Comparison of Cognitive Functions between First & Multi-Episode Bipolar Affective Disorder

Thesis Submitted for partial fulfillment of the M.D. degree in Psychiatry

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INTRODUCTION

Bipolar disorder, or manic-depressive illness, has been recognized since at least the time of Hippocrates, who described such patients as "amic" and "melancholic." In 1899, Emil Kraepelin defined manic-depressive illness and noted that persons with manic-depressive illness lacked deterioration and dementia, which he associated with schizophrenia **(Soreff, 2006).**

Bipolar disorder (manic-depression) impacts approximately 1% of the population, compared to a lifetime prevalence of 6% for unipolar depression, and is equally prevalent among men and women **(Soreff, 2006).**

Bipolar depression result in a greater overall burden on patients and families due to an earlier age at onset, more frequent episodes, and a greater proportion of time spent ill **(Bowden, 2001)**. Approximately 25-50% of individuals with bipolar disorder attempt suicide, and 11% actually commit suicide **(Soreff, 2006).**

The onset of bipolar disorder often occurs in what should be a particularly productive time of life. Regardless of age of onset, there is typically a five- to ten-year delay between onset and time of first treatment or first hospitalization **(Sachs et al., 2000).**

People with bipolar disorder usually see several doctors and, on average, spend more than eight years seeking treatment before receiving a correct diagnosis , which is likely to further influence outcome, as well as account for notable economic impact **(Ghaemi et al., 1999).**

Providing close daily contact and care to patients with bipolar disorder exacts a toll on their families and caregivers. Many patients with bipolar disorder divorce or experience marital problems. Not only must caregivers of patients with bipolar disorder deal with the impact of patients' symptoms, caregivers also feel the effects of patients' illness on their work and leisure time. The combination of missed work hours and lower productivity caused by stress adds a financial burden on the caregiver, as well as on society as a whole **(Ghaemi et al., 1999).** These all lead to recognizing BAD as the sixth leading cause of disability world wide **(Woods et al., 2000).**

The etiology and pathophysiology of bipolar disorder have not been determined, and no objective biological markers exist that correspond definitively with the disease state. However, twin, family, and adoption studies all indicate strongly that bipolar disorder has a genetic component. In fact, first-degree relatives of a person with bipolar disorder are approximately 7 times more likely to develop bipolar disorder than the rest of the population **(Parbakaran, 2004).**

Brain imaging studies of persons with bipolar disorder show abnormal myelination in several brain regions associated with this illness. Neuroimaging also shows evidence of cell loss or atrophy in brain regions as the frontal lobe and the hippocampus. This suggests that damage to cells of critical brain circuitry might be the cause of the illness **(Parbakaran, 2004).**

Abnormally large brain ventricles have been reported frequently, albeit inconsistently, in bipolar disorder **(Strakowski et al., 2002)**. Groups with less chronic or severe illness may be less likely to have ventriculomegaly. For example, first-episode or adolescent patients have only somewhat larger ventricles than healthy subjects **(Botteron et al., 1995)**. In addition, Hauser et al. **(Hauser et al., 2000)** found lateral ventriculomegaly in bipolar disorder type I but not bipolar disorder type II, suggesting that the severity of the manic phase, which differentiates these subtypes, may be associated with ventriculomegaly. Therefore, lateral ventriculomegaly might progress with repeated affective episodes and greater illness severity in bipolar disorder. The neuropathologic meaning of large ventricles is unclear but may reflect small volumes of periventricular brain regions. Several periventricular structures (e.g., striatum, thalamus, hippocampus) appear to modulate mood and cognition and so may be relevant to the expression of affective symptoms. With these considerations in mind, we predicted that the multiple-episode patients would have larger ventricles than the first-episode patients and that the volumes would be associated with course of

illness. Consequently, cognitive deterioration might be present along with ventriculomegally occurring with the progression of illness.

Post, 2003 proposed a mechanism involving electrophysiological kindling and behavioral sensitization processes, a method that also resonates with the previous hypothesis based on neuronal injury. Post asserts that an individual who is susceptible to bipolar disorder experiences an increasing number of minor neurological insults, perhaps caused by drugs of abuse, excessive glucocorticoid stimulation resulting from acute or chronic stress, or other factors, which eventually result in mania. Subsequently, sufficient brain damage might persist such that mania could recur even with no or minor environmental or behavioral stressors. **(Soreff, 2006).**

There is a growing consensus that persistent cognitive deficits are common in patients with bipolar affective disorder even when they are euthymic. Information about onset and course of cognitive deficits is, however, scarce. Apart from certain exceptions, studies of remitted patients have generally reported deficits in several cognitive domains. However, many of these studies have not controlled for residual affective symptoms, which could have a substantial bearing on their results. When this has been done enduring deficits have been observed in either memory or executive functions, or a combination of these areas. More specifically, there have been reports of impairment in

visuospatial memory, verbal learning, executive functions **(Thompson et al., 2005)** and sustained attention **(Clark et al., 2002)** among euthymic patients of Bipolar affective disorder (BPAD) **(Nehra et al., 2006)**.

