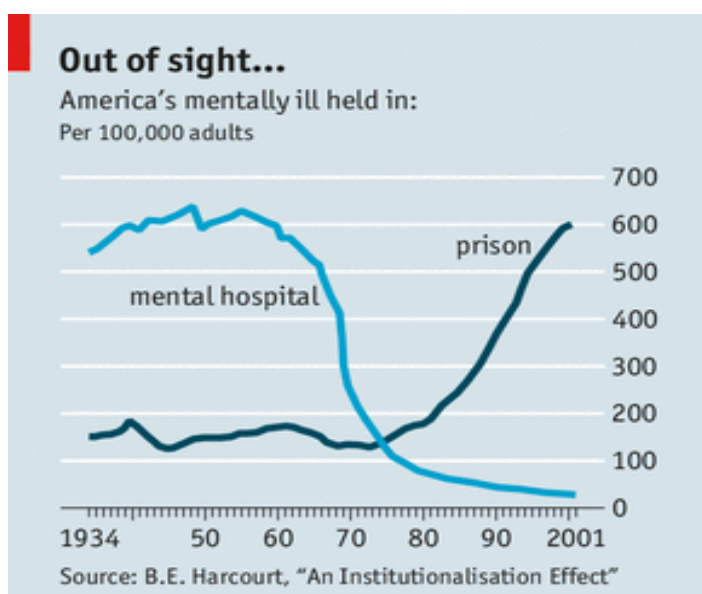


Figure 7. Trans-institutionalization over the last 70 years in the U.S.

Figure taken from B.E. Harcourt, "An Institutionalization Effect".

Demographics

- [Figure 8](#) and [Figure 9](#) illustrate some demographic information regarding Canada's correctional population (based on age and ethnic group).
- Notably, the Indigenous population is over-represented in Canada's correctional system
 - Make up 4-5% of Canada's population
 - 28-30% of correctional inmates
 - As high as 75% in Manitoba and Saskatchewan

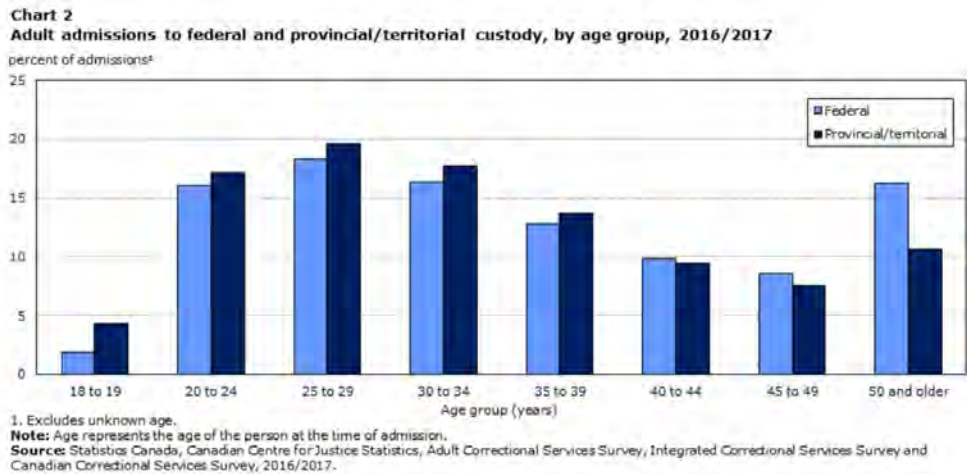


Figure 8. Distribution of adult admissions to federal and provincial/territorial custody, by age group, from 2016 to 2017.

Figure taken from Integrated Correctional Services Survey and Canadian Correctional Services Survey, 2016/2017.

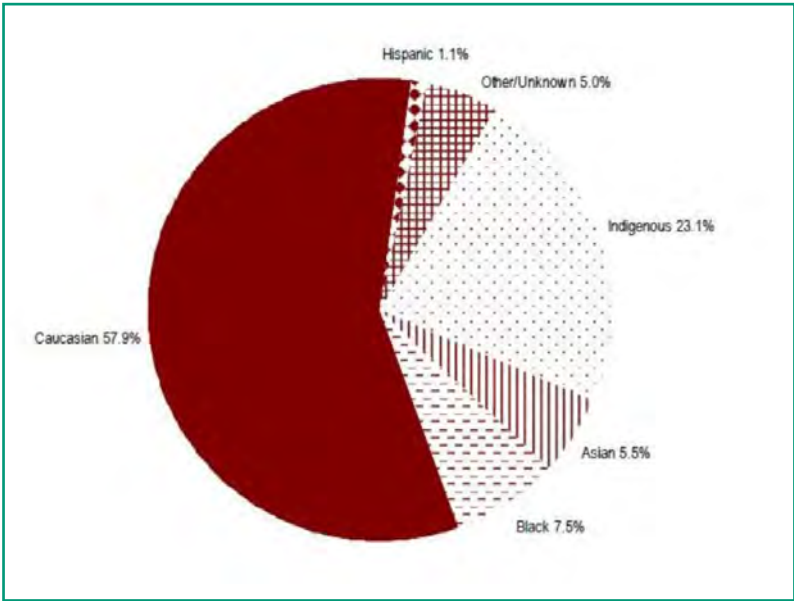


Figure 9. Percentages of total offender population by ethnic group.

Figure taken from Health in Corrections Bootcamp Lecture.

Health status of Canadian prisoners

- More than 75% of people incarcerated in Canada's jails and prisons have a substance use disorder, about 20% have a mood disorder and 4-5% have a psychotic disorder.
 - Lifetime prevalence rates of all mental disorders are 2-4x higher in custody.
- 20% of men in provincial jails were homeless at the time of admission.
- 55% of people admitted to Federal custody have less than a grade 10 education (2011).
- Suicide rate in custody is approximately 7x greater than in the general population.
- $\frac{2}{3}$ of adults in custody are current smokers (compared to ~16% of the general population).
- Infectious disease: up to 30% Hepatitis C rates and 1-2% HIV rates; rates of tuberculosis are ~5x greater than in the general population.
- Reproductive health: more than half of adults in custody have children; women in provincial custody have an average of four pregnancies, 5% currently pregnant.
- Chronic disease: poorly studied but clearly higher rates of CVD, diabetes, asthma and COPD.

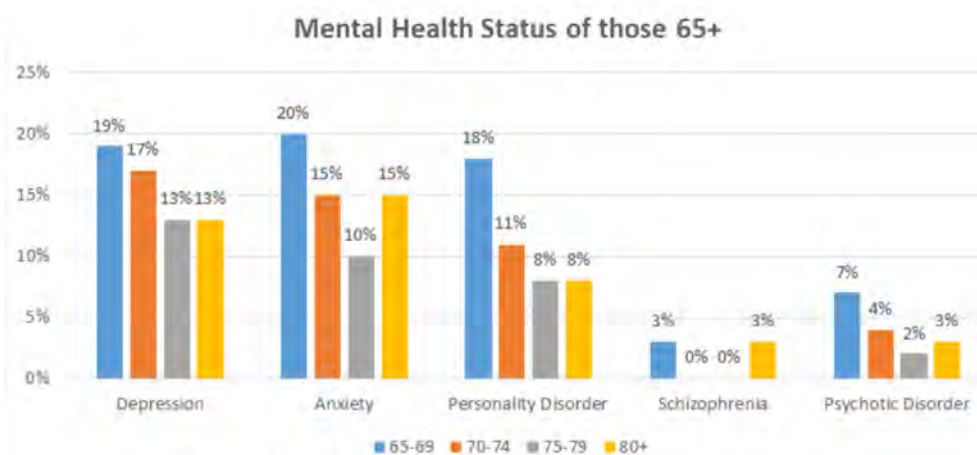


Figure 10. Prevalence of various mental disorders amongst those aged $\geq 65+$ in federal custody.

Figure taken from *Aging and Dying in Prison: An Investigation into the Experiences of Older Individuals in Federal Custody*.

Clinical challenges

- Correctional health is a greatly under-serviced area of medicine.
- Complex, comorbid patients.
- Often negative views about physicians/healthcare
 - Childhood experiences (e.g. parental abuse, unwanted treatment)
 - Often brought to hospital by police
 - Slow to develop trust
- Length of stay unpredictable.
- Very hard to arrange follow-up.
- Limited access to family, supports and resources.
- Diversion of medications (especially psychotropics) is widespread.



Figure 11. Comparison between prisoners with no ACEs and those with 4 or more ACEs.

Figure taken from the Prisoner ACE Survey.

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Review Questions

1. You are a primary care provider seeing a 35-year-old patient, relatively new to your practice, who appears to have multiple medical and mental health issues. You decide to screen for ACEs, as you know that addressing them will help improve health outcomes. Which of the following would be TRUE about screening for ACEs in this patient?
 - a) Screening for ACEs is a low yield because you cannot change the past.
 - b) You can ask the nurse/receptionist to give them a screening questionnaire to fill out before they see you.
 - c) You should ask ACE screening questions as part of a clinical interview, and if anything is positive, fully explore the details of their trauma.
 - d) You shouldn't ask about past trauma during a primary care encounter because you don't have time to do anything about it.
 - e) It is better to focus on the medical issues rather than past traumas.

(p. 1)
Answers:

ADHD, Oppositional Defiant Disorder, and Conduct Disorder

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Attention-Deficit/Hyperactivity Disorder (ADHD)

General features

- Disorder characterized by marked inattention (i.e. inability to sustain attention, follow through on instructions, finishing tasks, organizing tasks, etc) and/or hyperactivity (i.e. excessive talking, fidgeting, etc) and/or impulsivity (i.e. blurts out answers, interrupts others, etc).
- Classified under “Neurodevelopmental Disorders” in the DSM-5.

DSM-5 Criteria for Attention-Deficit/Hyperactivity Disorder

- A. Inattentive symptoms ($\geq 6/9$), and/or hyperactive-impulsive symptoms ($\geq 6/9$) (for age 17 and older at least 5 symptoms are required) - see [Table 1](#).
- B. Several symptoms must have been present <12 years of age.
- C. Several symptoms must be present ≥ 2 settings (home, school, work, friends, other activities).
- D. Clear interference in functioning (school, social, family, work).
- E. Symptoms not better explained by another mental health disorder or medical condition.

Presentations

- **Combined presentation:** 6 or more symptoms of inattention and 6 or more symptoms of hyperactivity-impulsivity
- **Predominantly inattentive presentation:** 6 or more symptoms of inattention
- **Predominantly hyperactive-impulsive presentation:** 6 or more symptoms of hyperactivity-impulsivity

Inattention (9)	Hyperactivity (6)	Impulsivity (3)
Inattention to details/ careless mistakes	Fidgets, taps hands/feet, or squirms in seat	Blurts out answer
Does not sustain attention	Leaves seat when expected to remain seated	Has difficulty awaiting turn
Does not seem to listen when spoken to directly	Runs about or climbs where it is inappropriate	Interrupts or intrudes on others
Does not follow through on instructions/ finishing	Not quiet during leisure activities	
Has difficulty organizing tasks, activities	"On the go"/ acts as if "driven by a motor"	
Has difficulty with sustained mental effort	Talks excessively	
Loses things		
Gets easily distracted		
Is forgetful		

Table 1. Break-down of ADHD symptomatology categories.

Differential diagnosis

- Not every inattentive or disruptive child has ADHD.
- A child may be inattentive or act out because of other psychiatric or medical conditions.
- Psychiatric conditions to rule out:
 - Learning problems, intellectual disability
 - Oppositional defiant disorder, conduct disorder
 - Mood (depression, disruptive mood dysregulation disorder, or bipolar disorder)
 - Anxiety, post-traumatic stress disorder (PTSD)
 - Reactive attachment disorder
 - Autism spectrum disorder
 - Sleep problems
 - Substance-related disorder not otherwise specified
 - Medication-induced symptoms of ADHD
 - Impaired hearing or vision
 - Personality change due to a general medical condition
 - Age-appropriate behaviours in active child
 - Under-stimulating environment (gifted child)

- Medical conditions to rule out:
 - Hyperthyroidism
 - Asthma
 - Iron-deficient anemia
 - Poorly controlled diabetes mellitus
 - Seizure disorder/epilepsy

Epidemiology

- Prevalence of ADHD
 - School age children: 6-9%
 - Adult 4.4%
- ADHD accounts for 30-50 % of mental health referrals
- Prevalence of different ADHD presentations in children:
 - Combined (50-75%)
 - Inattentive (20-40)
 - Hyperactive-impulsive (<5-15%)
- Gender differences:
 - Diagnosed in 9.0% of boys (4-16 yrs old) and 3.3% of girls (4-16 yrs old).
 - Boys: more commonly present with hyperactive-impulsive type.
 - Girls: more commonly present with inattentive type (and can be missed as a result).

Etiology

- Genetics accounts for ~0.76 of the variance in ADHD.
- Child of a parent with ADHD has a 50% chance of having ADHD.
- Non-genetic factors: low birth weight/prematurity, maternal smoking or drinking alcohol in pregnancy, psychosocial adversity.
- Parenting is not a cause of ADHD, but parenting influences the outcome of ADHD.
- Polygenic disorder (many genes involved).
- Dysfunction in cortico-striatal-thalamic-cortical loops.
- Catecholamine dysfunction (norepinephrine and dopamine).

CLINICAL PEARL

Comorbidity is the rule, not the exception, in individuals with ADHD.

Many have psychiatric comorbidities including anxiety disorders, mood disorders, oppositional defiant disorder, and conduct disorder. (See [Figure 1.](#))

Assessment in children and adolescents

- Parent interview, including developmental history.
- Child/adolescent interview.
- Information from teachers and other sources.
- Rating Scale (available at www.caddra.ca)
 - Useful to support clinical evaluation and monitor progress, but should not be used on their own to make a diagnosis.
 - Conner's Rating Scale-Revised (Parent/Teacher)
 - SNAP-IV Teacher/Parent Rating Scale
- Medical evaluation
 - Rule out hearing/vision, sleep, head injuries, seizures.
 - Labs such as CBC, TSH.

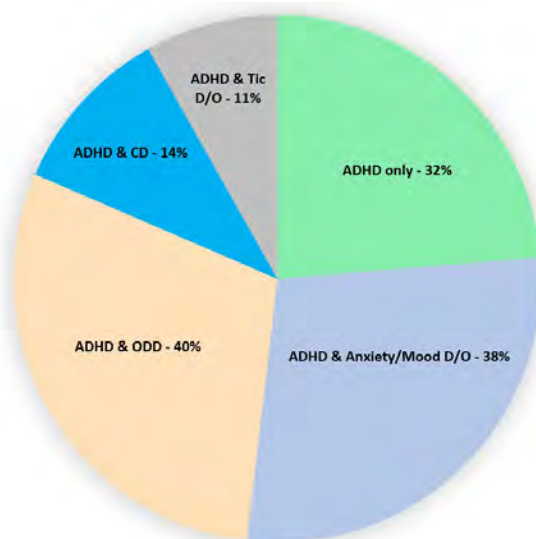


Figure 1. Comorbidities associated with ADHD.

Figure adapted from data from Jensen PS, 2001.

Treatment

Psychosocial

Psychoeducation

- Explain the rationale for the diagnosis.
- Explain that ADHD is mainly a genetically and neurobiological based disorder.
- Review the natural course of ADHD.
- Provide a sense of hope since ADHD is one of the most treatable psychiatric conditions.

CLINICAL PEARL

Questions to ask during the parent interview

- Does he/she get easily distracted? (telephone, noise)?
- Does he/she daydream excessively to the point that he/she zones out all the time?
- Gaps in memory in regards to what the teacher is saying during class?
- How organized is he/she? Room? Assignments? Desk at school/home? Agenda? Loses things easily? Projects (planning, getting things done in order)?
- Difficulty sitting still? Energy level? (hyperactivity)
- Acts before he/she thinks, dare devil? (impulsivity)
- How long can he/she play alone? Quietly?
- How does he/she behave during sports/extracurricular activities (e.g. piano, soccer, baseball, swimming)?

Behavioural Parent Management Training

- Improved compliance with parental commands; improved parental understanding of behavioral principles; high levels of parental satisfaction with treatment.

Behavioural School and Academic Intervention (ES 0.61)

- Improved compliance with classroom rules; decreased disruptive behavior; improved work productivity.

Biological

- See [Figure 2](#) and [Table 2](#).
- Medications are first line in the treatment of ADHD, specifically stimulants, which include:
 - Methylphenidates (Biphentin, Concerta, Ritalin, etc.)
 - Amphetamines (Adderall, Vyvanse, Dexedrine, etc.)
- Stimulants are available in both short-acting and long-acting forms; long-acting forms are preferred due to reduced abuse potential.
- Non-stimulants, such as:
 - Atomoxetine:
 - Selective norepinephrine (NE) reuptake inhibitor (NRI)
 - Atomoxetine had been studied as a potential treatment for depression, but was found to be ineffective.
 - Unlike stimulants, is not a controlled substance and may be used for children/adolescents who poorly respond to stimulants.
 - Selective alpha-2-adrenergic agonists (guanfacine and clonidine)
 - Both guanfacine and clonidine have similar side effect profiles, but clonidine has higher risk of sedation and hypotension
 - Only medication recommended as an adjunctive therapy to psychostimulants for patient with suboptimal treatment response.

FYI

Review the [CADDRA guidelines](#) for additional information on biological treatment options for ADHD.

Prognosis

- 70-80% of children with ADHD continue into adolescence.
- 65% continue into adulthood.
- Hyperactive-impulsive symptoms are more likely to improve or become internalized (e.g. changed into nervous tension).
- Inattentive symptoms are more likely to persist.

ADHD in Adults

Diagnostic challenges

- Difficult to diagnose, compared to ADHD in children and adolescents
 - Low levels of identification and treatment (<20% compared to >50% in children and adolescents)
- Diagnosis requires presence of ADHD symptoms in childhood (before 12 years)
- ADHD shares symptoms with other diagnoses
- Comorbidity complicates presentation

Comorbidities

Any Mood Disorder: 38%
 Major Depressive Disorder: 19%
 Any Anxiety Disorder: 47%
 Social Phobia: 29%
 GAD: 8%
 Any Substance Disorder : 15%

Assessment

- Screening questions for ADHD in adults:
 - “Were you ever diagnosed with ADHD as a child?”
 - “Do you have a family member with ADHD (first degree relative)?”
 - “Do you have a lifelong history of distractibility, inattention or disorganization?”

Diagnosis

1. Focused biopsychosocial history
 - Rule out medical and/or psychiatric disorders
 - Assess exacerbating factors/stressors
2. Brief childhood history and childhood ADHD symptoms
 - Diagnosis of ADHD
3. Assess lifelong and current ADHD symptoms
 - Severity of adult ADHD

Findings on history that warrant high index of suspicion for adult ADHD

Organizational skill problems
Erratic work history or academic problems
Recurrent marital problems, parenting problems
Discrepancy between success and intelligence
Money management problems
Frequent accidents, involvement in risk-taking or extreme sports
Problems with driving, e.g. frequent driving violations
Treatment-resistant depression or anxiety
Anger control problems
Patients who are over-talkative, interrupt frequently or inappropriately
Substance use or abuse
Addictions such as hoarding, compulsive shopping, sexual avoidance or addiction, overeating, compulsive exercising, gambling
Lack of time sense; a history of missed appointments or being late for appointments
Family history of ADHD

Compensatory/avoidant efforts

- May hide symptom impact
- Patients opt out or defer challenging activities
- Compensation may be a burden
 - Efforts to maintain attention, control behavior
 - Reliance on organizational, reminder systems
 - Reliance on others for structure, deferred tasks
 - Long hours to compensate for inefficiency

ADHD in Adults (continued)

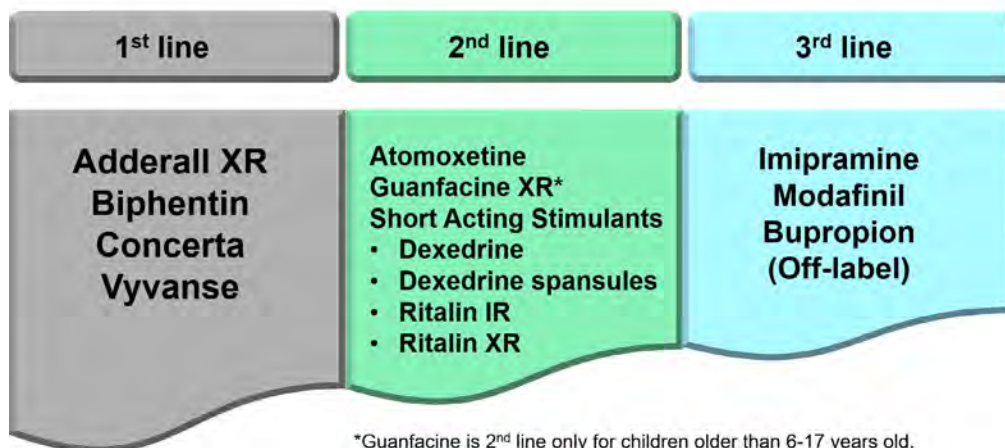
Treatment

Psychosocial

- Psychoeducation
 - Behavioural Intervention and Goal Setting
 - Assistive and Organizational Technologies
- Work place or academic accommodations
- Psychotherapy
 - CBT in combination with medication
 - Meta-cognitive therapy: a group-administered, cognitive-behavioral principles and training in executive self-management skills.
 - Other psychotherapies
 - Individual psychotherapy
 - Marital therapy

Biological

- Pharmacological treatment in adults is similar to that of children.
- Stimulants are first-line.



*Guanfacine is 2nd line only for children older than 6-17 years old.

Figure 2. Classification of medications used in the treatment of ADHD.

	Stimulants	Atomoxetine (ATX)	Alpha-2-adrenergic agonists (Guanfacine and Clonidine)
Advantages	Extensive data efficacy and safety	24-hr coverage - No potential for drug abuse - Little or no long-term effect on growth in children followed up to 5 years. - Possibly lower risk of exacerbating tics and may even improve tics.	- Not a controlled substance. - May also treat coexisting conditions (eg, sleep disorders, tic disorders). - Generic formulations available
Disadvantages	More side effects than non-stimulants	- May be less efficacious than stimulants. - Potential increased risk of suicidal ideation. - More time to steady state (up to two weeks for initial response; up to eight weeks for maximal effect). "Drug holidays" are not an option. - Drug interactions with 2D6 inhibitors (e.g. fluoxetine, paroxetine)	- May be less efficacious than stimulants. - More time to steady state (up to two weeks for initial response). "Drug holidays" are not an option.
Contra-indications	- Hypersensitivity - Within two weeks of monoamine oxidase inhibitor (MAOI) use - Glaucoma (narrow angle) - Advanced/symptomatic cardiovascular disease - Agitated states - Marked anxiety - Hyperthyroidism - Moderate-to-severe hypertension. - History of drug abuse *Note: Stimulants are not contraindicated in individuals with seizure disorders, autism spectrum disorders, or Tourette syndrome, but use is cautioned.	- Hypersensitivity - Within two weeks of MAOI use - Glaucoma (narrow angle) - Advanced/symptomatic cardiovascular disease - Pheochromocytoma	Hypersensitivity
Monitoring	- Height and weight on growth charts - Heart rate (HR) and blood pressure (BP) at baseline, with dose changes and periodically thereafter - Use parent and teacher rating scales to monitor response and side effects at different doses	- Height and weight on growth charts - HR and BP at baseline, with dose changes and periodically thereafter - Use parent and teacher rating scales to monitor response and side effects at different doses - For ATX: assess suicidal ideation. Baseline LFTs are not necessary, but LFTs should be done at the first symptom or sign of liver dysfunction.	- Height and weight on growth charts - HR and BP at baseline, with dose changes and periodically thereafter - Use parent and teacher rating scales to monitor response and side effects at different doses
Adverse reactions	*Note: Methylphenidate and Amphetamine have similar side effect profiles. Most common adverse effects: anorexia, weight loss, insomnia, xerostomia, headache, irritability. - Boxed warnings: - High potential for abuse (both) - Misuse may cause sudden death and serious cardiovascular adverse events (amphetamines).	- Most common adverse effects: Headache, insomnia, drowsiness, hyperhidrosis, xerostomia, nausea, anorexia, abdominal pain, vomiting constipation, erectile dysfunction. - Boxed warning: risk of suicidal ideation in rare cases.	- Note: Guanfacine has a longer half-life and fewer side effects than does clonidine. - Most common adverse effects: Somnolence, fatigue, drowsiness, headache and upper abdominal pain, and a lowering of pulse and blood pressure.
Efficacy	70% of children and adults respond to any given stimulant efficacious in both adults and children; 90% respond to both. - Helpful for treating ODD/CD symptoms and aggression associated with ADHD (overall effect size of 0.7-0.8).	- Improves ADHD symptoms in children (ES: 0.6) but less effective in adults (ES 0.3-0.4). - Less effective for ODD symptoms (ES: 0.3) - Poor quality of evidence for ATX being helpful in comorbid anxiety.	- Can be used as monotherapy or adjunct therapy to stimulants (respective ES are 0.6 and 0.3-0.4). - Helpful for treating comorbid ADHD and tics (ES: 0.7)

Table 2. Summary of medications used in the treatment of ADHD.

Conduct Disorder (CD)

General features

- Repetitive and persistent pattern of behavior violating basic rights of others or major societal norms or rules.
- Classified under “Disruptive Behavior Disorders” chapter in the DSM-5.

DSM-5 Criteria for Conduct Disorder

- A. A repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms/rules are violated, as manifested by the presence of >3 of the following 15 criteria in the past 12 months from any of the categories below, with >1 criterion present in the past 6 months:

Aggression to People and Animals

1. Often bullies, threatens, or intimidates others.
2. Often initiates physical fights.
3. Has used a weapon that can cause serious physical harm to others (e.g., a bat, brick, broken bottle, knife, gun).
4. Has been physically cruel to people.
5. Has been physically cruel to animals.
6. Has stolen while confronting a victim (e.g., mugging).
7. Has forced someone into sexual activity.

Destruction of Property

8. Has deliberately engaged in fire setting with the intention of causing serious damage.
9. Has deliberately destroyed others' property (other than by fire setting).

Deceitfulness or Theft

10. Has broken into someone else's house, building, or car.
11. Often lies to obtain goods or favors or to avoid obligations (i.e., “cons” others).
12. Has stolen items of nontrivial value without confronting a victim (e.g., shoplifting, but without breaking and entering; forgery).

Serious Violations of Rules

13. Often stays out at night despite parental prohibitions, beginning before age 13 years.
14. Has run away from home overnight at least twice while living in the parental or parental surrogate home, or once without returning for a lengthy period.
15. Is often truant from school, beginning before age 13 years.

