
Verapamil Treatment for Women with Bipolar Disorder

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Background: *Additional pharmacological treatments are needed for patients with bipolar disorder. We describe our experience with verapamil in an inclusive, sequential series of outpatient women (some pregnant) with bipolar disorder.*

Methods: *All women who were prescribed verapamil for bipolar disorder (n = 37) were included. We used the criterion of 50% reduction in scores on the Mania Rating Scale or the Hamilton Rating Scale for Depression to define response for women who were treated for an acute episode of bipolar hypomania/mania or depression, respectively. For euthymic women who chose verapamil maintenance treatment, we evaluated whether they met criteria for a recurrent episode during therapy.*

Results: *Treatment for acute episodes was initiated in 28 women. Of women with depression and mania, 39% and 100% responded, respectively. Seven of the nine patients (77%) with mixed states responded: all seven improved to response criterion on the mania scale, and two responded on the depression scales as well. Six of eight patients who received continuation therapy remained well.*

Conclusions: *These data provide evidence that verapamil is effective for mania. The response rate for mania compares favorably to that for other mood stabilizers. After decades of case reports and underpowered clinical trials, we must definitively study verapamil for efficacy and gender specificity in bipolar disorder.* Biol Psychiatry 2002;51:745–752 © 2002 Society of Biological Psychiatry

Key Words: Bipolar disorder, mania, depression, verapamil, women, pregnancy

Introduction

Bipolar disorder is a chronic disorder that affects 1% of our population. Lithium is the standard drug for treatment of both acute mania and maintenance therapy; however, it is ineffective or not tolerated by many patients. Divalproex sodium is increasingly used for the management of acute mania. Weight gain and hyperandrogenism in valproate-treated women with seizure disorder (Isojarvi et al 1993) render maintenance therapy worrisome for female patients, particularly adolescents (Piontek and Wisner 2000). The efficacy of carbamazepine also has been assessed in acute mania, but concerns about neutropenia and interactions with other drugs temper enthusiasm for its use as well. Information about the efficacy of additional treatments is needed urgently for patients who do not respond, have prohibitive side effects, or have medical disorders that complicate the use of lithium and anticonvulsants.

Reports of the use of calcium channel blockers (CCBs) for bipolar disorder have been published for two decades. In general medical practice, CCBs are used to treat states related to cellular hyperexcitability such as supraventricular dysrhythmias, vasospastic angina, hypertension, and premature labor (Dubovsky et al 1986). Safety data from observational studies and randomized clinical trials favor verapamil (VPM) among the CCBs (Opie et al 2000).

Verapamil has multiple effects in the brain. Doran et al (1985) demonstrated that VPM and its active metabolite norVPM are distributed to cerebrospinal fluid after oral administration. Ratios in cerebrospinal fluid/plasma for VPM and norVPM were 0.06 and 0.04, respectively. These ratios are similar to values in the lower range for valproate (0.076–0.25; Vajda et al 1981). Verapamil possesses clinically relevant dopamine antagonist properties as evidenced by its ability to increase prolactin release (Fearrington et al 1983). Both VPM and haloperidol decreased striatal dopamine concentrations after 3 weeks of treatment in rats (Stiges and Guarneros 1998). Verapamil has antiepileptic activity (Straub et al 1997) and has been demonstrated to have neuroprotective effects on cognitive deficits in an experimental model of Alzheimer's disease in rats (Popovic et al 1997). Similarly, the neuroprotective effects of lithium have been described by

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Manji and Lenox (2000). The effects of VPM on circadian rhythms are similar to other mood stabilizers. In hamsters, carbamazepine and VPM shortened the duration of locomotor activity and improved the stability of running activity patterns in a manner similar to that of lithium (Klemfuss and Kripke 1996).

Multiple case reports of the treatment of bipolar disorder with CCB have been published. The majority of studies have involved VPM. Gitlin and Weiss (1984) described a woman who had multiple antidepressant-induced manias despite prophylactic lithium treatment. She was able to maintain euthymia with the addition of VPM and trazodone over a 1-year period. She remained well after lithium was withdrawn. Solomon and Williamson (1986) described two patients who had rapid-cycling bipolar disorder. They were lithium responders who could not be treated secondary to hyperparathyroidism and noncompliance. At week 5 of VPM treatment, case 1, (a woman) developed a depression and was treated with trazodone with good result. Maintenance for 4 months on both drugs was successful. Case 2, a male patient, also responded and developed depression after 5 weeks of treatment. He was maintained for 4 months on VPM and an antidepressant with good result. Verapamil prevented mania in a woman who took phenelzine; mania recurred when VPM was withdrawn and remitted with reinstatement of VPM (Dubovsky et al 1985). These cases are interesting because the patients developed treatable depression after resolution of cycling during VPM therapy.

