

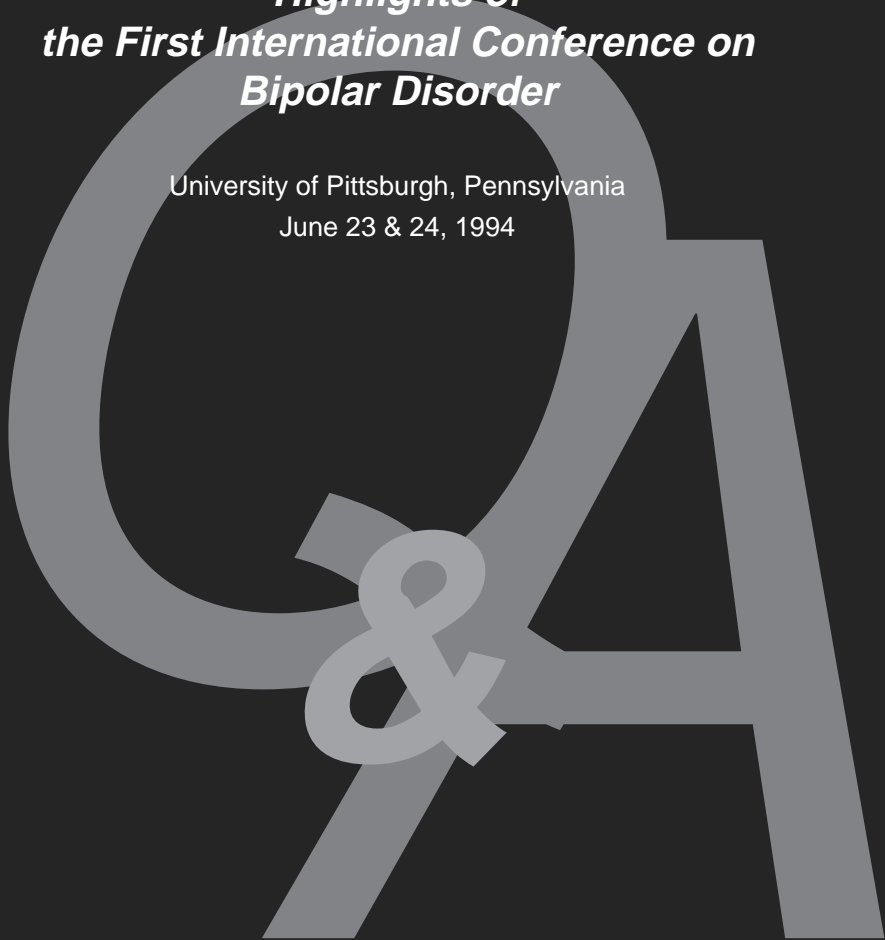


# Bipolar Depression

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*Highlights of  
the First International Conference on  
Bipolar Disorder*

University of Pittsburgh, Pennsylvania  
June 23 & 24, 1994



# Introduction

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Bipolar disorder is a chronic disorder that affects approximately one per cent of the world's population, afflicting both males and females. The onset of bipolar disorder usually occurs between 20 to 30 years of age, with a second peak in the mid-40s for women. Typically, a patient with bipolar disorder will experience approximately eight to ten episodes of mania or depression in his or her lifetime. Some patients, however, have rapid-cycling disorder and experience many more episodes of mania or depression.

Early recognition of bipolar disorder, which can be misdiagnosed as schizophrenia, personality disorder, or alcohol or drug abuse, and effective treatment of the acute episode are important due to the increased risk of suicide in untreated or inadequately-treated patients. For many years, the mainstay of treatment has been lithium, which acts to stabilize the cyclic nature of the disease. However, it has been reported that as many as 20 to 40 per cent of bipolar patients fail to respond to lithium therapy. Moreover, breakthrough depression commonly occurs in patients on lithium, which may necessitate the use of antidepressant drugs or electroconvulsive therapy. Alternative forms of therapy are anticonvulsant drugs such as carbamazepine or sodium valproate. These compounds are also associated with breakthrough depression.

The use of classical antidepressant drugs such as tricyclics and monoamine oxidase inhibitors (MAOIs) in patients with bipolar disorder has been found to increase the incidence of rapid-cycling. These drugs also carry the potential of serious side effects. For example, overdoses of tricyclics have been associated with cardiovascular toxicity, and the risk of hypertensive crisis is great in patients taking MAOIs with foods containing tyramine. Further studies are necessary to document greater efficacy for the selective serotonin reuptake inhibitors (SSRIs) in bipolar depression as compared to the tricyclics or MAOIs. SSRIs have fewer anticholinergic, sedative, hypotensive, and cardiac effects than the tricyclics, owing to their high selectivity for serotonin reuptake activity.

Many of these treatment findings and other aspects of the illness were presented at the First International Conference on Bipolar Disorder which was held in Pittsburgh, Pennsylvania on June 23 and 24, 1994. Approximately 500 clinicians and scientists from around the world gathered to learn more about the latest research findings from a distinguished faculty of investigators from the United States and abroad. As part of this conference's scientific program, seven experts were asked to present brief overviews of their area of expertise and to answer questions from the audience during informal "Ask the Experts" sessions. Occasionally questions were answered by members of the audience. This booklet contains a summary of each of these presentations and the question and answer periods that followed. Discussions addressed a breadth of issues, including diagnosis, genetics, and family intervention techniques. Particularly in the area of treatment, the opinions shared by the invited faculty offer the reader several strategies for the treatment of patients with bipolar disorder.

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# Differential diagnosis of bipolar disorder

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Two-thirds of bipolar episodes begin with depression; whenever you see a person who is depressed, you should ask yourself: 'Is this person going to be bipolar?'