- B. The disturbance in behavior causes clinically significant impairment in social, academic, or occupational functioning.
- C. If the individual is age 18 years or older, criteria are not met for antisocial personality disorder.

Specifiers:

- **Onset:**
 - Childhood-onset type: Individuals show at least one symptom characteristic of conduct disorder prior to age 10 years.
 - Adolescent-onset type: Individuals show no symptom characteristic of conduct disorder prior to age 10 years.
 - Unspecified onset: Criteria for a diagnosis of conduct disorder are met, but there is not enough information available to determine whether the onset of the first symptom was before or after age 10 years.
- **With limited prosocial emotions:** to qualify for this specifier, an individual must have displayed at least 2 of the following characteristics persistently over at least 12 months and in multiple relationships and settings.
- **Lack of remorse or guilt:** Does not feel bad or guilty when he or she does something wrong (*exclude remorse when expressed only when caught and/or facing punishment).
- **Callous—lack of empathy:** Disregards and is unconcerned about the feelings of others. The individual is described as cold and uncaring.
- **Unconcerned about performance:** Does not show concern about poor/problematic performance at school, at work, or in other important activities.
- **Shallow or deficient affect:** Does not express feelings or show emotions to others, except in ways that seem shallow, insincere, or superficial
- **Current severity:**
 - Mild: Few if any conduct problems in excess of those required to make the diagnosis are present, and conduct problems cause relatively minor harm to others (e.g., lying, truancy, staying out after dark without permission, other rule breaking).
 - Moderate: The number of conduct problems and the effect on others are intermediate between those specified in “mild” and those in “severe” (e.g., stealing without confronting a victim, vandalism).
 - Severe: Many conduct problems in excess of those required to make the diagnosis are present, or conduct problems cause considerable harm to others (e.g., forced sex, physical cruelty, use of a weapon, stealing while confronting a victim, breaking and entering).

Epidemiology

- One-year population prevalence between 2-10%, median of 4%.
- More common in males than in females (M:F = 4-12:1)

Etiology

- Temperamental: undercontrolled/difficult infant temperament, lower-than-average intelligence.
- Environmental: Parental rejection and neglect, inconsistent child-rearing practices, harsh discipline, physical or sexual abuse, lack of supervision, early institutional living, frequent changes of caregivers, large family size, parental criminality, and certain kinds of familial psychopathology (e.g., substance-related disorders).
- Genetic: More common in children of biological parents with alcohol use disorder, mood disorders, schizophrenia, ADHD, or conduct disorder.

Comorbidities

- Oppositional defiant disorder (ODD); in clinical samples, a very low rate of CD without ODD is observed.
- ADHD (common)
- Specific learning disorder, anxiety disorders, depressive or bipolar disorders, and substance-related disorders
- Academic deficits particularly in reading and other verbal skills, (may justify the additional diagnosis of specific learning disorder or a communication disorder)

Diagnosis

- Youth are the best informants of CD behaviours, regardless of age
- Collateral is important! (In some cases of CD, especially with limited prosocial emotion, patients will not readily admit to traits.)
- Parents are more aware of boys' than girls' CD behaviours (see sidebar)
- Checklists are useful for identifying symptoms; interviewing gets at the context
- Try to obtain age at onset and severity at that time

NOTE

Gender-related diagnostic issues in CD

- Males with a diagnosis of CD frequently exhibit fighting, stealing, vandalism, and school discipline problems.
- Females with a diagnosis of CD are more likely to exhibit lying, truancy, running away, substance use, and prostitution.
- Whereas males tend to exhibit both physical aggression and relational aggression (behavior that harms social relationships of others), females tend to exhibit relatively more relational aggression.

Differential Diagnosis

- ADHD
- Oppositional defiant disorder
 - Less severe, and does not include aggression toward individuals or animals, destruction of property, or a pattern of theft or deceit. ODD includes problems of emotional dysregulation.
- Depressive and bipolar disorders
 - Irritability, aggression, and conduct problems can occur in children or adolescents with major depressive disorder, bipolar disorder, or disruptive mood dysregulation disorder. The behavioral problems associated with these mood disorders can usually be distinguished from the pattern of problems seen in CD based on their course.
 - Persons with CD will display substantial levels of aggressive or non-aggressive conduct problems during periods in which there is no mood disturbance. In those cases in which both criteria for CD and a mood disorder are met, both diagnoses can be given.
- Adjustment disorders

Treatment

Psychosocial

- Parent management training
- Problem solving skills training
- Stop now and plan program (SNAP)
 - Community-based program for children (<12 years of age) who have come into contact, or are at risk of coming into contact with the criminal justice system and who display early signs of antisocial or aggressive behaviour.
- Multisystemic therapy (well evidenced-based)
- Multidimensional treatment foster care
- Anger replacement training
- CBT
- Family therapy
- Education/employment programs
- Social skills training

Biological

- Pharmacological therapy for comorbid disorders
- Offer methylphenidate or atomoxetine for the management of ADHD in children and young people with ODD or CD
- Consider risperidone for the short-term management of severely aggressive behaviour in young people with a conduct disorder who have problems with explosive anger and severe emotional dysregulation and who have not responded to psychosocial interventions.

Prognosis

- The majority of children with CD do not develop adult antisocial personality disorders, but are at risk of doing so (25% of girls and 40% of boys with CD).
- Individuals with conduct disorder are at risk for later-developing mood disorders, anxiety disorders, post-traumatic stress disorder, impulse-control disorders, psychotic disorders, somatic symptom disorders, and substance-related disorders as adults.
- Poor prognostic factors: early-age onset, low-intelligence, dysfunctional family environment, persistent criminality in parents, comorbid ADHD, early sexual activity, substance abuse.
 - Persistence is more likely for individuals with behaviors that meet criteria for the childhood-onset subtype and qualify for the specifier “with limited prosocial emotions”. The risk that conduct disorder will persist is also increased by co-occurring ADHD and by substance abuse.
- Favorable prognostic factors: treatment of comorbid ADHD (if present), proper school placements with assistance for learning (if learning difficulties present), higher verbal intelligence, and positive parenting.

CLINICAL PEARL

General guidelines for treating CD

- Diagnosis needs to consider more than symptom presence.
- Severity, age of onset, and persistence of disruptive behaviour symptoms predict different treatments and outcomes.
- Psychosocial and educational therapies are first-line and always indicated.
- Medications should be symptomatic treatment (e.g. ADHD symptoms if present, aggression, etc).
- **Do not offer pharmacological interventions** for the routine management of behavioural problems in children and young people with ODD or CD.

Oppositional Defiant Disorder (ODD)

General features

- Childhood disorder characterized by repetitive and persistent anger, irritability, arguing, defiance, or vindictiveness towards authority figures.
- Can have extremely negative effects on parent-child interactions
 - These children are at high risk for developing secondary mood, anxiety, impulse-control disorders
- Classified under “Disruptive Behavior Disorders” chapter in the DSM-5.

DSM-5 Criteria for Oppositional Defiant Disorder

- A. A pattern of angry/irritable mood, argumentative/defiant behavior, or vindictiveness lasting ≥ 6 months as evidenced by ≥ 4 symptoms from any of the following categories, and exhibited during interactions with at least one individual who is not a sibling.

Angry/Irritable Mood

1. Often loses temper.
2. Is often touchy or easily annoyed.
3. Is often angry and resentful.

Argumentative/Defiant Behavior

4. Often argues with authority figures or, for children and adolescents, with adults.
5. Often actively defies or refuses to comply with requests from authority figures or with rules.
6. Often deliberately annoys others.
7. Often blames others for his or her mistakes or misbehavior.

Vindictiveness

8. Has been spiteful or vindictive at least twice within the past 6 months.

- B. The disturbance in behavior is associated with distress in the individual or others in his or her immediate social context (e.g., family, peer group, work colleagues), or it impacts negatively on social, educational, occupational, or other important areas of functioning.
- C. The behaviors do not occur exclusively during the course of a psychotic, substance use, depressive, or bipolar disorder. Also, the criteria are not met for disruptive mood dysregulation disorder.

Epidemiology

- Prevalence ranges from 1%-11% with average prevalence of 3.3%.
- M:F 1.4:1 prior to adolescence; M=F after puberty
- Usually appears by age 8 (2nd peak 14-15 years)

Etiology

- Temperamental:
 - Temperamental factors related to problems in emotional regulation (e.g., high levels of emotional reactivity, poor frustration tolerance) have been predictive of the disorder.
- Environmental:
 - Harsh, inconsistent, or neglectful child-rearing practices are common in families of children and adolescents with oppositional defiant disorder, and these parenting practices play an important role in many causal theories of the disorder.
 - Families in which childcare is disrupted by a succession of different caregivers.

Diagnosis

- Screening questions sensitive (not specific) to ODD:
 - Child Behaviour Checklist (CBCL) (Achenbach)
 - Strengths and Difficulties questionnaire (Goodman)
 - Conner's rating scale for diagnosing comorbid ADHD
- Screening for comorbidities, such as the presence of ADHD and/or depression
- Assessment of language and cognitive developmental abilities
- Screening for trauma
- Assessment of attachment and goodness of fit (parenting style and child's temperament)

Differential diagnosis

- ADHD
- Conduct disorder
- Depressive and bipolar disorders
- Disruptive mood dysregulation disorder (DMDD)
 - Note that in DMDD:
 - The severity, frequency, and chronicity of temper outbursts are more severe
 - Persistent disruption in mood between outbursts
 - When the mood disturbance is severe enough to meet criteria for DMDD, a diagnosis of ODD is not given.
- Intellectual disability (intellectual developmental disorder)
 - A diagnosis of ODD is given only if the oppositional behavior is markedly greater than is commonly observed among individuals of comparable mental age and with comparable severity of intellectual disability
- Language disorder, parent child relational problem, social anxiety disorder, PTSD, reactive attachment disorder.

Treatment

Psychosocial

- Psychosocial intervention: therapy for anger management, self expression, cognitive behavioural therapy, family counseling, parent training

Biological

- Medication is not useful for ODD itself; pharmacotherapy is used for comorbid disorders.
- If ODD with ADHD, treat ADHD with frontline ADHD medication

Prognosis

- Resolves in most children.
- 70% of children with ODD will not have behavioural problems by age 18.
- 10% of children with ODD will develop conduct disorder.

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Review Questions

1. You are considering treating your 8-year-old patient with a psychostimulant medication for ADHD. In order to do this safely, which of the following should you rule out prior to initiating therapy?
 - a) Recurrent otitis media
 - b) Asthma
 - c) Cardiovascular diseases
 - d) Atopic dermatitis
 - e) Family history of kidney disease

2. The core symptoms of ADHD include all of the following, **except**:
 - a) Making careless mistakes
 - b) Poor academic performance
 - c) Losing things necessary for tasks and activities
 - d) Avoidance of tasks requiring focusing
 - e) Trouble organizing tasks

3. When treating Oppositional Defiant Disorder (ODD) the best evidence is for:
 - a) The use of risperidone
 - b) Treating the ADHD with Ritalin
 - c) Punishing the child for his/her behaviour
 - d) The use of Parent Management Training (PMT)
 - e) The use of dialectical behavioural treatment

Answers:
1. c)
2. b)
3. d)

Autism Spectrum Disorder (ASD)

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General Features

- Classified under “Neurodevelopmental Disorders” in the DSM-5.
- Affects social communication/ interactions, play, interests and behaviour.
- Can severely affect many aspects of a child’s life; emotional, behavioural, medical.
- Causes more stress on the family than any other disorder of childhood and requires an average of 1000 extra hours of care per year.
- ADHD is no longer an exclusionary criterion.

DSM-5 Criteria for Autism Spectrum Disorder

- A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:
1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
 2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures, to a total lack of facial expressions and nonverbal communication.
 3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

- B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least 2/4 of the following, currently or by history:
1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
 2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).
 3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).
 4. Hyper or hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).
- C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).
- D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
- E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay.

Specifiers:

- With or without accompanying intellectual impairment
- With or without accompanying language impairment
- Associated with a known medical or genetic condition or environmental factor
- Associated with another neurodevelopmental, mental, or behavioral disorder
- With catatonia
- Severity specifiers:
 - For both social communication and restricted, repetitive behaviours specify the level of severity:
 - Level one: requiring support
 - Level two: requiring substantial support
 - Level three: requiring very substantial support

Epidemiology

- Prevalence of at least 1% of the population.
- Male to female ratio: 4:1
- Between 50 to 75-80% will have an associated intellectual disability

Comorbidities

- 70% of autism patients have a comorbid mental disorder
- Common comorbid mental disorders:
 - Intellectual disability (ID)
 - Attention deficit hyperactivity disorder (ADHD)
 - Specific language impairment
 - Anxiety disorders, depressive disorders, obsessive compulsive disorder (OCD)
- Common comorbid medical disorders:
 - Motor disorder (eg. developmental coordination disorder, stereotypic movement disorder)
 - Epilepsy (17-35%, higher incidence in severe ID)
 - GI problems (eating problems, elimination problems)
 - Sleep wake disorders

Evaluation

- ASD specific assessments:
 - Screening questionnaires:
 - M-CHAT (Modified Checklist for Autism in Toddlers) - see [Figure 1](#).
 - Social communications Questionnaire (SCQ)
 - ABC (Autism Behaviour Checklist)- see [Figure 2](#).
 - Autism-specific diagnostic tools:
 - Autism Diagnostic Interview-revised (ADI-R)
 - Autism Diagnostic Observation Schedule (ADOS-G)
 - Childhood Autism Rating Scale (CARS)
 - Diagnostic Interview for Social and Communication Disorders (DISCO)

IMPORTANT

Early red flags in ASD

Social communication

- Little social smiling (occurs in most babies age 2-3 months)
- Limited social eye contact (occurs in most babies age 6-8 weeks)
- Little separation anxiety (occurs in most babies age 6-8 months)
- Impaired joint attention
- Important indicator of autism is the failure to develop joint attention which refers to the child's ability to share interests, pleasurable experiences, or requests by using gestures or verbal communication in combination with eye contact with another person

Non-verbal communication

- Speech delay cut-off: expect to see spontaneous two word phrases with a verb by 24 months in most babies
- No pointing/gestures (most children begin between age 9-14 months)
- No change in facial expression
- Can't guess what he/she wants
- Drags caregiver by the hand/uses them as a tool

- Can consider microarray/genetic referral
- Complete history:
 - Pregnancy, neonatal and developmental history, medical history, family and psychosocial factors, intervention history
- Observation of child, including play
- Collateral of observations of child in social settings
- Physical evaluation:
 - Identify dysmorphic features, neurological exam, measurement of head circumference, vision and hearing tests
- Psychological evaluation:
 - Cognitive testing, adaptive skills
- Speech/language/communication assessment
- Occupational therapy evaluation

M-CHAT

Please fill out the following about how your child usually is. Please try to answer every question. If the behavior is rare (e.g. you've seen it once or twice), please answer as if the child does not do it.

1. Does your child enjoy being swung, bounced on your knee, etc.?

☐ Yes ☐ No

2. Does your child take an interest in other children?

☐ Yes ☐ No

3. Does your child like climbing on things, such as upstairs?

☐ Yes ☐ No

Does your child enjoy playing peek-a-boo/hide-and-seek?

☐ Yes ☐ No

4. Does your child ever pretend, for example, to talk on the phone or take care of a doll or pretend other things?

☐ Yes ☐ No

5. Does your child ever use his/her index finger to point, to ask for something?

☐ Yes ☐ No

6. Does your child ever use his/her index finger to point, to indicate interest in something?

☐ Yes ☐ No

7. Can your child play properly with small toys (e.g. cars or blocks) without just mouthing, fiddling, or dropping them?

☐ Yes ☐ No

8. Does your child ever bring objects over to you (parent) to show you something?

☐ Yes ☐ No

9. Does your child look you in the eye for more than a second or two?

☐ Yes ☐ No

10. Does your child ever seem oversensitive to noise? (e.g., plugging ears)

☐ Yes ☐ No

11. Does your child smile in response to your face or your smile?

☐ Yes ☐ No

12. Does your child imitate you? (e.g., you make a face-will imitate it?)

☐ Yes ☐ No

13. Does your child respond to his/her name when you call?

☐ Yes ☐ No

14. If you point at a toy across the room, does your child look at it?

☐ Yes ☐ No

Does your child walk?

☐ Yes ☐ No

15. Does your child look at things you are looking at?

☐ Yes ☐ No

16. Does your child make unusual finger movements near his/her face?

☐ Yes ☐ No

17. Does your child try to attract your attention to his/her own activity?

☐ Yes ☐ No

18. Have you ever wondered if your child is deaf?

☐ Yes ☐ No

19. Does your child understand what people say?

☐ Yes ☐ No

20. Does your child sometimes stare at nothing or wander with no purpose?

☐ Yes ☐ No

21. Does your child look at your face to check your reaction when faced with something unfamiliar?

☐ Yes ☐ No

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Figure 1. M-CHAT screening questionnaire.
From Robins et al, 1999.

ABC Checklist

Name:

Date & Time	Antecedent What was happening JUST prior to the behavior occurring?	Behavior ____ Escape ____ Attention	Consequence What happened after the behavior to resolve the problem?	Duration	Intensity
	____ Alone	____ Did not follow instructions	____ Student ignored	____ >1 min.	1 LOW
	____ With peers	____ Disrupting class	____ Redirected	____ 1-5 min	
	____ Ending an activity	____ Clearing materials	____ Gave visual prompt	____ 5-10 min	2
	____ Participating in group	____ Screaming/yelling	____ Gave verbal prompts	____ 10-30 min	
	____ Asked do non preferred activity	____ Biting	____ Student lost privilege	____ 1/2 - 1 hr	3
	____ Told/asked "not to:"	____ Throwing	____ Limited choices from reward menu	____ 1-2 hr	
	____ Transitioning	____ Pushing	____ Went to his own area	____ 2-3 hr	4
	____ Working on academics	____ Pinching	____ Went to think time in class	____ 3+ hr	
	____ Being ignored	____ Running away	____ Movement break		5 HIGH
	____ Beginning an activity	____ Grabbing/pulling	____ Adapted the assignment		
	____ Other	____ Nudging	____ 1-2-3 count		
		____ Other	____ Physical assist/prompt		
			____ Went to resource room		
			____ Sent to school office		
			____ Other		

Notes:

Figure 2. ABC checklist screening questionnaire.
From Bravo Oro et al, 2014.

ADI-R	ADOS
Range of Facial Expressions Used to Communicate	Facial Expressions directed at others
Quality of social Overtures	Quality of Social Overtures
Appropriateness of social responses	Quality of Social Response
Conventional/instrumental gestures	Descriptive, conventional, instrumental, or informational gestures
Social verbalization/chat	Amount of reciprocal social communication
Reciprocal conversation	Conversation
Neologisms/idiosyncratic language	Stereotyped/idiosncratic use of words or phrases
Unusual preoccupations	Excessive interest in unusual or highly specific topics or objects
Circumscribed interests	Excessive interest in unusual or highly specific topics or objects
Hand and finger mannerisms	Hand and finger and other complex man-nerisms
Unusual sensory interests	Unusual sensory interest in play material/ person
Seeking to Share Enjoyment with Others	Shared Enjoyment in Interaction
Compulsions/Rituals	Compulsions/Rituals

Figure 3. Comparison between the criteria included on ADI-R vs. ADOS tools.
From Lemler, 2012.

Differential Diagnosis

- ADHD, oppositional defiant disorder (ODD)
- Learning disorder
- Intellectual disability without ASD
- Language disorders and social (pragmatic) communication disorder
- Anxiety disorders including selective mutism
- OCD
- Stereotypic movement disorder, Tourette's and tic disorders
- Schizophrenia
- PTSD, reactive attachment disorder
- Medical/neurological/genetic conditions (eg Rett's syndrome, fragile X, neurofibromatosis)
- Sensory impairments (especially hearing and visual impairment)

Treatment

- Multimodal
- Overall goals of treatment are for the individual to achieve functionality and competence (same quality of life as other individuals without ASD)
- ASD is a heterogeneous condition, thus there is not one treatment that is suitable for all.
- There is strong evidence for interventions that focus on early parent-child interactions.
- Important to:
 - Establish goals for educational interventions.
 - Establish target symptoms for intervention.
 - Prioritize target symptoms and/or co-morbid conditions.
 - Monitor multiple domains of functioning (behavioural adjustment, adaptive skills, academic skills, social/communicative skills, social interactions).
 - Monitor pharmacological interventions for efficacy and side-effects.
 - *Note that there is no medication to treat the core symptoms of autism.

NOTE

Common medical issues in ASD

- Seizures (two peaks of incidence: early childhood and adolescence)
- GI complaints (constipation/encopresis, gastroesophageal reflux disease)
- Dental caries
- Severe food restriction
- Allergies (especially food allergies)
- Minor injuries*
- Ear infections*
- Headaches*

*Note that individuals with ASD do not necessarily get more minor injuries, ear infections, or headaches, but they may not be able to verbalize that they are in pain, and this may affect their behavior. The same applies to any other illness. Often their pain threshold is elevated.

Psychosocial management

Applied Behavior Analysis (ABA)

- ABA is not a specific intervention, but an overall paradigm to develop and evaluate behavioral interventions.
 - Uses the principles of operant conditioning to teach specific social, communicative, and behavioural skills to children with ASD. It involves teaching new behaviours by explicit reinforcement of these behaviours with rewards
 - Problem behaviours are often addressed by carefully analyzing triggers or antecedents of the problem behaviour in order to change the factors in the environment that are contributing to the problems behaviour.
- ABC's of ABA
 - ABA uses the following 3 step process to understand behaviour and teach new skills:
 - **Antecedent/instruction:** What happens right BEFORE the behavior?
 - **Behavior/the child's response:** What the child does.
 - **Consequence/teacher feedback:** What happens right AFTER the behavior?

Behavioural treatments

- Intensive Behaviour Intervention (IBI) is a more intense form of ABA which has the most evidence
 - >25 hours per week, adult directed, 1-on-1
 - IBI is most beneficial when:
 - Treatment takes up 30-40 hours per week
 - Treatment is 1-on-1 (with therapist or parent)
 - Patients are > 2yrs
 - Treatment starts before the age of 5
- Treatment and Education of Autistic and related Communications Handicapped Children (TEACCH).
 - Looks at skills and strengths that patients have and builds on them.
 - Addresses problematic behaviours and gives patients more favourable behavioural options.

Developmental treatments

- More child-directed; focuses on child's developmental level
- More focused on social communication skills
 - E.g. Early Start Denver Model, pivotal response training, developmental individual difference relationship-based approach (DIR or Floortime)
- All ABA-based
- Current level of evidence is inconclusive

Other interventions

- Children with ASD often have unusual sensory sensitivity/responses such as hypersensitivity to certain noises, texture etc.
 - Sensory integration therapy uses techniques such as “brushing” of the skin and “swinging” to stimulate vestibular responses and pressure massage applied in an effort to calm the child. No strong research to show efficacy, but clinically highly useful.
 - Picture exchange communication system (PECS) is an intervention designed to promote early symbolic communication using visually helpful symbols with a trainer/facilitator. Popular for non-verbal children (ASD and/or ID).
- Social skills (groups and social stories).

Pharmacological management

- There is no pharmaceutical treatment for core symptoms of social and relationship problems in ASD.
- Risperidone (5-16 years) and aripiprazole (6-17 years) are FDA-approved for aggressivity in children and adolescents with autism.
- Periodic attempts to decrease or discontinue medication used for aggressivity and irritability is prudent since most require long-term treatment.
- Melatonin can be used for sleep needs
- Stimulant and alpha agonists such as guanfacine can be used to treat comorbid ADHD

CLINICAL PEARL

For any medication used in the ASD population, the “start low and go slow” approach is recommended.

Potential targets of pharmacotherapy

- Comorbid psychiatric diagnoses such as depression, anxiety, OCD, and ADHD
- ASD symptom domains:
 - Hyperactivity and inattention
 - Repetitive behaviors
 - Aggressive behaviours/irritability
 - 40-60% of parents report significant aggression

Treatment of comorbid ADHD

- ADHD symptoms are common in ASD (>60%).
- 40% meet full criteria for ADHD
- Methylphenidate (MPH) is commonly prescribed for children and adolescents with ASD but few controlled trials of MPH have been conducted in this population.

Prognosis

- ASD has varying degrees of functionality, and this often dictates prognosis and the types of supports required.
- Early detection and early intervention carries more favorable outcomes.
- Poor prognostic indicators include severe core symptoms, low IQ, poor/absent language skills, late initiation of treatment.
- Majority of patients remain dependent on family and familiar surroundings, even as adults.
- 10% of ASD patients without an associated intellectual disability will lose the diagnosis as adults, but subtle social and communication difficulties will persist.

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Review Questions

1. For which medication is there evidence for the treatment of social deficits for adolescents with ASD?
 - a) Risperidone
 - b) Aripiprazole
 - c) Naloxone
 - d) A and B
 - e) None of the above

2. Which genetic syndrome is NOT associated with ASD?
 - a) Fragile X syndrome
 - b) Neurofibromatosis type 1
 - c) Klinefelter syndrome
 - d) Rett's syndrome
 - e) Down syndrome

3. Which risk factor is NOT associated with an increased risk of autism?
 - a) Maternal obesity
 - b) In utero exposure to traffic-related air pollution
 - c) Younger parental age (> 35 years)
 - d) Maternal hypertension
 - e) In utero exposure to pesticides

Answers:

1. e)

2. c)

3. c) In fact, *older* parental age is associated with an increased risk.

Substance-Related and Addictive Disorders

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Introduction

Substance-related disorders are a group of disorders subclassified into:

- Substance use disorders, and
- Substance-induced disorders

Substance Use Disorder

Substance use disorders (SUD) describe a cluster of cognitive, behavioural, and physiological symptoms which indicate that an individual continues to use a substance despite it causing problems. These problems can include inability to control use of the substance, social impairment, and use during or leading to hazardous situations. Diagnosis is based on a pathological pattern of behaviours related to use of the substance.

DSM-5 Criteria for Substance Use Disorder

- A. A problematic pattern of substance use leading to clinically significant impairment or distress, as manifested by at least 2 of the following, occurring within a 12-month period.
1. Substance is often taken in larger amounts or over a longer period than was intended.
 2. There is a persistent desire or unsuccessful effort to cut down or control substance use.
 3. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.
 4. Craving or a strong desire or urge to use the substance.
 5. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to alcohol use; substance-related absences, suspensions, or expulsions from school; neglect of children or household).

