Treatment-Resistant Bipolar Disorder

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***Abstract*—Bipolar disorder comes n many varieties, which often requires combined approaches. Medication and psychotherapy together usually show more effective in clinical practice than medication alone. The objective needs to be the full remission of symptoms. On the medication side, this may mean prescribing more than one drug. On the psychological side, a communication-oriented approach is helpful to improve the internal and external communication of the patent, which facilitates an individualized treatment plan, improves compliance and raises quality of life over the long-term.**

***Index Terms*—bipolar disorder, treatment resistant, treatment, psychotherapy psychiatry**

I. Introduction

Bipolar Disorders types I and II affect about 2% of the world's population. Including various forms of cyclothymia, a subthreshold form of bipolar disorder, the total rises to 4% or 160 million people given the current world population of eight million. Since affective conditions can have serious consequences for an individual's personal and professional life, the individual suffering and loss to the economy is enormous. Effective treatment of this condition can therefore have a very real and considerable effect in the world. In 2009, for example, the direct and indirect costs of bipolar disorder were estimated in the US to be $151 billion.

Even with treatment, about a third of patients relapse into depression or mania within one year, and around 60% within two years. Probably twice as many of these recurrences are of depressive polarity rather than of manic polarity.

One Condition: Mood Instability

Mood instability rather than separate episodes of depression and mania is probably the most accurate description of the dynamics in affect underlying bipolar disorder. As in many other psychiatric conditions the changes along a spectrum of states are typical and specific to the disorder. Yet a lack of change in affective or emotional states or cognitive processes can be as descriptive of a mental health condition, such as in the case of a severe chronic depression. Describing the dynamics of these changes is thus an important part of an assessment and very valuable when considering medication or which psychotherapeutic approach and techniques to use.

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Communication as the Key to Treatment

Treatment of bipolar disorder conventionally focuses primarily on acute stabilization, in which the goal is to bring a patient with mania or depression to a symptomatic recovery with a 'normal' stable mood. Often, the goal is then on functioning in private and professional life. However, these narrow goals may also contribute to the problems.

The major cause of the problems in a patient's life are due to how the condition effects internal communication and the communication with the rest of the world. (Haverkampf, 2010, 2012, 2013, 2014, 2015, 2016) Both the medication and the psychotherapy help synergistically. Unfortunately, frequently only one treatment approach or the other are used.

Despite a substantial expansion of research into bipolar disorder and potential treatments during the past 2 decades, true advances have been few. However, one aspect that is often overlooked This applies, for example, to communication between patient and therapist as a basic mechanism which can maintain and contribute to the intensity of a manic episode, as well as a depressed episode.

Treatment as a Challenge

The treatment of bipolar depression is a major challenge, with few treatments of proven efficacy and, in particular, substantial controversy about the role of antidepressant drugs. Authors of guidelines and consensus statements on this topic often ponder why antidepressants are so commonly used despite the scarce evidence for efficacy. Until recently, after the work of Emil Kraepelin, bipolar depressive episodes were deemed phenomenologically and biologically similar to unipolar depressive episodes. Even as late as the 1990s, inclusion and exclusion criteria in clinical trials of antidepressants in patients with depressive disorder did not usually either select or stratify according to polarity. Earlier trials suggested that when given with antimanic treatment,

selective serotonin reuptake inhibitor antidepressants were more effective and no more likely to induce mania than placebo and were less likely to induce mania than tricyclic antidepressants. In 2007, a large trial found no benefit associated with the addition of paroxetine or bupropion to a mood stabilizer; another reported that paroxetine was no better at achieving a durable recovery than placebo.

Learning from Others

Most newly introduced treatments for bipolar disorder, whether pharmacological or psychological, have been based on an extension of use from another disorder—e.g. antipsychotics in mania and antidepressants or cognitive-behavioral therapy for bipolar depression. However, lithium remains unique because its main therapeutic use is in bipolar disorder, and investigation of its mechanism of action has, and remains, crucially important in the identification of future targets.

II. Bipolar Depression

Often in the treatment of bipolar disorder a latent or subthreshold depression may be overlooked, which may have a multiplier effect. When an underappreciated depression interferes with a patient's personal and professional life, this can have knock on effects on the depression, which can worsen it and the affective stability in general. Even patients who receive adequate pharmacotherapy have lengthy and debilitating periods of subthreshold depressive symptoms after major episodes. Longitudinal studies estimate that patients with bipolar disorder type I spend as many as 3 weeks depressed for every 1 week (hypo)manic, while this is lower in type II.

