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# Case 1

Jimmy Mcavoy is a 23 year old man who is brought to the GP by his sister who is concerned about his increasingly bizarre behaviour. She says he talks about voices no one else can here and the voices tell him to ‘barricade the house’. He also believes that ‘someone is watching him’. His sister thinks that he is having a psychotic episode.

**She asks you ‘what are the main categories of symptoms that define psychosis and some examples of each?’**

* **“Positive' symptom** - are changes in thoughts and feelings that are “added on” to a person's experiences (e.g., paranoia or hearing voices).
  + **Hallucinations -** involve seeing, hearing, feeling, smelling or tasting something that is not actually there. These experiences appear entirely real to the person who is experiencing them. The most common type of hallucination involves hearing things – such as voices or particular sounds.
  + **Illusions -** An illusion is a misperception resulting from a trick of the senses, or something that is not as it appears.
  + **Delusions -** Delusions are very firmly held, false beliefs that are not consistent with one’s culture. These beliefs cannot be shaken despite reason or proof to the contrary.
* **“Negative” symptom** - are things that are “taken away” or reduced (e.g., reduced motivation or reduced intensity of emotion).
* **Disorganized**
* **Speech -** slipping off-topic, going off on a tangent, answering a question in a way that doesn’t make sense to the other person, talking about things that seemed unrelated to the conversation
* **Disorganized behaviour -** behaviours that don’t fit the situation
* wearing clothing that doesn’t fit the weather
* displaying an inappropriate emotional response to the situation (e.g., laughing in response to hearing about a person’s tragedy)
* difficulty performing activities of daily living such as cooking or self-care
* not responding or reacting to their environment

|  |  |  |
| --- | --- | --- |
| **Positive symptoms** | **Negative symptoms** | **Disorganized** |
| Hallucinations (auditory is most common type)  Illusions  Delusions | Flat affect  Alogia  Anhedonia  Apathy  Asociality | Loose associations  Word salad  Neologisms  Tangential speech |

**Discuss the difference between an illusion vs delusion vs hallucination.**

* Delusion: fixed, false beliefs which cannot be corrected by logic and are not consistent with the culture and education of the patient
* Hallucination: false sensory perceptions experienced without real external stimulus e.g. seeing a goblin sitting next to you, when nothing is actually there. Can be visual, auditory, tactile, taste.
* Illusions: Misperception of real external stimulus. E.g. looking at a cloud formation - see a goblin

**Jimmy is diagnosed with schizophrenia and is commenced on olanzapine. What class of drug does olanzapine belong to and what are its major side effects?**

**Olanzapine is an atypical antipsychotic (second generation)**

* Metabolic side effects very common with second generation antipsychotics
  + Dyslipidaemia, weight gain, hyperglycaemia and diabetes mellitus
  + Will need to monitor J’s waist circumference, fasting glucose, lipid profile and BP
* Anticholinergic side effects: dry mouth, constipation, urinary retention
* Cardiovascular SEs: QT prolongation and cardiomyopathy
* Sexual side effects: reduced libido, erectile dysfunction, anorgasmia
* Sedation: due to antihistamine action
* Hyperprolactinaemia due to D2 receptor antagonism
  + Dopamine secretion from the hypothalamus inhibits prolactin secretion. Therefore, anti-dopaminergic activity removes the inhibition of prolactin secretion.
  + Leads to elevated serum prolactin, which causes galactorrhea in women, gynecomastia in men, and symptoms of hypogonadotropic hypogonadism
* + many more - antipsychotics are a pharmacological nightmare

**Jimmy’s sister had heard about another drug used to treat schizophrenia called haloperidol, compare its drug class to that of olanzapine drug class in terms of:**

|  |  |  |
| --- | --- | --- |
|  | **Typical antipsychotics (first generation)** | **Atypical antipsychotics (second generation)** |
| Drug examples | Haloperidol, Fluphenazine, Perphenazine, Trifluoperazine, Pimozide | Olanzapine, Clozapine, risperidone, quetiapine |
| MOA | Strong dopamine receptor antagonism | Weaker dopamine receptor antagonism  Antagonist for serotonin, histamine and alpha-adrenergic receptors |
| Adverse effect profile | HIGH YIELD   * **Extrapyramidal side effects (EPSE) - more common in 1st gen** * Tardive dyskinesia * Hyperprolactinemia * Prolonged QT interval * Metabolic and anticholinergic effects less pronounced * Neuroleptic syndrome | HIGH YIELD   * **EPSE less common in 2nd gen** * Sedation * Hyperprolactinemia (< typicals) * Prolonged QT interval * Metabolic effects most prominent (weight gain, hyperglycemia, dyslipidemia) * Anticholinergic and anti-sympathetic effects * Neuroleptic malignant syndrome |
| Indications | Generally used as second line aside from acute presentations of the following psychiatric disorders   * Schizophrenia * Bipolar disorder * Acute psychosis * Delirium | More used first line and are the only antipsychotic medications with evidence for long-term treatment in the following psychiatric disorders   * Schizophrenia * Bipolar disorder * Acute psychosis * Delirium * Anxiety disorders * Huntington’s disease |
| Contraindications | Parkinsons - Any antipsychotics may aggravate the condition  Lewy Body dementia - any antipsychotics (even low dose) can cause deterioration in cognitive and motor function + increase agitation  Seizures - use with caution may lower seizure threshold | |