NOTE

The DSM 5 no longer uses the terms "substance abuse" or "substance dependence/addiction".

Instead, it recognizes **substance-related disorders** resulting from the use of ten separate classes of drugs:

- Alcohol
- Caffeine
- Cannabis (primarily marijuana)
- Hallucinogens
- Inhalants
- Opioids
- Sedatives
- Hypnotics
- Anxiolytics
- Stimulants (e.g. cocaine and amphetamines)

6. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.
7. Important social, occupational, or recreational activities are given up or reduced because of the substance use.
8. Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use).
9. Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
 - a. A need for markedly increased amounts of substance to achieve intoxication or desired effect.
 - b. A markedly diminished effect with continued use of the same amount of the substance.
11. Withdrawal, as manifested by either of the following:
 - a. The characteristic withdrawal syndrome for the substance.
 - b. The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.

Specifiers:

- **Early Remission:** This specifier is used if, for at least 3 months, but for less than 12 months, the individual does not meet any of the criteria 1-3, 5-11 for a substance use disorder (i.e. none of the criteria except for Criterion 4, “Craving or a strong desire or urge to use a specific substance”).
- **Sustained Remission:** This specifier is used if none of the criteria 1-3, 5-11 for a substance use disorder have been met at any time during a period of 12 months or longer (i.e. none of the criteria met except for Criterion 4, “Craving or a strong desire or urge to use a specific substance”).
- **Severity:**
 - 0 criteria or 1 criterion: No diagnosis
 - 2-3 criteria: Mild substance use disorder
 - 4-5 criteria: Moderate substance use disorder
 - 6 or more criteria: Severe substance use disorder

Terminology

- “**Physical dependence**” refers to a state of adaptation that arises from a drug withdrawal syndrome due to abrupt cessation or reduction in dose of a drug, or administration of an antagonist.
 - Individuals may be physically dependent on a drug without meeting the criteria for substance use disorder if they are not preoccupied with obtaining the drug and it does not impair the individual’s ability to fulfill their occupational and social roles.
- The term “**addiction**” is omitted from the official DSM-5 substance use disorder diagnostic terminology due to having an uncertain definition and potentially negative connotation.
 - It is defined by the Canadian Mental Health Association Ontario as a condition that leads to compulsive engagement with a stimulus, despite negative consequences. Addictions can be either substance related or process-related (such as gambling or internet addiction).

MNEMONIC

The 4 C’s of Addiction

- **C**raving
- Loss of **C**ontrol of amount or frequency of use
- **C**ompulsion to use
- **C**ontinued substance use despite consequences

Substance use in adolescents

- Cannabis is the most common substance of daily use by youth
- Median age of onset for SUD is 15 years with a steep increase thereafter
- Substance use over time has moved into adolescent population and younger age groups
- Major psychosocial challenges (transition) + maturational neurodevelopmental brain changes = vulnerability to the effects of substance use
- Multi-drug use in adolescence increases the risk for SUD in young adulthood
- Early initiation of substance use (<15yo) increases the risk for:
 - Development of SUD by young adulthood
 - More rapid progression to severe SUD
- Will often have comorbid psychiatric illnesses including but not limited to attention deficit hyperactive disorder (ADHD), mood and/or anxiety disorders
- Cannabis and other substance use can lead to adolescents presenting with substance-induced disorders such as depression, anxiety and psychosis
- Negative consequences of adolescent SUD:
 - Disruption of developmental tasks (changes in school performance and peer groups, insomnia, unexplained weight loss, and involvement in illegal activities)

- Experimentation is common in adolescence
- Peer influence is the strongest determinant of initial substance use

Substance use in adults

- Adults will present with physical and psychological consequences
 - Hypertension, fatigue, insomnia, depression, weight loss, suicidality
- Often have difficulties with work and relationships

Substance use in the elderly

- As the population ages, so does the number of elderly individuals with problems related to substance use
- Although older adults use substances less frequently than younger adults, those who do tend to experience more harms
 - This is due to age-related changes in physiology, as well as higher rates of polypharmacy
- Chronic pain, depression, and isolation are common problems in elderly individuals that can predispose them towards benzodiazepine use and resultant dependence
 - The risk of dependence increases with age

Comorbidities

- Major depression has a lifetime prevalence of 15-50% in individuals with substance use disorder
- ADHD rates in individuals with substance use disorder are 2-3 times higher than the general population
- In individuals with bipolar disorder, 40% have substance use disorder
- In individuals with schizophrenia, 47% have a lifetime experience with a substance use disorder
- Individuals with PTSD are 2-4 times more likely to have a substance use disorder

Taking a substance use history

- Ask about *specific* substances
- Extent of usage for each - onset, usage, frequency, route
- Setting of use, alone/with peers
- Last usage
- Intoxication or withdrawal symptoms
- Rehab or detox history
- Risky use - e.g. driving, overdosing, selling, exchanging sex for drugs

Tools for Quantifying Drug Use

- **CAGE questionnaire** (see sidebar)
 - A 4-item questionnaire used for screening for alcohol use disorder
- Other tools to assess for substance use disorder and impact on functioning:
 - Desire for Drug Questionnaire
 - 13-item tool to measure intention to use drugs, negative reinforcement, and control over desire to use drugs
 - Obsessive Compulsive Drug Use Scale
 - 12-item tool to measure thoughts about drugs and interference, desire and control, and resistance against thoughts and intention to use drugs
 - Global Assessment of Functioning
 - A scale from 0 to 100 that can quantify psychosocial functioning
 - Personal and Social Performance Scale
 - A scale from 0 to 100 which tests functioning in self-care, social useful activities, personal and social relationships, and disturbing and aggressive behavior
- Screening tools for adolescent substance use:
 - CRAFFT – N
 - A 7-item substance use screening tool for adolescents aged 12-21.

CLINICAL PEARL

The CAGE Questionnaire

- Have you ever felt you should **cut down** on your drinking?
- Have people **annoyed** you by criticizing your drinking?
- Have you ever felt bad or **guilty** about your drinking?
- Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (**eye-opener**)?

Score each item a 0 (if no) or a 1 (if yes). A score of 2 or more is considered clinically significant.

Substance	Notes
Alcohol	1 standard drink = 13.6 grams - Wine (12% alcohol): 5oz or 142mL 1 bottle = 750mL = 5 standard drinks - Hard liquor (40% alcohol): 1.5 oz or 43mL 1 "Mickey" = 13 oz = 8 standard drinks 40 oz = 27 standard drinks - Beer (5% alcohol): 12oz or 341mL
Marijuana	Usually quantified in grams. 1 gram = approximately 2 joints, cost ~\$10 1 ounce = 28 grams *Ask how many grams they are using daily.
Cocaine	- Comes in powder or crack form - Crack is smoked; powder is snorted or injected - Costs \$80-100 per gram - Speedball: combination of cocaine and heroin "8 ball" = 3.5 grams *Ask how many times a week they are using. *Ask how many grams on each occasion or how much money they are spending.
Opioids	- Popular sources are fentanyl patches, powder fentanyl, heroin, dilaudid, and oxycodone - Can be sourced from personal prescriptions, family member prescriptions, and illicit sources - Even if patient says they started taking opioids for pain, do not assume that it was from a physician's direction *Ask how they take the medication: swallowed, crushed, snorted, or injected. *Ask how often they use and how much.
Benzodiazepines (BZD)	- Popular forms are Ativan (lorazepam) tablets, clonazepam tablets, Xanax (alprazolam) tablets - Xanax "bars" or "street xanax" are often pressed forms including other substance such as fentanyl *Ask about total amount used per day and method of use. *Ask source of medication. *If prescribed, asked how many tablets are prescribed per month and if they take medications spaced throughout day as prescribed or all at once.

Table 1. Summary chart of key characteristics and pearls when asking about frequency and amount of use for different common substances.

Substance-Induced Disorders

Definition

- Substance-induced disorders include **substance intoxication**, **substance withdrawal**, and **other substance or medication-induced mental disorders** (e.g. substance-induced psychotic disorder, substance-induced depressive disorder).
- Symptoms must develop during or soon after substance intoxication or withdrawal.
- The disorders should disappear after a period of abstinence from the involved substance.

Substance	Psychotic disorders	Bipolar disorders	Depressive disorders	Anxiety disorders
Alcohol	Intoxication or withdrawal	Intoxication or withdrawal	Intoxication or withdrawal	Intoxication or withdrawal
Sedatives, hypnotics, anxiolytics	Intoxication or withdrawal	Intoxication or withdrawal	Intoxication or withdrawal	Withdrawal
Opioids	-	-	Intoxication or withdrawal	Withdrawal
Stimulants	Intoxication	Intoxication or withdrawal	Intoxication or withdrawal	Intoxication or withdrawal
Cannabis	Intoxication	-	-	Intoxication

Table 2. Causative potential of substance-induced disorders by substance classification.

Substance	Time (Intoxication)	Time (Withdrawal)
Alcohol	During or shortly after	Several hours to a few days
Sedatives, hypnotics, anxiolytics	During or shortly after	Several hours to a few days
Opioids	During or shortly after	Minutes to several days
Stimulants	During or shortly after	Within a few hours to several days
Cannabis	Within 2 hours	Within approximately 1 week

Table 3. Timing of intoxication and withdrawal by substance classification.

Alcohol intoxication

DSM-5 Criteria for Alcohol Intoxication

- A. Recent ingestion of alcohol.
- B. Clinically significant problematic behavioral or psychological changes (e.g., inappropriate sexual or aggressive behavior, mood lability, impaired judgment) that developed during, or shortly after, alcohol ingestion.
- C. ≥ 1 of the following signs or symptoms developing during, or shortly after, alcohol use:
 - 1. Slurred speech
 - 2. Incoordination
 - 3. Unsteady gait
 - 4. Nystagmus
 - 5. Impairment in attention or memory
 - 6. Stupor or coma
- D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance.

Differential diagnosis

- Sedative, hypnotic or anxiolytic intoxication
- Diabetic ketoacidosis
- Cerebellar ataxias
- Multiple sclerosis (and other neurological conditions)

Clinical course

- Intoxication typically occurs as an episode which develops over minutes-hours and lasts several hours
- Average age at first occurrence is in mid-teens
- Early symptoms are talkativeness, a sensation of well-being, and a bright expansive mood
- As blood alcohol levels drop, symptoms include becoming more depressed, withdrawn, and cognitively impaired
- The body metabolizes approximately one drink every hour
- High blood levels of alcohol can cause inhibition of respiration and pulse and death

Management

- Treatment is primarily supportive
- Intravenous thiamine (vitamin B1) followed by intravenous glucose
 - Thiamine is an essential nutrient which must be acquired through food, and is required by all tissues in the body
 - The nervous system is particularly sensitive to thiamine deficiency, leading to Wernicke-Korsakoff syndrome which consists of the short-term and severe Wernicke's encephalopathy and the long-term debilitating Korsakoff's psychosis
- Induction of emesis or gastric lavage are not typically indicated as alcohol is absorbed quickly
- Lorazepam or haldol can be used for agitation

IMPORTANT

ALWAYS protect the airway in someone with alcohol intoxication!

Alcohol withdrawal

DSM-5 Criteria for Alcohol Withdrawal

- A. Cessation of (or reduction in) alcohol use that has been heavy and prolonged.
- B. ≥ 2 of the following, developing within several hours to a few days after the cessation of (or reduction in) alcohol use described in Criterion A:
 1. Autonomic hyperactivity (e.g., sweating or pulse rate greater than 100 bpm)
 2. Increased hand tremor
 3. Insomnia
 4. Nausea or vomiting
 5. Transient visual, tactile, or auditory hallucinations or illusions
 6. Psychomotor agitation
 7. Anxiety
 8. Generalized tonic-clonic seizures
- C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

Specifiers:

- With or without perceptual disturbances
 - **NOTE: This specifier applies in the rare instance when hallucinations (usually visual or tactile) occur with intact reality testing, or if auditory, visual, or tactile illusions occur in the absence of a delirium.*

Differential diagnosis

- Sedative, hypnotic, or anxiolytic withdrawal
- Hypoglycemia
- Diabetic ketoacidosis
- Essential tremor

Clinical course

- Typically other aspects of an alcohol use disorder have developed before the first signs of withdrawal manifest
- Starts when blood alcohol concentration declines quickly after alcohol use has been stopped or reduced
- Peak of intensity at 48-72 hours, improving by the 4th or 5th day
- Less than 10% develop severe symptoms including severe autonomic hyperactivity, tremors, and delirium
- Fewer than 3% develop grand mal seizures

Management

- Fixed dose method: Benzodiazepines given at predetermined intervals and doses
- Front-loading method: High doses of medication given in early course of withdrawal
- Symptoms-triggered method: Uses Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A)
- All patients receive thiamine 100mg IM then 100mg PO for 3 days
- Generalized seizures will typically resolve without intervention
- Severe or repeated seizures can be treated with IV diazepam 5-10mg
 - Uncomplicated seizures due to alcohol withdrawal do not require long term antiepileptic

CLINICAL PEARL

Delirium tremens is a severe form of alcohol withdrawal marked by disturbances in consciousness and cognition, with visual, tactile, or auditory hallucinations.

It requires constant observation in hospital, and the most effective treatment for it is IV benzodiazepines.

Benzodiazepine intoxication

Differential diagnosis

- Alcohol intoxication
- Multiple sclerosis (and other neurological conditions)
- Progressive dementia (in the elderly)
- Prior head injury (subdural hematoma)

Clinical course

- Medication may originally have been prescribed for treatment of anxiety or insomnia
- Dependence typically involves young individuals in teens or 20s that escalate occasional use
 - This is more likely among individuals with other substance use disorders

IMPORTANT

Individuals with alcohol dependence are at greater risk of BZD intoxication, as they may receive prescriptions for BZDs due to alcohol-related anxiety or insomnia.

Management

- Maintain airway and provide ventilatory support when necessary
- Activated charcoal for recent ingestion
- Flumazenil can reverse the sedative effects of benzodiazepines
 - This produces a rapid benzodiazepine withdrawal and thus carries a risk of causing seizures

Benzodiazepine withdrawal

Differential diagnosis

- Alcohol withdrawal
- Intoxication with amphetamines or cocaine
- Hyperthyroidism
- Panic disorder
- Generalized anxiety disorder

Clinical course

- Time course of withdrawal symptoms depends on the half-life of the specific substance used
 - Short acting drugs (e.g. lorazepam, alprazolam) will have onset of withdrawal within 24 hours, peak severity in 1-5 days, and total duration of 7-21 days

- Long acting drugs (e.g. diazepam, clonazepam) will have onset of withdrawal in 7 days, with peak severity in 1-9 days, and total duration of 10-28 days
- Longer duration of substance use and higher doses increases the likelihood of severe withdrawal
- Generalized tonic clonic seizures may occur in up to 20-30% of individuals undergoing withdrawal without treatment
- Tactile, auditory, and visual hallucinations can also occur

Tapering of Benzodiazepines

Outpatient tapering

- Outpatient tapering is preferred for patients taking <50mg/day of diazepam equivalents.
- For 50-100mg/day of diazepam equivalents, outpatient tapering should only be considered if the patient is:
 - Not physically dependent on other drugs
 - Medically and psychiatrically stable
 - Unlikely to use other sources of benzodiazepines

Inpatient tapering

- If patient is on >100mg/day diazepam equivalents, inpatient taper is advised.
- Rebound symptoms is a possible outcome of benzodiazepine tapering
 - It involves development of symptoms that are similar to the disorder for which the drugs were originally prescribed
 - Symptoms are of short duration and self-limited, but can be more intense than the original symptoms before use of benzodiazepines

Opioid intoxication

DSM-5 Criteria for Opioid Intoxication

- A. Recent use of an opioid.
- B. Clinically significant problematic behavioral or psychological changes (e.g., initial euphoria followed by apathy, dysphoria, psychomotor agitation or retardation, impaired judgment) that developed during, or shortly after, opioid use.
- C. Pupillary constriction (or pupillary dilation due to anoxia from severe overdose) and one (or more) of the following signs or symptoms developing during, or shortly after, opioid use:
 - 1. Drowsiness or coma
 - 2. Slurred speech
 - 3. Impairment in attention or memory
- D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance.

Specifiers:

- With or without perceptual disturbances

Differential diagnosis

- Alcohol intoxication
- Sedative, hypnotic, or anxiolytic intoxication

Clinical course

- Symptoms will typically last for several hours, dependent on the half-life of the drug used
- Severe intoxication can lead to coma, respiratory depression, pupillary dilation, unconsciousness, and death

Management

- Naloxone is an opioid antagonist which reverses neurologic, cardiac, and respiratory depression within minutes, given in dose of 0.4-0.8mg IM
 - Higher doses of naloxone over a longer period of time may be needed for stronger or longer-acting opioids such as fentanyl and

CLINICAL PEARL

Lack of response to a naloxone challenge and absence of pupillary constriction suggests intoxication that is NOT opioid-related.

IMPORTANT

Use of naloxone will cause withdrawal symptoms!

methadone respectively

- Advanced cardiac life support may be necessary

Opioid withdrawal

DSM-5 Criteria for Opioid Withdrawal

- A. Presence of either of the following;
 1. Cessation of (or reduction in) opioid use that has been heavy and prolonged (i.e., several weeks or longer).
 2. Administration of an opioid antagonist after a period of opioid use.
- B. ≥ 3 of the following, which must develop within minutes to several days after Criterion A:
 1. Dysphoric mood
 2. Nausea or vomiting
 3. Muscle aches
 4. Lacrimation or rhinorrhea
 5. Pupillary dilation, piloerection, or sweating
 6. Diarrhea
 7. Yawning
 8. Fever
 9. Insomnia
- C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

Differential diagnosis

- Sedative, hypnotic, or anxiolytic withdrawal

Clinical course

- Typically not life threatening
- Onset is 6-12 hours for short acting opioids and 2-4 days for long acting opioids

CLINICAL PEARL

The presence of rhinorrhea, lacrimation, and pupillary dilation are highly suggestive of opioid withdrawal over withdrawal from other substances.

- Peak of withdrawal is typically 2-3 days with total duration of 5-10 days
- Acute symptoms include anxiety, restlessness, aching pain in back and legs, craving and drug-seeking behaviour, irritability, and increased sensitivity to pain
- Anxiety, dysphoria, anhedonia, insomnia, and drug craving are symptoms that can last for weeks to months

Management

- Substitution of opioid with methadone or suboxone is the standard of care for moderate-severe opioid use disorder
 - **Suboxone** (buprenorphine/naloxone) is the first line treatment
 - Buprenorphine is a partial opiate agonist which displaces morphine and other full opioid agonists from the mu receptor
 - It is taken under supervision at a pharmacy for the first 2 months
 - **Methadone** is a synthetic opioid that reduces drug cravings and withdrawal symptoms without sedation or euphoria
 - Maintenance methadone is indicated for individuals with physical and psychological dependence in high daily doses of opioids, individuals with a long history of opioid dependence, and individuals who have failed at other forms of treatment or unwilling to try
- Non-opioid medications can also be used to manage opioid withdrawal:
 - Clonidine
 - Antidiarrheals
 - Antinauseants
 - Analgesics
 - Trazodone for sedation at night

Stimulant intoxication

DSM-5 Criteria for Stimulant Intoxication

- A. Recent use of an amphetamine-type substance, cocaine, or other stimulant.
- B. Clinically significant problematic behavioral or psychological changes (e.g., euphoria or affective blunting; changes in sociability: hypervigilance; interpersonal sensitivity: anxiety, tension, or anger; stereotyped behaviors: impaired judgment) that developed during, or shortly after, use of a stimulant.
- C. ≥ 2 of the following signs or symptoms, developing during, or shortly after, stimulant use:
 1. Tachycardia or bradycardia
 2. Pupillary dilation
 3. Elevated or lowered blood pressure
 4. Perspiration or chills
 5. Nausea or vomiting
 6. Evidence of weight loss
 7. Psychomotor agitation or retardation
 8. Muscular weakness, respiratory depression, chest pain, or cardiac arrhythmias
 9. Confusion, seizures, dyskinesias, dystonias, or coma
- D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance.

Specifiers:

- Specify the specific intoxicant (i.e., amphetamine-type substance, cocaine, or other stimulant).
- With or without perceptual disturbances.

Differential diagnosis

- Amphetamine intoxication (cocaine)
- Cocaine intoxication (amphetamines)
- Phencyclidine intoxication
- Schizophrenia paranoid type

- Bipolar disorder
- Panic disorder
- Generalized anxiety disorder

Clinical course

- Onset is typically in 10 seconds for crack cocaine users, with euphoria wearing off after 5-15 minutes
- Cocaine, when snorted, will typically have onset of effects after 1-2 minutes
- Onset of amphetamine symptoms is typically within minutes, but may range from seconds to 1 hour depending on the drug and method of use
 - Methods include swallowing, chewing, snorting, and injecting
- Severe intoxication can cause convulsions, cardiac arrhythmias, hyperpyrexia, and death

Management

- Cocaine can have acute cardiovascular effects including severe hypertension, cardiac dysrhythmias, angina, myocardial infarction, stroke, and sudden death
 - First line treatment includes nitrates, benzodiazepines, oxygen, and aspirin
- Treatment of amphetamine intoxication is primarily supportive
 - Amphetamine-induced psychotic disorder can be treated acutely with haloperidol

IMPORTANT

Cardiovascular protection is THE most important immediate goal when treating cocaine intoxication!

Stimulant withdrawal

DSM-5 Criteria for Stimulant Withdrawal

- A. Cessation of (or reduction in) prolonged amphetamine-type substance, cocaine, or other stimulant use.
- B. Dysphoric mood and ≥ 2 of the following physiological changes, developing within a few hours to several days after Criterion A:
 1. Fatigue
 2. Vivid, unpleasant dreams
 3. Insomnia or hypersomnia
 4. Increased appetite
 5. Psychomotor retardation or agitation
- C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

Specifiers:

- Specify the specific substance causing the withdrawal syndrome (i.e., amphetamine-type substance, cocaine, or other stimulant).

Differential diagnosis

- Major depression
- Amphetamine withdrawal (cocaine)
- Cocaine withdrawal (amphetamines)

Clinical course

- Cocaine withdrawal develops within hours of cessation
 - Symptoms typically end within 18 hours for mild-moderate use and after a week for heavy use
 - Acute withdrawal symptoms (“crash”) typically seen after “binges” with repeated high dose
- Amphetamine withdrawal develops within hours to days of cessation or reduction after heavy and prolonged amphetamine use

- Symptoms peak at 2-4 days and resolve after 1 week
- Crash will typically follow an episode of high-dose use (“speed run”)
- Depressive symptoms and suicidal ideation or behaviour are most concerning

Management

- Treatment of stimulant withdrawal is supportive with a particular focus on safety and suicide prevention.

Cannabis intoxication

DSM-5 Criteria for Cannabis Intoxication

- Recent use of cannabis.
- Clinically significant problematic behavioral or psychological changes (e.g., impaired motor coordination, euphoria, anxiety, sensation of slowed time, impaired judgment, social withdrawal) that developed during, or shortly after, cannabis use.
- ≥2 of the following signs or symptoms developing within 2 hours of cannabis use:
 - Conjunctival injection
 - Increased appetite
 - Dry mouth
 - Tachycardia.
- The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance.

Specifiers:

- With or without perceptual disturbances

Differential diagnosis

- Low dose hallucinogen intoxication
- Dysthymic disorder in chronic intake
- Acute adverse reactions can appear similar to:
 - Panic disorder
 - Major depressive disorder

- Bipolar disorder
- Schizophrenia paranoid type
- Delusional disorder

Clinical course

- Euphoric effects appear within minutes of use and peak in 30 minutes, lasting 2-4 hours
- Motor and cognitive effects last for 5-12 hours

Cannabis withdrawal

DSM-5 Criteria for Cannabis Withdrawal

- A. Cessation of cannabis use that has been heavy and prolonged (i.e., usually daily or almost daily use over a period of at least a few months).
- B. ≥ 3 of the following signs and symptoms develop within approximately 1 week after Criterion A:
 1. Irritability, anger, or aggression.
 2. Nervousness or anxiety.
 3. Sleep difficulty (e.g., insomnia, disturbing dreams).
 4. Decreased appetite or weight loss.
 5. Restlessness.
 6. Depressed mood.
 7. At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache.
- C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance

Differential diagnosis

- Panic disorder
- Generalized anxiety disorder

Management

- Insomnia can be treated with non-addictive medication
- Treat any underlying anxiety or depression

Principles of Treating Substance-Related Disorders

- Programs that include all or some of the following components seem to work best:
 - Medications
 - Counselling
 - Family therapy
 - Interventions that help increase motivation to stay in recovery
- Long-term follow up of any treatment is recommended (i.e. “got well ≠ stay well”)

Pharmacological management

- Alcohol
 - Naltrexone is an opioid receptor antagonist and thus inhibits the euphoric effects of alcohol and reduces cravings
 - Acamprosate reduces withdrawal symptoms from alcohol use. It is believed to block glutaminergic NMDA receptors.
 - Disulfiram inhibits acetaldehyde dehydrogenase and thus the metabolism of alcohol, causing negative effects such as redness, nausea, and dizziness. This is to disincentivize drinking when around alcohol
- Opioids
 - Opioid substitution therapy
 - Buprenorphine is an opioid partial agonist which is used in substitution treatment for opioid use disorder. Once substituted for stronger opioids, the dose is tapered down.

- Methadone is a synthetic opioid agonist which does not produce euphoria at treatment doses and also blocks euphoria from other opioids. It is used as maintenance therapy.

Psychosocial management

- Motivational interviewing (MI) is a patient-centered, directive counseling style that builds on intrinsic motivation.
- *Remember: We are not responsible for whether or not patients change, but for helping them decided if they want to or can change, and if so, how to do so.*

FYI

For further information on motivational interviewing, visit: <https://www.ncbi.nlm.nih.gov/books/NBK64964/>.

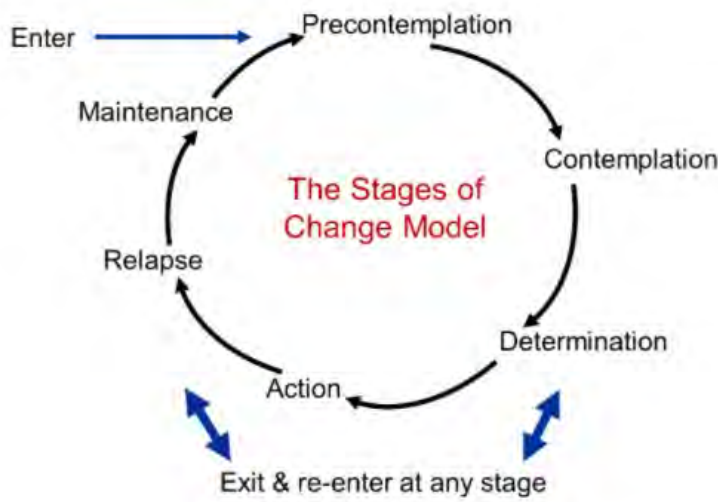


Figure 1. The Stages of Change model.
From Saveland, C.'s lecture notes on Substance Use.