Recommendation in clinical practice guidelines for treatment-resistant bipolar depression are still often based on extrapolation from the evidence on augmentation and switching strategies in unipolar major depression. This situation might lead to an underestimation of the attendant risks of treatment-emergent hypomania or mania in patients with bipolar disorder.

III. Medication

The pioneering trials of lithium and chlorpromazine were done in the 1970s and were followed by a focus on antiepileptics, primarily valproate and carbamazepine, in the 1980s and 1990s.

None of the medication is specific 'bipolar medication'. This is not necessarily due to the fact that there are still major questions about the biological causes of the condition, but that several types of medication can stabilize mood. This also allows prescribers some latitude in picking medication that addresses the bundle of symptoms most adequately and lowers the side effects, particularly those that are more likely to decrease the quality of life of the individual patient. However, this requires spending enough time on assessing the patient to pick the right medication.

Neurobiology

Dopamine antagonism seems to be a potential target for antimanic treatments, but the scarce convincing evidence that increasing serotonergic transmission improves symptoms in bipolar depression shows the need for development of bipolar-specific validated targets for novel treatments. After evidence of dysfunction in the N-methyl-D-aspartate–receptor complex in the glutamatergic system, two crossover trials found that infusion of the N-methyl-D-aspartate antagonist ketamine produced rapid alleviation of depressive symptoms in bipolar depression.

An important approach for elucidating underlying biological etiologies and developing new medications is 'reverse engineering' by identifying molecules which seem to relieve symptoms, and then deriving potential anomalies in receptors and other building blocks and processes of the various neurotransmission systems. Ebselen is such an example, which did not prove useful in stroke treatment, but as a potential lithium mimetic may affect the neural system as various points.

There are several new techniques to enhance research into the neurobiology induced pluripotential stem cells to provide in-vitro models of neural systems, the identification of genetic and epigenetic factors, and the use of optogenetics to develop more precise animal models.

Clarification of the mechanisms by which different mood stabilizers and atypical antipsychotics affect sleep and circadian rhythms and their relationship with daily mood fluctuations is another path to explore.

Short vs Long Term

For manic episodes, severe acute ones, the antipsychotics, primarily olanzapine, risperidone, aripiprazole and haloperidol, are often preferred in clinical practice to anticonvulsants and lithium. However, for long-term maintenance treatment lithium and the anticonvulsants are usually considered as a baseline treatment, which can be augmented with antipsychotics for manic episodes. Important is to note that there are differences between the antipsychotics and the antiepileptics, as well as among individual drugs, in the stabilizing effect patients notice. This makes it even more important to assess the condition the patient is suffering from thoroughly, as well as individual aspects that are not directly related to the bipolar condition.

COMBINATIONS

Combinations can make much sense pharmacologically in individual cases. In the BALANCE trial, for example, combination treatment with lithium plus valproate was identified as more effective than treatment with valproate monotherapy. One needs to carefully consider three aspects when considering communication:

- the desirable and undesirable effects of the medication in the individual patient
- the various positive and negative effects of the specific medication
- medical considerations applying to the specific medication in the specific medication with his or her individual medical history and current somatic condition
- the personal and professional environment of the patient

A. Lithium

Lithium, introduced by John Cade in 1949, remains an important class of medication in itself for long-term treatment for bipolar disorder. However, since it can take months to work in several cases, other medication to stabilize the effect may be necessary in beginning of treatment. A meta-analysis of five placebo-controlled lithium maintenance trials involving 770 patients showed that lithium reduced the risk of manic relapse by close to 40% and depressive relapse by close to 30%. It is also the only medication known to have a more or less direct ant-suicidal effect, which has also been confirmed in randomized studies on suicidal ideation.

However, the benefits of lithium are restricted by adverse effects and a low therapeutic index. There is a risk of renal impairment and the discussion about end-stage renal failure has not yet subsided.

The risk of congenital malformations in the babies of mothers who have taken lithium during pregnancy may be lower than previously thought, but a risk probably remains. Although, the risk of valproate in pregnancy is certainly higher. The balance of risks should be considered before lithium is withdrawn during pregnancy, including a possible increase in suicidal thoughts.

