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Early Symptom Improvement as a Predictor of Response to Extended Release Quetiapine in Major Depressive Disorder

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Abstract: The aim of this post-hoc analysis was to determine whether early symptom improvement with extended release quetiapine (quetiapine XR) may predict treatment outcome in patients with major depressive disorder. Data were from 6, double-blind, placebo-controlled studies of quetiapine XR (2 fixed-dose and 2 flexible-dose monotherapy and 2 adjunct studies) in adult patients with major depressive disorder. Montgomery-Åsberg Depression Rating Scale (MADRS) and Clinical Global Impression-Severity Score (CGI-S) were assessed at baseline, weeks 2, 4, and 6. Hamilton Rating Scale for Depression (HAM-D) was assessed at baseline and week 6. The MADRS improvement at week 2 (15%, 20%, 25%, 30%) was used to predict response and remission, based on MADRS (50% improvement; total score ≤ 12) or HAM-D (50% improvement; total score ≤ 7). The CGI-S improvement (1 point) at week 2 was used to predict final outcome (CGI-S score ≤ 2). The predictive value for early improvement with quetiapine XR was found to be "very strong" (Yule's Q coefficient, a combined measure of sensitivity and specificity) using 30% MADRS improvement as the threshold. This was relatively comparable for response and remission and for fixed-dose, flexible-dose, and adjunct studies. This was also observed for placebo. Exceptions were: adjunct studies (where predictivity was lower for ongoing antidepressant/placebo), and for remission (predictivity for remission appeared lower than for response with placebo). In conclusion, outcome at week 6 with quetiapine XR for a major depressive episode could be predicted by 30% improvement after 2 weeks, a finding that could give doctors confidence to continue treatment and may facilitate adherence in patients.

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Despite multiple options for treating major depressive disorder (MDD), response rates following initial antidepressant treatment vary, and estimates suggest that around two-thirds of patients will not achieve full symptomatic remission with an initial agent.[1,2] Common strategies used to improve efficacy in patients who have not responded to initial antidepressant therapy include switching to another antidepressant (usually a different class) and augmentation with a nonantidepressant.[3] Early identification of unresponsive patients can reduce the burden of MDD on patients/family and limit healthcare resource use.

A particular challenge when introducing a new antidepressant is that symptomatic response to therapy can be heterogeneous in terms of presence and timing.[4] For most patients, symptom resolution takes several weeks and a trial period of 4 to 8 weeks is generally required to determine whether an agent is likely to be efficacious for a patient.[5] Treatment guidelines reflect this, suggesting that the dose should be increased or treatment switched if partial response has not occurred after 4 to 8 weeks.[5]

Information that could help predict whether individuals will achieve symptomatic remission (or response) within a shorter time frame to a given antidepressant would be of considerable clinical relevance. Emerging evidence suggests that symptom improvement in the first 1 to 2 weeks of conventional antidepressant therapy is predictive for patients who will ultimately respond.[6–11]

The efficacy and tolerability of extended release quetiapine (quetiapine XR) fumarate for the treatment of MDD have been reported in 4 acute monotherapy studies in adults,[12–15] 1 acute monotherapy study in the elderly,[16] 1 maintenance monotherapy study in adults,[17] and 2 acute adjunct-therapy studies in adults.[18,19] This analysis used pooled data from the acute monotherapy and adjunct studies in adults to identify early predictors of symptomatic improvement with quetiapine XR and assess feasibility of providing guidance to clinicians monitoring patients newly starting quetiapine XR for MDD.

METHODS

Patient Population

This post-hoc analysis included 6 multicenter, double-blind, randomized, parallel-group, placebo-controlled studies in patients with MDD described previously.[12–15,18,19] The quetiapine XR dose varied across the following studies: fixed-dose monotherapy (50, 150, and 300 mg/d), monotherapy with dose-doubling (150–300 mg/d) for inadequate response, and adjunct therapy (150 and 300 mg/d) for inadequate response to an original antidepressant (amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine).[12–15,18,19]

Data from each pair of studies were pooled to assess the question of interest. Therefore, results are provided for the following 3 populations: (1) fixed-dose (studies 1 and 2), (2) flexible-dose (studies 3 and 4), (3) adjunct therapy (studies 6 and 7). The quetiapine XR 50 mg/d treatment group in study 1 was not included in this analysis. Data for patients randomized to placebo were analyzed for qualitative comparison. The analysis approach was modified intention-to-treat. This included all patients in the analysis who had a baseline measure of disease severity, at least 1 dose of treatment, and 1 postbaseline measure of disease severity. Missing data were imputed by using the last observation carried forward.

