Post-Stroke Neuropsychiatric Disorders

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Disclosure Statement

- I do not have any financial relationships with any commercial interest or any proprietary entity producing health care goods or services.

- I *will* discuss off-label use of medications (there are no medications with specific FDA-approved indications for post-stroke neuropsychiatric disorders).

Learning Objectives

- Identify common post-stroke neuropsychiatric disorders
- Understand that individuals with a history of stroke are at higher risk for suicide
- Recognize that psychiatric disorders and stroke may share a bidirectional relationship (i.e., one can increase the risk for the other)

Post-stroke neuropsychiatric disorders

- Defined in various ways, but for purpose of this talk:
  - Psychiatric disorders which occur following stroke and which are believed to be due to the direct effects of the stroke on the brain
- Examples: depression, apathy, anxiety disorders, impulse control disorders/personality change
- Post-stroke depression represents the most-studied and best-understood post-stroke neuropsychiatric disorder
  - But even here much research remains to be done
  - Knowledge base for other post-stroke neuropsychiatric disorders is even more limited
  - Can occur following ischemic or hemorrhagic stroke, but most research has been done in ischemic stroke
- Post-stroke neuropsychiatric disorders are common, clinically significant, and treatable—so important to recognize and diagnose them!

Post-stroke neuropsychiatric disorders are common—important to look for them in all patients with a history of stroke

Disorder	Prevalence
Apathy	36%
Depression	29%-33%
Anxiety disorders	24%
PTSD	23%
Irritability	12%-53%
Pathologic laughing and crying	8%-32%
Impulse control disorders	6%-76%
Mania	≤2%
Psychotic disorders	<1%-10%

Why do post-stroke neuropsychiatric disorders matter?

- Post-stroke neuropsychiatric disorders are common, affecting 1/3 or more of patients with stroke
- Patients with post-stroke neuropsychiatric disorders have worse health outcomes, increased mortality, and poorer quality of life
- However, appropriate treatment of post-stroke neuropsychiatric disorders may improve these outcomes

- Hard to treat a disorder if you don't know it's there—so, important to screen patients with stroke for depression and other psychiatric disorders, and treat if found

Which strokes can produce psychiatric sequelae? All of them!

- Both ischemic and hemorrhagic strokes can cause neuropsychiatric disorders
- Laterality of stroke (probably) doesn't matter
  - No clear association between location of stroke and specific psychiatric manifestations
- Strokes do NOT have to cause severe neurologic deficits to cause psychiatric sequelae
  - Not just a reaction reaction to disability or increased awareness of one's mortality
  - Even strokes which do not produce significant functional impairment can cause depression or other psychiatric sequelae
  - Direct neurophysiologic effects of stroke can cause psychiatric disorders
    - Older adults with "asymptomatic" ischemic white matter disease and no history of clinical stroke show higher rates of depression

Stroke and psychiatric disorders: a bidirectional relationship?

- Evidence thus far indicates that stroke is a risk factor for subsequent psychiatric disorders, and psychiatric disorders are a risk factor for subsequent stroke

- Stroke increases the risk of depression, anxiety, and mania
- People with idiopathic depression, anxiety, and bipolar disorder face an elevated risk of stroke, even after controlling for conventional vascular risk factors (such as smoking, HTN, etc)

Could stroke and psychiatric disorders represent different manifestations of a shared underlying cause?

- Stroke and psychiatric disorders may share common etiologic factors
  - Nothing definitively proven, but proposed common mechanisms include:
    - Inflammation
    - HPA axis dysregulation
    - Serotonin-mediated effects on platelet and endothelial function
    - Excessive sympathetic tone

Stroke and suicide

- A history of stroke is a risk factor for suicide!
- Up to 7% of patients with stroke will ultimately die by suicide, a far higher rate than in the general population
- Elevated suicide risk may persist for 5 years after the stroke
- Risk factors for post-stroke suicide:
  - Depression (highest risk)
  - Young age
  - *Less* severe stroke
  - Fatigue (possibly)
- Important for all physicians—including neurologists!—to screen patients with a history of stroke (or depression or other psychiatric disorders, or other neurologic disorders associated with increased risk) for suicidality
  - Almost half of patients who die by suicide saw a non-psychiatrist physician within one month of their death; assessing for suicidality is every clinician's responsibility