The key factor in the differential diagnosis of bipolar depression is the age of the patient at onset. Depression in adolescents, particularly psychotic depression, predicts an outcome of bipolar illness so reliably that one might almost say any patient who has a psychotic depression in adolescence is suffering from bipolar disorder until proven otherwise. In fact, there is often a bipolar element to any psychotic episode in adolescents. For example, a certain number of adolescents have attention deficit disorder, which may actually be an early manifestation of bipolar illness.

Since the onset of schizophrenia usually occurs between the ages of 20 and 30 years, schizophrenia must be high on the list of differential diagnoses in patients who become ill in early adulthood. However, the race of the patient should be taken into account in making the diagnosis. For example, African-Americans tend to be over-diagnosed as schizophrenic and under-diagnosed as manic. One must, therefore, guard against labelling a psychotic individual as schizophrenic when he or she might be bipolar. Also, in the early-adult age group, women who have post-partum depression are at particular risk of developing bipolar illness.

In the elderly, primary mania has to be differentiated from confusion. About one-third of patients with mania are disoriented during their manic episodes, and so a confusional psychotic state that is not alcohol- or drug-related may be primary mania with an underlying diagnosis of bipolar disorder. Most elderly people who become manic with a diagnosis of bipolar illness have a history of depression earlier in life. They may have their first episode of mania in their 60s but they probably have a history of major depression in their 40s or 50s. In the elderly age group, it is necessary to exclude secondary mania due to an underlying organic disorder. Co-morbidity is also an important issue, particularly in the elderly.

The correct diagnosis of bipolar depression is clearly not easy. Recreational drug use and alcohol abuse are relatively common among bipolar patients and add to the difficulty by masking the underlying condition. Some doctors believe that certain symptoms such as hypersomnia and increased appetite differentiate patients with bipolar disorder from patients with schizophrenia or personality disorders and from alcoholics and drug abusers. Family history tends to provide the best validation of the diagnosis. Family members of most individuals with bipolar disorder have a history of depression rather than mania, whereas there is less mania and depression in the family history of schizophrenic patients, for example.



## Questions and answers

**Q** How do you distinguish hypomanic episodes in bipolar disorder from normal 'hypomanic' feelings such as falling in love or winning the lottery?

**A** Firstly, even if someone feels happy or joyful about something, the feeling does not normally remain constant over a whole day or for two to three days as in hypomania. Secondly, patients with true hypomania are very distractible, they do not follow through on anything, and can be incapacitated for three or four days as a result. Such euphoria and distractibility, possibly combined with talking too much and too loudly, or having fast thoughts, indicate true hypomania. It is useful, however, to try and obtain some collateral information rather than relying solely on the patient's own account of their symptoms. Ask for example, 'Has anyone else commented on your mood being abnormal; said you are talking too much, too loudly, being a pain?'

**Q** How do you differentiate between an episode of normal acute grief and an episode of major depression?

**A** It would be hard to distinguish major depression from bereavement during the first month after the loss of a child, a spouse or a parent. Not many patients who are grieving normally have symptoms of retardation or psychotic symptoms, so either of these would indicate a treatable condition. Three to four months after the bereavement, the symptoms of grieving should be diminishing. At this stage, feelings of worthlessness and hopelessness are not part of normal acute grief. Somatic symptoms of depression such as disturbances of sleep and appetite can occur, however, and may be persistent, with sleep disturbance continuing for up to two years.

**Q** Do you think that the very low rates of co-morbid personality disorder in bipolar illness are genuine, given that rates are much higher in major depression?

**A** There is a personality difference between patients with bipolar disorder and those with unipolar depression. Studies have shown that patients with unipolar depression tend to have depressive personalities, even after 15 years' follow up (when patients were no longer sick). Compared with patients with unipolar depression, patients with bipolar depression have more normal personalities, though they tend to rate themselves a little more highly and to think that their sexual activities are better. I think they do have a tendency to be obsessional, but they are by-and-large more stable than patients with unipolar disorder.

**Q** How do you make the differential diagnosis between bipolar disorder and cluster B personality disorders, predominantly narcissism and borderline states?

**A** Bipolar disorder is an episodic illness. It is also seasonal, with depression occurring more often in the autumn or winter and mania in the spring or summer. So seasonality or an episodic course are more associated with bipolar illness than a borderline state. Personality disorder is a more constant feature; as it is a part of the individual, it tends not to fluctuate in this way. Hyperactivity and over-talkativeness are other good diagnostic symptoms for bipolar disorder which are not usually features of a borderline personality.



## Questions and answers

**Q** How would you classify schizo-affective patients who started out with a clearly bipolar illness and developed a chronically psychotic illness over time? Are they truly bipolar or has their diagnosis changed?

**A** Chronically psychotic patients are more likely to be schizophrenic than bipolar. I cannot think of many patients who started off with a clear diagnosis of bipolar disorder and subsequently became schizo-affective. From the point of view of family history and age of onset, for example, schizo-affective mania usually looks like mania. However, on follow up many patients with schizo-affective depression turn out to be schizophrenic. Of course, grandiosity can be misleading. It may sometimes seem to be a sign of mania, but it is also among the characteristics traditionally ascribed to schizophrenia. The core elements of mania are the characteristic hyperactivity and pressure of speech.

**Q** Observation of a mood-incongruent delusion or hallucination often leads to a diagnosis of schizophrenia, particularly in adolescents. What are your views on mood-incongruent psychotic symptoms in bipolar patients?

**A** DSM-III, -III-R and -IV classification systems all allow for mood-incongruent psychotic symptoms in bipolar disorder. A key consideration is that mania is an acute illness, so that a person who is well and then suddenly gets sick in their teenage years is more likely to be manic than schizophrenic. In contrast, the onset of schizophrenia is usually more insidious: patients initially have some anxious or depressive symptoms, then they begin behaving in a peculiar way, and later you can elicit evidence of strange ideas.

