See article by Nierenberg et al

A Brief Commentary on the Bipolar CHOICE Study

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A number of elements can be admired in the study by Nierenberg and colleagues.[1] Treatments in bipolar disorder and bipolar depression are notoriously limited and merit examination, especially in real-world patients. In this light, the Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness) study[1] investigators set out to study an important question: How will established medications compare in "usual practice" over a longer time than the typical brief timeframe in a placebo-controlled trial? This question is central for clinical practice, but current clinical trials methodology has not adequately addressed it. The researchers also ask whether a strategy using a widely prescribed US Food and Drug Administration (FDA)–approved medication for the treatment of bipolar disorder, quetiapine, offers advantages over one using the first medication approved by the FDA specifically for bipolar disorder, lithium.

The authors evaluated two end points in this large randomized study of the strategy of adding either lithium or quetiapine to usual care (here referred to as "adjunctive personalized medications" by the researchers) for the treatment of patients with bipolar disorder who were at least mildly ill in any phase of the illness—a potentially typical kind of patient entering treatment. The coprimary outcome measures were the Clinical Global Impressions (CGI)-Efficacy Index and a novel outcome (originally developed for the Lithium Treatment Moderate-Dose Use Study [LiTMUS][2]), necessary clinical adjustments (NCAs), defined as medication adjustments due to tolerability or inadequate response.[3] Consistent with real-world practice, there were few exclusions to study participation other than the limitation in each group for medications to be tried of the same class as under examination (eg, no quetiapine or other second-generation antipsychotic [SGA] in the lithium group and no lithium or SGAs in the quetiapine group). Any other treatments could be changed or initiated within this limitation during the 6-month trial. Because of the open nature of the study, both the psychiatrists and the patients were aware of what the patients were prescribed, although clinical raters of the primary outcomes were blind to treatment assignment. This design could be very desirable, if effective, in telling us something about the medications under "comparison" in real-world practice. What is perhaps different about this study, and which raises a question about its methodological approach, is that the research plan included the option for the doctors to change any standard care medications while maintaining the study drugs for the duration of the study. These changes were captured via the NCA counts for all patients.

How did it turn out? Results were not significantly different between the treatment arms on primary and secondary outcomes: both groups improved overall, and there were about equal numbers of NCAs across groups. Nearly 75% completed the trial, although this value might be less than expected given the flexibility of changing treatment during the study. A few secondary outcomes suggested differences between groups, although, as appropriate for hypothesis-generating secondary outcomes, no correction for multiple comparisons was made. In sum, this large, well-coordinated study was completed with relatively few dropouts.

Perhaps we could infer medication impact by the achievement of reasonable dosages of the study medications. Dosing of quetiapine of a mean maximum dose of > 300 mg/d (± 170 mg) versus blood lithium levels ranging from mean of 0.5–0.6 mEq/L (± 0.3–0.4) suggests quetiapine dosing was closer to usual recommended clinical doses and lithium tended toward subtherapeutic levels. Could these differences contribute to side effect burden differences, or would these have been due to other medication changes? Could these blood level and dose differences also relate to the improved response of hypomanic symptoms to quetiapine? The Bipolar CHOICE study results carry some mystery. One is that the lithium group had fewer NCAs when anxiety scores were higher, an unexpected finding given that quetiapine is known from other studies (eg, Sheehan et al[4]) to significantly impact anxiety scores in bipolar disorder.

The researchers' effort to develop new methodology is a critical and important step in the difficult area of clinical trials and especially in longer term clinical trials in bipolar disorder such as the 6-month trial[1] presented here. Notable was the approximately equal numbers of NCAs for each group. Of some concern, though, is the question, Is it realistic to attribute the number of NCAs to treatment assignment? Importantly, How can we estimate each physician's views of the assigned medication? How might this inform or impact the choices clinicians made with their patients? The scientific method is founded on efforts to identify key outcomes while stabilizing other factors and is central to developing interpretable results. Clearly, there are intrinsic limitations to the scientific method given the complexity of

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human behavior and the brain, but against the background of chaos, the need for caution in not overstating meaning is ever more important. The researchers are appropriately thoughtful in this regard and, in fact, leave us with many questions. Would a different trial methodology perhaps have led to more interpretable results? A significant issue in the Bipolar CHOICE study[1] is that the randomized element—assignment to the quetiapine or lithium strategy—was kept steady while allowing a host of other factors to be fluid. We don't know why prescribers made the choices they did. What were the biases and reasons each brought to the trial regarding the 2 treatments under study? How did the lithium versus quetiapine assignment impact their other clinical adjustments? Does a count of NCAs provide adequate insight into decisions at the physician-patient interaction?

How could a pragmatic trial be conducted such that uncertainty and background noise are kept at a minimum? D'Avolio and colleagues[5] developed a recent innovation to usual restrictive, randomized-controlled trials: that of point-of-care randomization. In this approach, there are liberal inclusion and narrow exclusion criteria in order to capture a broad presentation of patients instead of the narrowly defined subjects often randomized into clinical trials. One of the strengths of D'Avolio and colleagues' approach[5] is that randomization occurs in the flow of usual care, where treatments considered in equipoise are offered to patients. Another strength of this approach is that conditions that might confound and obscure the relative benefit and harm of treatments under study are kept constant. This innovation is consistent with the Agency for Healthcare Research and Quality approach to comparative effectiveness and has been adopted in the game-changing US Department of Veterans Affairs (VA) Cooperative Study Programs (CSPs) throughout the United States. One example of this approach is a recent study (CSP #519)[6] that evaluated whether stopping smoking would be more effective for veterans with posttraumatic stress disorder when embedded in the usual care given in mental health clinics or when the veteran is referred to a separate smoking-cessation program. Perhaps we should not be surprised that, indeed, there is greater success in stopping smoking when smoking cessation is embedded with ongoing care. Importantly, if CSP #519 had found it made no difference where the smoking cessation program was based, then it would have impacted policy, just as the findings from the study are impacting future plans for such programs in the VA and throughout health care systems nationally.

Innovation in clinical trial design is needed to more effectively capture real-world response to medications and consider best treatment approaches to bipolar disorder, an illness requiring lifelong medication for many. At the end of the day, did we learn something that informs us about the illness or directs us to the next study? Certainly the ongoing and continuous medication changes implicit in the Bipolar CHOICE study inform us about the illness—it changes and keeps changing. This level of ongoing change needs to be considered in future studies, and ways to improve our methodology should be sought. The ability to quantify outcome does not guarantee meaningfulness in a chaotic world—though reassurance may be at least temporary that order is feasible.

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