Basic psychiatry and the patient with ESRD on dialysis

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Disclosures

I have no disclosures or known conflicts of interest

Disclosures

I know very little about dialysis or end stage renal disease/CKD

Objectives

Discuss the most common psychiatric presentations and describe if or how they can be different in the patient with ESRD on dialysis

Discuss suicide facts, risks, and referrals

Understand some basic psychopharmacology and the principles of medication management

Review the concepts of under-treatment, treatment failure, remission and partial remission

Identify psychiatric medications that are not ideal or contraindicated in the patient with ESRD

Recognize when you patient is having a psychiatric emergency and needs to be referred for a higher level of care

What are the specific mental health needs and concerns of the patient on dialysis?

In many ways their concerns mirror the general population

There are some distinct differences

Many studies have demonstrated that patients with CKD have a higher prevalence of psychiatric disorders than the general population

- anxiety
- depression

Depression

Patients with ONLY depressive episodes are said to have major depressive disorder (MDD) or unipolar depression

Depression has been described for thousands of years (old testament, Iliad, Hippocrates)

Common

Highest lifetime prevalence of any psychiatric disorder (17%)

Twice as common in women

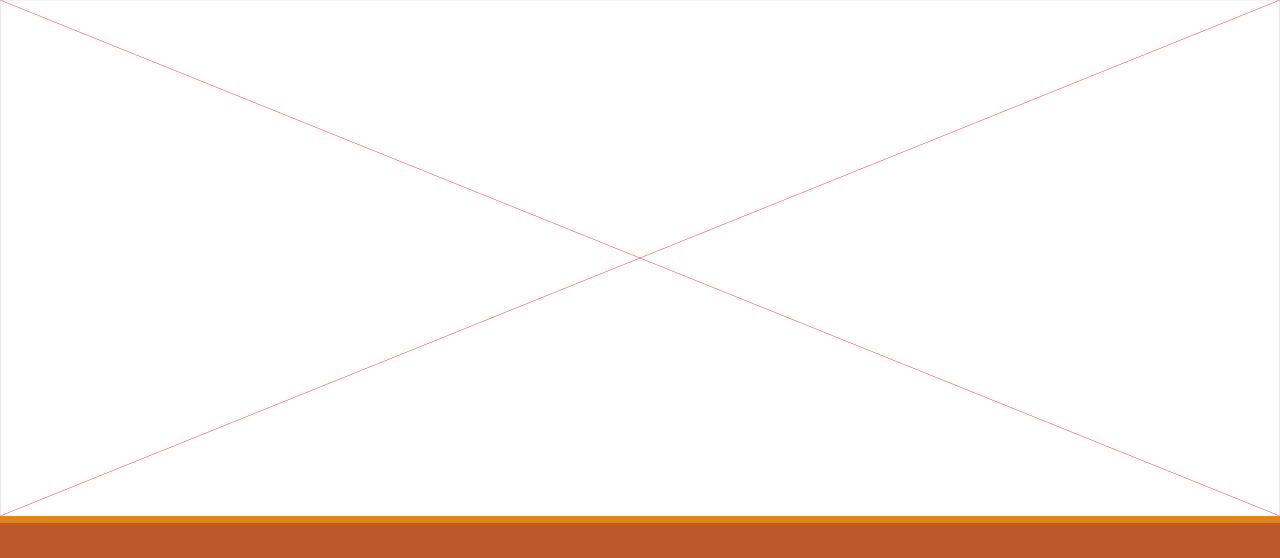
Biogenic amines: norepinephrine and serotonin are implicated in mood disorders (dopamine plays a role as well)

Depression

Criteria for diagnosis

Must last at least 2 weeks

at least 4 other symptoms besides low mood/lack of joy (wt loss or gain, appetite changes, changes in sleep and activity, lack of energy, feelings of guilt or worthlessness, problems thinking and making decisions, reoccurring thoughts of death or suicide) APA, 2014



Treatment of depression

What can we do?