The results of controlled studies have been inconsistent. In a 4-week, double-blind, randomized comparison of VPM with lithium in 20 patients with mania, Garza-Trevino et al (1992) found that both groups improved significantly within 3 weeks. No difference in efficacy between the two drugs was observed. Hoschl and Kozeny (1989) also treated 12 inpatients with mania with VPM, 24 with neuroleptics, and 11 with neuroleptics plus lithium. The responses of the three groups of patients were comparable. Dose et al (1986) used a placebo-controlled, double-blind A-B-A design to study the effect of VPM in patients with mania or schizomania. The response of seven of eight patients was rapid (within 3-7 days). Giannini et al (1984) compared the antimanic effects of VPM, lithium, and placebo in a crossover-designed study in men. The efficacy of VPM and lithium were similar, and both were more effective than placebo in mild to moderate mania. A double-blind crossover study of VPM compared with placebo showed that five of seven patients with acute mania responded to VPM (Dubovsky et al 1986).

Recent trials of VPM for bipolar disorder have been less encouraging. In a single-blind study, Walton (1996) found that lithium was significantly more effective on measures of mania and overall functioning than VPM in 40 inpa-

tients with severe mania. Janicak et al (1998) did not find differences in patients treated with VPM compared with placebo in a 3-week, double-blind, random-assignment, parallel-group trial of inpatients with mania; however, only nine of 32 subjects completed the 3-week trial.

Clinicians need alternative agents for use during pregnancy because valproate and carbamazepine are morphologic and neurobehavioral teratogens (Delgado-Escueta and Janz 1992). Although less teratogenic than implied by data from the Registry (Cohen et al 1994), lithium is associated with fetal growth enhancement (Jacobson et al 1992). Goodnick (1993) described the use of VPM in three women for the acute and maintenance treatment of bipolar disorder during pregnancy. The first woman had mania with psychotic features. She responded within 2 weeks to VPM, which was continued for the entire pregnancy. The second patient discontinued carbamazepine during previous pregnancies and became manic. She was treated with VPM during pregnancy and had mild hypomania. The third patient discontinued lithium during previous pregnancies and became manic with psychotic features. She was evaluated immediately after the discovery of pregnancy, discontinued lithium, and was treated effectively with VPM.

During pregnancy, VPM has been used for hypertension, maternal and fetal dysrhythmias, and tocolysis. Magee et al (1996) studied the safety of calcium channel blockers in human pregnancy with a prospective multicenter design. The teratogenicity of calcium channel blockers, most specifically VPM and nifedipine (41% and 44% of exposures, respectively), was examined. Seventy-eight women with first-trimester exposure were evaluated prospectively and compared with a control group matched for maternal age and smoking. The drugs were taken for hypertension, cardiac rhythm disturbances, and migraines. There was no increased risk for malformations in exposed fetuses. Neonatal health problems occurred at a similar rate in both groups.

Verapamil is a reasonable choice for women who choose to breastfeed their infants. Two cases of mother and breastfeeding infant serum levels of VPM have been published. In the first case, the infant was exposed in utero and during lactation to 240 mg VPM (Andersen 1983). The infant's VPM level was 2.1 ng/mL 4 days postpartum. In the second case, the mother received 240 mg VPM after birth, and no VPM or its metabolite norVPM could be detected in the infant's serum at 3 months postpartum. At typical doses, the neonatal intake of VPM would be about one hundredth of the maternal dose. Because newborns may be more sensitive to drug effects from small doses, concern about nursing has been expressed; however, the American Academy of Pediatrics (1994) considers VPM compatible with breastfeeding.

In this article, we present data from an inclusive naturalistic series of women treated in a specialized women's outpatient mental health care program. We frequently develop treatment plans for women who cannot tolerate or refuse to take lithium or anticonvulsants. Common clinical situations are: women who plan to conceive and require maintenance medication to prevent bipolar episodes; the emergence of mania or depression during pregnancy in women who have discontinued medication, since pregnancy offers no protective effect (Viguera et al 2000); and women who have recurrent episodes in the postpartum period (Wisner and Stowe 1997).

