Two definitions of early response as predictors of remission in a phase 3 depression program: informing augmentation trial design

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Methodological Question

Measures of early symptomatic improvement, their relative predictive power for longer-term remission, and the impact on phasic clinical trial designs in major depressive disorder (MDD).

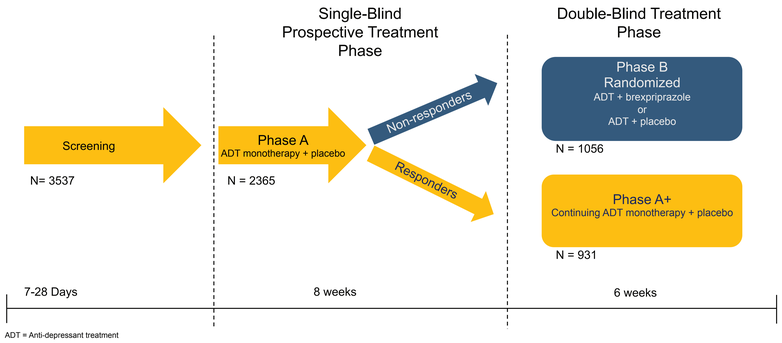
Introduction

Increasing evidence suggests that clinical course during the first weeks of antidepressant treatment (ADT) is a significant predictor of response and remission weeks later (e.g., Papakostas et al, 2006; Szegedi et al, 2009). These findings are useful supplements to existing treatment algorithms as they offer clinicians more confidence in early switching and augmentation. Furthermore, these data may inform design for trials that include phasic treatment periods (e.g. augmentation trials, maintenance trials) and a need to enrich the randomized sample with only those subjects who are not already on a response course and are not likely to respond to placebo. The current analysis will examine response data from two phase 3 brexpiprazole augmentation trials in MDD, and will aim to extend earlier findings by understanding the extent to which early response predicts response and remission after a full 14 weeks of ADT monotherapy.

Methods

The POLARIS (NCT01360632) and PYXIS (NCT01360645) trials evaluated adjunctive brexpiprazole vs placebo in subjects with MDD who had demonstrated inadequate response to 8 weeks of single-blind monotherapy ADT (Thase et al, 2015a and 2015b). Inadequate responders in the prospective treatment phase (Phase A) were randomized to brexpiprazole or placebo in the 6-week double blind treatment phase (Phase B). Responders in Phase A were assigned to a double-blind, 6-week continuation of the same ADT (Phase A+), for a total of 14 weeks of monotherapy ADT.

Figure 1: Design Schematic for the Combined POLARIS/PYXIS PROGRAMS



ADT = Anti-depressant treatment

For the current analysis, four different response definitions were applied to the POLARIS/PYXIS dataset, to include two early response definitions described in the literature (Szegedi et al, 2009, and Papakostas et al, 2009), the standard ≥50% improvement definition utilized in MDD research for decades (Frank et al, 1991), and the definition of adequate response applied in the POLARIS/PYXIS program (Thase et al, 2015 a & b). We explored each definition as a predictor of response (≥ 50% improvement from baseline in MADRS total score) and remission (MADRS ≤ 10) at endpoint (Phase A+, 14 weeks).

Figure 2: Definition of Phase A Response

PYXIS/POLARIS Adequate Response Thase et al,(2015 a/b)	Meets any of the following criteria: ≥ 50% reduction in HAMD-17 from baseline to Week 8, HAMD-17 total score of <14 at the week 8 visit, CGI-I score of 1 or 2 or ≥ 50% reduction in MADRS from baseline to any visit during the prospective treatment phase*
Standard (50%) Response (Frank et al, 1991)	>50% improvement from baseline to Week 8 on the MADRS Total Score
Early (20%) Improvement (Szegedi et al, 2009)	>20% improvement from baseline to Week 2 on the MADRS Total Score
Early Sustained Response (Papakostas et al, 2006)	>50% improvement from baseline to Week 2 with no subsequent worsening through Week 8 on the MADRS Total Score

MADRS = Montgomery Asberg Depression Rating Scale; HAMD-17 = 17-item Hamilton Depression Rating Scale; CGI-I = Clinical Global Impressions of Improvement

* Approximately 80% of all subjects were enrolled under these criteria. An earlier version of the protocol were slightly more liberal (Thase et al, 2015a & b)

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Results

Sample Characteristics

A total of 2365 subjects were enrolled into Phase A of the POLARIS/PXYIS trials. Demographic and clinical characteristics are shown in Table 1.