Post-stroke depression

- Can look like a classic major depressive episode as seen in idiopathic MDD, but can also take other forms
  - DSM 5 criteria based on idiopathic MDD; patients with post-stroke depression may not have all the symptoms listed in the DSM 5, but can still have clinically significant depression
  - Post-stroke depression can manifest as irritability
- Important to distinguish depression from apathy, as treatment may differ (but both can occur comorbidly)

Symptoms of depression

CORE SYMPTOMS

- Low mood
- Anhedonia
- Loss of interest in activities
- Irritability

SOMATIC SYMPTOMS

- Insomnia / hypersomnia
- Decreased / increased appetite
- Weight loss / weight gain
- Decreased energy *
- Psychomotor slowing *

OTHER PSYCHOLOGICAL SYMPTOMS

- Feelings of guilt or worthlessness
- Suicidal thoughts

COGNITIVE SYMPTOMS

Impaired concentration *

* Can be challenging to distinguish whether due to depression or other effects of stroke

Post-stroke depression and prior psychiatric history

- A history of previous depression significantly increases the risk for post-stroke depression, but people without any prior psychiatric history can also develop de novo depression following a stroke.

Timecourse of post-stroke depression

- Post-stroke depression can develop in the initial post-stroke period, or any time over the next year
- In up to half of patients with post-stroke depression, depression lasts for 1 year or more

Consequences of post-stroke depression

- Compared to nondepressed stroke patients, individuals with post-stroke depression show:
  - Increased mortality
  - Slower recovery from neurologic deficits
  - More disability
  - Worse quality of life

- However, treatment of post-stroke depression can improve these outcomes
  - Treatment can improve not only mood, but also:
    - Excess mortality risk
    - Degree of disability
    - Functional independence

Treatment of post-stroke depression: somatic interventions

- Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) shown to be effective for post-stroke depression in multiple randomized placebo-controlled trials
- SSRIs probably represent the best first-line choice for pharmacotherapy of PSD because individuals with stroke experience more vulnerability to adverse cognitive effects from anticholinergic medications such as TCAs
  - Robust and growing body of evidence that anticholinergic drugs directly and causatively increase risk for irreversible dementia in everyone
  - One case-control study found an increased risk of recurrent stroke in patients taking TCAs, especially if they stopped TCAs abruptly
- Some data that SSRIs given to nondepressed patients following stroke may actually prevent the development of depression, improve cognitive and motor outcomes, and reduce mortality—but other studies have not found this
  - Needs further investigation

SSRIs and bleeding complications

- Some but not all studies have found an increased risk of intracerebral hemorrhage in individuals in the general population who take SSRIs.
  - Increased risk in studies that found it was small: NNH = 10,000
- One study found that among individuals who had an ICH, those taking both warfarin and SSRIs/SNRIs were more likely to die than those on warfarin alone

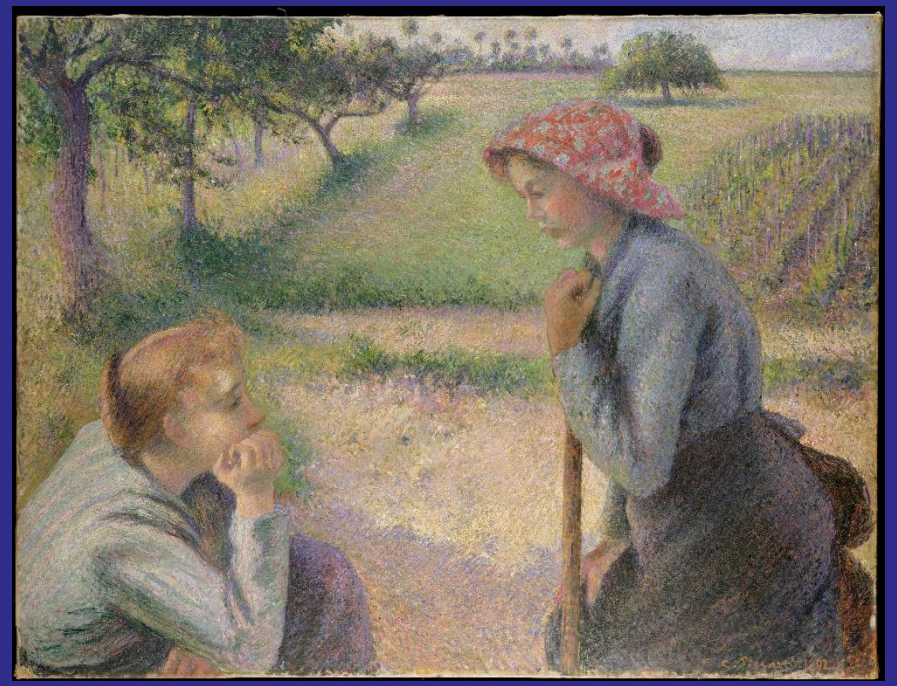
- Another study found that, among patients taking warfarin for A Fib, those who also took SSRIs had increased risk of major hemorrhage
- Correlation ≠ causation: these studies are epidemiologic—could be that depressed patients are more likely to have other risk factors for ICH (e.g., heavy alcohol use, smoking, etc)
- Other studies of SSRI/SNRI and NOAC found no increased bleed risk
- SSRIs + anticoagulation not contraindicated, but consider risks/benefits carefully: NOACs probably safer