Predictive and Outcome Measures

The severity of major depression was assessed at baseline, weeks 2, 4, and 6. Measures of disease severity included the following: (1) the Montgomery-Åsberg Depression Rating Scale (MADRS)[20] (at all time points), (2) the Hamilton Rating Scale for Depression (HAM-D)[21] (at baseline and week 6), and (3) the Clinical Global Impression-Severity (CGI-S) score (at all time points).[22]

Statistical Analyses

This analysis aimed to determine whether outcome after 6 weeks of treatment with quetiapine XR for MDD could be predicted by treatment response after 2 weeks. Response at 2 weeks to the MADRS (15%, 20%, 25%, and 30% improvement) was employed to predict final outcome on both the MADRS (50% improvement; total score ≤ 12) and HAM-D scales (50% improvement; total score ≤ 7). Response to the CGI-S (1 point) at 2 weeks was used as an early predictor of the final outcome on both the CGI-S (score ≤ 2) and HAM-D (50% improvement; total score ≤ 7). Yule's Q coefficient ([early improvers with a positive outcome × early nonimprovers with a negative outcome] − [early improvers with a negative outcome × early nonimprovers with a positive outcome] / the sum of these products), area under the curve (sensitivity vs 1-specificity), and 95% confidence intervals (CIs) were employed to show the balance between sensitivity and specificity and between positive and negative predictive values of the treatment response measures. Conceptually, Yule's Q coefficient is the number of pairs in agreement minus the number in disagreement divided by the total number of paired observations, and a coefficient value between 0.30 and 0.50 is considered "moderate," between 0.50 and 0.70 "strong," and more than 0.70 a "very strong" relationship between early marker and later response.[11,23] The following indices (and 95% CIs, calculated employing a normal approximation) were used to assess the predictive ability of the early measures of disease severity: (1) sensitivity = early improvers with a positive outcome / (early improvers with a positive outcome + early nonimprovers with a positive outcome) × 100, (2) specificity = (early nonimprovers with a negative outcome / [early nonimprovers with a negative outcome + early improvers with a negative outcome]), (3) positive predictive value = (early improvers with a positive outcome / all with a positive outcome), (4) negative predictive value = early nonimprovers with a negative outcome / all with a negative outcome, (5) false positives (100% − specificity), and (6) false negatives (100% − sensitivity). All analyses were conducted employing SAS version 8.2.

RESULTS

Patient Population

Baseline demographic and clinical characteristics for the 3 pooled study populations were well matched across treatment groups (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/JCP/A339). While the populations in the fixed-dose (studies 1 and 2) and flexible-dose monotherapy studies (studies 3 and 4) were similar with regard to sex, age, and ethnicity, the population in the adjunct-therapy studies (studies 6 and 7) was older and less racially diverse. Similarly, baseline disease severity (mean HAM-D and MADRS total scores) was similar between populations in the placebo and quetiapine XR arms of the fixed- and flexible-dose monotherapy studies but slightly lower for patients in the adjunct-therapy studies. There was a low incidence of missing data, which was evenly distributed across the treatment groups and was not deemed to bias the analysis.

Predictive Value of Early Improvement in Response to Quetiapine XR Therapy

Of the quetiapine XR regimens analyzed, the predictive value of early improvement with adjunctive therapy produced the highest efficiency for predicting outcomes, with Yule's Q coefficients of 0.81 to 0.84 for predicting 50% improvement in MADRS, for instance (Fig. 1). An improvement of 30% in MADRS at 2 weeks seemed to be the most efficient outcome