Stage	Description	Strategies
Precontemplation	Patients do not view their substance use as a problem.	• Provide health information such as low risk drinking guidelines • Inform patient of connection between their symptoms and substance use • Encourage patients to discuss the roles substance use plays in their life
Contemplation	Patients are weighing the pros and cons of changing their substance use patterns.	• Encourage patients to discuss benefits and risks of continuing substance use versus abstinence or cutting down
Determination/ Action	Patients are committed to changing their substance use.	• Present patient treatment options and allow them to decide their starting point
Maintenance	Patients have completed a treatment program and have maintained their treatment goals for 6 months.	• Discuss management of cravings and urges • Stress the importance of attending aftercare or mutual help meetings
Relapse	Patients have failed to maintain behaviour change over time.	• Avoid worsening patients' sense of guilt and self blame • Help patient to view the relapse as a learning experience • Develop new strategies to deal with craving • Intensify treatment program and provide more frequent follow up

Table 4. Features of each stage in the Stages of Change model and recommendations for strategies to pursue at each stage.

Harm reduction

- The goal of harm reduction is to decrease the health, social, and economic consequences of drug use without necessarily focusing on diminishing drug consumption.
- Strategies:
 - Provide a safer environment for substance use (e.g. supervised injection sites)
 - Provide a safer method for substance use (e.g. needle exchange programs)
 - Provide alternative safe substances (e.g. methadone maintenance treatment)
 - Manage related risky behaviours:
 - HIV/STD screening
 - Safe sex education
 - Condoms
 - Naloxone kits

FYI

There are a number of community resources and treatment centres available in Ontario and the Ottawa region for management of substance use disorders.

- [Ottawa Addictions Access and Referral Services](#)
- [SMART Recovery Ontario](#)
- [Alcoholic Anonymous](#)
- [Ottawa Withdrawal Management Centre](#)
- [Dave Smith Youth Treatment Centre](#)

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Review Questions

1. A 20-year old student with attention deficit disorder presented to the emergency room complaining of anxiety, tremor, nausea, and intermitted vomiting. He was taking no medication except for a “supplement” (last dose eight hours ago) for bodybuilding, and to “help him focus”. His condition deteriorated and he developed tachycardia, confusion, and extreme agitation, necessitating physical restraints and admission to the ICU. He was treated with diazepam and was discharged on day 11. The initial urine toxicology screen in the ER was negative. Which drug is most likely to be responsible for this clinical picture?
 - a) Deca-durabolin (nandrolone decanoate)
 - b) Gamma-hydroxybutyrate (“liquid XTC”)
 - c) Ritalin (methylphenidate)
 - d) Speed (amphetamine)
 - e) Dexedrine (dextroamphetamine)

2. While driving, a man with no previous history refuses to stop for the police. He is subsequently brought into the emergency room by them. He states that he was told by his radio that the police were FBI agents who were out after him, and thus he did not stop. He admits to a history of alcohol use. What is the most appropriate diagnosis?
 - a) Alcoholic hallucinosis
 - b) Delusional disorder, paranoid type
 - c) Delirium tremens
 - d) Dementia
 - e) Alcohol intoxication

3. A young male is admitted to the hospital. Two days later he experiences lacrimation, rhinorrhea, and dilated pupils. What was he using prior to admission?
 - a) Cocaine
 - b) Heroin
 - c) Benzodiazepines
 - d) Alcohol
 - e) Nicotine

Answers:
1. b)
2. a)
3. b)

Major and Mild Neurocognitive Disorders

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General Features

- Neurocognitive disorders (NCDs) can be classified as **major** or **mild**, depending on disease interference with functional independence in everyday activities (see Figure 1).
- Unique among DSM-5 diagnoses, as NCDs have underlying pathology that can be potentially determined in some cases.

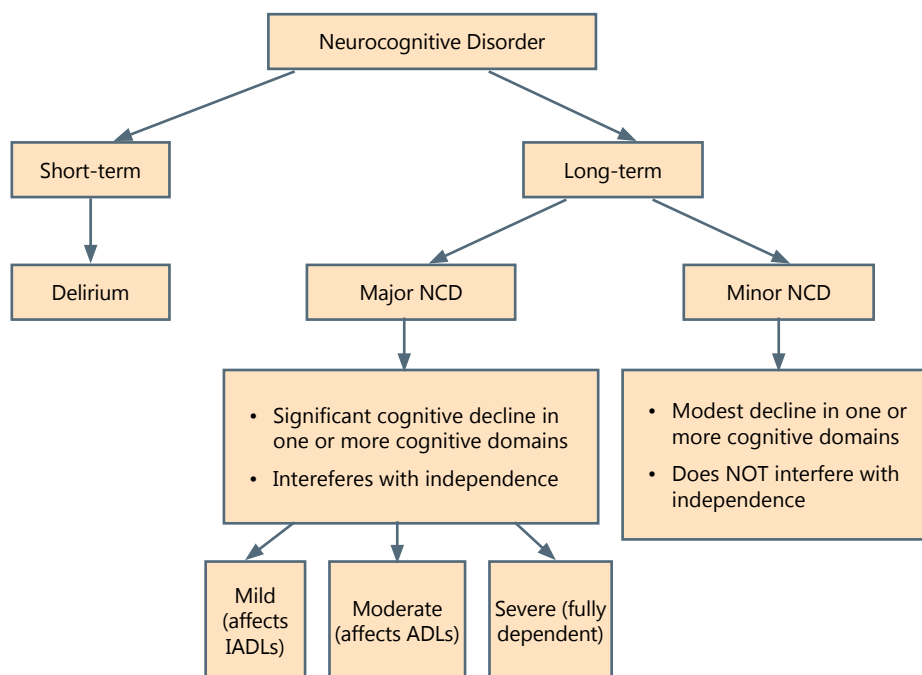


Figure 1. Classification of neurocognitive disorders.

DSM-5 Criteria for Major Neurocognitive Disorder

- A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (see side bar) based on:
 - 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function;
 - AND
 - 2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
- B. Cognitive deficits interfere with independence in everyday activities.
- C. The cognitive deficits do not occur exclusively in the context of a delirium.
- D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

MNEMONIC**Cognitive domains****"PALMES"**

Perceptual-motor
Complex **A**ttention
Language
Memory
Executive function
Social cognition

DSM-5 Criteria for Minor Neurocognitive Disorder

- A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (see side bar) based on:
 - 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and
 - 2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
- B. Cognitive deficits do not interfere with capacity for independence in everyday activities.
- C. The cognitive deficits do not occur exclusively in the context of a delirium.
- D. The cognitive deficits are not better explained by another mental disorder. (e.g., major depressive disorder, schizophrenia).

MNEMONIC**IADLs - "SHAFT"**

Shopping
Housekeeping
Accounting
Food preparation
Transportation (driving)

ADLs - "DEATH"

Dressing
Eating
Ambulating
Toileting
Hygiene

Specifiers (for both major and mild NCD):

- Etiology:
 - Alzheimer's disease (AD)
 - Frontotemporal lobar degeneration (FTD)
 - Lewy body disease
 - Vascular disease
 - Traumatic brain injury (TBI)
 - Substance/medication use
 - HIV infection
 - Prion disease
 - Parkinson's disease (PD)
 - Huntington's disease
 - Another medical condition
 - Multiple etiologies
 - Unspecified

FYI**Dementia vs NCD**

The term "dementia" was used in the DSM-IV but was taken out of the DSM-5. It is still used colloquially and can be thought of as synonymous with the DSM-5 diagnosis of major NCD.

"Dementia" = Major NCD

"Mild cognitive impairment" (MCI) = Minor NCD

Differential Diagnosis

- Delirium
- Drugs: new or recent changes, especially sedatives and anti-cholinergics
- Depression, or other psychiatric illnesses
- Infection (e.g. UTI, URTI)
- Pain (e.g. falls, fracture)
- Dehydration, weight loss
- Incontinence or constipation
- Sensory impairment
- Hypothyroidism
- Sleep disorder

MNEMONIC**DDx for NCDs****"The 4 D's"**

Delirium
Depression
Drugs
Diseases

	Alzheimer's disease	Vascular dementia	Lewy body dementia	Frontotemporal dementia (FTD)
General features	• Typical presentation: memory decline • Visuospatial and language are affected later (moderate-severe phase) • Social cognition preserved until late in the course of disease. • At least two domains of cognition are affected but one of them MUST be memory/learning • Mnemonic: The "4 A's and one D of AD" include Anterograde amnesia, aphasia, apraxia, agnosia, and disturbance in executive function"	• Presentation depends on what area of the brain is affected • Temporal relationship between CV events and cognitive decline • Prominent decline in complex attention (including processing speed) and executive function • May have depression/apathy	• Fluctuating cognition with pronounced variation in attention and alertness • Recurrent visual hallucination (systematic, well formed) • Worse attention and visual skills than AD • Suggestive features include REM sleep behavioural disorder and severe neuroleptic sensitivity • Spontaneous Parkinsonism symptoms after the onset of cognitive decline (usually within 1 year of each other)	• Relative sparing of memory learning, perceptual-motor function • Memory problems are generally not an issue until late in disease • Two variants: language variant and behavioural variant • Language variant presents with prominent decline in language ability, in the form of speech production, word finding, object naming, grammar or word comprehension • Behavioural variant presents with behavioural disinhibition, apathy/inertia, loss of sympathy or empathy, compulsive/ ritualistic behaviour and prominent decline in social cognition
Pathology	• Amyloid cascade hypothesis (-amyloid plaques) • Tauopathy (Neurofibrillary tangles) • Cortical dementia	• Vascular lesions: focal, multifocal, or diffuse • Subcortical dementia	• Alpha-synucleinopathy, Lewy body • More profound cholinergic deficit than AD • Cortical-subcortical	• Postsynaptic serotonin deficit, cholinergic system is relatively spared • Tauopathy • Cortical dementia
Epidemiology	F > M Most common form of dementia	M > F Second-most common form of dementia	M > F	Language variant: F > M Behavioural variant: M > F
Age of onset	8th and 9th decade	7th through 9th decade	6th through 9th decade	< 65 yrs
Years survival after diagnosis	~ 10		~ 5-7	~ 3-4
Onset and progression	Insidious, gradual	Sudden/abrupt onset and stepwise decline	Insidious, gradual	Insidious, gradual
Risk factors	• Age, • Genetic susceptibility polymorphism (APOE4) • Traumatic brain injury • Family history, • Down syndrome, • Low education • Vascular risk factors (see Clinical Pearl)	• Cerebrovascular event • Vascular risk factors	• REM sleep behaviour disorder	• Genetic factors • Family history of dementia or other psychiatric diagnosis.

Table 1. Summary table of the 4 most common types of dementia.

Epidemiology

- For major NCD:
 - 8% in patients aged >65; 50% in patients aged >85.
 - Prevalence doubles every 5 years.
 - For every vascular risk factor, risk doubles.

Investigations

Laboratory investigations

- Complete blood count (to rule out anemia).
- Thyroid stimulating hormone (to rule out hypothyroidism).
- Electrolytes (to rule out hyponatremia).
- Calcium (to rule out hypo/hypercalcemia).
- Fasting glucose (to rule out hypo/hyperglycemia).
- Vitamin B12.
- Folic acid (optional - celiac disease, inadequate diet).
- Genetic testing (e.g. Apolipoprotein E4) NOT recommended.

Imaging studies

- CT scan needed for the following indications:
 - Age <60 years.
 - Rapid (1-2 months) unexplained cognitive decline or function.
 - Short duration of dementia (less than 2 years).
 - Recent and significant head trauma.
 - Unexplained neurological symptoms.
 - History of cancer.
 - Use of anticoagulants or history of bleeding disorder.
 - Gait disturbance.
 - History of urinary incontinence and gait disorder early in the course of dementia (e.g. normal pressure hydrocephalus).
 - Any new localizing sign (e.g. hemiparesis).
 - Unusual or atypical cognitive symptoms (e.g. progressive aphasia).

CLINICAL PEARL

Vascular risk factors

- Hypertension
- Diabetes
- Smoking
- Hyperlipidemia (LDL)
- Atrial fibrillation
- Hyperhomocysteinemia
- Obesity
- End-organ damage from atherosclerosis (e.g. myocardial infarction, coronary artery disease, stroke)

Diagnostic Assessment

- Based on clinical assessment
- Patient interview – history of present illness, including cognitive symptoms
- Caregiver/or family interview
- Psychiatric history
- Medical history
- Substance use history
- Risk factors and protective factors
- Level of functioning (ADLs, IADLs)
- Brief cognitive test (e.g. Montreal Cognitive Assessment, Mini Mental State Examination).
- Physical exam.

	MMSE	MOCA
Duration	10-15 minutes to complete	15-25 minutes to complete
Cognitive domains tested	Memory, orientation, attention, language, visuo-construction, praxis	Memory, orientation, attention, executive function, language, visuo-construction
Sensitivity and specificity	Sensitivity 79%, specificity 88%	Sensitivity 100%, specificity 87%
Advantages and disadvantages	Copy-righted Lacks sensitivity to detect mild cognitive impairment	More sensitive than MMSE in detecting Alzheimer's disease and mild cognitive impairment

Table 2. Comparison between the Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MOCA).

Treatment

Non-pharmacological

- Cognitive stimulation: Small but consistent effect.
- Reminiscence therapy: Insufficient evidence.
- Reality orientation: Improved cognitive function.
- Music therapy: Insufficient evidence.
- Individualization is important!

Pharmacological

- Three cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and memantine
 - All are likely equivalent in efficacy (oral rivastigmine somewhat less well tolerated due to GI symptoms; rivastigmine patch improves tolerability)
- Consistent modest effects on cognition and caregiver global impression
- Delays progression (equivalent to 3-6 months)
- May delay emergence of apathy

MNEMONIC

Cholinesterase inhibitors

"Grandma Doesn't Remember"

Galantamine

Donepezil

Rivastigmine

Medication class	Medication name	Route of administration	Indication	Side effects
Cholinesterase inhibitor	Donepezil (Aricept)	Oral	Alzheimer's disease (mild, moderate, severe)	Nausea, diarrhea, muscle cramps, weakness, bradycardia, syncope, dizziness, bronchospasm (caution with poorly-controlled asthma and COPD), agitation and panic like state, urinary incontinence
	Galantamine ER (Reminyl)	Oral		
	Rivastigmine (Exelon)	Oral and transdermal	Also evidence for vascular dementia, Lewy Body dementia, Parkinson's dementia	
NMDA receptor antagonist	Memantine (Ebixa)	Oral	Moderate to severe AD Not indicated for FTD Can be combined with cholinesterase inhibitors (i.e. Namenda XR)	Dizziness, headache, constipation, confusion, hypertension, agitation, confusion, sedation/insomnia, urinary incontinence

NOTE

Untreated Alzheimer's typically progresses as a decline of 2-4 MMSE points per year.

Table 3. Summary table of cholinesterase inhibitors used to treat NCDs.

Neuropsychiatric Symptoms (NPS)

- Also known as "**behavioural and psychological symptoms of dementia**" (BPSD) and "**behavioural disturbances in dementia**"
- Occur in all types of dementia
- Includes behaviours such as: anxiety, apathy, depression, psychosis, aggression, agitation, disinhibition, irritability, sleep disturbance, inappropriate sexual behaviour
- Can be organized into five clusters: apathy, aggression, depression, agitation, psychosis
- Some types of dementias present with characteristic symptoms:
 - Lewy body - visual hallucinations.
 - Frontotemporal dementia (behavioural variation) - disinhibition.

Principles of management

- Assess to evaluate behavioural symptoms and define specific goals.
- Consider individual, social, and environmental factors to understand behaviours.
- Individualize intervention – non-pharmacological before pharmacological intervention.
- Select psychological and social interventions.
- If non-pharmacological management does not work, then consider psychotherapeutic medication treatment according to guidelines.
- Continue to assess whether the goals of treatments are being met.

Non-pharmacological	Pharmacological
Reduce social isolation: talking and singing, pet therapy, music, sensory stimulation, white noise, massage.	Modestly effective but carries significant risks.
Promote relaxation: music, sensory stimulation, white noise, massage.	Non-pharmacological intervention MUST be tried before medications, and informed consent MUST be obtained.
Increase positive engagement with physical and social environment: recreational activities, walking programs, group exercise.	Document your reason for using medications, any dose increases, and any switches to other medications.
	Attempt to discontinue periodically.
	Examples of medications used include SSRIs (e.g. Escitalopram) and antipsychotics (risperidone has the best evidence, followed by aripiprazole and olanzapine).
	Off-label options include: cholinesterase inhibitors (Parkinson's dementia, lewy body dementia), trazadone (anxiety and sundowning), carbamazepine (many side effects), benzodiazepines (perhaps only before bath/shower, many potential side effects), melatonin (sundowning), ECT.

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Review Questions

1. A 76-year-old woman with hypertension and angina and no known past psychiatric history is admitted for a knee replacement. Six hours after her surgery, she becomes agitated, is trying to climb out of her bed and says she is seeing birds in her room. Which of the following pharmacological treatments would be most appropriate?
 - a) Donepezil (Aricept) 5mg daily
 - b) Haloperidol (Haldol) 0.25mg BID
 - c) Diazepam (Valium) 10mg TID
 - d) Olanzapine (Zyprexa) 10mg TID
 - e) Chlorpromazine (Largactil) 25mg TID
2. A 60-year-old man is brought for assessment because of a history of memory complaints, which tend to fluctuate noticeably from hour to hour and day to day. During the evaluation, his wife comments that she frequently gets hit by him in his sleep because he is acting out dreams, usually in the early morning hours. He has a vague recall of dreams he is having during these times, often feeling like he is being chased by animals and fighting them off. His wife has also noticed that he moves more slowly, often shuffling his gait, with a noticeable decrease in his arm swing. What is the most likely diagnosis?
 - a) Neurocognitive disorder due to Alzheimer disease
 - b) Neurocognitive disorder due to Huntington disease
 - c) Neurocognitive disorder due to Lewy body disease
 - d) Neurocognitive disorder due to vascular disease
 - e) Neurocognitive disorder due to multiple etiologies
3. A 68-year-old woman with no past medical or psychiatric history presents with confusion. She is unable to recall the date or time, although she knows who she is. She is at times drowsy and difficult to wake up, and then can switch to being awake, agitated and restless. Her mini-mental status examination (MMSE) is 20/30 with points lost for orientation and short-term recall, although her long-term memory seems intact. Which of the following findings is most helpful in identifying the correct diagnosis in this patient?
 - a) Score of less than 20/30 on the Folstein MMSE
 - b) Fluctuating level of awareness
 - c) Inability to recall the date or time
 - d) Poor short-term memory with preservation of long-term memory
 - e) Early age of onset

Answers:
1. b
2. c
3. b

Geriatric Depression

Chapter Author: **Jessie Montanaro**

Faculty Reviewer: **Dr. Timothy Lau**, M.D., F.R.C.P.(C)., M.Sc.; Distinguished Teacher, Faculty of Medicine, Associate Professor, University of Ottawa; Director of Joy at Work Initiative, Department of Psychiatry; President of the Medical Staff, Clinical Lead, Geriatric Psychiatry Inpatient Unit, The Royal Ottawa Mental Health Centre.

Definition

- Major depressive disorder (MDD) diagnosed in an individual > 65 years.

Diagnostic Criteria

- ≥ 5 depressive symptoms (MSIGECAPS), 2 of which are depressed mood and loss of interest/pleasure
- ≥ 3 depressive symptoms (MSIGECAPS) = subsyndromal depression.
- Older adults are less likely than younger adults to endorse depressed mood symptoms.
- From DSM-5: “Memory difficulties may be the chief complaint and may be mistaken for early signs of dementia (“pseudodementia”). When the major depressive episode is successfully treated, the memory problems often fully abate. However, in some individuals, particularly elderly persons, a major depressive episode may sometimes be the initial presentation of an irreversible dementia.”

Epidemiology

- Most common mental health problem for geriatric patients (65 years and older).
- Prevalence in community is lower compared to younger population (1% and 7% respectively)
- Prevalence higher among geriatric patients in hospital and long term care
 - Long-term care: 15% MDD, 30% subsyndromal depression.

Differential Diagnosis

- Manic episodes with irritable mood or mixed episode
- Persistent depressive disorder (Dysthymia)
- Mood disorder due to another medical condition
- Substance/medication-induced depressive or bipolar disorder
- Adjustment disorder with depressed mood
- Bereavement
- Dementia

Symptom	Depression	Bereavement
Feeling	Worthlessness	Emptiness and loss Preoccupation with thoughts of deceased
Self-esteem	Poor Feelings of hopelessness	Generally preserved
Psychomotor changes	May have psychomotor retardation	None
Suicidal ideation	Suicidal ideation due to feeling worthless, undeserving of life, or unable to cope with pain of depression	Thoughts of joining the deceased
Frequency	Persistent	Dysphoria occurs in waves

Table 4. Comparison table between depression and bereavement.

Adapted from Chun S., Geriatric Depression bootcamp lecture.

Risk factors

- Recently bereaved
- Socially isolated
- Persistent complaints of memory difficulties
- Chronic disabling illness
- Recent major physical illness
- Persistent sleep difficulties
- Significant somatic concerns or recent onset anxiety
- Refusal to eat or neglect personal care
- Recurrent or prolonged hospitalization
- Diagnosis of dementia, Parkinson’s disease, or stroke
- Recent placement in nursing home

CLINICAL PEARL

Depression in the elderly vs. younger adults

Compared to younger adults, elderly individuals with depression tend to have:

- Fewer complaints of sadness
- More somatic symptoms
- More anxiety and agitation
- More cognitive problems
- More delusional symptoms
- More weight loss
- More melancholic features (early morning wakening, worse in the morning, loss of pleasure in most activities, lack of reactivity to usually pleasurable stimuli, excessive guilt, profound despondency, despair, empty mood, marked psychomotor agitation or retardation, significant anorexia or weight loss)

Screening Tools

- Without cognitive impairment: PHQ-9 or Geriatric Depression Scale (see Figure 1).
- With cognitive impairment: Cornell Caregiver Scale for Depression.

NOTE

The screening tools mentioned are used for follow-up (to monitor progress, measure response to treatment, etc.), and NOT for diagnosis.

Depression is primarily a **clinical** diagnosis that does not require use of tools.

Geriatric Depression Scale: Short Form

Choose the best answer for how you have felt over the past week:

1. Are you basically satisfied with your life? YES / **NO**
2. Have you dropped many of your activities and interests? **YES** / NO
3. Do you feel that your life is empty? **YES** / NO
4. Do you often get bored? **YES** / NO
5. Are you in good spirits most of the time? YES / **NO**
6. Are you afraid that something bad is going to happen to you? **YES** / NO
7. Do you feel happy most of the time? YES / **NO**
8. Do you often feel helpless? **YES** / NO
9. Do you prefer to stay at home, rather than going out and doing new things? **YES** / NO
10. Do you feel you have more problems with memory than most? **YES** / NO
11. Do you think it is wonderful to be alive now? YES / **NO**
12. Do you feel pretty worthless the way you are now? **YES** / NO
13. Do you feel full of energy? YES / **NO**
14. Do you feel that your situation is hopeless? **YES** / NO
15. Do you think that most people are better off than you are? **YES** / NO

Answers in **bold** indicate depression. Score 1 point for each bolded answer.

A score > 5 points is suggestive of depression.

A score ≥ 10 points is almost always indicative of depression.

A score > 5 points should warrant a follow-up comprehensive assessment.

Figure 1. Geriatric Depression Scale screening tool.

From Greenberg, 2012.

Investigations

- Labs may consist of any of the following, based on clinical discretion:
 - CBC differential
 - Electrolytes
 - Liver enzymes and function tests
 - Creatinine, urea
 - Vitamin B12, TSH, folate
 - CT head

Management

Psychotherapy and psychosocial intervention

- Cognitive behavioural therapy (CBT), interpersonal therapy (IPT), problem solving therapy, reminiscence therapy, acceptance and commitment therapy (ACT)
- Community involvement, exercise programs, and religious group association all help with connection and counter isolation.

Pharmacotherapy

- First-line agents: Selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitor (NDRIs) such as bupropion, noradrenergic and specific serotonergic antidepressants (NaSSAs) such as mirtazapine, serotonin antagonist and reuptake inhibitors (SARIs) such as trazodone.
 - Choice of antidepressant is based on: Clinical features, past response, family history of response, adverse effects, comorbidity, drug interactions, tolerability, cost and availability, patient preference, current medications.
- General guidelines:
 - *Start low and go slow, but keep going* (final dose may be similar to those in younger patients).
 - Adequate plasma levels or dosages
 - Treat for sufficient length of time
 - Expect some improvement in two weeks
 - Clinical response (usually defined as 50% of greater reduction) may not be evident until four to eight weeks (or even longer)

IMPORTANT

Antidepressant risks in the elderly

- Falls: SSRIs lower risk than others
- GI bleeds: with SSRIs, greater risk with advanced age
- Hyponatremia (secondary to SIADH): SSRIs, SNRIs
- Mortality: trazodone, mirtazapine, venlafaxine
- High-dose tricyclic antidepressants are associated with increased mortality, falls, seizures, and fractures.

- If no response in two to four weeks, intervene (optimize or switch)
- Recurrence is very common.
- Maintain antidepressant treatment at the same dose that was effective for treatment
- Treat for two years minimum even after remission is achieved.

