Geriatric Journal Club
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Title: Effect of Antidepressants on the Course of Disability Following Stroke

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Background:

- Stroke is associated with dependence in ADLs
- Stroke is also associated with high incidence of depression
- Treatment of post-stroke depression with antidepressants is associated with greater ADL recovery in patients whose depression remits compared to non-remitters.
- Recent placebo-controlled trials of citalopram and fluoxetine *in non-depressed patients* after stroke showed greater motor recovery over 1-3 months
- Accumulating evidence that antidepressant drugs produce signaling cascades that result in increased neurotrophic factors, inhibition of inflammatory cytokines, and proliferation of neural and glial precursor cells, increased axonal sprouting, and development of new synapses
- These investigators conducted a 1-year study of antidepressant effects on recovery of function after stroke, *independent of depression status*.

Importance:

- Chose to present this study because it addresses *possible non-mood effects of antidepressant drugs*, e.g, on CNS recovery and functioning

Specific aims:

- To assess whether antidepressants would augment stroke recovery independent of depression
- *Hypothesis:* Recovery from disability would be greater at 1-yr follow-up among patients administered either fluoxetine or nortriptyline, independent of depression, compared to patients given placebo.

Methods:

<u>General design</u>

- Randomized, 3-arm, double-blind, placebo-controlled trial
- Randomized independent of depression status at baseline to 3 months of treatment with fluoxetine titrated up to 40 mg/d, nortriptyline up to 100 mg/d, or placebo
- Quarterly follow-up over 9 months post-treatment

Sample

- Screened 343 patients, ages 18-85 (**Fig. 1**)
- Recent stroke (mean time from stroke to enrollment ~1month)
- Excluded patients w/signif medical illness that could impede stroke recovery or cognitive deficits that precluded verbal interview
- 56 depressed and 48 non-depressed subjects recruited, mostly from inpatient rehab unit in Iowa
- 21 excluded from analysis because of lack of analyzable modified Rankin Scale (mRS) data
- For analyses, n=83 at baseline, n=61 at 12-month follow-up (22 dropouts)

Measures/Outcomes

- DEPRESSION: Present State Exam (PSE) and 17-item HDRS score >or=12
- DISABILITY: Modified Rankin Scale (mRS), 0 (no sx) to 6 (dead)
- ADL IMPAIRMENT SEVERITY: Functional Independence Measure (FIM), 18-item, 72-point scale (higher score=less impairment)
- STROKE TYPE AND LOCATION: CT or MRI of brain
- STROKE SEVERITY: NIH Stroke Scale (NIHSS)
- INTENSITY OF REHAB CARE: Total hours of physical therapy per week, summed over quarterly visits

Statistical Approach

- Fisher's exact test for categorical variable comparisons
- Mann-Whitney U test for continuous variable comparisons
- Mixed model analysis of repeated measures to evaluate treatment effects over time, adjusting for covariates (age, baseline NIHSS & HDRS scores, hrs of PT)
- Kendall's tau-b for (non-parametric) mRS scores over time
- ANCOVA with tau-b coefficients, covariates were age, baseline NIHSS and HDRS scores, hrs of PT

Results:

Participants (**Table 1**)

- Mean age of treatment group < placebo group
- Rehab hours for placebo group > treatment group

Disability and ADL outcomes

- Mixed model analysis: significant treatment*time effect (**Table 2**)
- Age and stroke severity also independently associated with mRS change
- mRS scores improved over time in both treatment groups; placebo flat (**Fig 2**)
- ANCOVA found same outcome using nonparametric analysis (log transformed tau-b as outcome variable) (**Table 3**)
- FIM scores improved but treatment*time interaction not significant. (**Table 4)**
- Age, baseline NIHSS score, and hours of rehab were significantly related to FIM outcomes

Author's Conclusions:

- Antidepressant medication is associated with physical recovery from stroke over 1 year, *independent of depression*, after controlling for age, baseline stroke severity, total hours of PT
- Interpretation of results limited by high dropout rates and small group sizes
- Generalizability may be limited by homogeneity of subjects (white, married, educated, mid-high SES) and predominance of single site for recruitment
- Possible that antidepressant inhibition of microglial production of inflammatory cytokines and augmentation of neurogenesis contributes to recovery after stroke.

Reviewer's Comments:

- Strength of this study was repeated measures of disability over long follow-up period
- Characteristics of larger refuser and dropout groups are unknown
- Would have been useful to do sensitivity analysis comparing drug-placebo differences in disability outcomes in the depressed vs non-depressed groups
- Tolerability of treatment not reported

Practice Implications:

- Elderly patients with stroke-related disability might benefit from antidepressant treatment within the first 3-4 months after stroke, independent of the presence of depressive sx.
- Caveat: epidemiological studies from UK and Taiwan have reported association between antidepressant drug use and subsequent risk of stroke