# Treatment of refractory and rapid-cycling bipolar disorder

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In the early 1970s, publications began to appear suggesting that patients with more than four cycles of bipolar disorder per year did not respond very well to lithium. 'Rapid-cycling' was therefore recognised as a lithium-resistant subgroup of bipolar disorder and alternative modes of treatment were tried. First among these was the anticonvulsant carbamazepine. Around 1975 we published a series of some 90 cases of bipolar disorder, half of whom did not respond to lithium. Sixty-five per cent of the lithium-resistant patients responded to carbamazepine. More recently, we published a series in which 60 to 80 per cent of patients who did not respond either to lithium or to carbamazepine responded to sodium valproate. The addition of these two compounds to the choice of drugs used to treat bipolar disorder significantly extended the range of patients who could be successfully treated. There is no strict algorithm for lithium-resistant patients. Some patients do well on either carbamazepine or sodium valproate, others respond to one and not the other.

There are also, of course, patients who are either unresponsive to, or intolerant of, both these agents. What is the next step? A number of patients who do not respond to either carbamazepine or valproate alone do respond to a combination of the two. However, this combination can be problematic, because blood levels of valproate are rapidly decreased due to the enzyme induction caused by carbamazepine. Sodium valproate, on the other hand, may displace protein-bound carbamazepine, increasing free serum levels and thereby also increasing liability to toxicity.

A third group of drugs that has been used more recently is the calcium channel blockers (CCBs). In my experience, CCBs have sometimes achieved responses when added to existing therapy. A CCB with preferential absorption in the brain should be selected. If the patient fails all of these approaches, the question arises: 'When do you reach for the neuroleptics?' If a patient has a psychosis associated with recurrences of their bipolar disease, or is not able to be successfully managed by other measures, the use of a neuroleptic is appropriate.

Electroconvulsive therapy (ECT) should also be considered, even if only as an emergency measure. It can be hard to persuade patients to continue with maintenance ECT, but it can be effective in refractory mania or in cycling or suicidal depression.



## Questions and answers

**Q** There have been reports of the successful use of high-dose thyroxine for the treatment of refractory bipolar disorder. Could you comment on these?

**A** Initial reports from Norway as long ago as the 1930s concerned the use of high-dose thyroxine in what might be called a thyroid shock treatment. My own experience with thyroxine has been rather disappointing but there have been reports that in some patients with long histories of bipolar disorder, doses of thyroxine of the order of 500  $\mu\text{g}$  have blocked rapid-cycling. Some practitioners have titrated to 150 per cent of normal serum levels of thyroxine but this strategy carries a risk of endocrinological disturbance and has been criticized by endocrinologists. Lower doses of thyroxine in the range 100 to 125  $\mu\text{g}$  are, therefore, more commonly used but there are absolutely no reliable data to support the efficacy of this approach.

**Q** In refractory patients taking lithium and anticonvulsants, can either be stopped?

**A** I have patients for whom I can justify empirically keeping them on lithium, carbamazepine and sodium valproate. Once I have a patient on all three drugs and I am getting a good result I am reluctant to stop any of these agents because the patient may relapse and subsequently be difficult to stabilize. There are, however, some patients who find it difficult to tolerate lithium. If that is the case, I would certainly discontinue lithium and continue with anticonvulsant therapy.

A frequent clinical situation involves a young female patient who wants to stop taking medication because she wishes to become pregnant. It is important to consider in detail with the patient the risks of relapse if medication is discontinued and the likely consequences for the family as a whole. This can be particularly difficult if the consultation follows the first episode, when the patient's perception may be that recovery has occurred and there is no further need of medication. The psychiatrist's view might be that the course of the disease in a patient with early onset is likely to be recurrent and prophylaxis is needed.

**Q** What proportion of bipolar disorder can be identified as refractory to lithium and how are these cases characterized? Are they all rapid-cycling?

**A** The proportion of bipolar disorder that is resistant to treatment with lithium seems to be increasing, although this apparent increase may be an artifact. In the early 1970s the use of lithium was regarded by some psychiatrists not only as treatment but as a diagnostic tool: if the disease did not respond to lithium it was not bipolar disorder. This false point of view could certainly have led to a substantial under-diagnosis of bipolar disorder, with a corresponding failure to recognize the true incidence of lithium-refractory disease. One other possible reason is that an increasing number of resistant forms of the illness may be emerging. There was an epidemic of substance abuse during the 1960s and 1970s, first with amphetamines and later with cocaine; we know that there is a high degree of substance abuse in patients with bipolar disorder, and also a lot of alcoholism, either of which may make the illness worse.



## Questions and answers

Rapid-cycling is not the only category of bipolar disease that tends to be refractory to treatment. Mixed dysphoric mania, for example, which is as prevalent as rapid-cycling, can also be difficult to treat. Not all patients with either of these characteristics are necessarily resistant to lithium, but a high proportion of them are likely to be.

**Q** What are the current views about the association between the use of antidepressants and the onset of mania or rapid-cycling?

**A** Most psychiatrists would agree that there is a risk of precipitating mania or rapid-cycling in bipolar disorder with the use of certain antidepressants. It is difficult to estimate the rate at which this occurs because in the research-setting one tends to see a highly selected population made up mainly of the more problematic patients. However, I would put the risk of triggering rapid-cycling with classical antidepressants at about 15 to 20 per cent in general psychiatric practice, rising to around 50 per cent in specialist research units and clinics for refractory patients.

Most of the evidence concerning induction of rapid-cycling relates to tricyclic antidepressants, but there are now some reports of a similar triggering of mania or rapid-cycling with other classes of antidepressants, such as monoamine oxidase inhibitors (MAOIs), heterocyclics and some selective serotonin reuptake inhibitors (SSRIs).