Methods and Materials

Subjects

Women who met criteria for bipolar affective disorder according to the Structured Clinical Interview for DSM-IV (SCID) were identified. Those who chose to discontinue standard therapies (lithium and anticonvulsants) because of side effects, pregnancy, or refusal for personal reasons were included for study ($n = 37$). They were subjects in this sequential series if they accepted a trial of VPM therapy and if they had no cardiac pathology, no previous untoward reaction to any CCB (e.g., major cognitive disturbances), and no other active medical condition (e.g., insulin-dependent diabetes, hyperthyroidism). All subjects were advised that VPM treatment is not FDA-approved therapy for mania or depression. The Institutional Review Board approved this study.

Most women ($n = 29$) were ill at the time of entry into the series, and they were conceptualized as receiving acute treatment with the goal of symptom reduction. These subjects had 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton 1960) scores of ≥ 15 and/or a Mania Rating Scale (MRS) score of ≥ 12 (derived from the Schedule for Affective Disorders and Schizophrenia) (Endicott et al 1978). Some patients were given the Bech-Rafaelson Mania Rating Scale (BRMS) (Bech et al 1979); these patients had a score of ≥ 10 . In some of the initial subjects, the Inventory to Diagnose Depression (IDD) (Zimmerman et al 1986) was used to assess depression symptom level. This instrument was used in one of our clinical trials with a similar population, and we estimated the HRSD score from the IDD based on linear regression: $\text{HDRS} = 2.93 + 0.44 (\text{IDD})$. If no score was available (usually due to psychosis), the MRS was scored from observation and/or reports from significant others.

Subjects also fulfilled DSM-IV criteria for an episode of bipolar 1 disorder (depressed, mixed, or manic type), or bipolar 2 disorder (hypomanic or depressed type). Women with bipolar 1 or 2 disorder who were stable (did not fit the above criteria for an acute episode at the time of entry into

the series; $n = 8$) were considered to be in maintenance treatment.

Selection and Dosing of Verapamil

We chose VPM as the CCB for multiple reasons: VPM is the drug for which the majority of efficacy data for bipolar disorder has been published; an experience base for use of VPM during pregnancy has been established; and a long-term safety profile of VPM has been established. The doses of VPM used to treat bipolar episodes in published studies have been variable.

Our review provided data to support the use of doses of 240 mg/day (Gitlin and Weiss 1984; Garza-Trevino et al 1992), 320 mg/day (Solomon and Williamson 1984; Giannini et al 1984; Giannini et al 1985; Barton and Gitlin 1987), to the maximum recommended dosage (by the manufacturer) of 480 mg/day (Dubovsky et al 1986; Dose et al 1986; Hoschl and Kozeny 1989). Because response is likely to be related to dose, we chose to minimize the risk of failing to find an effect due to inadequate dose. We employed the following VPM dosing pattern: 80 mg b.i.d. for the first week, then 120 mg b.i.d. for the second week. If tolerated, the dose was increased slowly (by no more than 80 mg/day for a minimum of 7 days) to a maximum of 480 mg/day if response was not achieved. Our dosing was less aggressive than that of some studies because women are more sensitive than men to the side effects of medications (Yonkers et al 1992) and specifically more sensitive to VPM (Krecic-Shepard et al 2000). Additionally, the sample was drawn from outpatients, who could not be monitored as closely as inpatients.

Definitions of Response and Episodes

In the women who were treated for an acute episode, 50% reduction in depression or mania scores on the HDRS or MRS (or both in the case of mixed state occurrence) was used to quantify response. In women who chose to start VPM when they were not in an active episode, the criterion for recurrence of an episode was the SCID and severity criteria identified above for admission to acute treatment (a recurrence). A withdrawal occurred when a patient was removed from the series before assessing response (because of side effects) or when she refused to take the drug after prescription. All withdrawals in the sequential sample were included in the data set. The cases are presented in detail in Tables 1 and 2. Some women who entered acute treatment were pregnant ($n = 9$); these women are presented separately from the nonpregnant women ($n = 20$), Table 1).

Data Analysis

We explored the responses of women to VPM in this naturalistic sample by comparing them with drug and

