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# Choline in the Treatment of Rapid-Cycling Bipolar Disorder:

## Clinical and Neurochemical Findings in Lithium-Treated Patients

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*This study examined choline augmentation of lithium for rapid-cycling bipolar disorder. Choline bitartrate was given openly to 6 consecutive lithium-treated outpatients with rapid-cycling bipolar disorder. Five patients also underwent brain proton magnetic resonance spectroscopy. Five of 6 rapid-cycling patients had a substantial reduction in manic symptoms, and 4 patients had a marked reduction in all mood symptoms during choline therapy. The patients who responded to choline all exhibited a substantial rise in the basal ganglia concentration of choline-containing compounds. Choline was well tolerated in all cases. Choline, in the presence of lithium, was a safe and effective treatment for 4 of 6 rapid-cycling patients in our series. A hypothesis is suggested to explain both lithium refractoriness in patients with bipolar disorder and the action of choline in mania, which involves the interaction between phosphatidylinositol and phosphatidylcholine second-messenger systems.*

**Key Words:** Choline, magnetic resonance spectroscopy, brain, lithium, bipolar disorder, rapid cycling, human

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### Introduction

Choline, lithium, and bipolar disorder are linked by interactions at several levels. Clinically, there is evidence that the choline precursor lecithin (phosphatidylcholine) is

moderately effective in some patients with mania (Cohen et al 1980, 1982; Schreier 1982; Leiva 1990). In addition, lithium exerts a potent and specific inhibitory effect on human choline transport (Stoll et al 1991). This has led to the suggestion that choline administration in lithium-treated patients could lead to particularly high brain concentrations of choline-containing compounds (Millington et al 1979a and b). We hypothesized that this “choline trapping” through the simultaneous administration of choline and lithium may be a more effective antimanic therapy than either agent alone, and that lithium will substantially improve the efficacy of choline or choline precursors in the treatment of mania. Based on this hypothesis, choline bitartrate was administered to a con-

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secutive series of 6 treatment-refractory rapid-cycling bipolar patients who were already receiving lithium.

## Methods

Six treatment-refractory rapid-cycling bipolar patients who were maintained on lithium and other medications received open treatment with oral choline bitartrate. Four of the 6 patients were able to self-rate their mood symptoms twice daily (for best and worst mood state), on a standard form used in our centers to track mood changes over time. The patients could rate their mood as normal, depressed (mild, moderate, or severe), or manic (mild, moderate, or severe).

Choline was administered in capsules of 780 mg choline bitartrate (Solgar Vitamin Co., Inc., Lynnbrook, NY), each supplying the equivalent of 350 mg of free choline. Patients received 2-4 g of free choline per day initially, usually in a b.i.d. schedule, increasing to 3-8 g of free choline per day as a maintenance dosage, also in divided dosages. This dosage range for choline was chosen based on recent work indicating that choline dosages as low as 50 mg/kg produce a substantial rise in the brain choline magnetic resonance signal (Stoll et al 1995).

Five of 6 patients underwent at least two proton magnetic resonance spectroscopy ( $^1\text{H-MRS}$ ) scans: one pre-choline and at least one during choline treatment. The determination of the clinical response to choline treatment was made blind to  $^1\text{H-MRS}$  findings. The basal ganglia was chosen as the region to study due to its rich innervation with cholinergic neurons, high levels of choline metabolites in animal studies (Millington and Wurtman 1982), and other MRS research in the literature examining this brain area in patients with mood disorders (Charles et al 1992; Renshaw et al 1994). The  $^1\text{H-MRS}$  methods are described in detail elsewhere (Stoll et al 1995).

## Results

### Case 1

Mr. A is a 49-year-old single man with a 30-year history of mood symptoms. He did not improve during trials of maprotiline and fluoxetine. His subsequent course included rapid-cycling bipolar symptoms with psychosis. Lithium, with and without tranylcypromine, produced only an early temporary improvement in mood symptoms. He later presented to our center as an outpatient, with rapid-cycling symptoms. Mood charting over the next month revealed improvement as the tranylcypromine was tapered and discontinued. A 3.5-month valproate trial

(1500 mg/day; serum level 101 mg/L) in combination with lithium (1500 mg/day; serum level 1.1 mEq/L) was not helpful. Laboratory studies, including thyroid-stimulating hormone (TSH), were normal.