**Extrapyramidal side effects (EPSE) -** umbrella term for a wide variety of movement disorders. **TRAPS**

* **Acute syndromes** - those that develop generally within hours or days of treatment
  + **Acute dystonia**: involuntary muscular contraction which results in abnormal posture or movement. Typically involve muscles of the head and neck. Occurs more commonly in young adults and may appear after only a few doses. These are acute and painful and need immediate treatment sometimes with Intramuscular anticholinergics.
  + **Parkinsonism**: tremor, rigidity, bradykinesia. Symptoms generally emerge within a few days of starting the offending drug but may emerge slowly over several weeks. Anticholinergic drugs are usually effective.
  + **Akathisia**: sensation of inner restlessness, a compulsion to keep moving. Patients may be observed repeating purposeless movements. Acute akathisia is often associated with irritability, agitation and violent outbursts. Responds to treatment with propranolol.
* **Chronic or tardive syndromes** - those that develop after a sustained period of exposure
  + **Tardive dyskinesia:** rhythmic involuntary movements of tongue face and jaw. Develops following long-term use of antipsychotics. May be irreversible. Clozapine has been shown to be an effective treatment.
* [**https://www.youtube.com/watch?v=ucrV4ljDKuE**](https://www.youtube.com/watch?v=ucrV4ljDKuE)

**Jimmy’s GP is unfortunately a UQ graduate and decides to listen to Jimmy’s sister’s WebMD advice and swaps Jimmy to Haloperidol (typical antipsychotic).** **Two weeks after Jimmy’s acute psychosis, he comes to see the doctor because of difficulty with movements and a tremor. Neurological examination shows a shuffling gait, increased tone in the upper extremities and a tremor of the hands which improves with activity. The mental status examination is normal.**

**What is going on here and what is the mechanism?**

This is drug-induced pseudoparkinsonism (bradykinesia, muscle rigidity, resting tremor) – it is a collection of movement disorders due to disruption of dopaminergic pathways in the basal ganglia. It caused by anti-dopaminergic activity of antipsychotic drugs and usually onsets 1-4 weeks after starting antipsychotics.

**Key features include** Cogwheel rigidity (jerking muscle resistance and relaxation in response to passive movement)**,** Stiff gait**,** Tremor, Bradykinesia - A decreased speed of voluntary and involuntary movements.

**How might you resolve this issue for Jimmy?**

* Lower the dose **OR** switch to an antipsychotic drug with a lower risk of EPSEs (2nd gens)
* If dose reduction or switching is not possible or not tolerated, consider also prescribing:
  + Dopamine agonist (e.g., amantadine)
  + Anticholinergic (e.g. benztropine)

**What if Jimmy had been prescribed clozapine instead? What else would the doctor need to consider when prescribing him this?**

* **Clozapine** is reserved for:
  + Chronic: Treatment-resistant schizophrenia and schizophrenia associated with persistent suicidality
  + Acute: Psychotic symptoms caused by medication for Parkinson disease(dopamine agonists)
* **Risks:** Can cause **neutropenia or agranulocytosis**, may potentially also cause myocarditis in the early weeks of treatment.
  + Mechanism not fully understood but it has been postulated that **clozapine is metabolised to a nitrenium ion**. The binding of this ion to neutrophils may result in agranulocytosis.
* **Requires additional Monitoring!!!**
* In general, clozapine monitoring should include systematic evaluation of the following parameters:
  + **white blood cell and neutrophil counts** for at least the first 18 weeks
  + **cardiac parameters**, including regular measurement of body temperature, pulse rate, blood pressure and respiratory rate. Troponins and C-reactive protein should be measured weekly for the first 4 weeks. Further investigations, including electrocardiogram (ECG) and echocardiogram, are recommended at baseline and should be repeated on the basis of the other observations and results
  + **metabolic parameters**, including weight, body mass index (BMI), waist circumference, blood glucose concentration and lipid profile
  + **NOTE:** Brand substitution is not allowed, as each brand manufacturer has its own monitoring service (Clozapine Patient Monitoring System [CPMS] for Clozaril or Clopine Connect for Clopine)