Table 1. Verapamil Treatment of Acute Bipolar Episodes in Pregnant Women

Case	Diagnosis Severity when Verapamil Started	Verapamil Treatment ^b	Verapamil Augmentation	Results of Treatment (Post-Scores)
1	Bipolar II, depressed MRS = 0 HRSD = 15	80 mg/day (15 days)	None	Withdrew: Side effects (headaches)
2	Bipolar II, depressed Bulimia MRS = 8 HRSD = 24	300 mg/day (2.5 months)	None	MRS = 4 HRSD = 24
3	Bipolar II, depressed BRMS = 4 HRSD = 18	300 mg/day (7.5 months)	None	BRMS = 0 HRSD = 2 ^a
4	Bipolar I, depressed MRS = 10 HRSD = 30	160 mg/day (1 month)	T ₄	MRS = 10 HRSD = 35
5	Bipolar I, mixed Rapid Cycling BRMS = 17 HRSD = 19	200 mg/day (2 months)	None	BRMS = 0 ^a HRSD = 14
6	Bipolar I, depressed MRS = 6 HRSD = 19	240 mg/day (3 months)	Sertraline	MRS = 2 HRSD = 20
7	Bipolar I, manic MRS = 22 HRSD = 3	360 mg/day (2 months)	Trazodone Haldol discontinued	MRS = 1 ^a HRSD = 12
8	Bipolar I, depressed MRS = 0 HRSD = 25	360 mg/day (5 months)	None	MRS = 0 HRSD = 6 ^a
9	Bipolar I, mixed BRMS = 13 HRSD = 30	160 mg/day (1.5 months)	None	Withdrew: Non-compliance
10	Bipolar I, mixed MRS = 20 HRSD = 15	300 mg/day (3 months)	None	MRS = 0 ^a HRSD = 14
11	Bipolar I, Mixed Rapid Cycling prior to Menses BRMS = 12 HRSD = 21	360 mg/day; menstrual cycle days 12-20-increase to 440 mg/day (45 months)	Desipramine Valproate Zolpidem Lorazepam	BRMS = 0 ^a HRSD = 16
12	Bipolar I, depressed MRS = 9 HRSD = 24	160 mg/day (1 month)	Valproate	MRS = 0 HRSD = 7 ^a
13	Bipolar II, depressed MRS = 5 HRSD = 22	240 mg/day (1 month)	Lorazepam Bupropion	MRS = 0 HRSD = 5 ^a
14	Bipolar I, depressed Rapid Cycling MRS = 7 HRSD = 22	240 mg/day (2 months)	Carbamazepine	MRS = 0 HRSD = 17
15	Bipolar I, mixed MRS = 19 HRSD = 27	240 mg/day (4 months)	Trazodone	MRS = 4 ^a HRSD = 5 ^a
16	Bipolar I, mixed MRS = 16 HRSD = 17	300 mg/day (4.5 months)	None	MRS = 2 ^a HRSD = 5 ^a
17	Bipolar I, depressed with psychotic features MRS = 2 HRSD = 22	240 mg/day (4 months)	Perphenazine	Decrease in psychotic symptoms MRS = 3 HRSD = 16
18	Bipolar I, hypomania rapid cycling BRMS = 12 HRSD = 13	320 mg/day (6 months)	Gabapentin	MRS = 5 ^a HRSD = 19
19	Bipolar I, mixed with psychotic features MRS = 17 HRSD = 25	300 mg/day (4 months)	Haloperidol Buspirone Methylphenidate Gabapentin	MRS = 0 ^a HRSD = 22
20	Bipolar I, depressed with psychotic features MRS = 5 HRSD = 20	240 mg/day (4 months)	Valproate	MRS = 6 HRSD = 31
21	Bipolar II, depressed MRS = 0 HRSD = 16	300 mg/day (7 months)	None	MRS = 0 HRSD = 5 ^a
22	Bipolar I, mixed BRMS = 16 HRSD = 22	240 mg/day (2 months)	None	BRMS = 6 ^a HRSD = 16
23	Bipolar II, depressed MRS = 0 HRSD = 29	200 mg/day (1 month)	Nardil	MRS = 0 HRSD = 13 ^a
24	Bipolar I, depressed MRS = 9 HRSD = 17	240 mg/day (2 months)	None	MRS = 8 HRSD = 10
25	Bipolar II, depressed MRS = 10 HRSD = 20	160 mg/day (10 days)	None	Withdrew: Side effects (Rash)
26	Bipolar I, mixed MRS = 15 HRSD = 15	90 mg/day (2 months)	None	Withdrew: Non-compliance
27	Bipolar II, depressed MRS = 0 HRSD = 25	240 mg/day (8 months)	Sertraline	MRS = 0 HRSD = 0 ^a
28	Bipolar I, depressed MRS = 0 HRSD = 15	360 mg/day (5 months)	Fluoxetine	MRS = 18 HRSD = 20
29	Bipolar II, depressed MRS = 11 HRSD = 18	320 mg/day (2 months)	None	MRS = 0 HRSD = 17

BRMS, Bech-Rafaelson Mania Rating Scale; HRSD, 17-item Hamilton Rating Scale for Depression; MRS, Mania Rating Scale.

