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Multidimensional Assessment of Functional Outcomes in Schizophrenia: Results From QUALIFY, a Head-to-Head Trial of Aripiprazole Once-Monthly and Paliperidone Palmitate

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Abstract

Background: QUALIFY was a 28-week, randomized, open-label, head-to-head trial that assessed improvements across multiple measures in stable patients with schizophrenia with aripiprazole once-monthly 400 mg vs paliperidone palmitate.
Methods: Secondary effectiveness assessments included physician-rated readiness for work using the Work Readiness Questionnaire, the Clinical Global Impression–Severity and Clinical Global Impression–Improvement scales, and quality of life with the rater-blinded Heinrichs-Carpenter Quality of Life Scale. Patients assessed their treatment satisfaction and quality of life with Subjective Well-Being under Neuroleptic Treatment–short version and Tolerability and Quality of Life questionnaires.
Results: Odds of being ready for work at week 28 were significantly higher with aripiprazole once-monthly 400 mg vs paliperidone palmitate (adjusted odds ratio, 2.67; 95% CI, 1.39–5.14; P=.003). Aripiprazole once-monthly 400 mg produced numerically or significantly greater improvements from baseline vs paliperidone palmitate in all Quality of Life Scale items. With aripiprazole once-monthly 400 mg vs paliperidone palmitate at week 28, there were significantly more Clinical Global Impression–Severity and Clinical Global Impression–Improvement responders (adjusted odds ratio, 2.26; P=.010, and 2.51; P=.0032) and significantly better Clinical Global Impression–Improvement scores (least squares mean treatment difference, –0.326; 95% CI, –0.60 to –0.05; P=.020). Numerically larger improvements with aripiprazole once-monthly 400 mg vs paliperidone palmitate were observed for patient-rated scales Subjective Well-Being under Neuroleptic Treatment–short version and Tolerability and Quality of Life. Partial correlations were strongest among clinician-rated and among patient-rated scales but poorest between clinician and patient-rated scales.

Conclusions: Consistently greater improvements were observed with aripiprazole once-monthly 400 mg vs paliperidone palmitate across all measures. Partial correlations between scales demonstrate the multidimensionality of various measures of improvement. More patients on aripiprazole once-monthly 400 mg were deemed ready to work by the study end.

Trial registry: National Institutes of Health registry, NCT01795547, https://clinicaltrials.gov/ct2/results?id=NCT01795547)

Keywords: aripiprazole once-monthly, paliperidone palmitate, quality of life, functioning, schizophrenia

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Significance Statement

The QUALIFY study (QUAlity of LIfe with AbiliFY Maintena) compared aripiprazole once-monthly 400 mg with paliperidone palmitate across multifaceted clinical and functional scales addressing changes in symptoms, quality of life, and functional capacity. Overall, our findings show consistently greater improvements with aripiprazole once-monthly 400 mg vs paliperidone palmitate across scales reflecting a broad range of symptoms and functioning, regardless of whether the raters were blinded or not and whether the scale was rated by the patient or clinician. These results across multiple domains of health-related quality of life and functioning and in enhanced work readiness help to differentiate aripiprazole once-monthly 400 mg and paliperidone palmitate, 2 long-acting injectable antipsychotics with different pharmacologic profiles. Aripiprazole is a partial agonist at dopamine D_2 and serotonin $5HT_{1A}$ receptors and an antagonist at $5HT_{2A}$ receptors while paliperidone is an antagonist at D_2 and $5HT_{2A}$ receptors. Our results may help provide guidance to clinicians when choosing between antipsychotic treatments and psychosocial options for their patients with schizophrenia.

Introduction

The chronic nature of schizophrenia often requires continuous treatment to prevent relapse and maintain or improve functioning and quality of life over the long term (Kreyenbuhl et al., 2010; Hasan et al., 2013). Longitudinal studies demonstrate that early symptomatic improvement may have an enduring benefit regarding quality of life and that quality-of-life improvement affects long-term outcomes, such as symptomatic remission and functional recovery (Boden et al., 2009; Lambert et al., 2009, 2010; Karow et al., 2014). Patients who do not achieve symptomatic remission are more likely to report poor quality of life, to receive low scores on physician-rated scales of functioning (Boden et al., 2009), and to remain unemployed (Haynes et al., 2012).

Atypical (second-generation) antipsychotics offer the opportunity to individualize and optimize treatment, and this is reflected in more ambitious treatment goals that encompass quality of life and other relevant patient outcomes. Given the low degree of overlap between quality-of-life measures and clinician-rated assessments of psychopathologic symptoms, multifactorial assessment should be considered essential in clinical trials of antipsychotic drugs (Naber et al., 2005; Chen et al., 2011). Moreover, measurement of quality of life and functioning is of great importance given the role these can play in treatment adherence and satisfaction as well as clinical outcomes and prognosis in patients with schizophrenia (Boyer et al., 2013). Assessing patients' quality of life, functioning, and key milestones such as returning to work or school or maintaining employment (Schennach et al., 2012) can differentiate the benefits of different atypical antipsychotics, which have distinct pharmacologic and tolerability profiles (Fervaha et al., 2014a, 2014b, 2015, 2016) as well as identify areas for psychosocial intervention.