Table 1: Demographic and Clinical Characteristics for the Combined POLARIS/PYXIS Trials

	Enrolled in Prospective ADT Treatment Phase (Phase A) N = 2365
Demographics (at screening)	
Age, mean (SD)	44.11 (11.93)
BMI, kg/m^2, mean (SD)	29.68 (7.01)
Female sex, n (%)	1639 (69.3%)
White, n (%)	1975 (83.5%)
Clinical characteristic (at phase A baseline)	
Duration of current episode, months, mean (SD)	15.98 (29.42)
Recurrent episodes, yes, n (%)	2082 (88.0%)
No. of lifetime episodes, mean (SD)	3.60 (3.31)
MADRS total score, mean (SD)	29.95 (4.73)
Assigned antidepressant treatment (at phase A baseline)	
Escitalopram, n (%)	480 (20.3%)
Fluoxetine, n (%)	253 (10.7%)
Paroxetine CR, n (%)	255 (10.8%)
Sertraline, n (%)	391 (16.5%)
Duloxetine, n (%)	549 (23.2%)
Venlafaxine, n (%)	437 (18.5%)

Quantification of Responders Under Different Definitions

A total of 1987 subjects completed the 8-week prospective ADT Phase (Phase A), and of those, 1056 were randomized to adjunctive brexpiprazole or placebo in Phase B. The remaining 931 subjects were assigned to Phase A+ (continuing ADT for 6 additional weeks) because they had responded to ADT in Phase A, under the Adequate Response definition highlighted in Figure 2.

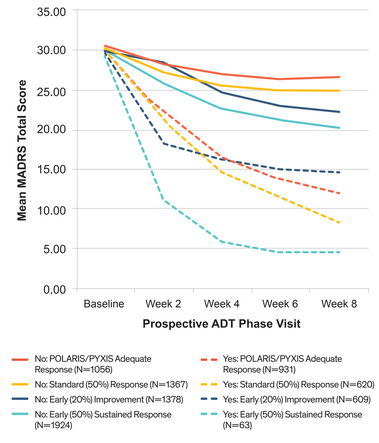
Table 2: Number (%) of Subjects Meeting Criteria for Response After 8 Weeks Prospective ADT, Under Four Different Definitions of Response

	Subjects Who Met Criteria in Prospective ADT Treatment Phase (Phase A) N = 1987
Adequate Response per POLARIS/ PYXIS Protocols	931 (46.9%)
Standard (50%) Response	620 (31.2%)
Early (20%) Improvement	609 (30.6%)
Early Sustained Response	63 (3.17%)

The POLARIS/PYXIS Adequate Response definition yielded the greatest proportion of subjects compared to other response definitions. Under the assumption that Adequate Response is highly predictive of those patients who might continue to respond to ADT monotherapy at endpoint, POLARIS/PYXIS prevented 931 subjects (47% of all enrolled subjects) from entering the brexipiprazole vs placebo augmentation phase of the study and impacting signal detection. In contrast, the Early Sustained Response definition was by far the most difficult to satisfy, such that only 63 (3%) of enrolled subjects met criteria at the end of the prospective ADT phase. Application of this definition would have allowed 868 subjects who appeared to be non-responders to prospective ADT into the randomized augmentation phase of the trial.

Quantification of Responders Under Different Definitions

Figure 3: MADRS Total Score Trajectory During 8 Weeks Prospective ADT, Under Four Different Definitions of Response



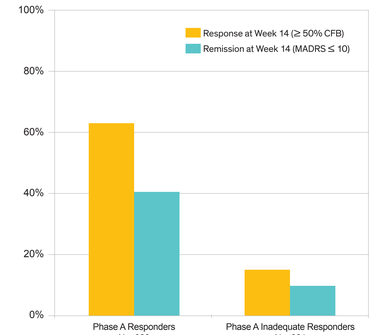
Visual inspection of symptom severity over the 8-week prospective ADT phase shows symptom trajectories consistent with the response criteria for each category. Severity level at the end of this phase was significantly different depending on how a responder was defined. Notably, the definition of prospective ADT response applied in the POLARIS/PYXIS was associated with significantly higher Week 8 MADRS scores, with lower variability, than in any other group ($p < 0.0001$).

Table 3: Mean (SD) MADRS Total Score for Subjects Not Meeting Criteria for Response After 8 Weeks Prospective ADT, Under Four Different Definitions of Response

	Mean (SD)
POLARIS/PYXIS Adequate Response (N=1056)	26.57 (5.55)
Standard (50%) Response (N=1367)	24.97 (6.15)
Early (20%) Improvement (N=1378)	22.07 (8.62)
Early (50%) Sustained Response (N=1924)	20.26 (9.32)

8-Week "Adequate Response" as a Predictor of 14-Week Response/Remission to ADT Motherapy

Figure 4: Response/Remission after 14 Weeks ADT Monotherapy in POLARIS/PYXIS



Of those subjects who met the POLARIS/PYXIS definition of prospective phase ADT response, 63.0% were considered responders and 40.7% were considered remitters after a full 14 Weeks of ADT monotherapy. Subjects not meeting Adequate Response criteria, and then assigned to placebo in the randomized augmentation phase, were far less likely to respond or remit with placebo augmentation (response: 14.7%; remission: 10.0%).