- Other options (though with much less robust evidence base than SSRIs):
  - Serotonin-norepinephrine reuptake inhibitors (SNRIs)
  - Mirtazapine
  - Stimulants
  - Repetitive transcranial magnetic stimulation (rTMS)
  - Electroconvulsive therapy (ECT)

- Whatever medication is chosen, antidepressant treatment should continue for at least 2 years—earlier discontinuation can worsen post-stroke depression

Treatment of post-stroke depression: other interventions

- Evidence-based options:
  - Psychotherapy
    - Behavioral activation therapy
    - Problem-solving therapy
    - Behavior therapy (for patients with post-stroke depression and aphasia)
    - Other modes of psychotherapy may also be effective, but not yet studied for post-stroke depression
  - Regular vigorous exercise
  - One RCT found that patients with stroke or TIA who underwent intensive vascular risk factor modification had less depression at 1 year follow-up
    - A good idea anyway!



Post-stroke apathy

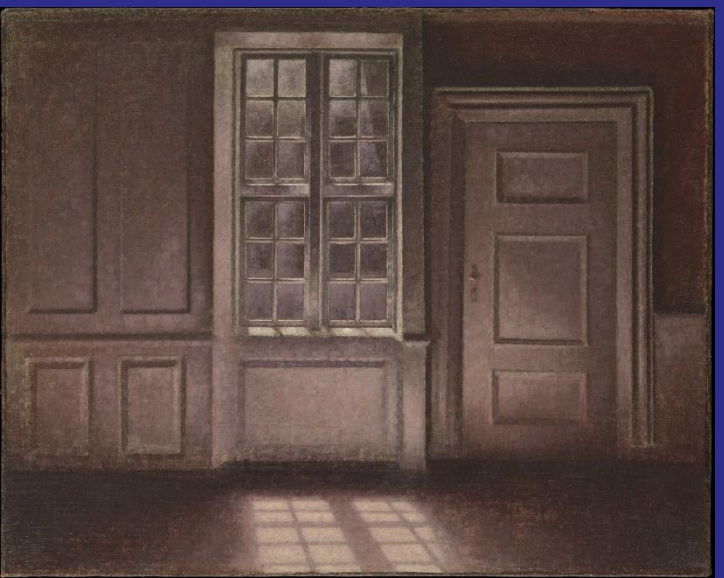
- What is apathy?
  - Lack of motivation
  - Impairment of goal-directed activity
  - Loss of spontaneity and initiative
  - Decreased interest
  - Emotional blunting
- Apathy ≠ depression
  - But they can occur together
  - Apathy also increases risk for depression
- Rule of thumb: depression bothers the patient, apathy bothers the family

Apathy vs Depression

Apathy	Depression
• Decreased initiative in undertaking activities, but may enjoy activities when others initiate/facilitate participation	• Loss of interest in activities, not improved when others encourage/facilitate participation
• Patient denies low mood or sadness	• Patient describes mood as low, sad, or down
• Mood generally unreactive (not sad, just not much of anything)	• Frequent tearfulness
• Family more concerned than patient about symptoms	• Patient distressed by symptoms

Prevention and treatment of apathy: medications

- One RCT found that that prophylactic poststroke treatment with a SSRI or problem-solving therapy reduced the incidence of apathy
- In general, apathy (whether from stroke or other etiology) responds less to treatment than depression does
- No RCTs for poststroke apathy treatment with drugs readily available in US
- Case reports / small series: dopamine agonists and stimulants improve post-stroke apathy
  - These agents have some evidence for treating apathy due to other causes
- RCTs for apathy in other conditions: evidence for stimulants, DA agonists, cholinesterase inhibitors, ginkgo biloba