SSRIs

Selective serotonin reuptake inhibitors

Most evidence for use in depression

1st line



Side effects and psych meds

patients typically experience side effects before they experience clinical improvement

Side effects can be immediate, benefit may take days or weeks

rapport

patience

trust

education

Antidepressants that require dose adjustments in renal impairment and should start at low doses with slow titrations:

SNRI (serotonin, norepinephrine reuptake inhibitors)

Venlafaxine

Desvenlafaxine

Duloxetine

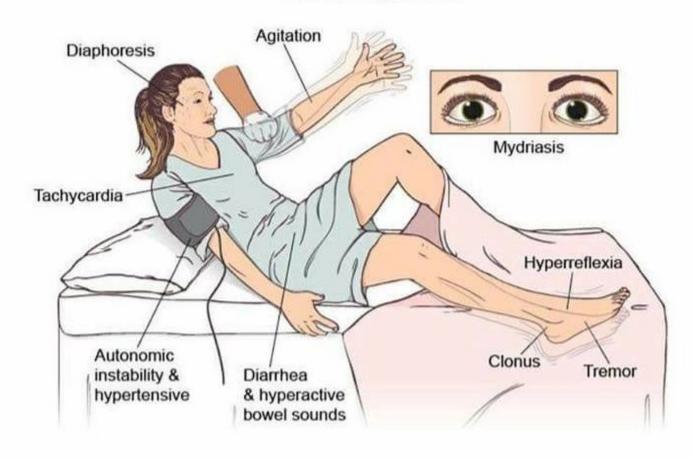
Levomilnacipran

Bupropion

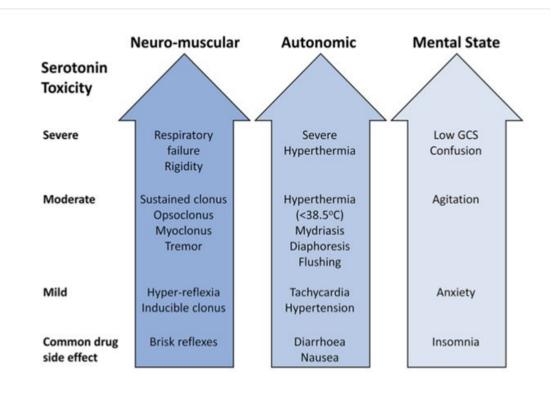
Paroxetine (SSRI)

Mirtazapine

Serotonin syndrome



Serotonergic meds/Serotonin syndrome (Brown, 2010)



SSRIs Miscellaneous Citalopram Buspirone Fluoxetine Carbamazepine Fluvoxamine Cocaine Olanzapine/fluoxetine Cyclobenzaprine Paroxetine Dextromethorphan Ergot alkaloids **SNRIs** Fentanyl Duloxetine 5-Hydroxytryptophan Sibutramine Linezolid Venlafaxine Lithium L-Tryptophan Triptans Meperidine Almotriptan Methadone Eletriptan Methamphetamine Frovatriptan Methylene blue Naratriptan Metoclopramide Rizatriptan Mirtazapine Sumatriptan Ondansetron Phenelzine Zolmitriptan Selegiline St. John's wort Tramadol

Tranylcypromine Trazodone

Valproic acid

Tricyclic antidepressants

Suicide

Some researchers suggest that suicidal behavior may be related not only to environmental psychosocial factors and health status, but also to a lack of coping strategies to reduce stress during the dialysis treatment

The etiology of depression in dialysis appears to be multifactorial, and depends on several psychological, social, and biological factors. Biological mechanisms include genetic predisposition, increased levels of cytokines, and dysregulation of neurotransmitters. The psychological and social factors include feelings of hopelessness, loss of job, impairment in social and family relationships and perceptions of loss, and lack of control (Pompili, et. al, 2013)

Suicide

Suicide was the 8th leading cause of death among New Mexico residents.

Among those 15-17 years, suicide was the leading cause of death by age group, tied with unintentional injuries.

Among those 5-14 and 18-34 years, suicide was the second leading cause of death by age group

35-44 years, it was the third leading cause.

♦ New Mexico had the second highest suicide rate in the U.S. in 2018

Suicide prevention

Suicides Are Preventable

Generally, a suicidal crisis is both transient and treatable.

90% or more of the people who attempt suicide do not go on to die by suicide

If you do not know what to do- REFER

Suicide is a Leading Cause of Death in the United States

According to the Centers for Disease Control and Prevention (CDC) WISQARS Leading Causes of Death Reports, in 2018: Suicide was the tenth leading cause of death overall in the United States, claiming the lives of over 48,000 people.

Suicide was the second leading cause of death among individuals between the ages of 10 and 34, and the fourth leading cause of death among individuals between the ages of 35 and 54.

