REVIEW ARTICLE

The Manic Syndrome: Factors Which May Predict a Patient's Response to Lithium, Carbamazepine and Valproate

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Studies suggest that 80% to 90% of all patients in the manic state respond to lithium provided that they are relatively free of dysphoria ("pure mania"). In contrast, less than 40% of individuals in the manic state who cycle rapidly or are substantially dysphoric ("dysphoric mania") respond to lithium. These patients appear to be more responsive to carbamazepine and valproate. The authors conclude that carbamazepine and valproate are the drugs of choice if one desires to treat a rapidly cycling individual or patient with dysphoric mania with just one agent. However, they emphasize that a prospective study designed to identify the predictors of response of primary mania to lithium, carbamazepine and valproate is required. Studies assessing the relative value of lithium, carbamazepine or valproate as prophylactic agents in the care of patients with specific subtypes of mania are also needed. These studies would address the most important issues confronting researchers interested in the drug treatment of mania.

Key Words: affective disorders, bipolar disorder, carbamazepine, lithium, mania, valproate

INTRODUCTION

Jean Pierre Falret (1854) vividly described a disorder of mood characterized by the recurrence of depressive and manic episodes, but his article was not published in English until 1983 (Sedler and Dessain 1983). Emil Kraepelin (1921) is consequently credited for having drawn one of the most fundamental distinctions in the history of psychiatry. Rare perspicacity lead him to recognize (as did Falret) that there are disorders of mood for which periodicity is the *sine quanon*. He distinguished these disorders from dementia praecox (schizophrenia) and labelled them as "manic-depressive insanity." All persons suffering recurrent episodes of depression, mania, or depression and mania were considered to have manic-depressive insanity. Leonhard et al (1962) later proposed that individuals who merely have recurrent episodes of depression have a disorder that is different from that afflicting persons with episodes of mania and depression. Mania and depression were thereafter referred to as unipolar and bipolar disorder, respectively.

Periodicity is elemental to both the concept of mood disorders and the care of those afflicted. Restoring patients with depression and mania to a state of euthymia is not generally a challenge. However, medicine is still deficient in its capacity to deal with all episodes of acute illness, let alone

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the enormous challenge of short-circuiting the processes which cause periodicity. In this paper, studies of the selection of pharmacological agents for the treatment of acute mania, given particular information about course of illness and clinical features on cross-section will be reviewed.

Mania can be devastating. A morbid risk of 1.2% (Weissman et al 1988) places it, by epidemiological standards, among common disorders. Although it has been a topic of study for much of this century, little is known about the clinical characteristics or attributes of the course of the illness which predict a patient's response to treatment. This constitutes a serious void in clinical medicine.

Introduction of lithium as a treatment for mania

Lithium was the first pharmaceutical to be recognized as having both antimanic properties and the capacity to favorably affect the periodicity of bipolar disorder (Angst 1970; Cade 1949; Prien et al 1973; 1988; Schou et al 1954). However, lithium is ineffective in the treatment of approximately 30% of those who endure episodes of mania. Many individuals who experience an acute antimanic response to lithium find its side-effects intolerable (Maarbjerg et al 1988; Polatin and Fieve 1971). This may render it useless as a prophylactic agent because of patients' non-compliance with treatment. There are also those unfortunate persons who have an excellent antimanic response to lithium and find its side-effects acceptable but for whom it is an inadequate prophylactic agent. All of these factors create a need for additional treatments that possess antimanic properties and are efficacious as prophylactic agents.

The ability of clinicians to predict whether a patient will not respond to lithium and will respond to other agents would clearly benefit the 30% who do not respond to lithium. Clinicians now have information at their disposal which makes this possible. The relevant studies are reviewed below.

Circumstances predicting a non-response to lithium

Lithium is of minimal utility for patients who cycle rapidly (Dunner and Fieve 1974; Dunner et al 1977) and who are concurrently depressed and manic (Himmeloch and Garfinkel 1986; Hemmelhoch et al 1976; Prien et al 1988; Secunda et al 1985; Swann et al 1986). The implications of these findings for clinical practice and directions for research will be discussed below.