In addition to known effects of lithium on the thyroid, the risk of hyperparathyroidism is increased, and calcium concentrations should be checked before and during treatment.

B. Anticonvulsants

The antiepileptic drug lamotrigine was investigated in patients with bipolar depression after a clinical benefit was seen after treatment with the drug in patients with bipolar disorder. A meta-analysis of individual patient-level data from five trials of lamotrigine in bipolar depression reported a modest treatment effect; however, no one trial showed statistically significant benefits of treatment with lamotrigine in comparison with placebo. Thus, the place of lamotrigine in acute treatment remains uncertain. However, lamotrigine has been associated with a decrease in relapse by more than a third over eighteen months.

C. Antidepressants

Antidepressants as an add on in bipolar patients with more pronounced depressive episodes can be helpful. However, one should avoid the SNRIs, particularly venlafaxine, which in clinical practice seems more likely to push patients into a manic episode. (Haverkampf, 2015) The less activating SSRIs may be a better choice in combination treatment. However, they should be titrated up slowly and gradually to catch a budding medication induced (hypo)manic state. Sometimes, one finds a single dose which protects against the depressive episode while not triggering (hypo)manic episodes. (Haverkampf, 2015)

D. Atypical Antipsychotics

As mentioned, atypical antipsychotics are particularly helpful in the more acute manic phase of bipolar disorder. The more serotonergic antipsychotic olanzapine, as well as quetiapine and probably lurasidone, are helpful in cases of bipolar depression. Quetiapine is also used in unipolar depression.

Because antipsychotics are the most potent treatments in acute mania, in many clinical situations, it will seem reasonable to continue them after remission from the acute episode. However, there are few long-term trials, most use enrichment designs, and none have the same degree of independent replication of efficacy as lithium. Thus, the role of antipsychotics as long-term mood stabilizers remains uncertain.

OLANZAPINE

Olanzapine when combined with fluoxetine leads to more symptomatic improvement than does olanzapine or placebo alone, which could suggest that fluoxetine is an effective treatment of acute bipolar depression or that the combination of fluoxetine and olanzapine is synergistic. However, this effect may extend to other SSRIs, such as sertraline as well.

QUETIAPINE

Treatment with quetiapine leads to more symptomatic improvement in patients with bipolar depression than do placebo, paroxetine, and lithium. The reasonably fast onset of action of quetiapine is clinically useful because it provides

clinicians and patients with a treatment that can be initiated early in the course of a worsening depression in the same way that antipsychotics are used for emerging manic symptoms. Some evidence exists of a reduced risk of recurrence in patients who respond to acute-phase treatment and continue quetiapine rather than switch to placebo.

ARIPIPRAZOLE

Aripiprazole is probably ineffective in bipolar depression if used by itself. However, this non-specificity and scarcity of convincing evidence of long-term disease modification by known mechanisms suggests that the effects are mediated by short-term alleviation of symptoms. Nonetheless, because bipolar depression is very difficult to treat, this relief is often useful for patients and clinicians. Further, combinations of atypical antipsychotics with selective serotonin-reuptake inhibitors, or with agents that have medium-term to long-term effects on depression (e.g. lamotrigine) are often used in clinical practice and warrant investigation in clinical trials.

E. Other Medication

Very little evidence exists of effective strategies for patients who do not respond to first-line treatments. It is still too early to say how ketamine or lamotrigine may be helpful in bipolar depression, while electroconvulsive therapy has been helpful in individual cases of bipolar depression but is often regarded as too invasive and the question whether it may induce manic states remains.

IV. PSYCHOTHERAPY

As already mentioned, communication plays an important role in the treatment of bipolar disorder. Helping the patient gain more insight into internal and external communication improves social functioning and reduces symptoms in the long-run.

Treatment guidelines mostly suggest that optimum management of bipolar disorder needs integration of pharmacotherapy with targeted psychotherapy. Randomized trials on the effectiveness of combined treatment are also becoming more frequent and all so far show its superiority.

Psychosocial stressors, including excessive family discord or distress, negative life events, or events that disrupt sleep and wake rhythms are associated with relapses and worsening symptomatic states. Thus, one element of psychotherapy is to help the patient conceive strategies for the management of stress, the identification and intervention of early signs of recurrence, and how to keep regular lifestyle habits, including exercise and stress. It should not be overlooked, however, that strategies are of limited help if underlying psychological dynamics make it difficult to develop and maintain them. In the long-term work on internal and external communication patterns helps to shape foundations which enable the patient to formulate better strategies herself or himself.

