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TITLE

Incidence and characteristics of the nocebo response from meta-analyses of the placebo arms of clinical trials of olanzapine for bipolar disorder

RUNNING TITLE

Nocebo effects in bipolar disorder

AUTHORS

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ABSTRACT

Objectives: In the clinical setting, the nocebo phenomenon is where clinical worsening or adverse events occur as a response to a treatment, where conditioning from previous treatment exposure and/or expectations of sickness or symptoms lead to sickness and symptoms in a conditioned or expectant individual. The nocebo response may thus be a confounder in clinical treatment and clinical research. There is a need to know how to predict if an individual is likely to be a nocebo responder, and how significant and commonplace the nocebo effect might be.

Methods: An analysis was conducted on nine placebo-controlled, randomised clinical trials of olanzapine for the treatment of bipolar disorder using data from placebo treated study participants only. Data was analysed to identify participant or study characteristics associated with a nocebo event, defined as any treatment emergent adverse event (TEAE) or an increase in score from baseline to endpoint for primary measures of clinical symptoms.

Results: A total of 1,185 participants were randomised to placebo, of which 806 (68%) reported a TEAE. Hamilton depression rating scale (HDRS) data was available was only available for 649 placebo treated participants, of which 321 (49.5%) demonstrated worsening. Nocebo events were significantly associated with; not being treatment-naïve, younger age, being located in the USA, being a participant in an earlier study, and being classified as obese compared with normal weight.

Conclusions: A pattern to identify nocebo responders did not emerge, although some prognostic variables were associated with a greater probability of nocebo response. There was some evidence to support the role of expectancy as a cause of nocebo reactions.

KEYWORDS

Nocebo, placebo, clinical trial, meta-analysis, olanzapine, adverse events, side effects.

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INTRODUCTION

Administering an essentially inert substance to a patient or a study participant can influence clinical outcomes such as symptom severity, including improvement or worsening, and may elicit treatment emergent adverse events. These phenomena, known as the placebo (improvement) or nocebo (worsening or adverse events) effects, occur commonly and are of varying intensity, challenging to predict, and may be difficult or impossible to distinguish from the natural progression of some illnesses or naturally occurring adverse events (1, 2). This concept has been extended to include not only inert substances, but also non-inert or pharmacologically active substances that are not considered to be effective for the index symptoms being treated (3).

Nocebo and placebo responses have been attributed to expectancy, conditioning, learning, memory, motivation, somatic focus, reward, anxiety reduction, and "placebo by proxy" induced by clinician and family members (2). Conditioning has been used to induce a nocebo response in one study (4) and to minimise it using counterconditioning in another (5). Nocebo has been associated with neurobiological factors including decreased dopamine and opioid neurotransmission (6). A nocebo response may occur as a synergy of psychological and biological mechanisms (6).

The role that placebo and nocebo phenomena play in influencing outcomes of clinical treatment and research requires further investigation. In clinical research, where randomised, placebo controlled trials have become the definitive tool for characterising treatment efficacy and tolerability, placebo and nocebo effects can be a driver of spurious trial results. The underlying assumption that placebo response rates contribute equally to both placebo and active treatment study arms is untested, and may be false (7). In the same way, a significant nocebo response in an RCT may mask genuine adverse events by increasing the rate of adverse events in both placebo and active treatment arms. A nocebo response of clinical worsening to an active treatment in an RCT will reduce the probability of detecting a statistically significant difference in clinical outcomes between placebo and active treatment arms.

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In clinical treatment these nocebo phenomena may result in patients not receiving optimal therapy, as a potentially effective treatment may be incidentally altered in response to nocebo related worsening. There is a paucity of evidence-based research to guide clinical approaches to identifying and then managing and treating suspected nocebo response patterns. Indeed, it may be effective to employ targeted adjunctive psychological therapies that address the nocebo response.

The ability to differentiate a nocebo adverse event from an adverse event that is either coincidental or mechanistically caused by the treatment, or to distinguish nocebo clinical worsening from the natural progression of illness, remains elusive. Studies have investigated variables associated with the nocebo effect revealing some important insights, but have left many questions unanswered. A systematic review of 89 studies of people exposed to inert substances reported that the strongest predictors of nocebo effects were: a higher perceived dose of exposure, explicit suggestions that the exposure triggers arousal or symptoms, observing people experiencing symptoms from the exposure, and higher expectations of symptoms (8). Elsewhere, participant characteristics including neuroticism, pessimism and type A personalities have been associated with nocebo response (1). Understanding the propensity of an individual towards a nocebo response may be useful from a perspective of person centred medicine, where is can be addressed on an individualised basis (9).

