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Adequate evidence to support improved outcomes in depression by primary care physicians compared to psychiatrists when using combinatorial pharmacogenomics

To the Editors:

We appreciate the letter to the editor by Rosenblat and colleagues with regard to the recent IMPACT study publication, in which greater improvement in patients' depression outcomes was observed among those treated by primary care providers versus psychiatrists following combinatorial pharmacogenomic testing. We agree that there are several limitations to the IMPACT study and we note that Rosenblat et al. have pointed out similar limitations that we discussed in the manuscript.

We agree that there is a need for controlled trials in order to demonstrate the utility of pharmacogenomic testing, and the forthcoming GUIDED randomized controlled trial will address this (Greden et al., 2018). The naturalistic IMPACT study was not designed to provide evidence that pharmacogenomics is more effective than treatment as usual. Instead, our analysis was designed to compare outcomes (symptom improvement, response, and remission) in patients with moderate-to-severe depression who were treated by primary care providers versus patients who were treated by psychiatrists. Rosenblat et al.'s statement that we "do not provide sufficient evidence to support the conclusion that 'use of combinatorial pharmacogenomic testing improves patient outcomes in major depressive disorder (MDD)'" has been stated out of context. Our conclusion was that the findings from the IMPACT study add to the body of evidence that, as a whole, supports the use of combinatorial pharmacogenomics in MDD. We have not claimed that the IMPACT study proves combinatorial pharmacogenomic testing is superior to treatment as usual; in a one-arm study, we observed a significant improvement in patients' symptoms (% change in BDI) across the duration of the study. The IMPACT study is not a standalone effort, but rather, as stated by Rosenblat et al. "adds to our understanding of pharmacogenomics".

In addition to the necessary randomized controlled trials to demonstrate the utility of combinatorial pharmacogenomics for MDD, there is great value in supplementing the evidence from randomized controlled trials with real-world, naturalistic evidence. The IMPACT study as a whole includes more than 10,000 patients, with a subset of 1,871 patients with moderate-to-severe depression. As a large, prospective, naturalistic, un-blinded study, IMPACT supports the implementation of pharmacogenomic testing across different treatment settings and shows that pharmacogenomics can be utilized in primary care settings treating depression. While randomized controlled clinical trials are designed to determine efficacy, they may not adequately inform practice. Consequently, healthcare payers have requested studies such as IMPACT to ensure knowledge translation into practice, and to enable similar benefits across all settings in which patients with MDD may be treated (Kogan et al., 2018). The naturalistic study design complements the strict design of a randomized controlled trial and provides support for the generalizability of the use of combinatorial pharmacogenomic testing (Frieden, 2017).

A key limitation of naturalistic, un-blinded clinical studies is the inability to control for placebo effect. However, a recent meta-analysis by Rosenblat and colleagues reported minimal differences in response and remission rates between blinded and un-blinded studies of pharmacogenomic testing in patients with MDD "suggesting that the enhanced placebo effect in un-blinded studies is likely minor" (Rosenblat et al., 2018).

Our initial conclusions, rooted in the data from this clinical study, provide adequate evidence to demonstrate better patient outcomes in primary care settings compared to psychiatric care settings when combinatorial pharmacogenomics is used. In combination with the many other completed trials, the current data provide an important contribution to the field of pharmacogenomic testing in psychiatry. We thank Rosenblat et al. for providing an additional platform to further discuss the methodological differences in clinical trial designs and for a call to action to understand the importance of information gained from a variety of well-controlled and real-world trials.

Disclosures

JAT, PED, and BMD were employed by Assurex Health at the time of this study. JLK is an unpaid member of the Assurex Health Scientific Advisory Board. All other authors declare no conflicts of interest.

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