Rate to Placebo (RRP) are needed to complete this calculation. In addition, the relapse rate in people who responded to medication (RLM) and the relapse rate in people who responded to placebo (RLP) must be obtained from the continuation phase of the study. Once this data is collected, the rate of relapse that may be attributable to initial placebo responding can be estimated.

In a hypothetical study, 150 patients received medication, and 100 of them responded, (RRM=66%). These 100 medication responders were continued on medication in the continuation phase where 30 patients relapsed (RLM=30%). 150 patients received placebo and 50 of them responded. (RRP=33%) These 50 were continued on placebo in the continuation phase where 25 of them relapsed (RLP=50%)

First, an estimate of the rate at which patients displayed a placebo response despite receiving active medication (ePR) is calculated by dividing the RRP by the RRM.

ePR = RRP/RRM, in our case 33%/66% = 50% of medication responders are actually placebo responders

Second, how many patients treated with active drug in the continuation phase, who were responders in the acute phase, are presumptive placebo responders (PPR)? To get this figure, the number of patients receiving active medication in the continuation phase is multiplied by the placebo response rate calculated in the first step.

PPR =
ePR * The number of PTs receiving active medication in continuation phase or 50% * 100 patients = 50 patients who are presumptive placebo responders.

The number of patients treated with active medication in the continuation phase who have responded, but are expected to relapse because they are presumptive placebo responders (eRLP) can then be calculated by multiplying the PPR by the RLP.

eRLP = PPR * RLP, or 50 * 50% or 25 patients

Finally, what percentage of relapse can be attributable to initial placebo responding? This final calculation is obtained by taking the number of presumptive placebo responders on active medication that have relapsed (ie,eRLP) and dividing by the total number of patients who relapsed on medication in the continuation phase.

eRLP / N 25/30, or 83%.

Thus the in this study, presumably 83% of the patients who relapsed after responding to medication and continuing on medication in the continuation phase actually relapsed because they were placebo responders.

Using this method, researchers and clinicians may more accurately determine who is truly responding to their choice of medication versus those who may merely be placebo responders and, thus, more likely to "poop-out" during the latter portion of their treatment.

Tamoxifen Treatment of Bipolar Disorder

Protein kinase C (PKC) is a family of enzymes involved in phosphorylation and cellular messaging. A growing body of evidence suggests that PKC inhibition may be a possible mechanism to treat bipolar disorder. Both lithium and valproate (commonly used mood stabilizers) inhibit PKC (Hahn GG et al. *J Psychiatr Res* 2005;39(4):355-63). In preclinical models, stimulants have been shown to activate PKC (Einat H et al. *BiolPsychiatry* 2006;59(12):1160-71) and when compared to normal controls, platelets from patients with bipolar disorder have higher levels of PKC (Friedman E et al. *Biol Psychiatry* 1993;33(7):520-5). Tamoxifen, an antiestrogen used in breast cancer treatment, is currently the only PKC inhibitor capable of penetrating the central nervous system. In a pilot study of 7 patients with bipolar disorder, tamoxifen

significantly decreased manic symptoms (Bebchuk JM et al. *Arch Gen Psychiatry.* 2000;57(1):95-7). In animal models, tamoxifen normalized stimulant-induced risk taking behaviors and hyperactivity (Einat H. *Neuropsychobiology.* In press).

Aysegul Yildiz-Yesiloglu, MD, Dokuz Eylul University, Turkey, presented data from a randomized, double-blind, placebo-controlled study of tamoxifen in patients with bipolar disorder conducted at a single center. Subjects aged 18 to 65 with a diagnosis of bipolar disorder and a Young Mania Rating Scale (YMRS) score >20 were eligible to enroll in the study. Subjects were randomized to receive either tamoxifen or matching placebo tablets for 3 weeks. The initial dose of tamoxifen was 20 mg BID, titrated to a target dose of 80 mg/day in divided doses; the placebo group received similar dose adjustments to maintain the blind. Lorazepam was administered if needed to relieve clinical symptoms. Efficacy measures included the YMRS, Hamilton Depression Scale (HAMD), the Montgomery Asberg Depression Rating Scale (MADRS), Clinical Global Impressions, and the Positive and Negative Syndrome Scale (PANSS).

A total of 66 subjects were randomized, 35 to tamoxifen and 31 to placebo. Six (17%) of the tamoxifen group and 10 placebo patients (32%) discontinued from the study, all due to lack of efficacy. There were no statistically significant differences between the treatment groups in any baseline demographic characteristic. There was one suicide attempt in each group. Other reported adverse events in the tamoxifen group were acne (2), flushing on face (1), headache (2), dry skin (1), urticaria (1), and loss of appetite (1). The tamoxifen YMRS and PANSS demonstrated significant improvement at 3 weeks compared to baseline (both p<0.01; Figure 1). The amount of lorazepam used was significantly less in the tamoxifen group at week 3 (p=0.02).

Although these data are promising, they must be viewed cautiously in light of limitations noted by Dr.Yildiz-Yesiloglu. The placebo response in this study was quite low (approximately 5%) when compared to more typical placebo response rates of 8-1% for

Figure 1. YMRS and PANSS Scores at Baseline and Endpoint.
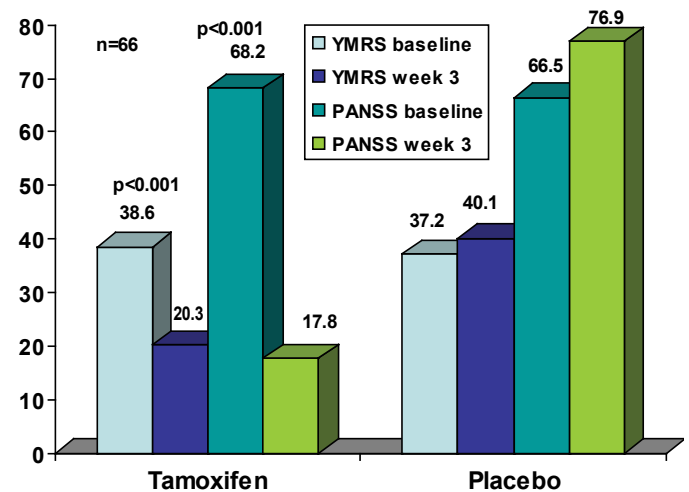
single sites. Patients in the tamoxifen group had a significantly higher proportion of medication free days in the month prior to randomization when compared to placebo subjects (p=0.014). The study design required a 24-hour washout of prior medications before randomization, so it is possible that the placebo patients experienced more drug discontinuation effects, especially because more placebo patients were taking psychotropic drugs prior to randomization. Despite these limitations, tamoxifen demonstrated anti-manic effects and PKC pathways remain attractive research targets in bipolar disorder.