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Early treatment response affects signal detection in a placebo-controlled depression study

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ABSTRACT

We examined the effect of early treatment response on the Quick Inventory of Depressive Symptomatology ($QIDS\text{-}SR_{16}$) within 2 weeks following randomization on the eventual treatment outcome at 6 weeks in a double-blind study of subjects with major depressive disorder randomly assigned to a combination treatment (buspirone 15 mg with melatonin SR 3 mg), buspirone 15 mg, or placebo (Clinicaltrials.org: NCT 007005003).

The extent of $QIDS\text{-}SR_{16}$ score improvement between baseline and week 2 was significantly associated with higher treatment response rates at week 6 ($\geq$50% $QIDS\text{-}SR_{16}$ improvement from baseline) regardless of treatment assignment.

Thirty-two of 123 subjects (26.0%) were $QIDS\text{-}SR_{16}$ treatment responders by week 2 and were excluded in a post-hoc analysis of five clinical metrics: $QIDS\text{-}SR_{16}$, the Inventory of Depressive Symptomatology (IDS-c30), clinical global impression of severity and improvement scales, and Hamilton rating scale for anxiety.

The effect size favoring the combination-treatment over buspirone and/or placebo increased on each of the 5 clinical metrics in the remaining 91 subjects with < 50% $QIDS\text{-}SR_{16}$ improvement at week 2. For instance, the effect size favoring the combination treatment over the pooled buspirone and placebo groups improved from 0.33 in the mITT population to 0.64 for the $QIDS\text{-}SR_{16}$, and from 0.37 to 0.58 for the IDS-c30. Further, the statistical significance favoring the combination treatment improved from p = .055–.017 for the $QIDS\text{-}SR_{16}$.

This was a post-hoc analysis of a small MDD study, but it is clear that future studies need to explore the mediating factors that affect signal detection and influence individual treatment response.

Introduction

The achievement of signal detection is particularly challenging in trials of major depressive disorder (MDD) where the placebo response has increased over the past three decades [1–5].

The inherent conditions of the clinical trial itself may facilitate symptomatic improvement and impede the detection of a true drug effect [4–15]. The informed consent process differentiates the willing from the unwilling subject, and the decision to consent may foster unrealistic expectations about the treatment outcome. The perception of illness severity, possible frustration about previously unsuccessful treatment interventions, or a sense of urgency for help may motivate some potential study subjects to exaggerate their symptoms to qualify for a clinical trial. Some site-based raters may inflate some rating scores in order to achieve study eligibility thresholds [16]. Further, a study subject may respond to queries differently as he or she gains increasing familiarity with the questions that measure symptom severity, and the natural course of the acute major depressive episode (MDE) may contribute to clinical improvement during the clinical trial [8]. Regardless of the etiology, the severity of each individual's depressive symptoms often attenuates shortly after the randomization visit regardless of treatment assignment, which may impede signal detection [2–3,5–8,17].

Early symptomatic improvement may influence the eventual treatment response [2–6,17–21]. In a meta-analysis of 4 randomized, double-blind, placebo-controlled depression trials, Evans and colleagues reported that improvement of the pre-randomization scores of the Hamilton rating scale for depression ($HamD_{17}$) between screen and baseline was associated with a higher placebo response rate and poorer drug–placebo separation at the end of these trials [19]. In an analysis of 8 double-blind MDD trials, Altin and colleagues reported that a 20% improvement of the total $HamD_{17}$ score within 2 weeks post-randomization yielded higher response and remission rates in both the duloxetine and placebo treated groups than in the subjects with < 20% improvement [20]. Thus, early symptomatic improvement may obscure the true drug effect and impede signal detection in clinical trials.

