White Paper

Placebo Response in Psychiatry Trials — Truth or Myth

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Introduction

Over the years there have been a few studies/analyses claiming increased placebo response in psychiatry clinical trials in specific geographies. A concern was raised over higher placebo response in Indian patients, hence further discussion was required to understand whether it was truly the case versus a perception. There is no specific meta-analysis available focusing on data from India as compared to other countries.

IQVIA conducted an advisory board involving four leading Psychiatrists from across the country on July 8, 2023 to discuss the above.

- To understand placebo response in Indian patients in Psychiatry clinical trials and factors that could impact placebo response.
- To discuss possible mitigation strategies to minimize placebo response.

Discussion on placebo response in Indian patients

Literature review

Primarily, three published articles were the main references to discuss the perceptions of placebo response in psychiatry trials. A Journal of American Medical Association publication by Walsh et. al. 2002[1] included a study of 75 clinical trials from 1981 to 2000. The authors included controlled clinical trials published between 1981 and 2000 in which adult out-patients of major depressive disorder were randomly assigned to receive placebo or medication. Out of the 75 trials which met the criteria the mean proportion of patients in the placebo group who responded was 29.7% (range, 12.5%-51.8%). Most studies examined more than a single active medication, and, in the active medication group with the greatest response, the mean proportion of patients responding was 50.1% (9.0%) (range, 31.6%-70.4%.

The authors concluded that the response to placebo in published trials of antidepressant medication for major depressive disorder was highly variable and often substantial. It increased significantly in recent years, but so has the response to medication. These observations support the view that the inclusion of a placebo group has major scientific importance in trials of new antidepressant medications. The JAMA study led to a debate and created perceptions about placebo response though there has been a change in evidence as supported by two other more recent publications. This was followed with another publication from Innovations in Clinical Neuroscience, 2019 (Whitlock et. al.[2]). This was a meta-analysis which attempted to re-examine whether higher placebo response in major depressive disorder trials was truly concerning. More number of trials had been conducted by then and Montgomery Asberg Depression Rating Scale (MADRS) was used as compared to the Hamilton Depression Rating Scale (HAM-D) in clinical trials. The authors reviewed the data from 122 major depressive disorder trials conducted between 1983 to 2010.

They concluded that both placebo responder rates and active responder rates increased up to 1998. They identified no noticeable increase in the average placebo response since 1998.

