Neuropsychiatric Issues Following Stroke

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Learning Objectives

• To recognize the neuropsychiatric sequelae of stroke, with a focus on post stroke depression

• To understand approaches to treatment and related safety considerations

• To appreciate the impact of post stroke neuropsychiatric issues, and treatment, on stroke recovery and survival
Overview

• Stroke Facts
• Post Stroke Depression (PSD)
• Role of antidepressants in PSD prevention, physical recovery & survival
• Other Neuropsychiatric Sequelae of Stroke
  • Post Stroke Anxiety
  • Pathological Affect
  • Apathy
  • Catastrophic Reaction
  • Delirium
Stroke: Definition

- An episode of neurological dysfunction caused by cerebral, spinal or retinal focal infarction
- Objective evidence of ischemic injury in a defined vascular distribution
- Clinical symptoms persisting $\geq 24$ hours or until death
- Other etiologies excluded

Sacco et al. Stroke 2013
Stroke Pathophysiology

• Ischemic (85%)
  • Interruption of blood supply to the brain → cell death
  • Thrombosis or embolism

• Hemorrhagic (15%)
  • Focal collection of blood within the brain
  • Vascular anomaly or hypertension
Impact of Stroke: Canada

• > 60,000 strokes per year
• 3rd leading cause of death → 13,000 die per year
• > 400,000 live with long-term stroke disability
• Incidence expected to grow

Impact of Stroke: United States

- >795,000 per year
- 3rd leading cause of death → 128,978 die per year
- Permanent disability: 66%
- Annual cost: $65 Billion

Heart Disease and Stroke Statistics – 2016 Update
Mozaffarian et al. Circulation 2016
Impact of Stroke: Israel

• 16,000 strokes per year
• 60% do not reach hospital in time for acute treatment
• Majority remain disabled and in need of rehabilitation and assistance for basic functioning

State of Israel Ministry of Health 2016
1.9 MILLION BRAIN CELLS DIE EVERY MINUTE AFTER STROKE
Death rate in-hospital following a stroke is decreasing (per 100,000 people)
Consequences of Stroke

- Motor
- Sensory
- Language problems
- Cognitive problems
- Emotional disturbances...
Post Stroke Neuropsychiatric Disorders

• Depression: 35%
• Anxiety: 25%
• Pathologic affect: 20%
• Apathy: 20%
• Catastrophic reaction: 20%
• Delirium > 30%
• Dementia > 25%
• Mania or Psychosis: rare

Chemerinski and Robinson Psychosomatics 2000
Post Stroke Depression (PSD)

- Prevalence: 20 - >65%
- Most recent meta-analysis: 31% developed depression at any time point up to 5 years following stroke

1) Depression Measurement:
   - self-administered scales vs. structured interviews

2) Population:
   - prevalence in hospital 30-40% vs. 10-20% in community samples

3) Timing:
   - acute vs. rehab vs. months later

Hackett and Pickles  Int J Stroke 2014
Depression in Medical Illness

- Stroke: 20-65%
- Parkinson’s Disease: 40-50%
- HIV: 44%
- CAD: 40%
- Cancer: 33%
- Diabetes: 27%
Post Stroke Depression: Risk Factors

- Severity of functional dependence *
- Psychiatric or medical history
- Social isolation
- Genetics
- Female Gender ?
- Stroke characteristics & lesion location ?
Post Stroke Depression: Cause

Theory #1: Biological Mechanism

- brain injury affects mood regulation
  - lesion location
  - inflammation
  - depression after stroke > other illnesses
  - occurs even in ‘silent’ stroke
Lesion Location (LL) in PSD

• Systematic Review:
  • 26 original articles reviewed
  • Multiple methodological differences noted

• Findings:
  • Left hemisphere LL is associated with PSD in hospital inpatient studies
  • Right hemisphere LL is associated with PSD in community studies

• Recommendations:
  • More standardized evidence required

Bhogal et al. Stroke 2004
Post Stroke Depression: Cause

Theory #2: Psychosocial Mechanism

→ reaction to major life/death event
  • looks like depression
  • risk factors unrelated to stroke
  • biological mechanism inconsistently replicated
Post Stroke Depression: Recovery & Survival