Quality of Life with Abilify Maintena (QUALIFY; NCT01795547) is the first head-to-head randomized study of 2 atypical long-acting injectable antipsychotics (LAIs) with different pharmacologic profiles, aripiprazole once-monthly 400 mg (AOM 400) and paliperidone palmitate once-monthly (PP), and the first to directly compare treatment effectiveness on a measure of health-related quality of life and functioning as the primary outcome (Naber et al., 2015). These 2 LAIs have different pharmacologic activities: aripiprazole is a partial agonist at dopamine D_2 and serotonin $5HT_{1A}$ receptors and antagonist at $5HT_{2A}$ receptors (Abilify Maintena Prescribing Information, 2016), whereas paliperidone is an antagonist at D_2 and $5HT_{2A}$ receptors (Invega Sustenna Prescribing Information, 2015). Patients in QUALIFY were stable at baseline but, in their physician's judgment, needed a change from their current oral antipsychotic and might benefit from LAI treatment. Compared with PP, AOM 400 showed noninferiority and met prespecified superiority criteria vs PP on the primary endpoint, which was changed from baseline to week 28 on the rater-blinded Heinrichs-Carpenter Quality of Life Scale (QLS). The clinician-rated QLS assesses function and health-related quality of life in patients with schizophrenia. It comprises a semistructured interview assessing 21 items in 4 domains: interpersonal relations (e.g., capacity for intimacy, avoidance, and withdrawal tendencies), instrumental role (e.g., satisfaction from work/school/parenting, level of accomplishment), intrapsychic foundations (e.g., sense of purpose, motivation, empathy), and commonplace objects and activities (e.g., engagement in regular/everyday activities) (Heinrichs et al., 1984). The QLS was originally designed in part to measure deficit symptoms of schizophrenia not adequately captured by symptom scales like the Positive and Negative Syndrome Scale. In QUALIFY, significantly greater improvements with AOM 400 compared with PP were also observed for the rater-blinded Investigator's Assessment Questionnaire (IAQ) (Naber et al., 2015), which measures medication effectiveness relative to prior antipsychotic medication (Tandon et al., 2005), and the clinician-rated Clinical Global Impression—Severity of Illness scale (CGI-S), which assesses the clinician's impression of current disease severity (Guy, 1976).

QUALIFY included multifaceted clinical and functional scales addressing changes in symptoms, quality of life, and functional capacity. Here, we report the effects of AOM 400 and PP on validated measures of clinical effectiveness, quality of life, functioning, and tolerability and their relationship to readiness to work, as measured by the Work Readiness Questionnaire (WoRQ), a newly developed clinician-administered assessment of the functional capacity to work in patients with schizophrenia, independent of their current employment status or opportunities (Potkin et al., 2016).

Methods

Study Design

Details regarding the study design were previously described (Naber et al., 2015). Briefly, this was a multicenter, open-label, rater-blinded, 28-week, randomized study (NCT01795547). The study took place from February 2013 through September 2014 (last patient enrolled February 2014; last visit occurred September 2014) and adhered to the principles of Good Clinical Practice and the Declaration of Helsinki; protocol approval was obtained from the relevant ethics committees by the national coordinating investigator for each country (EU) or the principal investigator at each site. Patients provided written informed consent after receiving a complete description of the study.

Study investigators enrolled patients at 71 study sites in 10 countries (Canada, Czech Republic, Estonia, France, Germany, Italy, Spain, Sweden, United Kingdom, and United States). Patients were randomized 1:1 to AOM 400 (option to reduce to 300 mg if patients experienced tolerability issues) or PP (flexible dosing, per label, with 50–150 mg/mo as paliperidone [EU and Canada], equivalent to 78–234 mg/mo as paliperidone palmitate [US]). Following randomization, patients' treatment was first converted to oral aripiprazole (5–30 mg/d) or paliperidone (3–12 mg/d) during 3 weeks while discontinuing their prior antipsychotic (oral conversion phase), followed by administration of the respective LAI formulation (LAI continuation phase) (Naber et al., 2015).

Randomization and Masking

Randomization was stratified by age (≤35 years or >35 years) and was achieved using an interactive voice response system using block randomization to ensure that equal numbers of patients entered each treatment group within each stratum. Treatment was not masked, because the objective was to design a study closely reflective of clinical practice, and AOM 400 and PP differed in appearance, available dose strengths, dose initiation regimens, and administration site (at the time of the QUALIFY study, Abilify Maintena (aripiprazole once-monthly) was approved for gluteal administration only). Nevertheless, raters for 2 outcome measures (QLS and IAQ) were unaware of (blinded to) the patient's treatment assignment.

Patients

Patient inclusion and exclusion criteria were previously described (Naber et al., 2015). Briefly, eligible patients included men and women, aged 18 to 60 years, with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* diagnosis of schizophrenia. Eligible patients were stable, were treated with an oral antipsychotic for at least 3 months before screening, and, in the opinion of the investigator, required a treatment change from their oral antipsychotic because of inadequate response, poor tolerability, or lack of adherence, and might benefit from LAI therapy. At screening and baseline visits, CGI-S scores ≥3 (mildly ill) and ≤5 (markedly ill) were required. Key exclusion criteria were an Axis I disorder or psychiatric disorder other than schizophrenia, a substance use disorder that might confound assessment (other than nicotine use), or treatment with an atypical LAI within 6 months before study screening (Naber et al., 2015).