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We examined the impact of early symptomatic improvement on eventual treatment outcome in a small, phase II clinical trial of subjects with major depressive disorder (MDD) who received a combination treatment of buspirone 15 mg with melatonin sustained release (SR) 3 mg. In pre-clinical studies, neurogenesis-based data has suggested that low buspirone doses (15 mg) combined with melatonin might yield an antidepressant effect [22]. We have previously reported that this combination treatment was significantly better than a pooled group of buspirone 15 mg and placebo-assigned subjects on the primary measure, the clinical global impression of improvement (CGI-I) scale, but not on the patient-rated Quick Inventory of Depressive Symptomatology (QIDS-SR_{16}) score [23–26].

For the current post-hoc analysis, the extent of the QIDS-SR_{16} score improvement within 2 weeks of randomization was used to examine subsequent treatment outcome in this study. We found that early symptomatic improvement of the QIDS-SR_{16} score within 2 weeks of randomization was associated with markedly higher treatment response rates across all treatment assignments and that early treatment response actually impeded signal detection.

Material and methods

Study design and study participants

This analysis was done as part of an investigator initiated clinical trial (CBM-IT-01; BCI NCT 007005003) conducted by the Clinical Trials Network at Massachusetts General Hospital and funded by BrainCells Inc. (San Diego, California). The methods and overall results of this study have been described elsewhere [25,26]. The core study was a randomized, 6-week, double-blind, placebo-controlled evaluation of a combination treatment of buspirone 15 mg combined with melatonin sustained release (SR) 3 mg) in patients with Major Depressive Disorder (MDD). Eligible subjects were randomized at baseline (Week 0) to receive either the combination treatment, buspirone 15 mg as monotherapy, or placebo in a 2:1:1 ratio for 6 weeks. Post-randomization study visits were done at weeks 2, 4, and 6 (the study endpoint).

The primary efficacy measures were the CGI-I and QIDS-SR_{16} [23,24]. Subjects required a QIDS-SR_{16} score ≥14 at screen and baseline for study eligibility.

Secondary variables included the Clinical Global Impression of Severity (CGI-S), Hamilton Rating Scale for Anxiety (Ham-A) and the Inventory of Depressive Symptomatology-30 item clinician version: IDSc30 [23,27,28]. Site-based raters administered the CGI-S at every study visit (screen, baseline, and weeks 2, 4, and 6. The IDSc30 and Ham-A instruments were administered at baseline and week 6 only.

All potential study subjects agreed in writing to participate in the study after reading and reviewing the IRB-approved informed consent. All sites obtained IRB approval prior to initiating the study.

Subjects between 18 and 65 years of age who met DSM-IV-TR criteria for major depressive disorder (MDD), as determined by the Mini-International Neuropsychiatric Interview (M.I.N.I.) and psychiatric evaluation were eligible for this study [29,30]. Female patients of childbearing potential needed to be taking a reliable, medically acceptable form of contraception for at least 30 days prior to screening and throughout the study. Subjects meeting criteria for other Axis-I disorders as their primary diagnosis, had a history of eating disorders, obsessive-compulsive disorder, psychotic disorder, bipolar disorder and/or mental retardation and those with alcohol or substance abuse or dependency were excluded from the study. The use of antidepressant, antipsychotic, or anxiolytic medications or drugs with known psychotropic properties was prohibited for 1 week (4 weeks for fluoxetine) prior to screening and throughout the study. Subjects who used substances that are known inhibitors or inducers of CYP3A4 were also excluded.

142 patients meeting DSM-IV-TR criteria for MDD confirmed by the M.I.N.I. and meeting minimum QIDS-SR_{16} score criteria (≥14) were enrolled in this study from 9 clinical trial sites located within the United States. This post-hoc analysis was conducted with the 123 subjects in the modified intent to treat (mITT) population with QIDS-SR_{16} assessments completed at week 2.

Statistical analyses

We examined the effect of QIDS-SR_{16} score improvement within 2 weeks of randomization on the eventual treatment outcome of all clinical metrics at the study endpoint. Treatment response at the study endpoint (week 6 or the last observation carried forward, LOCF) was defined as ≥50% QIDS-SR_{16}, IDSc30 or Ham-A total score improvement from the baseline visit.