Choline was begun at the equivalent of 4000 mg/day of free choline, and was increased to 6000 mg/day, because of ongoing symptoms, including insomnia. Mr. A had a dramatic, favorable response to choline therapy, as revealed in his mood ratings (Figure 1).

Before choline treatment, the choline-to-creatine resonance ratio in his basal ganglia was 0.63, which increased to 0.83 (31.7% increase) following 1 week of choline administration (Figure 2).

### Case 2

Mr. B is a 36-year-old man, with bipolar disorder, panic disorder with agoraphobia, and a past history of alcohol abuse. In the preceding year, he had two complete biphasic mood episodes. Lithium 1200 mg/day, clonazepam 0.75 mg/day, and several trials of antidepressants, including desipramine, were ineffective. Fluoxetine and paroxetine caused ataxia and tremor, and venlafaxine led to a recurrence of severe panic.

In the month prior to choline, he had 60 of 60 ratings in the depressed range. Choline bitartrate was added to the ongoing lithium and clonazepam treatment, beginning at the equivalent of 1000 mg b.i.d. of free choline, and increased to 1000 mg t.i.d. after 3 days. After 4 days of choline therapy, he had a complete remission of depressive symptoms, and no abnormal mood elevation (Figure 1). He has remained euthymic for 16 weeks, and denies any adverse reactions to choline treatment.

MRS was not performed.

### Case 3

Ms. C is a 30-year-old single woman with 11 years of bipolar disorder, including rapid-cycling illness for the last 2 years. The rapid cycling may have been precipitated by trials of clomipramine and later, phenelzine. The patient also carried diagnoses of anorexia nervosa and possible borderline personality disorder. Trials of neuroleptic drugs (chlorpromazine, haloperidol, perphenazine, and thiothixine) in various combinations with lithium, carbamazepine, valproate, and clonazepam were only partially helpful.

At the time of referral to our center, she was receiving haloperidol 6 mg/day, lorazepam 2 mg/day, lithium carbonate 900 mg/day (1.2 mEq/L), and carbamazepine 600 mg/day. Laboratory studies, including TSH, were all normal. She agreed to a trial of choline bitartrate to treat her rapid-cycling symptoms, and up to 1800 mg q.i.d. of free choline was added to her regimen.