All existing forms of psychotherapy for bipolar disorder include psychoeducation. The identification of mechanisms of change—e.g., regulation of sleep and wake rhythms, reductions in family conflict, consistency of adherence to drugs, or the ability to intervene early with prodromal symptoms—might lead to the development of briefer treatments with more durable effects. Further identification of psychological processes underlying mood instability, such as the role of imagery in increasing anxiety and mood instability, might lead to more focused psychological interventions. However, it is important to remember that underlying many of the techniques that work routinely, whether psychoeducation or cognitive therapy, is a new relationship with a therapist or others, exposure to new meaningful communication and a consequent change in internal and external communication patterns.

A. Psychosocial interventions

Common objectives of psychosocial interventions for bipolar disorder include:

- Improving the ability to identify and intervene early with warning signs of recurrences
- Increasing acceptance of the presence and the nature of the illness, while creating awareness for the many ways of treating it, reducing its symptoms and its impact in everyday life
- Enhancing the psychopharmacological compliance
- Arranging everyday life in ways that reduces stress in personal and professional life, which may be increased by the symptoms
- Stabilizing sleep and wake rhythms and other daily routines
- Reengaging with social, familial, and occupational roles
- Improving family communication and relationships
- Reducing self-medication with alcohol and drugs

Evidence-based models of psychotherapy include cognitive-behavioral therapy, family-focused therapy, interpersonal and social rhythm therapy, group psychoeducation, and systematic care management. Psychodynamic psychotherapy has also shown effectiveness. All these therapeutic approaches have in common that they affect internal and external communication patterns, which brings about adaptive and positive change over the long-term.

B. Adjunctive psychotherapy in acute treatment

Patients in acute manic episodes are not likely to respond well to intensive psychotherapy because of insufficient insight or rejection of help. In the STEP-BD study, over 1 year,

patients in intensive therapy recovered more rapidly and were more likely to be clinically well in any study month than those in brief treatment. Effects extended to relationship functioning and life satisfaction. No differences emerged between the three intensive modalities in symptoms or psychosocial functioning over one year. Interestingly, patients with depression in STEP-BD who were treated with mood stabilizers and randomly assigned to adjunctive anti-depressant treatment did not recover faster than patients who were assigned to adjunctive placebo treatment. Therefore, psychosocial treatment might be a more effective adjunct to mood stabilizers than antidepressants after a bipolar depressive episode.

C. Family-focused therapy

Stress in the communication dynamics within a family, mostly brought about by unresolved issues, an inability to discuss issues or emotions. Family-focused therapy involves the patient and caregivers (parents or spouse) in up to 21 sessions of psychoeducation, communication skills training, and problem-solving skills training.

In the one to two years after a manic, mixed, or depressive episode, patients with bipolar disorder who received family-focused therapy with medication have been shown to have a third less relapses and hospital stays, as well as less severe symptoms than those who were only 'case managed'. This is not surprising since family-focused therapy addresses external communication dynamics in the patient's immediate environment which also has a beneficial effect on the internal communication in the patient and others close to him or her.

Children and adolescents who received family-focused therapy and pharmacotherapy seem to recover more rapidly from depressive episodes than do children and adolescents wo are only treated with brief psychoeducation and psychopharmacotherapy.

The education of caregivers about bipolar disorder might translate into benefits for patients, even if patients do not attend educational sessions. Adjunctive family interventions have the potential to lengthen periods of stability and alleviate residual symptoms in maintenance care.

Family-focused therapy does seem an appropriate add-on to other psychotherapeutic approaches. It covers an important area of a patient's relevant external relationships and communication networks. In conjunction with a therapy that addresses underlying internal issues and general maladaptive communication patterns, it can have a synergistic effect.

D. Cognitive-Behavioral Therapy (CBT)

Cognitive-behavioral therapy presumes that recurrences of mood disorder are determined by pessimistic thinking in response to life events and core dysfunctional beliefs about the self, the world, and the future. Cognitive-behavioral therapy to treat depression has been adapted for patients with bipolar disorder with recognition that manic episodes are often associated with excessively optimistic thinking. In clinical practice, patients who receive at least ten to twenty sessions of cognitive-behavioral therapy are less likely to have depressive episodes and display better social functioning than patients in routine care. However, there is doubt how long this effect lasts in the long-run, especially if the therapy is less individualized, more manualized, and it focuses more on psychoeducation about strategies rather than bringing about changes and innovations in internal and external communication patterns in the individual patient.