Statistical analyses used an analysis of covariance (ANCOVA) model, with change from baseline as the dependent variable, the baseline value as a covariate, and treatment group as the factor with three values (placebo, buspirone, and the combination treatment). Additional analyses included X^2 tests with Yates correction for continuity and Cohen's d for effect size analyses where appropriate [31].

By design, the planned statistical analyses for this small study included a secondary pooling of the buspirone and placebo treatment groups on the expectation that these groups would not differ on the mean CGI-I at endpoint by more than 0.04 points [25]. This expectation was in fact realized, as the CGI-I score difference between buspirone and placebo was 0.04 at week 6. Thus, the buspirone and placebo groups were subsequently pooled for further ANCOVA and treatment response analysis against the combination treatment.

Table 1
Demographic and baseline clinical characteristics of MDD subjects.

	mITT Population	Combination[1]	Buspirone[2]	Placebo
n	123	60	31	32
Age (all) Mean ± SD	42.4 ± 12.0	43.3 ± 12.1	40.7 ± 12.3	42.2 ± 11.8
Gender (Female)%	82 (66.7%)	40 (66.7%)	19 (61.2%)	23 (71.9%)
Weight (lbs.)	203.9 ± 54.0	201.9 ± 56.5	215.8 ± 57.0	196.0 ± 54.3
BMI[3]	32.7 ± 8.3	32.2 ± 8.4	34.8 ± 9.1	31.6 ± 7.00
Baseline Clinical Metrics				
CGI-S (Mean ± SD)	4.50 ± 0.58	4.50 ± 0.60	4.55 ± 0.57	4.44 ± 0.56
IDSc30	41.3 ± 8.0	41.2 ± 8.1	42.3 ± 7.2	40.4 ± 8.7
QIDS-SR_{16}	17.1 ± 3.0	17.1 ± 3.1	17.0 ± 2.3	17.3 ± 3.4
Ham-A	20.1 ± 5.8	19.8 ± 6.0	20.2 ± 5.6	20.5 ± 5.6

[1] Combination treatment of buspirone 15 mg with melatonin 3 mg-SR.
[2] Buspirone monotherapy 15 mg daily.
[3] BMI = body mass index defined as weight (kg) divided by the subject's height in meters squared (m^2).

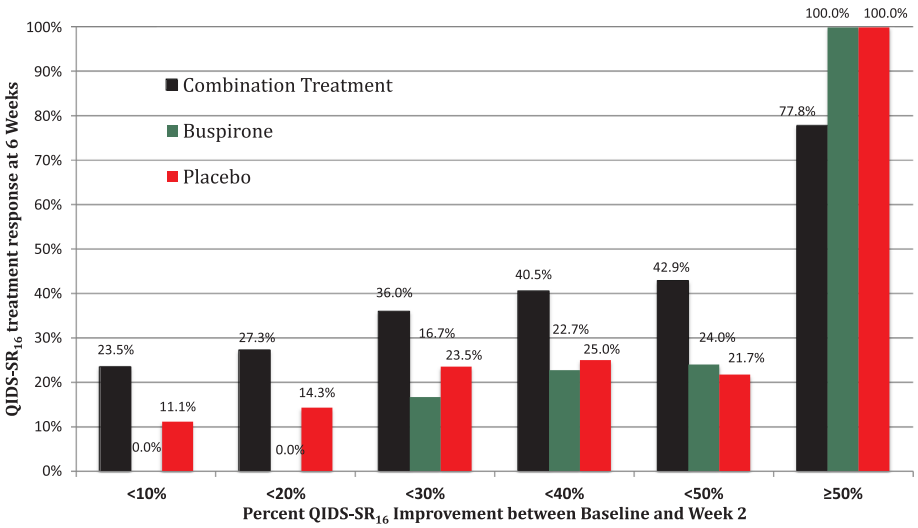

Fig. 1. Early QIDS-SR_{16} improvement and eventual treatment response*. *Early improvement reflects the change of total QIDS-SR_{16} score between baseline and week 2. QIDs-SR_{16} treatment response at 6 weeks is defined as ≥50% improvement from baseline.

