Comorbidity and Misdiagnosis of Pediatric Bipolar Disorder among a Sample of ADHD Children and Adolescents

Thesis

Submitted for partial fulfillment of M.D degree in Psychiatry

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LIST OF ABBREVIATION

ADD	: Attention Deficit Disorder.
ADHD	: Attention Deficit Hyperactivity Disorder.
BAD	: Bipolar affective disorder.
BAD NOS	: Bipolar affective disorder not otherwise specified.
BD	: Bipolar disorder.
BADI	: Bipolar affective disorder type I.
BADII	: Bipolar affective disorder type II.
BDNF	: Brain derived neurotrophic factor.
CABF	: Child and adolescent bipolar foundation.
CBT	: Cognitive behavior therapy.
CD	: Conduct disorder.
CMRS	: Child Mania rating scale.
CPRS-L	: Conner's Parent Rating Scale -revised -long version.
CPT	: Continuous performance test.
DSM-IV	: Diagnostic and statistical manual of mental disorders IV.
ECT	: Electroconvulsive Therapy.
EF	: Executive functions.
FDA	: Food and drug administration.

GAF	: Global assessment of functioning.
IQ	: Intelligence quotient.
JBPD	: Juvenile onset bipolar disorder.
K-SADS-PL	: Kiddies Schedule for Affective Disorders and Schizophrenia, Present and Lifetime versions.
MPH	: Methylphenidate.
MTA	: Multimodal treatment study of children with ADHD.
NEAs	: Neurological examination abnormalities.
MDD	: Major depressive disorder.
ODD	: Oppositional defiant disorder.
PANESS	: Physical and Neurological Examination for Soft Signs.
PBD	: Pediatric bipolar disorder.
PEA-BP	: Pre-pubertal and early-adolescent bipolar.
PDD	: Pervasive developmental disorder.
ROC	: Receiver operating characteristic.
SCID-I	: Structured clinical interview for DSMIV.
SR	: Sustained-release.
SPSS	: Statistical package for social sciences.
SSRIS	: Selective serotonin reuptake inhibitors.
WISC	: Wechsler Intelligence Scale for Children.

Introduction

Attention deficit hyperactivity disorder (ADHD) is the most common psychiatric disability in childhood, with an estimated incidence of 8–10% for children aged 6–12 years. Approximately 60% of these will persist into adolescence, and approximately 4–5% of adults will have ADHD **(Hershoin, 2006).**

ADHD is often accompanied by one or more co-occurring psychiatric disorders, regardless of the age of the patient. The type of co-morbidity varies and includes learning problems, anxiety disorders, unipolar and bipolar mood disorders, conduct and antisocial personality disorders, and substance use disorders **(Wilens et al., 1994).**

Most recently, Adler and colleagues reported data from the National Comorbidity Study Replication, indicating that 32% of ADHD patients also meet criteria for unipolar depression; 21.2% meet criteria for bipolar disorder; and 9.5% meet criteria for anxiety disorders **(Adler et al., 2006).**

On the other hand, the number of children and adolescents receiving a diagnosis of bipolar disorder has increased markedly during the past decade in the United States. Bipolar disorder was once thought to occur only

rarely in youths, especially children. However, there has been a shift in how the disorder is defined in juveniles. Although current DSM-IV nosology does not distinguish age-specific criteria for bipolar disorder (**American Psychiatric Association, 2000)**, the patterns of illness and symptom definition described in children often vary from the classic description of the disorder in adults (i.e., a cyclical illness characterized by distinct phases of mania and depression) **(McClellan et al., 2007).**

One of the most controversial issues in the diagnosis and treatment is the extent to which bipolar disorder and ADHD co-occurs. The rates of bipolar disorder in children with ADHD vary widely and depend in part on how the diagnosis of bipolar disorder is made, although most recognize that there is a subgroup of children who present with affective liability that is especially challenging for the clinician **(Pliszka, 2003).**

The forms of this co-occurrence could be BPD symptom expression leads to overdiagnosis of ADHD in BPD youth, ADHD is a prodromal or early manifestation of pediatric-onset BPD, the use of psychostimulants in the treatment of ADHD leads to the onset of pediatric BPD or ADHD and BPD share an underlying biological etiology (a common familial or genetic risk or underlying neurophysiology) **(Singh et al., 2006).**

To aid in early diagnosis of bipolar disorder, a study at the National Institutes of Mental Health in Mental

Health Association of Greater St. Louis in USA cited five key symptoms of grandiosity, suicide gesture, irritability, decreased need for sleep and racing thoughts. The diagnosis of pediatric bipolar disorder is important for the treatment of co-morbid ADHD and bipolar disorder. Several studies have shown that concomitant treatment with a mood stabilizer (such as divalproex sodium) and an approved ADHD medication (such as Atomoxetine) can be effective for treating symptoms of both disorders and reducing the impairment **(Scheffer et al., 2005).**

Much controversy remains to be resolved regarding the prevalence, phenomenology, and treatment of co-morbid or missed bipolar disorder within context of ADHD in children and adults. Clinicians need to be aware that these conditions can co-occur and should carefully consider pharmacologic options for patients presenting with both disorders (**Kollins, 2007).**

Hypothesis

The study hypothesizes that there is a great overlap between pediatric bipolar disorder and ADHD in form of comorbidity or misdiagnosis. There is also increased percent of bipolar spectrum disorders in parents of ADHD diagnosed children and this could be an indicator of comorbid or misdiagnosed bipolar disorder. These psychiatric problems are not well revealed, at least in the Egyptian patients.

Subjects and Methods

I- Study design

This study is a cross-sectional study.

II- Site of the study

The cases were selected from the outpatient child psychiatry clinic in the institute of psychiatry Ain Shams University Hospital which is characterized by:

- It is located in East Cairo.
- It serves both urban and rural areas.
- It is subdivided into private and free sections so the patients would represent middle and low social strata.

That's why it was selected as the site of the study.

III- Subjects

Sixty patients and their both parents participated in this study. All patients were selected during a one year interval from May 2008 to May 2009.

A-The patients group

A sample of sixty patients attending the outpatient clinic of Ain Shams University Hospital Institute of Psychiatry, and their both parents were included in the study.

1) Selection of sample

a) Inclusion criteria:

The study included Egyptian patients with the following criteria:

- Children and adolescents diagnosed clinically to have ADHD in the outpatient clinic.
- Age range is between 6-16 years old.
- Both sexes will be included.

The parents should give written consent for their children's participation in the study.

b) Exclusion criteria:

- IQ score below 80.
- The presence of neurological disabilities.

2) Choice of cases

The cases were from the outpatient clinic (either newly diagnosed or follow up cases). All cases fulfilling the selection criteria attending the Child outpatient psychiatric clinic during the time interval of the study were included.

IV- Tools

1) Wechsler Intelligence Scale for Children (WISC) Arabic version (Wechsler, 1991)

Aim: Assessment of intellectual abilities and cognitive functions.

- The Wechsler scale provides information about the most important aspects of the subject's intellectual functioning. It was chosen in our study to:
    - Determine the general level of intelligence.
    - Explore the difference between verbal and performance scales.
- **Description:** Wechsler Intelligence Scale is a battery comprising 13 subtests, each is scored on its own which are divided into two parts: **1) Verbal Scale Subtest;** for verbal I.Q., and is based on six verbal subtests. **2) Performance Scale Subtests;** for performance I.Q. and is based on five performance subtests. Both scored yield the **Full Scale I.Q.,** which is the average index of general intellectual functioning.

- **Choice of version:** We used the standardized Arabic version of the test **(Ismail and Melika, 1999)**. This is one of a series of standardized tests to evaluate the cognitive and intellectual abilities of children and adults.
- **Choice of subjects:** In this study, it was used to assess children and adolescents from 6- 16 years old (as inclusion criteria).
- **Verbal subscales were used:** information, vocabulary, Comprehension arithmetic, similarities and digit-span.
- **Performance subscales were used**: Picture completion, Picture arrangement, Block design and object assembly, coding, mazes and symbol search.
- So accordingly verbal, performance and total IQ were calculated.
- The test was administrated by the clinical psychologist in the institute of psychiatry Ain Shams University.

2) <u>The Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime versions (K-SADS-PL) (Kaufman et al., 1997)</u>

Aim: confirming diagnosis of ADHD and its subtypes, diagnosing mood disorders and any co-morbid other disruptive behavioral disorder.

- The Schedule for Affective Disorders and Schizophrenia for School age Children (K-SADS) was

originally developed in 1977 on the basis of Endicott and Spitzer's Schedule for Affective Disorders and Schizophrenia (SADS) for adults. The K-SADS is an interviewer-based, semi-structured interview for children age, 6-18. Its primary goals is to assess current and life time history of psychiatric disorders, assess episodes of psychopathology and to make categorical diagnosis by directly interviewing children and adolescents and their parents, according to DSM-III-R and DSM-IV criteria.

- The K-SADS-PL is administered by interviewing the youth; the mean administration time is 80-90 minutes. It is preceded by an unstructured introductory interview which takes about 10-15 minutes to complete. In this section, demographic, medical data and presenting complaint. The screening interview assesses the primary symptoms of the different diagnoses of the K-SADS-PL. Positive scores (a score of 3 on any of the screened symptoms) in the screening interview mandates completion of the corresponding supplement questionnaire.

- Supplement completion checklist: The K-SADS-PL contains 5 diagnostic supplements for the psychiatric disorders assessed, namely: affective disorders, psychotic disorders, anxiety disorders, behavioral

disorders and substance abuse and other disorders supplement, culminating in confirmation of the diagnosis.

- The majority of the items in the K-SADS-PL are scored using a 0-3 point-rating scales as follows:

0 indicates no available information.

1 the symptom is not present.

2 subthreshold intensity of symptomatology.

3 threshold criteria.

Whereas other points are scored on a 0-2 point rating scale on which

0 implies no available information.

1 the symptom is not present.

2 the symptom is present.

- The Arabic version of the K-SADS-PL used in this study was translated and validated through previous research conducted by **(Ibrahim et al., 2000)** in the Institute of Psychiatry, Ain Shams University.

3) Structured Clinical Interview for DSM-IV (SCID- I) *(First et al., 1995)*

Aim: the mood disorders subscale was used to assess both parents for any mood disorders spectrum

- Structured clinical interview for DSM-IV: the SCID was developed in the early 1990s to provide a standardized DSMIII- R axis I diagnosis based on an efficient but thorough clinical evaluation. It has since been updated for DSM-IV.
- The semistructured diagnostic interview begins with a section on demographic information and clinical background. Then there are 7 diagnostic modules, focused on different diagnostic groups: mood, psychotic, substance abuse, anxiety, somatoform, eating and adjustment disorders. Both required and optional probes are provided, and skip outs are subjected when no further questioning is warranted.

- All available information, including that from hospital records, informants, and patient's observation should be used to rate the SCID. The SCID is designed to be administered by experienced clinicians and is generally not recommended for use by lay interviewers. In individuals without symptoms, the interview takes approximately 1 hour, but it may take up to 3 hours in individuals with extensive symptomatology.

- It is considered the standard interview to verify diagnosis in clinical trials and is extensively used in other forms of psychiatric research.
- The Arabic version of the SCID-I used in this study was translated and validated through previous research conducted by **(El Missery et al., 2003)** in the Institute of Psychiatry, Ain Shams University.

4) Conner's Parent Rating Scale-revised; long version (CPRS-L) (Conner, 1997)

Aim: it is applied to assess severity of ADHD, and assess scores in co-morbid cases of ADHD and bipolar disorders to compare to cases with ADHD only.

- It is an 80 item questionnaire with an average administration time of 25- 30 minutes. It scores the parents' report of their child's behavior during the past month on a 4-point-response scoring, namely:

0: Not true or seldom true

1: Just a little true, occasionally

2: Often true, quite a bit

3: Very often true, very much true

- Despite its ability to score youths' behavior between the ages of 3-17 with strong confidence and outlining the profile of possible comorbidities, however its main use is in assessment of the severity of ADHD,

response to treatment, follow up studies, and DSM-IV diagnostic correspondence.

- Items are scored on 14 subscales of symptoms namely: oppositional, cognitive problems and inattention, hyperactivity, anxious shy, perfectionism, social problems, psychosomatic, ADHD index (screening test for inattention), Conners' global index: restless impulsive, emotional liability, total index: (screening test for hyperactivity), DSM-IV: inattentive, hyperactive-impulsive and total score.

- **T score guideline:**

1- Average, typical score 45-55.