Assessments

The QLS and IAQ were administered by trained raters who were blind to treatment assignment (Naber et al., 2015). Clinicians rating the additional secondary effectiveness measures (CGI-S, CGI-I, and WoRQ) were not blinded. The CGI-S scale quantifies the rater's impression of the patient's current illness severity on a scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill patients) (Guy, 1976). CGI-S response was defined as a decrease of ≥1 point from baseline to week 28. The CGI-I scale quantifies the clinician's impression of patient improvement or worsening relative to baseline on a 7-point scale ranging from 1 (very much improved) to 7 (much worse) (Naber et al., 2015). CGI-I response was defined as a score of 1 or 2 at week 28. WoRQ comprises 7 statements rated by the clinician on a 4-point scale (strongly agree to strongly disagree) based on the clinician's perception of the patient's ability or capacity to engage in daily activities; interact with others including co-workers, customers, and supervisors; maintain adherence to treatment; and of the patient's appearance, behavior, and impulse control with others (Potkin et al., 2016). Following rating of the 7 statements, a global yes/no question based on the clinician's judgment of the patient's readiness to work is answered; individual ratings for the 7 statements are used to aid the clinician in determining whether or not the patient is ready for work. Combined scores for the 7 statements constitute the WoRQ total score (Potkin et al., 2016). The judgment on readiness to work or not is made separately from the total score. Work is defined as an independent effort that merits pay and does not include supported work or job coach.

Patient-rated measures included the Subjective Well-Being Under Neuroleptic Treatment–short version (SWN-S) (Naber et al., 2001) and Tolerability and Quality of Life questionnaire (TooL) (Lindström et al., 2009). The SWN-S provides patients with a scale to rate the subjective effects of their neuroleptic drugs on psychopathology, quality of life, and adherence over the past 7 days. The scale contains 10 positive and 10 negative statements that comprise 5 subscales (mental functioning, self-control, physical functioning, emotional regulation, and social integration; 4 items per subscale). Items are rated on a 6-point Likert scale ranging from 1 (not at all) to 6 (very much). When calculating the total score, negative statements are reverse scored (e.g., $6 = 1$, $5 = 2$). Possible total scores range from 20 to 120 (4 to 24 for each subscale), with higher scores indicating better well-being (Naber et al., 2001). The TooL asks patients to rate the impact of antipsychotic side effects on their quality of life on 8 domains (mood [worry/upset], function/capabilities, fatigue/weakness, weight gain, stiffness/tremor, physical restlessness, sexual dysfunction, dizziness/nausea) using a 4-point scale ranging from 1 (no impact) to 4 (maximum impact); possible total scores range from 8 to 32, with lower scores indicating less impact of side effects on quality of life.

Safety and tolerability were assessed throughout the study, with a safety follow-up visit 4 weeks after completion of, or withdrawal from, treatment. The safety and tolerability of AOM 400 and PP in QUALIFY were previously reported (Naber et al., 2015).

Statistical Analyses

Effectiveness analyses were performed using the full analysis set (FAS), which included all randomized patients who took at least 1 dose of oral antipsychotic medication and had a valid baseline and post-baseline assessment of the QLS total score. All statistical hypothesis tests of endpoints were 2-sided tests performed on a 5% significance level, and no adjustment for multiplicity was made.

Preplanned secondary analyses included mean total CGI-I and IAQ scores at week 28 and changes from baseline in SWN-S and TooL at week 28. In addition, posthoc analyses of the change

from baseline in QLS items at week 28, the proportion of CGI-S responders at week 28, and the proportion of CGI-I responders were performed. Mean changes from baseline in SWN-S, TooL, and QLS items at week 28 were calculated using a mixed model for repeated measures. To compare AOM 400 with PP, region, baseline score-by-visit interaction, geographical region, age group, visit, and treatment-by-visit interaction were included as fixed effects, using an unstructured covariance matrix and Kenward-Rogers method for handling degrees of freedom. The proportions of CGI-S and CGI-I responders at week 28 were compared in AOM 400 and PP treatment groups using logistic regressions adjusting for baseline score, region, and age group. Change from baseline at week 28 in WoRQ total score was analyzed using an ANCOVA model adjusting for baseline score, region, and age group. In addition, a shift analysis of the WoRQ readiness-to-work question (shifts from not ready to work to ready to work) was performed, and the odds of being ready for work at week 28 were estimated with logistic regression adjusted for baseline status of work readiness.

To examine the relationships between assessments, mixed model for repeated measures was used to derive baseline adjusted partial correlations of changes from baseline to week 28 for QLS, CGI-S, WoRQ, TooL, and SWN-S, and between scores at week 28 for IAQ, and CGI-I. Partial correlation analyses were performed for each treatment group.

Safety was assessed in all treated patients (AOM 400, n = 144; PP, n = 137); adverse events were summarized using descriptive statistics and were previously reported in detail (Naber et al., 2015).

Results

There were 295 patients randomly assigned to AOM 400 (n = 148) or PP (n = 147). Of those randomized, 67.6% (100/148) of patients in the AOM 400 group and 56.5% (83/147) of patients in the PP group completed 28 weeks of treatment (Naber et al., 2015). The FAS included 136/144 (94.4%) treated patients in the AOM 400 group and 132/137 (96.4%) treated patients in the PP group (Naber et al., 2015). Baseline demographics and disease severity characteristics were similar between treatment groups (Table 1). Across treatment weeks, most patients in the AOM 400 treatment group (i.e., >84%) were treated with the 400-mg dose, and most patients in the PP treatment group (i.e., >74%) were treated with the 100-mg or 150-mg dose (as paliperidone, equivalent to 156 mg or 234 mg paliperidone palmitate) (Figure 1). In addition to study drug, 39 (27.1%) and 33 (24.1%) patients in the AOM 400 and PP treatment groups, respectively, received concomitant benzodiazepines (most frequently lorazepam, diazepam, and alprazolam), while 20 (13.9%) and 14 (10.2%) received concomitant non-benzodiazepine hypnotics (zolpidem or zopiclone). Concomitant anticholinergic medications, most often benztropine, were taken by 18 (12.5%) and 12 (8.8%) patients in the AOM 400 and PP treatment groups, respectively.