^aResponder = 50% reduction in symptoms from baseline to assessment.^bTime from initiation of verapamil to assessment of response.

placebo response rates in acute trials as defined in a meta-analysis by Keck et al (2000). Similar to Keck et al, we used the criterion of 50% reduction in mania or depression scale scores to define response. In the continuation phase, we evaluated whether patients at baseline (not acutely ill and not meeting identified threshold symptom levels) developed threshold symptoms for either mania or depression across time.

Results

Women With Acute Bipolar Episodes

Acute treatment response data are displayed in Table 3. Two of two women who had mania or hypomania responded (100%), and seven of nine (77%) women with mixed states responded in at least one state domain. Seven of these seven women responded with resolution of manic

Table 2. Continuation Treatment

Case	Diagnosis Severity when Verapamil Started	Treatment	Verapamil Augmentation	Results of Treatment (Post-Scores)
30	Bipolar II, Rapid Cycling PTSD BRMS = 11 HRSD = 5	Verapamil 300 mg/day (2 months)	Decrease in Clonazepam dose	BRMS = 11 HRSD = 0
31	Bipolar II, SAD MRS = 0 HRSD = 12	Verapamil 320 mg/day (14 months)	Bupropion, winter Valproate 250 mg for migranes	MRS = 1 HRSD = 2
32	Bipolar I, mixed with psychotic features MRS = 11 HRSD = 14	Verapamil 320 mg/day (9 months)	Lorazepam Valproate	MRS = 12 ^b HRSD = 24 ^b
33	Bipolar I, MRS = 2 HRSD = 13	Verapamil 160 mg/day (4 months)	None	MRS = 0 HRSD = 10
34	Bipolar II, Rapid Cycling MRS = 10 HRSD = 14	Verapamil 240 mg/day (2 months)	Sertraline	MRS = 6 HRSD = 12
35	Bipolar II, MRS = 0 HRSD = 0	Verapamil 160 mg/day (2 weeks)	None	Withdrew: Side effects (palpitations)
36	Bipolar I, rapid cycling OCD BRMS = 6 HRSD = 12	ECT ^a Maintenance Verapamil 240 mg/day (2 months)	Lithium (no ECT)	BRMS = 0 HRSD = 11
37	Bipolar I, MRS = 0 HRSD = 12	Verapamil 300 mg/day (3 months)	Lithium	MRS = 0 HRSD = 11

HRSD, 17-item Hamilton Rating Scale for Depression; MRS, Mania Rating Scale; BRMS, Bech-Rafaelson Mania Rating Scale; ECT, Electroconvulsive Therapy; OCD, Obsessive Compulsive Disorder.

^aTime from initiation of verapamil to assessment of response.

^bReached threshold symptom level and diagnosis.

symptoms, and two of the seven also had resolution of depression. Women who were depressed had the lowest responsivity, with seven of 18 (39%) meeting the criterion for response. Women who were pregnant responded similarly to those who were nonpregnant. For subjects who completed the acute trial, the treatment duration was a minimum of 1 month (median 3 months, mode 2 months, respectively).

Women in Maintenance Treatment

Six of these nine women remained well while taking VPM. The two recurrences that occurred were a mixed state and a breakthrough depression. For the eight patients in the maintenance treatment group (one withdrew), the treatment duration was 2 months to 14 months (median 2 months, mode 2 months).

Table 3. Acute Treatment Response Profiles

Episode Type	Baseline		Recovery Based on Symptom Scales						
	Number	Withdrew		HRSD < 15		MRS < 12		HRSD < 15 and MRS < 12	
		<i>n</i>	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>
Acute depression only (MRS < 12, HRSD ≥ 15)	18	2	11	7	39				
Patients who completed	16			7	44				
Acute manic only (MRS ≥ 12, HRSD < 15)	2	0	0			2	100		
Acute manic and depression (MRS ≥ 12, HRSD ≥ 15)	9	2	22	2	22	7	78	2	22
Patients who completed	7			2	29	7	100	2	29
Non-pregnant patients	22								
Acute mania	8	1				7	88		
Patients who completed	7					7	100		
Acute depression	19	2		7	37				
Patients who completed	17			7	41				
Mixed	7	1		2	29	6	86	2	29
Patients who completed	6			2	33	6	100	2	33
Pregnant patients	15								
Acute mania	3	1				2	67		
Patients who completed	2					2	100		
Acute Depression	8	2		2	25				
Patients who completed	6			2	33				
Mixed	2	1		0		1	100		
Patients who completed	1			0		1			

HRSD, 17-item Hamilton Rating Scale for Depression; MRS, Mania Rating Scale.

