Post-Stroke Depression: Detection, Differential Diagnosis and Treatment

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Disclosure Information

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Post-Stroke Depression

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All medications

Neuropsychiatric complications of stroke

Symptom	Frequency
Depressed Mood	***61%***
Irritability	33%
Appetite changes	33%
Agitation	28%
Apathy	27%
Anxiety	23%
Sleep Disturbance	16%
Disinhibition	10%
Hallucinosis / delusions	3%

Dafer et al, *Top Stroke Rehab*, 2008

PSD - So What?

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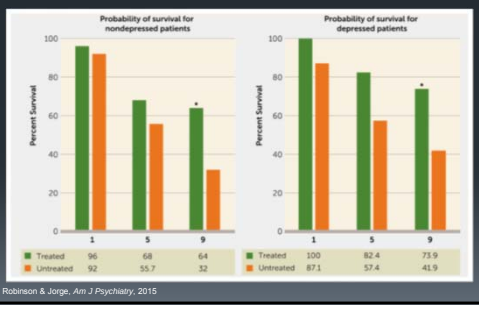

Robinson & Jorge, *Am J Psychiatry*, 2015

DSM-5: MDD

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- Core features: 1) Depressed mood *or* 2) loss of interest;
- AND ≥ 5 associated symptoms for 2+ weeks:
  - **Depressed mood** most of the day;
  - Markedly diminished interest or **anhedonia**;
  - Significant **weight loss** (not intestinally trying);
  - **Insomnia** (typical) or **hypersomnia** (atypical)
  - **Psychomotor** agitation or retardation;
  - **Fatigue** or anergia;
  - Feelings of **worthlessness** or excessive / inappropriate **guilt**;
  - Diminished ability to think, **concentrate**, make decisions;
  - Recurrent thoughts of death or **suicidal ideation.**

PSD

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- "Post-stroke Mood Disorders"
  - With depressive features, major depression-like episode, mixed
- "Vascular Depression" (DSM-5)
  - ⇧Age, ⇧cognitive impairment, ⇧physical impairment, less likely FH/personal Hx, poorer response to Tx, relapsing
  - More often related to leukoariosis
- Unique and common features: **burden (guilt)**, **behavioral inertia**

- Associated lesions (outdated, inconsistent data):
  - Left fronto-polar / latero-dorsal frontal corticies
  - Left basal ganglia / CSTC loops (frontal>temporal>parietal)
  - Anterior cingulate (more apathy)
  - Left >> Right hemisphere lesions

Evolving Understanding of Depression as a Systemic Disorder

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- AHA – Depression is a **risk factor for CAD and Stroke**
- Depressive symptoms ⇧ risk of death from IHD, MI, CVAs[1]
- Excessive platelet reactivity[2]
- Depression reduces survival in metastatic breast CA[3]
- Elevated IL-1, IL-6, TNF-α, CRP, chemokines, and adhesion molecules in MDD[4]

[1]Wassertheil-Smoller, *Arch Intern Med*, 1996; [2]Musselman et al, *Am J Psychiatry*, 1996; [3]Gise-Davis et al, *J Clin Onc*, 2010; [4]Nemeroff, unpublished data/personal communication

PSD: Incidence, Morbidity, Mortality, and Functional Outcome

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- ~1/3 develop PSD (meta-analysis, 61 studies, N=25,488[1)]
  - Pooled frequency = 31% (2008 review = 33%, p>0.05)
- ⇧mortality by 3.4x at 10 yr[2]
- Correlated with severity of impairment, disability,cognitive impairment, and recovery of ADLs/I-ADLs[1,3,4]
- Protracted cognitive impairment[5]
- Fluoxetine improved motor recovery (FLAME Study[6])
- Acute treatment with low-dose escitalopram (PSD + non-depressed) improved RBANS at 12 months[7]

[1]Hackett & Pickles, *Intl J Stroke*, 2014; [2]Robinson & Spalletta, *Can J Psychiatry*, 2010; [3]Ayrbe et al, *Br J Psychiatry*, 2013; [4]Johnson et al, Nursing, 2006;[5]Robinson, *The Clinical Neuropsychiatry of Stroke*, pp 470, 2006;[6]Chollet et al, Lancet Neurol, 2011;[7]Jorge et al, *Arch Gen Psychiatry*, 2010