Clinician-Rated Outcomes

Among QLS items, numerically greater improvements from baseline were observed with AOM 400 treatment compared with PP treatment on all items, and sense of purpose, aimless inactivity (both items of the intrapsychic foundations domain), and social initiative improved significantly more with AOM 400 than with PP (P < .05 for both comparisons) (Figure 2).

At week 28, a greater proportion of patients in the AOM 400 treatment group compared with the PP treatment group were classified as responders on the clinician-rated CGI-S

Table 1. Patient Baseline Demographics and Disease Severity

	AOM 400	PP
Randomized patients	n = 148	n = 147
All-patients-treated set	n = 144	n = 137
Full analysis set	n = 136	n = 132
Baseline demographics[a]		
Mean (SD) age, y	42.6 (10.9)	41.2 (10.7)
Mean (SD) age at schizophrenia onset, y	28.5 (10.7)	26.8 (9.5)
Mean (SD) schizophrenia duration, y	14.1 (10.5)	14.4 (10.7)
Male, n (%)	86 (59.7)	82 (59.9)
Baseline scale scores[b]		
QLS total score, possible range 0–126 (higher = better)		
Mean (SD)	66.0 (21.7)	62.9 (21.5)
CGI-S score, possible range 1–7 (lower = better)		
Mean (SD)	4.0 (0.65)	4.0 (0.65)
WoRQ total score, possible range 7–28 (lower = better)		
Mean (SD)	14.5 (3.45)	15.3 (3.25)
SWN-S total score, possible range 20–120 (higher = better)		
Mean (SD)	83.6 (15.9)	85.2 (14.6)
TooL total score, possible range 8–32 (lower = better)		
Mean (SD)	14.4 (4.4)	14.3 (3.9)

Abbreviations: AOM 400, aripiprazole once-monthly 400 mg; CGI-S, Clinical Global Impression–Severity of Illness; QLS, Heinrichs-Carpenter Quality-of-Life Scale; PP, paliperidone palmitate once monthly; SWN-S, Subjective Well-Being Under Neuroleptics–short version; TooL, Tolerability and Quality of Life Questionnaire; WoRQ, The Work Readiness Questionnaire.
[a]Baseline and demographic data are from the all-patients-treated set.
[b]Baseline scale scores are from the full analysis set.

(62.7% vs 43.5%, respectively; adjusted odds ratio (OR), 2.26; P = .010) and on the clinician-rated CGI-I (52.0% vs 29.4%; adjusted OR, 2.51; P = .0032) (Figure 3). Patients treated with AOM 400 also demonstrated significantly lower (better) CGI-I scores compared with patients treated with PP, indicating greater clinical improvement with AOM 400 (least squares mean treatment difference at week 28, –0.326 [95% CI, –0.60 to –0.05]; P = .020).

Change from baseline at week 28 on the WoRQ total score was significantly greater with AOM 400 compared with PP treatment (least squares mean treatment difference [standard error of the mean] at week 28, –1.162 [0.399] 95% CI, –1.96 to –0.37; P = .004). At baseline, similar percentages of patients in the AOM 400 and PP treatment groups (32.7% and 29.6%, respectively) were perceived by clinicians as being ready for work. At week 28, a numerically larger percentage of patients in the AOM 400 group (52.7%) was rated as being ready for work compared with the PP treatment group (32.7%) (Figure 4a). Furthermore, a greater percentage of patients receiving AOM 400 shifted from No (not ready to work) at baseline to Yes (ready to work) at week 28 (26.4%) compared with those receiving PP (12.2%) in the FAS population. Among patients who were not ready to work at baseline (n = 74 patients in the AOM 400 treatment group and 69 patients in the PP treatment group), 39.2% of patients who received AOM 400 and 17.4% of patients who received PP were rated by clinicians as being ready for work at week 28 (Figure 4b). The adjusted odds of being ready for work at week 28 were significantly higher for patients treated with AOM 400 compared with patients treated with PP (adjusted OR at week 28, 2.67 [95% CI, 1.39–5.14]; P = .003).

Patient-Rated Outcomes

At baseline, mean SWN-S total scores indicated that patients in both treatment groups had a relatively positive perception of their well-being on their current medication (Table 1).
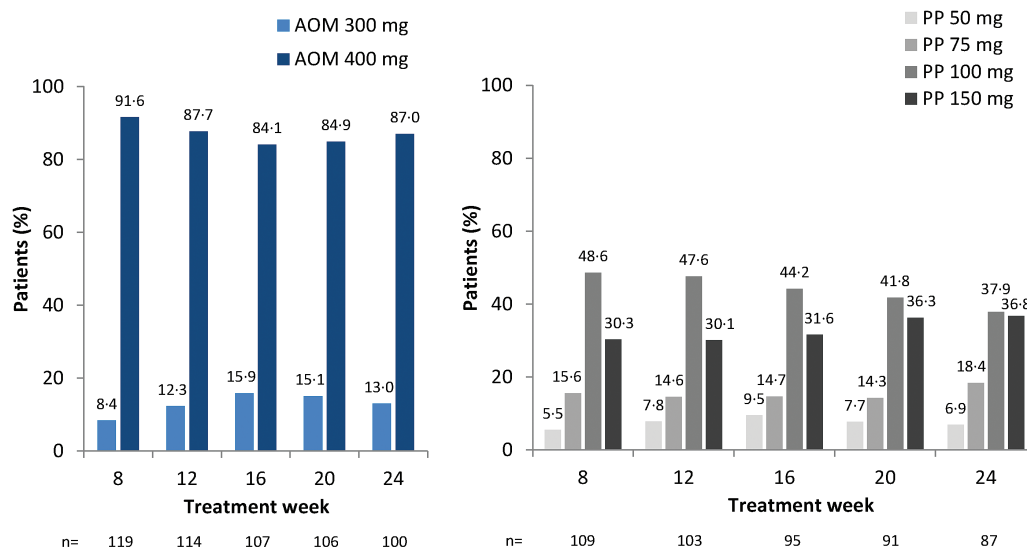
Figure 1. Distribution of aripiprazole once-monthly 400 mg (AOM 400) and paliperidone palmitate once-monthly (PP) doses by treatment week in the all-patients-treated set (i.e., all patients randomized who took ≥1 dose of study medication). Percentages of patients receiving each dose is given above each bar, numbers below the axes refer to number of treated patients in the given treatment week. PP doses refer to paliperidone (50, 75, 100, and 150 mg [EU]) equivalent to paliperidone palmitate (78, 117, 156, and 234 mg [US]).

