See article by Correll et al

Functional Outcomes of an Antipsychotic Medication in Schizophrenia:
A Generalizable or Specific Effect?

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Most published articles reporting on the effects of medications indicated for schizophrenia focus on the psychopathological symptoms and/or prevention or delay of relapse. Often the authors will remind us that symptoms and hospitalizations represent significant barriers to improvements in community functioning, a logical proposition. Is that proposition supported by data?

In a study comparing oral and long-acting injectable fluphenazine conducted during the 1970s, my colleagues and I examined the course of social functioning in the subgroup of patients who did not experience relapse during the 12-month trial regardless of which treatment they received.[1] We saw an interesting pattern. Between the first assessment when patients were hospitalized and acutely symptomatic and the second when they were in the community 3 months later, there was significant improvement. However, there was no further improvement over the remaining assessments at 6, 9, and 12 months after baseline. The same pattern was observed for work and school, family relations, and overall social functioning. And, most important, the actual level of functioning was poor. Our conclusion: although antipsychotic medication prevented relapse and re-hospitalization, it did not facilitate improvement in social and role functioning. A narrative review published in 1984 suggested that the finding was not specific to fluphenazine.[2] That review focused on clinical trials that reported significantly greater efficacy of the antipsychotic compared to placebo in preventing relapse. In those studies that assessed social functioning as well, there was no significant advantage for antipsychotic medication compared to placebo.[2]

These reports predate the development and availability of second-generation antipsychotics (SGAs). A landmark study that compared clozapine to chlorpromazine resulted in the 1990 approval of clozapine for treatment-refractory schizophrenia.[3] That approval launched a search for antipsychotic medications with improved efficacy and a more favorable side effect profile that would not be limited to treatment-refractory schizophrenia. Since then, 12 antipsychotic medications have received US Food and Drug Administration (FDA) approval for schizophrenia. In addition to short-term studies to show efficacy compared to placebo, long-term relapse prevention studies comparing them to placebo have been conducted with virtually all of these agents. Many of these studies were stopped prematurely when the number of relapses required to evaluate the difference was reached. In all of these cases, the number was significantly higher in the placebo arm than in the antipsychotic medication arm. As a result, the availability of data to evaluate long-term functioning in these studies is limited. In addition, the interest in such evaluation has also been limited.

The study reported by Correll and colleagues in this issue of the *Journal* represents an infrequent and welcome opportunity to examine the effects of an SGA, brexpiprazole, on functional outcomes.[4] The article has a number of methodological strengths. The authors examined functioning measures in detail. They accessed a number of studies that compared brexpiprazole to placebo, including both short- and long-term outcome measures. They have been careful to explain their data sources and that their analyses are post hoc and therefore cannot be considered as hypothesis testing. The title of the article includes the phrase "post hoc analysis," clearly stipulating that the report does not present results of well-powered hypothesis testing. The measures used translate to terms that have clinical applicability. The short-term trials used the Personal and Social Performance Scale (PSP).[5] The long-term relapse prevention trial compared to placebo used the Global Assessment of Functioning (GAF) that is familiar to many as an Axis of the *DSM-5*.[6]

In general, the findings indicate that brexpiprazole offers schizophrenia patients significantly better functional outcomes than placebo. The report raises two interesting clinical questions.

The first is, How good is statistically significant greater benefit? The results are quite consistent for both the PSP and the GAF. For the short-term studies that used the PSP, the mean total score at baseline was 44, which reflects marked difficulties in 3 of the 4 areas of functioning: socially useful activities, personal and social relationships, self-care, and aggressive behavior. After acute treatment of 6 weeks, or whenever treatment was stopped, the mean score in the

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brexpiprazole group was 56, which reflects marked difficulty in 1 area. Good functioning in all 4 areas (score range of 81–90) is defined as "presence of only common problems or difficulties." Results for the GAF are comparable. The mean GAF total when patients had completed a stabilization phase that defined their readiness for maintenance treatment was 63.6. That score reflects "moderate symptoms or moderate impairment in social and occupational or school functioning." After 52 weeks, the patients who were still receiving brexpiprazole had maintained their gains. Benefit compared to placebo still leaves patients with substantial impairment. Further, the GAF that was used to index long-term functioning includes symptoms as well as functioning.

The report also raises the question, Is the effect specific to brexpiprazole? The brexpiprazole maintenance data are remarkably consistent with the findings described above with fluphenazine.[1] There is initial improvement from the point of acute symptoms and then maintenance of the effect rather than the hoped-for goal of continued improvement in functioning when maintenance antipsychotic medication continues for a year without a relapse or re-hospitalization.

What about the effects on functioning of another SGA antipsychotic? Fluphenazine, a first-generation antipsychotic, is not widely prescribed today, and, as noted above, there are 11 other available SGAs. Fleischhacker and colleagues[7] examined the effects on self-report of functioning outcomes for long-acting injectable risperidone over the course of a year. Their findings are remarkably congruent with the findings for fluphenazine and brexpiprazole: initial improvement followed by plateau and at levels that are substantially below those of normative samples assessed with the same measure.

Correll and colleagues[4] remind us that functional outcomes are important and valuable to assess. Families and patients have told us that for as long as we have been willing to listen to them. Shortly after clozapine had become available in our community, I was presenting the results of the landmark study[3] that was the basis for the FDA approval to an audience that included family members. I noted that about 30% of patients who received clozapine in the trial had improved and that the side effect burden and need for weekly blood draws suggested that if patients did not receive benefit from clozapine after an adequate trial, they should not continue to receive it. After my talk, a mother in the audience came up to let me know that although her son's doctor felt that he had not improved and should not continue to receive clozapine, he was indeed much better. They could now go out for dinner together.

Despite the enormous value of antipsychotic medications in the treatment of schizophrenia and improvement in functional outcomes, those outcomes continue to lag behind the improvements in symptoms and reductions in relapse.

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