Table 4: Predictive Power of the POLARIS/PYXIS Adequate Response Definition

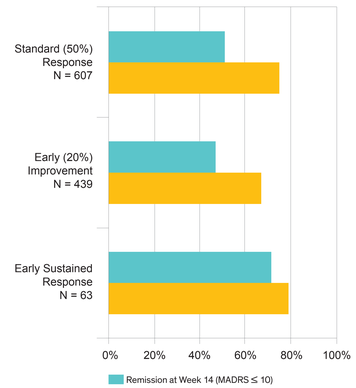
N = 882	Endpoint (Week 14) Response	Endpoint (Week 14) Remission
Sensitivity (95% CI)	91.1 (89.5 to 92.6)	90.8 (89.2 to 92.4)
Specificity (95% CI)	48.8 (46.1 to 51.5)	38.6 (35.9 to 41.2)
Positive Predictive Value (95% CI)	63.0 (60.4 to 65.7)	40.7 (38.0 to 43.3)
Negative Predictive Value (95% CI)	85.0 (83.1 to 87.0)	90.0 (88.4 to 91.7)
False-Positive Rate (95% CI)	26.1 (23.7 to 28.5)	42.0 (39.3 to 44.7)
False-Negative Rate (95% CI)	4.4 (3.3 to 5.5)	2.9 (2.0 to 3.8)

"Early Improvement" and "Early Sustained Response" as Predictors of 14-Week Response/ Remission to ADT Monotherapy

An exploration of 14 Week ADT response and remission rates, by alternate definitions, resulted in several interesting findings.

- Of the two early response definitions (Early Improvement and Early Sustained Response), both were strongly associated with full remission at Week 14 (EI: $X^2 = 14.24$, $p < 0.001$, OR: 1.67; ESR: $X^2 = 29.23$, $p < 0.001$, OR = 4.19).
- Positive predictive value (PPV) was highest for Early Sustained Responders, where 78.0% (95% CI: 75.2 to 80.7%) meeting ESR criteria were responders at the 14 week endpoint, and 69.5% (95% CI: 66.5 to 72.5%) were remitters at the 14 week endpoint. Negative predictive value (NPV), on the other hand, was 39.7% in this group (95% CI: 36.5 to 43.0.7%), showing that of those patients not classified as early sustained responders, 60% would eventually respond by the 14 week endpoint.
- For Early Improvers, PPV of response at the 14 week endpoint was 65.6% (95% CI: 62.4% to 68.7%), and NPV was 42.2% (CI: 39.0 to 35.5%).

Figure 5: Response/Remission after 14 Weeks ADT Monotherapy for Phase A Early Responders



Note that PPV and NPV results presented here should only be interpreted in the context of the POLARIS/PYXIS trials, given that satisfaction of POLARIS/PYXIS Adequate Response criteria was a condition of assignment to Phase A+. The strength of these early response definitions, therefore, are relative to one another and not relative to the POLARIS/PYXIS ADT prospective responders.

Conclusions

- The Adequate Response criteria in the POLARIS/PYXIS trials were extremely effective at identifying those subjects who would maintain a response to 14 weeks of ADT monotherapy. These criteria successfully excluded 931 ADT responders (46.9% of all enrolled subjects) from the randomized brexpiprazole vs placebo augmentation phase (Phase B) of the trial.
- For clinicians, early assessment of medication effectiveness for an individual patient is among the highest priorities, such that PPV is often considered the most useful guide for clinical decisions. In this program, nearly 80% of subjects with Early Sustained Response after 8 weeks of ADT monotherapy were still considered responders six weeks later at Week 14, and 70% were remitted.
- For clinical researchers, however, this level of certainty must be balanced against operational feasibility. Application of the very conservative Early Sustained Response criteria in this clinical program would have identified only 63 responders in the prospective ADT phase (3% of all subjects enrolled), yielding a higher randomization rate and a faster trial overall, but ultimately requiring a much larger randomized sample to show drug/placebo separation with more modest effect sizes.
- The most informative response definition for augmentation trials is the one that prevents ADT monotherapy responders from entering the randomized phase. Such high-yield definitions ensure that investigational drug vs placebo comparisons are free of subjects who might already be responding to ADT monotherapy, and further protects patients by minimizing medication burden where ADT alone is sufficient.
- The NPV data for Adequate Response in the POLARIS/PYXIS program showed that 85% of subjects who were inadequate responders in the ADT prospective phase, and who were assigned to placebo in the randomized augmentation phase, did not respond by the 14 -week Endpoint. This translated to an extremely low 14.7% placebo response rate not often observed in multi-site global depression trials.

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Disclosures

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