Table 2
Effect size analyses comparing the combination treatment versus buspirone and placebo-assigned groups.*

	n	ΔCGI-I	ΔCGI-S	ΔIDSc30	ΔQIDS-SR_{16}	ΔHam-A
All subjects	123					
Combination	60					
vs. buspirone	31	0.365	0.440	0.282	0.423	0.388
vs. placebo	32	0.386	0.399	0.480	0.230	0.365
vs. pooled group**	63	0.374	0.421	0.373	0.326	0.350
< 50% QIDS-SR_{16} improvement*	91					
Combination	42					
vs. buspirone	26	0.533	0.734	0.468	0.654	0.529
vs. placebo	23	0.469	0.662	0706	0.625	0.638
vs. pooled group**	49	0.503	0.701	0.579	0.641	0.580
≥50% QIDS-SR_{16} improvement*	32					
Combination	18					
vs. buspirone	5	−0.528	−0.678	−0.570	−0.282	−0.471
vs. placebo	9	0.377	0.000	0.219	−0.310	0.056
vs. pooled group**	14	0.054	−0.242	0.063	−0.300	−0.132

* Effect size analyses examine the difference between the score changes (Δ) of the combination treatment versus other assigned groups for the CGI-S, IDSc30, QIDS-SR_{16}, and Ham-A measures after 6 weeks of treatment (the double-blind study endpoint) and the final mean CGI-I score; Positive values favor the combination treatment.

** Pooled group includes subjects assigned to buspirone monotherapy or placebo.

*** Post-hoc analyses evaluating the impact of < 50% or ≥50% QIDS-SR_{16} improvement between the baseline and week 2 visits on eventual treatment outcome at 6 weeks.

Results

Table 1 describes the demographic and clinical characteristics of the study population. The full study results have been reported elsewhere and are not the subject of this communication [25,26].

The study population for this analysis included the 123 subjects who had week 2 QIDS-SR_{16} assessments (60 subjects randomized to the combination treatment, 31 subjects to buspirone 15 mg monotherapy, and 32 subjects to placebo). As noted above, the planned statistical analyses for this small study included a secondary pooling of the buspirone monotherapy and placebo treatment groups. Subjects who received the combination treatment did significantly better than the pooled group of buspirone monotherapy and placebo-assigned subjects on the CGI-I (p = .038), CGI-S (p = .015), Ham-A (p = .017) and IDSc30 (p = .030), and revealed a non-statistically significant trend favoring the combination treatment on the QIDS-SR_{16}. (p = .055) at the study endpoint (week 6).

Early QIDS-SR_{16} score improvement and eventual treatment outcome

Fig. 1 displays the association of increasing percentages of QIDS-SR_{16} score improvement between baseline and week 2 on the eventual treatment response at the study endpoint (6 weeks). There was a significant association between the extent of early QIDS-SR_{16} improvement at week 2 and eventual treatment response. For instance, subjects with < 20% QIDS-SR_{16} score improvement by week 2 had significantly less QIDS-SR_{16} treatment response at week 6 than subjects with ≥20% improvement (X^2 = 7.3; df = 1; p = .007). The most significant difference was noted between the subjects who had < 50% versus ≥50% QIDS-SR_{16} score improvement by week 2 (X^2 = 27.3; df = 1; p < .0001).

Signal detection in subjects with < 50% QIDS-SR_{16} score improvement at week 2

Thirty-two of the 123 subjects (26.0%) achieved a treatment response (≥50% QIDS-SR_{16} score improvement) within two weeks of randomization. Eighteen responders had been randomly assigned to the combination treatment, 5 to buspirone, and 9 to placebo.

At the study endpoint (week 6), 28 of the 32 early QIDS-SR_{16} treatment responders (87.5%) were still treatment responders. In a post-hoc analysis, we excluded the 32 subjects who had ≥50% QIDS-SR_{16} score improvement at week 2.

