STATE OF THE ART IN THE MANAGEMENT OF BIPOLAR DISORDER *

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Abstract :In this paper there is a revision of the classification and prevaience of mood disorders, with the emphasis on the higher rates of prevalence of Bipolar Disorders in recent studies. The clinical phenomenology is updated with some discussion of the misunderstood classification and inconsistant diagnosis and treatment worldwide. The managements in psychiatry generally and in Bipolar disorder in particular has been discussed. The pharmacotherapy of Bipolar Disorder is reviewed. Lithium, Novel antipsychotics and the management of acute mania or mixed episodes as well as acute depression and rapid cycling also maintenance treatment is clarified, without forgetting the importance of psychosocial intervention. The conclusion calls for more research in the field.

Introduction

An application of DSM-IV criteria (Zurich cohort) produced prevalence for mania and hypomania of 5.5% by age 35. In a recent study, Angst (1 998) reported that, while 13 epidemiologic studies since 1980 had persistently found a low lifetime prevalence of mania (0.0-1.7%), the application of DSM-IV criteria by trained clinical psychologists produced a prevalence for mania and hypomania of 5.5% by age 35. A broadening of diagnostic criteria to include other aspects of the bipolar spectrum (hypomania, cyclothymia, and bipolar disorder not otherwise specified) in six studies since 1978 yields a prevaience ranging between 3.0 and 8.8%. Depression usually causes more subjective distress than does mania. Hence, patients are more likely to seek help for depression than for mania. This high prevalence suggests that bipolar disorder is a general health problem with significant social and economic sequel, a fact of which policy makers should be aware.

Clinical Phenomenology of Bipolar Subtypes.

Akiskal and Pinto (1999) broadened the bipolar spectrum and suggested several subtypes as follows:
Bipolar 1: Full - Blown Mania
Bipolar 1 1/2 : Depression with protracted hypomania
Bipolar 2: Depression with hypomania
Bipolar 2 1/2 : Cyclothymic depression
Bipolar 3: Antidepressant associated hypomania.
Bipolar 3 1/2: Bipolarity Masked and unmasked by stimulant abuse.
Bipolar 4: Hyperthymic Depression.
Bipolar V & VI: Not yet defined.

Mixed states

Mixed states, also called dysphoric mania, constitute 5 - 7 % of cases. This category has been recently acknowledged as a distinct entity of bipolar disorder, occupying an intermediate position on a spectrum between mania and depression. It is a severer form of bipolar disorder and its phenomenology consists of a superimposed independent mania and depression

Morbidity and Social Cost

Bipolar disorder is the 6th leading cause of disability worldwide and is a recurrent illness in more than 90% of patients. Suicidal ideation is present in 25-50 % in cases of mixed mania. At least 25% of bipolar patients attempt suicide, while the actual suicide rate is estimated between 11-19 %. Co morbid substance abuse or other psychiatric diagnoses (McElroy et al., 2001) and/or medical conditions (Strakowski et al., 1994) are highly prevalent in bipolar disorder.

Functional recovery often lags behind symptomatic and syndromal recovery. Recurrent episodes may lead to progressive deterioration in functioning and the number of episodes may affect subsequent treatment response and prognosis, hence the importance of early identification and intervention.

Psychosocial disability from bipolar disorder remains extensive and encompasses multiple domains, including work and social functioning, independent community living, family adjustment, premature mortality, and diminished quality of life.

In an Egyptian retrospective study of a sample of bipolar patients, Okasha et al.,(In Press) found that the syndromic recovery was almost double that of functional recovery, including work, domestic and interpersonal relationships.

Goldberg et ai. (1995) found at both 2- and 5-year follow-ups that fewer than one-quarter of bipolar patients with affective relapses had steady work performance, and that affective relapse led to impaired work functioning more profoundly among bipolar than unipolar patients. At least one quarter of euthymic bipolar patients show impaired insight and an inability to recognize affective prodromes.

The economic burden of treatment of bipolar disorder is poorly understood. A recent study (Johnstone et al., 2001) discussed the direct cost of care for bipolar disorder in an employer claims database representing the health care experience of approximately 1.6 million covered lives. The study examined the estimated cost of care including expenditures for hospitalisation, hospital outpatient services, outpatient medications, psychiatric day/night facilities, nursing home facilities, office visits, laboratory tests, substance abuse treatment, and other services. The prevalence of bipolar disorder in the population was 5.5 patients per 1000 eligible members. These patients incurred significant annual expenditures, totaling $ 13,402 in 1995, $ 11,856 in 1996, and $ 11,146 in 1997. These expenditures were comparable te the costs of treatment for schizophrenia in the same population during this period. Annual costs for outpatient use of mood stabilizers and antipsychotic medications increased by $ 168 (42%) over the study interval, totaling $ 568 in 1997. However, other costs of care for these patients decreased by $ 2,424 (i.e., more than 80%) during the same period.