There were more than two and a half times as many suicides (48,344) in the United States as there were homicides (18,830)

Who dies by suicide in NM?

In 2015 Whites and American Indians have the highest rates

Whites 32.5/100,000

Steady increase among American Indians/Alaska Native

Highest rate among 35 and older

American Indians 25.2/100,000

Highest rate among those younger than 35 years

Suicide rate for men is more than 3 times that as for women

The rate was highest for males 75 years and older and for females 45-54 years old

53% of those who died by suicide from 2011-2015 used a firearm.

The male firearm suicide rate in 2015 was six times higher than the female firearm suicide rate

Suicide in Rural Areas

Suicide rates are higher in rural America than in urban America.

The gap in suicide rates between rural and urban areas grew steadily from 1999 to 2015.

White Non-Hispanics have the highest suicide rates in urban areas (metropolitan counties)

American Indian and Alaska Native Non-Hispanics have the highest rates in rural areas.

Findings by age group revealed increases in suicide rates for all ages with the highest rates and greatest rate increases in rural counties

CDC.gov 2019

Risk Factors Suicidality

Current and/or past suicidality: suicide intent, plan, rehearsals, preparation, and/or self-injurious behavior

Recent diagnosis and/or flare-up of mental and/or substance use disorder chronic and/or life-threatening physical illness (New to dialysis)

Currently or will soon be isolated or alone

Perceived burdensomeness to others

Access to firearms or other lethal means: preferred method currently or easily available

Motivated to under-report/lie about risk

Current stressors: Recent interpersonal losses; recent exposure to suicide in media/community; recent disciplinary and/or legal crises

Transitions (change) in treatment/level of care, especially recent discharge from psychiatric hospital

Family history (of suicide, attempts, or severe mental illness requiring hospitalization)

Risk Factors Key Symptoms

PSYCHOLOGICAL PAIN: Hurt, anguish, or misery in your mind

STRESS: Feeling of being pressured or overwhelmed

AGITATION: Emotional urgency; feeling that you need to take action

HOPELESS: Expectation things will not get better no matter what you

do

SELF-HATE: Disliking yourself; having no self-esteem / self-respect

Comorbidity

More than 90% of people who die by suicide have a mental health disorder or substance abuse disorder or both

More than 50% of suicides are associated with a major depressive disorder

Approximately 25% of suicides are associated with a substance abuse disorder

Ten percent of suicides are associated with psychotic disorders

When do I need to refer my patient for a higher level of care?

Have a plan and intent- must be sent to the hospital for stabilization

Thoughts of dying, a plan but no intent requires a safety plan, referrals to behavioral health

Thoughts "better off dead"- but no plan or intent needs treatment, support, suggests depression, referrals should be provided

Where to refer in NM

ER

UNM Psych ER/ Psychiatric Urgent Care

Haven

Lovelace

Kaseman

NM Crisis Line 1-855-NM CRISIS (662-7474)

National Hotlines 1-800-273-TALK (7255)

Cessation of dialysis

- Patients can decide against dialysis; most would argue this is not suicide
- Rational motives for a patient to refuse continuation of dialysis are many
 "Especially if they are not transplant candidates, dialysis patients suffer
 significant discomfort, inconvenience, and progressive functional disability, in
 return for which they may sometimes expect a limited prolongation of life on the
 saw-toothed edge of uremia. It is understandable that the risks and injuries
 attendant to long-term dialysis may eventually outweigh the perceived benefits."
- At least one third or even one half of dialysis discontinuation decisions are reached by staff and proxies for patients who can no longer meaningfully participate in the determinations

Refusal of treatment

Most feel this is not suicide but is a patient's right

Srettabunjong Figure 1. A cut on one end of the temporary haemodialysis catheter that had been secured on the right side of the patient's neck was detected at the death scene.

(Srettabunjong, 2019)

Treatment of depression on dialysis

Many psychiatric medications are metabolized and excreted by the liver and are therefore used in patients on dialysis

Non-pharmacologic treatment- therapy, yoga, exercise, light therapy

Psychotherapy

CBT- Cognitive Behavior Therapy

DBT-Dialectical Behavior Therapy

BA-Behavioral Activation

Remission, partial remission and treatment resistance/failure

Remission: primary goal (symptoms are gone)

Partial remission: A little better. Measure this with screening tests like PHQ 9 and GAD 7 for instance, good predictor of medication efficacy with objective values

• Function- eating better, sleeping better, more goal directed activities, less disruption in the patient's life

Treatment failure: a medication is taken for at least 4-6 weeks, at FDA approved level

Under-treatment: common

Treatment resistance: tried 2 med classes at FDA approved dosage and over 4-6 weeks (no agreed definition!)

