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A four week randomised control trial of adjunctive medroxyprogesterone and tamoxifen in women with mania

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Summary Emerging research has suggested that hormone treatments such as selective oestrogen receptor modulators (SERMs) or progestins may be useful in the treatment of mania. The current pilot study compared the use of the SERM tamoxifen and the progestin medroxyprogesterone acetate (MPA), as an adjunct to mood stabiliser medications, for the treatment of mania symptoms in 51 women in a 28-day double blind, placebo controlled study. The primary outcome was the change between baseline and day 28 mania scores as measured by the Clinician Administered Rating Scale for Mania (CARS-M). Adjunctive MPA treatment provided greater and more rapid improvement in mania symptoms compared with adjunctive placebo and tamoxifen treatment. Adjunctive therapy with MPA may be a potentially useful new treatment for persistent mania, leading to a greater and more rapid resolution of symptoms compared with mood stabiliser treatment alone.

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1. Introduction

Mania is characterised by a prolonged period of excessively elevated or irritable mood (American Psychiatric Association, 2000). It is the hallmark of bipolar affective disorder (BPAD) and is also seen in schizoaffective disorder. Currently, the biological processes involved in mania pathophysiology are unclear, and its treatment remains complex (Geddes and Miklowitz, 2013). Women with BPAD experience fluctuating mood across the menstrual cycle, with an exacerbation of symptoms reported during the premenstrual period (Rasgon et al., 2003, 2005; Payne et al., 2007; Dias et al., 2011). Further, evidence suggests that women with BPAD have an increased risk of mood disorder during menopause, a time of decreasing oestrogen levels (Freeman et al., 2002; Marsh et al., 2012). Thus, in women, there is suggestive evidence that endogenous oestrogen levels may mediate manic symptoms.

In previous work, we found that a small subgroup of schizoaffective women with acute mania who received 50 mcg of adjunctive transdermal estradiol for 28 days experienced a worsening of manic symptoms (Kulkarni et al., 2001). We hypothesised this as the effect of an increase in Central Nervous System (CNS) oestrogen exposure. This hypothesis is supported by case reports of improvement in mania with treatments that reduce estradiol levels by inducing anovulation, such as danazol (Goldstein, 1986; Nelson, 1988) and medroxyprogesterone acetate (MPA: Chouinard et al., 1987). In early animal studies, MPA has been shown to cause down regulation of oestrogen receptors in the hypothalamus and pituitary (Blaustein and Brown, 1984) and has an 'anti-estrogenic' effect in the brain generally (Irwin et al., 2011).

Tamoxifen is a selective oestrogen receptor modulator (SERM), with tissue specific effects on oestrogen receptors as well as second messenger pathways (Lam, 1984). Tamoxifen has mainly 'anti-estrogenic' effects in many parts of the CNS, although studies are largely inconclusive (Paganini-Hill and Clark, 2000; Buwalda and Schagen, 2013). Several small studies have also demonstrated a clinical benefit of tamoxifen in the treatment of mania (Manji and Lenox, 1999; Bebchuk et al., 2000; Zarate et al., 2007; DiazGranados and Zarate, 2008; Yildiz et al., 2008; Amrollahi et al., 2011; Yildiz et al., 2011). A small study found tamoxifen to be superior to MPA and clomiphene in preventing amphetamine induced hyper locomotion in an animal model of mania (Pereira et al., 2011).

Our group has previously reported results of a three arm pilot study comparing adjunctive tamoxifen, MPA and placebo in the treatment of 13 women with manic symptoms (Kulkarni et al., 2006). The women treated with tamoxifen had a greater improvement than the MPA group, and both groups showed a greater improvement than placebo. While both tamoxifen and MPA have oestrogen antagonism effects, tamoxifen is also known to be a potent protein kinase-C (PKC) inhibitor. Elevated PKC levels are seen in mania, and the resolution of mania is associated with reductions in PKC levels (Friedman et al., 1993; Kulkarni et al., 2006; Einat et al., 2007; DiazGranados and Zarate, 2008).

The study reported here expands our pilot study. The aim was to compare the use of two adjunctive agents (tamoxifen and MPA) in a 28-day three-arm double blind, placebo-controlled study in the treatment of acute mania or hypomania to further explore dosing effects in larger sample. Extrapolating from our pilot results, we hypothesised that tamoxifen therapy would be associated with a significant reduction in mania symptoms compared to the MPA and placebo groups. We also attempted to understand more about the mechanisms underpinning any reduction in mania symptoms. In particular, we were interested in exploring whether tamoxifen reduced mania symptoms through PKC inhibition or by oestrogen antagonism. To do this we included the MPA arm as a direct comparator for an ''anti -estrogen'' effect, and examined for changes in PKC levels across the trial.

2. Method

This three arm double blind randomised controlled trial was approved by The Alfred Hospital Ethics Committee and Barwon Health Research and Ethics Advisory Committee (Alfred Project Number 77/02). All participants provided written informed consent. The registration number of this trial (at clinicaltrials.gov) is NCT00206544.

2.1. Participants

Women were assessed for eligibility across two Australian sites (the Alfred Hospital, a tertiary hospital and Barwon Health, a regional hospital) between 2004 and 2007. Eligible women were aged between 18 and 65; able to give informed consent; taking a mood stabiliser (lithium, sodium valproate or carbamazepine) and/or a mood — stabilising antipsychotic and had a diagnosis of schizoaffective disorder or BPAD made by their treating psychiatrist which was confirmed by the Structured Clinical Interview for DSM-IV Disorders (SCID-IV). Participants were also required to be currently manic as defined by a score of 15 or above on the *Clinician Administered Rating Scale for Mania* (CARS-M). Women were excluded if they were receiving oestrogen or progestin therapy including the oral contraceptive pill; were pregnant or lactating; had a history of hyperthyroidism or any unstable neurological or other serious medical condition; were taking drugs known to interact with tamoxifen or MPA including warfarin, aminoglutethimide, diuretics, methyldopa, theophylline, fluoxetine, calcium channel blockers and non-steroidal anti-inflammatory drugs; or had a history of substance abuse or dependence in the previous six months. Six of the final sample of 51 women were postmenopausal, as classified by a baseline FSH of more than 25 (Harlow et al., 2012) and amenorrhoea.

2.2. Treatment

All participants were randomised by the Alfred Clinical trials pharmacy to receive either *tamoxifen* 40 mg daily (n = 15); *MPA* 20 mg daily (n = 18); or *placebo* capsules (n = 18) according to a computer generated randomisation list.[1] Bebchuck et al. (2000) reported that a dose of up to 80 mg of oral tamoxifen was effective in reducing manic symptoms in both

[1] The same doses of tamoxifen and MPA were used in our pilot study (see Kulkarni et al., 2006).