In addition, prior experiences may also increase the risk of a nocebo response. Prior adverse events or dissatisfaction with medical services may cause negative expectations. Similarly, people with adverse early life experiences or trauma histories may have negative expectations (1). A study of 2,457 clinical trial participants randomised to placebo found that people who had previously used complimentary medicines were more likely to report treatment emergent adverse events (TEAEs) (10). The same study found little evidence to suggest other predictive variables, including sex, age, or previous antidepressant exposure. Nevertheless, TEAEs were reported by 63.9% of participants, 11.2% showed worsening of their Hamilton Depression score and 4.7% of participants discontinued from the study due to TEAEs, with all participant treated with placebo only, suggesting that the nocebo effect is common but covert. Compared to the previous study with a similar study design (10), similar results were reported for TEAEs (63.9% vs 68%), study discontinuation due to TEAE (4,7% vs 4,6%) but dissimilar results for Hamilton scale worsening (11.2% vs 49.5%) as in the current study only one trial was for the treatment of bipolar depression and the other trials were mania,

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mixed and relapse prevention. In contrast, the other meta-analysis cited was from trials where all participants had major depression at baseline. It is not unexpected that Hamilton scale worsening has occurred more frequently in the study where participants started with lower scores at baseline.

This study aims to explore patterns and predictors of nocebo events, both worsening of clinical symptoms and/or treatment emergent adverse events, in the placebo arms of randomised controlled trials comparing olanzapine or placebo for the treatment of bipolar disorder.

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MATERIAL AND METHODS

Data included in the meta-analysis

Included data comprised of multi-site, randomized, placebo-controlled clinical trials (RCTs) commenced between 1996 and 2007. Studies were conducted in patients with bipolar disorder, and included at least one arm of olanzapine monotherapy and one arm of placebo monotherapy. Nine industry-sponsored studies, including seven published studies (11-17) and two unpublished studies (Study ID codes HGGW and HGHL), were identified that met selection criteria and data was obtainable for all nine studies by request. The length of study duration for which participants were treated with placebo ranged from three weeks to 18 months (Table 1). Table 1 also states the study ID codes for each of the nine studies, used to identify individual studies in this paper. Three of the nine studies had three treatment arms, one with a haloperidol comparator, another with a divalproex comparator, and another with an olanzapine and fluoxetine combination comparator. All studies were either Phase III or Phase IV trials for the treatment of bipolar disorder, including mania, mixed episodes, depression and relapse prevention. Six studies were conducted exclusively in the USA, and three studies were conducted in both the USA and other regions.

Only data from study participants randomised to placebo were included in the meta-analyses. Data from participants randomised to active treatments were not utilised. Young mania rating scale (YMRS), clinical global impression – bipolar (CGI-BP), treatment emergent adverse

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events (TEAE) and demographic data were available for all nine studies. Hamilton depression rating scale (HDRS) was available for six of the nine studies. For the purpose of these analyses, clinical symptoms were evaluated using HDRS total score, YMRS total score, and CGI-BP total score. A worsening was defined as an increase in score from baseline to endpoint. TEAEs were collected according to international guidelines and were defined as any event that occurred or worsened during placebo treatment. Endpoints analysed included any TEAE and any discontinuation due to a TEAE.

Statistical Analyses

Baseline characteristics of the study participants were analysed with respect to demographics including age, gender, smoking status and BMI; disease characteristics including prior medication, previous episodes and previous hospitalizations for bipolar disorder. Effect size and statistical significance was evaluated based on a two-sided significance value of .05. Descriptive statistics were used to describe incidence of adverse events, as well as the time to first treatment emergent adverse event. The influence of various factors was analysed using a logistic regression with study as a fixed-effect and the following study characteristics as random effects: age quintile, BMI, year of protocol, patients who are treatment-naïve and location as Asia or USA. SAS software version 9.2 or higher was used for the analyses (SAS Institute Inc., Cary North Carolina, USA).