Following the post-hoc exclusion of 32 subjects who had ≥50% QIDS-SR_{16} score improvement by week 2, the calculated effect size favoring the combination treatment was enhanced on each of the 5

Table 3
Impact of early QIDS-SR_{16} treatment response on the QIDS-SR_{16}, IDSc30, and Ham-A treatment response rates at the study endpoint.[1]

	n	QIDS-SR_{16} Response At Week 6	IDSc30 Response At Week 6	Ham-A Response At Week 6
mITT population (All subjects)	123	57 (46.3%)	51 (41.5%)	47 (38.2%)
Combination	60	32 (53.3%)	29 (48.3%)	23 (38.3%)
Buspirone	31	11 (35.5%)	12 (38.7%)	13 (41.9%)
Placebo	32	14 (43.8%)	10 (31.3%)	11 (34.4%)
Pooled group[2]	63	25 (39.7%)	22 (34.9%)	24 (38.1%)
< 50% QIDS-SR_{16} improvement at week 2	91	29 (31.9%)	28 (30.8%)	26 (28.6%)
Combination	42	18 (42.9%)	16 (38.1%)	12 (28.6%)
Buspirone	26	6 (23.1%)	7 (26.9%)	8 (30.8%)
Placebo	23	5 (21.7%)	5 (21.7%)	6 (26.1%)
Pooled group[2]	49	11 (22.5%)	12 (24.5%)	14 (28.6%)
≥50% QIDS-SR_{16} improvement at week 2	32	28 (87.5%)	23 (71.9%)	21 (65.6%)
Combination	18	14 (77.8%)	13 (72.2%)	11 (61.1%)
Buspirone	5	5 (100.0%)	5 (100.0%)	5 (100.0%)
Placebo	9	9 (100.0%)	5 (55.6%)	5 (55.6%)
Pooled group[2]	14	14 (100.0%)	10 (71.4%)	10 (71.4%)

[1] Early QIDS-SR_{16} treatment response is defined as ≥50% total QIDS-SR_{16} score improvement between the baseline and week 2 visits. Study endpoint is week 6 or LOCF.
[2] Pooled group includes subjects assigned to buspirone monotherapy or placebo.

clinical metrics used in the study (Table 2). For instance, the calculated effect size favoring the combination-treatment over the pooled buspirone and placebo groups increased from 0.326 in the mITT population to 0.641 on the QIDS-SR_{16} in the subjects with < 50% QIDS-SR_{16} score improvement by week 2 (Table 2).

As shown in Table 3, 18 of the 42 combination-treated subjects (42.9%) with < 50% QIDS-SR_{16} score improvement at week 2 were QIDS-SR_{16} treatment responders at week 6 in contrast to 11 of 49 subjects (22.5%) in the pooled group ($\chi^2 = 3.45$; df = 1; p = .063). This result slightly improved upon the non-significant trend noted for the larger mITT population ($\chi^2 = 1.79$; df = 1; p = .181).

In the post-hoc analysis of score differences over the 6-week double-blind period, the statistical significance favoring the combination treatment over the pooled groups improved on all 5 clinical metrics at the study endpoint (Tables 4 and 5). The mean QIDS-SR_{16} score difference favoring the combination treatment over the pooled group increased from 1.7 to 3.3 points and achieved statistical significance (F = 5.96; p = .017) in the 91 subjects with < 50% QIDS-SR_{16} score improvement at week 2. Fig. 2 displays the mean QIDS-SR_{16} score trajectories for the combination-treated, buspirone monotherapy, and placebo-assigned treatment groups at each study visit in the mITT population and in the subjects with < 50% QIDS-SR_{16} score improvement at 2 weeks. Similarly, the mean IDSc30 score difference favoring the combination treatment over the pooled group increased from 4.6 to 7.3 points from baseline to endpoint (F = 5.89; p = .017) and improved upon the IDSc30 result found in the mITT population (F = 4.48; p = .030).