**Q** Can neuroleptics trigger mania or rapid-cycling in the way that tricyclic antidepressants have been reported to do?

**A** Tolerability of neuroleptics can be an issue with bipolar patients, but I have not encountered mania or rapid-cycling induced by neuroleptics. However, I have the impression that, on occasion, depression might have been triggered in a patient with bipolar disorder by the use of a neuroleptic.

Some doctors have suggested that patients with bipolar disorder are 'neurochemically brittle' and have a propensity to suffer side effects not only with antidepressants but also with neuroleptics. Those who subscribe to this view suggest that low doses of either class of drug may be both sufficiently effective and better tolerated in patients with bipolar disorder.

# Genetic counseling in bipolar disorder

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Genetic counseling is currently used more in North America than Europe. Even in North America, though, the link between genetic counseling and psychiatry is only now beginning to be made. What this new association can offer is an approach to risk analysis for families with a history of psychiatric conditions. As bipolar disorder is among the psychiatric illnesses that run in families, it is obviously a condition in which genetic counseling is directly relevant. The only center of genetic counseling devoted specifically to genetic risk-assessment of psychiatric conditions is at Washington University in St Louis. A psychiatric risk-assessment model based on empirical data about family histories is being developed. By entering details of age, gender and family psychiatric history of an individual, this model will give an estimate of the risk for an individual to develop a psychiatric condition during the next five years and in subsequent five-year intervals. The risk to family members and for intended children can also be determined.

Use of genetic counseling in psychiatry differs from some of the other traditional genetic models in that the risk assessment is not as precise (there is no blood- or gene-test available); however, for many of the psychiatric conditions a treatment does exist. With Huntington's Disease, for example, accurate predictions can be made but there is no treatment. The use made of the information is clearly affected by these differences. The development of gene tests for some psychiatric disorders may be expected during the next 10 years or so. However, it is unlikely that the model for a given psychiatric disorder will be a simple one of a single gene or of transmission from generation to generation. There will be complex interactions between hereditary and environmental factors. Both will figure in the construction of computerized models such as that being developed at Washington University. In this way, gene tests will complement empirical information by enabling the development of a more accurate and complete risk assessment.



## Questions and answers

**Q** What is the likelihood that a gene will be identified for bipolar disorder?

**A** There is probably a genetic component in bipolar disorder, but this is almost certainly polygenic, meaning that a single gene is unlikely to be identified. In any single individual, a combination of genetic factors needs to be present and to be acted upon by one or more environmental factors. If some or all of the genetic elements are identified, it may be possible to offer appropriate tests and to counsel individuals accordingly on their risk of developing bipolar disorder. Healthy individuals with a family history suggesting a risk of bipolar disorder, for example, may wish to know whether they themselves carry genes which put them at particular risk. Once the genetic part of this equation is clarified it may also help to define the environmental part, which in turn may aid the development of scientifically based treatment and prevention.

**Q** What do you tell people who ask you about their genetic risk of bipolar disorder?

**A** I always explain that there is no definitive answer to this kind of question. I say that in many families a bipolar condition can be inherited. I try to give up-to-date empirical data, which changes over time, and is affected by the sex of the individual and the number of their relatives who are affected. I start from a position of 50:50 risk and modify it accordingly. However, the computerised models on bipolar disorder are not yet sufficiently robust to allow us to use them to give accurate risk predictions.

**Q** Gene therapy is already in clinical trials for cystic fibrosis. Could gene therapy work for a psychiatric disorder like bipolar disorder?

**A** The defect in cystic fibrosis is one involving multiple deletions (missing pieces of DNA) in a single gene. Affected individuals have two defective copies of the same gene. This gene is responsible for the production of proteins with key roles in the normal functioning of the gut and the lung. One of the affected areas, the lung, is readily accessible and its surface is susceptible to certain viruses which can be used as vectors for the insertion of DNA into cells. This is the basis upon which this condition was chosen for trials in gene therapy. Theoretically, under these circumstances a definitive genetic correction could be made. Unfortunately, early research indicates that the effect of gene therapy in cystic fibrosis is not as long term as hoped for.

Psychiatric conditions are likely to differ from the cystic fibrosis model of gene therapy in several important respects. Firstly, they are likely to involve more than one gene. Secondly, the affected organ is not easily accessible. Thirdly, the genetic defects may not be simple deletions or may involve irreversible abnormalities. If, for example, a defect had occurred in a developmental gene, it may be that the brain was 'wired' in an abnormal way during its growth, such a defect could not be corrected by the subsequent replacement of a protein. By contrast, if there was a simple deficiency of a certain type of receptor, for example, that was determined by a single gene, one might envisage a role for gene therapy.



## Questions and answers

**Q** How aware is the general public about genetic issues in psychiatry? Can the lay public be educated on this field or is the subject too complex?

**A** The most current journals on genetics in the United States are Newsweek and Time, which have both been publishing information about the latest genetic discoveries in psychiatry. As a result we get calls from patients and their families, asking whether we can perform particular genetic tests, or if not who can, and so on. I believe people can be educated. In about an hour, it is possible to impart the basic principles about inheritance and risk and the perception of risk to the majority of people. Having understood it, however, some people do not wish to take risk assessment any further and people should have the right not to be tested.

# Bringing family members into the treatment alliance

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A psychotic episode like bipolar disorder in a relative can be disastrous for the whole family. It produces a state of disorganization in individual family members and in the family as a whole. Relatives are not only important resources to aid in treatment but also people with needs themselves who have to deal with very serious problems. Family involvement should, therefore, be a routine part of the post-hospitalization care of every patient. We use a psychoeducational model to assist in the re-organization of the family system, including the patient, following the disruption caused by a psychotic episode.