RESULTS

Participant disposition

The total number of randomised participants from the nine studies was 4680, of which 1,185 participants were randomised to placebo treatment. The study characteristics are listed in Table 1. The mean (±*SD*) duration of placebo treatment ranged from 12.2 ±6.8 days to 81.5 ±106.7 days

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(Table 1). Six of the nine studies (*n*=649) collected HDRS data and all studies (*n*=1,185) collected TEAE, discontinuation due to a TEAE, CGI-BP and YMRS data.

A total of 806 (68.0%) placebo-treated participants reported a TEAE; 54 (4.6%) discontinued due to a TEAE. A worsening of HDRS, CGI-BP or YMRS total score was observed in 321 (49.5%), 278 (23.5%) and 585 (49.4%) placebo-treated patients, respectively. The most frequently reported TEAEs are listed in Table 2. The reporting frequency by MeDRA preferred term is shown in Figure 1.

The median time for a placebo-treated participant to report a TEAE was 16 days (Table 3). Studies HGGW and HGFU had the shortest median time to TEAE reported (five and six days respectively), while Study HGMP had the longest time to TEAE report (37 days). Examination of the type of TEAE reported revealed that 32.7% of placebo-treated participants reported at least one TEAE that was listed in the participant information (PI) or consent form (CF).

Demographic and Baseline Clinical Characteristics

Of the 1,185 placebo treated participants, 665 (56.1%) were female, 769 (64.9%) were located in the USA, 239 (20.2%) in Asia and 177 (14.9%) elsewhere. The mean (±*SD*) age of participants was 38.8 ±12.63 years. There were 318 (26.8%) treatment-naïve participants and the other 867 (73.2%) had previous treatment with medications for bipolar disorder. The most common previous treatments were; benzodiazepines for 521 (60.1%) participants, antidepressants for 400 (46.1%) participants, mood stabilisers 375 (43.3%) of participants and 222 (25.6%) participants had received previous treatment with an atypical antipsychotic. Prior to the index episode, 62.3% of participants reported previous episodes and 19.5% had been previously hospitalized. A full description of the demographic and baseline characteristics for placebo treated participants included in these meta-analyses is provided in Table 4.

Relationship between Clinical Characteristics and Adverse Outcomes

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Prognostic variables for placebo-treated participants who reported HDRS worsening, TEAEs, or who experienced study discontinuation were analysed (Figure 2). The adverse outcome TEAEs were significantly associated with: not being treatment-naïve, being located in the USA, being a participant in an earlier study, and being classified as obese compared with normal weight. TEAEs were reported by: 55.0% of treatment-naïve participants (175 of 318) compared to 72.8% of participants who were not treatment-naïve (631 of 867) (p<.001), 75.9% of USA participants (584 of 769) compared to 53.4% of Asian and other participants (222 of 416) (p=.016), 88.9% of participants in studies commenced prior to the year 1999 (217 of 244) and 52% of participants in studies commenced after the year 2002 (195 of 374) (p<.001), 70.4% of obese participants (244 of 318) compared to 59.8% of normal weight participants (260 of 435) (p<.05) with data from underweight (43), overweight (334) and missing data (55) not included.

HDRS worsening was significantly associated with: younger age (p=.001), being located in the USA (p<.001), and being a participant in an earlier study (p<.001) in unadjusted and adjusted statistical models. When adjusted for age, year of protocol, baseline BMI and Country categorized (Asia, USA and other), patients who were treatment-naïve had a reduced odds of having HDRS Worsening Status (0.68; 0.48-0.96 p=0.03).

At least one nocebo event was reported by 806 participants, reporting a total of 1,119 nocebo event. Participants who reported TEAEs tended to more commonly report HDRS worsening (29.7% vs. 21.6%; p=.004), CGI-BP worsening (25.7% vs. 18.7%; p=.008) or YMRS worsening (55.0% vs. 37.5%; p<.001).

There was no significant association for gender and adverse outcomes, with negligible numerical difference between males and females for each adverse outcome. There was no significant association for smoking status and adverse outcomes. Smokers consistent reported more adverse outcomes than non-smokers, however, smoking status data was only available for 259 of 1,185 participants so the possibility of a type I error cannot be ruled out. There was no significant association between any clinical characteristic and study discontinuation due to a TEAE, with only 54 participants in this category, again suggesting the possibility of type I error.

