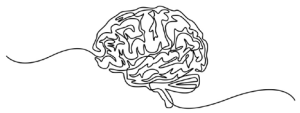
THE WARREN ALPERT Medical School
BROWN UNIVERSITY

Jointly Provided By

Comprehensive Stroke Center
Rhode Island Hospital
BROWNHealth
UNIVERSITY

Mood Disorders After Stroke and Their Impact on Outcome

Colin Harrington, MD
Professor of Psychiatry and Human Behavior, Clinician Educator
Professor of Medical Science, Clinician Educator
Professor of Medicine, Clinician Educator
The Warren Alpert Medical School of Brown University
Director, CNS-Psychiatry Clerkship and Consultation Psychiatry Fellowship
Director, Consultation Liaison Psychiatry
Brown University Health
Providence, RI



Rhode Island Stroke Symposium

Financial Relationship Disclosure(s)

Colin Harrington, MD

- Nothing to disclose

Post Stroke Depression

epidemiology, psychobiological mechanisms, and treatment

Brown Health Neurology Conference – Sept 2025

Colin Harrington, M.D.
Consultation Psychiatry and Neuropsychiatry
Professor, Clinician Educator
Departments of Psychiatry and Medicine
Alpert Medical School of Brown University

Post Stroke Depression
PSD

PSD

- Diagnosis
- Inclusive vs exclusive → literature favors inclusive
- Somatic / vegetative vs psychological

Depression and Stroke (PSD)
epidemiology

- The most common psychiatric sequelum of stroke
- Estimated 30-35% of patients: more than half of these meet criteria for MDD
- More common in stroke patients than in orthopedic and medical patients w/ similar levels of disability
- Associated with:
  - greater cognitive impairment
  - poorer physical health
  - poorer motor and functional outcome (greater disability)
  - Interference with rehab efforts
  - reduced QOL
  - Increased readmission rates
  - increased mortality rates

Depression and Stroke (PSD)
screening

- Center of Excellence designation requires screening for and ability to Tx PSD
- Screening tools
  - PHQ
  - Other
  - Role of aphasia (VAM)
- Definition – timing - adjustment disorder
- Hypokinetic delirium

PSD
epidemiology

- What and how Dx
  - Major depression
  - Minor depression
  - Adjustment do
- Where and when Dx
  - Rehab
  - Acute inpatient
  - > 3 months post stroke
  - Later
- Estimates of PSD range from 19-31%

PSD
epidemiology

- Cobley et al – MDD 19%, subthreshold 22%
- Robinson et al -
  - Acute or rehab setting
    - Major depression 22%
    - Minor depression 17%
  - OP clinics
    - Major depression 24%
    - Minor depression 24%
- Meta-analysis 51 studies and 25,000 patients
  - 31% depression at any point up to 5 years post stroke
- Meta-analysis 21,000 patients
  - 29% depression at 15 years post stroke

PSD
epidemiology

- Estimates based upon overt strokes
- Silent strokes 5 x more common
- Burden of chronic, accumulating small vessel disease
- Vascular depression – akin to vascular cognitive impairment (VCI)

- PSD associated with worse
  - QOL
  - Functional status
  - Mortality
  - Physical and cognitive recovery post stroke
  - Interfere with rehab efforts

PSD
RF

- Size
- Level / severity of disability and decline in ADLs
- Aphasia
- Imaging markers of premorbid chronic sm vs ds – microangiopathic changes
- Personal Hx depression
- Family Hx depression
- Gender – no
- Age - no

PSD
DDx

- Adjustment disorder
- Catastrophic Rx – aphasia - Stroke Aphasia Depression Questionnaire – Hospital Version (SADQ-H)
- Psychomotor slowed patient:
  - Delirium – hypokinetic
  - Catatonia
  - Akinetic mute
- Apathy – frontal-subcortical circuits (mesial-cingulate cortex role in motivated behavior)
- R-hemisphere paralinguistic language deficits
- Pseudobulbar affect (PBA) – pathologic affect