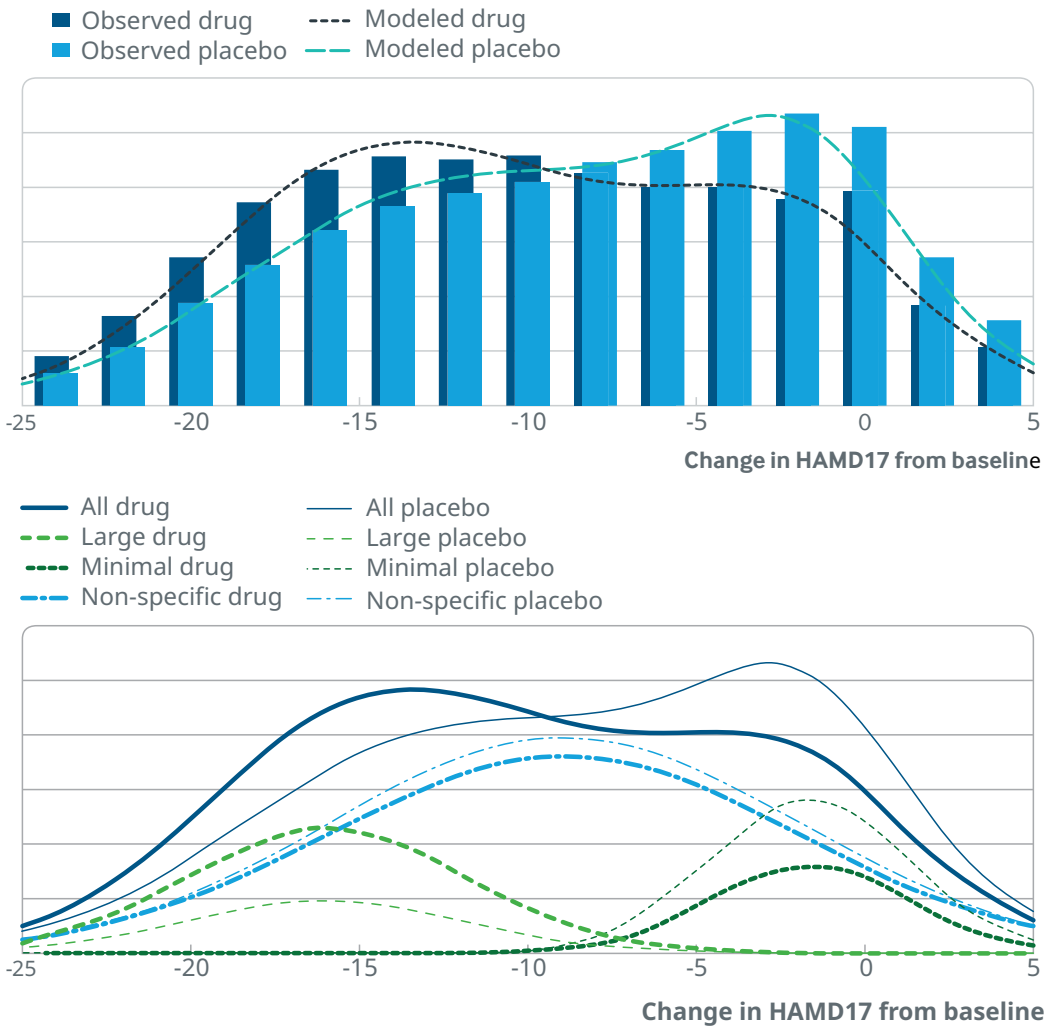
Third study dated 2022 which is the most recent analysis characterizing individual participant level response distributions to acute monotherapy for major depressive disorder (Stone et al British Medical Journal3). Individual

participant data from 232 randomized double blind, placebo-controlled trials of drug monotherapy for major depressive disorder submitted by drug developers to the FDA between 1979 and 2016 was analyzed. This comprised data of 73,388 adult and child participants meeting the inclusion criteria for efficacy studies on antidepressants.

The authors converted the responses to Hamilton Depression Rating Scale (HAMD 17) equivalent scores where other efficacy measures were used.

One of the findings during data analysis showed that small increments or improvements are more likely with placebo. Antidepressants and placebo both showed a trimodal response. However, larger, or more significant clinical improvement was observed with active drug/ antidepressants. This is depicted in the graph below by the authors.

Figure 1: Change in HAMD17 score from baseline



Distribution	Mean change from baseline	SEM	SD	Estimated proportion of overall population			
				Active drug	95% CI	Placebo	95% CI
Large	-16.00	0.22	4.22	24%	20% to 29%	10%	6% to 13%
Minimal	-1.68	0.11	2.99	12%	10% to 14%	21%	19% to 24%
Non-specific	-8.94	0.15	6.96	63%	58% to 69%	69%	65% to 73%

Source: Marc B Stone et al. BMJ 2022;378:bmj-2021-067606[3]