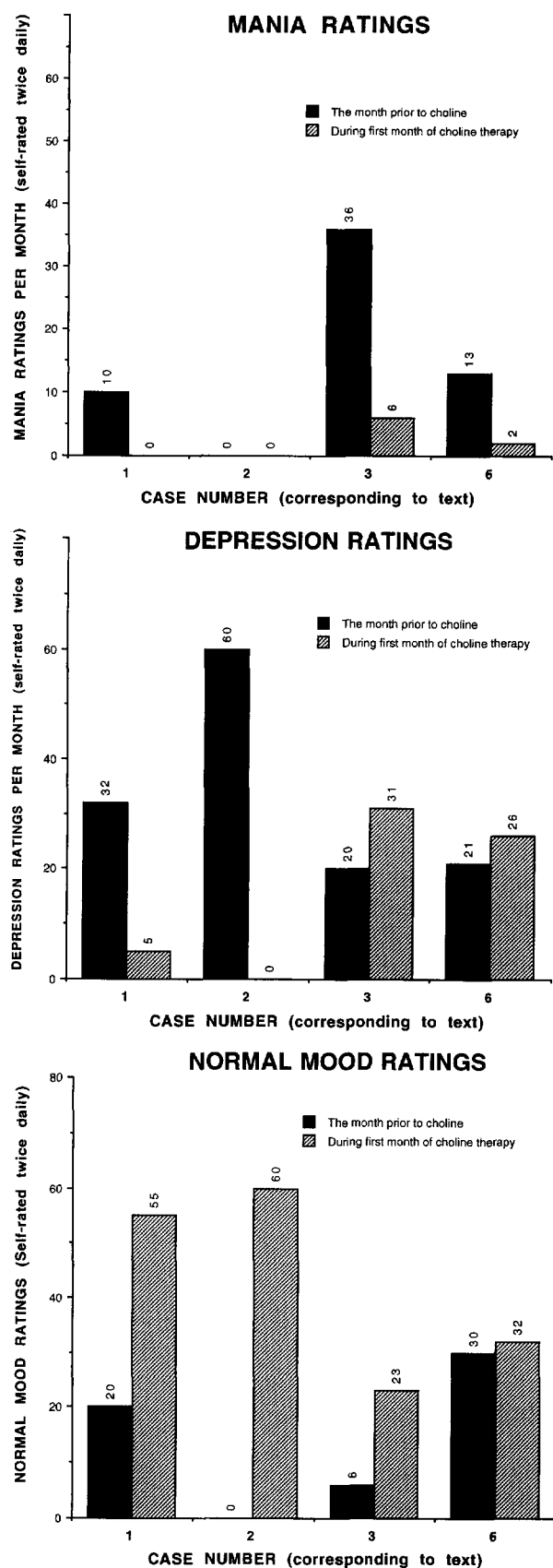


Figure 1 depicts her mood ratings in the 1 month prior to choline administration and in the first month of choline therapy. She exhibited substantially more normal ratings and less mania ratings during choline treatment. The depressive ratings increased somewhat, however, and due to continued dysphoria, her referring psychiatrist discontinued choline and restarted the phenelzine. Within 10 days, the patient was hospitalized for another manic episode, and has not been seen for follow-up in our center.

On MRS, the patient exhibited approximately a 50% increase in the choline-to-creatine resonance ratio in her basal ganglia (from 0.662 to 0.920) after 1 week of choline administration (Figure 2).

#### Case 4

Mr. D is a 33-year-old man with a history of probable cyclothymia, beginning at age 15, followed by a full-blown manic episode at age 23. Despite this and multiple other episodes, he received no treatment for many years. Following referral to our center, lithium was started (level up to 1.4 mEq/L). While receiving lithium, clonazepam 1 mg/day, and propranolol for tremor, he improved only slightly and continued to experience several mood cycles per week. Valproate, in combination with lithium, caused severe diarrhea. He would not keep a mood diary, so his progress was based on frequent prospective clinical assessments.

Choline bitartrate was introduced at the equivalent of 4600 mg of free choline, in a single AM dose on an empty stomach. The single dose was due to his unwillingness to take medication while at work. At a choline dosage of 6000 mg/day (free choline), his colleagues noted a fishy odor on his breath. The fishy odor resolved after the dosage was reduced to 5000 mg/day. The patient reported improved mood stability by the end of the first week, and his mood completely normalized by 10 days. Over the next 3 months, he had 1 day of feeling slightly "giddy," and 1 day several weeks later, where he was slightly depressed. Due to mild diarrhea and abdominal discomfort, the choline was reduced to 3000 mg/day, and he has maintained his improvement.

MRS revealed that the choline/creatine resonance ratio in his basal ganglia increased from 1.02 prior to choline to 1.73 (69.6% increase) following 1 week of choline administration (Figure 2).

Figure 1. Mood ratings before and during choline therapy. Patients self-rated their mood twice per day, using a standard form in the month prior to choline and during the first month of choline therapy. For case 6, the mood ratings during choline therapy and following discontinuation of high-dose thyroxine are shown.