PSD
lesion location

- Early reports suggested increased rates of depression post-stroke associated with:
  - (L) > (R) lesions
  - more anterior lesions
  - cortical and subcortical (BG)
- Mechanisms proposed to explain early findings:
  - hemispheric lateralization of emotion (including finding that TMS is only effective when delivered to the L dorso-lateral cortex – esp in vascular depression)
  - asymmetric representation of mono-aminergic NT anatomy
- Early studies criticized for inconsistency in:
  - definition of depression
  - time post-stroke at which depression measured
- Early studies CT dependent for stroke Dx (vs MRI)

Robinson RG, Starkstein SE, Price TR - multiple references

PSD

- More recent data do not support the notion of increased rates of PSD in (L) hemisphere stroke patients
- Newer conclusions:
  - (L) hemisphere lesion predominance in depression 1-3 months after stroke
  - no clear hemispheric predominance in depression > 3 months out from stroke
- Deficit in awareness (anosognosia) from (R) hemisphere lesion may account for under-reporting / under-ascertainment of depression Sx / Dx after (R) sided stroke
- Versus over and mis-Dx of depression after R sided stroke due to loss of para-linguistic aspects of language (gesture, prosody, inflection) which leads to appearance of blunted affect and unemotional speech/language

Carson AJ et al, Lancet 2000

Secondary Mania

- More specific association b/w R sided lesions / injury and secondary manic-spectrum syndromes and behavior
- Akin to behavioral variant FTD (bvFTD) more common with R predominant disease vs sematic dementia / aphasia with L predominant disease
- Hemispheric lateralization and antagonism:
  - R primary/evolutionarily-survival/basic (anger, fear, hedonic, other)
  - L secondary socialized emotions (language)
  - L stroke → unopposed R = negative valence affect/mood/behavior
  - R stroke → unopposed L = social, approach, engage

- REFERENCES

PSD
proposed mechanisms

- Ascending mono-aminergic systems (asymmetric)
- HPA axis derangement
- Perturbation of frontal-subcortical networks relevant to mood and motivated behavior
- Elevated inflammatory factors post stroke
- Alterations in
  - Neuroplasticity
  - Glutamatergic neurotransmission

PSD
treatment

- First randomized placebo controlled double-blinded (DBPC) study
  - Lipsey (1984)
  - NTI > placebo
- First DBPC study of SSRI
  - Andersen (1994)
  - Citalopram > placebo
- Meta-analysis of 16 RCTs
  - 12 medications, 4 nonpharmacologic
  - 1655 patients
  - Benefit of antidepressant medications demonstrated
  - Psychotherapy not more effective than placebo – which should not suggest lack of benefit for psychotherapy approaches for many patients and families

PSD
treatment

- Evidence of PSD Tx benefit with:
  - nortriptyline
  - trazodone
  - fluoxetine
  - citalopram
  - sertraline
  - mirtazapine
  - psychostimulants (methylphenidate)
  - duloxetine (more recent)

- Recent trials:
  - L dorsolateral prefrontal cortex rTMS
  - L dorsolateral prefrontal cortex transcranial direct current stimulation (tDCS)

PSD
prevention

- Evidence of PSD prevention with:
  - sertraline
  - mirtazapine
  - fluoxetine (FOCUS)

- Meta-analysis prevention trials – 8 RCTs – 776 patients – nondepressed post stroke – benefit of antidepressant Tx:
  - Primarily SSRIs
  - > 1 year

PSD
treatment - nonpharmacologic

- Small studies
- Environmental enrichment (virtual reality)
- CBT
- Behavioral activation
- Group based acceptance and commitment therapy (ACT)
- Psycho-education

PSD

cerebrovascular effects of SSRIs - theoretical considerations

- Clear evidence of anti-platelet effect of SSRIs
- Reports of increased bleeding risk in observational and CC studies in patients with GIB, orthopedic surgery, other (no Black Box)
- Less clear evidence of excessive bleeding with SSRI post stroke
- Depression in CAD - pleiotropism welcome

- 5HT reuptake inhibition and effect on platelet function:
  - protect against ischemia (CAD)
  - increase risk of ICH ?