2 week/20% rule: improvement of 20% after 2 weeks of treatment, may predict positive outcome

How to dose: Start low, increase every 2 weeks until remission or intolerable. Use FDA maximum dosing guidelines.

If partial remission: Augment

DE prescribing is an important art as well

Goldberg & Stahl, 202

Treatment of "treatment resistant" depression

TMS



TMS/Neuromodulation

Effect neurons electrically (magnetic)

Applied to the cerebral cortex

Induce electrical fields in the brain with external magnets-causes neurons to fire=behavioral effects (activation)

Can have immediate and or lasting effects

TMS

TMS:

- Criteria: fail 2 medications from 2 different classes, and alternative treatment modality for a total of 3
- DX: treatment resistant depression or dysthymia
- UNM: TMS clinic, Dr. Quinn
 - Actively involved in research
- STAR*D study: 70-80% positive effect, 50% remission (George et. al., 2010)

TMS

Done at UNM, VA, Sage Neuroscience

Non-invasive

Relatively benign- can cause unintended seizure



Ketamine

Dissociative anesthetic agent

Can cause hallucinations or a dissociative state

No respiratory depression, does cause cardiac stimulation (tachycardia, hypertension)

Metabolized by the liver, excreted in urine



Ketamine

Antagonizes NMDA receptor in the CNS producing dissociative analgesia and sedation

Exact mechanism of action is unknown

Rapid infusion of ketamine may reduce suicidality but it is not long-lasting

Ketamine combined with an antidepressant improved symptoms in the long-term

Intranasal Eskatamine (Spravato): one dose of 50mg improved symptoms within 40 minutes (Lapidus et. al., 2014)

Cost: \$590-\$885 per 2 sprays

Ketamine comes in other cheaper forms as well (IV, oral wafer)

ECT

Electroconvulsive therapy

"high voltage synchronous neuronal firing"

The gold standard of treatment in treatment resistant depression

Given in a controlled setting under general anesthesia (VA, UNM)

Studied since 1500 (Induce seizure to treat psychiatric illness)



ECT

Indications for electroconvulsive therapy (ECT)

Definitely effective
Unipolar major depression
Refractory or resistant to antidepressant therapy
Need exists for rapid treatment response, such as in pregnancy, persistent suicidal intent, or food refusal leading to dehydration or nutritional compromise
Medical comorbidities prevent the use of antidepressant medication
Previous response to ECT
Psychotic features (eg, delusions or hallucinations)
Catatonia
Persistent suicidal intent
Bipolar depression or mania

Bipolar disorder/Bipolar depression

Rare 1%

Equally as common in men and women

Frequent misdiagnosis

What bipolar disorder is not-

Moody, irritable
"Hot and Cold" "off and on"
Nice one day, angry or mean the next

MANIA and then MAJOR DEPRESSION

Mania

"elevated, expansive or irritable mood"

Euphoric, impulsive

Can have devastating consequences

alcohol poisoning

gambling

outlandish dress and jewelry

inattention to details (not hanging up the phone)

disrobing in public

financial ruin

dangerous sex/STI which can destroy relationships

erratic behavior at work or not going to work leading to loss of employment

Mania cont.

A manic patient is often preoccupied by odd beliefs

religious

political

sexual

financial

persecutory ideas that can evolve into complex delusion

rarely play in their urine and feces

**Anxiety, depression, alcohol misuse, substance use disorder typically coexists

Bipolar disorder

Mood disorders:

Mania	Hypomania			
Lasts at least 7 days	Lasts at least 4 days			
Causes severe impairment in social or occupational functioning	No marked impairment in functioning			
May necessitate hospitalization ro prevent harm to self or others	Does not require hospitalization			
May have psychotic features	No psychotic features			

Lithium (Sadd

(Saddock, Saddock and Ruiz, 2015)

excellent at mood stabilization in acute mania and beyond, also helpful in depression, schizophrenia, many others

under utilized

prophylaxis and treatment of mania/bipolar disorder

distinct risks and side effects (80% of patients have side effects) hypothyroid, wt gain, hair loss, GI, tremor, arrhythmia, birth defects