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Prognostic Factors and Heterogeneity Across Individual Studies

The prognostic factors of age, BMI and whether a patient was treatment-naïve were analysed by study (Supplementary Figure 1). Heterogeneity was observed across studies.

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DISCUSSION

There are a number of unresolved questions pertaining to the nocebo effect. These include: how common is the nocebo effect; how much impact it has on outcomes; in whom is it likely to occur and when; and is there any way in which it can be predicted in individuals or distinguished from clinical worsening or adverse events that are not precipitated by treatment?

A majority of placebo treated participants reported a TEAE and many reported worsening of clinical symptoms, suggesting that the non-pharmacological related adverse events and hence the nocebo effect is very common. A nocebo experience is a stressor, and can generate anxiety in a bidirectional manner (18). A nocebo response may create negative expectation to future treatments (19), and potentially damage the therapeutic alliance between the doctor and the patient (18), and its likelihood is also increased by negative experiences of prior treatment. Such an effect is associated with reduced treatment adherence, as well as treatment discontinuation, and may perturb clinical outcomes (1).

Predictive variables for the nocebo effect included both study and participant characteristics. Study characteristics associated with an increased nocebo response included earlier year of protocol and studies conducted in the USA. An increased nocebo response with earlier protocols was also shown in prior studies (10). A possible explanation for this may be found in the expectancy hypothesis in that early phase studies would be perceived to be more risky than more recent studies, however, positive or negative expectancy was not measured in clinical trial participants leaving this hypothesis unanswered. Evidence supporting the expectancy hypothesis was suggested by the finding that approximately one third (32.7%) of participants reported at least one TEAE that was mentioned in the participant information and consent form (PICF). The PICF has the

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potential to illicit a nocebo response through suggestion, and can heighten an expectation of a TEAE that matches what the participant has read in the PICF.

A greater nocebo response in USA based studies has also been previously reported (10), but is not explained by either the expectancy or conditioning hypotheses. This finding could possibly be explained by cohort specific variables rather than a study characteristic per se, although this would require further investigation to clarify, and is beyond the scope of this analysis.

Younger age was a significant predictor of a worsening HDRS score, but not of a TEAE. Having experienced a previous episode of illness was also associated with HDRS worsening, whereas being treatment-naïve was protective against a TEAE. Notably obesity, as indicated by a BMI of $\geq$30 kg/m^2, was associated with worsening for all clinical symptom measures and a TEAE. Obesity is associated with poorer outcomes in general (20).

In this study, gender was not significantly associated with a nocebo response, nor was tobacco smoking status. It is worth noting however, that tobacco smoking status was only available for three of the nine studies, and was underpowered to demonstrate statistical significance as a prognostic variable. Further investigation with a larger sample is required to determine whether smoking is associated with the nocebo effect.

The median time to the first TEAE was 16 days, which may be helpful for discerning a genuine nocebo response from a naturally occurring adverse event. A TEAE that appears early in the course of treatment may have a greater possibility of being a nocebo response compared to a TEAE that emerges following extended treatment. This is consistent with the current understanding of the psychological drivers of the nocebo phenomena, where if an individual is primed for a nocebo response that response is likely to happen after exposure to a stimulus rather than after a long time period of exposure to that stimulus.

A limitation of this study is that all clinical worsening and TEAEs are included in these analyses, without the ability to discern that these outcomes are responses to the placebo treatment rather than the natural progression of illness.

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Although there were significant findings identifying characteristics associated with a nocebo effect, it must be noted that these were generally weak associations. Characteristics that may be useful for identifying participant who may be more susceptible to nocebo remain unclear. It is also important to note that this study included participants selected for a treatment trial for bipolar disorder and randomised to a placebo study arm. As such, the results of these analyses may not be generalizable outside of this cohort, and should be interpreted with caution. It is also worth noting that this study did not assess the severity of the nocebo response.

Further research is still needed to characterise the nocebo response. While sometimes envisaged as an uncommon response amongst people susceptible to negative expectations (21), this data suggests that the nocebo response is more likely a common response that, similar to the placebo response, is an expected consequence of exposure to a therapeutic intervention (18).