Rapid cycling

Rapid cycling is operationally defined as a course of illness marked by four or more episodes of mania and depression in one year (Dunner and Fieve 1974). From the time of its initial description, rapid cycling was perceived to predict that a patient' would not respond to lithium (Dunner and Fieve 1974; Okuma et al 1975). Kukopoulos et al (1983) reported that only ten percent to 15% of their patients with mania who cycled rapidly responded to lithium. In contrast, Post et al (1987) reported that patients with frequent episodes during the preceding year were more likely to respond to carbamazepine (CBZ) than those who did not respond to CBZ. Similarly, Okuma et al (1979) reported that 78% of their patients who responded to CBZ cycled rapidly. They also noted that only 35% of their patients who cycled rapidly responded to lithium.

These studies suggest that rapid cycling predicts that a patient will respond positively to CBZ. Other studies have yielded conflicting results. Only about one-third of the rapid cycling subjects in some studies respond to CBZ (Joyce 1988; Kishimoto and Okuma 1985). The differences in rate of response between studies may be the result of many factors. Rapidly cycling patients may constitute a heterogenous population of individuals who share an attribute of course. Several pathogenic processes may produce rapid cycling. Response to treatment may be contingent on pathogenesis. The existing data do not allow researchers to address this possibility. Comorbidity of substance abuse, chronicity, age and prior treatment may also be related to a lack of response to CBZ.

Recent reports suggest that valproate (VPA) may be more effective than lithium in the treatment of manic patients who cycle rapidly (McElroy et al 1988a; Calabrese and Delucchi 1989). However, published data on the effectiveness of VPA, with two exceptions (Freeman et al 1992; McElroy et al 1988b), are exclusively from open and uncontrolled studies.

Rapid cycling patients have an interesting variant of the illness. The challenge posed by this phenomenon has attracted the attention of many clinicians. However, it is still important to note that rapid cycling patients represent a minority of those who do not respond to lithium (Keller et al 1986). The prevalence rate of rapid cycling ranges from five percent to 20% (Kukopoulos et al 1983).

Mixed states

Kraepelin (1921) and Falret (1854) observed that patients can be simultaneously manic and depressed. Kraepelin (1921) recognized that patients in mixed states were among the most severely ill of those suffering from affective disorders. This observation has been confirmed by contemporary students of psychopathology. Kotin and Goodwin (1972) reported finding a positive correlation between the severity of manic symptomatology and depressive symptomatology. Recent studies have also suggested that patients with concurrent depressive and manic syndromes or significant depressive symptomatology respond poorly to lithium (Himmelhoch and Garfinkle 1986; Prien et al 1988; Secunda et al 1985; Swann et al 1986).

There are now three common definitions of "mixed" or "dysphoric" mania. The first definition is the most stringent; it defines mixed mania as a state in which full depressive and manic syndromes coexist. For instance, we define mixed

mania as a state in which a patient simultaneously meets the criteria for both major depressive disorder (MDD) and mania, as defined in the Research Diagnostic Criteria (RDC). The RDC stipulate that the signs and symptoms of a depressive syndrome must persist for at least seven days to warrant the diagnosis of MDD. "Manic dysphoria" is characterized by the concurrence of the manic syndrome and depressive symptoms. A patient need not meet the operationally defined criteria for a depressive syndrome. Patients with manic dysphoria often meet all the criteria for a depressive syndrome except the duration of the illness. Finally, extreme rapid cycling is characterized by several shifts between the manic and depressed state in the course of the day.

Responsiveness of dysphoric mania to lithium

Goodwin and Jamison (1990) reported that 40.1% of 506 subjects from eight major studies published between 1969 and 1989 were in a mixed state. Their review included one study in which the prevalence rate of mixed mania was only 16% (n = 61) (Winokur et al 1969). Particularly stringent criteria were employed. The incidence of mixed mania among the 506 subjects rose to 48% if less stringent but typical criteria were used to classify the subjects. Six major studies assessing the efficacy of lithium as a treatment for mania were published after 1971 (Beigel and Murphy 1971; Himmelhoch and Garfinkel 1986; Prien et al 1988; Post et al 1989; Secunda et al 1985; Swann et al 1986). Two of these studies (Prien et al 1988; Post et al 1989) were included in the eight studies (151 of the 506 subjects) reviewed by Goodwin and Jamison. Forty-seven percent (range = 31% to 57%) of the patients in these outcome studies were categorized as having mixed or dysphoric mania.