There is some discussion whether CBT is appreciably more effective than psychoeducation in bipolar patients in relapse prevention. From a communication perspective, this is

E. Psychodynamic Psychotherapy

Psychodynamic psychotherapy derived from psychoanalysis, the original "talk therapy". The psychodynamic approaches place emphasis on the why of a condition. They may not work as rapidly as CBT. However, clinical experience shows that if the therapy is carried out by an experienced therapist, the effect can be more enduring than the of CBT.

F. Communication-Focused Therapy (CFT)

CFT was developed by the author to work with a focus on communication, processes many psychotherapeutic interventions use, but to do so more directly. (Haverkampf, 2010) In clinical practice, this seems to be a very helpful approach as it combines working on the internal and external communication a patient uses to get own needs, values and aspirations met. This can lead to a greater sense of efficacy, confidence, a better sense of self and stabilize affect and emotions.

G. Interpersonal and social rhythm therapy

Substantial evidence exists that mood instability in bipolar disorder is related to changes in circadian rhythms. The relation between sleep and mood disturbances seem to be bidirectional. Polymorphisms in CLOCK genes are related to circadian mood fluctuations and recurrences in bipolar disorder. In one promising animal model, mice with mutations in CLOCK genes behaved in ways that resembled manic behavior in people (e.g. increases in activity and decreased sleep); these behaviors were reversed upon treatment with lithium.

Interpersonal and social rhythm therapy, an adaptation of the interpersonal psychotherapy for depression, uses a

problem-solving approach to interpersonal problems by encouraging patients to maintain and regulate daily routines and sleep and wake rhythms. These approaches may be of little use in acute situations, but can be an important add on to psychopharmacology, and in themselves contain elements which may can be useful in establishing a working relationship with the patient, lower anxiety and However, patients who received interpersonal and social rhythm therapy in the acute phase had longer times to recurrence and better vocational functioning in the maintenance phase than did patients who received clinical management during the acute phase. Moreover, the effects of interpersonal and social rhythm therapy in the delay of recurrences were most pronounced in patients who had been able to stabilize their daily or nightly routines during acute treatment. Thus, to help patients to stabilize their sleep and wake rhythms after an acute episode might have downstream effects on the prevention of future mood instability.

H. Group psychoeducation

In view of the many patients who could benefit from psychoeducation, group approaches following a predesigned curriculum have been proposed. The Barcelona approach emphasizes awareness of illness, treatment adherence, early detection of recurrences, and sleep and wake regularity. In clinical practice, patients who had received the structured groups have fewer relapses and are ill for less time than those who are in unstructured groups. Less hospital stays seem necessary.

I. Neurocognitive Training

Neurocognitive training aims to improve cognitive functioning of patients in their everyday life, which can be useful if cognitive deficits are evident and the medication is very slow acting, such as lithium, or residual symptoms remain even with optimization of the medication and psychotherapeutic approach. Exercises for memory, attention, problem solving, reasoning, and organization are all elements of neurocognitive training. The primary objective is to raise the quality of life through better interactions with oneself and the environment, helping to improve social relationships and making it easier for patients to get what they need, value and aspire to in the world, which reduces stress, additional psychological pressures and stabilizes affectively and emotionally.

J. Systematic care management

Systematic care management combines protocol-driven pharmacotherapy, group psychoeducation, and intensive patient monitoring by a nurse care manager. The frequency of relapse may not be lower, but patients in systematic care probably spend fewer weeks in manic episodes than those In a Veterans Administration study, patients in collaborative care also had improved social functioning and quality of life over 2 years.

V. Conclusion

Clearly, more research is needed to provide clinicians with better guidance in making treatment decisions, especially in light of accumulating evidence that the longer patients are unsuccessfully treated, the worse their long-term prognosis tends to be. However, with the clinical experience and the study results we have so far, a lot can be done, particularly in the combination of psychotherapy and medication, to alleviate the suffering of patients.

Conflicting Interests

The author reports no conflicting interests.

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