- SSRIs and apathy
  - Initial concern in general population that SSRIs could cause/worsen apathy
  - However, one small open-label study of older adults with idiopathic MDD found SSRIs improved comorbid apathy, though less so symptoms of depression

Treatment of apathy: psychosocial interventions

- No studies of psychotherapy or other psychosocial interventions for post-stroke apathy
- Studies of apathy due to dementia indicate that animal therapy, music therapy, and participation in activities may help
  - Likely worth trying in post-stroke atrophy: may help and unlikely to hurt
- Provide psychoeducation to family that patient isn't depressed or lazy; explain what apathy is and why it's not a deliberate behavior

- Apathy is very distressing to families, especially if they don't understand what it is
- Can counsel families that they should initiate activities for the patient and encourage him/her to participate in things rather than waiting for the patient to do things on his/her own
  - Patients often enjoy activities and participate when prompted, but won't do on their own

Post-stroke anxiety disorders

- Data primarily on post-stroke generalized anxiety disorder (GAD) and panic
- Core symptom of GAD: excessive worry about multiple different issues
    - Associated symptoms: poor sleep, fatigue, muscle tension, restlessness, inability to relax, poor concentration, irritability
- Panic attack: sudden severe anxiety, fear, or discomfort; accompanied by tachycardia, palpitations, SOB, chest pain / discomfort, diaphoresis, tremulousness, GI upset, dizziness / lightheadedness, choking feeling, paresthesias, depersonalization / derealization, fear of losing control / going crazy, and / or fear of dying
    - Peaks in 5-10 minutes (can have mild residual symptoms for longer, but panic attacks don't last for hours)
    - DDx: TIA, MI, PE, seizure

Post-stroke anxiety disorders: other clinical features, significance, and treatment

- Often comorbid with post-stroke depression
- Worsen quality of life
- Treatment options supported by some evidence:
  - SSRIs
  - SSRIs plus supportive psychotherapy
  - Buspirone
- Prevention of post-stroke GAD
  - One study found that SSRI or problem-solving therapy reduced rates of post-stroke GAD
- *Avoid anticholinergics and benzodiazepines!!!*
  - Anticholiergics causatively increase risk of irreversible dementia
  - Benzodiazepines associated with increased falls, and all-cause mortality; also have dependence liability
  - NEITHER shown to be effective long-term for anxiety in any population

Post-stroke PTSD

- PTSD begins after a potentially life-threatening event (stroke certainly qualifies!)
- Core symptoms of PTSD: intrusive, frequent, and unwanted reexperiencing of past trauma
  - Flashbacks, nightmares, intrusive thoughts, severe distress at reminders of trauma
- Associated symptoms: poor sleep, hypervigilance, excessive startle, inability to recall part of trauma, poor concentration, irritability / anger, self-destructive / reckless behavior, loss of interest in activities, sense of detachment from others, excessive self-blame related to trauma, avoiding thinking of / reminders of trauma, loss of positive emotions, excessive negative emotions, excessively negative outlook

Post-stroke PTSD: significance and treatment

- Patients with post-stroke PTSD showed worse adherence to secondary stroke prophylaxis
  - Places them at increased risk for future stroke
- No data specifically on treatment of post-stroke PTSD
  - For now, should base treatment on standard treatment for PTSD from other etiologies:
    - SSRIs
    - Prazosin for PTSD nightmares
    - Psychotherapy
      - Individual and/or group
    - Avoid benzodiazepines: shown to worsen outcomes in PTSD, in addition to the other risks they pose
- Make sure to inquire about and assist patients with adherence to secondary stroke prophylaxis interventions

Post-stroke neuropsychiatric disorders: conclusions

- Post-stroke neuropsychiatric disorders are common
  - But can go undiagnosed and untreated if you don’t look for them
- Lead to poorer health outcomes and quality of life
- However, treatment can improve outcomes
- SSRIs may be the best option for many post-stroke neuropsychiatric disorders
- Consider psychosocial interventions (psychotherapy, family education, encouraging exercise, etc) as well
- Stroke is a risk factor for suicide—make sure to screen for suicidality and take action to improve safety and reduce risk when needed
- Post-stroke neuropsychiatric disorders are a serious problem, but we can intervene to improve outcomes for our patients

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Questions?