Caveats in International Classification
Bipolar disorder, however, remains ftequently misunderstood, leading to inconsistant diagnosis and treatment. Bipolar disorder is under diagnosed and under recognized and frequently misdiagnosed as unipolar major depressive disorder, which can increase the burden of the disorder. Reasons for under diagnosis include patients' impaired insight into mania, failure to involve family members in the diagnostic process, and inadequate understanding by clinicians of manic symptoms. Slavish adoption of the DSM- IV and ICD-10 definitions may have hindered research into the etiology of mental disorders and contributed to the high degree of short-term diagnostic instability for many disorders. The concrete use of DSM-IV and ICD-10 entities where they are considered to be equivalent to "diseases" is more likely to obscure rather than elucidate research findings. In recent years, much progress has been made in the diagnosis and treatment of schizophrenia and depression. The work by Berrettini (1996) indicating that three of the putative susceptibility loci associated with bipolar disorder also contributes to the risk of schizophrenia. Bipolar disorder however remains frequently misunderstood, leading to inconsistant diagnosis and treatment. The states of diagnosis and treatment in bipolar disorder are suboptimal. More diagnostic attention to manic criteria is necessary.

Management strategies
Lack of treatment specificity is the rule rather than the exception. The current pattern of use of antidepressant use in bipolar disorder needs to change. Antidepressants are probably overused and mood stabilizers underused.
Why is this the case? Many fondamental aspects of the therapeutics of bipolar disorders remain remarkably underdeveloped and require further systematic study.

Goals of Management in Psychiatry
Any psychiatric management attempts to fulfill a series of objectives. Initially there is the objective to establish and maintain a therapeutic alliance, which is a prerequisite for any doctor patient relationship. There is also a need to monitor the patient's psychiatric status, provide education regarding bipolar disorder, enhance treatment adherence, and promote regular patterns of activity and sleep. On the preventive side a sound management plan should be able to anticipate stressors, early identify indicators for new episodes and seek to minimize functional impairments.
In the case of bipolar mania, specific goals involve control of dangerous symptoms such as suicide, agitation and psychosis, stabilize mood, i.e. control mania without provoking depression. Treatment should target all faces of mania including depressive, anxious and psychotic elements. The most important guideline in the above process is to monitor overdose and protect patient from harmful side effects such as severe toxicity and teratogenicity. The long-term objective of treatment of bipolar mania is to restore patient's premorbid functioning. This entails a simplification of patient's daily routines, enhancement of compliance through simple dosing, avoiding annoying side effects or dulling and limitation of needs for medical procedures.
To meet the above requirements we are in need of an "Ideal Mood Stabilizer" which is effective over 'Time and across episodes. Such ideal medication should have a rapid efficacy for mania, treat psychotic symptoms white at the same time have a broad efficacy spectrum (e.g. mixed, rapid cycling). At the same time is should reduce depressive symptoms, maintain favorable cognitive fonctions, enjoy long-term usefulness, be easy te use, safe and well tolerated, and, ideally, affordable.

Pharmacotherapy in bipolar disorder
Mood-stabilizing Agents that have been developed or used in an attempt te achieve the above recipe are variable. The most classic is Lithium. But then there are also the anticonvuisants: Carbamazepine (Tegretol), and oxycarbazepine (Trileptal), Valproate (Depakene, Depakote), Lamotrigine (Lamictai), Gabapentin (Neurontin), Topiramate (Topamax), Benzodiazepines such as Clonazepam or Klonopin and finally conventional (e.g. Haloperidol) and novel antipsychotics (e.g. Clozapine, Olanzapine, Risperidone) and others. Valproate is recognized by the American guidelines to be antimanic and can be used as a mood stabiliser. Gabapentin and Topipromate proved te be effective as an add on drug, especially in maintenance treatment. Lamotrigine showed favorable response in resistant bipolar depression.

Lithium
The antimanic effect of lithium is supported by recent evidence. Different authors estimate the range of efficacy of lithium in the treatment and prevention of bipolar disorder between 49-70%. The onset of action of lithium takes 5-21 days as a therapeutic medication and about 6 months as a preventive one. Predictors of lithium responsiveness include a diagnosis of classic mania, manie-depressive illness and fewer numbers of episodes. A drastic reduction of affective morbidity is very frequent in bipolar patients receiving lithium prophylaxie regularly for several years. Lithium does seem to be efficacious also in bipolar disorders with mood- incongruent psychotic features at least in the large majority of patients. It also seems to exert an antisuicidal effect in bipolar patients. Despite its powerful therapeutie and preventive effect, lithium use is hampered by its high side effect profile, which includes neurocognitive, renal, gastrointestinal, endocrinological side effects and weight gain. In addition there is an increased recurrence risk in the months following its discontinuation.

Novel Antipsychotics in Bipolar Disorder
Novel antipsychotics have been recommended both in the treatment of acute mania, dépression with psychotic features and as maintenance treatment in recurrent bipolar disorder. Their advantages include a reduced risk of extra pyramidal side effects, reduced risk of Prolactin elevation and reduced risk of tardive dyskinesia. Novel antipsychotics used in the treatment of acute mania include Clozapine (open trials and many double-blind comparison trial), Risperidone (1 add-on comparison trial), Olanzapine (2 double-blind, placebo-controlied trials; 1 lithium comparison trial), Quetiapine (anecdotal reports) and Ziprasidone (preliminary evidence in bipolar schizoaffective patients).