CONCLUSION

The nocebo effect is an important yet surreptitious factor in both clinical trials and clinical practice. The nocebo response is seemingly common when defined as any TEAE or clinical worsening in people treated with a placebo. This study offers some evidence associating the nocebo response with variables including: not being treatment-naïve, younger age, and being classified as obese compared with normal weight. Being located in the USA and being a participant in an earlier study was also associated, suggesting that context and environment can also influence the nocebo response. These associations however, were very weak and the ability to accurately predict that an individual may be a nocebo responder for now, remains elusive. Collectively, the evidence presented in this study suggests that the nocebo response is common, and requires both clinical attention and research clarification.

ACKNOWLEDGMENTS AND DISCLOSURES

Ethical Standards

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The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Conflict of interest

SD has received grants/research support from the Stanley Medical Research Institute, NHMRC, Beyond Blue, ARHRF, Simons Foundation, Geelong Medical Research Foundation, Fondation FondaMental, Eli Lilly, Glaxo SmithKline, Organon, Mayne Pharma and Servier, speaker's fees from Eli Lilly, advisory board fees from Eli Lilly and Novartis, and conference travel support from Servier. AJW has no conflicts of interest. AJMB owns shares in and is an employee of Eli Lilly and Company, Australia. NH is an employee of Macrostat Clinical Research, China. AB is a former employee of Eli Lilly and Company, Australia. MB has received Grant/Research Support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, MBF, NHMRC, Beyond Blue, Rotary Health, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Meat and Livestock Board, Organon, Novartis, Mayne Pharma, Servier and Woolworths, has been a speaker for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Merck, Pfizer, Sanofi Synthelabo, Servier, Solvay and Wyeth, and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck Merck, Pfizer and Servier.

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TABLES

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Table 1. Studies Included in the Analyses

Study ID	Clinical Trial Identifier	Protocol Title	Year of Protocol	Phase	Study Design	Number of placebo-treated participants	Lead-In	HDRS Data Available	Length of Acute Phase	Mean (SD) Duration of Placebo Treatment	Cross-Regional Study[a]
HGEH	1028[b]	Olanzapine vs. Placebo in the Treatment of Mania Associated with Bipolar I Disorder	1996	3/4	Parallel	69	None	Yes	3 weeks	12.2 (6.8)	No
HGHL	2354[b]	Olanzapine vs. Placebo in the Prevention of Relapse in Bipolar Disorder	1999	3	Parallel	136	6-12 weeks olanzapine	Yes	Up to 12 months	81.5 (106.7)	No
HGFU	1035a[b] 1035b[b]	Olanzapine Added to Mood Stabilizers in the Treatment of Bipolar Disorder	1997	3	Parallel	115	None	Yes	6 weeks (acute) 18 months (extension)	67.6 (110.7)	Yes
HGGW	1729[b]	Olanzapine vs. Placebo in the Treatment of Bipolar Disorder, Manic or Mixed	1997	3/4	Parallel	60	None	Yes	4 weeks	16.9 (9.9)	No
HGGY		Placebo-Controlled Olanzapine Monotherapy in the Treatment of Bipolar I Depression	2000	3	Parallel	377	None	No	8 weeks	39.1 (17.9)	No
HGIU	4360[b] NCT00050206[c]	Olanzapine vs. Placebo in the Treatment of Mania in Adolescents with Bipolar I Disorder	2002	4	Parallel	54	None	No	3 weeks	19.0 (4.9)	No
HGKQ	7029[b] NCT00094549[c]	Olanzapine vs. Divalproex and Placebo in the Treatment of Mild to Moderate Mania Associated with Bipolar I Disorder	2004	4	Parallel	105	None	No	3 weeks	18.0 (6.0)	Yes
HGMP	NCT00510146[c]	Efficacy and Safety of Olanzapine in the Treatment of Patients with Bipolar I Disorder, Depressed: A Randomized, Double-Blind Comparison with Placebo	2007	3	Parallel	171	None	Yes	6 weeks	35.7 (12.2)	Yes
BMAC	NCT00129220[c]	Placebo- and Haloperidol-Controlled Double-Blind Trial of Olanzapine in Patients with Manic or Mixed Episode of Bipolar I Disorder	2005	3	Parallel	98	None	Yes	3 weeks	17.9 (6.0)	No

[a] Cross-regional studies are those performed in the United States and in other regions (Europe, Asia and others).

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[b] lillytrials.com/results/Zyprexa.pdf Study identification number.

[c] Clinicaltrials.gov Study Identification Number.