Signal detection in subjects with morbid obesity and < 50% QIDS-SR_{16} score improvement at week 2

In a previous analysis, we demonstrated that morbid obesity affected signal detection in this same MDD study population [32]. We examined the effect size resulting from combining the moderating factor (morbid obesity) with the mediating factor of early QIDS-SR_{16} treatment response. The post-hoc exclusion of 16 additional mITT subjects with body mass index (BMI) ≥40 (the World Health Organization standard for morbid obesity) in the subject sub-group with < 50% QIDS-SR_{16} improvement enhanced the effect size from 0.641 to 0.744 for the QIDS-SR_{16}, from 0.579 to 0.782 for the IDSc30, and from 0.350 to 0.715 for the Ham-A.

Table 4
Impact of early QIDS-SR_{16} treatment response on the eventual treatment outcome of 5 clinical metrics in an MDD trial.[1]

mITT population	n	Δ CGI-S	CGI-I	Δ IDS-C30	Δ QIDS-SR_{16}	Δ HAM-A
Mean	123	−1.12	2.67	−16.61	−7.59	−7.41
± SD		1.14	1.14	12.42	5.33	7.73
Combination	60	−1.37	2.45	−18.98	−8.48	−8.80
Buspirone	31	−0.87	2.87	−15.65	−6.26	−6.32
Placebo	32	−0.91	2.88	−13.09	−7.22	−5.88
Pooled[2]	63	−0.89	2.87	−14.35	−6.75	−6.10
< 50% QIDS-SR_{16} improvement[1]	91					
Combination	42	−1.34	2.59	−18.91	−8.47	−9.16
Buspirone	26	−0.58	3.15	−13.00	−5.15	−4.88
Placebo	23	−0.65	3.09	−10.00	−5.30	−4.00
Pooled[2]	49	−0.61	3.12	−11.59	−5.22	−4.47
≥50% QIDS-SR_{16} improvement[1]	32					
Combination	18	−1.56	1.94	−17.56	−10.89	−11.00
Buspirone	5	−2.40	1.40	−18.20	−12.00	−13.80
Placebo	9	−1.56	2.33	−17.33	−12.11	−10.67
Pooled[2]	14	−1.86	2.00	−17.64	−12.07	−11.79

[1] Early treatment response is defined as ≥50% QIDS-SR_{16} score improvement between the baseline and week 2 visits. Treatment outcome reflects the mean total score change (Δ) for CGI-S, IDSc30, QIDS-SR_{16}, and Ham-A and the final mean CGI-I value for each of the three treatment groups at week 6 (the double-blind study endpoint) or the last observation carried forward (LOCF).
[2] Pooled group includes subjects assigned to buspirone monotherapy or placebo.

Table 5
Post-hoc statistics following the exclusion of early QIDS-SR_{16} treatment responders on 5 clinical metrics in an MDD trial.[1]

(Combination treatment versus pooled group[2])				
	mITT population		QIDS-SR_{16} < 50% improvement[1]	
n	60	63	42	49
	F	p	F	p
CGI-S*	6.09	0.015	9.03	0.003
CGI-I**	4.38	0.038	5.13	0.030
IDSc30*	4.48	0.030	5.89	0.017
QIDS-SR16*	3.68	0.055	5.96	0.017
Ham-A*	5.87	0.017	7.00	0.010

[1] Post-hoc sub-group excludes 32 subjects from the mITT population who achieved ≥50% QIDS-SR_{16} score improvement (treatment response) between the baseline and week 2 visits.
[2] The pooled group includes subjects assigned to buspirone monotherapy or placebo.
* ANCOVA for treatment changes from baseline to endpoint (or last observation) for CGI-S, IDSc30, QIDS-SR_{16}, and Ham-A measures.
** ANOVA for CGI-I.

Discussion

In this analysis, early QIDS-SR_{16} improvement within 2 weeks of randomization was associated with significantly higher treatment response rates *regardless* of treatment assignment at the end of a 6-week double-blind placebo-controlled, clinical trial in MDD subjects.