Our guiding principle is that, in contrast to traditional family therapy, we need to try to put things back together, rather than unravel what is going on. This requires a fairly structured approach. Our 'psychoeducational model' involves more than just giving out information, it includes using psychotherapeutic skills to deal with the emotions that the information often stirs up. We also attempt to restore basic communications within the family; people are often no longer sure whether they can talk without triggering extreme reactions.

We do not consider that patients with bipolar disorder have recovered when they leave hospital. We think they are usually in partial remission, and that recovery takes place during the ensuing months. They are unstable, and unless you have a psychosocial support plan in addition to medication, recovery does not proceed smoothly. During the recovery period, we have five underlying objectives:

- 1 The family and the patient need to integrate the psychotic experience. This means having a degree of understanding, and not denying or burying the experience. This is achieved through promoting open family dialog.
- 2 The family and the patient need to accept that there is a vulnerability to future episodes. This can be a tremendous narcissistic injury and requires skillful handling by the therapist.
- 3 The individual has to accept dependence on psychotropic medication for symptom control.
- 4 The patient and the family should try to identify stressful life-events as potential triggers for the onset of the disorder (and therefore for recurrences). People often do not make these connections of their own accord.
- 5 Finally, it is vital that the person be helped to appreciate their assets and valuable qualities that are not part of the disorder.



## Questions and answers

**Q** When do you start to deal with the family, and how long do you spend with them? How do you approach the objectives you have set yourself?

**A** We meet the patient and the families while the patient is still in hospital and we follow them for a year. During the initial recovery period - say the first three months - we try not to make too many demands; no big decisions. We concentrate on getting the patient to feel better, and getting the family back into a routine. In the longer term we then try to improve coping skills, stress management, problem-solving and communications. We encourage open dialogue about bipolar disorder, which is where education comes in, and try to integrate the family's recent experience. This can lead to quite heated argument in the family. We also, therefore, have a role as mediator. Later we focus on life events as potential triggers, and we use a very systematic approach to this, with checklists of likely events drawn from the literature. Finally, and this is the major element of education in our strategy, we present a vulnerability-stress model of bipolar disorder to the family, saying that we see at least two pieces to the puzzle: one being a biological or chemical vulnerability and the other being an environmental stress which, when they interact precipitate episodes of mania or depression. This leads us naturally on to discuss the likelihood that there may be a recurrence. To counterbalance this negative aspect, we go through the ways that the family and the patient have of controlling the bipolar disorder: mainly medication and the management of stress.

**Q** Patients and their families are often very resistant to the idea that there may be a recurrence. How do you deal with that?

**A** We tend to use psychotherapeutic techniques. We normalize the desire not to accept this information by saying things like 'We realize this is very painful. We realize no one likes the idea that in the future they may be vulnerable to another episode and you should struggle with this. This is a healthy and normal struggle for you to be having.' In this way, we give people room to deal with it, rather than saying 'You just have to accept what we say; that's the way it is'.

We approach potential compliance problems the same way, by saying 'It is healthy to struggle against medication and try to manage yourself without taking biological agents. That's a normal struggle that anybody goes through with hypertension, diabetes, and so forth.' If you don't bring out these issues as normal struggles with personal identity, self-control, desire to be autonomous and so forth, then you may suddenly find you have somebody who is non-compliant and not participating.



## Questions and answers

**Q** What is your success rate?

**A** Firstly, we don't have any dropouts. I think the reason for this is that the family makes sure the patient gets to the sessions. Secondly, the rate of medication compliance during our programme is extremely high, and most of these people are in much better clinical shape at the end of it. However, there may be certain individuals for whom a one-to-one approach may be better, with the family staying out of the programme, except perhaps to receive some education separately.

We have been using this approach for about four years now, and although we are not yet ready to give a definitive report on its success or otherwise, we are pleased with the results achieved so far.

**Q** Isn't your program very costly?

**A** In Los Angeles it costs \$1000 a day to keep a patient in the hospital. Most of our patients have not been hospitalized during the year they spend in our program, and very few in the year after the program. Our program may indeed appear costly because it is labor intensive: patients and families may be seen 20 times at \$100 an hour. But this only represents the cost of two days' hospitalization. Seen in this perspective, the program may be considered cost-effective.

# General clinical approach to bipolar patients

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Lithium has been the mainstay of treatment for bipolar disorder since its introduction in the 1960s. The key function of lithium salts is to stabilize the characteristic cycling in bipolar disorder. Even in stabilized patients, however, breakthrough episodes of mania or depression may still occur, and these require specific therapy. Some 20 to 40 per cent of patients with bipolar disorder are unresponsive to lithium and a certain number of other patients are unable to tolerate the drug due to side effects such as thirst, polyuria, edema, weight gain, nausea and diarrhea.

Anticonvulsant drugs are now widely used, either as adjuncts to lithium or as substitutes for lithium in the treatment of bipolar disorder. The most commonly used are carbamazepine and sodium valproate. Failure to respond to one of these does not preclude a response to the other, and some patients require both. The response rate to these anticonvulsants is about 50 per cent in lithium-resistant patients and there is some evidence that patients who respond poorly to lithium are more likely to respond to carbamazepine. Other compounds with anticonvulsant properties which have been used in bipolar disorder include phenytoin, acetazolamide, verapamil, clonazepam and lorazepam.

Both lithium and the anticonvulsants are more effective in controlling mania and in stabilizing cycling than in treating the depression of bipolar disorder. It is, therefore, often necessary to use an antidepressant drug in this condition. Unfortunately, there is evidence that use of some antidepressants in bipolar disorder carries with it a significant risk of precipitating mania or rapid-cycling, which can then be difficult to control. Initially this induction of rapid-cycling was linked mainly with the use of tricyclic antidepressants, but there have been reports of the same problem with monoamine oxidase inhibitors (MAOIs). The novel antidepressant bupropion and some selective serotonin reuptake inhibitors (SSRIs), such as paroxetine, may be associated with a lower risk of inducing rapid-cycling. Patients with bipolar depression can present with psychotic symptoms that require the use of neuroleptics. However, many practitioners consider that patients with bipolar depression are particularly susceptible to the extrapyramidal side effects of neuroleptics.