Abbreviations: HDRS = Hamilton Depression Rating Scale.

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Table 2. Treatment-Emergent Adverse Events with an Incidence of >3% in Placebo-treated patients

Preferred Term	Frequency N = 1185	Incidence (%)
Headache	140	11.8
Insomnia	108	9.1
Somnolence	82	6.9
Anxiety	76	6.4
Nausea	75	6.3
Diarrhoea	65	5.5
Irritability	64	5.4
Agitation	60	5.1
Depression	55	4.6
Dizziness	55	4.6
Dry Mouth	54	4.6
Sedation	42	3.5
Constipation	41	3.5
Fatigue	41	3.5
Tremor	41	3.5
Increased appetite	40	3.4
Vomiting	40	3.4
Weight increased	40	3.4

Table 3. Time to First Treatment-Emergent Adverse Event by Study

Study ID	Number of Patients with Events, n (%)	Median (95% CI), days
Overall	673 (58.1)	16 (14, 19)
HGEH	30 (43.5)	12 (8, NA)
HGHL	78 (57.4)	11 (8, 15)
HGFU	100 (87.0)	6 (3, 8)

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HGGW	28 (84.8)	5 (3, 7)
HGGY	221 (58.6)	19 (15, 29)
HGIU	30 (55.6)	15 (7, NA)
HGKQ	46 (43.8)	NA
HGMP	88 (51.5)	37 (22, NA)
BMAC	52 (53.1)	19 (12, NA)

Note: Time to first TEAE is the time from the date of randomization to the date of the first TEAE. Patients without experiencing TEAE were censored for the analysis at the earliest date of death or discontinuation of study treatment.

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Table 4. Patient Demographics, Clinical Characteristics and Study Characteristics for Placebo-treated Patients

Characteristic	Total N = 1185	Any TEAE N = 806	Discontinued Due to TEAE N = 54	HDRS Total Score Worsening N = 321[a]	YMRS Total Score Worsening N = 585[b]	CGI-BP Total Score Worsening N = 278[b]
Female, n (%)	665 (56.1)	469 (58.2)	34 (63.0)	169 (52.6)	335 (57.3)	160 (57.6)
Age, mean (SD), y						
>0 and ≤ 26.6	238 (20.1)	149 (18.5)	10 (18.5)	36 (11.2)	104 (17.8)	42 (15.1)
>26.6 and ≤35.6	234 (19.7)	168 (20.8)	11 (20.4)	74 (23.1)	113 (19.3)	52 (18.7)
>35.6 and ≤42.6	241 (20.3)	175 (21.7)	8 (14.8)	69 (21.5)	109 (18.6)	63 (22.7)
>42.6 and ≤49.8	236 (19.9)	163 (20.2)	13 (24.1)	79 (24.6)	131 (22.4)	65 (23.4)
>49.8 and ≤84.4	236 (19.9)	151 (18.7)	12 (22.2)	63 (19.6)	128 (21.9)	56 (20.1)
BMI, mean (SD), kg/m^2						
< 18.5	43 (3.6)	22 (2.7)	1 (1.9)	10 (3.1)	15 (2.6)	7 (2.5)
≥18.5 and <25	435 (36.7)	260 (32.3)	22 (40.7)	110 (34.8)	195 (33.3)	85 (30.6)
≥25 and <30	334 (28.2)	230 (28.5)	13 (24.1)	91 (28.3)	185 (31.6)	82 (29.5)
≥30	318 (26.8)	244 (30.3)	17 (31.5)	109 (34.0)	189 (32.3)	104 (37.4)
Geographical region, n (%)						
United States	769 (64.9)	584 (72.5)	31 (57.4)	229 (71.3)	405 (69.2)	210 (75.5)
Asia[c]	239 (20.2)	125 (15.5)	15 (27.8)	73 (22.7)	91 (15.6)	38 (13.7)
Other	177 (14.9)	97 (12.0)	8 (14.8)	19 (5.9)	89 (15.2)	30 (10.8)
Year of protocol, n (%)						
<1999	244 (20.6)	217 (26.9)	6 (11.1)	122 (38.0)	71 (12.1)	40 (14.4)
1999-2002	567 (47.8)	394 (48.9)	30 (55.6)	125 (38.9)	378 (64.6)	183 (65.8)
>2002	374 (31.6)	195 (24.2)	18 (33.3)	74 (23.1)	136 (23.2)	55 (19.8)