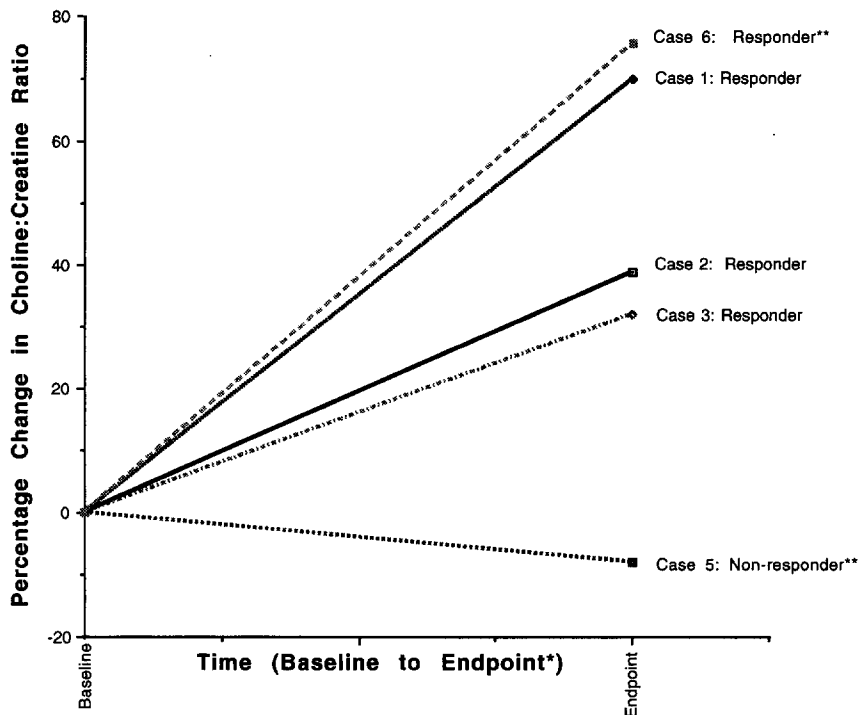


Figure 2. Change in basal ganglia choline:creatine resonance ratio after oral choline and lithium. The human brain choline resonance was determined by  $^1\text{H}$ -MRS. Two major resonance signals were examined: Choline (Cho) and Creatine (Cr). The Cr resonance is composed of creatine and phosphocreatine (Frahm et al. 1989), and is used as an internal standard. Thus, the relative concentrations of Cho were determined using the ratios of the Cho resonance intensity to the Cr resonance intensity. \*One week, except for cases 5 and 6, who each had several MRS studies. Only the first and last MRS results are shown. \*\*Both cases 5 and 6 were receiving supratherapeutic thyroxine. In case 6, the thyroxine was discontinued, and the patient subsequently responded to choline and exhibited a marked rise in the concentration of choline-containing compounds in his basal ganglia.

### Case 5

Ms. E is a 55-year-old married mother of three. She has a long history of psychiatric difficulties dating back to childhood, and was hospitalized at age 22 for a postpartum depression. At her second admission, 15 years later, she presented with acute mania and thyroid cancer was also diagnosed. She underwent a total thyroidectomy, and has been maintained on 0.3–0.4 mg/day of thyroxine since that time. For 14 years, she had 4–6 mood episodes per year, but largely refused treatment. She has been unable to tolerate therapeutic levels of lithium, valproate, and carbamazepine; however, she has continued lithium at 300 mg/day for many years, because upon complete discontinuation of lithium, she suffers the abrupt onset of depression and mania.

Choline was begun at 1000 mg b.i.d. (free choline), which was increased to 2000 mg b.i.d after 1 week. The patient stopped the choline after 6 weeks due to lack of improvement. A mood chart was not maintained. Figure 2 illustrates that her brain choline/creatine resonance intensities did *not* increase over the course of the study.

She has subsequently responded well to paroxetine. There were no gastrointestinal or other side effects to choline.

### Case 6

Mr. F is a 35-year-old man with a history of repeated medical evaluations for episodic sadness and somatic symptoms since age 5. Despite the chronic and recurrent nature of his symptoms, his high intelligence and periods of exceptional productivity enabled him to succeed vocationally. During graduate studies he was referred for psychiatric treatment; however, after 2 weeks of treatment with fluoxetine, he experienced his first full manic episode. Despite immediate discontinuation of fluoxetine, he required psychiatric hospitalization for a 6-week manic episode.

Over the next 7 years, he continued to suffer dozens of mood episodes each year, despite trials of more than 50 medications. His mood episodes typically consisted of an initial phase of depression lasting 3–7 days, followed by 1–2 days of extreme irritability during which his temper was violent. He was referred to a bipolar disorder specialty clinic, where hypermetabolic thyroid supplementation was recommended. He reported improvement with thyroxine 0.4 mg/day, added to his ongoing regimen of lithium (serum level 1.2 mEq/L), carbamazepine (serum level 9.2 ng/mL), and thioridazine (50–100 mg/day). His medical record from previous treaters documented clear worsening on two attempts to lower his dose of thyroxine, as well as

a history of severe behavioral dyscontrol when treated with benzodiazepines.

The patient developed cognitive impairment, but no apparent benefit from increasing dosages of lithium and carbamazepine. Additional trials of clonidine, propranolol, valproate, and risperidone were unsuccessful. The patient received 4 weeks of choline bitartrate at the equivalent of 6000 mg/day of free choline; however, there was no improvement in his mood symptoms. Repeat MRS at 2 weeks of choline treatment revealed *no* change in his brain choline resonance.