2- Slightly atypical, borderline 56-60.

3- Mildly atypical, possible problems 61-65.

4- Moderately atypical, evident significant 66-70 .

5- Markedly atypical, significant problem > 70 .

- The Arabic versions of the Conner's rating scales revised, long versions, parent form used in this study were translated and validated through previous research conducted by ***(El Sheikh et al., 2003)*** in the institute of psychiatry, Ain Shams University.

5) The child mania rating scale (Pavvuluri et al., 2006a)

Aim: to diagnose any missed cases of mania, and differentiate it from ADHD alone.

- The CMRS is a parent report screen measure for child and adolescent mania. It is also able to differentiate ADHD alone from manic episode alone yet it can't differentiate co-morbid ADHD and bipolar from only bipolar cases.

- It is based on DSMIV criteria for mania, 21 items, employs a single focus for each item to minimize error in reporting, indicates the degree each symptom is interfering with the child functioning, and incorporates age-specific items applicable to an age range 5-17 years. It also includes psychotic symptoms that could be missed unless queried. The cutoff point is 20, each item is assessed as follow:

0: never or very rare.

1: sometimes.

2: often.

3: Very often.

V- The procedure

A) Pilot study

Time:

The pilot study was done from May 2008 to August 2008.

Objectives:

- Determine any problems that can face the study proper.
- Determining the size of the sample.
- Identify suitability of tools used with respect to the setting.
- To design the researcher sheet according to the important points to be covered during interviews.
- To assess the reliability, validity and applicability of the chosen tools.
- To test the applicability and feasibility regarding time of administration and linguistic simplicity of the tools.
- To be trained on applying the tools and become acquainted with their ways of administration.

Results of the pilot study:

a- We were able to identify and deal with some problems:

We found it is a must to refer the cases for IQ assessment and Conner's parents rating scales before doing other steps, to exclude cases with IQ below 80.

b- Sample size: during 3 months period of the pilot study, 27 cases were assessed. 5 were excluded due to epilepsy, and 8 due to IQ below 80 or age under 6 years old. Only 14 cases were fit to be included, so it was decided that 60 patients could be assessed with their parents over one year interval.

c- Regarding the reliability of the diagnosis and ascertainment procedures:
During the pilot study the interviewer of this work was observed by an experienced supervisor in the first interviews.

d- Regarding the applicability and feasibility of the assessment tools:
The researcher had to give clear instructions and to clarify the questionnaires to patients participating in the research.

e- Regarding the child mania rating scale, it wasn't used as Arabic version before, so the following steps were done:

1) Translation and back translation twice by the researcher and two supervisors.
2) Application on the patients through pilot study to modify any questions according to Arabic culture.

3) Comparing its results with the KSADS-PL the mania rating scale, the KSADS Arabic version has been translated and validated through previous research conducted by **(Ibrahim et al., 2000)** in the Institute of Psychiatry, Ain Shams University. This comparison was done to measures shown in table (2) and figure (1).

   - Construct validity (which is the evidence of the extent to which the measure is measuring what it was designed to measure). It correlated with the KSADS-MRS as 0.965.

   - Criterion related validity on the receiver operating characteristic (ROC) analysis found that cut off score 22, resulted in sensitivity 93.3 and specifity 100.

Table (2): The ROC curve between KSADS and CMRS.

ROC curve between KSADS and CMRS					
Cutoff	**Sens.**	**Spec.**	**PPV**	**NPV**	**Accuracy**
> 22	93.3	100.0	100.0	97.8	0.965

It shows that at a cutoff point 22, the sensitivity in comparison to KSADS-PL is 93.3%, and specifity is 100%, the positive predictive value is 100% and negative predictive value is 97.8% leading to accuracy 0.9654.

Figure (1): The sensitivity and specifity of CMRS Arabic version.

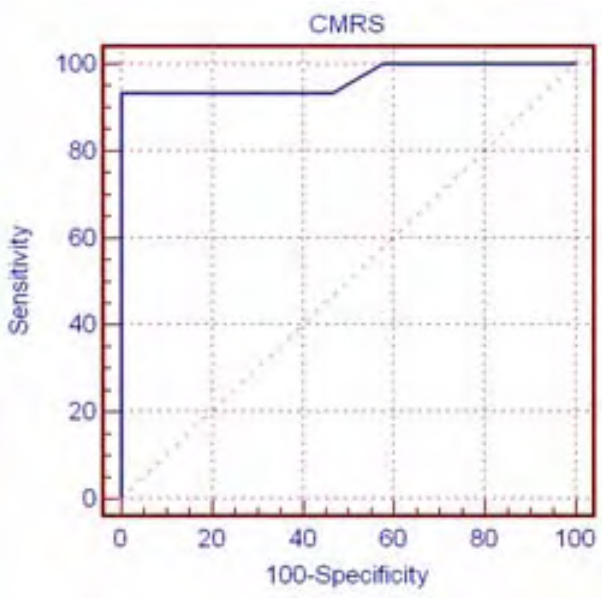
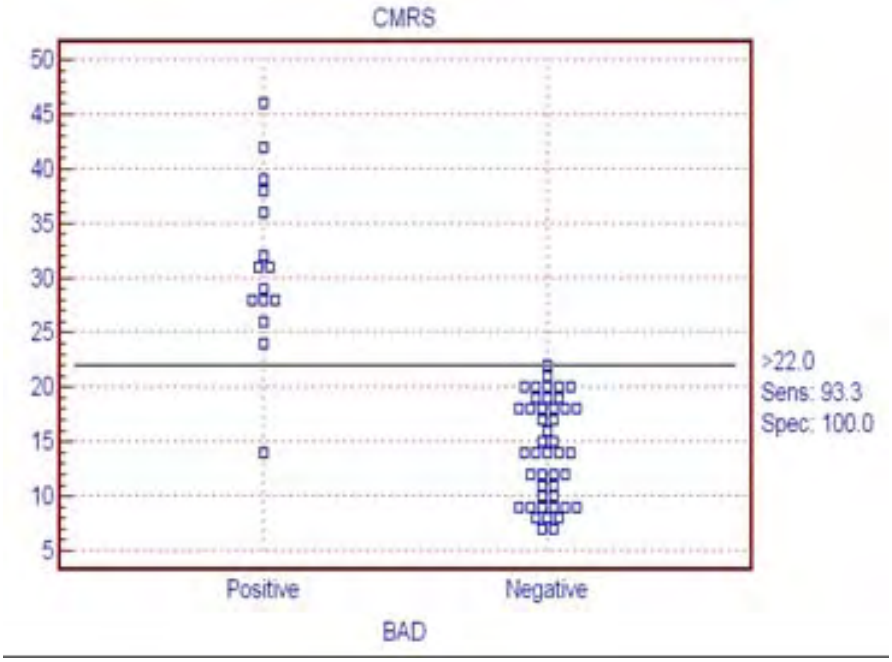


Figure (2): The cutoff point for CMRS Arabic version



f- During this period the researcher became acquainted with the research tools and was well trained on applying them.

B) Study proper

The cases diagnosed as ADHD in the outpatient clinic and fulfilling the selection criteria were subjected to the following steps:

- An informed consent was obtained from the parents of the patients. Then the patients were assessed in the following steps:

i. The First step:

The cases were referred to the clinical psychologist to perform:

- Evaluation of IQ (verbal, performance and total) using Wechsler Intelligence Scale translated form **(Ismail and Melekia, 1999).**
- If they are above 80 as regards total IQ, The Conner's parents rating scale long version **(El Sheikh et al., 2003)** was applied to assess the severity of the symptoms.

ii. The second step:

The child and both parents are interviewed as following:

- The Interviewer was the researcher.

- Clinical interview to fulfill the items of the sheet designed by the researcher that include all relevant demographic data.
- The Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime versions (K-SADS-PL) **(Kaufman et al., 2007),** translated form **(Ibrahim et al., 2000)**. It was used to confirm diagnosis of ADHD, determine which type, to diagnose mood disorders and search for other co-morbid disruptive behavioral disorders.
- The child mania rating scale **(Pavvuluri et al., 2006a)** in its Arabic translated version was used to search for any missing cases with a manic episode in children and adolescents, also it help differentiating ADHD from manic episodes which is difficult due to presence of many shared diagnostic criteria according to DSMIV.

iii. <u>The third step:</u>

Both parents were interviewed separately for:

- Full family history of ADHD or Mood Disorders.
- The structured clinical interview for DSMIV axis I disorders (SCID-I) clinical version, the section of

mood disorders was applied on them to detect any form of mood disorders in them.

The assessment of each patient and the parents consumed around 2-3 hours according to the cooperation of the patient and his family. The assessment was done through 1-2 settings.

VI- Statistical Methods

Statistical analyses were done by the statistical package for social sciences (SPSS), version 16. The results were tabulated, grouped and statistically analyzed using the following tests:

1) Pearson chi square test: to detect whether there is significant association between different categorical variables.
2) Student t Test: for comparison between means of different group of patients.
3) Multiple logistic regression analysis: used to examine the extent to which a set of variables independently predicts a dependent variable.

4) P value: used to indicate the level of significance
P > 0.05: insignificant.

P < 0.05: significant.

P >0.01: highly significant.

P< 0.001: very highly significant.

Aim of the work:

The study is designed to verify the study hypothesis by:

1. Investigating the presence of cases of pediatric bipolar disorder that are misdiagnosed as ADHD.

2. Investigating the co-morbidity of ADHD and bipolar disorders in children and adolescents.

3. Investigating the presence of a positive family history of mood disorders spectrum among parents of ADHD children and its correlation to appearance of comorbidity or misdiagnosis of bipolar disorder in their offsprings.

Results

There has been a continued debate in the last decade about the diagnoses of pediatric bipolar disorder in children and adolescents, and on the degree of similarity in symptoms and signs profile between it and ADHD leading to misdiagnosis and comorbidity between them. Our present study aims at studying the prevalence of these forms of comorbidity and misdiagnosis, besides studying the parents of these children for any mood disorders spectrum.

Results in this chapter were grouped to cover the following questions:

1. Description of the whole sample included in the study.
2. The prevalence of co-morbidity or misdiagnosis of Pediatric Bipolar disorder among ADHD cases.
3. The clinical profile of ADHD cases suggesting co-morbidity with Pediatric Bipolar disorder.
4. The co-morbidity with other disorders as Oppositional defiant disorder and Conduct disorder.
5. Is there a relation between positive mood disorders in parents and Bipolar disorder in their children?
6. The predictive factors for possible Bipolar disorder co-morbidity in ADHD cases.

Section I

Description of the whole sample included in the study

The study is designed to investigate the prevalence of co-morbidity and misdiagnosis of pediatric bipolar disorder among (60 cases) of ADHD (newly diagnosed or follow up cases) in the outpatient clinic, in addition their both parents were studied for mood disorders spectrum.

I- Socio-demographic data

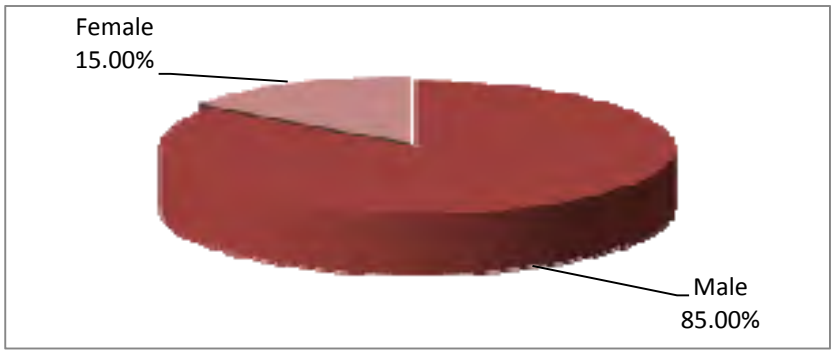
- **Age**

  We found that the mean age of the sample was 8.03 with standard deviation 1.50.

- **Sex**

  The sample was 85% (n=51) males and 15% (n=9) females as shown in figure (3).