- Social withdrawal
- Worsened quality of life
- Increased caregiver burden

- Poor rehabilitation outcome
- Poor cognitive recovery
- Increased mortality
Post Stroke Depression: Impact on Survival

• Depressive symptoms after stroke are associated with higher mortality:
  • Large VA study: 10% higher risk mortality at 3 years
  • Association with 12- and 24-month mortality
  • Higher mortality 29 years later
  • 3.5 – 8 x higher mortality 15 months & 10 years later

Possible Mechanisms

- Medication adherence
- Lifestyle modification
- Smoking, substances
- Direct biological effects:
  - Cytokines
  - Altered autonomic nervous system activity
  - HPA-Axis
Onset of Depression

- Peak 3-6 months
- Risk remains > 2 years
- Can become chronic:
  - 19% of patients remained depressed at 2 years
  - 29% at 3 years

Astrom et al. Stroke 1993
Importance of Recognition

“Despite the devastating consequences of untreated poststroke depression, it is vastly undertreated. . . .

. . . early and effective treatment of depression is perhaps even more crucial in this patient population, given the need for full mobilization for occupational and physical therapy and other functional retraining early in the course of recovery.”

Huffman and Stern  Psychosomatics 2003
There is no universally accepted screening tool for PSD

- CES-D - Center for Epidemiological Studies-Depression Scale
- HADS - Hospital Anxiety Depression Scale
- BDI - Beck Depression Inventory
- GDS - Geriatric Depression Scale
Screening Tools

- PHQ-9
- PHQ-2
- “Are you depressed?”

- Valid, easy, useful, free

**Patient Health Questionnaire (PHQ-9)**

<table>
<thead>
<tr>
<th>Problem</th>
<th>Not at all (0)</th>
<th>Several days (1)</th>
<th>More than half the days (2)</th>
<th>Nearly every day (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Little interest or pleasure in doing things.</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>b. Feeling down, depressed, or hopeless.</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>c. Trouble falling/asleep, sleeping too much.</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>d. Feeling tired or having little energy.</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>e. Poor appetite or overeating.</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>f. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down.</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>g. Trouble concentrating on things, such as reading the newspaper or watching TV.</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>h. Moving or speaking so slowly that other people could have noticed. Or the opposite; being so fidgety or restless that you have been moving around more than usual.</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>i. Thoughts that you would be better off dead or of hurting yourself in some way.</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

2. If you checked off any problem on this questionnaire so far, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all
- Somewhat difficult
- Very difficult
- Extremely difficult

TOTAL SCORE

Turner et al. Stroke 2012
Post Stroke Depression: Challenges in Diagnosis

• Time
• Communication difficulty
• Cognitive impairment
• Anosognosia = lack of awareness
• Overlap of depression & medical illness
• Overlap of depression & other syndromes
  • Apathy
  • Pseudobulbar affect
• Stigma
Major Depression
DSM-V Diagnostic Criteria

• ≥ 5 symptoms, 2 week period, change in function
• * must include 1 of these symptoms

• Depressed mood, most of the day, for most days *
• Marked reduction in interest or pleasure in activities *
• Decreased/increased appetite/weight
• Insomnia or hypersomnia
• Psychomotor agitation/retardation
• Loss of energy/fatigue
• Feelings of worthlessness/inappropriate guilt
• Loss of concentration
• Recurrent thoughts of death or suicide
Post Stroke Depression Case: Ms. Z

• 71 yo single female
• No Psychiatric History
• PMHx:
  • DM Type I, HTN, Hyperlipidemia
• Left MCA stroke
  • Right hemiparesis
  • Expressive aphasia
Ms. Z

• Crying ++
• Despair; death wishes
• “It’s too much; I need help”
• Multiple losses:
  • Independence
  • Job/$$
  • House
  • Friends
  • Hobbies....
Ms. Z
Treatment

• Medication:
  • Citalopram 60 mg – partial response
  • Mirtazapine 30 mg – akathisia
  • Nortriptyline 100mg – good effect

• Supportive Therapy

• Future Goals: Rehab, Social links
Post Stroke Depression: Treatment

- Psychosocial
- Biological
- Medication broadly
  - Prevention
  - Physical recovery
  - Mortality
Psychotherapy

• Loss of independence
• Physical limitations
• Identity & body image issues
• Loss of employment
• Financial strain
• Less access to social supports
• End of life issues
Psychotherapy: Evidence

• Little positive research
• Talk-therapy combined with medication
• Focus on problem-solving, goals, coping skills, psycho-education, family support
• Cochrane Review 2009: “Results do not provide strong support for the use of psychotherapeutic interventions in this population.”