The experience with case 5 was similar, in that the failure of choline to improve mood symptoms was accompanied by lack of increase in the brain choline resonance and with high-dose thyroxine treatment. Based on these possible associations, Mr. F's choline, lithium, and carbamazepine were continued, and his thyroxine was reduced to 0.3 mg/day. After 2 weeks, a significant improvement occurred and his thyroxine was further reduced to 0.2 mg/day. On his mood chart during the subsequent month, only one brief period of moderate dysphoria was evident, with some persistent mild depressive symptoms (Figure 1). The following month, his thyroxine was gradually discontinued, and he has continued to experience a substantial remission of mood symptoms. His mood charting reveals little or no manic symptoms, but with intermittent mild to moderate depressive symptoms, which he finds tolerable.

Repeat MRS approximately 6 weeks after discontinuing his thyroxine while continuing choline and lithium treatment revealed a marked rise in his choline/creatine resonance, from a baseline value of 0.75 to 1.32, an increase of more than 75% (Figure 2).

## Discussion

The results of this case series suggests that oral choline in combination with lithium is an effective therapy for some patients with treatment-refractory rapid-cycling bipolar disorder. Five of the 6 patients experienced clinically significant antimanic responses to choline therapy. Two patients experienced sustained normalization of mood soon after the initiation of choline treatment. The effect of choline on depressive symptoms was variable, with some patients experiencing continued, intermittent depression following choline, whereas others experienced complete resolution of depressive symptoms. The effects of choline on mania appeared earlier and were more robust than the effects on depression. In addition, for the patients who responded, the mood-stabilizing effects of choline were accompanied by a rise in the basal ganglia choline resonance, as determined by <sup>1</sup>H-MRS.

Two of the 6 patients did not initially respond well to choline. The 2 patients who did not initially improve with choline also did not exhibit a rise in the brain resonance of choline-containing compounds with sustained coadministration of choline and lithium. This is in contrast to the 4 cases with an early response to choline, where the brain choline resonance rose rapidly with ongoing choline and lithium therapy. Moreover, the 2 patients who did not respond were also the only 2 cases receiving supratherapeutic thyroxine; however, 1 of these patients (case 6) did appear to respond well following the deliberate discontinuation of his thyroxine. In addition, following the discontinuation of thyroxine in this case, his brain choline resonance rose substantially. Supporting the validity of this finding are several reports that have observed that in animals, increasing thyroid activity was associated with diminished concentration of choline in brain (Toide et al 1993; Cornatzer et al 1984).

Strengths of the present study include the twice-daily, systematic ratings of mood for 4 of the 6 patients in this consecutive series, as well as the blind determination of the <sup>1</sup>H-MRS data; however, the major weakness of the present study is the open-label design, which is susceptible to bias by both patients and investigators. Although the patients served as their own controls, with the expectation that patients with rapid-cycling bipolar disorder would have a low rate of spontaneous remission or placebo response (Roy-Byrne et al 1984), a sustained placebo response cannot be ruled out.

It remains unproven whether the administration of lithium plus choline causes a greater rise in the brain choline resonance than choline administration alone; however, the neurochemical findings appear to corroborate one of the main hypotheses of the study: Continuous oral administration of choline in the presence of ongoing lithium will produce a rise in the brain choline resonance in humans ("choline trapping"). Furthermore, the precise neurochemical significance of choline in bipolar disorder remains unclear. Lithium has powerful inhibitory effects on the phosphatidylinositol-associated second-messenger system. Hydrolysis of membrane-associated phosphatidylinositol-containing molecules by phospholipase C, through a specific receptor-linked G-protein mechanism, leads to the release of the second messenger molecules inositol triphosphate and diacylglycerol (Berridge et al 1982). Recent data have shown that phosphatidylcholine is also an important source of second-messenger diacylglycerol (Beterman et al 1986; Exton 1990; Zeisel 1993). Although the acyl groups in the diacylglycerol species derived from phosphatidylcholine and phosphatidylinositol differ, both have similar actions in the cell-signaling cascade (Exton 1990). The main difference between the