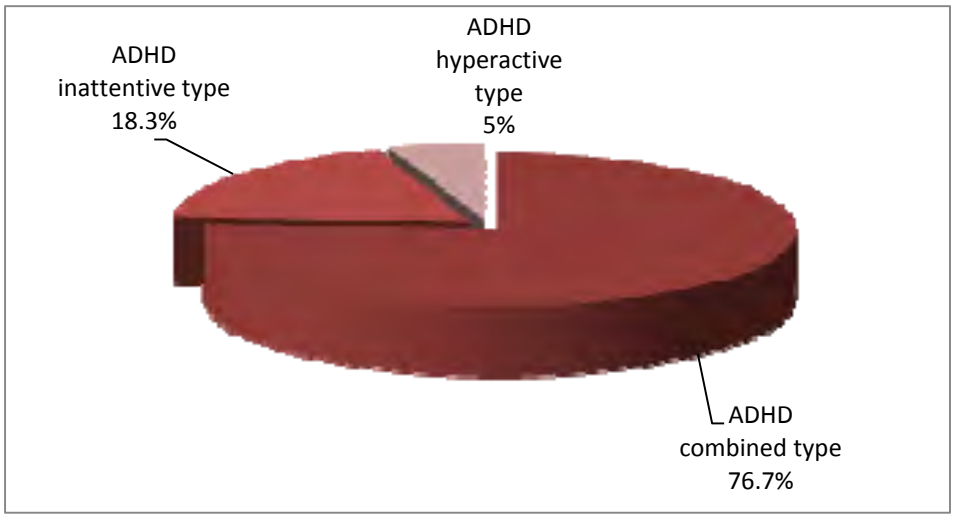
Fig (3): Sex distribution among the sample.



II- ADHD types

As shown in figure (4), the referred cases were 76.7%(n= 46) diagnosed as ADHD combined type, 18.3%(n=11) as ADHD inattentive type and 5%(n=3) as ADHD hyperactive impulsive type.

Fig (4): The types of ADHD among the sample.



III- Intellectual quotient

The mean total IQ of the sample was 99.17 ± 9.46, as regards verbal IQ 98.63 ± 8.71 and performance IQ 98.90 ± 10.15.

IV- Age of onset of ADHD

The mean age of onset of ADHD was 4.45±1.17.

V- Medications

There were 78.3% (n=47) of the sample newly diagnosed and not on treatment, 11.7% (n=7) were on Ritalin and 10% (n=6) on other medications as presented in figure (5). The 11.7% on Ritalin was distributed 5% in non comorbid group and 6.7% in comorbid ADHD and bipolar group. On comparing the two groups there were statistically significant difference (p=0.03), the comorbid group was more to be associated with Ritalin treatment as shown in table (3).

Fig (5): The medications distribution in the sample.

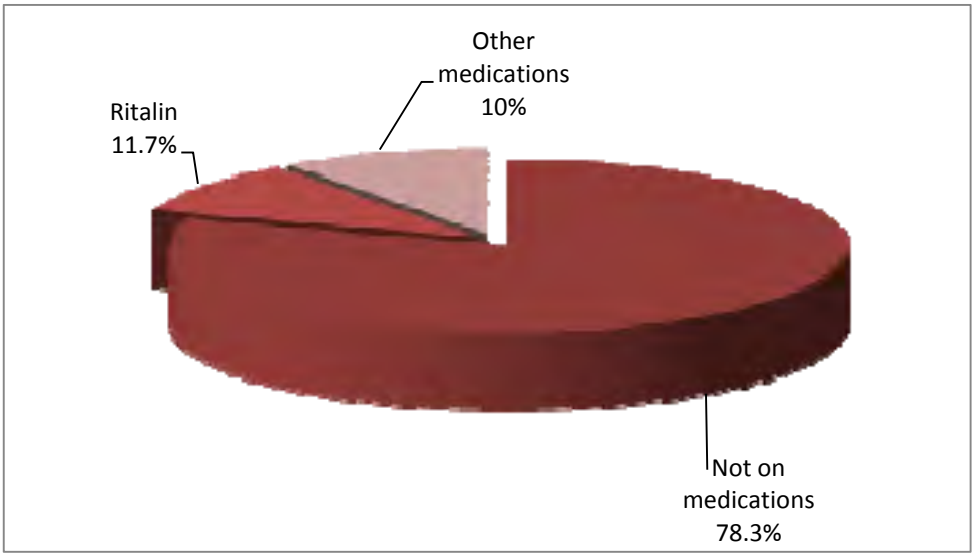


Table (3): Ritalin treatment in both groups.

Ritalin treatment		Comorbid ADHD & BAD		
		Non comorbid	comorbid	Total
On ritalin	N	3	4	7
	%	6.67	26.67	11.67
Not on ritalin	N	42	11	53
	%	93.33	73.33	88.33
Total	N	45	15	60
	%	100.00	100.00	100.00
Chi-square	X^2	4.36		
	P-value	0.03*		

VI- Family history of psychiatric illness

A- Family history of Mood disorders

As regard the family history of mood disorders, the majority of the sample have no family history that represent 93.33% (n=56), only 6.66% (n=4) cases have FH of mood disorders, as shown in table (4).

Table (4): Family history of Mood disorders in the sample.

Family history of mood disorders	N	%
Positive FH of mood disorder	4	6.66
No FH of mood disorder	56	93.33
Total	60	100.00

B- Family history of ADHD

As regard ADHD, 80% (n=48) have no family history of ADHD, while 20% (n=12) of the cases have positive FH of ADHD (9 of them were the brothers, 2 cases the cousin and one case the mother), as shown in table (5). On comparing family history of ADHD in comorbid bipolar and ADHD group to only ADHD group no statistically significant correlation was found (p=1) as shown in table (6).

Table (5): Family history of ADHD in the sample.

Family history of ADHD	N	%
Positive FH of ADHD	12	20.00
No FH of ADHD	48	80.00
Total	60	100.00

Table (6): Family history of ADHD in comorbid and non comorbid groups.

Family history of ADHD		Comorbid ADHD & BAD		
		Non comorbid	comorbid	Total
Positive FH of ADHD	N	9	3	12
	%	15.00	5.00	20.00
No FH of ADHD	N	36	12	48
	%	60.00	20.00	80.00
Total	N	45	15	60
	%	80.00	20.00	100.00
Chi-square	X^2	0.000		
	P-value	1.000		

C- SCID-I of the parents for Mood disorders

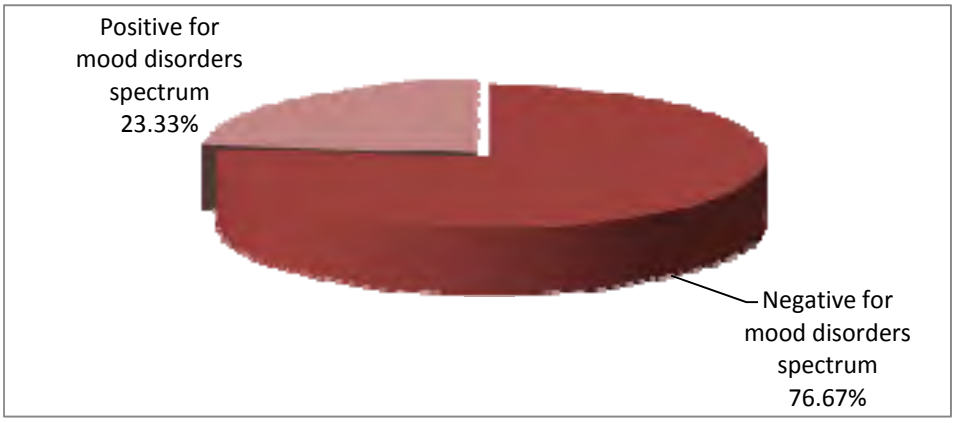
- **SCID-I of the mothers:**

As table (7) and figure (6) reveal, there were positive mood disorder spectrum cases in 23.33% of the mothers (n=14, 9 cases were major depressive disorder, 3 cases were bipolar affective disorder and 2 cases were cyclothymic disorder), and 76.67% (n=46) of the mothers were with no mood disorders spectrum according to SCID-I.

Table (7): SCID-I results for Mood disorders section in mothers.

SCIDI for mood disorder in mothers	N	%
Negative for mood disorders spectrum	46	76.67
Positive for mood disorders spectrum	14	23.33
Total	60	100.00

Fig (6): SCID-I results for Mood disorders section in mothers.



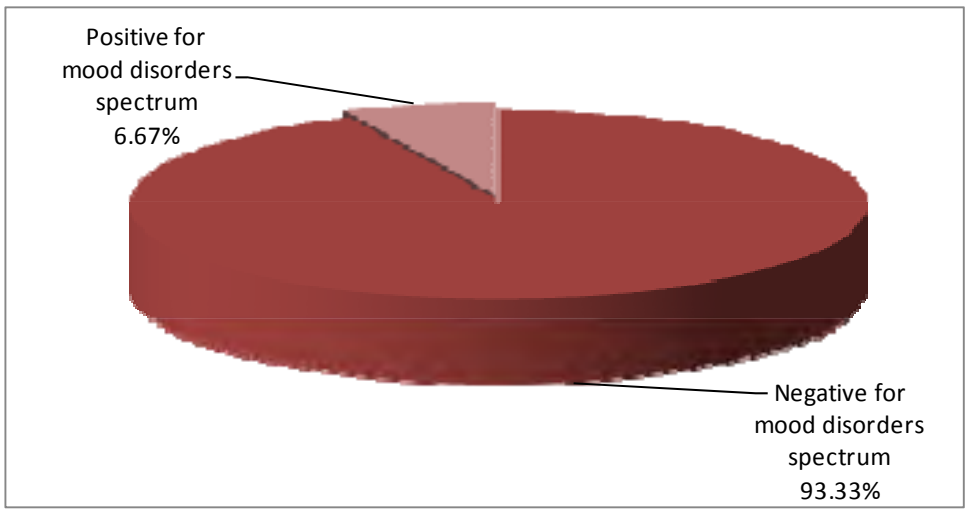
- **SCID-I of the fathers**

As shown in table (8) and figure (7), there were 6.67% cases having positive mood disorder spectrum disorders (n=4, one with cyclothymic disorder, 1 case bipolar affective disorder and 2 cases major depressive disorder). The fathers with no mood disorders spectrum represents 93.33% (n=56).

Table (8): SCIDI results for Mood disorders section in fathers.

SCIDI for mood disorder in fathers	N	%
negative for mood disorders spectrum	56	93.33
positive for mood disorders spectrum	4	6.67
Total	60	100.00

Fig (7): SCIDI results for Mood disorders section in fathers.



D- The disorders categorization according to the KSADS-PL results

The cases after diagnosis by KSADS-PL were divided into the category of disruptive behavior disorders (43 cases which represent 71.67% of the sample), and the category of comorbid disruptive behavior disorders and affective disorders (17 cases which represent 28.33% of the sample) as shown in table (9) and figure (8).

As regard the disruptive behavior disorder category, 18 cases were only ADHD, 23 cases were ADHD and comorbid oppositional defiant disorder and 2 cases ADHD and comorbid conduct disorders as shown in table (10).

For the comorbid affective and disruptive behavior disorders category, 14 cases were comorbid bipolar affective disorder (BAD) and ADHD, 2 cases were comorbid ADHD and major depressive disorder and 1 case was BAD comorbid with oppositional defiant disorder as shown in table (10).

Table (9): The disorders categorization of the sample according to KSADS-PL.

Disorders categories	N	%
Disruptive behavioral disorder	43	71.67
Comorbid disruptive and affective disorders	17	28.33
Total	60	100.00

Fig (8): The disorders categorization of the sample according to KSADS-PL.

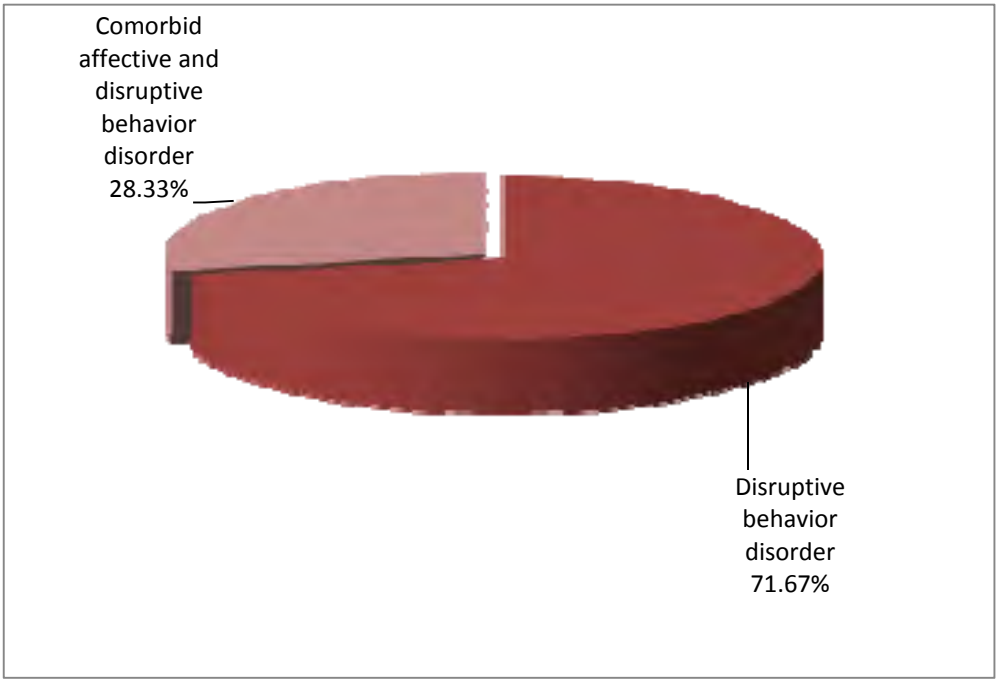


Table (10): The results of the KSADS-PL of the whole sample.