Panel discussion

Panelists agreed that raters would have to be meticulous in their ratings to avoid small changes in scores. Panelists agreed that the anchors in the rating scales like Montgomery Asberg Depression Rating Scale (MADRS) to be closely taken in to account. MADRS is a 10-item rating scale, and each item is scored on 7-point scale (0-6). Anchor points are specified for scores/ratings of 0, 2, 4 and 6. Scores/ratings of 1,3 and 5 do not have textual rating of severity. ISCTM (International Society for CNS Clinical Trials and Methodology5) convened a working group of MADRS experts from academia and industry recommended use of a structured interview like SIGMA as a complementary means to add to the data quality. Panelists commented on the use of complementary and alternative medicine (CAM) that could impact the placebo response. One of the panelists informed about a survey undertaken in the city of Pune. Besides a diagnosis of MDD, the survey included people with non-communicable diseases including diabetes mellitus, major depression, thyroid disorders. 85% of responders reported the use of complementary and alternative therapies ranging from yoga to homeopathy. This is not specifically enquired or probed during routine clinical practice as well as during clinical trials. Physical activity, meditation or other complementary therapies are likely to contribute to efficacy due to various reasons.

Another observation was the higher levels of inflammatory markers like C-reactive protein (CRP) as a contributing factor towards response to active drug. Higher levels of C-reactive protein are observed in almost all non- communicable diseases including depression. Patients with major depression also have higher levels of C reactive protein. It is now understood that at least one-third of patients with major depression have high inflammatory markers. It is implied that patients with higher levels of inflammatory markers are less likely to respond to treatment (Orsilini et al[4]. This does not necessarily fall under the unstable physical co-morbidities which are exclusionary in most clinical trials. Some patients have high insulin resistance.

This has been observed in their clinical practice. This sub-set of patients had anxiety symptoms and the origin of anxiety was in insulin resistance, higher fasting insulin levels. These patients responded to an anti-depressant only after metformin was added to the treatment regimen. Similarly, some MDD patients have high autonomic dysfunction which contributes to allostatic load. This in turn could contribute to less than satisfactory response to active drug in clinical trials.

The panelist then suggested that sponsors could factor-in these aspects while designing a protocol. Another issue raised was that of compliance. This includes non-compliance with study medication as well as dose adjustments made by the participants without informing the study team. Investigational Product (IP) compliance should go beyond the counting from the IP kit. Self-made dose adjustments, intake of over-the-counter medications for sleep, anxiety should be specifically enquired at every visit.

With regards to major depression (more so as compared to other indications) the attention and time with the treating doctor, quicker access to treating doctor/study teams, much less waiting time in out-patient department (large hospitals) could contribute to placebo response.

Another aspect which could be further investigated was different responses in endogenous and exogenous major depression. Exogenous major depression would more likely respond to placebo. The sponsors could choose a rating scale which has provision to identify whether a particular participant has exogenous/endogenous depression. The 2014 study by Spanemberg et al6 demonstrated that thirty three patients with depression showed higher Interleukin -4 (IL-4), Interleukin -6(IL-6) and protein carbonyl content (PCC) values as compared to healthy controls. 39% of their sample size marked as endogenous depressives by CORE measure had higher levels of interleukin 6 as compared to non-endogenous/non-melancholic and healthy controls. Clinical trials have a limitation as these sub-types are not considered and this could also affect the primary efficacy endpoint outcome.

It is unlikely that a response to active drug would be observed within first 2-3 days of treatment. Hence an early response observed in the first few days is likely not due to active treatment/molecule. Additionally, placebo responses appear to be small responses which do not increase over time. A method to analyze data which permits such an evaluation of response over time or distribution of response over time would provide a clearer picture. Another area of discussion was the course of major depressive episode itself. The time point during major depressive episode when the patient was enrolled in a trial also would affect the response to treatment/IP. An early response would be observed if the depressive episode is in natural remission mode. A method to quantify improvement after 6th week of treatment in an 8-week trial could possibly address this issue. Having a higher cut-off for primary efficacy measure scales might not help to identify/separate such patients.

To summarize there are four broad categories which could influence placebo response as well response to active drug. Rater related issues, concurrent use of complementary and alternative therapies, inflammatory markers, trial participants responding due to increased and frequent attention by treating physician. Hence, not all factors are rater related. Moreover, data included from 232 clinical trials for review in Stone et. al. study indicates that placebo response is a global phenomenon and culturally agnostic factors also have to be taken into account.