Electroconvulsive therapy (ECT)

- Indications as first-line treatment:
 - Depression with psychotic features
 - Treatment-resistant depression
 - Catatonia
 - Acute and severe suicidal ideation
 - Previous treatment response
 - Lack of treatment adherence with other available treatments and severe illness
 - Repeated medication intolerance
 - Pregnancy
 - Rapidly deteriorating physical status
 - Patient choice
- Contraindications:
 - No absolute contraindications
 - Unstable/severe cardiovascular disease (e.g. untreated and severe HTN, myocardial infarction less than two weeks ago)
 - Space occupying lesion with raised intracranial pressure
 - Recent stroke/bleed
 - Bleeding/unstable vascular aneurysm
 - Unstable pulmonary condition
- Side effects:
 - Common and benign side effects (headache, nausea, muscle pain)
 - Cognitive impairment
 - Fracture and dislocation
 - More serious complications: myocardial infarction, tachycardia, cardiac rupture, transient ischemic attack
 - Death 1:10,000

Suicide in the Elderly

- Suicide rate increases with age.
- Elderly people are less likely to endorse suicidal ideation but more likely to attempt
- Higher rates of completed suicide (23/100,000) compared to younger population (12/10,000)
- Suicide attempt: completion = 4:1 in elderly men (compared to 20:1 in younger population)
- White, older men at the highest risk
- Lethality increases with age
- Method of suicide:
 - Elderly men: firearms and hanging
 - Elderly women: poisoning and hanging

Course and Prognosis

- Average length of untreated depression: nine months (same as younger age groups)
- Frequency of episodes increases with age and can even merge into a chronic condition (increased relapse rate)
- Prognosis is similar to the younger population: 70% recovery with meds and response rates of up to 80% with meds and psychotherapy.
- Depressive symptoms are a risk factor for mortality in elderly people, particularly in physically healthy individuals.
- Chances of achieving remission are greatest in the first six months of disease onset (50% remission rate vs 5% 13-15 months after disease onset).
- Late-onset depression is thought to be a prodrome to dementia.

FYI

For further reading on the management of geriatric depression (suggested by chapter reviewer Dr. Lau), check out the [Canadian Network for Mood and Anxiety Treatments \(CANMAT\) 2016 guidelines for the management of special adult populations with major depressive disorder](#), section on "Late-Life Depression".

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Review Questions

1. 73 year old woman who presents with 2 month history of tearfulness, loss of energy, apathy, inability to get out of bed in the morning, and insomnia with early morning awakenings. She describes increasing anxiety, an inability to cope, forgetfulness, problems reading or even watching TV, a 30 lb weight loss and feels very constipated. She expresses a concern that something is wrong with her stomach. Her lower back has also been bothering her more. She lost her husband about 3 months ago.

What would be the most likely diagnosis?

- a) Unspecified medical condition
 - b) Bereavement
 - c) Alzheimer's disease
 - d) Depression in late life
 - e) Generalized anxiety disorder
2. Which of the following are uncommon "reasons for consultation" by elderly who have their first depressive episode?
 - a) "Nerves"
 - b) Excessive fatigue
 - c) Increased appetite
 - d) Digestive problems
 - e) Fear of Alzheimer's disease
 3. An 85 year old man whose wife passed away 2 months ago presents with a six week history of sadness that comes in waves, numbness, a loss of appetite, and feelings of poor self-worth. He has repeatedly thought he heard his wife calling for him, often while drifting off to sleep. He has expressed a wish to join his wife.

Which of the following symptoms is most consistent with bereavement?

- a) Active suicidal ideation
- b) Prominent psychotic symptoms
- c) Profound feelings of guilt
- d) Crying spells when he thinks of his deceased wife.
- e) Being unable to attend to her usual daily activities 3 months after the death of his wife

3. (d)
2. (c)
1. (d)

Answers:

Delirium

Chapter Author: **Jessie Montanaro**

Faculty Reviewer: **Dr. Barb Deren**, BSc, MD, FRCPC; Child & Adolescent Psychiatrist, Children's Hospital of Eastern Ontario (CHEO); Clinical Lecturer, University of Ottawa.

Definition

- Syndrome caused by a physiological disturbance
- Marked by a fluctuating course with impairments in consciousness, attention, and perception
- Can be thought of as “brain failure”
- Is a signifier of underlying medical illness
- Causes increased morbidity and mortality

DSM-5 Criteria for Delirium

- A. Disturbance in:
 - Attention – ability to direct, focus, sustain and shift attention
 - AND
 - Awareness – orientation to the environment
- B. Disturbance:
 - Develops over a short period of time (usually hours to days)
 - Represents a change from baseline attention and awareness
 - Tends to fluctuate in severity during the course of the day
- C. Any one additional disturbance of cognition (ex: memory, disorientation, language, visuospatial ability and/or perception)
- D. Disturbances in criteria A and B:
 - Are not due to another pre-existing established or evolving neurocognitive disorder
 - Do not occur in the context of a severely reduced level of arousal (ex: coma)
- E. Evidence from the history, physical examination or investigations that it is a direct physiological consequence of:
 - Another medical condition
 - Substance intoxication
 - Substance withdrawal
 - Exposure to a toxin
 - Multiple etiologies

Specifiers:

- Duration:
 - Acute – Lasting a few hours or days
 - Persistent – Lasting weeks or months
- Type:
 - Hyperactive - Hyperactive level of psychomotor activity; mood lability; agitation; and/or refusal to cooperate with medical care.
 - Hypoactive – Hypoactive level of psychomotor activity; sluggishness; and/ or lethargy that approaches stupor.
 - Mixed level of activity – Normal level of psychomotor activity with disturbed attention and awareness. May have rapidly fluctuating activity level.
- Etiology:
 - Delirium due to another medical condition
 - Medication-induced delirium
 - Substance intoxication delirium
 - Substance withdrawal delirium
 - Delirium due to multiple etiologies

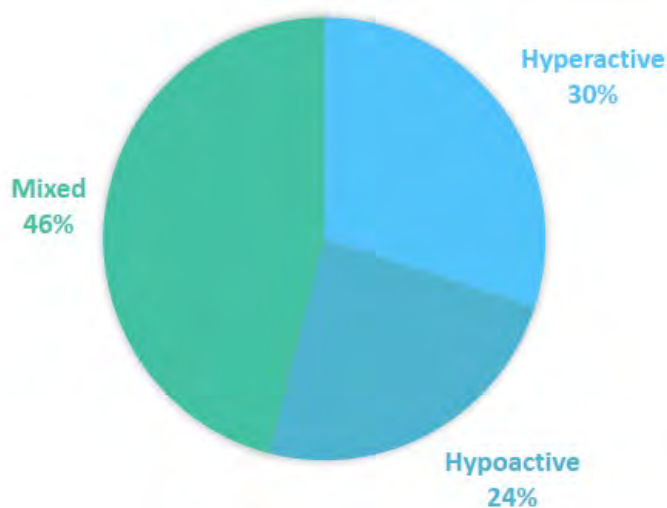


Figure 1. Breakdown of the types of delirium.

From Chun S., Deren B., Delirium bootcamp lecture.

Clinical Features

General clinical features	Hyperactive delirium	Hypoactive delirium
Fluctuating symptoms	Hypervigilance/	Lethargic
Fluctuating alertness	Restlessness	Sparse/ Slow speech
Inattention	Fast/ Loud Speech	Apathy
Disorientation	Calling out	Decreased motor activity
Impaired memory	Anger/ Irritability	Quiet
Impaired cognition	Combativeness	Decreased alertness
Emotional disturbance	Impatience	Starring
Hallucinations	Uncooperative	
Difficulty with verbal expression	Laughing	
Sleep-wake cycle disturbance	Swearing/ Singing	
Autonomic instability	Euphoria	
Re-emergence of primitive reflexes	Wandering	
	Distractibility	
	Nightmares	
	Persistent thoughts	

Table 1. Summary table of clinical features of delirium.

Epidemiology

- Community prevalence:
 - General – 1 to 2%
 - >85yo – 13%

Population	Prevalence of delirium
Medically-ill hospitalized patients	10-30%
Open heart surgery patients	30%
Hip replacement surgery patients	50%
Long-term care	60%
Intensive care unit	70-85%
End-of-life care	80%

Table 2. Prevalence of delirium in various patient populations.

Risk Factors

Predisposing factors

- Dementia/ cognitive impairment
- History of delirium
- Male sex
- Age >75 years old
- Vision/hearing impairment
- Medical comorbidity
- History of TIA/ stroke
- Substance use
- History of depression, bipolar, or schizophrenia

Precipitating factors

- Medications (>3)*
- Use of physical restraint
- Dehydration
- Malnutrition
- Sleep deprivation
- Pain
- Infection
- Surgery
- Bladder catheter in situ

* Especially anticholinergics, antihistamines, antiparkinsonian agents, muscle relaxants, antipsychotics, anti-muscarinics, benzodiazepines, corticosteroids, tricyclic antidepressants, histamine type-2 receptor antagonists, narcotics.

Etiology

- (See sidebar mnemonic for common etiologies of delirium.)
- In 10-20% of patients, no cause is identified.

MNEMONIC

Etiologies of delirium

"I WATCH DEATH"

Infection

Withdrawal

Acute metabolic

Trauma

CNS pathology

Hypoxia

Deficiency (e.g. vitamins)

Endocrinopathies

Acute vascular

Toxins/Drugs

Hheavy metals

Pathophysiology

- Largely unknown but most accepted hypothesis is that of “network disconnectivity” and “neurotransmitter dysregulation”.
- Other hypotheses include: neuronal aging, oxidative stress, neuroinflammation, cerebral hypoxia, neuroendocrine dysregulation.
- Acetylcholine plays a key role in mediating consciousness and attention process.
- Other neurotransmitters may include: dopamine, glutamate, GABA, melatonin likely also play a role

Differential Diagnosis

- Other neurocognitive disorders
- Psychotic disorder
- Bipolar/depressive disorder with or without psychotic features
- Acute stress disorder
- Catatonia
- Epilepsy – Absence or non-convulsive status epilepticus
- Medication and or substance intoxication/withdrawal

Work-up

History

- Clarify baseline cognitive function and time course of any changes in mental status
- Review all medications, including over the counter and herbal remedies, recent medication changes, and drug-drug interactions
- Review substance use history
- Assess for pain
- Review medical history and treatments
- Review safety (harm to self and others)
- Assess for capacity

IMPORTANT

Patients with suspected delirium may be unreliable, so getting **collateral history** from family, caregivers, friends, neighbours, etc. is key!

Physical examination

- Vital signs: heart rate, blood pressure, temperature, oxygen saturation, and glucose.
- Full physical exam: focus on signs of infection, sepsis, hydration, nutritional status, and neurological exam.

Mental Status Examination (MSE)

Screening tools

- Confusion Assessment Method (CAM) - see sidebar
- Delirium Symptom Interview
- Delirium Rating Scale
- Clinical Institute Withdrawal Assessment for Alcohol (CIWA)

Investigations

- Routine – CBC, electrolytes, calcium, magnesium, phosphate, albumin, creatinine, urea, liver enzymes and function tests, TSH, random glucose, urinalysis, urine/blood toxicology screen, CXR, EKG and HIV/syphilis testing.
- As indicated – urine, blood, cerebral spinal fluid cultures, vitamin B12, folate, CT/MRI head. EEG may be considered if suspicions of seizures and would show diffuse slowing in delirium. Lumbar puncture may be considered if fever, headache, meningeal signs or suspicion of encephalitis A.

CLINICAL PEARL

Confusion Assessment Method (CAM)^{1,2}

After seeing the patient and reviewing the history of cognitive changes, was there:

1. Acute onset and fluctuating course
2. Lack of attention
3. Disorganized thinking
4. Altered level of consciousness

Screening is positive for delirium when 1 AND 2 are present, PLUS either 3 or 4.

¹ Best for use in medical/surgical units and in the emergency room.

² Use caution in interpreting screening results in patients with dementia (chronic confusion) or patients with primary psychotic symptoms. CAM has not been validated in younger populations.

Management

Non-pharmacological

- Priority is to identify and treat the underlying cause.
- Discontinue medications contributing to delirium.
- Optimize physiological stability and modifiable risk factors
 - Hydration, cardiovascular stability, electrolyte balance, pain, control sleep pattern, treat constipation.

- Reorientation strategies:
 - Frequent reorientation, clocks and calendars, appropriate lighting, minimize sensory deprivation (e.g. glasses, hearing aids), avoid room transfers, consistent staff providing care, familiar photos, and provide meaningful activities to maintain function and self-esteem.
- Mobilize early
- Decrease tethers (e.g. IV, foley, physical restraints)
- Alliance
 - Calm, supportive approach
 - Avoid confrontation
 - Distract if needed
- Involve family and friends and provide psychoeducation about delirium.

Pharmacological

- *NOTE: All medications are off-label!
- Consider pharmacotherapy if there are safety concerns for patient or others, significant patient agitation or psychosis, and if non-pharmacological approaches have been ineffective.
- Medications are not indicated for hypoactive delirium without psychosis or for wandering.
- General approach:
 - Aim for monotherapy
 - Start at lowest possible dose
 - Discontinue as soon as possible (less than one week)
- Treatments of choice:
 - Haloperidol (0.25 to 0.5mg OD or BID)
 - Atypical antipsychotics (see Evidence-Based Practice sidebar box)

IMPORTANT

Avoid benzodiazepines and anticholinergic agents in patients with delirium.

EVIDENCE-BASED PRACTICE

Atypical antipsychotics in the management of delirium

There is better evidence for risperidone and quetiapine, while there is only limited data for olanzapine and aripiprazole.

Prognosis

- Increased mortality – up to 50% one year mortality rate.
- Increased hospitalization/prolonged hospitalization (average five to ten days longer).
- Functional decline persisting over six months after the discharge.
- PTSD from perceptual/delusional experiences.
- Increased placement to long term care.

Feature	Delirium	Dementia	Depression
Onset	Acute	Insidious	Variable
Course	Fluctuating	Slowly progressive	Diurnal variation (worse in the morning, improves during day)
Duration	Days to weeks	Months to years	Variable
Consciousness	Impaired, fluctuates	Clear until late in course of illness	Unimpaired
Attention	Inattentive	Without marked inattention	Difficulty concentrating
Memory	Impaired	Impaired	Memory intact/ minimally impaired
Affect	Variable	Variable	Depressed; anhedonia
Sleep-wake	Always disrupted	May be disrupted	Often disrupted

Table 3. Comparison table between delirium, dementia, and depression.

References

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Review Questions

1. A 65 year old widower reports seeing worms in his apartment for the last two days and now reports spiders crawling on his body over the last 24 hours. What is the most important information to obtain in your initial assessment?
 - a) Developmental history
 - b) Social history
 - c) Psychiatric history
 - d) Medical history
 - e) Medication allergies

2. Which of the following features is most indicative of delirium?
 - a) Memory impairment
 - b) Inattention
 - c) Psychomotor agitation
 - d) Confusion
 - e) Insomnia

3. A previously healthy 76 year old gentleman is admitted to the orthopedic surgery service after undergoing hip ORIF following a fall at home. The RN calls you and reports that the patient is wandering in the hallways and is observed heading towards the exit on numerous occasions. Which management approach is most appropriate at this time?
 - a) Lorazepam 0.5mg IM
 - b) Haloperidol 0.5mg po
 - c) Physical restraints
 - d) Redirect the patient to his room and remind him it is time for bed
 - e) Complete a Form 1

4. Which investigation would you order to differentiate between delirium and a primary psychotic disorder?
 - a) CT head
 - b) Lumbar puncture
 - c) Electroencephalogram
 - d) Blood work, including lipid panel
 - e) None of these

Review Questions (continued)

Answers:
1. d)
2. b)
3. d)
4. c)

Personality Disorders

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Introduction

Personality disorders are generally defined as an *enduring pattern* of inner experience and behaviour which deviates markedly from the expectations of the individual's culture which is:

- Pervasive and inflexible
- Stable over time
- Traced back to adolescence or early adulthood
- Causative of distress or impairment
- Manifested in two or more of the following: cognition, affectivity, interpersonal functioning, impulse control

Personality disorders are divided into three clusters in the DSM 5:

- **Cluster A: Eccentric Disorders**

- Paranoid: A pattern of distrust and suspiciousness such that others' motives are interpreted as malevolent
- Schizoid: A pattern of detachment from social relationships and a restricted range of emotional expression
- Schizotypal: A pattern of acute discomfort in close relationships, cognitive or perceptual distortions, and eccentricities of behaviour

- **Cluster B: Dramatic Disorders**

- Borderline: A pattern of instability in interpersonal relationships, self-image, and affects, and marked impulsivity
- Antisocial: A pattern of disregard for, and violation of, the rights of others
- Histrionic: A pattern of excessive emotionality and attention seeking
- Narcissistic: A pattern of grandiosity, need for admiration, and lack of empathy

- **Cluster C: Anxious Disorders**

- Avoidant: A pattern of social inhibition, feelings of inadequacy, and hypersensitivity to negative evaluation
- Dependent: A pattern of submissive and clinging behaviour related to an excessive need to be taken care of
- Obsessive-compulsive: A pattern of preoccupation with orderliness, perfectionism, and control

MNEMONIC

Personality Disorder Clusters

Cluster A: "**A**typical"

Cluster B: "**B**old"

Cluster C: "**C**oncerned"

Personality can also be described using the dimensional model, with personality traits described along a continuum from no to severe dysfunction.

- The most widely used model is the NEO Personality Inventory which consists of 5 traits:
 - Openness to experience: Active seeking and appreciation of experiences
 - Conscientiousness: Degree of organization, persistence, control, and motivation in goal-directed behaviour
 - Extraversion: Quantity and intensity of energy directed into the social world
 - Agreeableness: Tendency towards pro-social behaviour
 - Neuroticism: Tendency towards experiencing and acting on psychological distress
- Personality dysfunction occurs at extremes of these dimensions.
 - Generally people with personality disorders will have high neuroticism, low agreeableness, and low conscientiousness.
 - As we age, our personality characteristics tend to move away from the extremes due to biological, psychological and social factors.

MNEMONIC

**The 5 traits of the NEO
Personality Inventory**
"OCEAN"

Epidemiology

- Personality disorders as a whole are estimated to be prevalent in 9-16% of the population.
- Estimates suggest a prevalence of 1.6-6.8% for Cluster A disorders, 1.2-6.1% for Cluster B, and 2.6-10.6% for Cluster C
- Personality disorders are more common in certain groups, such as individuals with psychiatric diagnoses and in the incarcerated population
 - Comorbid personality has been associated with a poorer response to treatment for many psychiatric conditions
- Onset of personality disorders tends to be in adolescence with full development by early adulthood
 - If a personality change occurs later in life, it is suggestive of another mental disorder, a neurocognitive disorder, or a disorder caused by a medical condition or substance use
 - Some individuals may not come to clinical attention until later in life despite onset in adolescence

Etiology

- Childhood abuse and neglect are associated with a risk for personality disorders, and most known for their association with antisocial and borderline personality disorders
- Most personality disorders have evidence of heritability
 - There is evidence for shared heritability of schizotypal personality disorder and schizophrenia
 - Antisocial and borderline personality disorders have a strong genetic component

Diagnosis

- Longitudinal and collateral history are important for all personality disorder diagnoses
- Ideally diagnosis should be avoided on a single assessment
- If a personality disorder is to be diagnosed in an individual younger than 18 years of age, the features must be present for at least 1 year
 - Antisocial personality disorder is an exception, as it cannot be diagnosed in individuals younger than 18, and they must show signs of conduct disorder since before the age of 15
- If evaluating someone of a different background, it can be helpful to obtain additional information from individuals familiar with the cultural background

Treatment

- Psychotherapy is the primary form of treatment in the outpatient or community setting
- Day hospital programs can also be useful for individuals with personality disorder
 - These programs utilize cognitive behavioural therapy (CBT) and mindfulness skills and focus on developing coping skills, building self-worth, social connectedness, finding life balance, and navigating conflict in relationships
- Medications, unless used to treat a comorbid psychiatric diagnosis, are adjunctive and off-label

Prognosis

- Personality disorders are often associated with difficulties in social, interpersonal, and occupational functioning
- Rates of unemployment, homelessness, divorce, domestic violence, traumatic accidents, substance misuse, healthcare utilization, and suicide are higher among individuals with personality disorders
- Almost all individuals with a personality disorder have at least one comorbid psychiatric disorder
 - Major depressive disorder is most common, with other mood, anxiety, substance use, and eating disorders being common as well
- Personality disorders generally improve over time. However symptoms tend to improve more than functioning

Cluster A Disorders

	DSM-5 criteria
Paranoid personality disorder	A. A pervasive distrust and suspiciousness of others such that their motives are interpreted as malevolent, beginning by early adulthood and present in a variety of contexts, as indicated by ≥ 4 of the following: 1. Suspects, without sufficient basis, that others are exploiting, harming, or deceiving him or her. 2. Is preoccupied with unjustified doubts about the loyalty or trustworthiness of friends or associates. 3. Is reluctant to confide in others because of unwarranted fear that the information will be used maliciously against him or her. 4. Reads hidden demeaning or threatening meanings into benign remarks or events. 5. Persistently bears grudges (i.e., is unforgiving of insults, injuries, or slights). 6. Perceives attacks on his or her character or reputation that are not apparent to others and is quick to react angrily or to counterattack. 7. Has recurrent suspicions, without justification, regarding fidelity of spouse or sexual partner. B. Does not occur exclusively during the course of schizophrenia, a bipolar disorder or depressive disorder with psychotic features, or another psychotic disorder and is not attributable to the physiological effects of another medical condition. *Note: If criteria are met prior to the onset of schizophrenia, add “premorbid,” i.e., “paranoid personality disorder (premorbid).”
Schizoid personality disorder	A. A pervasive pattern of detachment from social relationships and a restricted range of expression of emotions in interpersonal settings, beginning by early adulthood and present in a variety of contexts, as indicated by ≥ 4 of the following: 1. Neither desires nor enjoys close relationships, including being part of a family. 2. Almost always chooses solitary activities. 3. Has little, if any, interest in having sexual experiences with another person. 4. Takes pleasure in few, if any, activities. 5. Lacks close friends or confidants other than first-degree relatives. 6. Appears indifferent to the praise or criticism of others. 7. Shows emotional coldness, detachment, or flattened affectivity. B. Does not occur exclusively during the course of schizophrenia, a bipolar disorder or depressive disorder with psychotic features, another psychotic disorder, or autism spectrum disorder and is not attributable to the physiological effects of another medical condition. *Note: If criteria are met prior to the onset of schizophrenia, add “premorbid,” i.e., “schizoid personality disorder (premorbid).”
Schizotypal personality disorder	A. A pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships as well as by cognitive or perceptual distortions and eccentricities of behavior, beginning by early adulthood and present in a variety of contexts, as indicated by ≥ 5 of the following: 1. Ideas of reference (excluding delusions of reference). 2. Odd beliefs or magical thinking that influences behavior and is inconsistent with subcultural norms (e.g., superstitiousness, belief in clairvoyance, telepathy, or “sixth sense”: in children and adolescents, bizarre fantasies or preoccupations). 3. Unusual perceptual experiences, including bodily illusions. 4. Odd thinking and speech (e.g., vague, circumstantial, metaphorical, overelaborate, or stereotyped). 5. Suspiciousness or paranoid ideation. 6. Inappropriate or constricted affect. 7. Behavior or appearance that is odd, eccentric, or peculiar. 8. Lack of close friends or confidants other than first-degree relatives. 9. Excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears rather than negative judgments about self. B. Does not occur exclusively during the course of schizophrenia, a bipolar disorder or depressive disorder with psychotic features, another psychotic disorder, or autism spectrum disorder. *Note: If criteria are met prior to the onset of schizophrenia, add “premorbid,” i.e., “schizoid personality disorder (premorbid).”

Table 1. DSM-5 criteria for Cluster A personality disorders.

Paranoid personality disorder

- Individuals with paranoid personality disorder are chronically suspicious and distrust others.
 - As such they rarely seek treatment, and the disorder is often first diagnosed when the individual seeks treatment for a mood or anxiety disorder
 - These individuals do not have frank delusions
- Prevalence of this disorder is estimated to be 1-4% in the general population
- Antipsychotics may have some effects in reducing paranoid thoughts, but use remains off-label

CLINICAL PEARL

When managing paranoid personality disorder, clinicians should be supportive and listen to the patient's complaints.

Once rapport is established, then alternative explanations can be suggested for the patient's misperceptions.

Schizoid personality disorder

- Individuals with schizoid personality disorder tend to prefer solitary activities and have few close relationships
 - They tend not to experience or display strong emotions and have little desire for sexual experiences
- Prevalence of this disorder is estimated to be 3-5% in the general population
- Individuals with schizoid personality disorder rarely seek psychiatric care, and as such will typically present due to comorbid psychiatric disorder
 - They also tend to lack the insight and motivation needed for individual psychotherapy and are not inclined towards the intimacy of group therapy settings
 - Day programs and drop-in centres may be appropriate means of treatment for these patients

IMPORTANT

Group therapy should be avoided for individuals with paranoid personality disorder, as they have a tendency to misinterpret statements and situations that may come about during the sessions!

Schizotypal personality disorder

- Schizotypal personality disorder is characterized by a pattern of peculiar behaviour, odd speech and thinking, and unusual perceptual experiences
- Individuals with this disorder tend to be socially isolated, have "magical" beliefs, mild paranoia, social anxiety, and inappropriate or constricted affect
- Prevalence of this disorder is estimated to be 4-5% in the general population
 - Comorbid mood, substance use, and anxiety disorders is common

- Family, twin, and adoption studies suggest that there is a genetic link between schizotypal personality disorder and schizophrenia
- Treatment focuses on the issues that the individual seeks treatment for such as feelings of alienation or isolation, or paranoia
 - They may find exploratory and group psychotherapies to be threatening
 - Social skills training may be useful to help the individual develop an understanding of what behaviours others may find to be odd, and to develop skills to assist the individual in making interactions with others more productive and satisfying
 - Second-generation antipsychotics may help to reduce anxiety, paranoia, and unusual perceptual experiences

Cluster B Disorders

	DSM-5 criteria
Antisocial personality disorder	A. A pervasive pattern of disregard for and violation of the rights of others, occurring since age 15 years, as indicated by ≥ 3 of the following: 1. Failure to conform to social norms with respect to lawful behaviors, as indicated by repeatedly performing acts that are grounds for arrest. 2. Deceitfulness, as indicated by repeated lying, use of aliases, or conning others for personal profit or pleasure. 3. Impulsivity or failure to plan ahead. 4. Irritability and aggressiveness, as indicated by repeated physical fights or assaults. 5. Reckless disregard for safety of self or others. 6. Consistent irresponsibility, as indicated by repeated failure to sustain consistent work behavior or honor financial obligations. 7. Lack of remorse, as indicated by being indifferent to or rationalizing having hurt, mistreated, or stolen from another. B. The individual is at least age 18 years. C. There is evidence of conduct disorder with onset before age 15 years. D. The occurrence of antisocial behavior is not exclusively during the course of schizophrenia or bipolar disorder.
Borderline personality disorder	A. A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity, beginning by early adulthood and present in a variety of contexts, as indicated by ≥ 5 of the following: 1. Frantic efforts to avoid real or imagined abandonment. (*Do not include suicidal or self-mutilating behavior covered in Criterion 5.) 2. A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation. 3. Identity disturbance: markedly and persistently unstable self-image or sense of self. 4. Impulsivity in at least two areas that are potentially self-damaging (e.g. spending, sex, substance abuse, reckless driving, binge eating). (*Do not include suicidal or self-mutilating behavior covered in Criterion 5.) 5. Recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior. 6. Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days). 7. Chronic feelings of emptiness. 8. Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights). 9. Transient, stress-related paranoid ideation or severe dissociative symptoms.
Histrionic personality disorder	A. A pervasive pattern of excessive emotionality and attention seeking, beginning by early adulthood and present in a variety of contexts, as indicated by ≥ 5 of the following: 1. Is uncomfortable in situations in which he or she is not the center of attention. 2. Interaction with others is often characterized by inappropriate sexually seductive or provocative behavior. 3. Displays rapidly shifting and shallow expression of emotions. 4. Consistently uses physical appearance to draw attention to self. 5. Has a style of speech that is excessively impressionistic and lacking in detail. 6. Shows self-dramatization, theatricality, and exaggerated expression of emotion. 7. Is suggestible (i.e., easily influenced by others or circumstances). 8. Considers relationships to be more intimate than they actually are.
Narcissistic personality disorder	A. A pervasive pattern of grandiosity (in fantasy or behavior), need for admiration, and lack of empathy, beginning by early adulthood and present in a variety of contexts, as indicated by ≥ 5 of the following: 1. Has a grandiose sense of self-importance (e.g., exaggerates achievements and talents, expects to be recognized as superior without commensurate achievements). 2. Is preoccupied with fantasies of unlimited success, power, brilliance, beauty, or ideal love. 3. Believes that he or she is "special" and unique and can only be understood by, or should associate with, other special or high-status people (or institutions). 4. Requires excessive admiration. 5. Has a sense of entitlement (i.e., unreasonable expectations of especially favorable treatment or automatic compliance with his or her expectations). 6. Is interpersonally exploitative (i.e., takes advantage of others to achieve his or her own ends). 7. Lacks empathy - is unwilling to recognize or identify with the feelings and needs of others. 8. Is often envious of others or believes that others are envious of him or her. 9. Shows arrogant, haughty behaviors or attitudes.