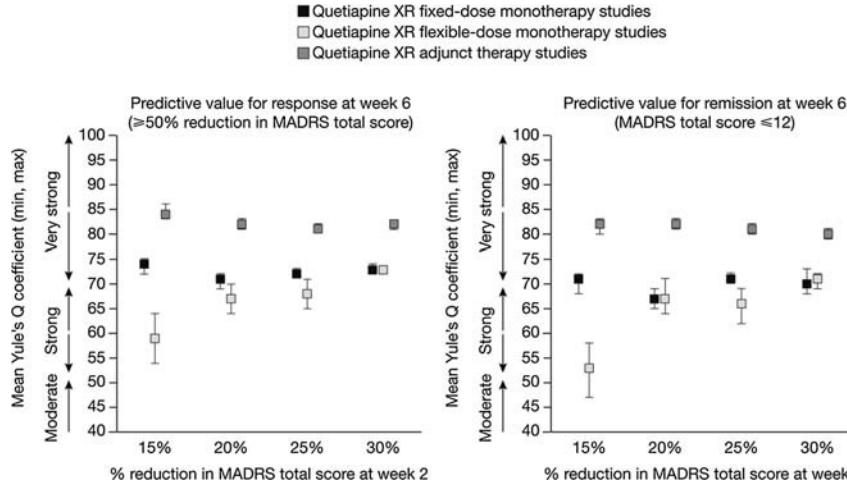

FIGURE 1. Predictive value for treatment response (≥50% reduction in MADRS total score) or remission (MADRS total score ≤ 12) to quetiapine XR, according to the level of improvement at week 2 (% reduction in MADRS total score): fixed dose, flexible dose, or as an adjunctive treatment in MDD.

for predicting MADRS response at 6 weeks. For the fixed-dose monotherapy population, early improvement at 2 weeks was highly predictive of treatment outcome with quetiapine XR at 6 weeks (50% improvement on MADRS), with Yule's Q values of 0.71 to 0.74. In the flexible-dose population, modification of the quetiapine XR dose seemed to lead to a slight decrease in predictivity of early response compared with the fixed-dose regimen, as indicated by comparatively lower Yule's Q values for MADRS improvements of 15% to 30% at 2 weeks (0.59–0.73 for the flexible-dose regimen and 0.71–0.74 for the fixed-dose regimen). Data for quetiapine XR and placebo are given in Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/JCP/A339 and Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/JCP/A340.

Predictive Value of Early Improvement in Response to Placebo Therapy

For the adjunctive placebo plus antidepressant therapy population, the Yule's Q coefficient for the predictive value of 15% or more improvement on MADRS at 2 weeks for eventual MADRS response at 6 weeks was lower than the corresponding predictive value for quetiapine XR; the Yule's Q coefficient ranged from 0.72 to 0.76 (Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/JCP/A340 and Supplementary Table 3, Supplemental Digital Content 3, http://links.lww.com/JCP/A341). Remission (MADRS total score ≤ 12) at 6 weeks was most efficiently predicted by a 30% improvement on MADRS at 2 weeks in this group. In the fixed- and flexible-dose placebo populations, an improvement on MADRS at 2 weeks was highly predictive of response (50% improvement on MADRS) at 6 weeks, with Yule's Q values of 0.73 to 0.77 and 0.69 to 0.75, respectively. In the fixed-dose population, a 30% improvement on MADRS at 2 weeks appeared more efficient than 20% improvement for predicting response at 6 weeks, with a correspondingly higher Yule's Q value (0.77 vs 0.73, respectively). However, in the flexible-dose placebo population, a greater level of early improvement did not seem to correspond to greater predictivity for response or remission (lower Yule's Q for 25%–30% improvement on MADRS at 2 weeks compared with 15%–20% improvement at 2 weeks; Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/JCP/A340 and Supplementary Table 3, Supplemental Digital Content 3, http://links.lww.com/JCP/A341).