Improvements from baseline to week 28 on SWN-S total score were reported in both treatment groups, and the difference between treatment arms did not reach statistical significance (Figure 5a). Improvements were noted on all SWN-S subscales in the AOM 400 treatment group at week 28 and 4 of 5 subscales in the PP group (Figure 5a). Improvements numerically favored AOM 400 over PP on the subscales of mental functioning, physical functioning, and self-control.

Likewise, mean TooL scores were relatively low (i.e., minimal impact of side effects on quality of life) at baseline (Table 1). The impact of antipsychotic side effects on quality of life improved at week 28 in both treatment groups, with numerically greater improvement in mean changes from baseline in TooL total scores for AOM 400 vs PP (P = .10) (Figure 5b).

Partial Correlations between Assessments

Posthoc analysis of responses to treatment based on clinician- and patient-rated scales indicated that, in general, the clinician-rated assessments (i.e., CGI-S, IAQ, CGI-I) were modestly correlated with change from baseline in the patient-rated TooL and SWN-S scales (Table 2). Change from baseline on the WoRQ total score was correlated with the clinician-rated scales of symptom severity (i.e., CGI-S, IAQ, CGI-I, and QLS) and patient-rated TooL or SWN-S scales (Table 2). Likewise, change from baseline on the clinician-rated QLS total score was modestly correlated with change from baseline on the WoRQ total score, and improvements in QLS were correlated with clinician-rated measures of symptom severity (CGI-S, CGI-I, IAQ) and modestly correlated with patient ratings of well-being and quality of life (Tool, SWN-S) (Table 2).

Safety and Tolerability

Safety and tolerability results were previously reported (Naber et al., 2015). In both treatment groups, there were no new safety signals detected, and no deaths occurred during the study.

Discussion

Here we report endpoints from the QUALIFY study in patients with schizophrenia, demonstrating consistent and multidimensional improvements in patients on AOM 400, particularly in functional measures including readiness for work. Patients with schizophrenia are often unemployed, and those with chronic schizophrenia are more likely to be unemployed than patients with first-episode schizophrenia (Marwaha et al., 2007). In QUALIFY, there were significantly greater improvements in the WoRQ total score as well as significantly higher odds of being rated as ready for work at week 28 in patients treated with AOM 400 compared with those treated with PP. The improvement on the WoRQ shows that this questionnaire is sensitive to drug effects and may be appropriate as a scale of functioning in future clinical trials. In particular, the simplicity of administering the WoRQ questionnaire makes it potentially useful in clinical practice as a good indicator of functioning.

As previously reported, patients treated with AOM 400 had significantly greater mean improvements from baseline to week 28 in the QLS total score compared with patients in the PP treatment group, and the mean change from baseline at week 28 was numerically greater with AOM 400 for all 4 QLS domains, reaching statistical significance for the intrapsychic foundations domain (Naber et al., 2015). The current analysis demonstrated numeric improvements with AOM 400 vs PP on all items, indicating that improvements in the QLS total score and domain scores resulted from improvements across QLS items. Specific items across domains, including sense of purpose and aimless inactivity (both items of the intrapsychic foundations domain) as well as social initiative, improved significantly more with AOM 400 than with PP. Improvement on these items and in the intrapsychic foundations domain of the QLS indicates improved motivation and goal-oriented thoughts, thus addressing key negative symptoms that underlie impaired functioning in patients with schizophrenia (Milev et al., 2005; Gard et al., 2009; Konstantakopoulos et al., 2011; Fervaha et al., 2014c; Robertson et al., 2014).