ADHD without comorbid mood disorder	N	%	ADHD with comorbid mood disorder	N	%
ADHD predominantly inattentive	8	13.33%	BAD mixed+ ADHD combined	1	1.67%
ADHD predominantly hyperactive	1	1.67%	BAD NOS+ ADHD combined	2	3.33%
ADHD combined type	9	15%	BAD depression+ ODD	1	1.67%
ADHD hyperactive+ODD	2	3.33%	BAD manic+ADHD combined+ODD	2	3.33%
ADHD inattentive+ODD	2	3.33%	BAD mixed+ADHD combined+ODD	3	5%
ADHD combined type+ODD	19	31.67%	BAD NOS+ ADHD combined type+ODD	3	5%
ADHD combined+ conduct disorders	2	3.33%	BAD manic+ADHD combined type+conduct	1	1.67%
			BAD mixed+ADHD combined type+conduct	1	1.67%
			BAD NOS+ADHD combined+conduct	1	1.67%
			Major depressive disorder+ADHD combined+ODD	1	1.67%
			Major depressive disorder+ADHD inattentive type	1	1.67%
Total	43	71.66%		17	28.33%

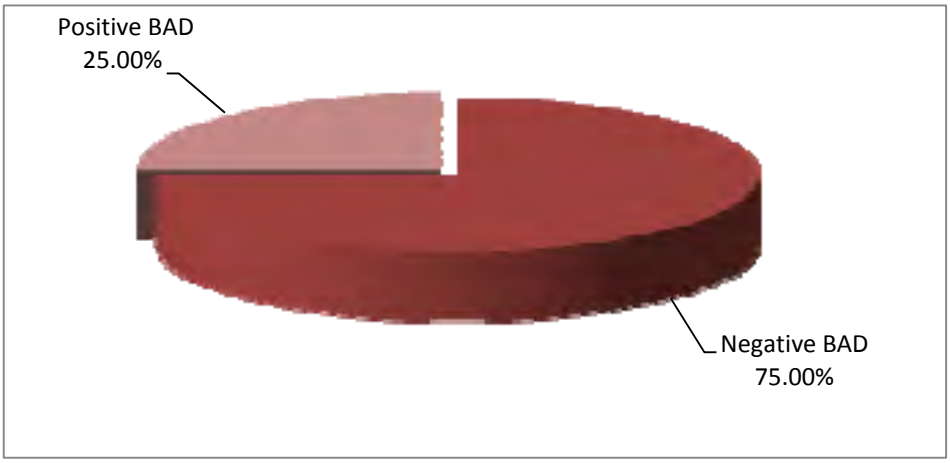
Description of the Bipolar Affective Disorder cases

As shown in table (11) and figure (9), The bipolar affective disorder represents 25% of the sample (n=15, 14 comorbid with ADHD and one case was misdiagnosed as ADHD but on KSADS it was diagnosed as BAD depression and oppositional defiant disorder).

Table (11): The prevalence of bipolar affective disorder in the sample.

BAD cases	N	%
Non BAD	45	75.00
Positive BAD	15	25.00
Total	60	100.00

Figure (9): The bipolar affective disorder cases in the sample.



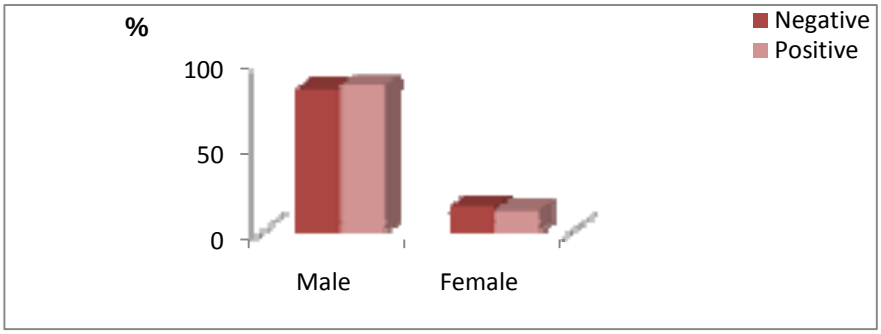
1) Sex

As shown in table (12) and figure (10), 86.67% of the bipolar cases were males (n=13) and 13.33% females (n=2), the comparison between the bipolar and non bipolar cases revealed no statistically significant difference (p=0.834).

Table (12): Sex distribution among bipolar and non bipolar children.

Sex		Bipolar Affective Disorder		
		Non bipolar	Bipolar	Total
Male	N	38	13.00	51
	%	84.44	86.67	85.00
Female	N	7	2.00	9
	%	15.56	13.33	15.00
Total	N	45	15.00	60
	%	100.00	100.00	100.00
Chi-square	X^2	0.04		
	P-value	0.834		

Fig (10): Sex distribution among bipolar and non bipolar children.



2) Age

As shown in table (13), the mean age of this group was 7.464 with standard deviation 1.611.

3) IQ

As shown in table (13), the total IQ was 104.786 with standard deviation 11.116, the verbal IQ 102.538 with standard deviation 10.055, and performance IQ 103.385 with standard deviation 11.737.

4) Age of onset of ADHD

As shown in table (13), the age of onset of ADHD in the bipolar cases was 3.464 with standard deviation 0.843.

5) Age of onset of bipolar disorder

As shown in table (13), the mean age of onset of the bipolar disorder was 4.8 with standard deviation 1.6.

Table (13): Descriptive data of the bipolar cases.

Descriptive data	Bipolar cases
	Mean ± SD
age	7.464 ± 1.611
total IQ	104.786 ± 11.116
verbal IQ	102.538 ± 10.055
performance IQ	103.385 ± 11.737
age of onset of ADHD	3.464 ± 0.843
age of onset of BAD	4.857 ± 1.692

Section II

The prevalence of co-morbidity and misdiagnosis of bipolar affective disorder among ADHD cases

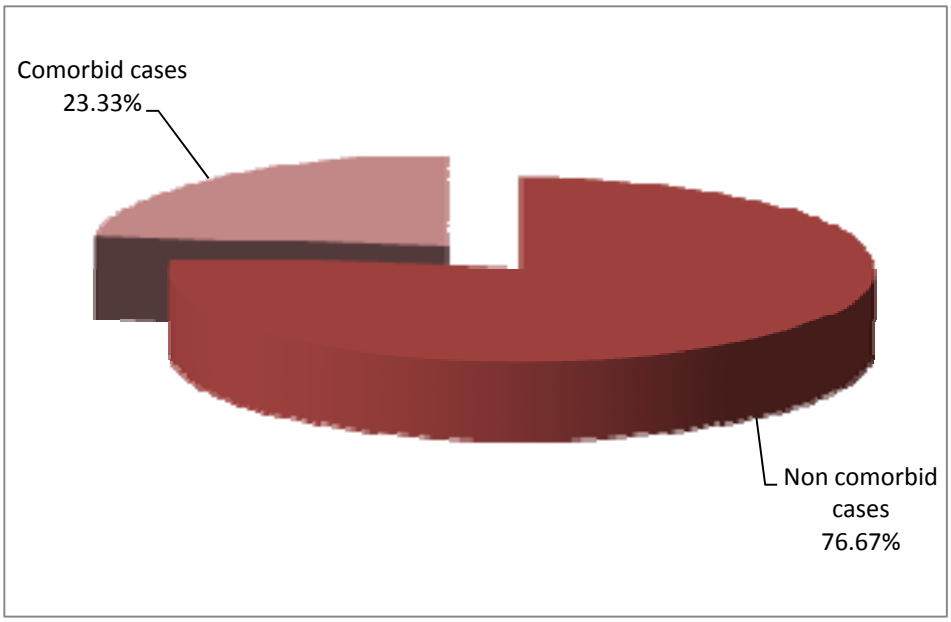
1) The prevalence of comorbidity of bipolar affective disorder and ADHD:

As table (14) & figure (11) reveal, the prevalence was 23.33% (n=14) comorbid bipolar affective disorder and ADHD cases.

Table (14): The prevalence of comorbid ADHD & BAD cases.

Co-morbid BAD and ADHD	N	%
Negative	46	76.67
Positive	14	23.33
Total	60	100.00

Fig (11): The prevalence of co-morbid ADHD & BAD cases.



2) The prevalence of misdiagnosis

There was only 1 case bipolar affective disorder currently depression misdiagnosed as ADHD, represents 0.6% of the sample.

Section III

The clinical profile of ADHD cases suggesting comorbidity with BAD

The comparison between the group of comorbid bipolar affective disorder and ADHD and the group of ADHD without comorbid bipolar disorder revealed the following:

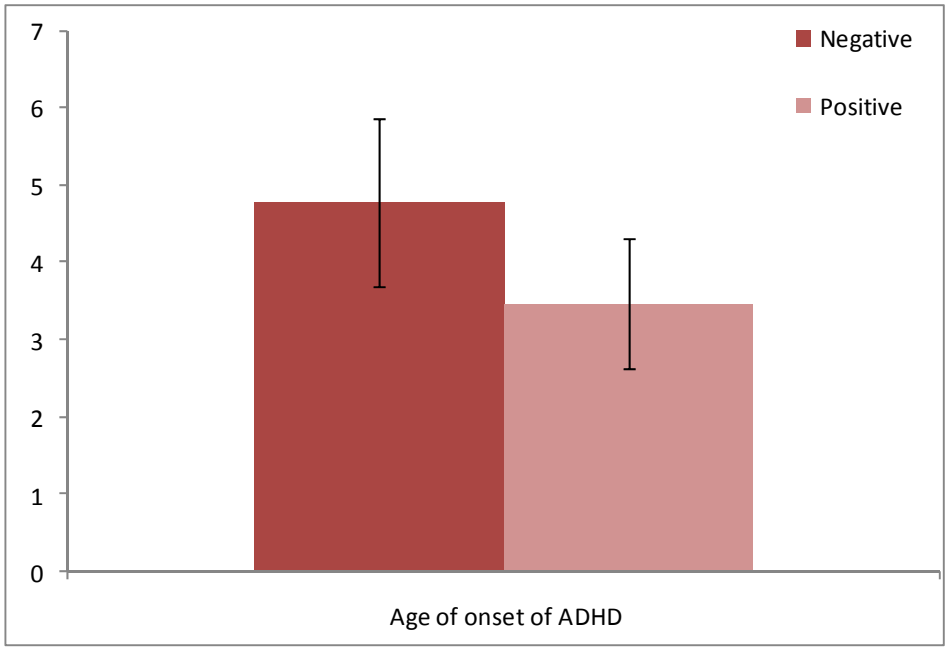
Table (15): Comparison between comorbid ADHD & BAD and non comorbid groups.

Data	Comorbid ADHD & BAD			
	Non comorbid	comorbid	T-test	
	Mean ± SD	Mean ± SD	t	P-value
age	8.207 ± 1.432	7.464 ± 1.611	1.650	0.104
total IQ	97.457 ± 8.296	104.786 ± 11.116	-2.666	0.010*
verbal IQ	97.522 ± 8.077	102.538 ± 10.055	-1.872	0.066
performance IQ	97.600 ± 9.394	103.385 ± 11.737	-1.848	0.070
age of onset of ADHD	4.767 ± 1.088	3.464 ± 0.843	4.092	0.000*

1) Age of onset of ADHD

As figure (12) and table (15) reveal, the cases with comorbid bipolar affective disorder and ADHD age of onset of ADHD were 3.46 ± 0.843 and the cases without comorbid bipolar disorder age of onset of ADHD were 4.767± 1.088. On comparison the cases of comorbid bipolar disorder had earlier age of onset of ADHD with very highly statistically significance (p= 0.000).