State of the Art in the Management of Bipolar Disorder

I. Acute mania or mixed Episode
Treatment selection should depend on illness severity, associated features such as rapid cycling or psychoses, and where possible, patient preference. For patients not yet in treatment for bipolar disorder and who suffer severe mania or mixed episodes, treatment is best initiated with lithium in combination with an antipsychotic or valproate in combination with an antipsychotic. For less ill patients, monotherapy is recommended. Lithium, Valproate, or an antipsychotic may be sufficient. In the latter case atypical antipsychotics are preferred

over typical ones. Short-term adjunctive treatment with a benzodiazépine may also be helpful. For mixed episodes, valproate may be preferred over lithium. Alternatives include Carbamazepine or Oxcarbazepine, Ziprasidone or Quetiapine. Antidepressants should be tapered and discontinued if possible. For the best effect, pharmacotherapy should be coupled with psychosocial therapies.

"Breakthrough" manic or mixed episode while on maintenance treatment

In the case of a recurrence of a manic or mixed episode while on maintenance treatment, the medication dose should be optii-nized to achieve a higher serum level. Sometimes it is necessary to resume the use of an antipsychotic. If the breakthrough episode is not adequately controlied within 10 to 14 days of treatment with optimized doses of the first-line medication regimen, another first-line medication should be added. For example adding Carbamazeoine or Oxacebazepine in lieu of an additional first-line medication (Lithium, Valproate, antipsychotic drug) or changing ftom one antipsychotic to another. Clozapine may be particularly effective in reftactory illness. Electro convulsive therapy (ECT) may also be considered for manic patients who are severely ill or whose mania is treatment resistant. For psychoses during a manic or mixed episode, patients should be prescribed an antipsychotic medication and ECT may also be considered.

II. Acute Depression

In the case of bipolar patients who are not yet in treatment for bipolar disorder, medication is best initiated by either lithium or Lamotrigine. Treatment initiation can also be donc with both lithium and an antidepressant simultaneously. However, antidepressant monotherapy is not recommended. Again, ECT can be considered. Interpersonal therapy and cognitive behavior therapy may be useful when added to pharmacotherapy.

Breakthrough depressive episode while on maintenance treatment

Again, the medication dosage should be optimized in the case of a breakthrough depressive episode while on maintenance treatment of bipolar disorder. The dose adjustment should target a higher serum level of the drug, which however should bc maintained in the therapeutie range. Psychotic features require an antipsychotic medication and ECT might be considered. If the patient fails to respond to optimized maintenance treatment, consider adding Lamotrigine, Bupropion, or Paroxetine. Alternative next steps include adding another newer antidepressant (e.g. another (SSRI) or venlafaxine) or a monoamine oxidase inhibitor (MAOI).

Tricyclic antidepressants may carry a greater risk of precipitating a switch.

III. Rapid Cycling

In the case of rapid cylcers one should start with an attempt to identify and treat medical conditions such as hypothyroidism or drug or alcohol use that may contribute to rapid cycling. If possible, medications (particularly antidepressants) that may contribute to cycling should be tapered. For initial treatrnent, lithium or valproate should be used. An alternative treatment is Lamotrigine. For many patients, combinations of medications are required. This may be a combination of two of the agents mentioned above or one of them in addition to an antipsychotic.

IV. Maintenance Treatment

The decision on maintenance treatment and even more the tailoring of maintenance treatment is one of the biggest challenges in the fields of psychiatry. Long-term maintenance treatment in bipolar disorder cases should be considered once the patient develops more than two episodes in the first two years of the history of his/her illness.

Although maintenance therapy with atypical antipsychotics may be considered, there is as yet no definitive evidence that their efficacy in maintenance treatment is comparable to that of other agents discussed above.. The rule is that antipsychotic medications should be discontinued unlessthey are needed for control of persistent psychoses or prevention of recurrence of mood episodes. If a patient faits to respond, i.e. continues to experience subthreshold symptoms or breakthrough mood episodes, another maintenance medication could be tried such as an atypical antipsychotic, or an antidepressant. There are insufficient data to support one combination over another. Maintenance ECT may also be considered for patients who respond to ECT during an acute episode.

Psychosocial intervention

Concomitant psychosocial interventions addressing illness management (i.e. adherence, lifestyle changes, and early detection of prodromal symptoms) and interpersonal difficulties are likely to be of benefit. Supportive and psychodynamic psychotherapies are widely used in combination with medication. Group psychotherapy and family therapy may also help. Support groups are helpful in providing participants with useful information.

Finally, we need to encourage a research agenda on bipolar disorder that goes beyond our current ways of thinking to a dimensional approach addressing issues of under diagnosis and misdiagnosis. More emphasis should be made on the bipolar spectrum and rnore diagnostic attention given to manic criteria.

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