The need for prophylactic treatment during periods of remission, when the patient is stable and may consider him or herself recovered, is a problematic aspect of the clinical management of bipolar disorder. Patients may decide to discontinue medication just when it is most effective. This is challenging to the psychiatrist, who knows that withdrawal and reintroduction of previously effective treatment is often associated with the onset of refractoriness.



## Questions and answers

**Q** Could you illustrate the point you made about withdrawal and reintroduction of medication being followed by refractory states?

**A** This has been shown to occur both with lithium and with antidepressants. The MAOIs are particularly liable to become ineffective if withdrawn and then reintroduced. To give an anecdotal example, a patient may have to undergo a minor operation; they stop their MAOI, have their operation, start taking the MAOI again and never get their response back. This phenomenon is well recognized empirically, even though the mechanism is not understood. It may reflect a state of altered receptor sensitivity induced by the drug itself. The effect is not restricted to MAOIs, it has also been reported with tricyclics and SSRIs. One might speculate that the body makes homeostatic adjustments to any drug with a powerful effect, and occasionally those adjustments may actually offset the effects of the medication.

**Q** If patients discontinue an antidepressant during a period of remission in bipolar disorder, what is the risk that the same treatment will be ineffective in a subsequent episode?

**A** Interruption and re-starting of treatment for any reason carries with it a risk of subsequent non-response in bipolar disorder. The published evidence suggests that 10 to 15 per cent of patients who responded to treatment A in episode A will not respond to treatment A in episode B. Data from our studies show that people who suffer recurrences, in spite of receiving drug treatment, are much more non-compliant than those who did not relapse, suggesting an association between interruption of treatment and relapse. The latter is true not only for antidepressants but also for lithium.

**Q** Given that bipolar patients are particularly liable to develop tardive dyskinesia when given phenothiazines, is it best to avoid using them in this indication?

**A** Even though we may try hard never to use any kind of neuroleptic in bipolar patients, there is a subgroup in whom their use is unavoidable. These are patients who will not respond to lithium or to the anticonvulsants or to any combination. Generally they can be quite easily identified. In their first episode and if they are taken off their neuroleptic they become explosively delusional and manic in a very short period of time. In these patients there is no choice.

**Q** Which drugs would you personally use to treat pure depression in the context of bipolar disorder?

**A** Dr Himmelhoch: Personally I start off with low doses of lithium as my first antidepressant. Forty per cent of patients will respond to 450 to 900 mg of lithium. I would then add an MAOI to non-responders although I think that most other clinicians would add an SSRI at this stage. If they don't respond, the next step would depend on their vascular reactivity to tranylcypromine. If I cannot get the dose above 20 to 30 mg because of hypotension, I add amphetamine or methylphenidate hydrochloride to boost the blood pressure and to get a better antidepressant effect. If they are still refractory at this stage I would consider hospitalization and electroconvulsive therapy (ECT), or start again with a different antidepressant.



## Questions and answers

Dr Thase: I would agree about using a mood stabilizer first, whilst checking and optimizing thyroid function. I would encourage the use of an exercise schedule, and increased exposure to morning sunlight, and would restrict sleep if they were oversleeping. I would try to avoid using an antidepressant during the first three weeks, even though I may well use one eventually. I look for a non-sedating, potentially activating antidepressant. Bupropion is currently my first choice, venlafaxine my second choice, and tranylcypromine my third choice - even though from a data standpoint it may be the first choice. I would use an antidepressant for the natural length of an episode, probably between six and 12 months, bearing in mind that the risk of inducing cycling is more pronounced if the antidepressant is withdrawn and re-started during the episode.

**Q** Bipolar patients quite often have guilt feelings. What is the significance of these?

**A** Guilt feelings tend not to be a major feature of first episodes of bipolar disorder, but guilt and agitation can become prominent over time due to some of the things the patient does during the manic phases of this condition. Some practitioners would say that it is particularly common for patients with bipolar disorder with guilt feelings to commit suicide, and indeed suicidal ideation becomes more common as the fifth or sixth episode of bipolar disorder is reached. Guilt feelings with suicidal ideation in bipolar disorder would be an indication for the use of electroconvulsive therapy (ECT).

**Q** What is the current thinking on the relation of seizures to bipolar disorder?

**A** In a recent study, a comparison was made between 30 patients with severe temporal-lobe epilepsy with interictal affective states plus psychotic symptoms, and patients with bipolar disorder who had responded to anticonvulsants. It was clear from a clinical standpoint that the two populations were completely distinct. For example, if depression occurred in the patients with temporal lobe epilepsy, it responded rapidly and dramatically to treatment with tricyclics, which was not the case for the patients with bipolar disorder.

# Polypharmacy and the treatment of bipolar disorder

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Polypharmacy is a surprisingly old concept. The Oxford English Dictionary traces the origin of the word as far back as 1762. It means the use of many drugs or medicines in the treatment of a disease, but also suggests indiscriminate, unscientific or excessive prescription. Polypharmacy must be a bad thing, by definition, but for bipolar disorder, the issue is not that simple.

The classical view of bipolar disorder tends to be that it really ought to respond to lithium alone. In practice that does not always happen. But what constitutes polypharmacy in the treatment of this condition? My general rule would be that if you are using more than three drugs at once to treat bipolar disorder, then you should be looking more critically at how you are managing the case.