Mitigation strategies to minimize placebo response

Literature review

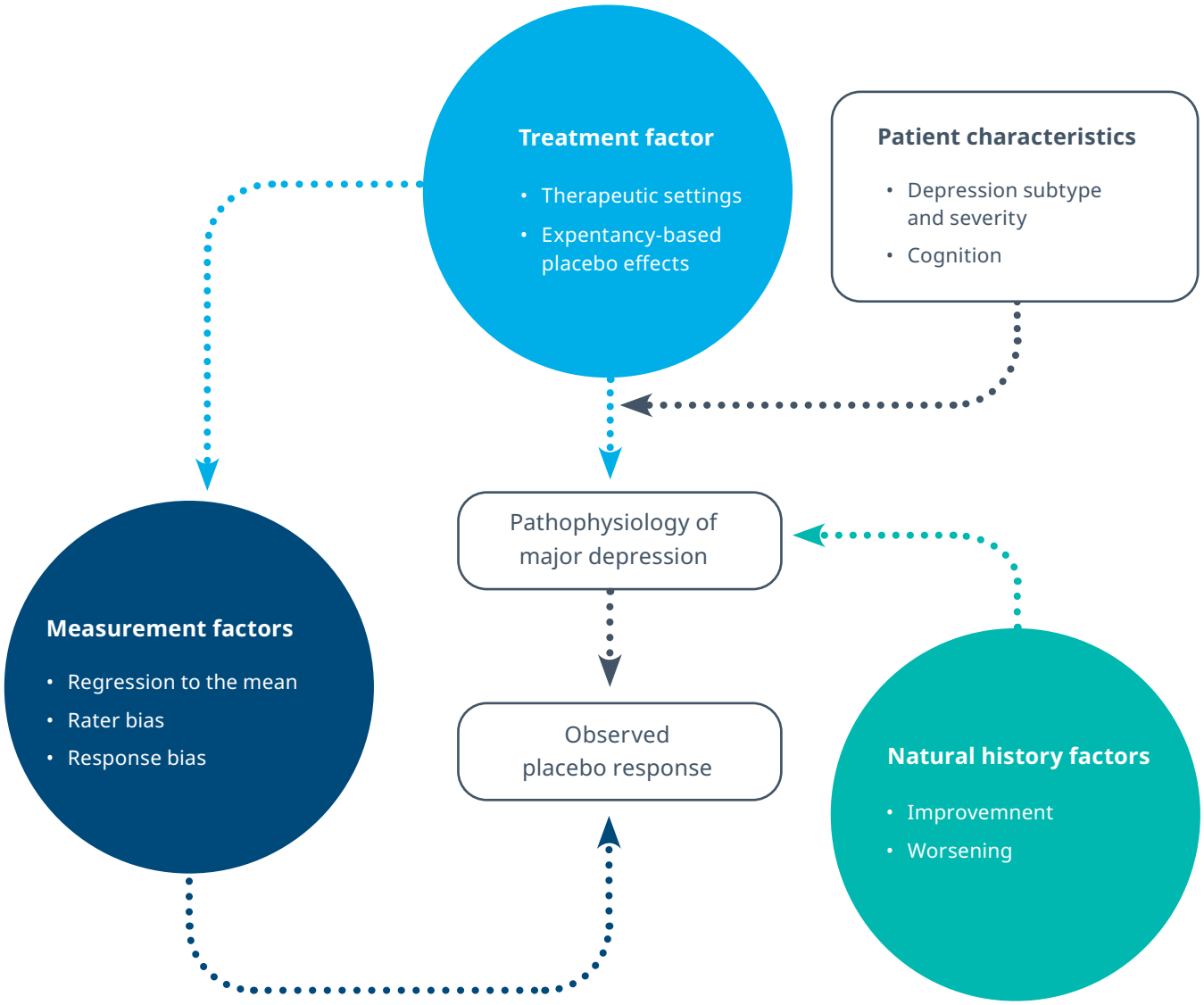
Rutherford et. al. have suggested that factors contributing to placebo response are treatment factors, measurement factors and natural history of major depressive disorder as highlighted in the table and chart below.