Robinson and Jorge Am J Psych 2016
Treatment: Antidepressant Medication

- Antidepressants are effective:
  - SSRIs & others
  - Tailor treatment to the patient
  - Takes weeks to work
  - Psychoeducation
Treatment: Antidepressant Medication

- TCAs
  - Nortriptyline
- Pro: Effective; Positive studies in PSD
- Con: Anticholinergic side effects
- Not 1st line
SSRI Side Effects

• Generally safe and well tolerated
• Common side effects tend to resolve:
  • GI upset
  • Headache
  • Sleep changes
• Rare but serious side effects:
  • Bleeding – includes hemorrhagic stroke
  • Hyponatremia
  • Falls
  • Seizures
  • Induction of mania or SI
Medication Interactions: Serotonergic Medication

- Beware of other serotonergic medications:
  - Tramadol
  - Linezolid
  - Herbal remedies

Serotonin syndrome can be life threatening.
Inform your patients about it.
Medication Interactions: Warfarin

- Warfarin mainly metabolized by CYP1A2, 2C9 and 3A4
- Most antidepressants inhibit at least one of these pathways

Highest Risk of Interaction:
- Fluoxetine
- Paroxetine
- Fluvoxamine

Lowest Risk of Interaction:
- Citalopram
- Escitalopram
- Sertraline

Careful warfarin management is necessary when an SSRI is initiated, altered, or discontinued.
Medication Interactions: Direct Thrombin Inhibitors

Theoretically, SSRIs and other drugs that inhibit serotonin uptake would increase the risk of bleeding when combined with other anticoagulants, but little information is available.
Health Canada Advisory
Citalopram & Escitalopram

Be aware of dose-dependent
QT prolongation
Health Canada Endorsed Important Safety Information on
CELEXA® (citalopram hydrobromide)

- A thorough QT study, conducted according to international standards, assessing the effects of citalopram 20 mg per day and 60 mg per day on the QT interval has shown that citalopram causes dose-dependent QT prolongation.

- Celexa® (citalopram hydrobromide) should no longer be prescribed at doses greater than 40 mg per day.

- 20 mg per day is the maximum recommended dose for patients with hepatic impairment, patients who are 65 years of age or older, patients who are CYP2C19 poor metabolizers, or patients who are taking concomitant cimetidine or another CYP2C19 inhibitor.

- Celexa® (citalopram hydrobromide) is contraindicated in patients with congenital long QT syndrome or known QT interval prolongation.
Treatment: Antidepressant Alternatives

- Stimulants
  - Limited research; maybe effective
  - Generally safe, but risks exist

- ECT
  - Effective treatment for serious cases
  - Previous stroke is not a contraindication
“It’s a new anti-depressant—instead of swallowing it, you throw it at anyone who appears to be having a good time.”
SSRIs For More Than Depression

• Prevention of Post Stroke Depression
• Physical/ Functional Recovery
• Survival
Advances in Prevention:

![Graph showing the percentage of original sample developing depression in various studies.]

<table>
<thead>
<tr>
<th>Study</th>
<th>Completers</th>
<th>Randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robinson et al. (79) (52 weeks)</td>
<td>134</td>
<td>176</td>
</tr>
<tr>
<td>Rasmussen et al. (90) (52 weeks)</td>
<td>67</td>
<td>137</td>
</tr>
<tr>
<td>Almeida et al. (91) (24 weeks)</td>
<td>56</td>
<td>92</td>
</tr>
<tr>
<td>Chollet et al. (50) (12 weeks)</td>
<td>88</td>
<td>113</td>
</tr>
<tr>
<td>Tsai et al. (82) (52 weeks)</td>
<td>56</td>
<td>111</td>
</tr>
</tbody>
</table>

- Escitalopram (10 mg <65 years; 5 mg >65 years)
- Problem solving therapy
- Sertraline (63 mg Rasmussen; 50 mg Almeida)
- Fluoxetine (20 mg)
- Milnacipran
- Placebo