Fig (12): Age of onset of ADHD in comorbid and non comorbid groups.



2) Type of ADHD

As shown in table (16), all the comorbid bipolar affective disorder and ADHD were having ADHD

combined type. On comparing the group of comorbid ADHD and BAD to the group without BAD, there were statistically significance that the comorbid group have ADHD combined type more than non comorbid group (p value= 0.012).

Table (16): The types of ADHD in comorbid and non comorbid groups.

ADHD type		Comorbid ADHD & BAD		
		Comorbid	Non comorbid	Total
Combined	N	14	31	45
	%	23.73	52.54	76.27
Inattentive	N	0	11	11
	%	0.00	18.64	18.64
Hyperactive	N	0	3	3
	%	0.00	5.08	5.08
Total	N	14	45	59
	%	23.73	76.27	100.00
Chi-square	X^2	8.857		
	P-value	0.012*		

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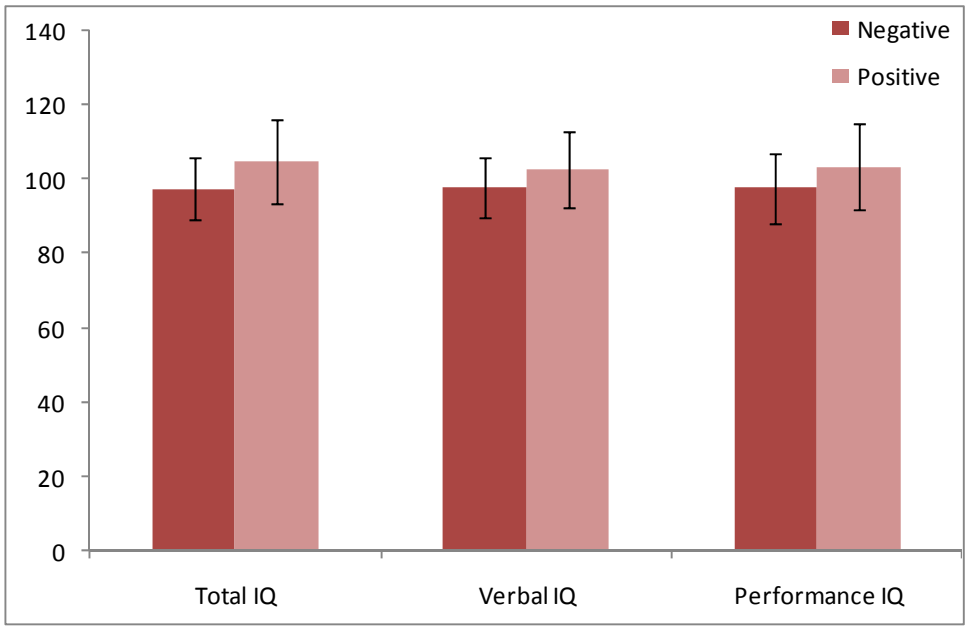
3) IQ

As shown in figure (13) and table (15), the cases with comorbid bipolar affective disorder and ADHD have total IQ 104.78± 11.11, verbal IQ 102.53± 10.05 and performance IQ 103.38± 11.73, cases without bipolar affective disorder have total IQ 97.45± 8.29, verbal IQ 97.52± 8.07 and

performance IQ 97.6± 9.39. On comparing the two groups there were higher total IQ in the bipolar group with statistical significance (p=0.010), yet for verbal and performance IQ there were no significant difference (p value 0.066 & 0.070 respectively).

Fig (13): The IQ results in comorbid and non comorbid groups.



4) Conner's parents rating scale (table 17, figure 14)

As regard the group with comorbid bipolar disorder and ADHD

a) Opposition subscale:

The mean T score is 74.08, which means significant problem.

b) Cognitive subscale:

The mean T score is 72.16, which means significant problem.

c) Hyperactivity subscale:

The mean T score is 83.66, which means significant problem.

d) Conner's ADHD index (inattention) subscale:

The mean T score is 75.5, which means significant problem.

e) Conner's global index (impulsive/restless):

The mean T score is 80.16, which means significant problem.

f) Conner's global index (emotional labiality):

The mean T score is 73.5, which means significant problem.

g) Conner's social problem subscale:

The mean T score is 83.92, which means significant problem.

As for anxious/shy, perfectionism and psychosomatic subscales T score revealed average value, which means no problem.

As regard the group without bipolar disorder

a) **Opposition subscale:**

The mean T score is 72.73, which means significant problem.

b) **Cognitive subscale:**

The mean T score is 81.28, which means significant problem.

c) **Hyperactivity subscale:**

The mean T score is 76.84, which means significant problem.

d) **Conner's ADHD index (inattention) subscale:**

The mean T score is 75.31, which means significant problem.

e) **Conner's global index (impulsive/restless):**
The mean T score is 75.55, which means significant problem.

f) **Conner's global index (emotional labiality):**

The mean T score is 69.46, which means significant problem.

g) **Conner's social problem subscale:**

The mean T score is 75.81, which means significant problem.

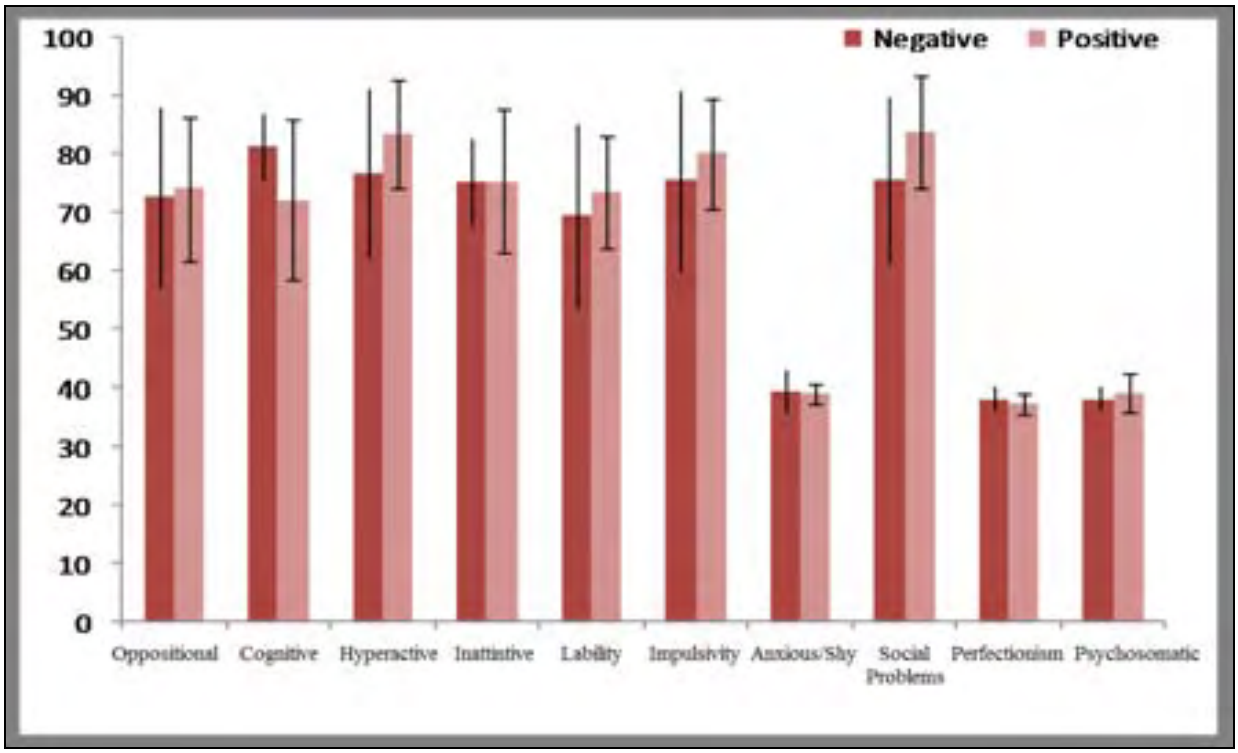
As for anxious/shy, perfectionism and psychosomatic subscales T score revealed average value, which means no problem.

As shown in table (17), on comparing the two groups, the cognitive subscale was found to be better in the comorbid group with statistical significance (p= 0.001), also on the social problem the comorbid group have more social problems with statistical significance (p= 0.027). On the other subscales there was no statistically significant difference between the two groups.

Table (17): The Conner's parent rating scale results of both groups.

Conner's subscale	Comorbid ADHD & BAD					
	Non comorbid		Comorbid		T-test	
	Mean ± SD		Mean ± SD		t	P-value
Conner's oppositional	72.733 ± 15.611		74.083 ± 12.450		-0.276	0.783
Conner's cognitive	81.289 ± 5.727		72.167 ± 13.776		3.504	0.001*
Conner's hyperactive	76.844 ± 14.461		83.667 ± 9.296		-1.546	0.128
Conner's inattentive	75.311 ± 7.437		75.500 ± 12.169		-0.068	0.946
Conner's emotional liability	69.467 ± 15.837		73.500 ± 9.700		-0.838	0.406
Conner's impulsivity	75.556 ± 15.576		80.167 ± 9.590		-0.974	0.334
Conner's anxious/shy	39.546 ± 3.682		39.077 ± 1.754		-0.442	0.660
Conner's social problem	75.818 ± 14.337		83.923 ± 9.810		2.332	0.027*
Conner's perfectionism	38.318 ± 1.877		37.539 ± 1.854		-1.329	0.199
Conner's psychosomatic	38.273 ± 1.969		39.385 ± 3.203		1.187	0.254

Fig (14): The Conner's parent rating scale results of both groups.



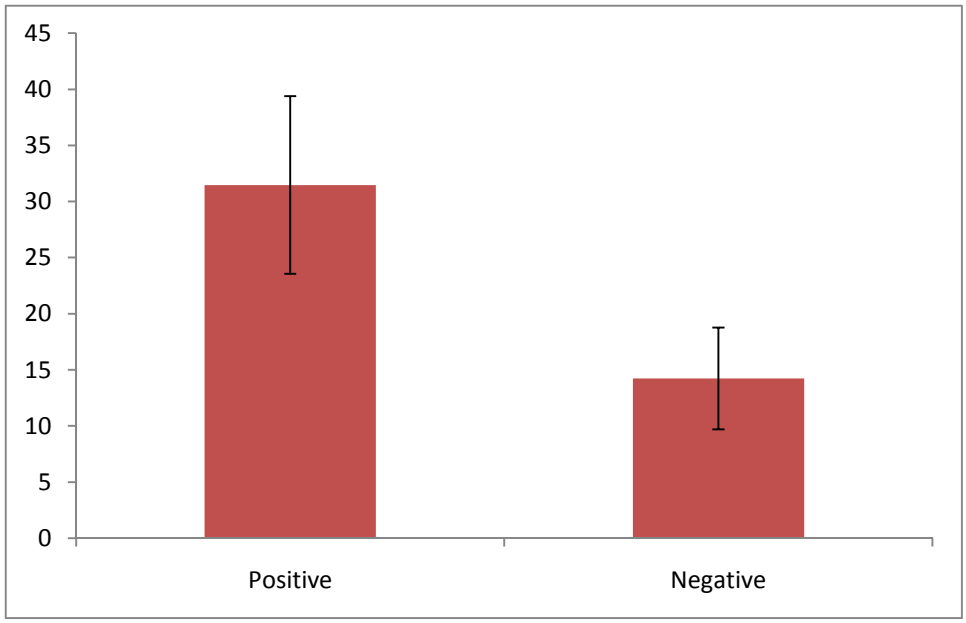
5) Child mania rating scale

As shown in table (18) and figure (15), The results of the child mania rating scale for the bipolar group were a mean of 31.46 and standard deviation of 7.9, for the non bipolar cases were a mean of 14.22 and standard deviation 4.54, with statistically very high significance (p value= 0.001).

Table (18): Child mania rating scale results in both groups.

BAD	CMRS			
	Range	Mean ± SD	T-test	
			t	P-value
Positive BAD	14.00 ± 46.00	31.4667 ± 7.9090	10.43	<0.001*
Negative BAD	7.00 ± 22.00	14.2222 ± 4.5422		

Fig (15): Child mania rating scale results in both groups.



