# Clinical meaningful changes in Alzheimer's disease: CDR progression and effect on MMSE, ADAS-Cog, RBANS and ADC ADLI

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## Objectives

The Clinical Dementia Rating (CDR) scale is commonly used to characterize Alzheimer's disease (AD) stages and disease progression. CDR Global score (GS) determines the presence of cognitive impairment/dementia and quantifies disease severity from MCI (CDR 0.5) to mild (CDR 1), moderate (CDR 2) and severe (CDR 3) dementia. Identifying a clinically meaningful change in cognitive and functional tests is essential when cognition is used as an outcome in clinical trials. There is still no consensus between the association of the CDR GS to a score change in other cognitive and functional scales widely used as key endpoints in AD trials. Our objective was to establish clinically important differences for commonly used cognitive and functional tests when subjects progress from MCI to mild dementia and from mild to moderate dementia.

## Methods

Effect sizes (ES) were calculated to estimate clinically important changes on the MMSE, ADAS-Cog, RBANS and ADCS ADLI when subjects progressed from MCI to mild dementia and from mild to moderate dementia. Clinically important changes were defined as mean change of MMSE, ADAS-Cog, RBANS and ADC ADLI in subjects rated for the first time CDR GS 1 and CDR GS 2 at 6 and 12 months since baseline. Data from these scales was analyzed for baseline, 6 and 12 months for 466 subjects with AD enrolled in four multinational double-blind,placebo controlled clinical trials.

## Results

The mean changes for CDR rated first time mild dementia (CDR 0.5 to 1) in the MMSE, ADAS-Cog, RBANS and ADCS ADLI were respectively: -2.34±3.77 (d=-0.72), 2.83±7.35 (d= 0.43), -4.23±11.58 (d=-0.38) and -3.90±6.78 (d=-0.65). The mean changes for CDR rated first time moderate dementia (CDR 1 to 2) in the MMSE, ADAS-Cog, RBANS and ADCS ADLI were respectively: -5.07±3.99 (d=-1.45), 5.61±8.77 (d= 0.68), -4.23±6.96 (d=-0.55) and -14.22±12.00 (d=-1.29).

## Conclusions

We have explored the effect sizes of change on these instruments associated with CDR reflecting mild and moderate dementia. All scales captured worsening effectively when there was progression from MCI to mild dementia but the MMSE and the ADCS ADLI demonstrated being more sensitive to capturing worsening when there's progression from mild to moderate dementia.

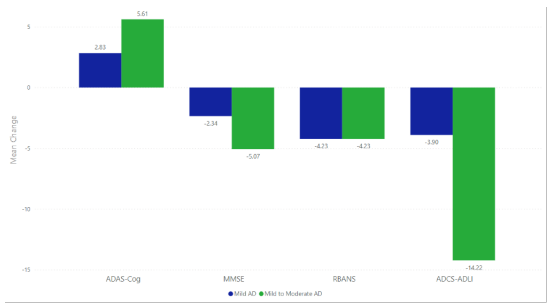


*Figure 1:* Mean change on ADAS-Cog, MMSE, RBANS and ADCS-ADLI when progresses from MCI to mild dementia and mild to moderate dementia

| Scale Name | Visit | Mean | Delta Mean | SD | N | Min Score | Max Score |
|---|---|---|---|---|---|---|---|
| CDR | Baseline | 1.00 | | 0.00 | 70 | 1 | 1 |
| ADAS-Cog | Baseline | 25.57 | | 7.80 | 69 | 12 | 47.33 |
| ADAS-Cog | Mild to Moderate | 31.19 | 5.61 | 8.77 | 64 | 15 | 56 |
| ADCS-ADLI | Baseline | 57.82 | | 9.95 | 45 | 35 | 72 |
| ADCS-ADLI | Mild to Moderate | 43.60 | -14.22 | 12.00 | 45 | 15 | 66 |
| MMSE | Baseline | 20.21 | | 2.95 | 70 | 13 | 28 |
| MMSE | Mild to Moderate | 15.14 | -5.07 | 3.99 | 70 | 5 | 24 |
| RBANS | Baseline | 54.92 | | 8.04 | 65 | 42 | 72 |
| RBANS | Mild to Moderate | 50.69 | -4.23 | 6.96 | 36 | 42 | 70 |

*Table 2:* Sample characterization when progression from mild to moderate dementia

| Scale Name | Visit | Mean | Delta Mean | SD | N | Min Score | Max Score |
|---|---|---|---|---|---|---|---|
| CDR | Baseline | 0.50 | | 0.00 | 396 | 0.5 | 0.5 |
| ADAS-Cog | Baseline | 17.15 | | 5.64 | 328 | 5.67 | 38 |
| ADAS-Cog | MCI to Mild | 19.98 | 2.83 | 7.35 | 321 | 5.67 | 46.67 |
| ADCS-ADLI | Baseline | 69.33 | | 5.19 | 88 | 54 | 77 |
| ADCS-ADLI | MCI to Mild | 65.43 | -3.90 | 6.78 | 87 | 41 | 77 |
| MMSE | Baseline | 23.70 | | 2.70 | 395 | 16 | 30 |
| MMSE | MCI to Mild | 21.35 | -2.34 | 3.77 | 345 | 9 | 30 |
| RBANS | Baseline | 66.35 | | 10.94 | 387 | 45 | 104 |
| RBANS | MCI to Mild | 62.12 | -4.23 | 11.58 | 276 | 43 | 100 |

*Table 1:* Sample characterization when progression from MCI to mild dementia

| Scale Name | Cohen MCI to Mild | Cohen Mild to Moderate |
|---|---|---|
| ADAS-Cog | 0.43 | 0.68 |
| ADCS-ADLI | -0.65 | -1.29 |
| MMSE | -0.72 | -1.45 |
| RBANS | -0.38 | -0.55 |

*Table 3:* Effect sizes for ADAS-Cog, ADCS-ADLI, MMSE and RBANS


## References

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M. Williams, M. Storandt, C. M. Roe, John C. Morris. Progression of Alzheimer disease as measured by Clinical Dementia Rating sum of boxes scores. Alzheimer's & Dementia, Journal of Alzheimer's Association, 2013; 9 (1S):39-44; https://doi.org/10.101/j.jalz.2012.01.005 3. Jamalian S, Dolton M, Chanu P, et al. Modeling Alzheimer's disease progression utilizing clinical trial and ADNI data to predict longitudinal trajectory of CDR-SB. CPT Pharmacometrics Syst Pharmacol. 2023; 12:1029- 1042. doi:10.1002/psp4.1297