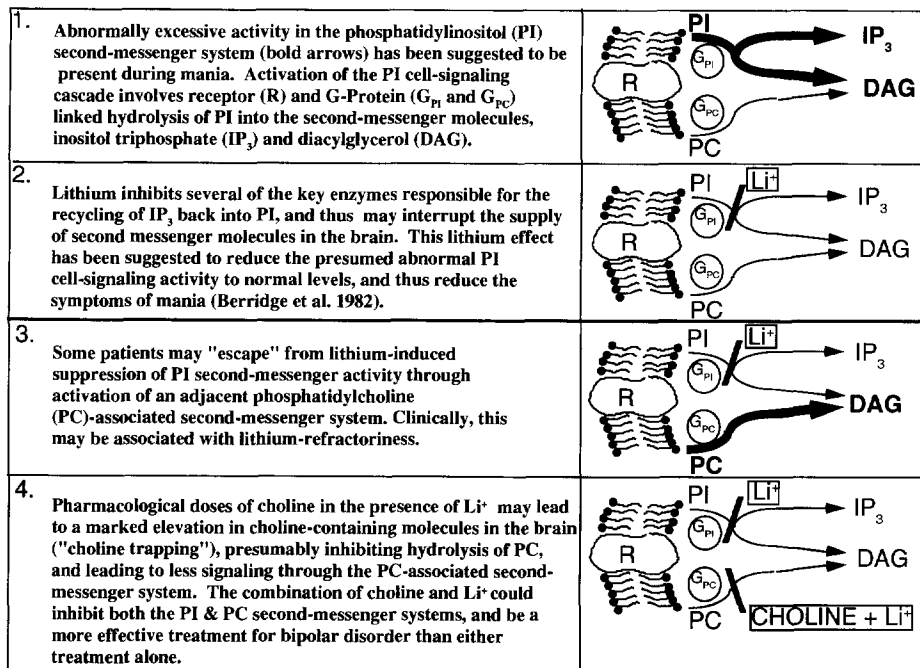


Figure 3. Hypothesis for choline and lithium action in refractory mania.

two second-messenger systems is that phosphatidylinositol hydrolysis occurs early, while phosphatidylcholine hydrolysis appears later and may be more sustained (Nakashima et al 1991).

It has been suggested that mania is associated with excessive activity in the phosphatidylinositol cell-signaling system, and that lithium treats mania by reducing phosphoinositol signaling to normal levels of activity (Berridge et al 1982). A study of activated macrophages has shown that if the phosphatidylinositol system is inhibited, the phosphatidylcholine system can compensate by becoming more active (Sands et al 1994). We hypothesize that during lithium-refractory mania some patients may "escape" from this lithium-induced suppression of the phosphatidylinositol system, by activating the phosphatidylcholine second-messenger system, which is less directly affected by lithium treatment (Figure 3). This mechanism could explain why some patients do not respond to lithium.

Increased brain choline concentrations due to pharmacologic treatment with choline may lead to enhanced synthesis of phosphatidylcholine and sphingomyelin, the two principal choline-containing phospholipids in neuronal membranes (Blusztajn and Wurtman 1983). Increasing the concentration of choline-containing membrane phospholipids, especially sphingomyelin, has been shown to alter membrane structure, and may lead to inhibition of phospholipase hydrolysis of phosphatidylcholine (Dawson et al 1985), and possibly less signaling through the

phosphatidylcholine system. Although it is speculative, we hypothesize that the combination of choline and lithium inhibits both the phosphatidylinositol and the phosphatidylcholine second-messenger systems, and may be a more effective treatment for mania than either therapy alone (Figure 3).

Choline is a precursor of the neurotransmitter acetylcholine, and this pathway provides an alternative explanation for the efficacy of choline precursors in mania. The "adrenergic-cholinergic balance" hypothesis suggests that mania is associated with cholinergic underactivity and adrenergic overactivity (Janowsky et al 1972). It has been suggested that administration of choline can enhance acetylcholine neurotransmission, and thus treat mania through this mechanism; however, recent data suggest that choline administration influences acetylcholine biosynthesis only when acetylcholine neurotransmission is active (Happe and Murrin 1993). Thus, if mania is associated with cholinergic underactivity, it appears uncertain whether acetylcholine activity would be significantly influenced by choline administration in this clinical state.

In summary, oral choline in the presence of lithium was an effective and well-tolerated antimanic agent and mood stabilizer in 5 of 6 consecutive patients with severe and chronic rapid-cycling bipolar disorder. Although it is unproven, lithium may be a crucial factor in the efficacy of choline in bipolar disorder. In addition, the 4 patients who responded rapidly to choline all exhibited a substantial rise in the resonance of choline-containing compounds in their

basal ganglia during choline therapy. The 2 initial nonresponders to choline did not exhibit a rise in the brain choline resonance during choline treatment, and were both also receiving suprathreshold thyroxine. In 1 of these cases the patient subsequently responded well to choline after reduction of thyroxine, and had an accompanying rise in his brain choline resonance. These findings require

confirmation in a double-blind, placebo-controlled protocol.

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