Section IV

The comorbidity with other disorders as oppositional defiant disorder and conduct disorder

1) The correlation to oppositional defiant disorder

As shown in table (19) and figure (16), the children with oppositional defiant disorder in the sample were 55% (n=33, 10 of them were in the group of bipolar cases and 23 in the non bipolar group), the children without oppositional defiant disorder were 45% (n=27, 7 in bipolar group and 20 in non bipolar group). On comparing the two groups there were no statistically significance as regard comorbidity with oppositional defiant disorder (p value= 0.7).

Table (19): Oppositional defiant disorder in both groups.

oppositional defiant disorder		Comorbid ADHD & BAD		
		Non comorbid	comorbid	Total
Yes	N	23	10	33
	%	53.49	58.82	55.00
No	N	20	7	27
	%	46.51	41.18	45.00
Total	N	43	17	60
	%	100.00	100.00	100.00
Chi-square	X^2	0.14		
	P-value	0.708		

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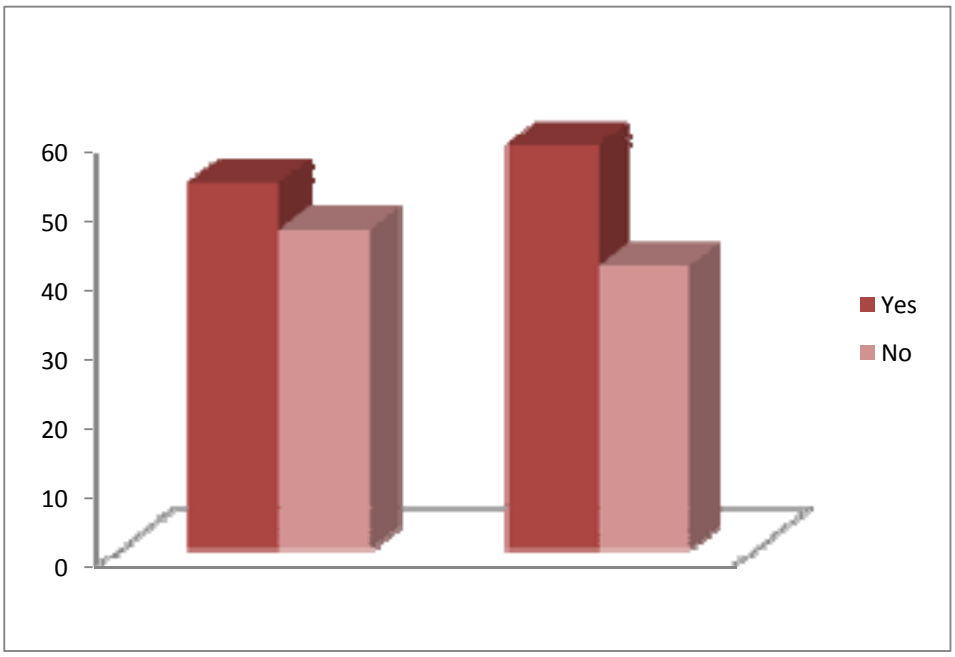
Fig (16): Oppositional defiant disorder in both groups.



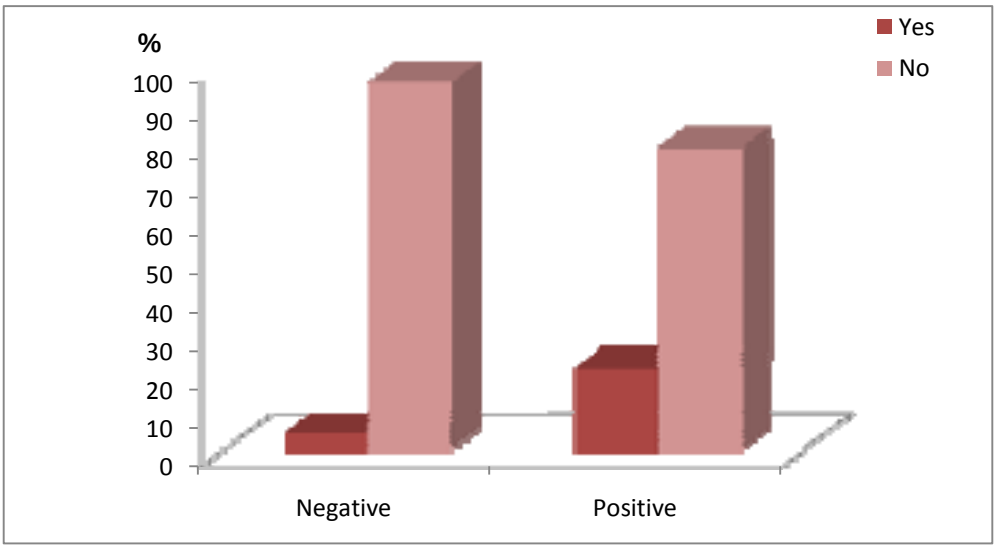
2) The correlation to conduct disorder

As shown in table (20) and figure (17), the cases of conduct disorder in the sample were 8.33% (n=5, 3 of them were in the group of bipolar cases and 2 in the non bipolar group), the cases without conduct disorder were 91.67% (n=55, 11 in bipolar children and 44 in the non bipolar children). On comparing the two groups there were statistically significant as regard comorbidity with conduct disorder in the comorbid group (p value= 0.043).

Table (20): Conduct disorder in both groups.

conduct disorder		Comorbid ADHD & BAD		
		Non comorbid	Comorbid	Total
Yes	N	2	3	5
	%	4.35	21.43	8.33
No	N	44	11	55
	%	95.65	78.57	91.67
Total	N	46	14	60
	%	100.00	100.00	100.00
Chi-square	X^2	4.099		
	P-value	0.043*		

Fig (17): Conduct disorder in both groups.



Section V

Is there a relation between positive mood disorder spectrum in parents and comorbid bipolar disorder in there offsprings?

1) The relation between positive family history of mood disorder and bipolarity in the children

As shown in table (21), the cases with positive family history of mood disorders were 6.67% (n=4, major depressive disorder in mother and 1 with bipolar affective disorder in mother). On comparing bipolar children group with non bipolar group no statistically significant difference regarding the family history was found (p value = 0.935).

Table (21): Family history of Mood disorders in Bipolar and non Bipolar children.

Family history of mood disorder		BAD		
		Non BAD	BAD	Total
positive	N	3	1	4
	%	6.52	7.14	6.67
negative	N	43	13	56
	%	93.48	92.86	93.33
Total	N	46	14	60
	%	100.00	100.00	100.00
	P-value	0.935		

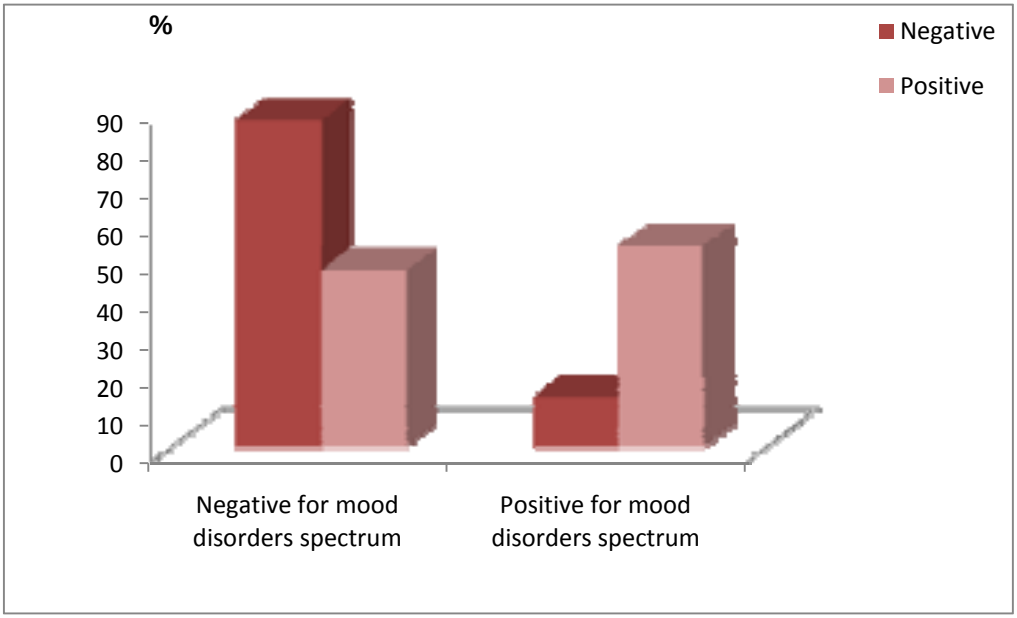
2) The relation between SCID-I for mood disorders spectrum of mothers and bipolar affective disorder in their children

As shown in table (22) and figure (18), the mothers with mood disorder spectrum were 23.33% (n=14, 8 of them had a child with positive bipolar disorder diagnosis and 6 with no bipolar disorder in their children), mothers with negative mood disorder spectrum were 76.67% (n=46, 7 with bipolar children and 39 without bipolar diagnosis in their children). On comparison of the two groups there are highly significant association between positive mood disorders spectrum in mothers and bipolar affective disorder diagnosis in children (p= 0.002).

Table (22): SCID-I for mood disorders in mothers of bipolar and non bipolar children.

SCIDI for mood disorder in mothers		BAD		
		Non BAD	BAD	Total
Negative for mood disorders spectrum	N	39	7	46
	%	86.67	46.67	76.67
Positive for mood disorders spectrum	N	6	8	14
	%	13.33	53.33	23.33
Total	N	45	15	60
	%	100.00	100.00	100.00
Chi-square	X^2	10.06		
	P-value	0.002*		

Fig (18): SCID-I for mood disorders in mothers of bipolar and non bipolar children.



3) The relation between SCID-I for mood disorder spectrum of fathers and bipolar affective disorder in their children:

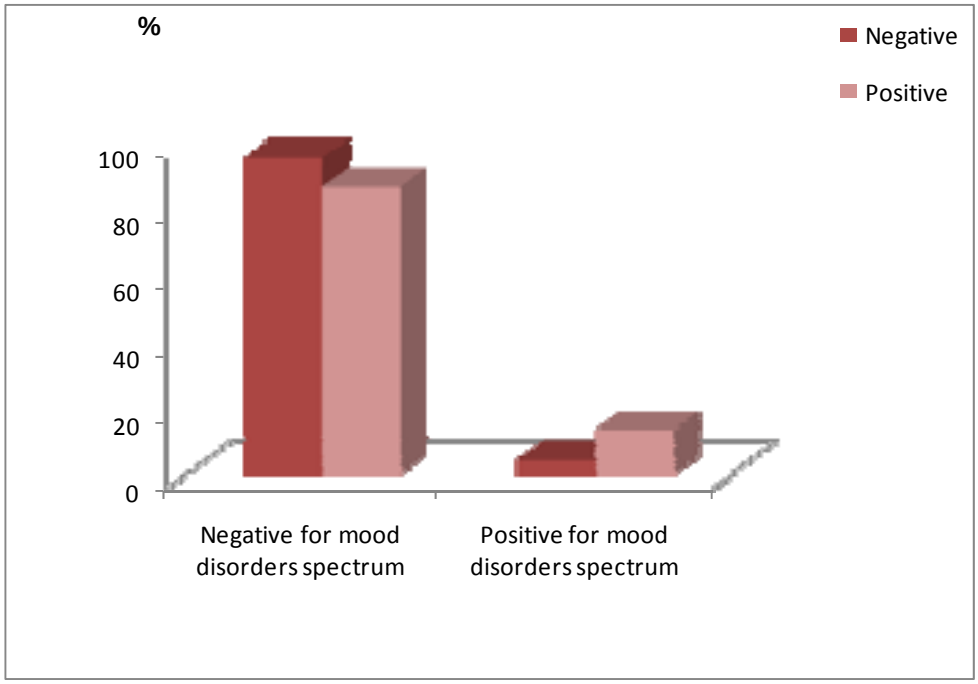
As shown in table (23) and figure (19), there were 6.67% (n=4) fathers with positive mood spectrum disorders diagnosis (2 had children with bipolar disorder and 2 with no bipolar disorder diagnosis in their children), and 93.33% without mood spectrum disorders (n=56) (13 with bipolar diagnosis in their children and 43 without). On comparison of the two groups there are no significant association between positive mood disorders spectrum in

fathers and bipolar affective disorder diagnosis in their children (p= 0.232)

Table (23): SCID-I for mood disorders in fathers of bipolar and non bipolar children.