Does not metabolize

Excreted unchanged by the kidneys

Equilibrium or steady state is reached in 5-7 days

Requires blood levels/monitoring

Lithium

Excellent in controlling suicidal thoughts, may be used in low dose in depression May be a lifesaving option

Highly dependent on Renal Excretion:

- requires dose reductions
- usually try to avoid with dialysis if possible
- Generally, will check a Li level immediately before dialysis and then give a dose after dialysis

Lithium and kidney damage

Lithium causes damage

- Collecting Tubule
- Nephrogenic DI
- Glomerulus
- Minimal change glomerulopathy nephrotic syndrome
- Tubulointerstitial Nephritis/ Nephropathy (rare, <1%)
- chronic use associated with kidney damage- can consolidate dosing to once at night has demonstrated kidney protection

Lithium

Lithium (Li) is the commonest drug causing hypernatraemia;

serum sodium levels as high as 196 mmol/L have been reported [18].

Li is used to treat bipolar (manic-depressive) disorders and has become the most frequent cause of drug-induced NDI.

NDI is evident in almost 50% of patients receiving prolonged lithium therapy [18]. Of those, 30% have a subclinical concentrating defect, while the remaining 20% suffer from polyuria that can take place within the first 8–12 weeks of treatment.

Lithium-induced NDI is usually reversible upon stopping therapy, but a few patients remain symptomatic long after discontinuation of Li [19].

In a series of 23 cases of Li intoxication, three patients developed hypernatraemia ranging from 155 mmol/L to 162 mmol/L [20].

Water loss due to impaired renal concentrating ability was implicated in the pathogenesis of hypernatraemia.

Catatonia

New diagnostic category in the DSM 5

Can cover a broad spectrum of mental disorders, most often in psychotic disorders and mood disorders (Schizophrenia or psychotic depression)

Can be caused by an underlying medical condition or substances (TBI, hyponatremia, status epilepticus, infection, hepatic encephalopathy, hypercalcemia. Medications include steroids, antipsychotic meds, immunosuppressants, ESRD)

"striking" behavioral abnormalities such as motoric immobility or excitement, profound negativism (freezing) or echolalia (mimicking of speech) or echopraxia (mimicking of movement)

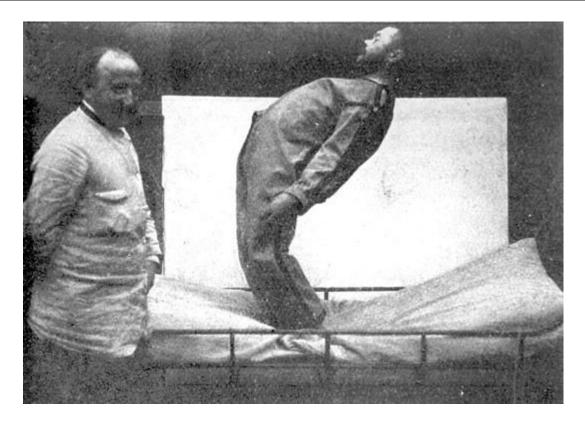
Uncommon

Treated with ECT, benzodiazepines

Catatonia









Anxiety

Rates of anxiety are HIGH in ESRD patients

Therapy as important if not more important than medications

The same meds that are used to treat depression are typically the best medications to treat anxiety

SSRI (fluoxetine, escitalopram, sertraline, paroxetine, citalopram) 1st line

SNRI (duloxetine, venlafaxine)

TCAs (clomipramine, imipramine, amitrptyline)

Buspirone

Mirtazapine

Rescue meds (hydroxyzine, propranolol, gabapentin, benzodiazepines)

Anxiety

Core of psychiatric theory

Associated with significant morbidity

Chronic

Resistant to treatment

Family of related but distinct mental disorders

panic

agoraphobia

specific phobia

social anxiety or phobia

Generalized anxiety disorder

genetic and environmental (trauma)

(Saddock, Saddock & Ruiz, 2015)

Pain and anxiety

Often co-occurring

Anxiety will be worse when a patient is in pain

Often treated with acetaminophen, gabapentin and pregabalin (Lyrica)

Pregabalin

Similar to gabapentin

CrCl 30-60= max dose of 75-300mg/day

CrCl 15-30= max dose of 25-150mg/day

CrCl <15: max dose of 25-75mg/day

Psychosis

Perceptual disturbances

Hallucinations- any of the 5 senses can be affected by hallucinatory experiences

auditory (voices) most common "You are stupid, you should kill yourself" obscene, threatening, accusatory