**In Schizophrenia psychotic symptoms such as hallucinations delusions, disorganised speech and grossly disorganised or catatonic behaviours are known as:**

|  |  |  |
| --- | --- | --- |
|  | a) | Negative symptoms |
|  | **b)** | **Positive symptoms** |
|  | c) | Mediating symptoms |
|  | d) | Catastrophic symptoms |

**In Schizophrenia when an individual believes they are in danger, this is referred to as:**

|  |  |  |
| --- | --- | --- |
|  | a) | Delusions of grandeur |
|  | **b)** | **Delusions of persecution** |
|  | c) | Delusions of control |
|  | d) | Nihilistic delusion  Grandiosity: The patient insists that they have special powers or importance  Persecutory: The patient insists that they are being cheated on, conspired against, or harassed.  Control: False belief that another person, group of people, or external force controls one's general thoughts, feelings, impulses, or behaviors  Nihilistic: delusional belief of being dead, decomposed or annihilated, having lost one's own internal organs or even not existing entirely as a human being. |

**‘Poverty of content' in Schizophrenia is when:**

|  |  |  |
| --- | --- | --- |
|  | **a)** | **Speech appears to be detailed in terms of numbers of words, but is grammatically incorrect** |
|  | b) | A tendency to jump from one topic to another within a sentence |
|  | c) | Poor use of vocabulary |
|  | d) | Poor use of grammar |

**Catatonic Behaviour in Schizophrenia is characterised by which if the following:**

|  |  |  |
| --- | --- | --- |
|  | a) | Resisting attempts to be moved |
|  | b) | Maintaining rigid, immobile postures |
|  | c) | Decrease in reactivity to the environment |
|  | **d)** | **All of the above** |

# Case 2

Anne is aged 40 years, divorced with two children, works casually and cares for her mother who has chronic kidney disease. She presents to you feeling stressed and worried about ‘anything and everything’. Upon further questioning, she notes that she has always worried about things, but it has gotten much worse during the last two years with COVID. She states that she no longer feels like she can control these thoughts.

She has no significant past medical history, other than being moderately depressed for 2 months following her divorce 5 years ago. Since then, she has made frequent appointments with you for no specific reason other than to check she is “well”. When worried she notes her heart races and sometimes she finds it difficult to breathe. Her sleep is poor with difficulty getting off to sleep due to worrying and frequent wakening. She feels tired and irritable. She does not drink any alcohol, smoke or take drugs.

**Based on her history you suspect that she may have some form of anxiety. Complete the table below comparing the different anxiety disorders.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Type** | **Generalized anxiety disorder** | **Panic Disorder** | **Social Anxiety Disorder** | **Specific Phobias** | **Substance/ Medication induced anxiety disorder** |
| **Definition** | **Prolonged and excessive anxiety** that:  1) **Is not focused on a single specific fear** but may revolve around themes (e.g., work)  2) Causes clinically significant distress  3) Is not caused by **substance use**, **medication**, or underlying medical condition | Recurrent **spontaneous**and **unexpected** panic attacks that often occur without a known trigger | Pronounced anxiety lasting ≥ 6 months of **social situations** that might involve scrutiny by others | **Persistent**(≥ 6 months)**and intense fears** of one or more **specific situations or objects** (phobic stimuli)  Always occurs during encounters with the phobic stimulus but may already surge in anticipation of an encounter | Prominent anxiety or panic attacks within 1 month of use of, or withdrawal from, a substance/medication that is capable of inducing anxiety symptoms |
| **Duration of symptoms required for Dx** | ≥ 6 months  >=3 Symptoms must occur on more days than not (see below) | **Panic attacks:** several minutes | ≥ 6 months | ≥ 6 months | Within 1 month of using or stopping the substance/medication |
| **Clinical Features** | Prolonged and excessive anxiety not focused on a single specific fear  **Symptoms for Dx:**   * Nervousness, restlessness * Irritability * Muscle tension * Somnolence, fatigue * Concentration difficulties * Insomnia | Recurrent unexpected panic attacks  Overstimulation of the sympathetic sys:  Sweating, palpitation, shaking, Paresthesias  Abdominal pain, nausea, Light-headedness, chest pain, Shortness of breath, choking sensation, Depersonalization, derealization | Blushing, **palpitations**, **sweating** during a social interaction  **Anticipatory anxiety**  Anxiety from **fear of embarrassment** and others noticing the reaction  **Avoidance of the aforementioned triggers** (e.g., not attending parties, refusing to attend school) | Persistent and intense fears of particular situations or objects | Prominent fear, anxiety or panic attacks after using or stopping a substance/medication  Palpitation, dizziness, shaking, shortness of breath, and sweating |
| **Triggers** | No definitive trigger or source | May not have an obvious trigger | Social interaction and/or performance of any actions in public | One or more specific situations or objects  Examples – spiders, heights, dogs, blood, needles, flying, enclosed spaces etc. | **Alcohol**, **Caffeine**  Anticonvulsants, opioids, Anticholinergics  Bronchodilators  Corticosteroids  Amphetamines,  cocaine, cannabis, hallucinogens |
| **Treatment** | **First line:**  SNRI/SSRIs; CBT, applied relaxation therapy, biofeedback  **Second line:**  Buspirone, TCAs, benzodiazepines (only until other drug takes effect) | **Acute panic attack:** short-acting benzodiazepines (e.g. alprazolam); breathing exercises  **Long-term management:**CBT, SSRIs, SNRIs, TCAs | CBT plus  First line: SSRIs/SNRIs  Second line – clonazepam or phenelzine (if hx of substance abuse)  **Performance-only SAD**: CBT + beta blocker or benzodiazepine (take before SAD event) | **First line:** CBT (desensitization therapy)  **Alternative:**  Benzodiazepine or SSRIs | Discontinuation of the substance/medication  CBT |