SCIDI for mood disorder in fathers		BAD		
		Negative	Positive	Total
Negative for mood disorders spectrum	N	43	13	56
	%	95.56	86.67	93.33
Positive for mood disorders spectrum	N	2	2	4
	%	4.44	13.33	6.67
Total	N	45	15	60
	%	100.00	100.00	100.00
Chi-square	X^2	1.420		
	P-value	0.232		

Fig (19): SCID-I for mood disorders in fathers of bipolar and non bipolar children.



Section VI

The predictive factors for possible bipolar comorbidity in ADHD cases

To evaluate the predictive value for the previously analyzed factors, we performed multiple logistic regression analysis test. We used bipolar comorbidity as dependant factor and for risk factors the following variables: age of onset of ADHD, family history of mood disorders, SCIDI-I for mother, SCIDI for father and conner's parents rating scale.

As shown in table (24), the results presented revealed that the significant correlate was SCID-I mood disorders section for mothers. On the other hand the age of onset of ADHD, family history of mood disorders, SCIDI-I mood disorders section of fathers and Conner's parents rating scale were statistically non significant and with no predictive value.

Table (24): Multiple regression analysis of variables predictive of Bipolar disorder in ADHD children.

Regression	B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
							Lower	Upper
Age of onset of ADHD	-0.750	0.542	1.916	1	0.166	0.472	0.163274	1.36608
Family history of mood disorders	4.458	3.628	1.509	1	0.219	86.284	0.070364	105807.6
SCIDI-I for mother	3.654	1.634	5.002	1	0.025*	38.642	1.571176	950.3905
SCIDI-I for father	0.756	2.208	0.117	1	0.732	2.130	0.028139	161.2874
Conner's cognitive subscale	-0.246	0.131	3.523	1	0.061	0.782	0.605315	1.010901
Constant	-0.279	87.824	0.000	1	0.997	0.757		

Discussion

In the past decade, interest and research on pediatric bipolar disorder (PBD) has increased substantially. The prevalence rates of the disorder have doubled in the outpatient settings, while twice as many research articles of PBD were published **(*Leibenlft and Rich, 2008*).** The unique pattern of comorbidity found in pediatric mania greatly complicates accurate diagnosis, the course of the disorder, and its treatment. The pattern of comorbidity is unique, especially its overlap with attention-deficit hyperactivity disorder (ADHD) and conduct disorder. Clinically, symptoms of mania have been discounted as severe ADHD or ignored in the context of conduct disorder.

A very important issue that needs focus is the degree of overlap between attention deficit hyperactive disorder (ADHD) and Pediatric Bipolar Disorder (PBD). Consequently, symptoms such as hyperactivity, impulsivity, aggressiveness, distractibility, and emotional liability overlap considerably, and confuse the differential diagnosis **(*Carlson et al., 2000 ; Pavuluri et al., 2005*).**

Accurate diagnosis is very important as the occurrence of false negatives (for example, failing to recognize ADHD in a bipolar child) may lead to underutilization of preventative interventions aimed at improving the long-term functioning. Overdiagnosis (false positives; for example, diagnosing bipolar disorder in a child who only had ADHD) has its own disadvantages

given the uncertainties about the short- and long-term effects of mood-stabilizing or antidepressant medications for children **(*Kim and Miklowitz, 2002*).**

Another important issue is that stimulants are commonly used to treat ADHD and may be prescribed to children who later develop manic symptoms **(*Wozniak and Biederman, 1996*).** While there seem to be no negative long-term effects of stimulants in children with ADHD, the effects of stimulants on children with or at risk for BPD have yet to be determined **(*Carlson et al., 1992 ; Gillberg et al., 1997*).** It seems that stimulants lead to early expression of manic symptoms only in vulnerable children that is why accurate diagnosis and excluding possibility of bipolar symptoms is very important for a successful management plan and better prognosis.

Therefore our study was designed to assess the presence of co-morbid or misdiagnosed bipolar disorder among ADHD diagnosed children. Also we tried to search for any factors that could direct our attention to suspect PBD in a child with ADHD, as the presence of mood disorder in the parents along with other factors that will be discussed in details.

Patients evaluated in the study were 60 child referred from the outpatient clinic with a diagnosis of ADHD with their both parents. The children were assessed by Wechsler intelligence scale for children Arabic version, Kiddie schedule for affective disorders and schizophrenia present and lifetime version (KSADS-PL),

Conner's parent rating scale and child mania rating scale. The parents were assessed with SCIDI the mood disorders section.

The mean age of the sample in the study was 8.03 years which is similar to the mean age of ADHD patients referred to the outpatient clinic in many other studies which was ranging from 8.6 to 8.7 years **(*Biedermann et al., 2002 ; Gershon, 2002*).**

The males represent 85% (n=51) and females 15% (n=9). Gender difference in the presentation of cases is very apparent, which goes in agreement with abundant researches showing ADHD to have male predominance **(*Faraone et al., 1999*).**

The misdiagnosis and co-morbidity between ADHD and pediatric bipolar disorder

Our study revealed that the prevalence of affective disorder in the sample represent 28.3% (n=17), of which 25% (n=15) are bipolar affective disorder and 3.3% (n=2) were major depressive disorder. The prevalence of comorbid ADHD and pediatric bipolar disorder was 23.3% and one case misdiagnosed as ADHD in a previous manic episode and came presented with bipolar affective disorder currently depression.

Our results for comorbidity between ADHD and pediatric bipolar disorder are similar to many researches done in this issue. A study by ***(Butler et al., 1995)*** was

done to assess the presence of bipolar disorder among newly diagnosed ADHD children; the study revealed 22% of them were comorbid with bipolar disorder.

In another study by ***(Biederman et al., 1996)*** DSM-III-R structured diagnostic interviews and blind raters were used to examine psychiatric diagnoses at baseline and 4-year follow-up in ADHD and control children. In addition, subjects were evaluated for cognitive, academic, social, school, and family functioning. The results revealed, BPD was diagnosed in 11% of ADHD children at baseline and in an additional 12% at 4-year follow-up with a whole prevalence of 23%. These rates were significantly higher than those of controls at each assessment. ADHD children with comorbid BPD at either baseline or follow-up assessment had significantly higher rates of additional psychopathology, psychiatric hospitalization, and severely impaired psychosocial functioning than other ADHD children.

(Biederman et al., 2004b) assessed 128 ADHD diagnosed boys age from 6-17 with the KSADS in independent interviews with the mothers and direct interviews of subjects, except for children younger than 12 years who were not directly interviewed. The study found 17% (n=22) comorbid bipolar disorder at baseline assessment and 6% (n=7) new cases during the 4 year follow up with a total 23% comorbid cases.

(Biedermann et al., 2004a) reviewed children 12 years or younger referred to child psychiatry services from

1995 to 2002 in a cohort II study and compared them to a cohort I before 1995. Results revealed very high rates of overlap between ADHD and pediatric bipolar disorder, 87% of bipolar children have comorbid ADHD and 20% of ADHD children have bipolar disorder. All studies mentioned above share our study in the prevalence of comorbid ADHD and pediatric bipolar disorder with percentage near 23%.

In a study by ***(Yousef et al., 2006***) they assessed 120 ADHD child aged 6-12 years old for bipolar affective disorder using DSMIV diagnostic criteria, conner's rating scale, child behavior checklist, young mania rating scale parents version and clinician administrated rating scale for mania. Their results revealed that 37.5% fulfilled diagnostic criteria for bipolar affective disorder; this is a higher percentage than ours. The difference could be explained by the difference in methodology of diagnosis as we used different tools as child mania rating scale and KSADS-PL, in addition we used the strict diagnostic criteria of KSADS-PL and no child acquired a diagnosis of bipolar unless having at least two cardinal features of bipolar disorder.

In a study by **(*Faraone et al., 2001)*** 140 ADHD girls and 122 controls and their first degree relatives were assessed for comorbid bipolar disorder and family history of ADHD or bipolar disorder. It revealed that 11% of ADHD cases had comorbid bipolar disorder. These results are different from ours may be due to the gender of the

sample was only females yet our study included both sexes predominantly males (86.6%).

All the above results prove the high incidence of comorbid pediatric bipolar disorder with ADHD could be missed during the child assessment leading to incorrect management plan and worsen the prognosis.

(***Sachs et al., 2000***) studied 56 adult bipolar subjects who were assessed by SCID-I to confirm diagnosis and retrospectively by KSADS-PL to diagnose past episodes of other comorbidities as ADHD and age of onset of ADHD and bipolar affective disorder. Results revealed that 81% of the sample having onset of bipolar disorder before 19 years old and 19% after 19 years old. On comparing the two groups' early onset bipolar disorder group had 62% comorbidity with ADHD and the late onset group no comorbidity with ADHD. Also age of onset of bipolar was younger in comorbid ADHD and bipolar group than non comorbid group ($p=0.01$). The study concluded that this gives a clue that ADHD in genetically loaded children might identify children at risk for later development of bipolar affective disorder.

To determine whether overlapping diagnostic criteria account for the high comorbidity rates between ADHD and BPD, (***Milberger et al., 1995***) devised a subtraction method, which involved subtracting overlapping symptoms and applying the same DSM-III-R criteria to the remaining symptoms. Because this method can be overly stringent and cause an overall reduction in

the number of possible symptoms, a proportion technique was also used that required the proportion of symptoms in the reduced set of symptoms to be at least as large as the proportion of symptoms required by the original DSM-IV criteria. After correction for overlapping symptoms using both the subtraction and the proportion method, 100% of 15 children and adolescents with co-occurring ADHD and BPD maintained the diagnosis of ADHD, suggesting that comorbid ADHD is not an artifact of overlapping symptoms between BPD and ADHD. In contrast, using the subtraction method about half (47%) of these children maintained the diagnosis of BPD, and using the proportion method 80% maintained the diagnosis of BPD. This suggests that among some, but not all, patients with BPD and ADHD, comorbid BPD may be an artifact of overlapping symptoms between mania and ADHD.

To challenge the assumption that symptoms of ADHD and BPD are indistinct, it is important to demonstrate that prototypic symptoms can be distinguished in both consecutive and comorbid cases. (***Geller et al., 1998)*** studied 60 bipolar affective disorder and 60 ADHD children aged from 7-16 years old using the Washington University at St. Louis Kiddie and Young Adult-Schedule for Affective Disorders and Schizophrenia — Lifetime and Present Episode Version-DSM-IV (WASH-U-KSADS). The results revealed that most cases have prebubertal onset of bipolar disorder. The comorbidity with ADHD in prebubertal children was 97% decreasing to 74.1% in postpubertal children. They suggested that ADHD can be a phenocopy as any child fulfilling criteria

for bipolar disorder can fulfill criteria for ADHD yet that decrease with aging. Also the study demonstrated that elated mood, grandiosity, hypersexuality, decreased need for sleep, racing thoughts, and all other mania items with the exception of increased energy and distractibility were substantially more frequent among youth with BPD compared with those with ADHD and can help avoiding overdiagnosis of bipolar disorder among ADHD cases.

We took that point carefully in consideration during assessment, no child was given the diagnosis of bipolar disorder unless at least two of the following mentioned criteria is present (euphoria, grandiosity, racing thoughts, hypersexulality and decreased need for sleep with increased activity). The most common were euphoria and grandiosity, followed by racing thoughts. For more confirmation another assessment tool the child mania rating scale which is a tool to screen for mania was applied to all cases, it help to differentiate ADHD alone from co-morbid ADHD and mania.

In children and adolescents, determining the polarity of a mood disorder presentation is a common clinical dilemma. Indeed, youth presenting with major depressive disorder (MDD) may go on to develop bipolar disorder, 47% of the bipolar individuals had MDD present prior to mania. In a study by ***(Wozniak et al., 2004***) they investigated 285 ADHD children aged 6-17 years old males and females for unipolar and bipolar depression. They found that unipolar depression were 109 and bipolar depression were 43 and 128 cases were only

ADHD. On comparing the groups they found that it is very difficult to differentiate the clinical presentation of unipolar from bipolar depression, they found that in contrast to unipolar depression, bipolar depression was more likely to present with severe impairment, suicidality, both irritability and sadness, and higher levels of comorbidity with Conduct Disorder and Oppositional Defiant Disorder. A family history of bipolar disorder was more likely to be present in bipolar (20%) vs. unipolar (8%) depressed youth. In addition, relatives of youth with bipolar depression had greater levels of MDD (62%) vs. unipolar youth (45%).