Prien et al (1988) reported that the percentage of patients with dysphoric and non-dysphoric (pure) mania who completed a course of therapy with lithium alone were 39% and 59%, respectively. Twenty-two percent of the dysphoric subjects and 94% of the non-dysphoric subjects eventually had a positive response to lithium. Secunda et al (1985) reported that 28% of their subjects with mixed mania and 90% of their subjects with pure mania ultimately responded positively to therapy with lithium alone.

A survey of the literature reveals that the relative rates of response of patients with dysphoric or mixed and pure mania to an optimal trial of lithium are 15% to 25% and 85% to 90%, respectively. These figures, coupled with estimates of the incidence of dysphoric mania among the subjects in the outcome studies published since 1971 suggest that patients with dysphoric mania constitute the largest group of subjects who do not respond to lithium.

The results of the National Institute of Mental Health collaborative study on the psychobiology of depression (Secunda et al 1980) indicated that the manic syndrome was generally more severe among subjects with mixed than among those with pure mania. Swann et al (1986) studied the responses of 19 manic subjects in this study. Repeated behavioral and biological evaluations were conducted during a 15-day placebo run-in period. The placebo run-in phase was followed by 24 days of treatment with lithium. Eight of the 19 patients had dysphoric mania. These individuals had nursing ratings of the global severity of depressive symptoms and Hamilton Rating Scale for Depression (HRSD) scores characteristic of depressed patients (Secunda et al 1985). Ten of the 11 subjects with pure mania and two of the seven subjects with mixed mania responded to lithium (Fisher's exact test, $p = 0.01$). One patient with mixed mania had an indeterminate response.

The subjects who did not respond to lithium had higher pre-treatment scores for anxiety, depression and somatization. The HRSD scores of the subjects who failed to respond to lithium were also higher than the scores of those who responded to lithium. The findings suggested that dysphoric mania is associated with a poor response to lithium (Swann et al 1986). However, the size of the sample did not allow the investigators to determine whether the poor response of the subjects with mixed mania was a function of the severity of the illness or other factors.

CONCLUSIONS

Studies suggest that the responses to lithium of patients with dysphoric or mixed mania are inferior to those of patients with pure mania. This could be the result of a biological characteristic that is unique to dysphoric mania or merely a function of the severity of the illness. Manic syndrome is generally more severe among dysphoric subjects than non-dysphoric subjects. The studies published to date involve too few subjects to determine whether or not dysphoria contributes independently to a lack of response to lithium.

Alternatives to lithium

Carbamazepine

The limitations of lithium as a treatment for acute mania provide an impetus to develop new agents and treatment strategies. Carbamazepine may be effective for many patients who do not respond to lithium. Potential predictors of response to CBZ are rapid cycling, a negative family history of mania and greater severity (Post et al 1987).

The results of retrospective studies of the efficacy of carbamazepine in the treatment of rapid cycling patients are far from definitive. Kishimoto and Okuma (1985) observed that only a minority of rapid cycling patients have a positive response when treated with CBZ for mania. The long-term outcome may be even more dismal (Wehr et al 1988).

Post et al (1987) retrospectively assessed the relationship between dysphoric presentation and response to CBZ. The subjects with dysphoric mania tended to have a better response to CBZ than the patients with pure mania. The

results of this study suggest that CBZ may be most effective for patients who generally respond poorly to lithium.

There is little information on the response of manic patients to CBZ and lithium. The available data suggest that the overall rates of response to these two agents are similar (Okuma et al 1975; Prien and Gelenberg 1989; Lerer et al 1987; Lusznat et al 1988). However, the critical issue now is not whether the rate of overall response to CBZ is equal to or greater than that to lithium; rather, it is whether or not manic subjects with certain clinical features or attributes of course tend to respond to a given agent. The results of a prospective study to address this issue have yet to be published.

Valproate

Recent results suggest that VPA may be an effective treatment for mania (Brennan et al 1984; Calabrese and Delucchi 1989; McElroy et al 1987; 1988a; 1988b; 1989; Pope et al 1991). A prospective study designed to address the issue of whether specific clinical features or characteristics of course predict a response to VPA has not yet been published. However, the case reports and results of retrospective studies are encouraging.

McElroy et al (1988a) reported that three rapid cycling patients who did not respond to lithium did well for periods of three to 25 months when treated with VPA. Calabrese and Delucchi (1989) reported that mixed and rapid cycling outpatients generally did well when treated with VPA.