Risk Factors for PSD

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- Genetic:
  - SERT polymorphisms and BDNF gene snp[1]
- Demographics:
  - Neither age nor sex consistently associated with PSD[2]
- PMH: **DM**, depression, anxiety[2]
- Stroke severity and functional impairment has strongest correlation with PSD[3]
- Weak association between PSD and type (ischemic vs hemorrhagic) or mechanism (embolic vs thombotic)
- Lesion localization: murky waters
  - Left frontal/basal ganglia = transient, ie, <2 months out

[1] Kim et al, *J Psychiatric Res*, 2013; [2]De Ryck. J Geriatr Psychiatry, Neurol, 2014; [3]Kutlubaev, *Int J Stroke*, 2014

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Predictors of acute PSD

- Age: <65 years, increased 2.3 fold
- Crying in first 5 days s/p stroke (*sans* coma)[1]:
  - Pathologic crying – NO predictive value
  - Appropriate crying ('emotionalism') – 41% develop PSD
  - Catastrophic reaction – 64% develop PSD
- Barthel Index Score of 60-90[2]
- Lesions in close proximity to left frontal pole[3]
  - TMS to left DLPFC is effective in MDD and PSD

[1]Carota et al, *Neurology*, 2005; [2]Wiley et al, *Stroke*, 2010; [3]Robinson et al, *Brain*, 1984

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Detection

- Not a trivial task
  - Overlap with disorders of motivation
  - Deficits may preclude clinical evaluation
  - Heterogeneity of screening measures
  - Lack of properly trained personnel
  - Vague complaints
- Clinical interview and history **with** collateral
- Standardized screening measures
  - Objective:
    - Utility limited by clinician
  - Self-report (when appropriate):
    - Sensitive but not specific; anosognosia, physical/cognitive impairments

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Self-Report Measures

- Beck Depression Inventory-2 (BDI-2)
- Hospital Anxiety and Depression Scale (HADS)
- **Center for Epidemiological Studies-Depression Scale (CES-D)***
- **Patient Health Questionnaire 9-item (PHQ-9)***
- Geriatric Depression Scale (GDS)#
- Visual-Analog Mood Scale (VAMS)#

* Appear to have best sensitivity and internal validity reliability
# Not validated in PSD

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Observational Measures

- **Hamilton Depression Rating Scale (HDRS)***
- Post-stroke Rating Depression Scale (PDRS)#
- Stroke Aphasia Depression Questionnaire (SADQ-H 21 or 10 item)
- Aphasia Depression Rating Scale (ADRS)
- Signs of Depression Scale (SODS; RN admin.)
- Montgomery-Asberg Depression Rating Scale (MADRS)

* Appear to have best sensitivity and internal validity
# Not validated in PSD

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JNNP

Screening for poststroke major depression: a meta-analysis of diagnostic validity studies

Nick Meader, Thirimon Moe-Byrne, Alexis Llewellyn, et al.

J Neurol Neurosurg Psychiatry published online February 5, 2013
doi: 10.1136/jnnp-2012-304194

Table 2 Evidence summary on meta-analysis of depression scales for any depression

Instrument	Total sample size (number of studies)	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)*	Negative predictive value (95% CI)*	Rule-in clinical utility**	Rule-out clinical utility**
BDI	940 (4)	0.86 (0.78 to 0.92)	0.64 (0.60 to 0.83)	0.54 (0.39 to 0.73)	0.90 (0.79 to 0.95)	Poor	Fair
CES-D	314 (4)	0.75 (0.60 to 0.85)	0.88 (0.71 to 0.95)	0.75 (0.56 to 0.89)	0.88 (0.78 to 0.93)	Fair	Good
HDRS1	1019 (7)	0.84 (0.75 to 0.90)	0.83 (0.72 to 0.90)	0.71 (0.57 to 0.82)	0.91 (0.85 to 0.95)	Fair	Good
YMRS-A	1250 (9)	0.80 (0.76 to 0.83)	0.93 (0.88 to 0.96)	0.77 (0.49 to 0.93)	0.90 (0.85 to 0.94)	Poor	Fair
HADS-T	483 (4)	0.72 (0.45 to 0.89)	0.86 (0.69 to 0.94)	0.72 (0.42 to 0.88)	0.86 (0.72 to 0.95)	Fair	Good
GDS-15	507 (4)	0.74 (0.55 to 0.87)	0.80 (0.72 to 0.87)	0.65 (0.49 to 0.77)	0.86 (0.76 to 0.93)	Fair	Good
MADRS	615 (4)	0.85 (0.78 to 0.90)	0.73 (0.70 to 0.86)	0.67 (0.56 to 0.76)	0.91 (0.87 to 0.93)	Fair	Good
PHQ-9	552 (3)	0.86 (0.70 to 0.94)	0.79 (0.60 to 0.90)	0.67 (0.46 to 0.82)	0.92 (0.86 to 0.97)	Fair	Good
PHQ-2	552 (3)	0.79 (0.55 to 0.92)	0.76 (0.62 to 0.85)	0.62 (0.42 to 0.75)	0.88 (0.74 to 0.96)	Poor	Good