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Smoking status yes, n (%)	137 (11.6)	99 (12.3)	9 (16.7)	90 (28.0)	93 (15.9)	80 (28.8)
Treatment-naïve patients, n (%)	318 (26.8)	175 (21.7)	8 (14.8)	65 (20.2)	151 (25.8)	56 (20.1)
Patients with previous episodes, n (%)	738 (62.3)	523 (64.9)	31 (57.4)	211 (65.7)	401 (68.5)	202 (72.7)
Patients with previous hospitalizations, n (%)	231 (19.5)	181 (22.5)	15 (27.8)	95 (29.6)	129 (22.1)	67 (24.1)

[a] Six studies (BMAC, HGEH, HGFU, HGGW, HGHL and HGMP) have information available.

[b] All nine studies have information available.

[c] Asia includes China, Japan, Korea and Taiwan.

Abbreviations: CGI-BP = Clinical Global Impressions scale for use in Bipolar Disorder; HDRS = Hamilton Depression Rating Scale; SD = standard deviation; TEAE = treatment emergent adverse event; YMRS = Young Mania Rating Scale; y = years.

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FIGURE LEGENDS

Figure 1. Distribution of the Occurrence Frequency of the MedDRA Preferred Terms reported for Placebo-Treated Patients

Figure 2. Odds Ratio (95% CI) of Prognostic Characteristics for Adverse Outcomes in Placebo-Treated Patients. Abbreviations: BMI = body mass index; HDRS = Hamilton Depression Rating Scale; SD = standard deviation; TEAE = treatment emergent adverse event; y = years

Supplementary Figure 1. Odds of TEAE Occurrence by Study According to Selected Patient Characteristics

