# Choosing the Appropriate Rating Scale for Patient Inclusion and Primary Endpoint Definition in MDD Trials: MADRS or HAMD?

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## METHODOLOGICAL ISSUE ADDRESSED

Is there an **association** between the **rating scale** we use as **severity measure for including** major depressive disorder (MDD) patients in a clinical trial, the rating scale we define as **primary endpoint**, and the **success of the trial**?

## INTRODUCTION & AIMS

Among the most established scales to rate severity in major depressive disorder (MDD) are the Hamilton Depression Rating Scale in its 17-item version (HAMD; total score 0-52) and the Montgomery Åsberg Depression Rating Scale (MADRS; total score 0-60 scored over 10 items). In clinical trials testing treatment efficacy in MDD patients, either one or both scales are usually used as inclusion criteria. Furthermore, the primary endpoint is often defined as change from baseline in one of these scales. By analyzing recent clinical trials, we explore the current practice in MDD trials and test associations between scales and trial outcome (i.e., a significant primary endpoint).

## METHODS

We identified relevant trials using a commercial clinical-trial intelligence platform (Citeline) by applying the following search algorithm:

For inclusion to the analysis set, trials had to be industry-sponsored, randomized Phase 2 or 3 clinical trials in major depressive disorder (including treatment-resistant depression) with start date ≥ 1 January 2017. Trials had to be registered with an NCT/EudraCT identifier, enrolled >19 patients. HAMD and/or MADRS had to be used as both inclusion criterion and as primary/key efficacy endpoint.

Trials enrolling bipolar or suicidal populations and open-label designs were excluded.

Using this search algorithm, we ultimately identified 110 trials. We then analyzed frequencies of trial design features and their associations with trial outcome.

## KEY RESULT 1: MADRS Most Frequently Used For Inclusion And As Primary Endpoint

Out of 110 included trials:

- **Population:** 57 (51.8%) included a TRD population, 52 (47.3%) included a MDD population, and 1 (0.9%) a mixed (TRD & MDD) population.
- **Phase:** 58 (52.7%) were Phase 2, 50 (45.5%) were Phase 3, and 2 (1.8%) was Phase 2/3
- **Treatment regimen:** 57 (51.8%) were monotherapy, 50 (45.5%) were adjunctive, 2 (1.8%) allowed both, and 1 (0.9%) was adjunctive, requiring co-initiation of an SoC ADT.

| inclusion scale | primary outcome scale | | Total |
|---|---|---|---|
| | HAMD | MADRS | |
| HAMD | 17 | 29 | 46 |
| MADRS | 5 | 56 | 61 |
| both | 1 | 2 | 3 |
| Total | 23 | 87 | 110 |

**Table 1.** Quantification of inclusion scale and primary endpoint scale in analysis population. Note 56 out of 110 trials (51%) use MADRS as inclusion scale and primary endpoint scale.

| inclusion > primary endpoint scale | N | % |
|---|---|---|
| MADRS > MADRS | 56 | 51 |
| HAMD >HAMD | 17 | 15 |
| MADRS >HAMD | 5 | 4.6 |
| HAMD >MADRS | 29 | 26 |
| both >HAMD | 1 | 0.9 |
| both >MADRS | 2 | 1.8 |
| Total | 110 | 100 |

**Table 2.** Quantification of relationship of inclusion scale (in) and primary endpoint scale (out) in analysis population

## MAIN CONCLUSION & DISCUSSION

While the practice of including on a different scale than the primary efficacy endpoint scale is relatively common (around one third of the trials), this approach is not associated with increased trial success.

Trials that use HAMD as an inclusion criterion appear to benefit from requiring a higher baseline total score for eligibility.

There are no clear recommendations for improving a clinical trial's success rate as the choice of inclusion criteria and outcome measure (HAMD vs MADRS) does not appear to affect outcomes.

Potential reporting bias should be noted as a limitation.

## KEY RESULT 2: Trial Success Slightly More Frequent In Studies With Same Scale For Inclusion And Outcome

Out of 110 included trials, 52 (47.3%) did not report whether the primary endpoint was met ("Trial Success"). Out of 58 included trials reporting primary endpoint outcome, 29 (50%) were positive and 29 (50%) were negative. The primary endpoint was met in 52.6% of trials that used the same scale and in 45% of trials that used different scales for inclusion and primary endpoint.

| inclusion scale | primary endpoint met | | Total |
|---|---|---|---|
| | no | yes | |
| different | 11 | 9 | 20 |
| same | 18 | 20 | 38 |
| Total | 29 | 29 | 58 |

**Table 3 (above).** Relationship between whether scales were switched between inclusion and primary endpoint and trial success.