Table 4. Comparison of Placebo and Drug Response Rates to Published Rates

					Likelihood of Our Observations with Keck et al's (2000) Estimates of Placebo and Drug Effects			
					For Mania			
Women with mania/hypomania	Number recovered		Proportion recovered	95% CI ^a	Average placebo	Maximum placebo	Average drug	Maximum drug
					.23	.43	.40	.65
All who started	11	9	.82	.48-.98	.0001 ^b	.01 ^b	.994 ^c	.80 ^c
Only completers	9	9	1.00	.66-1.00	.0000 ^b	.0005 ^b	.9997 ^c	.98 ^c

					For Depression			
Women with Depression	Number recovered		Proportion recovered	95% CI*	Average placebo	Maximum placebo	Average drug	Maximum drug
					.29	.38	.64	.86
All who started	27	9	.33	.17-.54	.38 ^b	.46 ^b	.001 ^c	.000 ^c
Only completers	23	9	.39	.20-.61	.20 ^b	.53 ^b	.013 ^c	.000 ^c

^aExact binomial confidence limits of the observed proportion recovered.

^bProbability that the observed results or more extreme results would be obtained with proportions from Keck et al (2000) as the standard. For the placebo effects, this tests whether the obtained results suggest the observed proportion ≤ the expected proportion.

^cProbability that the observed result could be obtained with the proportions from Keck et al (2000) used as the standard. For the drug effects, this tests whether the obtained results suggest that the observed proportion ≥ the expected proportion.

Comparison With Established Rates of Response (Table 4)

In acute mania studies, the criterion for response is defined as 40% to 50% reduction in the score from baseline to outcome assessment (Keck et al 2000). The mean percentage of placebo responders was 23% (± 11%; range 11-43%), with the comparison rate for drug responders of 40% (± 24%; range 8-65%). These authors found little justification for continuation of acute treatment trials for mania beyond 3 weeks. For women with bipolar depression, the mean percent of placebo responders was 29% (± 12%; range 13-38%) compared with 65% (± 24%; range 45-86%) of drug responders. The optimum treatment period for bipolar depression was 3 to 5 weeks. Separation of drug and placebo effect was apparent at week 5 on the HRSD. All women in our study were treated for at least 1 month, and all but four of the sample were treated for 6 weeks or longer before assessment of efficacy.

In Table 4, we display the significance of the response rates observed in our study compared with that of Keck et al (2000). Women who had mixed states are included in both the mania/hypomania and depression groups with the recovery rate for each individual state domain. The responses we observed for mania/hypomania are highly unlikely to be a placebo response in both the intent-to-treat and completer groups, even when the maximum placebo response (0.43) is used (all *p* values < 0.01 for intent-to-treat and completer groups). Conversely, our response rate is very likely to be a drug effect compared with the reported mean drug response rate of 0.40 or maximum

drug response rate of 0.65 (all *p* values ≥ 0.80 for intent-to-treat and completer groups). In women with depression, our response rates are very likely to be equivalent to a placebo response (at both the average and maximum rates) for intent-to-treat and completer groups (all *p* values ≥ 0.20) and unlikely to be a drug effect at the reported rates (all *p* values < 0.013).

Keck et al (2000) commented that placebo-controlled studies might be obviated by setting an effect size for an investigational treatment to achieve or exceed relative to an average placebo response, and suggested a value of 0.9. In our data, the effect size for patients in the mania/hypomania group was 3.66 (compared with 1.3 for drug responders in Keck et al). The effect size equals [(mean at base-mean at end point)/SD, where SD is a pooled SD from both time points or the SD of the change score; 15.44/4.22 = 3.66]. This effect size provides additional evidence that our observed response is unlikely to be equivalent to the placebo response rate. The effect size we observed for the depressed patients was 0.72, which is consistent with a placebo response.

Mother-Infant Serum VPM Levels

One mother who was breastfeeding her infant elected VPM therapy. The maternal serum levels were: R-VPM 161 ng/mL and S-VPM 37.7 ng/mL; for the metabolite nor-VPM: R-norVPM 162 ng/mL and S-norVPM 57.8 ng/mL. The infant's serum levels were < 1 ng/mL (the limit of quantifiability) for all VPM enantiomers.

Discussion

We were intrigued by the positive response to VPM of women who presented with manic/hypomanic or mixed states (100% and 77%, respectively) to our tertiary-care outpatient women's mental health clinic; however, the response of for depression in women whom we treated was lower (39%) and not convincingly different from a placebo response.