* Assumes depression prevalence of 25% based on an estimate from a systematic review on prevalence of any depression in stroke patients.
** See www.clinicalutility.co.uk for more information.
† All scales are self report except the HDRS and the MADRS which are clinician administered scales.
BDI, Beck Depression Inventory; CES-D, Center of Epidemiological Studies-Depression Scale; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scale; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery Asberg Depression Rating Scale; PHQ, Patient Health Questionnaire.

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Should everyone be screened?

YES

When should screening occur?

ACUTE & SERIALLY

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Differential Diagnosis

- Disorders of motivation (incidence: 25-60%)
  - Loss of spontaneity, sustainment of cognitive/motor activity, behavioral output
  - "Do you feel sad or down?" ➔ "No"
  - Do NOT treat with SSRIs
- Hypoactive delirium
- Dementia
- PBA
- Parkinsonism (hypomimia)

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Treatment

- "For any given patient with any given symptom on any particular day, they will respond *differently* to a specific drug at the same dose, given the same time, with the same serum levels, and the same lunar cycle."

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Treatment

- SSRIs considered 1st line
- TCAs equally effective but ⇧ side effects
- Stimulants **should be considered** (*but curiously are overlooked*)

- Psychotherapy – CBT
- Family-Based Interventions

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SSRIs and TCAs

- SSRIs
  - Good side-effect profile
  - Citalopram and sertraline most studied (evidence mounting for escitalopram)
  - Improved motor recovery with fluoxetine
  - AHA endorses use of SSRIs; 6+ months after remission
  - Risks: Bleeding, falls, standard SSRI side effects
- TCAs – no receptor left behind!
  - Poorly tolerated; dose-dependent side effects
  - Dirty drugs
  - Efficacy similar to SSRIs (nortriptyline)

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Escitalopram and the "others"

Drug	SERT	NET	DAT	α_1	H_1	M_1	5HT2A	5HT2C	σ_1
Celexa	+	-	-	+	+	-	-	-	-
Lexapro	+	-	-	-	-	-	-	-	-
Zoloft	+	+	+	+	-	+	-	-	+/-
Prozac	+	+	-	-	-	+	+	+	-
Paxil*	+	+	+	-	-	++	-	-	-
Luvox	+	-	-	-	-	-	-	-	+

(+) = K_i < 1000 nM

* M_{1-5}

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Other Options (mono- and adjunctive)

- **Stimulants**
  - **Rapid onset of action**
  - Improves engagement in rehabilitation
  - Likely augment plasticity, e.g., recovery from neglect
- SNRIs
  - Effexor (Pristique), Cymbalta, Savella (NET>>SERT)
- SARIs
  - **Serzone** and Trintellix
- NaSSA
  - Remeron ($\alpha_{1/2}$ antagonism; useful side-effects)
- Wellbutrin
  - SR formulation has best evidence for motivation and cognition

Prevention of PSD

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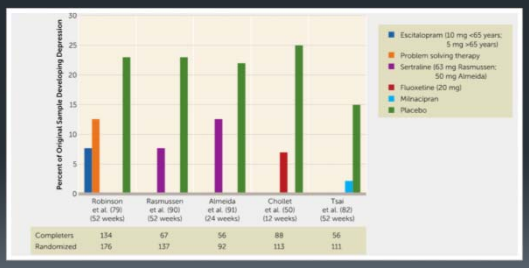

Robinson & Jorge, *Am J Psychiatry*, 2015

Psychotherapy

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- Evidence for psychological interventions is limited
  - Poor study design, poor efficacy of some modalities studied
- Cognitive Behavioral Therapy (thoughts drive behavior)
  - Fewer adverse effects than pharmacotherapy
  - Resource intense
  - Only 1 RCT with null results 2/2 methodological issues[1]
- Kookter et al., *Clinical Rehabilitation*, 2015
  - Stroke-specific 'augmented' CBT
  - Co-treatment with OT/PT/Movement therapy for 'goal-setting' and 'goal attainment'
  - Best structured therapy for PSD to date