Ramasubbu R, J Clin Psychiatry 2004

Cerebrovascular Effects of SSRIs
theoretical concerns

- WHO data base lists hundreds of cases of association b/w SSRI use and ICH:
  - bleeding at other sites investigated as well (GI, ortho)
  - causal relationship remains unclear

- 2 case-control studies failed to demonstrate association b/w SSRI use and ICH

Ramasubbu R, J Clin Psychiatry 2004

PSD
treatment *ischemic* stroke

- Initial use SSRI:
  - exploit possible platelet mechanism for secondary prevention

- Sertraline:
  - pharmacokinetically neutral
  - evidence of treatment and prevention benefit

- Other SSRIs
- Non-SSRIs

PSD

treatment *hemorrhagic* stroke

- What to do for depression in ICH patient?
- If avoiding SSRI:
  - TCA → Sz, cognition, cardiac
  - bupropion → Sz

- Reasonable use of serotonergic agent in ICH patients:

  - careful use w/ NSAID, asa, warfarin

  - agents less potent at 5HTT pump (citalopram) →
  - agents w/ no effect at 5HTT pump (mirtazapine) →

minimal platelet effect

Ramasubbu R, J Clin Psychiatry 2004

SSRI and Post Stroke Recovery

- FLAME

- FOCUS

Pseudobulbar Affect (PBA)

- Pseudobulbar affect (PBA)
- Pathologic affect
- Emotional incontinence
- Involuntary emotional expression disorder (IEED)

Pseudobulbar Affect (PBA)
definition / phenomenology

- Sudden, uncontrollable episodes of laughter or crying
- Emotional expression incongruent with internal mood state
- Any strongly felt internal emotion may drive the same / often incongruent emotional expression
- Spectrum – frequent involuntary expressed emotion of the same valence (congruent with) internal mood state but out of proportion to the trigger
- Often mis-diagnosed as depression (crying)
- Often ignored
- Significant functional impairment and difficult for family / caregivers

Pseudobulbar Affect (PBA)
anatomy

- Eary descriptions suggested occurrence with bi-frontal lesions ("batwing" menigiomas)
- Causes:
  - Stroke
  - MS
  - TBI
  - Tumor
- Sites / location:
  - Frontal
  - Pons
  - Cerebellum
  - Other

Pseudobulbar Affect (PBA)
treatment

- Earliest study – TCA / NTI
- SSRI – multiple – relevant as PBA can be co-morbid with depressive disorder
- Neudexta (dextromethorphan and quinidine):
  - Dextromethorphan – NMDA receptor / glutamate antagonist
  - Quinidine – inhibitor of dextromethorphan metabolism to support adequate serum level

RCVS

- Reversible cerebrovascular vasoconstriction syndrome
- SSRI use has been noted in association with these cases

