Aysegul Yildiz, M.D.
Associate Professor of Psychiatry
Department of Psychiatry, Dokuz Eylül University, Izmir, Turkey
Department of Psychiatry, Harvard Medical School and International Consortium for Bipolar Disorder Research, McLean Division of Massachusetts General Hospital, Boston, Massachusetts

Q1) What was the most important finding of your study?

This is the first reported proof of concept study on the role of 'protein kinase C–PKC' in development and treatment of mania with an adequate design and statistical power. This study along with all the previous genomic, preclinical, and clinical work represents an example of thoughtful drug development and improved understanding of the pathophysiology of bipolar disorder, which affects millions of both ordinary people as well as many well-known and highly gifted artists, writers, musicians, and scientists.

Q2) Exactly how much better was tamoxifen than placebo after 3 weeks?

In our study, tamoxifen resulted in 18.3 point mean improvement (47.4% improvement relative to the baseline score) in a mania rating scale, in contrast to 2.9 point worsening (7.8% worsening relative to the baseline score) with placebo after 3 weeks; yielding a contrast of 21.2 point between drug and placebo.

Q3) Were you surprised at all by this or other findings?

Given extensive experimental indications of a role of PKC inhibition in the actions of lithium and divalproex, and the central anti-PKC activities of tamoxifen, observed antimanic effect of tamoxifen was not a surprise. However, the extent of improvement with tamoxifen that was grounded on a target specific indication being apparently better than standard mood stabilizers may be considered as a surprise.
Given high placebo response rates in most of the previous reports we were surprised by the negative placebo effect. Yet, this finding is replicated by the smaller NIMH study by Zarate et al. 2007, which is the only other short-term single-site monotherapy trial conducted in mania within the last 15 years.

Q4) Why is it important to study tamoxifen as an anti-mania agent?

There is compelling pre-clinical data suggesting that PKC signaling is a target of mood stabilizing drugs. However, a suitable animal model of bipolar disorder is not currently available to study this possibility in greater detail. Peripheral tissues and postmortem brains from bipolar disorder patients are also of limited value in reflecting signaling disruption in the brain during mania. Thus, establishing clinical/therapeutic relevance of the findings on PKC system for such a complex human disease was only possible through clinical trials. Since

tamoxifen is the only central nervous system (CNS) penetrant PKC inhibitor available for human use we studied tamoxifen as an anti-mania agent.

Q5) How does tamoxifen differ from other anti-mania drugs (i.e lithium)?

Indeed, in a recent meta-analysis number-needed-to-treat (NNT) determined from random-effects meta-analysis by rate-difference was calculated as 2.4 [95%CI: 1.7–4.1] for tamoxifen, which was the lowest (indicator of better treatment) among all available antimanic agents. This obviously suggests strong antimanic properties with tamoxifen. Yet, data on tamoxifen should be interpreted as '***a proof of concept***', not a proposal of tamoxifen in its current formulation with hormonal effects as a new anti-manic treatment. We need pure PKC inhibitors for mania.

Q6) Do we really need another drug to treat mania?

This prevalent, complex and hard-to-treat illness leads to extreme and erratic shifts of mood, thinking, and behavior, with a very high risk of suicide. Currently available treatments for the disorder include lithium and some drugs developed for the treatment of epilepsy or schizophrenia. Most of these have been known for many years. Their benefits are substantial, but typically far from curative, as individuals usually get out of mania or out of their bad depressions, but they often do not go back to their normal levels of functioning in terms of education, work, or relationships.
Furthermore, antimanic effects lithium and valproate have first been discovered serendipitously, this consequently initiated research into their potential mechanisms of action. Now, this relation became bidirectional, as new treatment strategies are being investigated based on the proposed mechanism of action of the existing mood stabilizer drugs.
Understanding the biochemical targets of treatment in bipolar disorder as in the case of PKC, promise for development of new target specific treatment strategies, which can have a very rapid anti-manic effect. With such rapidly acting treatments patients may have the chance of preventing the emergence of full-blown mania once they sensed a manic episode coming on, and better functioning in their normal lives.

Q7) Do these findings mean that women with breast cancer being treated with tamoxifen are much less likely to be delusional or psychotic or manic?

As we know antidepressant or mood stabilizing drugs have no effect in affect & mood when given to individuals with no mood disorders. Yet, if a patient has a diagnosis of bipolar disorder and is being treated with tamoxifen for breast cancer, that patient would probably be less likely for being delusional or psychotic or manic.

Q8) Should psychiatrists be considering tamoxifen in their practices now?

Although, effective and quite safe for short-term treatment of mania, long-term use of tamoxifen is not recommended due to potential side effects such as transient thrombocytopenia, leukopenia, hot flushes, vaginal bleeding, vaginal discharge, peripheric

edema, menstrual irregularities, hepatotoxicity, and retinopathy which are all related with the drug's estrogen blocking properties. Psychiatrists should wait for development of new central nervous system penetrant selective protein kinase C inhibitors with no hormonal effect. However, if a patient is being treated with tamoxifen for breast cancer gets an axis I diagnosis of bipolar disorder, that patient may also benefit tamoxifen's antimanic properties, and her lithium and/or divalproex treatment can be monitored accordingly.