McElroy et al (1992) reviewed the results of 29 uncontrolled studies and five controlled studies of the efficacy of VPA as a treatment for mania. An estimated 419 of the 633 patients (63%) in the controlled studies had a significant response to VPA. Twenty-eight of the 45 subjects (62%) receiving VPA in the double-blind, controlled studies exhibited a marked or moderate response. Eighteen of the subjects receiving VPA participated in two studies reported during the last 18 months (Pope et al 1991; Freeman et al 1992).

Pope et al (1991) assessed the efficacy of valproate as an antimanic agent in a study of 43 subjects randomly assigned to receive either a placebo or VPA. Seventeen subjects who received VPA and 19 who received a placebo completed at least seven days of the trial. The subjects who received VPA exhibited a median reduction of 54% in their scores on the Young Mania Rating Scale (YMRS). The subjects receiving a placebo displayed a median reduction of only five percent in YMRS scores. An efficacy analysis was also performed using the entire sample of 43 subjects; it was found that the 20 subjects who received VPA had a significantly greater improvement as a group. Another analysis compared the response of 25 subjects who completed ten or more days of the study and whose final ratings were completed at least 24 hours after they had received a dose of lorazepam. Thirteen received VPA and 12 received a placebo. The VPA group once again had a significantly greater improvement.

Freeman et al (1992) conducted a double-blind study in which subjects were randomly assigned to either VPA or lithium for 21 days. Twenty-seven patients completed the study: 14 received valproate and 13 received lithium. A positive response was defined as a reduction in the Schedule for Affective Disorders and Schizophrenia – change version (SADS-C) mania factor and Brief Psychiatric Rating Scale (BPRS) scores to 40% of baseline. Nine of the 14 patients treated with VPA had a positive response. The subjects who responded to VPA had higher SADS-C depression factor scores before treatment (mean score of the VPA responsive and non-responsive subjects $\pm$ SD = 26.2 ± 4.9 and 7.1 ± 2.8, respectively; $t = 2.3$, $p < 0.05$).

Each of the four subjects with mixed mania responded to VPA, compared with only five of the ten subjects with pure mania. Twelve of the 13 subjects (82.3%) who were treated with lithium had a positive response. The one patient who failed to respond to lithium was in a mixed state. At the conclusion of the trial, the subjects with mixed mania who were treated with lithium had higher residual mania factor scores than the patients with pure mania (18 ± 4.5 mixed mania versus 6.7 ± 8 pure mania; $t = 2.3$, $p < 0.05$). This was true even of the subjects who had a positive response. These data suggest that VPA may be more effective for treating mixed mania than pure mania.

Questions raised

The studies reviewed raise many questions which can be addressed prospectively. Do specific attributes of course predict responsiveness to lithium, CBZ or VPA? Do patients who are responsive to lithium, CBZ or VPA differ with respect to the global severity of the manic syndrome? Is the severity of dysphoria related to responsiveness to lithium, as opposed to CBZ or VPA? Do specific characteristics of the manic syndrome other than dysphoria and severity predict a response to lithium, CBZ or VPA? Are there discernable differences between patients who respond to CBZ but not VPA and vice versa? What are the most useful operational definitions of "dysphoric" and "mixed" mania?

CONCLUSION

A highly significant proportion of patients with mania do not respond well to lithium. Many of these patients may have dysphoric mania. The anticonvulsants carbamazepine (Ballenger and Post 1978; 1980; Joyce 1988; Okuma et al 1979; 1981; Post et al 1983; 1984; 1985; 1986; 1987; 1989; Post and Uhde 1985) and valproate (Calabrese and Delucci 1989; Emrich et al 1980; 1985; McElroy et al 1987; 1988a; 1988b; 1989; Pope et al 1991; Freeman et al 1992) are now widely used to treat patients whose history and clinical presentation indicate that they will not respond to lithium.

The literature, albeit inadequate to generate conclusions, can justify some recommendations. CBZ and VPA may be the drugs of choice among the currently available pharmacological treatments should one opt to treat a patient with

dysphoric or mixed mania with one agent alone. It is important to note that there are as yet no adequate comparisons of the relative rates of response of patients with manic syndrome to lithium and CBZ or VPA in which possible clinical predictors of treatment responses are taken into account. The literature is also essentially devoid of information on the relative value of lithium, CBZ and VPA as prophylactic agents for patients with specific subtypes of mania. These are two of the more important practical problems confronting investigators interested in the pharmacological treatment of mania.

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