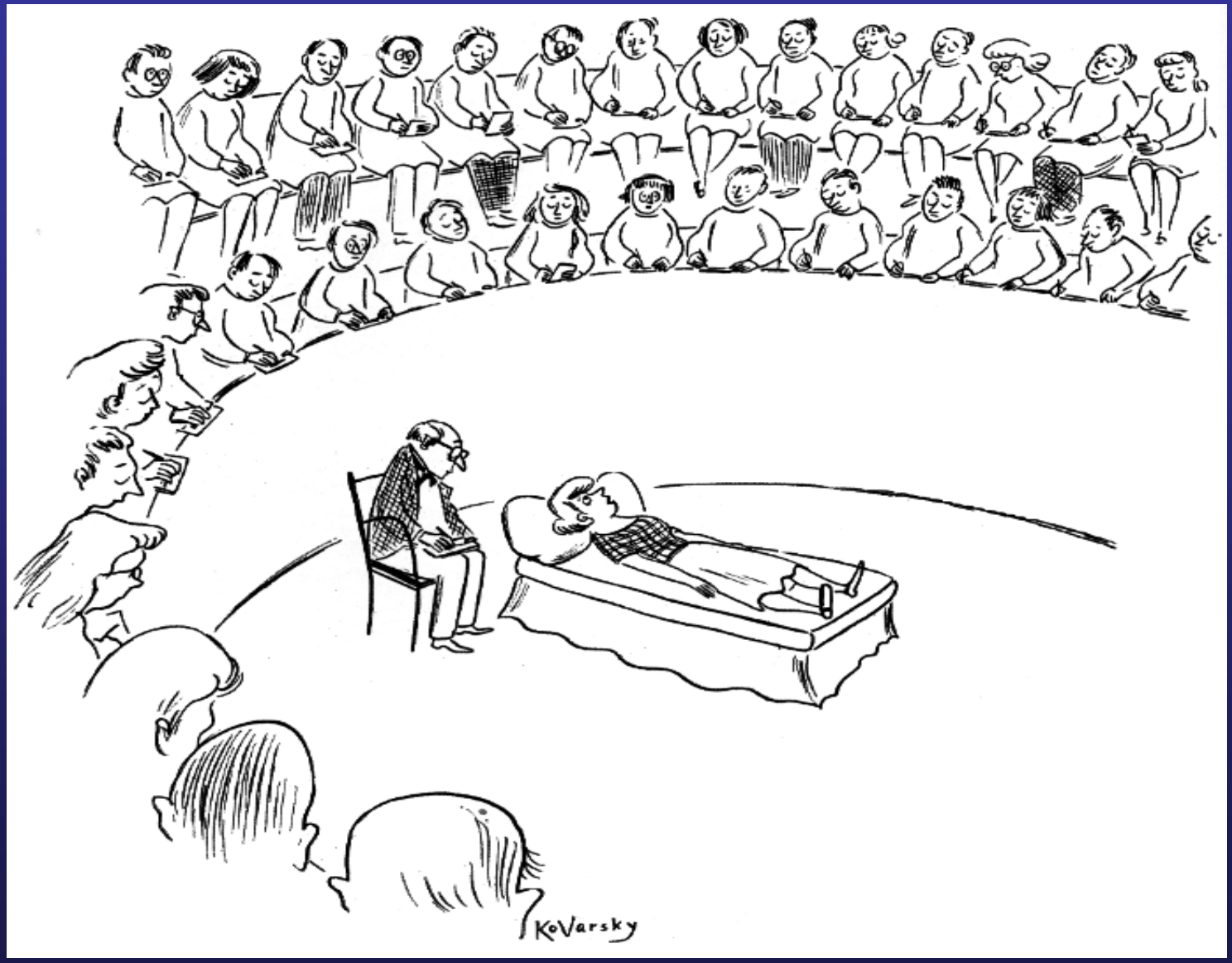
- Another note of caution on Tx of PSD?

References

- Robinson RG, Jorge RE, et al. Poststroke depression: an update. J Neuropsychiatry Clin Neurosci 2024, 36:22-35.
- Medeiros GC, Roy D, Kontos N, Beach SR. Post-stroke depression: a 2020 updated review. General Hospital Psychiatry 2020, 66:70-80.
- Chollet FC, Tardy J, et al. Fluoxetine for motor recovery after acute ischemic stoke (FLAME): a randomized placebo-controlled trial. Lancet Neurol 2011, 10:123-30.
- FOCUS Trial Collaboration. Effects of fluoxetine on functional outcome after acute stroke (FOCUS): a pragmatic, double blind randomized, controlled trial. Lancet 2019, 393:265-47.
- Liu L, Marshall IJ, et al. Natural history of depression up to 18 years after stroke: a population-based South London Stroke Register study. Lancet2024, 40:1-12.

QTc and Psychotropics

- Beach et al JACLP 2018


KoVarsky