The reason why I would consider up to three drugs justified is that when treating bipolar disorder, one is usually treating several different aspects of illness. In the first instance, there is acute treatment, and within that we may be faced with either mania or depression, but also there is maintenance treatment. The pharmacological strategy in the face of each of these distinct clinical problems is quite different.

In the classical original studies, the response rate to lithium alone was something like 80 per cent. More recent studies have had a much lower rate of response, with a half to one-third of patients responding. In my own institution, we have recently initiated a study of psychotherapy versus no psychotherapy in patients receiving optimal medical maintenance therapy for classical bipolar disorder. To date, about half of these classically bipolar patients had a good short- or long-term response to lithium alone. Some needed one additional drug (either an anticonvulsant, neuroleptic, or antidepressant). However, none of the patients needed three drugs or more.

I believe that patients with a classical bipolar manic-depressive profile respond better to lithium alone than those with atypical features. It is in treating the broader spectrum of bipolar patients with atypical symptoms and presentations that one may frequently encounter the need to prescribe two or three drugs in combination.



## Questions and answers

**Q** Do you find any difference in the response rate to lithium alone according to whether the index episode is manic or depressive?

**A** We have found it much easier to treat patients with an index episode of mania than those who present with depression. Patients presenting with mania get well more quickly than those with depression, and they tend not to switch into rapid-cycling. Treating depression in this bipolar context can be very difficult in our experience. Perhaps 50 per cent of the time the depression will respond to lithium but when it does not it is difficult to treat successfully. We used to try a tricyclic as our first-line treatment but had disappointing results. We have recently switched to tranylcypromine as our first-line drug and selective serotonin reuptake inhibitors (SSRIs) as our second-line agents.

**Q** Is lithium monotherapy usually sufficient to manage an acute manic episode?

**A** No. For one thing there may be a time-lag of a week or so before lithium works, and as people are potentially unmanageable and destructive during a manic episode, lithium monotherapy is not a practical proposition. The usual strategy would, therefore, be to use a neuroleptic early on to control manic symptoms, probably in addition to starting lithium.

**Q** Why are there so few published studies on the effects of multiple-drug combinations in comparison with single-agent therapy?

**A** \* A number of investigators have conducted studies in which lithium plus placebo has been compared with lithium plus (say) a calcium channel blocker (CCB) and the journals have refused to publish the papers because they objected to what they saw as polypharmacy. There is a general understanding in drug development that new therapies should be evaluated against placebo, and not as part of combination therapies. In my opinion, that principle is not really appropriate in bipolar disorder. It would be unethical to attempt to treat these patients with placebo alone. Addition of placebo or an active agent to a first agent is still a valid means of testing the benefit of the second agent. For example in epilepsy and cancer multiple-drug combinations are used commonly, and I believe new drugs are tested as part of combination therapies. The relative lack of papers on drug combinations in bipolar disorder might reflect the gap between the realities of clinical practice and the purely scientific stance adopted by some of the journals.

**Q** In patients on lithium with a bad depression, when would you add an antidepressant, and do you stop the antidepressant if the patient becomes manic?

**A** If a 33 per cent reduction of symptoms is not achieved within two weeks or a 50 per cent reduction within four weeks then I add an antidepressant to the lithium. If patients subsequently become hypomanic on the antidepressant I try not to withdraw it; I either increase the dose of the lithium or decrease the dose of the antidepressant. Dose titration is a lot safer and often more effective than starting drugs and then stopping them again if you don't get the right response immediately. Of course, if a patient becomes fully manic, the antidepressant should be discontinued.

\* Question answered by audience participant.



## Questions and answers

**Q** There is more and more pressure to cut costs by shortening hospital stays. What if there just isn't time to fine-tune the relative dosages of multiple-drug regimens?

**A** This is certainly a real clinical problem, but it is not new. Patients with bipolar disorder have always been coming out of hospital on multiple-drug regimens and requiring fine-tuning as outpatients. The real issue is that the length of time before discharge must be sufficient to stabilize these patients. Achieving the right combination of drugs and in the right doses is a delicate matter that requires time. Fine-tuning can be done on an outpatient basis but only if sufficient inpatient time has been spent to get the patient stable.

**Q** Do you have any recommendations concerning combined treatment for patients who are very aggressive and violent in the manic phase?

**A** \* I would control the aggressive and violent behavioral component of mania with a sedating neuroleptic. One can choose the degree of sedation required and prescribe accordingly, but I am not keen on using high potency neuroleptics such as fluphenazine, for example, unless there is a primary need to control psychotic symptoms. There are some trans-cultural differences in the choices typically made for this kind of patient. In Australia, thioridazine is often used in conjunctive treatment of acute mania: in Europe, the drug of choice for this tends to be haloperidol. Part of the rationale for using thioridazine is that it has calcium channel blocking activity as well, but in my opinion it is still controversial as to whether calcium channel blockers (CCBs) are effective antimanic drugs or not. Benzodiazepines such as clonazepam have also been used in this setting, and many people feel that the induction of sleep is therapeutically useful in mania, with a return of normal sleep pattern signifying recovery.

**Q** Is it acceptable to use more than one anticonvulsant agent in a combination regimen for bipolar disorder?

**A** You can certainly combine carbamazepine and sodium valproate. There is even some evidence in the literature to suggest that in combination they are somewhat synergistic. Moreover, if a patient with bipolar disorder does not respond to one or the other, there is a chance that they will respond to the combination.

# The American Psychiatric Association's guidelines for the treatment of patients with bipolar disorder

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The American Psychiatric Association's guidelines for the treatment of patients with bipolar disorder are aimed at practising psychiatrists. The guidelines are based as much as possible on data drawn from controlled clinical trials and represent the state-of-the-art in the management of bipolar disorder. Some of the key issues covered in the guidelines are summarized below.