Robinson and Jorge Am J Psych 2016
A Double-Blind, Placebo-Controlled Study of Sertraline in the Prevention of Depression in Stroke Patients

- N= 137 non-depressed
- <4 weeks post stroke
- Sertraline (50-150 mg) vs. placebo
- Rx - 1 year
- 10% sertraline vs. 30% placebo depressed @ 1yr

Rasmussen et al. Psychosomatics 2003
Escitalopram and Problem-Solving Therapy for Prevention of Poststroke Depression: A Randomized Controlled Trial

- 176 non-depressed stroke patients
- Escitalopram vs. placebo vs. PST started within 3 months of stroke
- Maintained for 1 year
- Placebo patients more likely to develop depression than patients on escitalopram (22.4% vs 8.5% P<.001)

Robinson et al. JAMA 2008
Prevention Clinically

- No guidelines currently recommend antidepressants for prevention
- Must weigh risks vs. benefits
SSRIs for Stroke Recovery

- Systematic review & meta-analysis of RCTs using SSRI in 1st year of stroke
- Dependence & Disability = primary outcomes
- 52 completed trials; 4059 patients
- “Tantalizing evidence” of disability benefits in non-depressed patients post stroke
- Large, well-designed trials needed to clarify

Mead et al. Cochrane Database Syst Rev 2012
Mead et al. Stroke 2013
Fluoxetine for motor recovery after acute ischemic stroke (FLAME): a randomised placebo-controlled trial

- 118 ischemic stroke patients
- Moderate-severe motor deficit
- Ages 18 - 85
- Fluoxetine 20 mg OD vs. placebo, 5-10 days post stroke
- All received physiotherapy
- Result: Fluoxetine significantly enhanced motor recovery

Distribution of modified Rankin scale scores at day 90

Chollet et al. Lancet Neurology 2011
Mortality and Poststroke Depression: A Placebo-Controlled Trial of Antidepressants

- 104 patients were randomly assigned to nortriptyline (100 mg/day), fluoxetine (40 mg/day), or placebo x 3 months
- Follow up for 9 years
- Survival rate with antidepressants was almost twice that of placebo (67.9% vs. 35.7% p=0.005)
- Antidepressants may modify pathophysiological processes associated with PSD & mortality

Jorge and Robinson Stroke 2003
Mortality and Poststroke Depression: A Placebo-Controlled Trial of Antidepressants

Probability of survival was significantly greater in the patients receiving antidepressants ($p=0.004$).

Jorge and Robinson Stroke 2003
Survival Rate for Patients Who Were Depressed and Nondepressed at 3 Months, Followed Over 9 Years

![Graph showing survival rate for patients who were depressed and nondepressed at 3 months, followed over 9 years. The graph compares the probability of survival for nondepressed and depressed patients, with data showing a significant difference (*) for treated and untreated groups at 9 years.]

Robinson AmJPsych 2016
Post Stroke Depression: Summary

• Depression is common after stroke
• Detection can be challenging, but is important
• Untreated depression can become chronic, can worsen functional outcome, and impact survival
• Biopsychosocial approach to treatment
• Medications are safe, but need to be monitored
• Potential of prevention
Something is Wrong...
But They’re Not Depressed

• Post-Stroke Anxiety
• Pathological Affect
• Apathy
• Catastrophic Reaction
• Delirium
Post Stroke Anxiety Case: Mr. S.

- 66 yo married male dentist admitted for stroke
- Emotional; crying; panicky
- Poor sleep, not eating, physical complaints
- Mood “not depressed”; enjoys family visits
- Lifelong “worrier; perfectionist”
- Refusing investigations due to fear
Mr. S.
Treatment

• Inpatient Medications:
  • Sertraline titrated to 150 mg OD
  • Zopiclone 7.5 mg QHS
  • Lorazepam 1mg prn

Outpatient Treatment:
• Integrative therapy – supportive, CBT principles
• Relaxation exercises; physical exercise
• Mindfulness Based Therapy Course
• Able to taper of medications within 2 years
Post Stroke Anxiety

