The role of artificial intelligence in decoding the placebo response – implications for clinical research and practice

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INTRODUCTION AND OBJECTIVE

- High placebo response rates can reduce the difference between active treatment and control groups in clinical trials and are a challenge in drug development[1].
- Placebo response rates are particularly high in neurological and psychiatric diseases[1].
- There is currently no consensus on how to statistically control for the placebo effect.
- Researchers can now use artificial intelligence (AI) methods such as machine learning and natural language processing to identify and model predictors of the placebo response at an individual patient level.
- This study provides an overview of AI methods used, research goals, and indications; and explores the implications for clinical research and practice.

METHODS

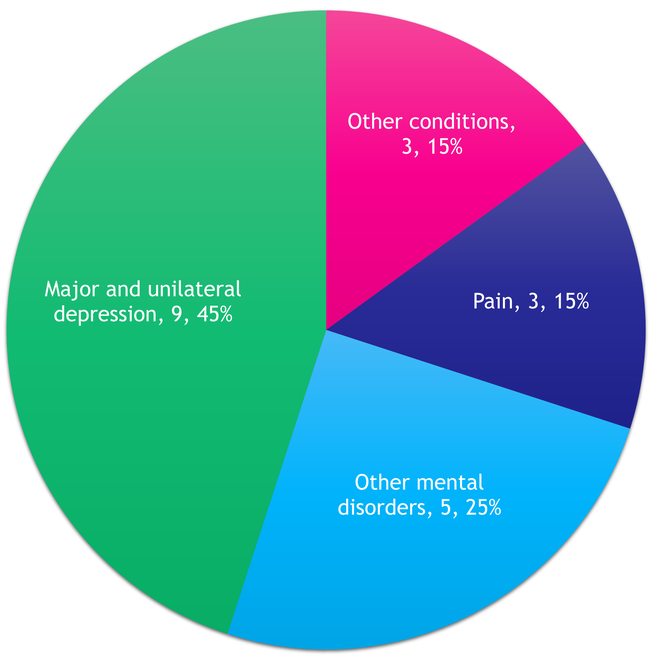
- This review was based on a search of MEDLINE, Embase, and PsycInfo databases via the ProQuest platform using title/abstract keywords and subject heading synonyms for AI, machine learning, natural language processing, and placebo and nocebo response/effect. The search date was 09 June 2023.
- Full-text studies evaluating AI methods to investigate the placebo response were eligible for inclusion.
- There was no time limit, but study selection was limited to English-language articles.
- Studies evaluating AI methods to predict responders to treatment were excluded unless data for placebo responders were provided or the study aimed at differentiating between treatment and placebo responders.

RESULTS

Overview of the evidence

- The initial search identified 92 records; two additional articles were identified via a bibliography review of the selected articles, resulting in 94 articles.
- After deduplication, 84 records remained; of these, 19 records (16 studies) met the eligibility criteria for inclusion in this review.
- **Figure 1** shows the number of retrieved records by indication (2 articles reported on more than one indication).

Figure 1. Number of records by indication



- The body of evidence was heterogeneous in terms of indication and modeling methods, and few studies were available for each indication.
- There were no studies attempting to model the nocebo response.
- Most studies reported on mental disorders (70% of records), including major depressive disorder (9 records), unilateral depression (2 records), and other neurobiological and psychiatric disorders (5 records). The remaining studies were on pain (3 records) or other conditions (3 records).
- Most studies (17/19 records) were published from 2018 to 2023, 1 record was published in 2012, and 1 record was published in 2016.
- Most studies (15/16 studies) utilized various machine learning methods to model the placebo response; only 1 study used natural language processing[20].
- Data were derived from randomized controlled trials in 14 studies and from systematic reviews in 2 studies[11, 13].
- All but 2 studies predicted placebo responders with fair to good accuracy. AI models did not predict the placebo response in studies evaluating attention-deficit hyperactivity disorder[14] or epilepsy[16].
- Two studies reported that AI methods could help assigning placebo responders to less invasive treatment [6,7]
- AI methods predicted different placebo effects across major depressive disorder, bipolar disorder, and schizophrenic disorder[11].
- **Table 1** provides key outcomes of the included studies.

