SMICA
SERIOUS MENTAL ILLNESS
CALIFORNIA ADVISER

Iatrogenic Aggression

While there are several commonly observed reasons why psychiatric patients may be aggressive (acutely psychotic or manic, in physical pain, severely personality disordered), **occasionally the reason is the treatment we provide or the symptoms we overlook.** Below are a few examples.

AKATHISIA

- Akathisia is a symptom that is usually defined by its 2 components:
    - the subjective component, which is described as a feeling of inner restlessness and an urgent need to move, and the objective component, which is manifested by characteristic abnormal movements, which predominate in the lower limbs with bending of the legs or feet, swaying of the leg while seated, rocking from one foot to the other, or walking in place.
- The subjective component is often difficult for patients to describe because there really is no other subjective state to which it can be compared. Some common phrases could include: *anxiety, discomfort, itching, heat, pain, stress, tension, vibration.*
- The subjective component can exist independent of the objective component, especially if the condition is mild (Lohr, 2015).
- Can use the Barnes Akathisia Rating Scale (BARS) to establish the diagnosis.
- Several studies have shown an association between akathisia and agitation including self-harm (Stubbs, 2000; Bjarke, 2022).
- **Is often underrecognized by clinicians** even though the prevalence of akathisia with treatment from typical antipsychotics ranges from 8-76% (Jouini, 2022) and atypical antipsychotics ranges from 0-50% (Lohr, 2015).
    - In the Jouini study of 124 inpatients, prescribed typical and/or atypical antipsychotics, there was a prevalence of 19.5% (n=24) and only 10% of those patients (n=2) were diagnosed with akathisia before the study.
- Risk factors may include higher dose or rapid dose increase, traumatic brain injury, cancer, and possibly bipolar disorder (Lohr, 2015).
- Most closely associated with antipsychotics, but can also occur with antidepressants particularly SSRIs and SNRIs (Akgoz, 2024), lithium (Demir, 2021), and the antibiotic azithromycin (Risselman, 2015).
- Treatment options include switching the medication, lowering the dose, or adding mirtazapine, biperiden, or vitamin B6 (Gerolymos, 2024); note that the evidence for all the add-ons are considered low quality.

CATATONIA

- A neuropsychiatric syndrome of motor signs.
- Initially thought to be a subtype of schizophrenia, but is now well-recognized to be associated with the ***undertreatment*** of an underlying condition such as mood disorders (the largest subgroup of patients who are diagnosed as meeting the criteria for catatonia per Fink, 2013), psychotic disorders, along with a multitude of other potential underlying causes (see Appendix I from Rogers, 2023).

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- Diagnosed by documenting 3 or more of the following: mutism, posturing, catalepsy, mannerisms, grimacing, negativism, waxy flexibility, stereotypy, stupor, agitation, echolalia, or echopraxia.
    - Staring, stupor, mutism, and posturing are most commonly observed.
    - Other symptoms, some of which are almost pathognomonic, are relatively rare: echolalia, echopraxia, waxy flexibility, catalepsy.
- Can use the Bush-Francis Catatonia Rating Scale to establish the diagnosis. Visit this website for training videos.
- Prevalence among psychiatric patients is estimated to be 9% based on a meta-analysis of 74 studies (Solmi, 2018).
- Often overlooked because catatonia can have an inconsistent and unpredictable presentation. The signs may emerge rapidly, reaching a maximum level within hours (in acute catatonia), or may develop slowly, over a period of days or weeks.
- Catatonic episodes may recur periodically or they may persist for years. Those who are in a stupor may engage minimally, making it even more difficult for the clinician to differentiate the negative symptoms of a psychotic disorder from catatonia.
- The psychomotor behaviors have been classified as akinetic/hypokinetic. (stupor/decreased), hyperkinetic (increased), and parakinetic (abnormal movements) but they can flip between these phenotypes especially akinetic and hyperkinetic (Rogers, 2023).
- Hyperkinetic episodes can present as unpredictable and purposeless agitation or aggression.
- Treatment options include a lorazepam challenge and ECT (Brar, 2017) but the underlying cause of ***the catatonia must be adequately treated otherwise catatonia will return once the lorazepam is stopped.***

PSYCHIATRIC MEDICATION CHOICES AND DOSING STRATEGIES

Certain neuropsychiatric medications are associated with an elevated risk of aggression and/or agitation. This includes:

- Levetiracetam (Keppra®):
    - Used to treat partial and generalized seizures, the Phase III studies of the drug initially reported more than 13% of a mixed group of both pediatric and adult patients were noted to have secondary symptoms of agitation, hostility, anxiety, depression, depersonalization, and emotional lability (Zhang, 2021).
    - Amongst all the antiepileptics, levetiracetam was noted to have the greatest rate (22.1%) of psychiatric and behavioral side effects including depressive mood, psychosis, anxiety, suicidal thoughts, irritability, aggression, and tantrum (Chen, 2017).
- Benzodiazepines:
    - While they can be temporarily used as an anxiolytic or hypnotic, they can cause disinhibition which leads to aggression (Bijl, 1991; Paton, 2002; Guina, 2022).
    - At greatest risk are patients with impulse control issues, learning disabilities, or neurocognitive pathologies and individuals younger than 18 or older than 65 (Gandotra, 2019).

