A Double Blind Study Examining the Efficacy of Protein Kinase C Inhibitor Tamoxifen in the Treatment of Acute Mania

Background

- Bipolar disorder (BD) is common, severe, chronic and can be life-threatening
- 10-20% of bipolar patients commit suicide
- Lithium is standard therapy, and has revolutionized the treatment of BD.
- Yet ~50% of patients with bipolar disorder do not respond to lithium.

Background

- Standard drugs for BD include Lithium and Valproic Acid; drugs in the same class but with different chemical structures

- The biochemical basis for the anti-manic and mood-stabilizing mechanisms of these drugs is not fully elucidated.

Background

- Data show these drugs affect the functional balance of interacting neurotransmitter systems

- Recent preclinical data suggest the protein kinase C (PKC) signaling pathway as a possible therapeutically relevant target. Both drugs inhibit PKC

Background

- Protein kinase C family of enzymes:
  - Highly enriched in brain especially pre-synpatic
  - Regulate pre- and post-synpatic aspects of neuro-transmission.
  - Intracellular mediator of external stimulation to cells.
  - Plays a role in regulation of synpatic plasticity in relationship to learning and memory.

Background

- Laboratory studies show abnormalities in PKC
  - Animal models of bipolar disorder show changes in PKC—more PKC activity
  - Treatment with lithium showed lower PKC activity and lower translocation in response to serotonin.
  - Higher PKC activity and translocation in brain samples from patients with bipolar disorder

Background

- Tamoxifen- a relatively selective and potent PKC inhibitor approved for use in humans

Background

- Tamoxifen
  - Used since 1977
  - Synthetic non-steroidal anti-estrogen
  - Crosses blood-brain barrier
  - Used in treatment and prevention of breast cancer in both women and men.
  - Some studies suggest it is associated with increase in depression.

Background

- A single, open-label study of TAM included 7 patients treated with 10-80 mg/day of TAM for 4-15 days.

- Result: significant decrease in manic symptoms in short, 3-7 day, time frame. One patient increase in depression.

Overall Research Purpose

- The purpose of this study is to test the hypothesis that PKC inhibition is part of the mechanism of effective anti-mania interventions, like lithium and valproic acid.

Aims

- Specific Aim #1: To assess the efficacy of 20-140 mg/day of TAM monotherapy compared with placebo in improving overall manic symptomatology.

- Specific Aim #2: To determine if the antimanic response to TAM is associated with attenuation of the PKC signaling pathway

Research Design

- Randomized double blind placebo controlled 3-week study of male and female inpatients meeting DSM IV criteria for a manic episode.
- 50 patients will be enrolled.
- 3 parts to the study

Research Design

- Period 1—Washout Screening 2-7 days.
  - Visit 1 screening tests, history, psychiatric and physical examination, EKG, laboratory tests.
  - Capacity assessment with MacCAT
  - Stop mania medications
  - Minimize risk of carry-over effect from previous treatments.

Research Design

- Period 2—Therapy period—3 weeks
  - Inpatients with daily visit from day 2 through 8
  - Patients get study medication—
    TAM or placebo.
  - TAM 20-140 mg/day
  - Daily EKG
  - Only other treatment is lorazepam up to 2 mg/day for anxiety and agitation in 1st 10 days of period 2

Research Design

- TAM monotherapy because no evidence of how it interacts with other psychotrophic drugs.
- TAM monotherapy to minimize confounding.
- Placebo because in acute mania placebo response rate averages 23%. Validity of results requires placebo.

Research Design

- Begin TAM at 20mg/day and titrate up rapidly based on side effects and response.
- Randomize patients until 20 have achieved 60 mg/day.
- TAM well tolerated up to 240 mg/day in cancer.
- By using up to 140 mg/day will see if any added benefit in mania from higher doses.
- In open-labeled TAM study went to 80mg/day with mean of 60mg/day.

Research Design

- Assessment
  - DSM IV criteria for bipolar I disorder
  - CBC
  - Electrolytes
  - Thyroid tests
  - Fasting blood sugar
  - LFTs
  - Toxic screen
  - Pregnancy test
  - HIV test
  - EKG

Research Design

- Assessment
  - Young Mania Rating Scale--YMRS
  - Hamilton Rating Scale for Depression
  - Montgomery Asberg Depression Rating Scale
  - Positive and Negative Syndrome Scale
  - Clinical Global Impressions Scale—bipolar
  - UKU side effect rating scale

Research Design

- Period 3—Open label TAM or clinical treatment—up to 3 weeks
  - After 3 weeks of treatment blind will be broken.
  - Placebo non-responding patients can get open label TAM for up to 3 weeks as inpatient
  - TAM and placebo responding patients get optimal clinical treatment for sufficient improvement to be discharged to appropriate follow-up care

Research Design

- Rating scales will be obtained daily Visits 2 through 8 and weekly visits 9 through 10.
- Response will be assessed based on results at end of week 3 or visit 10 ratings.
- Response is change in YMRS total score—responder is a patient who has a 50% or greater decrease from baseline to last measured value of study period 2.

Research Design

- Blood will be obtained at
  - Baseline
  - After TAM or placebo 5 days, 10 days and 21 days.
  - Isolate lymphocytes and platelets

Research Design

- Off Study criteria:
  - If daily EKG QTc>480 msec
  - Mood worsens based on rating scale
  - Clinical judgment
  - YMRS >30%
  - Lorazepam >2mg/day or beyond 10th day
  - Substance abuse

Eligibility

- Male or pre-menopausal female
- 18-65 years old
- Bipolar with acute mania
- Previously treated with bipolar drugs
- Willing to be hospitalized for 4 + weeks

Eligibility

- YMRS total score of ≥14 on visit 1 and 2
- No decrease during washout of YMRS of ≥20%
- Duration of manic episodes not >4weeks

Eligibility

- Ineligible if
  - Pregnant
  - QTc>450 msec
  - Anti-depressant within 4 weeks
  - Other medical condition—eg hyperthyroidism, heart, liver, or kidney disease
  - No history of uterine cancer or blood clots
  - No substance abuse within 30 days
  - No suicidal thoughts or plans

Consent

- Patients must voluntarily consent
- No durable power of attorney consent

Other

- Researchers report no conflicts of interest
- No DSMB

Statistical Analysis

- Sample size for Aim #1—
  - In preliminary study 71% of patients had 50% decrease in YMRS score with TAM
  - Placebo response of 24%
  - Power 0.80
  - One tailed α=0.05
  - Thus need sample size of 20 patients per cell.
  - Enroll 25 per cell for potential attrition.
- Utilize random regression analysis on YRMS score decline.
- Kaplan-Meier with log rank test for time to response analysis