• Prevalence: 25%
• Comorbid PSD: 75%

• Generalized Anxiety Disorder:
  • Excessive worry + 3 of:
    • Restlessness
    • Irritability
    • Poor energy
    • Poor concentration
    • Muscle tension
    • Sleep disturbance
Post Stroke Anxiety

• Negatively influences recovery & function
• Comorbid GAD prolongs PSD

• Treatment:
  • SSRIs and typical agents
  • Benzodiazepines often avoided post-stroke; may be indicated in short-term

Shimoda and Robinson 1998
Emotional Syndromes, With or Without Depression

- Pathological Affect
- Apathy
- Catastrophic Reaction
- Overlap with depression
Frequent & easily-provoked crying or laughter
- Exaggerated from underlying emotion
- “Uncontrollable”
- Inappropriate

Pseudobulbar Affect
- Emotional Incontinence
- Emotionalism
- Emotional Lability

“I know my face looks sad, but I'm not feeling sad at all.”
Pathological Affect

• Ask about:
  • Characterization of the episodes
  • Precipitants of the episodes
  • Associated emotions

• Treatment:
  • SSRIs
  • TCAs & other antidepressants
  • Dextromethorphan/Quinidine – 1st approved medication by FDA

Rosen and Cummings Annals of Neurology 2007
Apathy

- Loss of interest
- Loss of motivation
- Poor effort
- Indifference

“If I let him, he would sit in his chair all day doing nothing and he’d be perfectly content.”

1/5 - 1/3 of stroke patients
Apathy

• Risk Factors
  • Cognitive impairment
  • Age
  • Low educational level
  • No association with lesion location

• Diagnostic Approach
  • Collateral history
  • Informant rating scale – Apathy Evaluation Scale

Van Dalen et al. Stroke 2013
Apathy does not respond to SSRIs. Distinguishing between post-stroke apathy and depression is important clinically.

Apathy: Treatment

- Insufficient evidence for post-stroke apathy treatment
  - Bupropion
  - Methylphenidate
  - Cholinesterase inhibitor
  - Nefiracetam
Catastrophic Reaction

- Outburst when unable to perform simple tasks → anxiety, aggression, refusal
- Expressive aphasia
- Management:
  - Prevent and support
  - Be calm; explain what you’re doing
  - Look for triggers
  - Be watchful for comorbid depression

1/5 of stroke patients
Delirium: “The Great Imitator”

• “Confusion”

• Hyperactive Delirium:
  • Agitation
  • Hallucinations

• Hypoactive Delirium:
  • Lethargy
  • Sedation
  • Can look like depression
Referral from Inpatient Stroke Unit:

“77 yo female with depression, not participating in physiotherapy. Please advise on antidepressant.”
“83 yo male with new panic attacks and poor function. Started on Cipralex but refusing to take it. Please assess.”
Delirium: DSM-V Diagnosis

• Disturbance of consciousness with reduced ability to focus, sustain, or shift attention

• A change in cognition (ie. memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia

• Develops over a short period of time & fluctuates
Delirium: Impact

- Post stroke Delirium: 13-48%
- Worse functional & cognitive outcome
- Longer inpatient stay
- More likely to be discharged to nursing home
- Higher mortality in hospital than non-delirious stroke patients
- Higher mortality at 12 months

Shi et al. Stroke 2012
Delirium: Management

• Attend to Delirium first, before other psychiatric issues
• Actively investigate for underlying medical problems

• Supportive & Preventative Measures:
  • Immobility
  • Sleep deprivation
  • Vision impairment
  • Hearing impairment
  • Dehydration
  • Cognitive impairment
Delirium: Management

- Medication:
  - Low dose Haldol or atypical antipsychotics
  - No adequate evidence for benzodiazepines or cholinesterase inhibitors

- Educate family about Delirium
Summary: Post Stroke Neuropsychiatric Disorders

- Depression
- Anxiety
- Pathologic affect
- Apathy
- Catastrophic reaction
- Delirium
Take Home Points: Neuropsychiatry of Stroke

- Depression is the most common psychiatric issue following stroke
- PSD impacts recovery, morbidity & mortality
- Treatment can improve outcome & quality of life
- There is growing evidence that antidepressants may have a role in preventing PSD, assisting physical recovery & improving survival
- Distinguish overlapping neuropsychiatric syndromes to appropriately guide your treatment
Thank you!