Then again, it is not immediately clear whether cognitive impairment in BPAD is present right from the onset of the illness, or develops following repeated episodes. Some of the evidence such as **Danicoff et al., (1999)** suggests that recurring episodes of BPAD are associated with greater cognitive disturbance. It has been proposed that successive episodes cause subtle damage to key brain areas leading to the neurological and cognitive impairments observed in BPAD **(Altshuler, 1993)**. However, the evidence linking cognitive deficits with indicators of severity/progression of the illness is not always consistent. Moreover, some studies have also shown that patients with first episode BPAD perform significantly worse than normal controls on a wide variety of neuropsychological tests **(Albus et al., 1996).**

The most direct approach to determine the course of cognitive abnormalities in BPAD would be a longitudinal follow up of first episode subjects with repeated assessments of their cognitive function. This is usually difficult and expensive. Alternatively, cognitive functions of patients in their first episodes could be compared with patients who have already experienced multiple episodes. Such a strategy has been

successfully used in schizophrenia to demonstrate that cognitive profiles of first break patients are similar to those with chronic illness, pointing to the non progressive nature of cognitive dysfunction in schizophrenia **(Hyde et al., 1994).**

Rational

Cognitive impairment can have several adverse consequences for patients of BPAD in terms of disability, quality of life, and outcome. Individuals with bipolar disorder are at risk for an addiction. This creates the problem of a dual diagnosis and, therefore, complicates treatment. They are also at risk of committing suicide or homicide when acting on their delusions. Therefore, this must be a priority area for future research.

Apart from certain exceptions, studies of remitted patients have generally reported deficits in several cognitive domains. However, many of these studies have not controlled for residual affective symptoms, which could have a substantial bearing on their results. Therefore, cognitive assessment of BPAD after complete remission is essential in order to reach satisfactory results.

Hypothesis:

Cognitive dysfunctions are present in euthymic bipolar patients. Their onset is prior to the occurrence of illness and might be progressive with the occurrence of multiple episodes.

Aim of the work:

Theoretical part:

1. To review other literatures covering cognitive deficits in patients with single and multiple episode bipolar affective disorders.

Practical part:

1. Assess cognitive functions of a group of euthymic and stable bipolar patients with a single manic episode.
2. Compare and contrast cognitive profiles of single episode bipolar patients with those who had experienced multiple episodes, both while in remission.
3. Comparing results with a cross matched control group.

Methods

A. Site of research:

Out patient clinic in the institute of psychiatry (Ain Shams University) which represents a true random sample of the Egyptian population.

Subject's selection:

- Two random samples of BPAD in remission. Group I after a single episode and Group II after multiple episodes.
- A cross matched Control group will be selected, regarding age, sex, educational level and other sociodemographic factors.
- Written informed consent will be obtained from the subjects and one of their care givers about the nature and the aim of the study.

B. Operational definition:

First episode BPAD in remission:

Euthymic patients who had one single manic episode.

Multiple episodes BPAD in remission:

Euthymic patients who had 3 or more episodes of mania, hypomania, depression or mixed episode.

C. Inclusion criteria for both patient groups (single episode and multiple episode BPAD in remission) random input:

1. Age ranging from 20 – 40 years.
2. With a diagnosis of BPAD -I.
3. Patients have to be euthymic (Hamilton depression rating scale < 8; young mania rating scale < 6) and stable.
4. Read and write Arabic language.
5. Average IQ.

6. Have not done ECT in the 3-month period prior to inclusion.
7. Patient had been euthymic for at least 3 months prior to inclusion

D. Exclusion criteria for both patients groups:

1. No gross neurological disorder.
2. No co-morbid psychiatric disorder.
3. No mental retardation.
4. No substance abuse.
5. No organic cause.

E. Control exclusion criteria:

1. Gross neurological disorder.
2. Mental retardation.
3. Substance abuse.
4. Previous history of psychiatric illness.
5. Have a first degree relative with affective disorder.

Control group is going to be cross matched with the patients groups regarding; age, sex and educational level.

Tools:

1. Semi-structured sheet this sheet will be designed by the researcher under supervision of the supervisors including Sociodemographic factors, age, sex, marital status, religion, education level, past history, family history,

number of episodes, psychiatric treatment taken in previous episodes.

2. Wechsler IQ (WAIS) for all groups.
3. ICD-10 symptoms chick list for both patient groups.
4. Hamilton depression rating scale for both patient groups.
5. Young mania rating scale for all patient groups.
6. General health questioner for the control group.
7. Cognitive Assessment tests including:
    - Executive functions assessed using the Wisconsin card sorting test computerized version **(WCST, 1981)**, the trail making test B **(trail B; reitan, 1958)**.
    - Memory assessed using the Wechsler memory scale (WMS-R).
    - Attention and concentration assessed using the trail making test A **(trail A; reitan, 1958)**.

Procedures:

Pilot study:

Pilot study is going to be done for one month in order to determine the exact size of the sample and to find out any problem facing the study and try to solve it.

Study proper:

- The study contains 3 groups; group I fifty patient's single episode BPAD in remission. Group II, fifty patients with

multiple episodes BPAD in remission and fifty healthy control individuals.

- Any patient at the outpatient clinic fulfilling the inclusion criteria will be included in the study.
- Both groups of single episode and multiple episode BPAD will undergo:
    - **a)** Semi-structured sheet this sheet will be done by the researcher under supervision of the supervisor including Sociodemographic factors, age, sex, marital status, religion, education level, past history, family history, number of episodes, psychiatric treatment taken in previous episodes.
    - **b)** ICD-10 symptoms chick list.
    - **c)** Hamilton depression scale and YOUNG mania scale.
    - **d)** Cognitive Assessment tests including:
        a. WCST CV.
        b. Wechsler memory scale.
        c. Wechsler IQ.
        d. Trail A test.
        e. Trail B test.

For the control group:

- Semi-structured sheet this sheet will be done by the researcher under supervision of the supervisor including Sociodemographic factors, age, sex, marital status, religion, education level, past history, family history.

- Cognitive Assessment tests including:
    a. WCST.
    b. Wechsler memory scale.
    c. Wechsler IQ.
    d. Trail A test.
    e. Trail B test.
- General Heath Questionnaire.

❖ The data collected will be analyzed using the Statistical Package for the Social Sciences (SPSS) version 16.0 **(2007)** by a professional statistician.

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