- Benzodiazepine / opiate withdrawal
  - Either can precipitate periods of agitation, irritability, and/or anxiety (Arroyo-Novoa, 2020; Robertson, 2023).
  - Either can lead to delirium (Mader, 2020; Świderski, 2025) and even catatonia (Rosebush, 1996; Mader, 2020).
- Augmenting a potent D2 antagonist with aripiprazole (Abilify®)
  - Aripiprazole is a partial D2 agonist/antagonist, meaning that it binds to D2 receptors but works as a dimmer switch, behaving as an antagonist when dopamine levels are high and an agonist when dopamine levels are low.
  - Aripiprazole has 25% intrinsic D2 activity (agonism), meaning that the maximum antagonism it can provide is 75% D2 blockade. At 30 mg a day, aripiprazole occupies 86% of D2 receptors, resulting in 65% D2 blockade (75 x .86 = 64.5). Many severely mentally ill patients need 80+% D2 blockade (Meyer, 2021).
  - Has a stronger binding affinity for the D2 receptor compared to potent D2 antagonists; in essence, when you combine the two, the aripiprazole will be the agent that binds to the D2 receptor and exerts its effect, thus eliminating any benefit from the potent D2 antagonist. This can lead to a worsening of psychotic symptoms (Ma, 2022).
- Co-prescription of serotonin medications and/or inhibitor(s) leading to serotonin syndrome (Maitland, 2022).

<u>Abrupt discontinuation of medications as opposed to tapering can lead to an increased risk of aggression. This includes:</u>

- Anticholinergic medications
  - One of the most common reasons is when a patient is transferred to a medical facility and clozapine (highly anticholinergic) is not continued.
  - The abrupt discontinuation leads to cholinergic rebound, which can present as confusion and agitation (Bickerton, 2024).
- Antipsychotic medications:
  - Long-term exposure to potent D2 antagonists leads to a reciprocal increase in D2 receptor density, leading to dopamine supersensitivity (Nakata, 2017).
  - When the potent D2 antagonist is suddenly discontinued, supersensitivity psychosis can follow, which can present as agitation.
- Benzodiazepine / opiate withdrawal as previously described above.

<u>Not fully understanding how to interpret antipsychotic plasma levels:</u>

- While increasingly more practitioners are ordering antipsychotic plasma levels, most providers just check to see if the level is in the therapeutic range and many do not fully understand how to interpret them.
- An important concept to understand regarding antipsychotic plasma levels is the ***point of futility (POF)***, which is the plasma level where most patients will not receive any further clinical benefit from the medication but will likely experience increasing side effects (Meyer, 2021).

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  - For a potent D2 antagonist, levels near or above the point of futility can cause akathisia.
  - An important POF to remember is for haloperidol, at 18 ng/mL, although some patients will experience motor side effects well before reaching the POF.
- Another important concept to understand is that most antipsychotic plasma levels can naturally have 20% variability (with clozapine, it's 30%). If plasma levels on the same dose vary beyond the 20%, you should consider the possibility of intermittent non-adherence.
- If the patient's dosage has been adjusted, you can still check for the variability by calculating a CD ratio, which is the plasma **C**oncentration (i.e. plasma level) divided by the **D**osage and then check for the 20% variability amongst the CD ratios.
- Intermittent non-adherence can lead to an agitated patient in several ways:
  - When the patient is not taking the medication, they can be more symptomatic
  - When the patient resumes medication after several days of non-adherence, the rapid rise in plasma level can lead to akathisia or other side effects.
  - If the provider switches from an oral agent to a long-acting agent based on plasma levels without checking for variability and ruling out non-adherence, the average daily equivalent of the long-acting injectable may provide a higher plasma level than expected and lead to akathisia or other side effects.