Table 1: Study design features influencing placebo response in Antidepressant Clinical Trials

1 Increase placebo response	2 Decrease placebo response	3 Strength of evidence
More study sites	Fewer study sites	Strong
Poor rater blinding	Good rater blinding with blind assessment	Strong
Multiple active treatment arms	Single active treatment arm	Strong
Lower probability of receiving placebo	Higher probability of receiving placebo	Strong
Single baseline rating	Multiple baseline ratings	Medium
Briefer duration of illness in current episode	Longer duration of illness in current episode	Medium
More study visits	Fewer study visits	Medium
Sample of symptomatic volunteers	Sample of self-referred patients	Weak
Optimistic/enthusatic clinicians	Pessimistic/meutral clincians	Weak

Source: Rutherford et al[8]

Figure 2: A model of placebo response in Antidepressant Clinical Trials



Source: Rutherford et al[8]

Rutherford et. al. have cited response bias as well as rater bias as measurement factors contributing to placebo response. Response bias is more of a concern in antidepressant clinical trials as illness severity is rated based on subject responses. Rater bias especially inflation of baseline score is again observed in antidepressant clinical trials.

There are multiple approaches to minimize rater bias. A comprehensive ongoing rater training program in which inter rater reliability is measured closely and maintained at minimally acceptable level. Specifying a minimum depression severity score required for enrollment which is always a prerequisite in most psychiatry indication trials. Other strategies involve use of two separate rating scales; one to determine subject eligibility and another as a primary outcome measure as suggested by the author is already seen in clinical trials for major depression (Rutherford et al[8]).

Panel discussion

Panelist contributed that protocol design, choice of rating scales, rater training all contributes towards maximizing true effect of a study drug. Of these, the factor which could be addressed was rater training and rating scale administration. Rigorous rating scale administration training and refresher training to maintain certification irrespective of clinical trials was strongly recommended. This would involve use of rating scales commonly used as primary efficacy measures across various indications to be administered regularly.

Panelists also added that having an active comparator, placebo and investigational product (three-arm study) may help minimize the placebo response. The discussion which followed clarified that it is difficult to have instruments or rating scales which differentiate exogenous and endogenous depression. Beck's Depression Inventory may identify the quality of endogenous depression. Other factors which influence response to treatment are history of natural remission, duration of the MDD episode. Rating scales are not able to quantify this as most scales gather cross sectional data. A clinical trial is aimed at establishing efficacy of a molecule and are not aimed at optimizing the treatment response (as was studied as part of STAR*D study9). One of the points noted is that minimum duration of exposure to the study molecule/ IP should be re-evaluated.

Other mitigation strategies involved highlighting the differences between therapeutic alliance and research alliance to the site teams. This should also include sensitizing the clinical trial participants and caregiver to difference between therapeutic and research alliance. Clinical trial participants would have to educated about research alliance in which the psychiatrists and study team members would be more professional, not sympathetic, or overly supportive. The interaction will be restricted to study procedures and scales. Research alliance would help minimize the placebo response despite frequent contact and increased time spent with treating psychiatrist/site team.

Conclusion

Based on the discussion, experience sharing and review of available literature it was concluded that though increased placebo response is observed over the years it is not restricted to India. There are strategies which can be implemented to minimize placebo response. These include choosing an appropriate study design, ongoing and rigorous rater training, setting realistic expectations for the participants, and highlighting difference between therapeutic alliance versus research alliance.

Disclosure statement

Authors Medha Chaubal, Rupanwita Ghosh, Rashna Cama, Artem Klymenko are the employees of IQVIA, a contract research organization that provides scientific and technical services for clinical trials conducted by pharmaceutical companies involved in new drug development. Other than this, all authors declare no professional, academic, competitive, or financial conflicts of interest related to this article.

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