Greater improvement with AOM 400 compared with PP on clinician-rated scales was consistent across measures assessed by blinded (i.e., QLS, IAQ) and nonblinded raters (e.g., CGI-S and CGI-I). Effectiveness measures, including significantly better CGI-I scores at week 28 and significantly greater proportions of CGI-S and CGI-I responders, also demonstrated superiority of
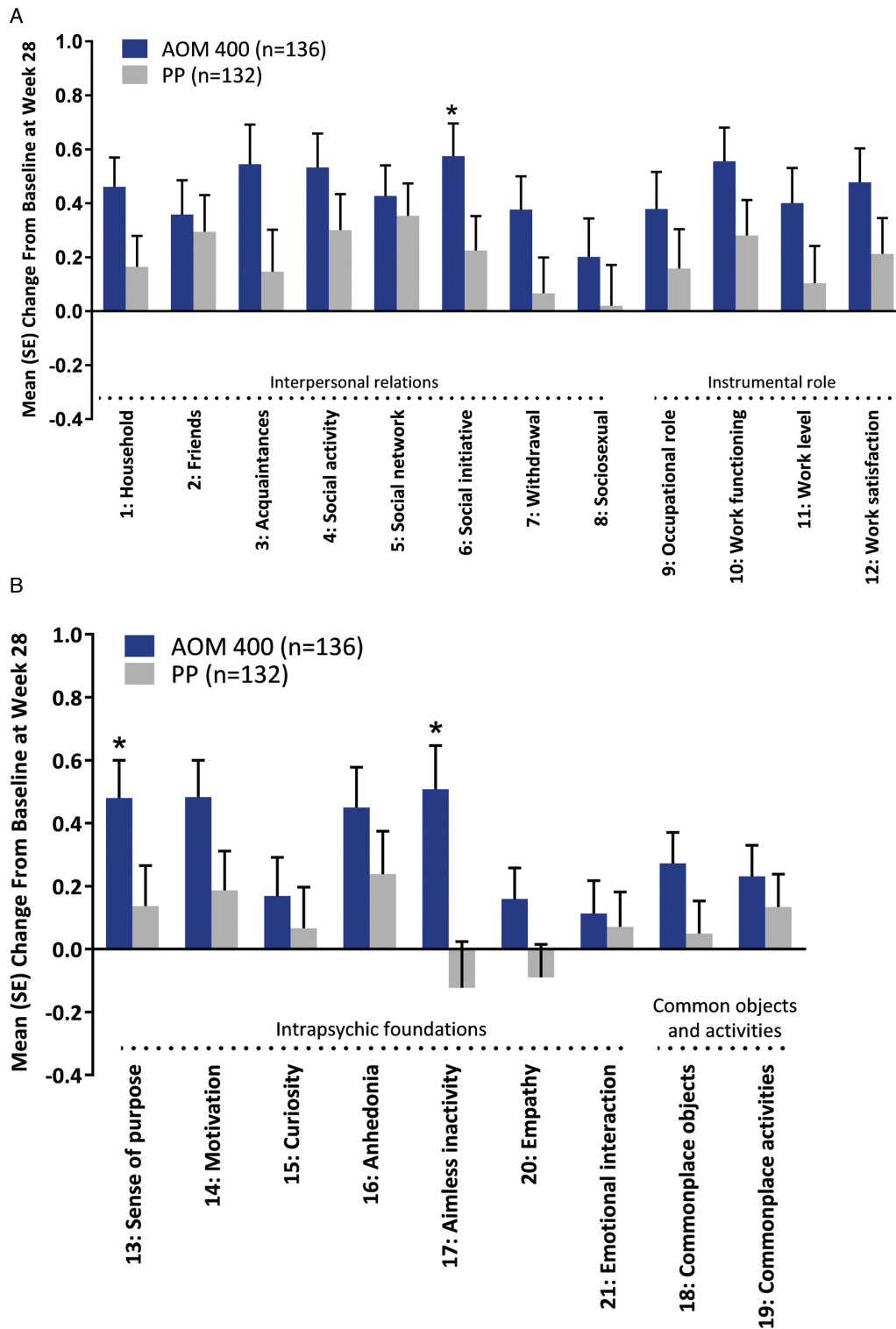
Figure 2. Change from baseline at week 28 on Heinrichs-Carpenter Quality of Life Scale (QLS) items. Full analysis set. Results are shown for (a) the first 12 items on the scale and (b) the last 9 items on the scale. AOM 400, aripiprazole once-monthly 400 mg; PP, paliperidone palmitate once-monthly. *P < .05.

AOM 400 vs PP. Numeric improvements with AOM 400 vs PP were observed on the patient-rated SWN-S scale. On average, patients rated their experience on their current neuroleptic drugs as relatively good at baseline, leaving less room for improvement after switching to the LAI test drug. Scores remained stable or improved modestly, indicating improved overall satisfaction with general functioning and with 28 weeks of treatment with either LAI.