Table 2. DSM-5 criteria for Cluster B personality disorders.

Antisocial personality disorder

NOTE

Evidence of conduct disorder before age 15 is a necessary criterion for diagnosis of ASPD.

- Individuals with antisocial personality disorder (ASPD) will report a history of childhood behaviour problems that would fulfill criteria for conduct disorder.
 - As adulthood approaches, these individuals develop problems such as uneven job performance and domestic abuse. Other common problems are reckless behaviour, inappropriate aggression, criminal behaviour, and pathological lying
- Prevalence of this disorder is estimated to be 2-4% in men and 0.5-1% in women
 - Prevalence is much higher in psychiatric hospitals and clinics, among the homeless and incarcerated, and among substance-abusing individuals
 - Comorbid substance-use disorders, mood and anxiety disorders, attention-deficit/hyperactivity disorders, other personality disorders, and gambling disorder are common
- Rates of death from suicide, accidents, homicides, and natural causes are higher in the population
- Aggression is the primary problem for many individuals with antisocial personality disorder, which can be treated with several drugs including lithium carbonate, valproate, and antipsychotics. However these are not routinely prescribed and are off-label.
 - Medications targeting comorbid mood, anxiety, or attention deficit/hyperactivity disorders can help to reduce their impact on the individual but may not reduce antisocial behaviour
 - There is some evidence that CBT can be helpful in those with mild symptoms who have good insight

IMPORTANT

Benzodiazepines should be avoided in the treatment of ASPD and BPD, due to potential for abuse and behavioural disinhibition.

Borderline personality disorder

- Individuals with borderline personality disorder (BPD) display a pattern of unstable relationships, emotional dysregulation, self-destructive impulsivity, chronic suicidality and self-harm, unstable sense of self, and intense fears of abandonment
 - They may also experience transient paranoid ideation or dissociative symptoms
- Prevalence of this disorder is estimated to be 6% in the general population
- More than 75% of individuals with borderline personality disorder engage in deliberate self-harm, and around 10% die by suicide
 - Better outcomes are associated with higher intelligence, self-

discipline, and social support

- Poor outcomes are associated with hostility, antisocial behavior, and suspiciousness. Substance abuse is most predictive of poor outcomes
- Long term prognosis is fairly good with 50% symptom remission at 2 years
 - Impulsivity tends to decrease the most
 - Only ⅓ achieve long-term employment or stable marriages
- Comorbid major depression, anxiety disorders, and substance abuse or dependence are common
- Several group treatment programs have been developed for borderline personality disorders
 - Dialectical behaviour therapy (DBT) is the most well-known program, which involves intensive year-long treatment including individual and group therapy
 - The Systems Training for Emotional Predictability and Problem Solving (STEPPS) program is a less-intensive 20-week alternative which involves psychoeducation and skills training
- Pharmacotherapy is directed at the patients' symptoms and comorbid conditions
 - SSRIs can be helpful in reducing depressive symptoms and suicidal ideation
 - Antipsychotics can treat perceptual distortions, poor anger control, suicidal behaviour, and mood instability

IMPORTANT

Exercise caution when prescribing any medication that could be dangerous in overdose such as lithium or tricyclic antidepressants, as suicide attempts are frequent in patients with BPD.

Histrionic personality disorder

- Individuals with histrionic personality disorder tend to display attention-seeking behaviour and excessive emotionality
 - These individuals can often be sociable and superficially charming but can also be manipulative, vain, and demanding
- Prevalence of this disorder is estimated to be 2% in the general population
- Individuals with histrionic personality disorder tend to seek out medical attention and frequently use health services
- A supportive problem-solving approach or CBT is recommended to help patients counteract their distorted thinking
- Group therapy may be useful in addressing provocative and attention-seeking behaviour, as patients may not have insight towards them

Narcissistic personality disorder

- Individuals with narcissistic personality disorder tend to display grandiosity, lack of empathy, and hypersensitivity to evaluation by others
 - These individuals tend to inflate their own accomplishments and are manipulative to those around them. They believe that they deserve special treatment and expect to receive admiration while having little empathy for others
 - They may appear outwardly charming but tend to have superficial and cold relationships
- Individuals with this disorder tend to have poor insight into their narcissism, often viewing themselves as caring and selfless
- Prevalence of this disorder is estimated to be 6% in the general population
- There is little data on treatment of narcissistic personality disorder
 - They can be difficult to treat as the narcissism can interfere with psychotherapy

CLINICAL PEARL

Narcissistic injury

Individuals with narcissistic personality disorder tend to seek help for what is termed a "narcissistic injury", wherein they feel anger or depression when deprived of something they feel entitled to.

This is a high-risk situation for suicidality!

Cluster C Disorders

	DSM-5 criteria
Avoidant personality disorder	A. A pervasive pattern of social inhibition, feelings of inadequacy, and hypersensitivity to negative evaluation, beginning by early adulthood and present in a variety of contexts, as indicated by ≥ 4 of the following: 1. Avoids occupational activities that involve significant interpersonal contact because of fears of criticism, disapproval, or rejection. 2. Is unwilling to get involved with people unless certain of being liked. 3. Shows restraint within intimate relationships because of the fear of being shamed or ridiculed. 4. Is preoccupied with being criticized or rejected in social situations. 5. Is inhibited in new interpersonal situations because of feelings of inadequacy. 6. Views self as socially inept, personally unappealing, or inferior to others. 7. Is unusually reluctant to take personal risks or to engage in any new activities because they may prove embarrassing.
Dependent personality disorder	A. A pervasive and excessive need to be taken care of that leads to submissive and clinging behavior and fears of separation, beginning by early adulthood and present in a variety of contexts, as indicated by ≥ 5 of the following: 1. Has difficulty making everyday decisions without an excessive amount of advice and reassurance from others. 2. Needs others to assume responsibility for most major areas of his or her life. 3. Has difficulty expressing disagreement with others because of fear of loss of support or approval. (*Do not include realistic fears of retribution.) 4. Has difficulty initiating projects or doing things on his or her own (because of a lack of self-confidence in judgment or abilities rather than a lack of motivation or energy). 5. Goes to excessive lengths to obtain nurturance and support from others, to the point of volunteering to do things that are unpleasant. 6. Feels uncomfortable or helpless when alone because of exaggerated fears of being unable to care for himself or herself. 7. Urgently seeks another relationship as a source of care and support when a close relationship ends. 8. Is unrealistically preoccupied with fears of being left to take care of himself or herself.
Obsessive-compulsive personality disorder	A. A pervasive pattern of preoccupation with orderliness, perfectionism, and mental and interpersonal control, at the expense of flexibility, openness, and efficiency, beginning by early adulthood and present in a variety of contexts, as indicated by ≥ 4 of the following: 1. Is preoccupied with details, rules, lists, order, organization, or schedules to the extent that the major point of the activity is lost. 2. Shows perfectionism that interferes with task completion (e.g., is unable to complete a project because his or her own overly strict standards are not met). 3. Is excessively devoted to work and productivity to the exclusion of leisure activities and friendships (not accounted for by obvious economic necessity). 4. Is overconscientious, scrupulous, and inflexible about matters of morality, ethics, or values (not accounted for by cultural or religious identification). 5. Is unable to discard worn-out or worthless objects even when they have no sentimental value. 6. Is reluctant to delegate tasks or to work with others unless they submit to exactly his or her way of doing things. 7. Adopts a miserly spending style toward both self and others; money is viewed as something to be hoarded for future catastrophes. 8. Shows rigidity and stubbornness.

Table 3. DSM-5 criteria for Cluster C personality disorders.

Avoidant personality disorder

- Individuals with avoidant personality disorder tend to have low self-esteem, are self-conscious, and fear being embarrassed in public
 - They tend to be hypersensitive to rejection, be socially awkward and timid, and be apprehensive and mistrustful
- The prevalence of this disorder is estimated to be 1.5-2.5% in the general population
- There are several psychotherapeutic strategies which can be used in treatment of avoidant personality disorder
 - Group therapy can aid in overcome an individual's social anxiety and develop interpersonal trust
 - Assertiveness and social skills training and systematic desensitization can be useful in addressing anxiety symptoms and introversion
 - CBT can help to correct dysfunctional attitudes
- Benzodiazepines can be used when a patient is attempting to enter previously avoided social situations
 - Use should be limited to short time periods when possible
- SSRIs can also be helpful in treating anxiety

FYI

There is significant overlap between avoidant personality disorder and anxiety disorders, with some experts believing the disorder is on a spectrum with the anxiety disorders.

Social anxiety disorder in particular can be difficult to distinguish from avoidant personality disorder.

Dependent personality disorder

- Individuals with dependent personality disorder excessively rely on others for emotional support
 - These individuals tend to have poor social and family ties as their dependency can accentuate interpersonal conflicts
- The prevalence of this disorder is estimated to be 0.5% in the general population
- There is little consensus on the treatment of dependent personality disorder
 - CBT can be used to promote emotional growth, assertiveness, effective decision making, and independence
 - Focused assertiveness and social skills training can also be beneficial
 - Marital counselling is useful when a patient's dependence on their spouse is causing marital issues

Obsessive-compulsive personality disorder

- Individuals with obsessive-compulsive personality disorder (OCPD) display perfectionism and inflexibility, as well as over-conscientiousness and constricted emotions
- Although initially thought that this disorder led to the development of obsessive-compulsive disorder (OCD), research has shown that most patients with OCD do not have a comorbid obsessive-compulsive personality disorder
 - Rates of OCPD in individuals with OCD have been reported between 15-28%
- The prevalence of this disorder is estimated to be 1-2% in the general population
 - This disorder is more common in those with higher levels of education and those in higher income brackets
 - There is frequent comorbidity with mood and anxiety disorders
- There is little literature on the treatment of obsessive-compulsive personality disorder
 - CBT may help individuals understand that reality is not defined by clear black and white lines of rigidly held beliefs
 - SSRIs can be useful in reducing the need for perfectionism and unnecessary ritualizing

NOTE

Individuals with OCD tend to view their symptoms as pathological, while individuals with obsessive-compulsive personality disorder tend to view their symptoms as desirable.

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Review Questions

1. A person with paranoid personality disorder says to you “my neighbours hate me and want me to move”. What is the defense mechanism displayed here?
 - a) Projection
 - b) Splitting
 - c) Egocentric thinking
 - d) Overgeneralization
 - e) Thought insertion

2. An individual with narcissistic personality disorder will routinely overestimate their abilities and inflate their accomplishments, and this is characterized by which of the following?
 - a) Unusual ideas of reference
 - b) An inability to monitor reality
 - c) A pervasive need for admiration
 - d) Impulsive behaviour such as drug abuse
 - e) Compete for empathy with the feelings of others

3. Personality disorders are an enduring patterns of behaviour that persist from childhood into adulthood and because of this fact, one of the best predictors of antisocial personality disorder in adulthood is a diagnosis of:
 - a) Conduct disorder
 - b) Attention Deficit Hyperactivity Disorder
 - c) Reactive Attachment Disorder
 - d) Childhood Anxiety Disorder
 - e) Autism Spectrum Disorder

Answers:
1. a)
2. c)
3. a)

Emergency Psychiatry

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Approach to Assessment

Collateral history and confidentiality

- It is important to obtain collateral history in the emergency psychiatry setting as not all patients will be reliable historians.
- Sources of collateral history include: police/ambulance reports, family members, hospital records/discharge summaries and family physicians.
- Can always *gather* collateral information without consent (as long as you are not *disclosing* any information).
- There are certain situations in which confidentiality must be broken:
 - Driving safety risk (e.g. suicidal ideation involving driving) → must report to the Ministry of Transport.
 - Abuse/neglect of children under the age of 16 → must report to CAS.

ED investigations

- Must rule out any other medical illnesses (e.g. intoxication, withdrawal, delirium).
- Basic investigations: CBC, lytes, Cr, urea, AST/ALT, TSH etc.
- Urine drug screen for common illicit drugs.
- Always order a set of vitals (especially temperature) → important to monitor for signs of autonomic instability in alcohol/benzodiazepine withdrawal, which can be life-threatening.
- Serum toxicology (common overdoses): alcohol level, acetaminophen level, TCA level, ASA level.
- Anticonvulsant drug levels (e.g. Epival level).
- If bipolar history or previously prescribed lithium, order a lithium level → can assess for compliance and rule out lithium toxicity.

Mental Health Act

Form 1: “Application for Psychiatric Assessment”

- Can be completed by any physician who has seen the patient within the week → police then have one week to bring patient into hospital for assessment.
- Person can be detained, observed and examined for up to 72 hours beginning when Form 42 is given to patient (may be cancelled after initial assessment).
- Patient does not have the right to apply to the Consent & Capacity Board (CCB) to contest.
- Patient must meet Box A and/or Box B criteria (see sidebar).
- Low threshold to place patient on Form 1 (err on side of safety).
- If patient admitted voluntarily, things to consider:
 - Acute safety risk?
 - Impulsivity? Ambivalence? Insight?
 - Psychosis or impaired judgement?

Form 2:

- Concerned family members can contact Justice of the Peace.
- Justice of the Peace completes a Form 2 (if Box A or Box B criteria are met).
- Allows police to apprehend and transport person to physician for assessment.
- Replaced by a Form 1 if physician believes this is necessary.

Section 17:

- Police can apprehend and transport person to be examined by physician if they believe Box A criteria are met (suspicion of a mental health issue).
- Replaced by a Form 1 if physician believes this is necessary.

When to hospitalize:

- Many patients may be chronically “psychiatrically unwell” at their baseline.
- Main reasons for admission:
 - Acute safety issues (SI/HI/self-care)
 - Diagnostic clarification
 - Complex treatment (i.e. ECT)

FYI

The **Mental Health Act** is an Ontario law which governs the administration of mental health care, specifically to regulate the involuntary admission of people into a psychiatric hospital.

NOTE

Box A Criteria

- Harm to self
- Harm to others
- Impairment of self

Past/present test: “has behaved/shown/caused...”

Future test: “will likely result in...”

Box B Criteria

- Previously received treatment
- Shown clinical improvement
- Incapable of consenting (& SDM consent has been obtained)
- Suffering from similar illness
- Likely to cause: harm to self/others/impairment of self

Safety and Aggression

Safety

Risk factors for violence

- Past history of violence (most important risk factor).
- Substance use.
- Antisocial personality disorder (criminality).
- Psychosis and/or mania.
- Agitation secondary to delirium or dementia.

Maintaining safety

- Speak calmly to de-escalate.
- Flexible, brief and focused interviews.
- Avoid wearing ties, stethoscopes, long necklaces etc.
- Don't assess anyone if it is an unsafe situation → if patient is agitated, get help right away to determine next steps.
- Make sure you are standing closest to the door and that nothing is obstructing your exit → make sure door swings both ways → can leave door open until you feel comfortable.
- Police or security guards can be present (upon request of the assessor) → either outside the door or even inside the room if that's what the physician/resident requires to complete the assessment (safety trumps privacy).
- Be aware of body language → if the patient stands during the assessment, stand up as well.

Safety Assessment

The following safety risks should be assessed in every patient presenting with a psychiatric emergency:

1. Any suicidal ideation vs. intent vs. plan?
2. Any homicidal ideation vs. intent vs. plan?
3. Any access to firearms? Any stockpiled medications?
4. Is the patient capable of adequately caring for themselves? Is there any risk of wandering, fire risk, etc.?
5. Is there risk of abuse and/or neglect of children under the age of 16? Risk of elder abuse?
6. Does the patient pose a driving risk?

**If the patient does pose a safety risk to themselves and/or others, a [Form 1](#) should be considered and the appropriate authorities should be notified (police, CAS, Ministry of Transport etc.).*

Agitation

Assessment of agitated patients

With agitated patients (who may require chemical or physical restraint), there are a number of things to assess prior to taking a complete history:

1. Nature and duration of agitation?
2. History of agitation (according to hospital records, collateral history etc.)? If so, how was it managed? Were there any major side effects?
3. Is the patient currently a threat to self or others? If yes, order stat medication and request additional help (nurses, security etc). Offer PO before IM if possible, order lowest dose possible, order physical restraints if necessary (only as last resort).
4. Is the patient on a Form 1 or meeting criteria to be brought into hospital?
5. Medical history.
6. Vital signs: any signs of substance intoxication or withdrawal?
7. Any change to LOC: overdose, delirium?
8. Medication history? Any new meds recently started?
9. Order appropriate observation and vitals (usually once daily for 72 hours).
10. Obtain collateral history.
11. Attempt to obtain a complete history only when it is safe to do so. Defer history if the patient is significantly agitated, aggressive, overly sedated or other acute safety issues are present.

Differential diagnosis of agitation

- Assess onset/timing: very acute onset suggests medical cause (i.e. delirium, intoxication).
- Barriers to communication (i.e. language barriers, cultural differences) → consider offering an interpreter.
- Stressors (i.e. being in hospital).
- Conflicts with family, friends, healthcare workers etc.
- Assess fall risk and rule out head injury.

IMPORTANT

Physical restraints **MUST** be accompanied by chemical restraint.

CLINICAL PEARL

Reasons to increase frequency of vitals

- Risk of withdrawal
- Signs of intoxication
- In elderly patients
- Patients with medical comorbidities
- Eating disorders
- Patients starting new medications
- Delirium

NOTE

Untreated agitation can lead to serious medical complications including dehydration, exhaustion, rhabdomyolysis and renal failure.

Psychiatric causes of agitation	Medical causes of agitation
Psychotic disorders	DELIRIUM
Depressive disorders	Intoxication/withdrawal
Bipolar disorders	Metabolic abnormalities
Anxiety disorders	Endocrine abnormalities
Personality disorders	Encephalopathy
Side effect of new medications (i.e. akathisia)	Stroke
Behavioural and psychological symptoms of dementia	Brain injury
	Space-occupying lesion
	Epilepsy

Table 1. Common psychiatric and medical causes of agitation.

Medical management of agitation

PRN medications for agitation:

- Haloperidol 5-10 mg PO/IM q6hr PRN (max 20 mg/24 hours).
- Lorazepam 1-2 mg PO/IM q4hr PRN (max 8 mg/24 hours).
- Olanzapine 5-10 mg PO/IM q6hr PRN (max 20mg/24 hours).
 - IM olanzapine is very expensive so only use if indicated (e.g. patient has allergy to Haldol, Parkinson's disease, etc.).
- Do NOT combine IM olanzapine with IM lorazepam → these agents are both sedating and can lead to respiratory depression.
- Consider loxapine 5-10 mg PO/IM q16hr in geriatric patients.
- For lesser agitation, can often use PO of patient's regular medication → can also be used for anxiety, insomnia etc.

Management of extrapyramidal symptoms (EPS)

- PRN medications for EPS should routinely be put in emergency orders in case patient develops an acute dystonic reaction (i.e. oculogyric crisis, laryngospasm) in response to PRNs for agitation.
- Benztropine (Cogentin) 2 mg IM.
- Lorazepam (Ativan) 2 mg IM.
- Diphenhydramine (Benadryl) 50 mg IM.
- Benztropine or diphenhydramine can be repeated after 10 minutes if symptoms are still very severe or life-threatening.
- If patient is on regular Cogentin at home, order this in hospital → can be effective for acute EPS.

CLINICAL PEARL

Patients who are agitated because of a primary psychiatric condition should have no fluctuation in LOC and should be fully alert. Consider a medical illness if fluctuation or decreased LOC are present.

NOTE

Anything that can cause delirium can cause agitation.

CLINICAL PEARL

5 mg of haloperidol and 2 mg of lorazepam are often given together in emergency situations.

Suicide

Approach to the suicide assessment

- Suicide should be screened for in every encounter → part of risk assessment along with violent/homicidal ideation → ask every patient, “Have you had any thoughts of wanting to harm or kill yourself?”
- Classify **ideation**:
 - Passive ideation: considers suicide, e.g. “I think about killing myself”.
 - Active ideation: active plan or intent for suicide, e.g. “I think about killing myself with a bottle of acetaminophen I just bought from the drugstore”.
- Assess **risk**:
 - Plan: “Do you have a plan as to how you would end your life?”
 - Intent: “Do you think you would actually carry out this plan? If not, why not?”
 - Past attempts: highest risk if previous attempt within the past year → ask about lethality, outcome, medical intervention.
- Assess **suicidal ideation**:
 - Onset and frequency of thoughts: “When did you start having these thoughts? How often do you have them?”
 - Control over suicidal ideation: “How do you cope with these thoughts?”
 - Intention: “Do you want to end your life?”
 - Intended lethality: “What do you think would happen if you took those pills?”
 - Access to means: “How will you get a gun?”
 - Time and place: “Have you picked a time and location? Is it isolated?”
 - Provocative factors: “What makes you feel worse?”
 - Protective factors: “What keeps you alive?”
 - Final arrangements: “Have you written a will? Given away your belongings?”
 - Practiced suicide or aborted attempts: “Have you ever put the gun to your head? Stood at the bridge?”
 - Ambivalence: “I wonder if there is a part of you that wants to live, given that you came here for help?”

IMPORTANT

ALWAYS ask about **access to firearms** when completing a safety assessment.

Assessment of suicide attempts

- Setting (isolated vs. presence of others/chance of discovery).
- Planned vs. impulsive attempt, stressors/triggers.
- Substance use/intoxication at time of attempt.
- Medical attention (brought in by other person vs. brought in by self to ED).
- Time lag from suicide attempt to ED arrival.
- Expectation of lethality at time of attempt.
- Reaction to survival (guilt/remorse vs. disappointment).

Epidemiology

- Suicide is a rare event (10-12 / 100,000).
- Attempted:completed = 20:1.
- M:F = 1:4 for attempts, 3:1 for completed.

Risk factors

Epidemiological factors

- Age: increases after age 14, highest rate of completion in persons >65 years.
- Sex: male.
- Race: white or Indigenous.
- Marital status: widowed/divorced.
- Living situation: alone, no children < 18 years in the household.
- Other: stressful life events, access to firearms.

Psychiatric disorders

- Mood disorders (15% lifetime risk in depression, higher in bipolar disorder)
- Anxiety disorders (especially panic disorder)
- Schizophrenia (10-15% risk)
- Substance abuse (especially alcohol - 15% lifetime risk)
- Eating disorders (5% lifetime risk)
- Adjustment disorder
- Conduct disorder
- Personality disorders (borderline, antisocial)

FYI

The **SAD PERSONS screening tool** is useful for assessing risk factors associated with suicide, though clinical assessment is still the gold standard.

- **S**ex (male)
- **A**ge (>60)
- **D**epression
- **P**revious attempts
- **E**thanol abuse
- Loss of **R**ational thinking (delusions, hallucinations, hopelessness)
- **S**uicide in family
- **O**rganized plan
- **N**o spouse (lack of social supports)
- **S**erious illness, intractable pain

CLINICAL PEARL

The most common psychiatric disorders associated with suicide are mood disorders and alcohol use disorder.

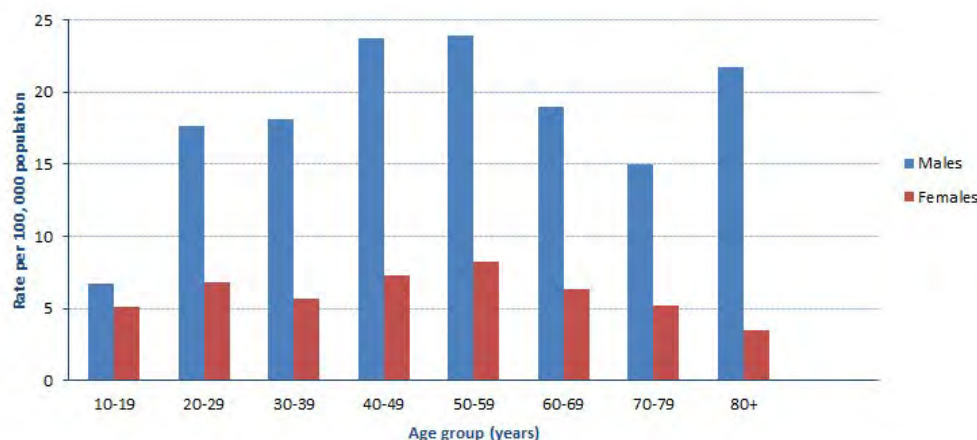


Figure 1. Death rates of suicide per 100,000 population in 2016 (by age and sex). Risk factors for suicide include male sex and age greater than 60.

Figure taken from Government of Canada: Suicide in Canada - Key Statistics (Infographic).