Visual- dark figures, shadows, can be more complex

Tactile, olfactory and gustatory are unusual

High risk for suicide

Risk of homicide is the same as the general population

Causes of psychosis

Dopamine imbalance (too much)

Many medical causes-

Schizophrenia

Depression

Treated with antipsychotic medication which blocks dopamine neurotransmission

Antipsychotics (Kujawski, 2019)

	1 st generation	2 nd generation		
A.K.A.	typical antipsychotics	atypical antipsychotics		
MOA	Primarily block D2 receptors only	Primarily block D2 and 5HT2A receptors		
Examples	haloperidolchlorpromazine	 aripiprazole olanzapine quetiapine risperidone clozapine 		
EPS	More likely to cause EPS (dystonia, akathisia, pseudoparkinsonism, and tardive dyskinesia)	Less likely to cause EPS and tardive dyskinesia (but can still occur)		
Metabolic abnormalities	Less likely to have metabolic abnormalities	More likely to cause metabolic abnormalities (elevated glucose, lipids, and weight gain)		

Antipsychotics

Not everyone on an antipsychotic has a psychotic disorder

- -aripiprazole (Abilify) often used as an adjunct in depression
- -quetiapine (Seroquel) often used for anxiety and sleep
- -olanzapine (bulimia nervosa) tic disorders
- -impulse control
- -aggression (risperidone)

Antipsychotics (Kujawski, 2019)

	EPS/TD	Dyslipidemia	Weight gain/T2DM	Elevated prolactin	Anticholinergic effects	Orthostatic hypotension	QTC prolongation
First generation*				20			
chlorpromazine	+	+++	+++	++	+++	+++	+++
haloperidol	+++	+	+	+++	+/-	-	++ (+++ if IV)
fluphenazine	+++	+	+	+++	+/-	-	+/-
Second generation	n*			05			
aripiprazole	+	-	+	-	-	-	+/-
asenapine	++	-	++	++	-	+	++
brexpiprazole	+	+	+	+/-	+/-	+/-	+/-
lurasidone	++	+/-	+/-	+/-	-	+	+/-
olanzapine	+	++++	++++	+	++	+	++
paliperidone	+++	+	+++	+++	-	++	++
pimavanserin	+/-	-	+	-	+	++	+
quetiapine	+/-	+++	+++	+/-	++	++	+++
risperidone	+++	+	+++	+++	+	+	++
ziprasidone	+	+/-	+/-	+	-	+	+++ (BBW!)
clozapine	+/-	++++	++++	+/-	+++	+++	++

Neuroleptic Malignant Syndrome

Neuroleptic= antipsychotic agents rarely metoclopramide and promethazine

Malignant = bad

Syndrome= constellation of symptoms

Neuroleptic malignant syndrome (NMS) is a life-threatening neurologic emergency associated with the use of antipsychotic (neuroleptic) agents and characterized by a distinctive clinical syndrome of mental status change, rigidity, fever, and dysautonomia

Mortality results directly from the dysautonomic manifestations of the disease and from systemic complications.

Incidence rates for NMS range from 0.02 to 3 percent among patients taking antipsychotic agents

Thought to be caused by <u>dopamine receptor blockade</u>. Treat with IV anticholinergics (benztropine and or diphenhydramine benzodiazepines)

FIGURE 1

Symptoms of Neuroleptic Malignant Syndrome

Primary Symptoms

Fever (often greater than 40°C)

Severe muscle rigidity (lead pipe presentation as opposed to cogwheeling)

Altered state of consciousness ranging from clouding of sensorium to coma

Autonomic instability

Labile pulse and blood pressure

Diaphoresis

Tachypnea

Secondary Symptoms

Autonomic Manifestations

Respiratory distress

Pallor

Flushing

Urinary retention

Other Motor Disturbances

Parkinsonian-like syndromes

Tremor

Sialorrhea

Dystonic reactions

Chorea

Occulogyric crisis

Dyskinesias

■ Neurological Symptoms

Dysphasia

Akinetic mutism

Aphonia

Dysarthria

Hyporeflexia

Ataxia

Extensor plantar responses

Posturing

Substance use disorder

Expect it

Can result in the need for dialysis

Many will be in remission (age)