**Table 4 (right).** Relationship between scale used for inclusion (inclusion) and primary endpoint definition (primary endpoint) and trial success.

| inclusion > primary endpoint scale | primary endpoint met | | Total |
|---|---|---|---|
| | no | yes | |
| MADRS > MADRS | 13 | 14 | 27 |
| HAMD > HAMD | 3 | 5 | 8 |
| MADRS > HAMD | 2 | 1 | 3 |
| HAMD > MADRS | 9 | 8 | 17 |
| both > HAMD | 1 | 0 | 1 |
| both > MADRS | 1 | 1 | 38 |
| Total | 29 | 29 | 58 |

| phase | primary endpoint met | | Total |
|---|---|---|---|
| | no | yes | |
| 2 | 18 | 13 | 31 |
| 2 / 3 | 0 | 1 | 1 |
| 3 | 11 | 15 | 26 |
| Total | 29 | 29 | 58 |

**Table 5.** The primary endpoint was more commonly met in identified Phase 3 trials (57.7%) than in identified Phase 2 trials (42%).

| adjunctive vs monotherapy | primary endpoint met | | Total |
|---|---|---|---|
| | no | yes | |
| adjunctive | 17 | 12 | 29 |
| adjunctive (co-initiation) | 0 | 1 | 1 |
| monotherapy | 12 | 16 | 28 |
| Total | 29 | 29 | 58 |

**Table 6.** The primary endpoint was more commonly met in monotherapy trials (57.1%) than in adjunctive trials (41.4%).

## KEY RESULT 3: Inclusion Threshold Associated with Treatment Success for HAMD but Not MADRS

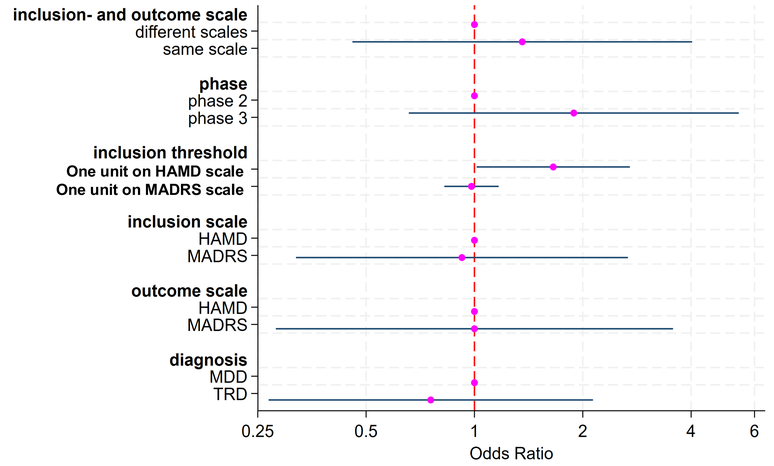


**Figure 1.** Associations between study design aspects and treatment success. Odds ratios >1 indicate a higher success rate. Categorical variables are tested against a reference group, continuous variables (inclusion thresholds are tested per one unit increase.

For the 34 studies who included on MADRS, there seems to be no association between inclusion threshold and treatment success.

However, for the 28 studies who included on HAMD, the Odds ratio of 1.66 indicates a higher success chance with higher inclusion threshold (p<0.044).

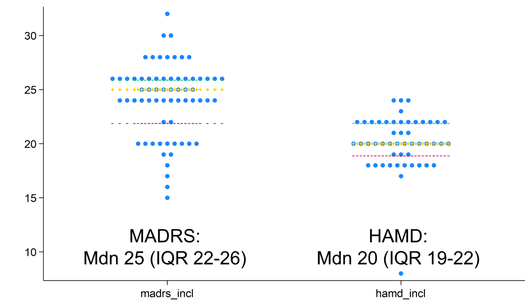


**Figure 2.** Quantification of the inclusion threshold (greater or equal to) for trial population. Blue dots indicate individual trials. Yellow line represents median, pink and green lines represent 25%- and 75% quantile, respectively.

## DISCLOSURES

CzE, JHu, CS, JHe, AG, and HE are employed by or consultants to HMNC Holding GmbH and may hold stock options; AK and XW are employed by Signant Health and may hold stock options.

BRAIN HEALTH

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