Past history

- Prior suicide attempt.
- Family history of suicide attempt/completion.

CLINICAL PEARL

The best predictor of suicide risk is a history of attempted suicide.

Management

- Proper documentation of clinical encounter and rationale for management is essential.
- **Higher risk** (hospitalization needs to be strongly considered):
 - Patients with plan/intent, access to means, recent social stressors and symptoms suggestive of psychiatric disorder.
 - If patient refused to be admitted, complete Form 1.
- **Lower risk:**
 - Patients who are not actively suicidal, no plan or access to lethal means.
 - Discuss protective factors, remind them of what they live for, promote coping skills that helped them through past crises.
 - Protective factors: good support network, stable home life, future orientation, motivation to engage in treatment, relief at surviving past suicide attempts.
 - Collaborate with patient on a safety plan including:
 - Distress tolerance or emotion regulation coping strategies that are effective for patient (i.e., grounding, focused breathing,

distraction etc.).

- Contact a friend or family member if feeling unsafe.
- Contact local crisis line or mobile crisis unit if in crisis.
- **Depression:** consider hospitalization if severe symptoms or psychotic features present.
- **Alcohol-related:** usually resolves with abstinence within a few days.
- **Personality disorders:** crisis interventions, hospitalizations are typically short-term for crisis stabilization.
- **Psychosis:** hospitalization may be necessary.
- **Self-harm:** long-term psychotherapy with brief crisis intervention when necessary. Dialectical behavioral therapy (DBT) has the best evidence in this population.

Discharge

- Make sure to arrange appropriate follow-up and make the necessary referrals.
- Try to offer patients and families something tangible and concrete to take with them → source of reassurance and validation
 - Prescription
 - Appointment date/time
 - List of resources (see next page for resources in Ottawa)
 - Outpatient referral form
- Try to manage the expectations of patients and their families → reach a collaborative decision regarding disposition.

Frequently-Used Mental Health Resources in Ottawa

General Mental Health

- [Mental Health Crisis Line](#)
 - Phone: 613-722-6914 in Ottawa;
1-866-996-0991 outside Ottawa
- **The Ottawa Hospital Mobile Crisis Team**
 - Follow-up Crisis Beds
- **Urgent Consultation Clinic (UCC)**
- **CMHA/ FSO Quick Access to Brief Counselling**
 - Phone: 613-822-6135
 - Fax: 613-737-4628
- **Walk-in Counselling Resources**
 - St. Paul's University
 - Catholic Family Services
 - Jewish Family Services
- **Day Hospital Program**
 - Intensive Full Day Stream
 - Transitional Skills Stream

Patient-Information/Self-Help

- [eMental Health](#)
- [Big White Wall](#)
 - Anonymous peer online support, online modules
- [Bounce Back](#)
 - Telephone coaching and workbooks, self-help videos
 - Phone: 1-866-345-0224
 - Fax: 1-905-430-1768
- [MoodGym](#)
 - Interactive self-help book for depression and anxiety

Addiction Resources

- [Quit Smoking Program at the Ottawa Heart Institute](#)
 - Room H2353
 - Tel: 613-761-5464
- **Ottawa Addictions Access & Referral Services (OAARS)**
 - 338 Montreal Road, suite 101, K1L 6B3
 - Phone: 613-241-5202
 - Fax: 613-241-5232
- **Alcohol Medical Intervention Clinic (AMIC)**
 - Monday to Friday, 8-11AM at the Royal Ottawa Mental Health Centre, Room 2141
- **Alcoholics Anonymous**
 - Al-anon family groups
- **Narcotics Anonymous**
 - Nar-anon family groups
- **Ontario Network for Borderline Personality Disorder**
 - Email: intake@on-bpd.ca

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Review Questions

1. Of the psychiatric disorders listed below, which one has the highest lifetime risk for completed suicide?
 - a) Schizophrenia
 - b) Alcohol use disorder
 - c) Eating Disorder
 - d) Borderline Personality Disorder

2. What type of withdrawal syndrome is potentially fatal?
 - a) Anticholinergic withdrawal
 - b) Benzodiazepine withdrawal
 - c) Cannabis withdrawal
 - d) Opioid withdrawal

3. An agitated 20 yo male presents in the ED with minimal history. Your resident asks what chemical sedation we should try. Which one should you AVOID?
 - a) Haloperidol 5mg + lorazepam 2mg IM
 - b) Loxapine 10mg IM
 - c) Olanzapine 5mg + lorazepam 2mg PO
 - d) Olanzapine 5mg + lorazepam 2mg IM

Answers:
1. b)
2. b)
3. d)

Psychopharmacology

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Antipsychotics

The dopamine receptors and pathways

There are 5 types of dopamine (DA) receptors: D1 and D5 are excitatory, while D2, D3, and D4 are inhibitory at the postsynaptic terminal. D2 and D3 may also be present in the presynaptic terminal as autoreceptors that regulate DA secretion. Most DA receptors in the cortex are D1. Most striatal DA receptors are D2.

There are 5 known major DA pathways in the brain:

- The **tuberoinfundibular** (hypothalamus to anterior pituitary) inhibits prolactin release.
- The **thalamic** (multiple sites to the thalamus), the functions of which remain unknown but maybe involved in sleep and arousal.
- The **nigrostriatal** (substantia nigra or SN in brain stem to the dorsal striatum in two pathways: direct to the globus pallidus interna activating D1 receptors, and indirect to the globus pallidus externa activating D2 receptors then via the subthalamic nucleus to the globus pallidus externa. From there, the pathway connects to the thalamus, then to the cortex – the cortico-striato-thalamo-cortical loop), through which DA stimulates motor movements.
 - A less well-understood subpathway of projections from the medial aspects of SN to the intermediate associative striatum is now thought to possibly play an important role in mediating positive symptoms of schizophrenia and therefore may have a role in regulating emotions and behavior.
- The **mesolimbic** (the midbrain ventral tegmental area or VTA to the nucleus accumbens in the ventral striatum which is part of the limbic system), through which DA release plays a role in motivation, pleasure and maybe the final common pathway for all reward and reinforcement.
 - Excessive DA activity in this pathway was hypothetically linked to positive symptoms of psychosis in the classic DA hypothesis. This hypothesis is being updated with the role of the nigrostriatal pathway described above and is referred to as the “integrative hub mesostriatal hyperdopaminergia” concept, in which the mesostriatal pathway refers to as a combination of the nigrostriatal and

mesolimbic pathways.

- Reduced DA activity in the mesolimbic pathway has been hypothetically linked to anhedonia, apathy and lack of energy. Presynaptic D3 autoreceptors in the VTA function as inhibitors of DA release.
- The **mesocortical** (midbrain VTA to dorsolateral and ventromedial parts of the prefrontal cortex (PFC)), through which the dorsolateral branch is thought to regulate cognition and executive functions, while the ventromedial branch is thought to regulate emotions and affect.
 - Reduced DA activity in this pathway is hypothetically linked to the cognitive and negative symptoms of schizophrenia.

Glutamatergic pyramidal neurons in the PFC regulate the activity of DA pathways via direct (stimulating) and indirect (inhibiting) projections.

Conventional antipsychotics

Antipsychotic drugs are also referred to as “neuroleptic” drugs, or drugs that induce neuroleptosis: slowness or absence of movements and behavioral indifference in experimental animals.

Conventional antipsychotics exert their effects through antagonism at the D2 receptor:

- D2 receptor blockade in the mesolimbic/mesostriatal pathway is able to attenuate the positive symptoms of psychosis, such as delusions, hallucinations and agitated behavior. For most antipsychotics, 60 to 80% D2 receptor occupancy in the mesolimbic pathway is needed for antipsychotic effect
- D2 receptor blockade in the mesolimbic pathway may cause drug-induced (secondary) negative symptoms of apathy, anhedonia and lack of motivation, or cause worsening of negative symptoms of schizophrenia
- D2 receptor blockade in the mesocortical pathway may cause worsening of cognitive and affective symptoms of schizophrenia
- D2 receptor blockade in the dorsal striatum (indirect nigrostriatal pathway) can cause drug-induced parkinsonism (muscular rigidity, tremor and/or bradykinesia), dystonia and akathisia – also known collectively as extrapyramidal symptoms (EPS)
 - Tardive dyskinesia (TD), a syndrome of abnormal hyperkinetic movements, can be produced with chronic blockade of D2 receptors in the dorsal striatum (nigrostriatal pathway) and is hypothesized to be secondary to the development of DA supersensitivity by upregulation of D2 receptors in the indirect nigrostriatal pathway

FYI

The first antipsychotic medications to be discovered were termed conventional antipsychotics, and can also be called typical, classical or first-generation antipsychotics.

- 5% of patients maintained on conventional antipsychotics (agents having little or no concurrent serotonin receptor action) will develop tardive dyskinesia every year
- Neuroleptic Malignant Syndrome can rarely occur with blockade of D2 receptors in the nigrostriatal pathway and is potentially fatal
- D2 receptor blockade in the pituitary (tuberoinfundibular pathway) can cause hyperprolactinemia

Conventional antipsychotics can also act at other receptors:

- Antagonism of muscarinic M1 receptors causes peripheral side effects including dry mouth, blurred vision, urinary retention and constipation, and central side effects such as cognitive dysfunction including problems with memory, concentration and slowing of cognitive processing
 - Conventional antipsychotics that cause fewer EPS tend to have stronger anticholinergic properties
 - DA inhibits acetylcholine (ACh) release from postsynaptic nigrostriatal cholinergic neurons. This then reduces the activity of GABAergic inhibitory neurons that would have resulted in inhibition of movement
 - When DA is inhibited by an antipsychotic, ACh becomes overly active, allowing inhibition of movement. This is associated with EPS
 - Antagonism of M1 receptors when D2 receptors are blocked can restore some of the DA/ACh balance in the nigrostriatal pathway, therefore reducing the inhibition of movement and reducing EPS.
- Antagonism of histamine H1 receptors can cause weight gain and sedation
- Antagonism of alpha1 adrenergic receptors causing norepinephrine (NE) blockade can cause sedation as well as cardiovascular side effects including orthostatic hypotension
 - The cortical arousal pathways involve ACh, histamine and NE. Given that many antipsychotics block these neurotransmitters, sedation is a powerful result.

NOTE

Antagonism of M1 receptors does not protect from or reduce akathisia.

Different conventional antipsychotics will have different binding properties and thus different side-effect profiles.

- Chlorpromazine has strong anticholinergic and antihistaminic activity while haloperidol comparatively does not.
- Historically conventional antipsychotics have been classified as “low potency” or “high potency”

- Low-potency antipsychotics (e.g., chlorpromazine) tend to have stronger anticholinergic, antihistaminic, and anti-alpha 1 adrenergic properties, while high-potency antipsychotics (e.g., haloperidol) have fewer sedating and anticholinergic side-effects but higher propensity for drug-induced parkinsonism.

Atypical antipsychotics

Atypical antipsychotics are named as such due to their clinical properties which differ from conventional antipsychotics.

- These drugs may be referred to as 5HT_{2A}/D₂ antagonists and are also known as second-generation antipsychotics. The 5HT_{2A} antagonism is the main property distinguishing conventional antipsychotics from atypical one.
- Atypical antipsychotics have approximately equal action to conventional antipsychotics in treating positive symptoms but with less incidence of EPS and hyperprolactinemia and fewer secondary affective symptoms
 - These drugs are also associated with significantly lower incidence of TD.

In addition to acting as D₂ receptor antagonists, atypical antipsychotic can have other pharmacologic properties:

1. Serotonin (5HT) receptors

- **5HT_{2A} receptors** are postsynaptic excitatory receptors.
 - 5HT_{2A} receptors are located on excitatory glutamatergic PFC neurons that directly innervate mesolimbic/mesostriatal DA neurons with activity resulting increase in DA release in this pathway, indirectly innervate (via inhibitory GABAergic interneurons) nigrostriatal DA neurons and indirectly innervate mesocortical DA neurons with a resulting decrease of DA release in these pathways.
 - 5HT_{2A} receptors are located in the pituitary lactotroph cells, and serotonergic activity at these receptors stimulates prolactin release (while these cells are inhibited from prolactin release by dopaminergic activity at their D₂ receptors).
 - Antagonism of 5HT_{2A} receptors theoretically decreases EPS and hyperprolactinemia as well as contributes to reduction of positive and negative symptoms of psychosis
 - 5HT_{2A} receptor antagonism will contribute antipsychotic effects on positive symptoms of psychosis by reducing downstream DA release in the mesolimbic/mesostriatal pathway

- 5HT_{2A} receptor antagonism will contribute antipsychotic effects on negative, affective and cognitive symptoms of psychosis and/or minimize secondary drug-induced negative and cognitive symptoms by stimulating downstream DA release in the mesocortical pathway
 - ▶ In practice, this effect is not consistent across all atypical antipsychotics, in some cases due to differences in potency of this effect and in others due to counteracting anticholinergic and antihistaminergic effects
 - 5HT_{2A} receptor antagonism stimulates downstream DA release in the nigrostriatal pathway
 - ▶ This serves to counteract the blockade from D₂ receptor antagonism that is responsible for EPS
 - 5HT_{2A} receptor antagonism also inhibits release of prolactin
 - ▶ This serves to counteract the effect of D₂ receptor antagonism to stimulate prolactin release
 - ▶ In clinical practice different atypical antipsychotics will reduce secretion of prolactin to different degrees, with some having no effect
- **5HT_{1A} receptors** can be presynaptic or postsynaptic, the latter are inhibitory and are present along with 5HT_{2A} on glutamatergic PFC neurons regulating nigrostriatal and mesocortical pathways
 - Partial agonism (intermediate signal response between full agonism and antagonism, effectively resulting in incomplete agonism) of 5HT_{1A} receptors theoretically decreases EPS through stimulating DA release in the nigrostriatal pathway
 - Partial agonism of 5HT_{1A} receptors is associated with antidepressant effects and reduced negative, cognitive and affective symptoms of psychosis through stimulating release of DA in the mesocortical pathway
- **5HT_{2C} receptors** are located in the PFC and the midbrain raphe, and are involved in regulating the release of DA and NE (they are also present in the suprachiasmatic nucleus (SCN) of the hypothalamus and involved in circadian rhythm regulation).
 - Antagonism of 5HT_{2C} receptors can have antidepressant and pro-cognitive functions through stimulating DA and NE release in the prefrontal cortex
- **5HT₇ receptors** are excitatory receptors found on GABAergic inhibitory interneurons that in turn function to inhibit serotonergic neurons in the raphe (with 5HT₇ activation resulting in an autoinhibition of serotonin release) and glutamatergic neurons in the PFC that stimulate downstream monoamine neurotransmitters

(with 5HT₇ activation resulting in indirect reduction of monoamine, including serotonin, release)

- 5HT₇ receptor antagonism can have antidepressant and pro-cognitive properties through disinhibiting release of serotonin
- **5HT₃ receptors** are excitatory receptors found on GABAergic inhibitory interneurons that in turn function to inhibit glutamate, ACh and NE neurons
 - 5HT₃ receptor antagonism is a disinhibitor of glutamate, ACh and NE, with resulting antidepressant action.

2. Alpha-adrenergic properties

- Some atypical antipsychotics have alpha₂-adrenergic antagonism properties, which may contribute to antidepressant effects as this receptor is often a presynaptic autoreceptor that reduces the release of NE and blocking it disinhibits NE release, such as in the raphe and the PFC.

3. D₂ receptor partial agonism

- Some atypical antipsychotics have partial agonist, rather than antagonist, action at D₂ receptors
- Partial agonism of D₂ receptors results in an intermediate signal response between full agonism and antagonism, effectively resulting in incomplete antagonism
 - Only a small amount of signal transduction is needed to reduce the likelihood of EPS, and thus partial agonism can treat positive symptoms of psychosis while reducing incidence of EPS

4. Metabolic side effects

- Metabolic side effects (weight gain and risk of obesity, dyslipidemia, and hyperglycemia/diabetes mellitus) are common with many atypical antipsychotics.
 - Some of these effects are mediated directly via increased appetite and weight gain resulting from antagonism at H₁ and 5HT_{2C} receptors
 - Another, yet unknown mechanism appears to be involved and through which insulin resistance and levels of fasting triglycerides are increased
 - Commonly used atypical antipsychotics with:
 - High metabolic risk include clozapine and olanzapine;
 - Moderate metabolic risk include risperidone, paliperidone, quetiapine and asenapine; and

- Low metabolic risk include ziprasidone, lurasidone and aripiprazole

Prescribing

- The choice of antipsychotic should be based on:
 - Previous response to antipsychotics
 - Side effect profile
 - Medical history
 - Concerns regarding compliance (for which long-acting injectable may be preferred)
 - Response, treatment resistance
- Starting with an atypical antipsychotic is recommended
- Patients should remain on antipsychotics for at least 18 months following a first episode of psychosis
- Patients should remain on antipsychotics for at least 2-5 years following resolution of positive symptoms if they have had multiple episodes of psychosis, and should likely continue indefinitely
- If a patient has failed two adequate trials (one trial being 6 weeks on adequate therapeutic dose) of antipsychotics, clozapine is recommended
 - Patients prescribed clozapine require regular monitoring due to risk of agranulocytosis and neutropenia
 - WBC and absolute neutrophil counts (ANC) should be repeated weekly for the first 26 weeks of clozapine therapy
 - If these remain acceptable ($\text{WBC} \geq 3500/\text{mm}^3$ and $\text{ANC} \geq 2000$), then WBC can be monitored once every 4 weeks
 - Clozapine is highly anticholinergic and thus has very low incidence of EPS
 - Sialorrhea and constipation are common side-effects
 - Sialorrhea can be treated with local muscarinic receptor antagonists including atropine and ipratropium

	Risperidone	Olanzapine	Quetiapine	Ziprasidone
Indication	Schizophrenia, acute mania, bipolar maintenance, and autism-related irritability in children.	Schizophrenia, acute mania, bipolar maintenance, and acute agitation associated with schizophrenia.	Schizophrenia, acute mania, bipolar maintenance, bipolar depression, and major depression.	Schizophrenia, acute mania, mixed mania, bipolar maintenance, and acute agitation in schizophrenia.
Mechanism of action	- Primarily acts as a D2 and 5HT2A receptor antagonist. 5HT7 antagonism may have antidepressant effects.	- Primarily acts as a D2 and 5HT2A receptor antagonist. 5HT2C antagonism may have antidepressant and pro-cognitive effects.	- Primarily acts as a D2 and 5HT2A receptor antagonist 5HT1A partial agonism (especially at moderate dosages), 5HT2C antagonism, 5HT7 antagonism and NE reuptake blockade may have antidepressant effects.	- Primarily acts as a D2 and 5HT2A receptor antagonist 5HT2C and 5HT7 antagonism with 5HT1A partial agonism may have antidepressant and pro-cognitive effects
Starting dose	Oral: 0.5-1 mg/day	5-10 mg/day	25-50 mg BID (increase by 25-50 mg BID each day)	20-60 mg BID with 500 calories
Target dose	Oral: 2-8 mg/day IM: 25-75 mg q2weeks	10-20 mg/day	600-800 mg/day for schizophrenia and mania. 300mg/day for depression.	40-200 mg/day
Special Notes	- Often preferred treatment for dementia with aggressive features or children with behavioural disturbances - Moderate metabolic risk - May have more sedation and weight gain in pediatric populations - Hyperprolactinemia is a common side effect	- Demonstrates greater effectiveness at moderately high dose compared to other antipsychotics at moderate doses - High potential for metabolic side effects	- Preferred antipsychotic for psychosis in Parkinson's disease and Lewy body dementia - Very little EPS or hyperprolactinemia - Potent sedative-hypnotic at low dosages due to potent H1 antagonism - Moderate metabolic risk	- Less weight gain and low risk of metabolic syndrome than most antipsychotics - Maybe activating at low dosages. Akathisia is common - Requires being taken with food for optimal bioavailability - Potential for QTc prolongation somewhat higher than other antipsychotics - Association with a rare serious skin condition known as Drug Reaction with Eosinophilia (DRESS)

(continued on next page)

	Paliperidone	Aripiprazole	Clozapine
Indication	Schizophrenia and schizoaffective disorder.	Schizophrenia, acute mania, mixed mania, bipolar maintenance, autism-related irritability in children, Tourette's disorder in children, and as an adjunct for depression.	Treatment-resistant schizophrenia.
Mechanism of action	- Primarily acts as a D2 and 5HT2A receptor antagonist. 5HT7 antagonism may have antidepressant effects.	- Primarily acts as a D2 partial agonist. - Partial agonism of 5HT1A receptors may have antidepressant effects. In addition, it has 5HT2A, 5HT2C and 5HT7 antagonism and lacks H1 and M1 antagonism.	- Primarily acts as a D2 and 5HT2A receptor antagonist. 5HT2C antagonism and 5HT1A partial agonism may have antidepressant and pro-cognitive effects.
Starting dose	Oral: 3-6 mg/day	10-15 mg/day for schizophrenia and mania 2-5 mg/day for other indications	25 mg, increase by 25-50 mg/day every 2-3 days as tolerated
Target dose	Oral: 6-12 mg/day IM (Sustenna): 75-150 mg q4weeks IM (Trinza): 175-525 mg q2weeks	15-30 mg/day (schizophrenia/mania) 2-10 mg/day (augmenting antidepressants) 5-15 mg/day (autism) 5-20 mg/day (Tourette's)	Target trough plasma level of at least 350 ng/mL
Special Notes	- Active metabolite of risperidone - Moderate metabolic risk - Hyperprolactinemia is a common side effect	- Less weight gain and low risk of metabolic syndrome than most antipsychotics - Less sedation than most antipsychotics, and can even be activating. Akathisia is common - Does not cause hyperprolactinemia	- Gold standard for refractory schizophrenia - All patients on clozapine must have regular monitoring bloodwork due to risk of agranulocytosis. WBC and ANC should be measured weekly for 6 months then monthly. - Baseline and weekly troponin and c-reactive protein are also recommended for the first 4-6 weeks due to rare risk of myocarditis. Annual ECG is recommended due to rare late-onset cardiomyopathy. - Higher metabolic risk than most antipsychotics - Lowers the risk of suicide in schizophrenia

Table 1. Summary table of commonly prescribed atypical antipsychotics.

Mood Stabilizers

General prescribing guidelines

(*See [Management section in Bipolar Disorders](#) chapter for further prescribing guidelines based on CANMAT 2018 recommendations.)

- Used as first-line monotherapy or in conjunction with atypical antipsychotics for acute episodes of depression and/or mania, or for long-term stabilization.
- Note that the label “mood stabilizer” is misleading. These medications vary in their ability to “treat” (reduce symptoms acutely) vs. “stabilize” (prevent relapse and recurrence) manic and/or depressive symptoms. These medications are often used in combination to achieve the desired outcome.
- Before initiating, get baseline: CBC with diff and platelets, ECG (if patient > 45 years old or cardiovascular risk factors), BUN, Creatinine, electrolytes and TSH.
- Screen for: pregnancy, thyroid disease, neurological, renal, liver, cardiovascular diseases.
- May take up to 2-4 weeks to exert full effect, may require acute coverage with benzodiazepines or antipsychotics.

Lithium

- Lithium is considered the “classic” mood stabilizer and has been used to treat bipolar disorder for more than 50 years.
- Lithium is an ion with an uncertain mechanism of action: candidates for its mechanism of action are various signal transduction sites beyond neurotransmitter receptors (i.e., the phosphatidyl inositol system, G protein modulation and regulation of gene expression for neuronal growth and plasticity factors via inhibition of GSK-3 and protein kinase-C).
- Proven effective in treating acute manic episodes and in maintenance of recurrence, especially for manic episodes and perhaps to a lesser extent for depressive episodes.
- It is used in the treatment of bipolar depression and as an augmenting agent in unipolar depression.

NOTE

Lithium has been shown to lower the risk of suicide in patients with mood disorders.

Anticonvulsants

A number of anticonvulsant medications have proven to be effective in treating mood disorders.

FYI

Anticonvulsants are also known as “antiepileptic drugs”.

- Ion channels
 - Ion channels are targets for many CNS-active drugs
 - There are 2 major categories of ion channels:
 - Ligand-gated ion channels, which are also receptors and maybe called ionotropic receptors (e.g. GABAA receptors, nicotinic cholinergic receptors and 5HT3 receptors)
 - Voltage-sensitive (or voltage-gated) ion channels, which open and close by voltage charge across the membrane.
 - Many anticonvulsants bind various sites on voltage-sensitive ion channels, which might contribute to the mechanism of their action as antiepileptic drugs and mood stabilizers.
- Valproic acid
 - Exact mechanism of action is unknown, various hypotheses exist, including: inhibition of voltage-sensitive sodium channels (VSSCs), potentiating GABA activity and regulating downstream signal transduction cascades (e.g. inhibiting GSK-3, activating BCL2).
 - Valproate is proven effective for the acute manic phase of bipolar disorder and is commonly used to prevent recurrence of mania (although this effect has not been as well established as its effect on acute mania).
 - Antidepressant actions of Valproate have not been well established.
 - Lower therapeutic doses of Valproate can be used in combination with other mood stabilizers such as Lithium to improve tolerability and compliance.
- Lamotrigine
 - Mechanism of action: inhibits VSSCs and is thought to reduce release of glutamate.
 - Lamotrigine is approved as a mood stabilizer to prevent recurrence of both mania and depression.
 - Often used as first-line treatment for bipolar depression.
 - Not indicated in acute mania → lamotrigine requires a slow up-titration due to the risk of life-threatening Stevens-Johnson syndrome (toxic epidermal necrolysis) and therefore cannot be used to treat an acute manic episode.