FIGURES

Figure 1

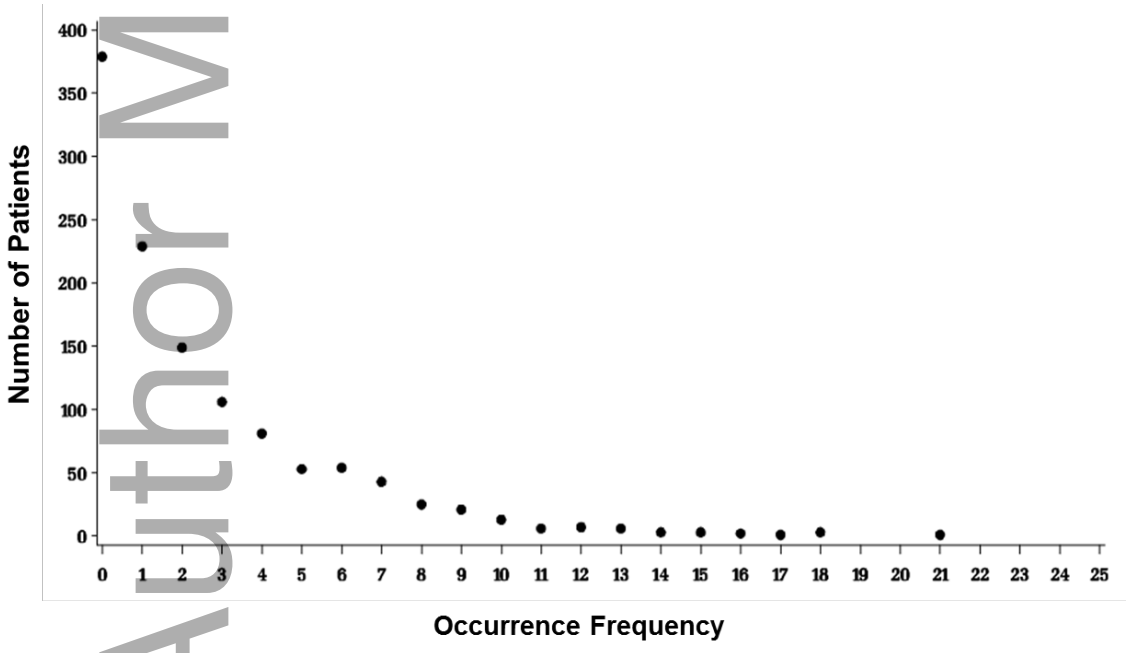

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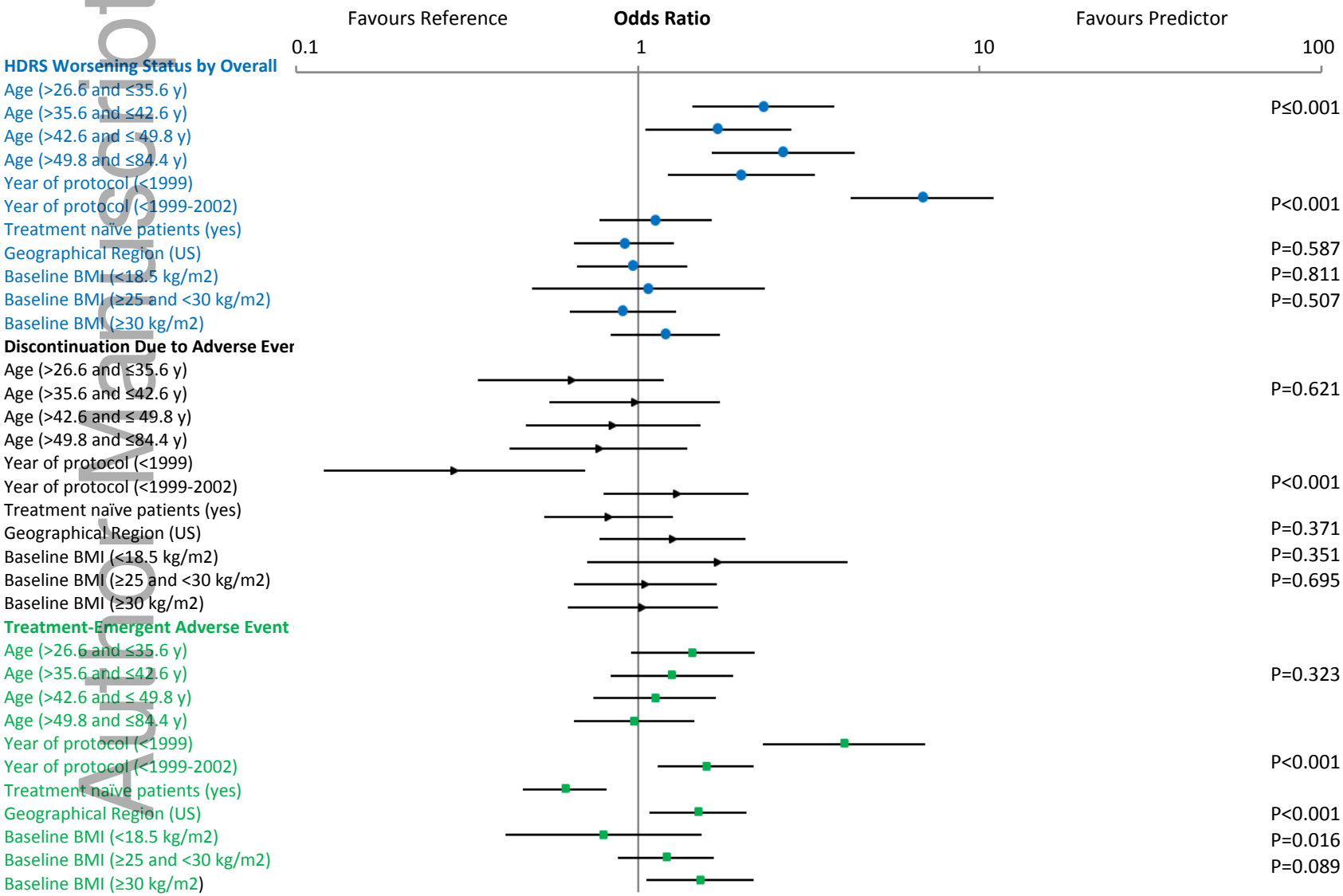
Figure 2: Odds Ratio (95% CI) of Prognostic Characteristics for Adverse Outcomes in Placebo-Treated Patients. Abbreviations: BMI = body mass index; HDRS = Hamilton Depression Rating Scale; SD = standard deviation; TEAE = treatment emergent adverse event; y = years



Reference: Age ≤26.6 years; Year of protocol >2002; Treatment-naïve patients = no; Geographical region = Other; Baseline BMI ≥ 18.5 and <25 kg/m^2

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