Researchers have identified several sources of bias in clinical trials that may lead to increased placebo response and decreased signal detection. One such bias, expectation bias, is of particular concern in CNS clinical trials due to the subjective nature of many (including primary) outcomes.

Expectation bias occurs when an individual’s expectations about an outcome influence one’s perceptions of one’s own or other behavior. In psychiatric clinical trials, both raters and subjects may enter the trial with the expectation of the outcome.

- Subject expectation bias may occur when subjects themselves expect to get better and/or report improvement in place of the rater.
- Rater expectation bias may occur when raters expect that subjects will improve (or fail to improve) over the course of the trial.

- Finally, in traditional trial designs rater and subject expectations may interact, creating an alliance resulting in increased placebo response and possibly decreased drug-placebo separation.

Next, we review several studies that illustrate the problem of subject and rater expectation bias.

Finally, we discuss how these studies suggest novel methodological approaches that may limit expectation bias in CNS clinical trials.

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**Introduction**

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**EVIDENCE OF SUBJECT EXPECTATION BIAS**

**Psychiatric Assessment**

- Psychiatrists, clinical psychologists and clinical graduate students listened to a psychiatrist acting as an ordinary everyday healthy person.
- Some raters saw the subject as very interesting because he looked normal but was actually quite psychotic.
- Results suggest that raters’ diagnoses may have been influenced by the expectation of seeing a “psychotic” patient, regardless of the symptoms the actual patient presents.

**Study Outcomes by Treatment Group**

**Ham-D Change from Baseline to Endpoint by Same vs. Different Rater**

- Placebo responders by rater type

**Pharmacokinetics**

- Raters who are blinded to study protocol details including inclusion/exclusion criteria and allocation percentages to drug vs. placebo may yield better signal detection and lower placebo response:
- The studies reviewed here suggest that subject expectations, rater expectations, and rater-subject relationships can increase placebo response and decrease signal detection.

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**CONCLUSIONS**

- Expectation bias may have an effect when subjects report higher or lower scores influencing the direction of improvement.
- The studies reviewed here suggest that subject expectations, rater expectations, and rater-subject relationships can increase placebo response and decrease signal detection.
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**References**

- For non-neurologists, interrater reliability was poor in both conditions (Rapapor S).
- Results suggest greater reliability and accuracy when raters are assigned to complete ratings in a pre-structured manner. This is suggested by the greater number of actual raters who actually rated patients as psychotic.
- Psychiatrists, clinical psychologists and clinical graduate students listened to a psychiatrist acting as an ordinary everyday healthy person.
- Some raters saw the subject as very interesting because he looked normal but was actually quite psychotic.
- Results suggest that raters’ diagnoses may have been influenced by the expectation of seeing a “psychotic” patient, regardless of the symptoms the actual patient presents.