Table 1. Key outcomes in the included studies

Indication	Predictor	Outcome
MDD[2-4] EMBARC study	Clinical and biological markers	• ML model predicted placebo responders with good accuracy (both area under the curve > 0.73). • Created an interactive calculator predicting the likelihood of placebo response at the individual level.
MDD[5]	Baseline imbalances	• A propensity model provided an unbiased strategy to make patients' data comparable across treatment arms and control for the placebo effect.
MDD[6]	Resting-state functional connectivity	• Increased resting-state functional connectivity predicted individual response to placebo. This correlation mainly occurred in the rostral anterior cingulate.
MDD[7] TADS study	Various clinical	• ML algorithm identified placebo responders and could be useful in guiding treatment assignment to CBT versus CBT plus medication.
UD[8-9]	Clinical and demographic	• ML algorithm identified placebo versus medication responders.
Anxiety, depression, SCZ, BD[10]	Disease severity clusters	• AI identified likely placebo response predictors. • Placebo responders were more likely to have less disease severity; there were potential placebo responders among those with highest disease severity (18% to 29%).
MDD, BD, SCZ[11]	Clinical rating scales and Clinical Global Impression scores	• ML analysis identified different placebo effects across MDD, BD, and SCZ.
ASD[12]	Various	• Commercial versus academic study locations, attention deficit hyperactivity disorder, and depression predicted increased placebo response. • Higher baseline Vineland-II 2DC and longer treatment duration predicted lower placebo response.
Binge eating disorder[13]	Less disease severity, no symptoms of general anxiety	• ML predicted placebo response with 88% sensitivity and 72% accuracy.
ADHD[14]	Various	• The ML models did not predict placebo response in ADHD.
NASH [15]	Clinical, histologic, and serum fibrosis markers	• ML identified lower disease severity at baseline as a predictor of spontaneous fibrosis improvement in patients receiving ineffective treatment or placebo.
Epilepsy[16]	Clinical features	• ML based on clinical features did not predict the placebo response. • ML of genetic and clinical data successfully predicted drug response.
Migraine without aura[17]	White matter tract microstructure	• White matter tract microstructure of the mPFC-amygdala could distinguish between patients with recovering and persisting migraine attacks in sham acupuncture with an accuracy of 84%.
Thermal pain in healthy participants[18]	Change in pain	• ML differentiated between placebo responders and non-responders and provided cut-off values.
Chronic pancreatitis pain[19]	Electroencephalographic biomarkers	• The model achieved up to 85.7% accuracy (P = 0.009) in classifying patients into the treatment and placebo groups.
Chronic low back pain[20]	Language patterns	• NLP model predicted a mean pain relief of 30% in placebo responders and 3% in placebo non-responders.

ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; BD, bipolar disorder; CBT, cognitive behavioral therapy; COPD, chronic obstructive pulmonary disease; MDD, major depressive disorder; ML, machine learning; mPFC, medial prefrontal cortex; NASH, nonalcoholic steatohepatitis; NLP, natural language processing; SCZ, schizophrenic disorder; TADS, Treatment of Adolescent Depression Study; UD, unilateral depression

Impact on clinical research and practice

- In medical practice, AI may help to assign placebo responders to less intensive treatment.
- In clinical trials, AI could be used to statistically control for placebo responders.
- The variability in placebo effects across MDD, BD, and SCZ might be considered in trial design.
- Interactive calculators could be a way to predict the likelihood of a placebo response at the individual level accessible to clinicians and researchers.

CONCLUSIONS

- AI methods can predict patients who are likely to respond to placebo. While the results are promising, there are only a small number of studies, the field is still evolving, and there are currently no accepted standards.
- Statistically controlling for the placebo effect could provide a more accurate estimate of treatment effect sizes in clinical trials.
- In medical practice, patients likely to respond to placebo could benefit from less intensive treatments.

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DISCLOSURES

The authors state no conflicts of interest.

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