Using the TooL, patients noted minimal impact of medication side effects on quality of life at baseline and modest improvements in medication side effects at week 28 that trended in favor of AOM 400 vs PP. For the IAQ, physicians rated efficacy
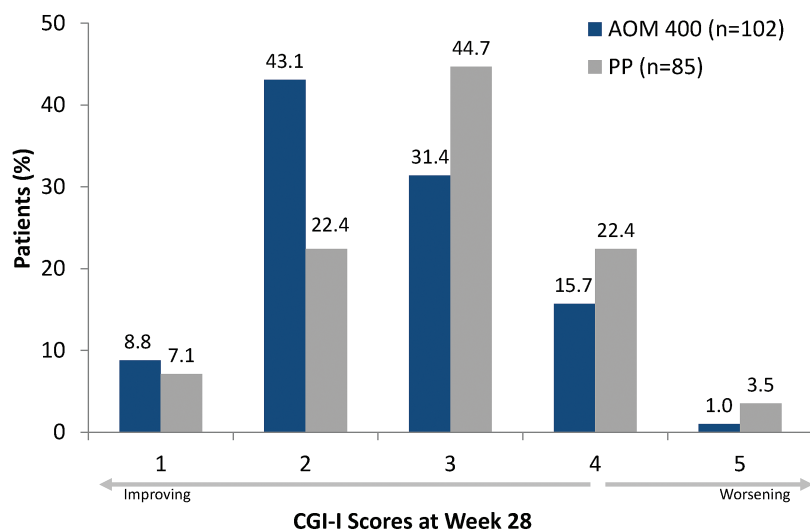
Figure 3. Distribution of Clinical Global Impressions–Improvement (CGI-I) scores at week 28. Full analysis set. 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse. Patients with CGI-I scores of 1 or 2 at week 28 were considered to be responders. AOM 400, aripiprazole once-monthly 400 mg; PP, paliperidone palmitate once-monthly.
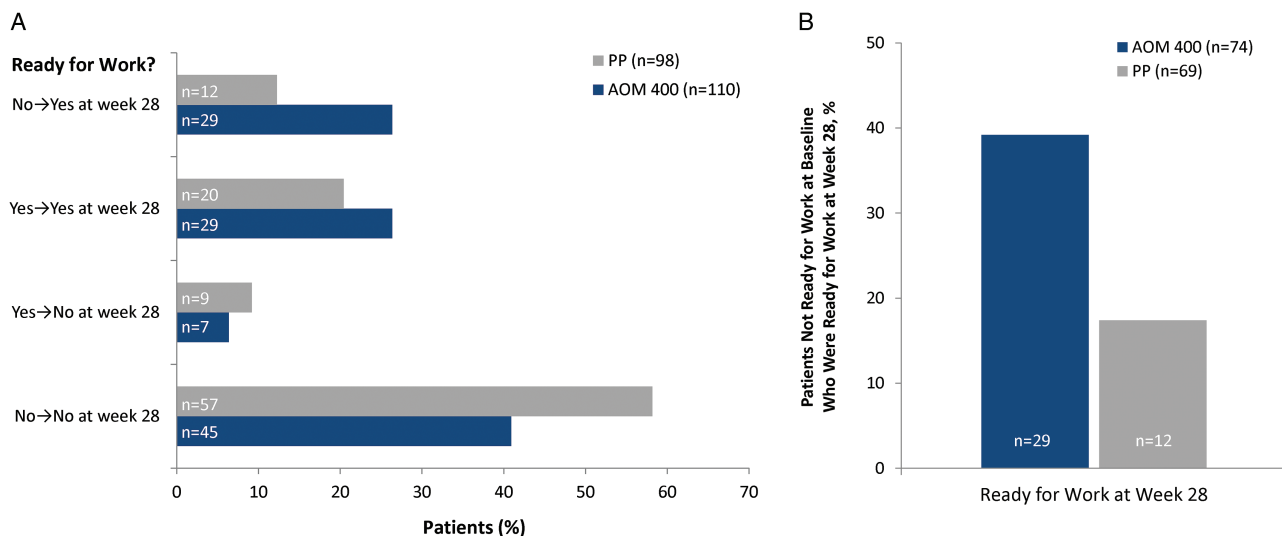

Figure 4. Shift from baseline in readiness for work status among (*a*) the full analysis set and (*b*) patients not ready for work at baseline. Shift analysis was based on the WoRQ readiness to work question (item 8) at baseline and week 28: Based on your clinical judgment, is this patient ready for work? AOM 400, aripiprazole once-monthly 400 mg; FAS, full analysis set; PP, paliperidone palmitate once-monthly; WoRQ, Work Readiness Questionnaire.

and tolerability of AOM 400 or PP as improved compared with prior antipsychotic therapy; greater improvements were noted with AOM 400 vs PP (Naber et al., 2015).

Correlations between scales indicated that different scales measure separate facets of schizophrenia. When comparing various assessment scales, the weakest correlations were observed between the clinician- and patient-rated scales, suggesting that patient and clinician perspectives provide distinct information and therefore, paying additional attention to the patient's perspective may be useful as it might not always be captured by the clinician-rated scales. The clinicians' rating of tolerability (i.e., IAQ) had a higher correlation with the patients' assessments (i.e., Tool and SWN-S) for AOM than for PP. However, the divergence of clinician and patient ratings could be best explored in a larger dataset with blinded ratings. WoRQ was modestly correlated with other clinician-rated scales but poorly correlated with patient-rated scales, suggesting that work readiness was

not related to patient subjective assessments. As a whole, correlations between scales were modest, which suggests that the assessments in QUALIFY measured different dimensions of schizophrenia. By virtue of this fact, this study can be considered to offer broader information than most randomized controlled trials that more narrowly focus on the assessment of psychopathologic symptoms using measures such as the Positive and Negative Syndrome Scale and CGI, which strongly correlate with one another (Levine et al., 2008) but less so with subjective measures of well-being and quality of life (Naber et al., 2005; Chen et al., 2011). Across the broad range of scales assessed in QUALIFY, AOM 400 produced numerical or statistically significantly greater improvements compared with PP.