Although lithium remains the usual first-line treatment for acute mania, the guidelines reflect the emerging evidence that valproate and carbamazepine are useful antimanic agents and that a combination of these drugs may be needed to control mania. Patients who are intolerant of, or unresponsive to, lithium may respond to these anticonvulsants. Patients with mixed features may respond better to valproate than lithium.

Although neither neuroleptics nor benzodiazepines have been shown to be specifically antimanic, both may be useful adjuncts in the treatment of acute mania because of their sedating properties, and in some patients they are also needed in the longer term. Traditionally, neuroleptics have filled this role more than benzodiazepines. The guidelines recommend the use of benzodiazepines, partly because of the serious side effect profile of neuroleptics in patients with bipolar disorder.

Depression in bipolar disorder is a neglected area in terms of the amount of research data available. Treating the depressive element is subject to a number of unique problems, not least of which is the risk of precipitating mania simply by giving an antidepressant drug. The guidelines recommend that depression in bipolar disorder is managed, wherever possible, with either psychotherapy alone, or with lithium or another mood-stabilizing agent alone - recognizing that it often takes a long time to obtain an antidepressant effect with lithium. It may nonetheless be necessary to use an antidepressant and in this case a mood stabilizer should be used to try and prevent the precipitation of mania. More research is needed on the treatment of depression in bipolar disorder.

Psychotherapy is indispensable in dealing with some of the sequelae of manic episodes, which can affect families. There is very little research in this area, but there are some new approaches, specific to bipolar disorder, that involve family members. They also involve education about the illness, and aim to foster control of it. Finally, the guidelines recognize that electroconvulsive therapy (ECT) can be life-saving in either severe depression or severe mania.

The guidelines are published in *The American Journal of Psychiatry* (December 1994), and will also be published and distributed independently.



## Questions and answers

**Q** How many people contributed to the guidelines?

**A** The guidelines were prepared by a task force of nine experts in bipolar disorder under the auspices of the American Psychiatric Association, and sent to over 600 individuals for review. Over 200 of the people who were invited to comment did so, and their input has been invaluable in preparing the final document. We are confident that the final document represents the state-of-the-art in the treatment of bipolar disorder.

**Q** Do the guidelines consider that one class of antidepressant is less likely to precipitate mania than any other?

**A** There is some evidence that selective serotonin reuptake inhibitors (SSRIs) may precipitate mania at a lower rate than do the tricyclic antidepressants, but we don't know this for certain. Therefore, the guidelines recommend that the therapeutic approach to depression in bipolar disorder should be: firstly, psychotherapy without medication, secondly, lithium – although it may take considerably longer than antidepressants to show an effect – and thirdly an antidepressant.

**Q** What recommendations do the guidelines make about maintenance levels of lithium?

**A** The guidelines do not recommend a specific level, but encourage maintenance levels as near as possible to those used during the acute phase of the illness. The available data seem to support this recommendation in principle. In each case, however, a cost-benefit assessment needs to be made in terms of balancing efficacy against side effects. Psychiatrists in different countries tend to disagree about maintenance levels of lithium. The British, for example, use lower levels of lithium during maintenance therapy than do the Americans. Lower levels are associated with fewer side effects. Nonetheless, the American guidelines do encourage lithium maintenance at levels in the acute range.

**Q** Should maintenance mean maintenance for life?

**A** In principle the answer is yes: maintenance therapy is for life. There may be exceptions though. For example, if one has a patient who has had only two episodes of bipolar disorder in six or eight years one would listen sympathetically if the patient wanted to discuss coming off therapy. Some practitioners prefer to discontinue therapy as a matter of co-operation, with regular monitoring, than have the patient stop their maintenance therapy of their own accord without telling anyone. However, there is a significant risk that having been stable for a long time, a patient who stops taking lithium can become ill again and be refractory to treatment with lithium. There is a series of such cases being followed at the moment. As yet it is uncertain whether this represents a reproducible phenomenon with a subgroup of people with bipolar disorder or whether it is just a series of idiosyncratic patients. While this uncertainty exists stable patients who want to discontinue lithium maintenance should be informed that lithium may not work next time if they need it again.



## Questions and answers

**Q** Is there any evidence that valproate differs from carbamazepine in terms of safety for long-term maintenance therapy?

**A** There have been no direct comparative studies in bipolar disorder, but there has been a study comparing these two agents for long-term treatment in epilepsy. Overall, there was no clinically significant advantage for either drug from the point of view of their side effect profiles. In terms of weight gain, tremor and hair loss, valproate appeared less well tolerated than carbamazepine whereas in terms of allergic reactions valproate was better tolerated.

**Q** What guidelines are given about treatment for bipolar disorder during pregnancy?

**A** All of the antimanic agents have teratogenic features and we recommend that they should not be taken by women who are pregnant, particularly during the first trimester, or by women who are trying to conceive. However, for some women with severe bipolar disorder, discontinuation of mood stabilizers will represent an unacceptable risk of increased morbidity. Under these circumstances, if the woman did discontinue her mood stabilizing drug therapy, ECT would still be available as an emergency treatment which can be administered safely during pregnancy. This would really be decided on a case-by-case basis, with a careful discussion with the patient and the family of the risks, benefits and alternatives. No guideline can be completely prescriptive in a matter such as this.

**Q** Will the guidelines impede progress by inhibiting psychiatrists from trying new therapies?

**A** No, because the guidelines are very up-to-date and will be regularly reviewed. They will, therefore, include a discussion of the newest approaches to the treatment of bipolar disorder. Of course, no printed medium is ever entirely current, but even if the guidelines were two years behind the latest developments in the field they would still represent more recent information than many practitioners would otherwise have. Any clinician who wants to try something outside the guidelines can do so, but would need to address why he or she is doing this and discuss it with the patient and the family.