Randomized, double-blind, placebo-controlled parallel group clinical trials have been the standard methods for establishing the efficacy of new treatments for patients with bipolar disorder (Keck et al 2000). The justifications for using placebo control groups are the fluctuating natural course of psychiatric illnesses, the wide variability in placebo responses across patient groups, and the influence of psychosocial factors upon treatment response (Keck et al 2000). Anecdotal and pilot data must provide evidence that a drug is promising to the degree that warrants intensive (and costly) study. Verapamil is a drug that has been viewed as a promising agent (to the extent that an NIMH contract was issued in 1995), but subsequently has lost momentum in our field. The issue is whether VPM studies in general provide enough of a "signal" to pursue a randomized clinical trial. In our opinion, VPM warrants definitive study because: 1) our clinical experience has been highly favorable, as this paper describes; 2) it is associated with not only fewer but also a different spectrum of side effects compared with lithium and anticonvulsants; 3) its tolerability and safety record with long-term use has been established; 4) as poly drug regimens become more commonly used to treat bipolar disorder, experience with additional agents is desirable; 5) the drug has actions similar to other agents known to be efficacious; 6) it has a favorable profile of low toxicity in pregnancy and lactation compared with other agents used to treat bipolar disorder; and 7) differences in responsivity related to gender (Leibenluft 1996) have not been evaluated. Verapamil exhibits higher bioavailability in women compared with men. Gender-related differences in drug metabolism exist at both the liver and the intestine and influence in vivo pharmacodynamic responses (Krecic-Shepard et al 2000).

The efficacy of VPM remains to be explored in randomized clinical trials of acute treatment with adequate power, and for maintenance therapy. Using the summary effect sizes estimated by Keck et al's (2000) meta-analysis, a randomized clinical trial of VPM versus placebo for mania with 60 completers in each cell would provide adequate power to detect a difference in proportions of 20% to 25%. In an area of psychiatry in which we have the need for new therapeutic agents, we cannot afford to either fail to identify a useful agent or to continue to use

one that is ineffective. A definitive randomized clinical trial for patients with bipolar disorder is compelling and urgently needed.

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References

- American Academy of Pediatrics (1994): The transfer of drugs and other chemicals into human milk. *Pediatrics* 93:137–150.
- Andersen HJ (1983): Excretion of verapamil in human milk. *Eur J Clin Pharmacol* 25:279–280.
- Barton BM, Gitlin MJ (1987): VPM in treatment-resistant mania: An open trial. *J Clin Psychopharmacol* 7:101–103.
- Bech P, Bolwig TG, Kramp P, Rafaelsen OJ (1979): The Bech-Rafaelsen Mania Scale and the Hamilton Depression Rating Scale: Evaluation of homogeneity and inter-observer reliability. *Acta Psychiatr Scand* 59:420–430.
- Cohen LS, Friedman JM, Jefferson JW, Johnson EM, Weiner ML (1994): A reevaluation of risk of in utero exposure to lithium. *JAMA* 271:146–150.
- Delgado-Escueta AV, Janz D (1992): Consensus guidelines: Preconception counseling, management, and care of the pregnant woman with epilepsy. *Neurology* 42:149–160.
- Doran AR, Narang PK, Meigs CY, Wolkowitz OM, Breier RA, Pickar D (1985): Verapamil concentration in cerebrospinal fluid after oral administration. *N Engl J Med* 312:1261.
- Dose M, Emrich HM, Cording-Tommel C, von Zerssen D (1986): Use of calcium antagonists in mania. *Psychoneuroendocrinology* 11:241–243.
- Dubovsky SL, Franks RS, Schrier D (1985): Phenelzine-induced hypomania: Effect of verapamil. *Biol Psychiatry* 20:1009–1014.
- Dubovsky SL, Franks RD, Allen S, Murphy J (1986): Calcium antagonists in mania: A double-blind study of verapamil. *Psychiatry Res* 18:309–320.
- Endicott J, Spitzer RL (1978): A diagnostic interview: The Schedule for Affective Disorders and Schizophrenia. *Arch Gen Psychiatry* 35:837–844.
- Fearrington EL, Rand CH, Rose JD (1983): Hyperprolactinemia-galactorrhea induced by verapamil. *Am J Cardiol* 51:1466–1467.
- Garza-Trevino E, Overall JE, Hollister LE (1992): Verapamil versus lithium in acute mania. *Am J Psychiatry* 149:121–122.
- Giannini AJ, Houser WL Jr, Loiselle RH, Giannini MC, Price WA (1984): Antimanic effects of verapamil. *Am J Psychiatry* 141:1602–1603.
- Giannini AJ, Loiselle RH, Price WA, Giannini MC (1985): Comparison of antimanic efficacy of clonidine and verapamil. *J Clin Pharmacol* 25:307–308.
- Gitlin MJ, Weiss J (1984): Verapamil as maintenance treatment in bipolar illness: A case report. *J Clin Psychopharmacol* 4:341–343.
- Goodnick PJ (1993): Verapamil prophylaxis in pregnant women with bipolar disorder. *Am J Psychiatry* 150:10.