The QUALIFY study is one of few randomized head-to-head studies of LAIs and is the first to compare 2 atypical LAIs with different pharmacologic profiles on health-related quality of life and functioning in patients with schizophrenia. Patients were
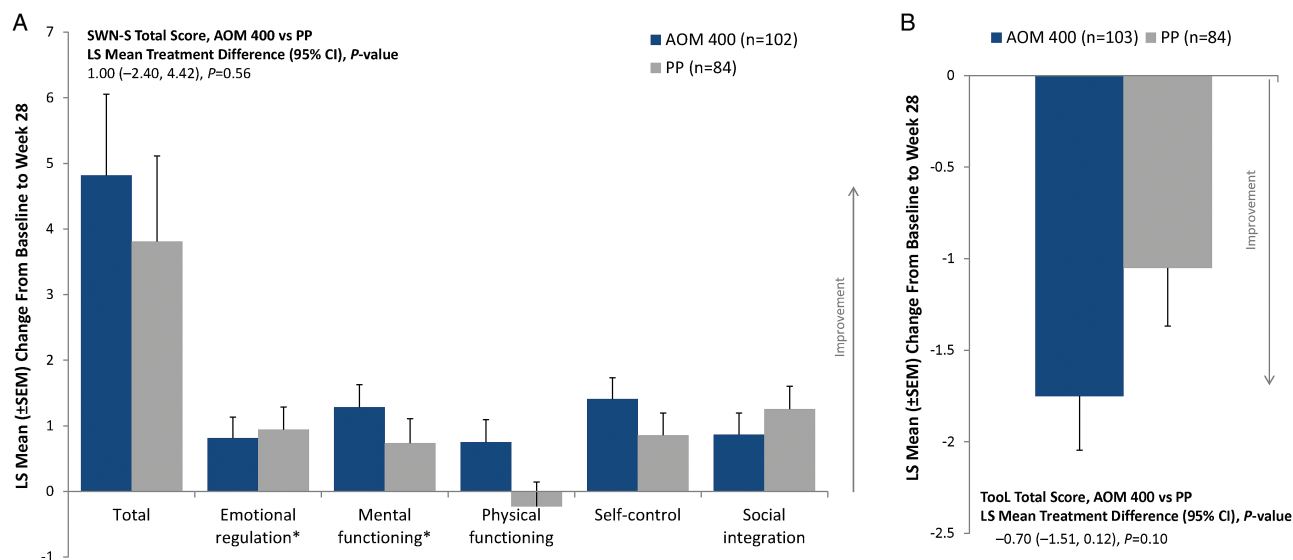
Figure 5. Change from baseline to week 28 in patient-rated (*a*) Subjective Well-Being Under Neuroleptics–short version (SWN-S) total and subscale scores and (*b*) Tolerability and Quality of Life (TooL) total score. Full analysis set. AOM 400, aripiprazole once-monthly 400 mg; FAS, full analysis set; LS, least squares. *n = 83 for the PP treatment group.

Table 2. Correlations between Change from Baseline to Week 28 (QLS, CGI-S, WoRQ, TooL, SWN-S) or Scores at Week 28 (IAQ, CGI-I) by Treatment

Correlation Estimates	QLS Total		CGI-S		IAQ Total		CGI-I		WoRQ Total		TooL Total	
	AOM 400	PP	AOM 400	PP	AOM 400	PP	AOM 400	PP	AOM 400	PP	AOM 400	PP
CGI-S	-0.598	-0.381										
IAQ-total	-0.587	-0.510	0.392	0.473								
CGI-I	-0.459	-0.400	0.765	0.715	0.459	0.578						
WoRQ-total	-0.322	-0.396	0.468	0.236	0.260	0.181	0.380	0.333				
TooL total	-0.374	-0.365	0.323	0.213	0.355	0.058	0.491	0.168	0.117	-0.158		
SWN-S total	0.375	0.376	-0.390	-0.355	-0.330	-0.259	-0.260	-0.348	-0.113	-0.064	-0.689	-0.557

Analyzed posthoc at patient level with MMRM to assess partial correlations between scales in the full analysis set. Abbreviations: CGI-I, Clinical Global Impression–Improvement; CGI-S, CGI–Severity; IAQ, Investigators' Assessment Questionnaire; MMRM, mixed model for repeated measures; QLS, Heinrichs-Carpenter Quality of Life Scale; SWN-S, Subjective Well-Being Under Neuroleptic Treatment–short version; Tool, Tolerability and Quality of Life Questionnaire; WoRQ, Work Readiness Questionnaire.
Higher QLS and SWN-S total scores indicate clinical improvements, whereas lower CGI-S, IAQ, CGI-I, WoRQ, and TooL scores indicate better clinical condition.

stable at enrollment, and thus our findings may not be applicable to patients experiencing an acute episode of schizophrenia (Naber et al., 2015). Study limitations were previously reported in detail—key limitations include the open-label study design in which raters of only the QLS and IAQ were blinded to study treatment (Naber et al., 2015). Also, the study was powered based on a 5-point noninferiority margin for the primary endpoint (Naber et al., 2015), which may have limited the ability to detect smaller statistically significant differences on some secondary and other endpoints, including QLS items. Finally, although the study findings were consistent across rater-blinded, rater unblinded, and patient-rated scales, the open-label design intended to more closely parallel clinical practice may have introduced some unmeasured bias.

Overall, our findings indicate consistently greater improvements with AOM 400 vs PP across all rater-blinded (i.e., QLS, IAQ) and unblinded (e.g., WoRQ, CGI-S and CGI-I) clinician- as well as patient-rated scales, reflecting a broad range of symptoms and functioning. These included significantly better CGI-I scores at week 28, significantly greater proportions of CGI-S and CGI-I responders, and significantly higher odds of being judged as ready for work. These multidimensional results extend our primary finding of superior improvement on the QLS total score with AOM 400 vs PP (Naber et al., 2015), demonstrating improvements across multiple domains of health-related quality of life and functioning and an additional important potential benefit of clinical and functional improvement in enhanced work readiness using the newly developed WoRQ. These results coupled with results from other studies may help to differentiate AOM 400 and PP, 2 LAI antipsychotics with different pharmacologic profiles: aripiprazole is a partial agonist at dopamine D_2 and serotonin $5HT_{1A}$ receptors and an antagonist at $5HT_{2A}$ receptors while paliperidone is an antagonist at D_2 and $5HT_{2A}$ receptors.. Our results may help provide guidance to clinicians when choosing between antipsychotic treatments and psychosocial options for their patients with schizophrenia.

Acknowledgments

Statement of Interest

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