**Which type of anxiety disorder do you think Anne has?**

Based on Anne’s history she most likely has a generalized anxiety disorder.

**How best could you treat this condition?**

As per ETGs guidelines

* **Psychosocial interventions**, including psychotherapy (eg cognitive behavioural therapy), are first-line treatments for generalised anxiety disorder in adults and young people.
  + Ongoing supportive psychosocial treatment is required in all patients.
  + Initial treatment for generalised anxiety disorder includes psychoeducation, and advice on coping skills and relaxation techniques. Implement stress management approaches such as:
    - activity scheduling
    - modifying lifestyle factors (eg engaging in good sleep practices, minimising alcohol consumption, eating a healthy diet [Note 1], undertaking adequate physical activity [Note 2])
    - problem-focused counselling
  + Use psychological therapies, if available; these should be provided by an experienced and trained clinician. Cognitive behavioural therapy (CBT) has the best evidence for generalised anxiety disorder.
* **Pharmacotherapy** may be used when psychotherapy is not available, not effective or not preferred, or if symptoms are severe.
  + If pharmacotherapy is appropriate, start an antidepressant for maintenance therapy (see Mental Health 1 worksheet for more info)
    - **SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) are first-line drugs for the treatment of generalised anxiety disorder**
  + Short-term treatment with a benzodiazepine may also be needed initially because it can take several weeks before an effect is seen with an antidepressant.

**Unfortunately, Anne did not take the medications you prescribed her, nor did she attend any appointments with a psychologist that you set up for her through a mental health care plan. Instead she decided to self-medicate with a bottle of wine per day at home, as it was easier to access.**

**12 months later Anne presents at the ED in a disoriented state. The intern conducts a full exam on her and states she has Wernicke encephalopathy.**

**What other signs/symptoms would the intern have observed to come to this**

**conclusion about Anne?**

* **The common triad for WE is:**
  + Confusion/disorientation
  + Oculomotor dysfunction (CN 3,4,6 invlovement)
    - Gaze-induced horizontal/vertical nystagmus (most common)
    - Diplopia – lateral rectus palsy
    - Conjugate gaze palsy
  + Gait ataxia: wide-based, small steps (combination of peripheral neuropathy, vestibular dysfunction, and cerebellar dysfunction)
* Other observations may include:
  + Autonomic dysfunction: hypotension, syncope, hypothermia
  + Peripheral neuropathy: paresthesia, foot drop,
  + Cardiovascular dysfunction: tachycardia, exertional dyspnea
  + Jaundice
  + Coma/stupor

**Explain why Anne would have developed this condition and how you would treat it.**

* Due to a Thiamine deficiency → decreased cerebral glucose metabolism and mitochondrial dysfunction → depleted ATP and increased free radicals → injury of neuronal elements (e.g., myelin sheaths, blood-brain-barrier, decreased neurotransmitters, etc.) →impaired axonal conduction → symptoms of Wernicke encephalopathy
* Thiamine is converted to Thiamine pyrophosphate which is its active form and used for enzymes in cerebral glucose and energy metabolism
* Treatment:
  + Immediate IV administration of **high-dose vitamin B1/thiamine** upon suspicion of Wernicke encephalopathy until symptoms recede, followed by a lower dose
  + Thiamine must be administered **before IV glucose infusions** because glucose administration without thiamine can worsen encephalopathy.
  + Long-term oral replacement of vitamin B1, vitamin B6, vitamin B12, and folic acid (vitamin B complex)
  + Abstinence from alcohol

**How could this progress if this was untreated?**

* If untreated this would lead to **Korsakoff syndrome**. The main features are:
  + Confabulation (unconscious production of fabricated memories to fill in real ones they forgot)
  + Anterograde and/or retrograde amnesia
  + Personality changes
  + Disorientation to time, place, and person
  + Hallucinations
* **This is NOT reversible.**

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