

How do threshold MADRS eligibility criteria influence MADRS scoring?

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INTRODUCTION

The aim of this study was to compare the impact of MADRS protocol inclusion criteria on MADRS total score in 3 similarly designed MDD studies that varied in their MADRS protocol inclusion criteria. We hypothesized that requirement criteria have potential to cause score inflation defined as a greater difference between Screening (SCR) and Baseline (BL).

METHODS

We selected the most recent study of three types (all initiated after 2012) that were double-blind, placebo-controlled, randomized Phase 2 and 3 adjunctive treatment trials investigating safety and efficacy of an investigational medicine in MDD patients with inadequate response to antidepressants in which MADRS was the primary efficacy outcome measure. The MADRS raters in all three studies were experienced clinical trial raters with at least 2 years of experience administering MADRS assessments. They were trained by the same vendor who also provided MADRS quality monitoring.

We defined three study types:

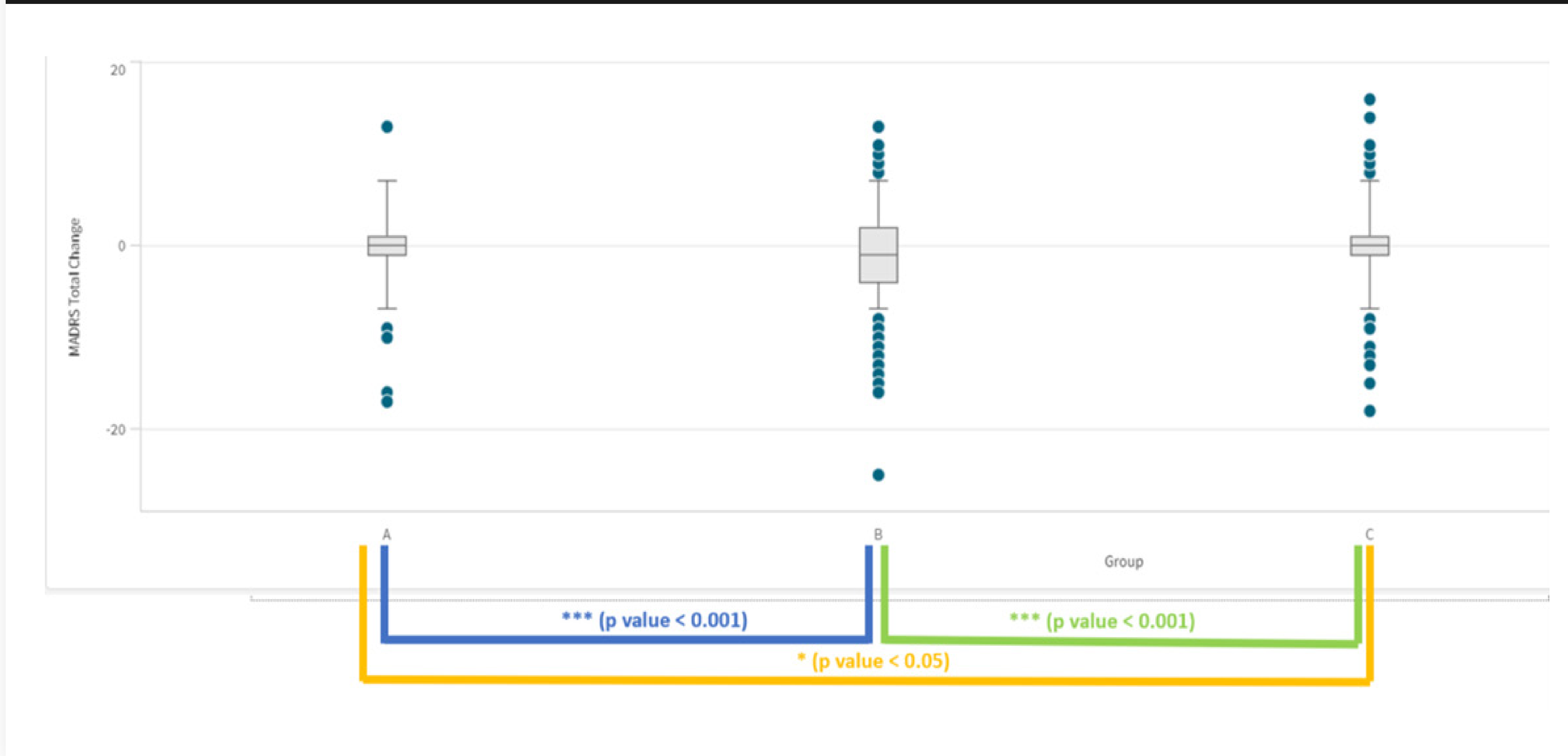
1. Type A: MADRS total score inclusionary criterion at Screening and Baseline.
2. Type B: MADRS total score inclusionary criterion only at Screening.
3. Type C: No MADRS total score as inclusionary criterion at Screening nor at Baseline.

We compared mean MADRS total score change from SCR to BL and the percentage of subjects with MADRS ratings meeting our operational definition of subsyndromal depression (fewer than 4 DSM-5 criteria confirmed by a MADRS rated 4 or greater).

RESULTS

- Study Type A (N=5052) had a 0.05 point increase in MADRS total score from SCR (mean=31.62, SD=3.59) to BL (mean=31.68, SD=3.74).
- Study Type B (N=273) had a 1.24 point decrease in MADRS total score from SCR (mean=34.11, SD=5.32) to BL (mean=32.85, SD=6.02).
- Study Type C (N=1500) had 0.2 increase in MADRS total score from SCR (mean=32.2, SD=4.87) to BL (mean=32.42, SD=4.95).
- Type B was found to be statistically significantly different from Type A and C using a t-test (Figure 1).
- The percentage of subsyndromal subjects in Study Type B increased from SCR (10.21%) to BL (16.78%), while for Study Type A and Type C, percentage of subsyndromal subjects decreased from SCR to BL (Type A =22.5% at SCR and 21.2% at BL, Type C = 22.6% (SCR) and 20.6% (BL)).

FIGURE 1



DISCUSSION

- The largest MADRS score change from SCR to BL was observed when threshold eligibility criteria were specified only for the screening visit. Consistent with this finding is that in this type of study, the percentage of subsyndromal patients increased from SCR to BL, suggesting that the subjects were scored with a higher symptom severity at SCR when it was required for inclusion, and then lower severity at BL when it was not. Our findings suggest that some raters and/or patients may be influenced by knowledge of the severity thresholds required for inclusion, whether consciously or not.
- Some limitations of our research include selecting only one study of each type, disparities in sample size between study types, and other protocol specifics which may have influenced our results. Future research is needed to replicate these findings and investigate whether they generalize to other pre-specified criterion, such as measures like the CGI-S that may or may not be used for inclusion.