DELIRIUM

- Delirium is the most common neuropsychiatric syndrome encountered by clinicians dealing with older adults and the medically ill and is best characterized by 5 core domains: cognitive deficits, attentional deficits, circadian rhythm dysregulation, emotional dysregulation, and alteration in psychomotor functioning (Maldonado, 2017).
- There are numerous causes for delirium but some of the most common ones in psychiatric patients are medication intoxication, sudden discontinuation and/or withdrawal, infection (especially urinary tract infections in the elderly who may be afebrile and otherwise asymptomatic), electrolyte imbalances, and thyroid conditions.
- Risk factors associated with delirium in patients with psychiatric illness primarily include advanced age, physical comorbid, types of psychiatric illness, antipsychotics, anticholinergic drug, Electroconvulsive therapy (ECT), and the combination of lithium and ECT (Huang, 2024).
- The estimated prevalence of delirium in an inpatient psychiatric setting is 15% (Huang, 2024).
- Rates of delirium misdiagnosis in many studies range from 41.8% to 64% (Hercus, 2020).

STAFF INTERACTION AND TREATMENT ENVIRONMENT

- Staff interaction includes understaffing, inconsistent boundaries, staff burnout, patient to staff rapport, unit/provider changes.
- Treatment environment includes regulation of daily life/activities, limited privacy, wait times in line, sensory overload (Stahl, 2014).
- Both staff and patients perceive therapeutic relationships to be protective against aggression. Nursing communication issues identified by patients as potential precursors to aggression included poor explanation regarding rules and inadequate listening (Fletcher, 2020).

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See APPENDIX I on the next page

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Table 3. Selected important medical conditions that may underlie catatonia.

Medical conditions associated with catatonia

CNS autoimmunity or inflammation
- Anti-NMDA receptor encephalitis
- Multiple sclerosis
- Other causes of autoimmune encephalitis, including paraneoplastic syndromes
- SLE

CNS infection
- Bacterial meningitis or encephalitis
- Cerebral malaria
- HIV encephalopathy
- Prion disease
- Subacute sclerosing panencephalitis
- Syphilis
- Viral meningitis or encephalitis

Endocrine
- Addison's disease
- Cushing's disease
- Hyperthyroidism
- Hypoparathyroidism
- Hypothyroidism
- Panhypopituitarism
- Phaeochromocytoma

Focal neurological lesions
- Lesions of varying pathophysiology to the frontal lobes, temporal lobes, parietal lobes, limbic regions, diencephalon, basal ganglia and cerebellum
- Space-occupying lesion
- Traumatic brain injury
- Tumour
- Vascular injury

Medication or drug administration or overdose
- Antiretroviral drugs
- Azithromycin
- Antipsychotics (see section 'Antipsychotic-induced catatonia')
- Baclofen
- Beta-lactam antibiotics
- Cannabis and synthetic cannabinoids
- Ciclosporin
- Corticosteroids
- CNS stimulants
- Disulfiram
- Fluoroquinolones
- Inhalants
- Ketamine
- Levetiracetam
- Lithium
- LSD
- Methoxetamine
- Opioids
- Phencyclidine
- Tacrolimus

Medication or drug withdrawal
- Alcohol
- Benzodiazepines
- Clozapine
- Gabapentin
- Zolpidem

Metabolic disorders and states
- Diabetic ketoacidosis
- Glucose-6-phosphate dehydrogenase deficiency
- Hepatic encephalopathy
- Homocystinuria
- Hyperammonaemia
- Hypercalcaemia
- Hyponatraemia
- Pellagra
- Porphyria
- Uraemia or renal failure
- Vitamin B12 deficiency or pernicious anaemia
- Wernicke's encephalopathy
- Wilson's disease

Neurodegenerative
- Dementia with Lewy bodies
- Frontotemporal dementia
- Parkinson's disease

Seizure
- NCSE

Toxins
- Bulbocapnine
- Carbon monoxide
- Coal gas
- Fluorinated hydrocarbons
- Isopropanol

Miscellaneous
- Burns
- Electrocution
- Extrapontine myelinolysis
- Narcolepsy
- Posterior reversible encephalopathy syndrome
- Postoperative, including post-transplant
- Respiratory failure
- Systemic infection or sepsis
- Toxic epidermal necrolysis
- Tuberous sclerosis

Source: Ahuja (2000), Carroll and Goforth (2004), Denysenko et al. (2018), Fink and Taylor (2003), Oldham (2018), Rogers et al. (2019), Tatreau et al. (2018), Yeoh et al. (2022).
CNS: central nervous system; HIV: human immunodeficiency virus; LSD: lysergic acid diethylamide; NCSE: Non-convulsive status epilepticus; NMDA: *N*-methyl-D-aspartate; SLE: Systemic lupus erythematosus.