Atypical antipsychotics

- Several atypical antipsychotics have been found to have mood-stabilizing properties and are indicated as first-line treatments for bipolar mania, depression as well as maintenance phases.
 - Notable examples: quetiapine, aripiprazole, paliperidone and asenapine.
- **See chapter on [Bipolar Disorders](#) for further information on indications for these medications in bipolar disorder.*
- **See the [Antipsychotics section](#) of this chapter for further information on prescribing of these medications.*

	Lithium	Valproic acid (Epival)	Lamotrigine (Lamictal)
Indications	Acute mania, depression, maintenance	Acute mania, maintenance	Depression, maintenance
Initial workup and ongoing monitoring	- CBC - Electrolytes, urea, creatinine - TSH - ECG - Serum level q5d until steady state, then at 3-6mos or with signs of dehydration or toxicity - Kidney function, TSH, and ECG q6-12mos	- CBC - Liver enzymes - Serum level weekly until steady state - Repeat tests q1mo x 6 mos, then q6mos or if symptoms	
Dosing	- Adults: 600-1500 mg/day; serum level 0.5-1.2 - Geriatric: 150-600 mg/day; serum level 0.4-0.8 Serum level is ▲ by: - NSAIDs - Thiazides - ACEi - Tetracyclines - Anticonvulsants Serum level is ▼ by: - Osmotic diuretics (mannitol) - Carbonic anhydrase inhibitors - Caffeine - High salt	Starting dose: 250 mg qhs (geriatrics) 250 mg bid-tid (adults) Dose range: 750-3000 mg/day, split into bid dosing Serum levels: 350-700 umol/L	Start at 25 mg/day, increase q2wks by 25-50 mg Usual maintenance dose: 100-200 mg, up to 500 mg, split into bid dosing
Side effects (drug levels within normal range)	- Lethargy - Insipidus (diabetes) - Tremor/Teratogen (increased risk of Ebstein's anomaly in 1st trimester, 0.1% vs. 0.005%) - Hypothyroid (5%) - Increased weight, increased WBC (transient) - Vomiting, GI upset - Miscellaneous: ECG changes (bradycardia, T-wave flattening or inversion; contraindicated in sick sinus syndrome), acne, rashes, alopecia	Acute: - Sedation (31%) - Tremor (10-30%) - Unsteadiness - Nausea, GI upset (20%) Longer term: - Appearance - Acne - Alopecia - Rashes (incl. SJS*) - Weight gain - Systemic - Blood dyscrasias – thrombocytopenia, anemia, agranulocytosis, coagulopathies - Liver dysfunction +/- elevated ammonia - Reproductive – menstrual irregularities, PCOS, teratogenicity	- Rash (incl. SJS) - Activation (3-8%) - Ataxia - Sedation and cognitive slowing - Sleep disturbances - Headache - Hypersensitivity reaction
Toxicity (drug levels exceeding normal range)	(Lithium >1.2 mEq/L) - Early: GI distress, hand tremor, fatigue, thirst, headache, impaired concentration - Late: ataxia, stupor, myoclonic jerks, hyperreflexia, seizure - Can lead to irreversible neurotoxicity including cognitive impairment, cerebellar dysfunction, peripheral neuropathy - Hospitalize for levels >2.0 or based on clinical symptoms		

Table 2. Summary table for commonly used mood stabilizers in bipolar disorders (same as Table 4 in the Bipolar Disorders chapter). PCOS: polycystic ovarian syndrome; SJS: Stevens-Johnson Syndrome

Anxiolytics

- Anxiolytics are defined as medications that reduce anxiety through acting on GABA, serotonin, or norepinephrine neurotransmitters.
- Numerous neurotransmitters contribute to regulating circuits underlying the anxiety disorders, but the main ones on which anxiolytics act are GABA, serotonin, or norepinephrine neurotransmitters.
 - There is substantial overlap between the circuits involved in regulating mood and affect (involved in depression) and those involved in generating fears and worries (involved in anxiety disorders).
 - The amygdala, with its extensive connectivity to areas such as the hypothalamus (endocrine output of fear), parabrachial nucleus (breathing output of fear), anterior cingulate gyrus and orbitofrontal cortex (affect of fear), periaquiductal gray of the brainstem (motor responses to fear, including avoidance), and the hippocampus (internal, memory and trauma-related induction of fear) has a central role in autonomic and affective aspects of anxiety disorders.
 - CSTC (cortico-striato-thalamo-cortical) circuits have major roles in the cognitive aspects of anxiety disorders such as generation of worries, apprehensive expectations, obsessions and catastrophic thinking.
 - GABAA receptors are ligand-gated chloride channels.
 - GABAergic action inhibits postsynaptic excitatory glutamatergic activity in both the amygdala and CSTC loop. Serotonergic neuronal activity inhibits activity in the CSTC loop and some amygdalar outputs. Noradrenergic activity activates both amygdalar and CSTC neurotransmission.
- First-line pharmaceutical treatment for generalized anxiety disorder, social anxiety disorder, panic disorder, and OCD is SSRIs/SNRIs.

CLINICAL PEARL

The most appropriate first-line treatments for both mild anxiety and insomnia include counseling, cognitive behavioural therapy, sleep hygiene, and self-help strategies.

NOTE

The anticonvulsants gabapentin and pregabalin, both of which are ligands acting on the voltage-sensitive calcium channels (VSCCs) resulting in reduced excitatory glutamate neurotransmission, are sometimes used as anxiolytics.

They do, however, have some potential for abuse.

Benzodiazepines

- General uses:
 - Panic disorder, insomnia, acute management of some causes of agitation, seizure disorder, alcohol withdrawal syndrome, induction of general anesthesia, procedural sedation.
- Mechanism of action:
 - Benzodiazepines potentiate binding of GABA to its postsynaptic (benzodiazepine-sensitive) GABAA receptors by positive allosteric modulation of the receptors. This enhances effects of phasic GABA

neurotransmission. Since GABAergic neurons generally act as inhibitory neurons, this causes decreased postsynaptic neuronal activity in a wide range of sites and neuronal circuits in the brain. The anxiolytic action of benzodiazepines is hypothetically linked to GABAA receptors within the amygdala and interneurons in the CSTC loop. The hypnotic action involves GABAergic projections from the ventrolateral preoptic nucleus (VLPO) of the hypothalamus to wake-promoting brain regions.

- Adverse effects:
 - Drowsiness, dizziness, slurred speech, memory problems, constipation, memory problems, physical dependency, risk of falls, decreased respiratory drive, etc.
- General guidelines:
 - Should be prescribed at the lowest possible dose and used for limited periods of time (2-4 weeks) to avoid tolerance and dependence.
 - Avoid taking with alcohol due to sedating effect.
 - Avoid prescribing as first-line agent for patients with generalized anxiety disorder.
 - Prescribing should be exercised with extreme caution in patients with concomitant substance use disorders.
 - Not appropriate for the treatment of short-term mild anxiety.
 - Exercise caution when prescribing with the extremes of age; may cause paradoxical effects in children. The only safe one in the elderly is Lorazepam because it bypasses the liver.
 - If prescribing for short-term insomnia, use intermittently for <1 week.
 - Patients with long-term use of benzodiazepines should be informed of negative effects and benefits of stopping (increased cognition and psychomotor functioning).

CLINICAL PEARL

Patients should be regularly offered to wean off benzodiazepines.

A slow, gradual taper is the most effective approach and reduces severity of withdrawal symptoms.

Azapirones (e.g. buspirone)

- Uses:
 - Generalized anxiety disorder. Can be used as adjunct treatment for social anxiety and depression,
- Mechanism of action:
 - Affects the serotonergic system via partial agonism at both presynaptic 5HT1A autoreceptors and postsynaptic 5HT1A receptors, resulting in enhanced serotonergic output. However, its action, which is delayed, is likely the result of adaptive neuronal and receptor events, rather than immediate change in serotonin release.

- Offers similar efficacy to benzodiazepines without the risk of dependence.
 - May be preferred over benzodiazepines because non-sedating, has no interaction with alcohol, and not prone to abuse.
- Onset of action is 2-4 weeks (similar to antidepressants).
- Adverse effects: dizziness, drowsiness, nausea, headache, nervousness, EPS.

Cyclopyrrolones (e.g. zopiclone)

- Uses:
 - Insomnia
- Mechanism of action:
 - Increases transmission of GABA in the CNS via positive allosteric modulation of benzodiazepine-sensitive GABAA receptors.
- May be preferred over benzodiazepines, because not as likely to cause dependency.
- Adverse effects:
 - Palpitations, bitter taste, confusion, daytime sedation, depression, dizziness, drowsiness, dysgeusia, euphoria, hypotonia, intoxicated feeling, memory impairment, nervousness, speech disturbance, diaphoresis, anorexia, constipation, increased appetite, sialorrhea, xerostomia, etc.
- Onset of action is typically within 1 hour.

FYI

Zopiclone - along with zaleplon, zolpidem, etc.
- are sometimes referred to as the "Z drugs", often used in the treatment of insomnia.

Class	Drug	Dose range (mg/d)	Half-life	Appropriate use
Long-acting	Clonazepam (Rivotril)	0.25-4	18-50	Seizure prevention, akathisia, generalized anxiety disorder, panic disorder. Adjunctive use in acute agitation of mania and psychosis, catatonia
	Diazepam (Valium)	2-40	30-100	Seizure prevention, muscle relaxant, alcohol withdrawal, generalized anxiety disorder.
	Chlordiazepoxide (Librium)	5-300	30-100	Alcohol withdrawal.
Short-acting	Alprazolam (Xanax)	0.25-4.0	6-20	Should be avoided due to high dependency rate.
	Lorazepam (Ativan)	0.5-6.0	10-20	Alcohol withdrawal (no first-pass liver metabolism), akathisia, short-term sedation for anxiety during procedures (i.e. CT or MRI), generalized anxiety; sublingual or IM for rapid action. Initial treatment of seizure/status epilepticus. Adjunctive use in acute agitation of mania and psychosis, catatonia
	Oxazepam (Serax)	10-120	8-12	Alcohol withdrawal (no first-pass liver metabolism), generalized anxiety disorder.
	Triazolam (Halcion)	0.125-0.5	1.5-5	Shortest half-life, rapid sleep without daytime sedation (i.e. overnight plan travel), but risk of rebound insomnia).
Azapirone	Buspirone	10-60	2-3	Most commonly used for generalized anxiety disorder; can be used for adjunct treatment in social anxiety and depression.
Cyclopyrrolone	Zopiclone (Imovane)	3.75-7.5	5	Insomnia

Table 3. Summary table for commonly used anxiolytics.

Antidepressants

- Pharmacotherapy is often considered first-line for patients experiencing a moderate to severe major depressive episode (MDE).
- For mild MDE, first-line recommendations include psychoeducation and psychotherapy.
 - Pharmacologic management may be considered for patients with mild symptoms in some cases, such as patient preference, previous response to antidepressants, or poor response to non-pharmacologic treatment.
- *Note that the label “antidepressant” is misleading:
 - Medications that are called “antidepressants” are used to treat a wide range of disorders, including anxiety disorders, eating disorders, obsessive-compulsive disorder, traumatic disorders, and pain.
 - Not all drugs labelled as antidepressants are used to treat all forms of depression - for example, they may not be good choices for bipolar depression or depression with mixed features as most antidepressants have poor efficacy in these cases and can potentially contribute to long-term mood destabilization in bipolar disorder.
 - Many drugs that are not labelled as antidepressants (e.g., some antipsychotics) may be used to treat certain forms of depression.
- Most medications approved for the treatment of depression have efficacy limitations. Most clinical trials of drug treatment of depression aim for a treatment “response” rather than complete remission and maintenance of improvement beyond the early treatment phase.
 - Response is when symptoms are reduced by at least 50%. Patients are better but not necessarily well.
 - Remission is when symptoms are sufficiently reduced so that criteria for the diagnosis are no longer met. Patients are generally no longer symptomatic or have minimal symptoms and their functioning level is at or close to the premorbid baseline.
 - Relapse is when depression returns before there is a full remission or after a brief remission of only a few months.
 - Recurrence is when depression returns after a full recovery (e.g., a remission lasting more than 9 months).

CLINICAL PEARL

In practice, about one-third of patients with unipolar depression achieve remission with the first trial of a drug from this class of medications (at therapeutic dose for 12 weeks), and up to 4 different trials may be necessary to achieve remission in two-thirds of patients.

Classification

There are multiple classes of antidepressants with varying mechanisms of action:

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Norepinephrine-dopamine reuptake inhibitors (NDRIs)
- Serotonin antagonist and reuptake inhibitors (SARIs)
- Serotonin partial agonist reuptake inhibitors (SPARIs)
- Tricyclic antidepressants (TCAs)
 - Block reuptake of monoamine neurotransmitters into the presynaptic neurons by blockade of transporters (NET and SERT). Some have stronger action at SERT (e.g., clomipramine), while others are stronger at NET (e.g., desipramine, nortriptyline). TCAs also have antagonist action at 5HT_{2A} and 5HT_{2C} receptors. This class of antidepressants is infrequently prescribed for the treatment of depression presently.
- Noradrenergic and specific serotonergic antidepressants (NaSSAs),
 - Block presynaptic α_2 adrenergic receptors (which mediate the feedback inhibition of NE release and some 5HT release), leading to increased release of NE and subsequently secondary increase of 5HT into the synaptic cleft. There is also specific blockade of certain serotonin receptors such as 5HT_{2A}, 5HT_{2C} and 5HT₃.
- Monoamine oxidase inhibitors (MAOIs) and reversible inhibitors of monoamine oxidase-A (RIMAs)
 - Inhibit monoamine oxidase (irreversibly and reversibly, respectively), leading to decreased destruction of monoamine NTs. Some MAOIs have amphetamine-like properties. MAOIs are now rarely prescribed for the treatment of depression.
- Some antidepressants are in classes of their own. For example:
 - Agomelatine has agonist effects on melatonin (MT₁ & MT₂) receptors and antagonist effects at 5HT_{2C} receptors, and no effects on monoamine reuptake.
 - Vortioxetine has multiple modes of action - it inhibits SERT and has antagonist actions at 5HT₃ and 5HT₇ receptors with agonist action on 5HT_{1A} receptor and weak partial agonist action at 5HT_{1B/D} receptors.
 - Brexanolone is an intravenously administered neuroactive steroid (a formulation of allopregnanolone) used for the treatment of postpartum depression, and it appears to work via potentiation of GABA activity through allosteric neuroactive steroid binding sites on benzodiazepine-insensitive GABA_A receptors. It also acts on

benzodiazepine-sensitive receptors.

- The anesthetic ketamine (and its intranasally administered S-enantiomer, esketamine) likely exerts its rapid-onset antidepressant action (when subanesthetic doses are infused slowly) through antagonism of the NMDA subtype of glutamate receptors, but has actions at sigma-1 (σ_1) receptors as well as mu (μ) opioid and other neurotransmitter receptors. The full mechanism of antidepressant action is not yet fully understood.
- The first antidepressants to be used include TCAs and MAOIs. These classes are now recommended as second or third line due to their side effect burden and safety concerns such as lower threshold for overdose.
- Newer classes, including SSRIs, are often recommended as first-line agents. Please see Table 7 in the [Depressive Disorders chapter](#) for a summary of the CANMAT recommendations.
- The antipsychotic medications quetiapine, olanzapine and aripiprazole are often used as adjuvants in the management of treatment-resistant depression. Other drugs, such as lithium, buspirone and thyroid hormone are also used as adjuvants in these cases.
- The antipsychotics quetiapine, olanzapine (in combination with fluoxetine), and lurasidone and the anticonvulsant lamotrigine are often used in the treatment of bipolar depression. Lurasidone is also used in depression with mixed features.

Class	Mechanism of action	Unwanted pharmacological action	Resulting side effects
SSRI	Selective inhibition of 5HT reuptake transporter (SERT) presynaptically (both at the somatodendritic areas and at the synapse) in serotonergic neurons. When treatment is initiated, SERT blockade increases 5HT (primarily in the somatodendritic areas) which activates 5HT_{1A} autoreceptors that reduce serotonin release. Over time, 5HT_{1A} are downregulated and desensitized leading to disinhibition of the serotonergic neuron. Presynaptic desensitization is correlated to onset of treatment response. There is gradual postsynaptic desensitization as well and is correlated with tolerance to the side effects of SSRIs.	Varies by agent: -Fluoxetine: has 5HT_{2C} antagonist effect which explains activation (but contributes to antidepressant effect) -Sertraline: has weak DA transporter (DAT) inhibitory effects (mildly activating) -Paroxetine: has muscarinic anticholinergic effects. Also inhibits nitric oxide synthase (contributes to sexual dysfunction) -Fluvoxamine: binds sigma-1 receptors—unknown function but may contribute sedative and anxiolytic effects -Citalopram: R-enantiomer has antihistaminic effects and may reduce efficacy of SERT inhibition and contribute to QTc prolongation at high dosages	GI: reduced appetite, nausea, constipation, diarrhea CNS: headache, insomnia, somnolence, anxiety, fatigue, tremor Sexual: delayed orgasm, anorgasmia Rare: prolonged QTc interval, UGI bleed, hyponatremia, serotonin syndrome, osteoporosis/fractures in elderly, SIADH, seizures, hallucinations
SNRI	Blockade of 5HT and NE reuptake transporters (SERT and NET)	More significant withdrawal reactions	In addition to SSRI side effects (see above), hypertension, sweating, nausea, dizziness, headache, dry mouth, insomnia
NDRI	Blockade of NET and DAT	CNS-stimulating effects may be problematic for some patients	Headache, agitation, anxiety, rash, emesis, insomnia, shaking, increased risk of seizures
NaSSA	5HT _{2A} , 5HT _{2C} , 5HT ₃ , sigma-2-adrenergic receptor antagonism	Histamine H1 blockade	Sedation, drowsiness, dry mouth, weight gain, constipation, increased appetite, nightmares Other: increased serum cholesterol Rare: neutropenia, agranulocytosis, serotonin syndrome, hepatotoxicity, SIADH
SARI	Powerful blockade of 5HT _{2A} and 5HT _{2C} receptors. Less potent inhibition of SERT	Histamine H1 blockade	Sedation, cognitive impairment, dry mouth
		Alpha-1 adrenoreceptor blockade	Postural hypotension, priapism Other: vivid dreams, may exacerbate arrhythmias
SPARI	Partial agonism at 5HT _{1A} autoreceptors SERT inhibition		GI: nausea/vomiting, diarrhea, dry mouth Headache, insomnia Rare: restlessness

(continued on next page)

Class	Mechanism of action	Unwanted pharmacological action	Resulting side effects
TCA	Blockade of SERT and NET (and DAT to a lesser degree)	Muscarinic blockade (anticholinergic)	Dry mouth, tachycardia, blurred vision, glaucoma, constipation, urinary retention, sexual dysfunction, cognitive impairment
		Alpha-1 adrenoreceptor blockade	Drowsiness, orthostatic hypotension, sexual dysfunction
		Histamine H1 blockade	Drowsiness, weight gain
		Fast Na channel blockade	QTc prolongation, reduced seizure threshold Overdoses: seizures, coma, cardiac arrhythmias/arrest. Note: One-month supply of a TCA may be lethal in overdose.
			Rare: Serotonin syndrome, SIADH, seizures, Torsades de Pointes
MAOI RIMA	Irreversible and nonselective monoamine oxidase inhibition	MAOIs: irreversible blockade of monoamine oxidase	Common: orthostatic hypotension, weight gain, sexual dysfunction, ankle edema Other: insomnia with daytime drowsiness, myoclonus, tremor, akathisia, paresthesia, dry mouth, urinary retention, increased sweating Rare: hypertensive crisis (e.g., after ingestion of dietary tyramine), serotonin syndrome (e.g., due to drug-drug interactions), blood dyscrasias, hepatotoxicity, seizures, teratogenicity
	Reversible and selective monoamine oxidase A inhibition	Numerous drug-drug interactions	

Table 4. Summary table for commonly used antidepressants.

Drug	Half-life (h)	Side effects					
		Sedation	Anticholinergic	Orthostatic hypotension	Sexual dysfunction	GI	Activation and insomnia
SSRIs							
Citalopram	35	VL	None	None	VH	H	VL
Escitalopram	25	VL	None	None	VH	H	VL
Fluoxetine	24-72	None	None	None	VH	H	VH
Fluvoxamine	15	M	None	None	VH	H	L
Paroxetine	20	L	L	None	VH	H	L
Sertraline	25	VL	None	None	VH	VH	M
Other antidepressants							
Agomelatine (melatonergic)	1-2	H	None	None	None	M-H	L
Bupropion (NDRI)	12	None	None	None	None	M	H
Desvenlafaxine (SNRI)	10	L	None	VL	H	VH	M
Duloxetine (SNRI)	8-17	VL	L	None	VL	H	L
Levomilnacipran (SNRI)	12	None	None	L	L	M	L
Mirtazapine (NaSSA)	20-40	H	None	L	None	VL	None
Nefazodone (SARI)	2-4	H	None	L	None	M	VL
Trazodone (SARI)	6-11	VH	VL	VH	None	M	L
Venlafaxine (SNRI)	3-5	L	None	VL	H	VH	M
Vilazodone (SPARI)	25	L	None	VL	VL	M	L
Vortioxetine (multimodal)	66	L	None	None	L-M	L-M	VL
TCAs							
Amitriptyline	9-46	VH	VH	VH	H	VL	None
Clomipramine	23-122	VH	VH	VH	VH	VL	None
Desipramine	12-28	M	M	M	H	VL	VL
Doxepin	8-25	VH	VH	VH	H	VL	None
Imipramine	6-28	H	VH	VH	H	VL	None
Nortriptyline	18-56	M	M	M	H	VL	None
MAOIs							
Isocarboxazid	-- ^a	M	L	H	H	VL	L
Phenelzine	-- ^a	L	M	VH	H	VL	L
Tranyl-cypromine	-- ^a	None	M	VH	L	VL	M
Moclobemide	1-4	None	None	L	None	VL	L

Table 5. Summary table of side effects associated with specific antidepressants, categorized by class.

GI = gastrointestinal; H = high; L = low; M = moderate; VH = very high; VL = very low.

^aMaximal inhibition by MAOIs is achieved in 5-10 days.

Table adapted from Black and Andreasen.

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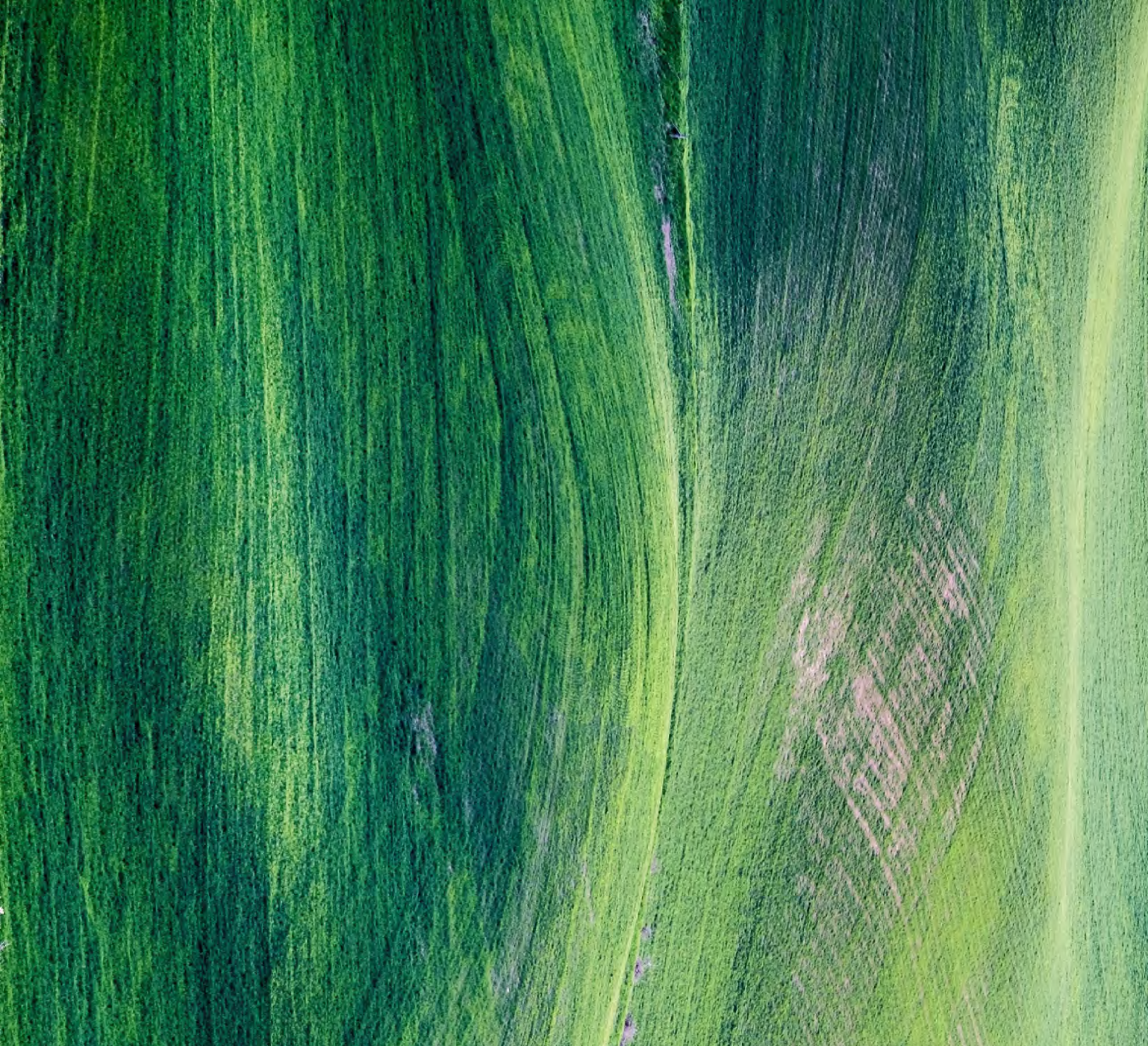
Review Questions

1. Clozapine has been shown to reduce the risk of suicide among patients with schizophrenia. Which of the following medications has been shown to reduce the risk of suicide in patients with mood disorders?
 - a) Quetiapine
 - b) Vortioxetine
 - c) Lithium
 - d) Fluoxetine
 - e) Valproate

2. A 31 year old man with a history of schizophrenia since his late adolescence and several inpatient admissions for treatment has been stabilized on olanzapine 15 mg daily for the past 3 years with no exacerbations of his illness. Previous trials of antipsychotic drugs included haloperidol, which was effective but developed severe muscle rigidity and could not tolerate it, and paliperidone, which was effective but discontinued by the patient when he developed mild gynecomastia. He is presently requesting a change of medication treatment as he has gained 18 kg since onset of olanzapine therapy and was told by his family physician that he is prediabetic and needs to be started on statins. Which of the following antipsychotics would be most suitable as an alternative to olanzapine for this patient?
 - a) Risperidone
 - b) Aripiprazole
 - c) Clozapine
 - d) Chlorpromazine
 - e) None of the above

3. A 26 year old woman with history of frequent daily panic attacks, anxiety and an increasing avoidance of open spaces has been receiving cognitive-behavioural therapy (CBT) for the past 3 months with modest improvement of her symptoms. Here therapist recommended that she consider a trial of medication while continuing her CBT sessions. Which one of the following medications can be considered as a first-line drug treatment in her case?
 - a) Alprazolam
 - b) Phenelzine
 - c) Buspirone
 - d) Quetiapine
 - e) Citalopram

Answers:
1. c)
2. b)
3. e)



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