Thirty-two of the enrolled acutely depressed MDD subjects (26.0%) met criteria for a full treatment response on the QIDS-SR_{16} at week 2

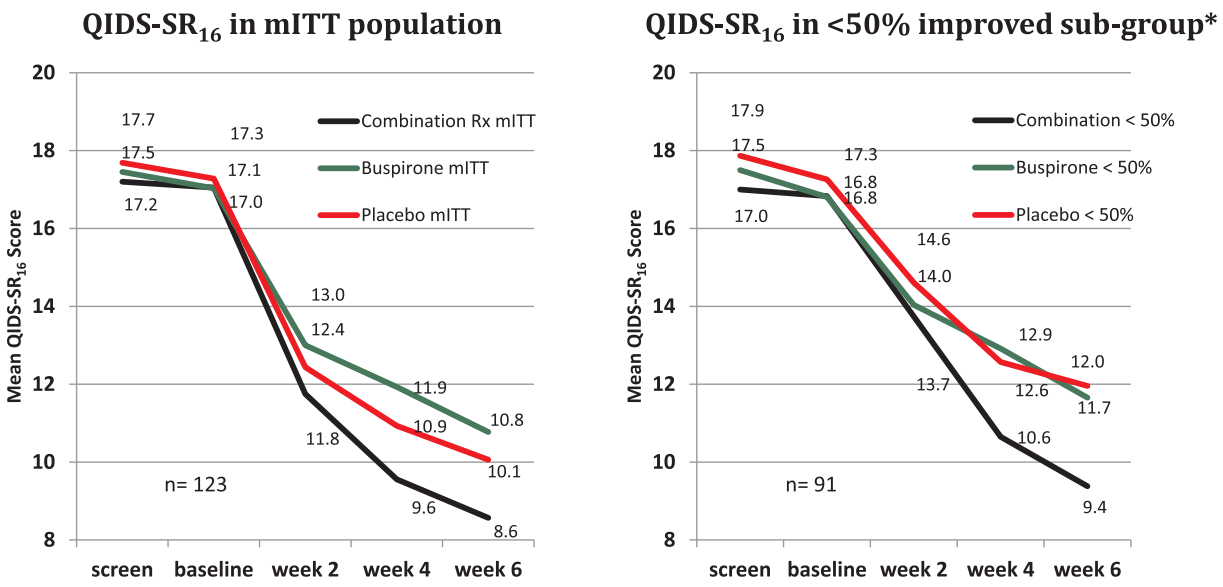

Fig. 2. Impact of early QIDS-SR_{16} treatment response on eventual treatment outcome. *post-hoc exclusion of 32 subjects with a conventional treatment response (≥50% QIDS-SR_{16} improvement from baseline) within 2 weeks following randomization (weeks 0–2).

regardless of treatment assignment. By week 6, 87.5% of these early QIDS-SR_{16} responders were still responders.

We excluded the 32 early QIDS-SR_{16} treatment responders in a post-hoc analysis. In the remaining sub-group of 91 subjects with < 50% QIDS-SR_{16} score improvement by week 2, there was an *enhanced* effect size favoring the combination treatment over the buspirone, placebo, and pooled treatment groups on all 5 clinical metrics compared to the larger mITT population and a statistically significant QIDS-SR_{16} treatment difference as well.

Our findings replicate previous studies that reported early symptomatic improvement during a double-blind placebo-controlled MDD trial [2,3,6,7,17–20]. An early treatment response significantly increases the likelihood of an eventual treatment response at the study endpoint regardless of treatment assignment (Fig. 1). Our findings are consistent with the study of Faries and colleagues and two independent meta-analyses of MDD trials that showed that early symptomatic improvement on the $HamD_{17}$ led to higher placebo response rates [18–20].

The early symptomatic improvement observed in some depressed subjects across all treatment groups may reflect the experimental condition as well as non-specific factors associated with study participation. The enhanced effect size favoring the combination treatment unmasked in the subjects who had < 50% QIDS-SR_{16} improvement at 2 weeks may reflect a truer drug effect in this study.