[1]Lincon and Flannhagan, *Stroke*, 2003

Family / Systems Therapy

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- Paucity of data despite clear impact on care givers

- Vallury et al., *Topics in Stroke Rehab*, 2015
  - 5 components of 'effective' family interventions:
    - ✓Multicomponent interventions with ACTIVE problem solving, goal setting, and skill development;
    - ✓Care coordination and adherence support;
    - ✓Structured but flexible programs;
    - ✓Early implementation;
    - ✓Duration was 12+ weeks, with at least weekly treatments

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- A 54 yo RH male with a PMH + for HTN, DM2, and a remote history of MDD, was admitted to the stroke service with a left anterior MCA ischemic infarction. He has a mild non-fluent aphasia and ideomotor apraxia, but no gross motor impairments. On hospital day 3 nursing staff note that he is tearful when family/friends leave, is not engaging in any therapy, reports worsening mood. He is scheduled to be transferred to a rehab facility on day 5.

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What would the most appropriate treatment be at this point?

A. SSRI
B. SSRI + Stimulant
C. TCA
D. Mirtazapine
E. Neudexta

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- A 71 yo RH women is transferred to a long-term acute care hospital after a right frontal ICH. She is withdrawn, flat affect, does not initiate conversation, has very little spontaneous motor or verbal output, and seems to have bouts of crying with no clear trigger. On the PHQ-9 she dose not endorse depressive symptoms. When asked, states “I feel fine”. She is not engaging in any therapeutic modality.

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What medication should be avoided in this patient?

A. Nudexta
B. Ritalin
C. Wellbutrin SR
D. Zoloft
E. Amantadine

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This image is:

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This image is:

A. Anatomic drawing of the thalamus
B. Milk Art by my 7 year old son
C. Cruel Rorschach meant to annoy neurologists & psychiatrists
D. All of the above
E. None of the above

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Thank you!

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Extra Slides for your Viewing Pleasure

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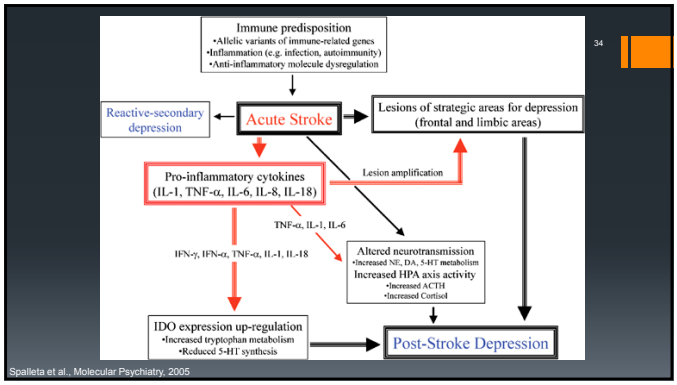
Clinical Observations

- Speeding up therapeutic efficacy with SSRIs
  - Buspirone > 5-HT1A sensitization
  - Stimulants > rapid antidepressant effects
- Improve tolerability: LOW, SLOW, BUT GO
- Remission less likely without psychotherapy
- Augment to target depressive symptoms
  - Modafinil / stimulants – fatigue, sleep/wake disturbance, engagement
  - Amantadine / bupropion – engagement in therapy, motivation
  - DA agonists – apathy, executive impairments
  - Hypnotics / Melatonin$_{1/2}$ agonists – insomnia, diurnal disturbance
  - Aripiprazole and brexpiprazole – rumination, perseveration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Immune predisposition
•Allelic variants of immune-related genes
•Inflammation (e.g. infection, autoimmunity)
•Anti-inflammatory molecule dysregulation
Reactive-secondary depression
Acute Stroke
Lesions of strategic areas for depression (frontal and limbic areas)
Pro-inflammatory cytokines (IL-1, TNF-α, IL-6, IL-8, IL-18)
Lesion amplification
TNF-α, IL-1, IL-6
IFN-γ, IFN-α, TNF-α, IL-1, IL-18
Altered neurotransmission
•Increased NE, DA, 5-HT metabolism
Increased HPA axis activity
•Increased ACTH
•Increased Cortisol
IDO expression up-regulation
•Increased tryptophan metabolism
•Reduced 5-HT synthesis
Post-Stroke Depression
Spalleta et al., Molecular Psychiatry, 2005