- Hamilton M (1960): A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56–62.
- Hoschl C, Kozeny J (1989): Verapamil in affective disorders: A controlled, double-blind study. *Biol Psychiatry* 25:128–140.
- Isojarvi JIT, Laatikainen TJ, Pakarinen AJ, Juntunen KTS, Myllyla VV (1993): Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. *N Engl J Med* 329:1383–1388.
- Jacobson SJ, Jones K, Johnson K, Ceolin L, Kaur P, Sahn D, et al (1992): Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. *Lancet* 339:530–533.
- Janicak PG, Sharma RP, Pandey G, Davis JM (1998): Verapamil for the treatment of acute mania: A double-blind placebo-controlled trial. *Am J Psychiatry* 155:971–973.
- Keck PE, Welge JA, McElroy SL, Arnold LM, Strakowski SM (2000): Placebo effect in randomized, controlled studies of acute bipolar mania and depression. *Biol Psychiatry* 47:748–755.
- Klemfuss H, Kripke DF (1996): Antimanic drugs stabilize hamster circadian rhythms. *Psychiatry Res* 57:215–222.
- Krecic-Shepard ME, Barnas CR, Slimko J, Jones MP, Schwartz JB (2000): Gender-specific effects on verapamil pharmacokinetics and pharmacodynamics in humans. *J Clin Pharmacol* 40:219–230.
- Leibenluft E (1996): Women with bipolar illness: Clinical and research issues. *Am J Psychiatry* 153:163–173.
- Magee LA, Schick B, Donnenfeld AE, Sage RR, Conover B, Cook L, et al (1996): The safety of calcium channel blockers in human pregnancy: A prospective multicenter study. *Am J Obstet Gynecol* 174:823–828.
- Manji HK, Lenox RH (2000): The nature of bipolar disorder. *J Clin Psychiatry* 61S:42–57.
- Opie LH, Yusuf S, Kubler W (2000): Current status of safety and efficacy of calcium channel blockers in cardiovascular diseases: A critical analysis based on 100 studies. *Prog Cardiovasc Dis* 43:171–196.
- Piontek CM, Wisner KL (2000): Appropriate clinical management of women taking valproate. *J Clin Psychiatry* 61:170–172.
- Popovic M, Caballero-Bleda M, Popovic N, Bokonjic D, Dobric S (1997): Neuroprotective effect of chronic verapamil treatment on cognitive and noncognitive deficits in an experimental Alzheimer's disease in rats. *Int J Neurosci* 92:79–93.
- Solomon L, Williamson P (1986): Verapamil in bipolar illness. *Can J Psychiatry* 31:442–444.
- Stiges M, Guarneros A (1998): Chronic verapamil modifies striatal and frontal cortex dopamine levels. *Eur Neuropsychopharmacol* 8:105–111.
- Straub H, Kohling R, Speckmann EJ (1997): Strychnine-induced epileptiform activity in hippocampal and neocortical slice preparations: Suppression by the organic calcium antagonists verapamil and flunarizine. *Brain Res* 773:173–180.
- Vajda FJ, Donnan GA, Phillips J, Bladin PF (1981): Human brain, plasma, and cerebrospinal fluid concentration of sodium valproate after 72 hours of therapy. *Neurology* 31:486–488.
- Viguera AC, Nonacs R, Cohen LS, Tondo L, Murray A, Baldessarini RJ (2000): Risk of recurrence of bipolar disorder in pregnant and nonpregnant women after discontinuing lithium maintenance. *Am J Psychiatry* 157:179–184. 7.
- Walton SA, Berk M, Brook S (1996): Superiority of lithium over verapamil in mania: A randomized, controlled, single-blind trial. *J Clin Psychiatry* 57:543–546.
- Wisner KL, Stowe ZN (1997): Psychobiology of postpartum mood disorders. *Seminars in Reproductive Endocrinology* 15:77–90.
- Yonkers KA, Kando JC, Cole JO, Blumenthal S (1992): Gender differences in pharmacokinetics and pharmacodynamics of psychotropic medication. *Am J Psychiatry* 149:587–595.
- Zimmerman M, Coryell W, Corenthal C, et al (1986): A self-report scale to diagnose major depressive disorder. *Arch Gen Psychiatry* 43:1076–1081.