The fact that many enrolled subjects have an early treatment response is not surprising and demonstrates the power of expectation and the inherent non-specific factors that can influence the experimental condition of the clinical trial. Kaptchuk and colleagues [12,13] have shown that the mere perception of support can generate therapeutic placebo responses comparable to known, effective treatments. Lambert [33] and Kirsch [10,11] have argued that most of the treatment response seen in placebo-controlled clinical trials of depression is due to non-specific factors and/or placebo responsiveness rather than a true drug effect. However, these arguments are tempered by recent studies that demonstrate how moderating and mediating factors can affect placebo response [3,17,34,35]. For instance, in a recent meta-analysis, Hieronymus and colleagues [35] demonstrated antidepressant efficacy over placebo after controlling for in-study adverse events (a potential mediating factor). In the current post-hoc analysis, the combined exclusion of both morbidly obese subjects (a moderating factor) and QIDS-SR_{16} treatment responders at week 2 (a mediator) further enhanced the effect size. Obviously, the objective is to identify the relevant pre-randomization factors at the screen visit as part of the subject selection process.

The findings reported in this post-hoc analysis were generated from a small depression study and must be interpreted with caution. Our findings might not be replicated in other, larger studies. It might also be argued that the very purpose of including a placebo control group is to engage, rather than avoid the non-specific factors that are part of the double-blind experiment in order to demonstrate that robust drug efficacy can overcome these factors and still achieve signal detection. Certainly, novel drugs with an early onset of antidepressant action (like esketamine or rapastinel) need to outperform early placebo responsiveness within the first week of treatment.

We believe our findings can inform future trial designs. Future clinical trial designs need to address the reality that double-blind treatment conditions can facilitate early symptomatic improvement that may, in turn affect signal detection. One design is to delay or stagger the start of randomization by adding a second, double-blinded study visit to identify subjects whose early responsiveness might adversely affect study outcome [18]. In fact, Quitkin and colleagues recommended a two-week placebo lead-in period to identify early responders prior to randomization over thirty years ago, although not all authors agree with this strategy [6,7,36]. An alternative strategy is the sequential parallel clinical design (SPCD) that has a 2-stage study design that anticipates early symptomatic change and subsequently re-randomizes non-responders in a second, presumably more robust double-blind stage [8]. The balanced crossover design is another innovative design model that attempts to address early placebo response as well [37]. Further, some phase II, exploratory trials might benefit by pre-specifying additional outcome analyses in the statistical analysis plan that anticipate and can adjust for the early symptomatic improvement.

Numerous efforts to manage the placebo response by using restrictive study eligibility criteria, site-independent subject selection, and innovative study designs have had only partial success in clinical trials [3,8,14–16,21,38,39]. This was a post-hoc analysis of a small MDD study, but it is clear that future clinical trials need to explore the moderating and mediating factors that affect signal detection. Hopefully, future studies will improve the subject selection process by using endophenotypic data or biosignatures based on specific clinical markers, genetic differences, biomarkers, and cellular disease mechanisms [34,40,41]. Further, a better understanding of the factors that affect individual treatment response may yield more personalized treatment strategies for depressed patients.

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Contributors

Dr. Targum participated in the design, implementation, and analysis of the original study and conceived, analyzed, and wrote the current post-hoc analysis reported in this manuscript. Mr. Catania assisted with the collection, collation, and analysis of the data relative to early symptomatic improvement and assisted with the preparation of the final manuscript.

Conflicts of interest

Dr. Targum was chief medical officer of BrainCells Inc. at the time of study execution but has received no compensation for the analysis or preparation of this specific manuscript. He has received consultation fees or vendor grants from Acadia Pharmaceuticals, Alkermes Inc., BrainCells Inc., Forum Pharmaceuticals, Functional Neuromodulation Inc., Intracellular Therapies, Inc., Johnson and Johnson PRD, Methylation Sciences Inc., Neurim Pharmaceuticals, Prana Biotechnology Ltd., Pfizer Inc., Resilience Therapeutics, Sophiris and Sunovion Pharmaceuticals.

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