Common in depression

High numbers in NM

Opioid Use Disorder-opioid agonists methadone buprenorphine/naloxone

Methamphetamine/Cocaine/Stimulant Use Disorder no replacements treat underlying mood disorders

Alcohol use disorder- meds that target cravings

Naltrexone- metabolized by the liver, excreted in the urine Acamprosate- caution in renal disease

Topiramate:

- requires dose reductions
- CrCl<70 requires slower titration

Gabapentin

- Eliminated primarily renally
- CrCl 30-59= dose of 400-1400mg/day
- CrCl>15-29= max dose of 700mg/day
- CrCl 15: max dose of 300mg/day--> but I have seen doses be given higher
- Will sometimes provide a supplemental dose after dialysis

Topirimate

Topiramate

- % with kidney stones in epilepsy study (2-4x incr risk)
- Carbonic anhydrase inhibitors promote stone formation by urinary citrate excretion and urinary pH.
 - Avoid with other carbonic anhydrase inhibitors
 - Hydrate
- Used in alcohol use disorder, binge eating disorder, migraines, epilepsy

Delirium

(intensive care psychosis, encephalitis, acute brain failure, toxic metabolic state) (Saddock, Saddock & Ruiz, 2015)

Can present like psychosis or a psychotic disorder (hint, you don't develop schizophrenia in your late 70s)

<u>Acute</u> decline in both level of consciousness and cognition with particular impairment in attention (confused)

Life threatening yet potentially reversible disorder of the <u>central nervous</u> <u>system</u>

Often involves perceptual disturbances, abnormal psychomotor activity, disrupted sleep

Often under recognized by healthcare workers

Delirium

Impaired consciousness

Impairment of cognitive function

language deficits

Mood, perception and behavioral abnormalities (hallucinations, delusions)

Tremor, asterixis (flapping tremor), nystagmus, incoordination, incontinence

brief and fluctuating course

Sudden onset

Rapid improvement when the underlying cause is corrected

Delirium

Common in the elderly

5-10% of elderly patients visiting the ER

15-21% of elderly patients admitted to the medical wards

30% open heart surgery patients

50% of patients with hip fractures

70-87% of the elderly in the ICU

83% of patients receiving end of life care

Severe burns, HIV, post-operatively, stroke, meningitis

Drugs- sedative hypnotics, anticholinergics, alcohol withdrawal

Environmental precipitating factors for delirium (Saddock, Saddock and Ruiz, 2015)

Admission to the ICU

Use of Restraints

Use of a bladder catheter

Use of multiple procedures

Pain

Emotional Stress

Prolonged sleep deprivation

Medical Causes of Delirium

Seizure Diabetes

migraine

dehydration or volume overload

head trauma nutritional deficiencies

electrolyte disturbance High altitude

Infection opiate pain medication

Trauma antibiotics, antifungals, antivirals

Burn serotonin syndrome

Pain herbs

heat stroke steroids, anesthesia

cardiac failure or arrhythmia

cardiac surgery

COPD with hypoxia

SIADH

adrenal crisis or failure

anemia or leukemia

renal failure, uremia

cirrhosis or hepatic failure

intoxication or withdrawal

Case study

Black Box Warnings

SSRIs- suicidality in "younger" patients

Aripiprazole (Abilify)- suicidality in children and young adults, increased mortality in elderly with dementia

Clozapine (Clozaril)- agranulocytosis, seizure, myocarditis, orthostatic or severe hypotension, respiratory arrest

Thioridazine- severe cardiac arrhythmia

Trazodone-suicidality in "younger" patients

Valproic acid (Depakote) hepatotoxic, teratogenic, pancreatitis

Lamotrigine- Steven Johnson's Syndrome

Stimulants-abuse, risk of sudden death, CV events

Atomoxetine-CVD events, death

Final thoughts "How can we help on our end?"

Everything has gotten harder and worse with COVID

Every patient is unique

A small phrase instilling hope is HUGE

The body keeps score

Be patient

Personality disorders- don't take it personally

Every brain is different

Many psych issues are genetic and environment- not in the pt's control

Duty to protect and help

Start low and go slow

Reach out and refer

Thank yous

Zwanet Hamming PMHNP ASAP (tables)

Amre Elamoud (PharmD/ Clinical pharmacist UNM Calm Clinic)

Lan Nguyen NP

Avi Kriechman (UNM Dept of Psychiatry).....Suicide slides are his

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