DISCUSSION

In the present study, symptomatic improvement with quetiapine XR at week 2 was shown, as expected, to be a very strong predictor of eventual response or remission in patients with MDD. A 30% decrease in MADRS total score at week 2 in the adjunct-therapy studies appeared to be the strongest indicator of eventual treatment response. Of interest is that the predictions were sustained—if not as strongly—even with placebo treatment. Adjunct-therapy study data indicate that predictivity is somewhat more obvious for quetiapine XR than placebo, although for those patients already receiving other pharmacotherapy, adding quetiapine XR or placebo gives a high predictivity of response during early treatment, so that if an improvement is evident after 2 weeks, there is a high probability of response. In the fixed-dose monotherapy population, improvement with quetiapine XR or placebo at 2 weeks was also strongly predictive for response or remission at week 6, suggesting that irrespective of treatment assignment, if improvement is shown after 2 weeks, the patient has a high probability of being a responder. The flexible-dose studies did not provide sufficiently clear data to support predictivity of early response in the context of treatment regimen modification. The remission data for this group suggest that the type of treatment the patient receives affects predictivity of the early data. In an analysis of patients separated into those who did and did not receive dose doubling, only a small number of patients increased their dose, such that no inference could be made from these data. In each patient population (fixed-dose, flexible-dose, and adjunct therapy), predictivity seemed to be higher where initial and final assessments used the same instruments; the predictive value of MADRS improvement at week 2 was higher for eventual MADRS response than HAM-D response and for MADRS remission over HAM-D remission. Indeed, using a common rating scale throughout treatment would be more reflective of general practice.

Our finding that early symptomatic improvement was predictive of response to placebo and active treatment is not new. Early improvement in MDD symptoms has been reported for placebo, where the time course of recovery from depression seems to be comparable with that of active treatment.[24] However, the reason for this similar pattern is unclear; there may be inherent differences in the biological response behind the observed symptomatic improvements, for example.[24] A meta-analysis that explored the predictivity of early treatment responses determined that the informativity of an early placebo response (odds ratio, 2.35; range, 1.89–2.92) was not as significantly important as an early response to active treatment (odds ratio, 4.11; range, 3.79–4.46).[11] There also seems to be a subset of patients in whom early treatment response is not predictive of remission.[8] Furthermore, we did not examine the relative contribution of quetiapine XR and placebo to the 2-week response. Previously, Katz et al[25] showed that there were differences in the nature of early responses to active and placebo therapy for MDD. The main difference was a consistent pattern of behavioral improvement with active therapy, whereas no such consistency was observed with placebo.[25] Our findings and those from these previous analyses highlight the need for more refined methodologies to detect early drug-induced specific changes in the disorder that go beyond the more general measures of "overall" symptom severity changes measured using the HAM-D or MADRS. Limitations were the variability in the designs of the 6 studies analyzed and the fact that the analysis was confined to only quetiapine XR. However, early symptomatic improvement has been shown to be a positive predictor for treatment outcome for other atypical antipsychotics in the treatment of MDD. Pooled data from 3 large, randomized, double-blind, placebo-controlled trials of aripiprazole adjunct to antidepressant found 20% or more improvement in MADRS total score at week 2 to be highly predictive of remission at week 6.[26] As in other studies of conventional antidepressants, including escitalopram and agomelatine,[9,11] evidence for lack of early response was a strong predictor for eventual nonresponse with quetiapine XR. In contrast, data from the Genome-Based Therapeutic Drugs for Depression study, in which patients with MDD received escitalopram or nortriptyline, revealed that a significant proportion of patients (44.5%) who failed to achieve a 20% reduction in symptoms at week 2 eventually had a response, suggesting that treatment discontinuation at week 2 in patients with no early symptom improvement would be premature. However, benefit was maintained in those patients who demonstrated improvement at week 2.

The clinical implications of identifying individuals with MDD who have been assigned to a treatment likely to be successful are largely axiomatic. Firstly, the earlier availability of information on the appropriateness of treatment could reduce patient distress and suffering and increase acceptability of treatment. Secondly, atypical antipsychotics have well-documented hazardous adverse events,[27] which are more likely to be observed with

greater duration of treatment exposure. Deciding whether the risk for adverse events is justified is informed by whether the chosen treatment is likely to mitigate target symptoms relevant to the patient.[28] Thirdly, determination of early improvement with treatment tacitly implies that measurement-based care occurs on a regular basis, which has been shown to improve patient outcomes in MDD.[29]

In conclusion, we found that assessment of early improvement at week 2 provided a powerful indicator of eventual treatment response or nonresponse with quetiapine XR in patients with MDD. In the adjunct-therapy studies, the positive predictive value of early improvement was very strong, and a 30% improvement in MADRS total score at week 2 gave the greatest predictive value for eventual response or remission.

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