(***Biederman et al., 2009***) designed a study to investigate whether ADHD is a risk factor for shift from unipolar depression to bipolar affective disorder. The study constitutes 280 ADHD males and females aged 6-18 years and 242 controls and their siblings. The males were assessed at baseline, 1, 4 and 10 years follow up and females at baseline and 5 year follow up. All cases with unipolar depression were followed up for shift to bipolar affective disorder. The results revealed that ADHD is a risk factor for shift from unipolar depression to bipolar affective disorder. The risk increases with the following factors presence of subthreshold bipolar symptoms, comorbid conduct disorder and positive family history of mood disorders. Our results revealed two cases with comorbid major depressive disorder and ADHD, they should be taken in consideration as they could be index episode for bipolar disorder if followed up.

The description of comorbid ADHD and bipolar cases in relation to non comorbid cases

Our study revealed that in the comorbid group the mean age was younger than non comorbid goup (7.46±1.6 vs 8.2±1.4), there were male predominance as the non comorbid group, (86.8% males and 13.3% females vs 84.4% males and 15.6% females).

The age of onset of ADHD in the comorbid group was earlier than non comorbid group (p=0.00), it was 3.46±0.8 in comorbid group vs 4.76±1 in non comorbid group. The age of onset of bipolar disorder was 4.85±1.7. As regards type of ADHD the comorbid cases were all the combined type (p=0.012).

In the study by ***(Faraone et al., 2001***) mentioned above 140 ADHD girls and 122 controls and their first degree relatives were studied for comorbid bipolar disorder and family history of ADHD or bipolar disorder. On comparing the comorbid and non comorbid groups, mean age of onset for bipolar disorder was 6.8 years, earlier age of onset of ADHD with mean 3.1 years old in comorbid group, which is also similar to our results as regards onset of ADHD but in our study age of onset of bipolar disorder was slightly younger.

In another study by ***(Biederman et al., 2004*b)** Conducted on 128 ADHD boys (6-17 years old) followed over 1 and 4 years follow up to detect comorbidity with bipolar. It revealed that 55% of children had onset of

bipolar disorder before 6 years, 27% between 6-10 years and 18% after 10 years old with mean age of onset of bipolar disorder 6.3±4.7 which is also older than results in our study. This could be attributed to that the mean age of the sample in the study by ***(Faraone et al., 2001)*** was 12.7±1.6 for comorbid ADHD and bipolar and 11.7± 3.3 for only ADHD, and in the study by **(Biederman et al., 2004b)** was 10.7±3 which is all older than the mean age of our sample (8±1.5), which was (7.46±1.6) in comorbid ADHD and bipolar group and (8.2±1.4) in only ADHD group.

In a study by (***Masi et al., 2006***) done on 98 referred bipolar child and adolescent (8-18 years old) followed over 6 months, to detect comorbid ADHD cases and compare the comorbid ADHD and bipolar group to only bipolar group it revealed that the mean age for comorbid cases was younger than only bipolar cases (mean age of comorbid group was 12±2). The age of onset of ADHD was 3.7±1.1, which is much similar to age of onset of ADHD in our study (3.46±0.8), also age of onset of bipolar disorder was 8.1±2.8 which is younger than only bipolar group 11.1±2.9 (p= 0.00) yet is older than age of onset in our study (4.8±1.7). This could be explained by difference in methodology as they compared only bipolar group to comorbid ADHD and bipolar disorder yet we compared them to only ADHD group, in addition the mean age of the sample in our study is younger than their study, in our study no children were older than 12 yet in study by Masi et al. 78.5% child were before 12 and 11.5% after 12 years old.

One of the explanations for high comorbidity and overlap between ADHD and bipolar disorder is that ADHD could be a prodromal presentation of early onset affective illness. Therefore, based on this explanation, it is expected that: individuals with early-onset BPD have higher rates of ADHD as compared to those with adolescent- and adult-onset BPD; the age at onset of BPD should be earlier in patients with BPD and ADHD than in BPD individuals without ADHD.

Prospective studies have also shown that ADHD may represent a developmental subtype or a marker for early-onset BPD. Specifically, a recent case-control, 10-year prospective study of youth with and without ADHD found that young adults diagnosed with ADHD in their youth had a greater lifetime prevalence for all categories of psychiatric disorders studied, and that BPD was over represented in ADHD children grown up ($p < 0.001$) **(*Biederman et al., 2006).***

So the results of our study in support to other studies mentioned above proved that in comorbid cases of ADHD and bipolar disorder there are earlier age of onset for ADHD in comparison to non comorbid ADHD cases, raising the possibility that ADHD in those children could be a prodromal presentation or a marker especially in genetically loaded children yet further research is still needed.

In a study done by (***Faraone et al., 1998),*** they found that bipolar disorder was highest among combined-type

youth (26.5%) but less elevated among hyperactive-impulsive (14.3%) and inattentive (8.7%) youth. In contrast to our study all comorbid cases were combined type of ADHD. The difference could be due to smaller sample size (301 in their study to 60 only in ours) with less number of each form of ADHD.

In a study conducted by ***(Del Bello et al., 2001***) to assess the relation between prior stimulant treatment and development of bipolar disorder in adolescents. The results revealed that bipolar adolescents with history of stimulant exposure prior to onset of bipolar disorder had earlier age of onset than those without prior stimulant exposure. They concluded that stimulants might cause earlier expression of bipolar disorder in vulnerable subjects.

Our results revealed that 78.3% of the sample were newly diagnosed and not on treatment, 11.7% on Ritalin and 10% on other medications mainly antipsychotics and antiepileptics. Also there were statistically significant difference between comorbid and non comorbid group as regards Ritalin treatment with more association between comorbid ADHD and bipolar disorder group and Ritalin treatment. These results are not reliable as we didn't take in consideration the correlation between onsets of bipolar disorder and starting Ritalin, also percentage of cases on ritalin represent a small percent from the whole sample.

Phenomenology of bipolar disorder in the comorbid group

The bipolar affective disorder cases represent 25% of the sample (n=15), 23.33% were comorbid with ADHD (n=14) and one case bipolar disorder currently depression was misdiagnosed as ADHD in a previous manic episode and came to us presented for the first time with depressive symptoms. Among the cases BADI represent 53.3% divided into BADI manic were 20% (n=3) and BADI mixed were 33.3% (n=5), and BAD NOS were 40% (n=6).

(***Axelson et al., 2006***) to investigate the phenomenology of children and adolescents with bipolar spectrum assessed 438 child and adolescent (7-18 years) according to DSMIV using the KSADS-PL. They found in agreement to our study that the most common form was BADI with percentage similar to ours 58.2% followed by BAD NOS with percentage 34.9% a little bit lower than ours. Also they found 6.8% BADII in agreement to 6.7% we found represented in the only misdiagnosed case. There are some methadological differences as they studied a bipolar sample yet we studied only comorbid and misdiagnosed ADHD and bipolar cases, also mean age of their sample was older than ours (12.7±3.3 in comparison to 7.46±1.6).

In another study by ***(Birmaher et al., 2006)*** assessment of 263 cases with bipolar spectrum disorder diagnosis aged 7-18 years old by KSADS-PL was done. The results revealed that the BADI represent 57.8%

(n=152) again similar to our results, BAD NOS 35% (n=92) and BADII 7.2% (n=19) which is also in agreement to our results. During follow up of cases 20% of BADDNOS shifted to BADI and 10% shifted to BADII making it a valid diagnosis that need to be carefully assessed so not to be missed that is why we took it in consideration in our study.

In our study we compared IQ as regards total, verbal and performance domains of the two groups and found that the comorbid ADHD and bipolar group have statistically significant higher total IQ in comparison to only ADHD group yet no significant difference on comparing verbal and performance IQ. As regards conner's parent rating scale long version there were only statistically significant difference in two domains cognitive subscale has worse scores in only ADHD group and this could be explained by lower total IQ and social problem scale was worse in comorbid group and this could be explained by the impact of comorbidity on the social functioning.

(Rucklidge, 2006) compared different neuropsychological functions of adolescents aged 14-17 years old with ADHD only, BAD only, comorbid ADHD and BAD and normal controls. They found that only ADHD group has lowest IQ than all other groups including the comorbid group which goes in agreement with our results yet no statistically significant difference was found on comparing them in contrast to our results. As regards Conner's parent rating scale all groups were

having significant scores with statistically significant difference on comparison to normal controls which we didn't do as we have no controls. They concluded in the end that ADHD has a great impact on bipolar disorder in comorbid group as regard neurocognitive functions. They found that only ADHD adolescents were having worse scores than comorbid and only bipolar groups. This study differs from ours as it took adolescents only; also we have no controls to compare to them as they did.

The comorbidity with other disruptive behavior disorders

In our study we investigated the comorbidity between other disruptive behavior disorders (oppositional defiant and conduct disorder) and pediatric bipolar disorder in the context of ADHD.

This was done through studying the comorbidity with oppositional defiant disorder and conduct disorder in the comorbid ADHD and bipolar group compared to only ADHD group. The results revealed that the rate of comorbidity with oppositional defiant disorder was high in both groups, 78.5% of comorbid ADHD and bipolar cases had comorbid oppositional defiant disorder and 58.7% of only ADHD cases have comorbid oppositional defiant disorder, on comparison no statistically significant difference was found.

The comorbidity between comorbid ADHD and bipolar disorder group and conduct disorder was 21.4%,

and comorbidity of ADHD alone and conduct disorder was 4.35%. On comparison there were statistically significant difference between the two groups (p=0.043), the comorbid ADHD and bipolar group was more to have comorbid conduct disorder than ADHD alone.

(***Biederman et al., 1997***) investigated140 ADHD probands and 120 controls aged 6-17 years old for any comorbidities. They found that 23% were bipolar disorder which is similar to our results, 15% (n=21) were comorbid ADHD, bipolar and conduct disorders. They concluded that comorbidity with conduct disorder increases with the presence of bipolar affective disorder within the context of ADHD.

In the same study mentioned before by (***Masi et al., 2006***) they assessed comorbidity with oppositional defiant disorder and conduct disorder. The study revealed that comorbidity with ODD & CD was higher in comorbid group in comparison to only bipolar group (p=0.032). The comorbidity with oppositional defiant disorder was 48.6% and conduct disorder was 13.5%. This study differs from ours as they compared only bipolar group to comorbid ADHD and bipolar while we compared them to only ADHD which might explain the difference in the results.

Parents in the sample

In our study, both parents (only one case with a dead father), were assessed with the mood disorders section in SCID-I. The results revealed that as regard the

mothers 23.33 %(n=14) had axis I mood disorder diagnosis, 9 of them have major depressive disorder, 3 have bipolar affective disorder and 2 have cyclothymic disorder.

On comparing the mothers of comorbid ADHD and bipolar disorder to mothers of only ADHD children, there was statistically significant association between mood disorder in mothers and bipolarity in their children (p=0.006).

As regard the fathers only 6.67% (n=4) were having axis I mood disorder, 2 were major depressive disorder, 1 with bipolar affective disorder and 1 with cyclothymic disorder. On comparing the fathers of comorbid ADHD and bipolar disorder to fathers of only ADHD children, there was no statistically significant association between mood disorders in fathers and bipolarity in their children (p=0.212).

(*Faraone et al., 2001*) when studied the first degree relatives of only ADHD children, comorbid ADHD and pediatric bipolar disorder and healthy controls, they found that bipolar affective disorder was significantly higher in relatives of comorbid group compared to only ADHD and healthy controls. ADHD was higher in relatives of both comorbid and only ADHD groups when compared to healthy controls yet when compared to each other no significant difference was found.

(Geller et al., 2006) examined the morbid risk of bipolar disorder in first degree relatives of prebubertal BAD children, ADHD and healthy controls. The risk for bipolar disorder in first degree relatives of bipolar children was statistically significant in comparison to ADHD and healthy controls (p=0.001). The morbid risk was statistically significant higher in female relatives in comparison to male relatives (p=0.002).

(Birmaher et al., 2009) in the Pitsburgh bipolar offspring study, assessed pediatric bipolar disorder in 388 offspring of 233 parents with bipolar affective disorder and 251 offsprings of 143 demographically matched controls. The study showed the statistically significant higher risk for pediatric bipolar disorder in offsprings of bipolar parents (10.6%) with onset before age of 12 years old.

(***Singh et al., 2007***) assessed 37 offsprings (aged 8-17 years old) of bipolar parents and were age and sex matched with 29 offsprings of parents free from axis I diagnoses. There were statistically significance higher rates of affective disorders in offsprings of bipolar parents, 38% were bipolar affective disorder (BAD I, II, NOS or cyclothymia), in addition to significant higher rates of disruptive behavior disorders, also higher rates of comorbidities especially between mood disorder and disruptive behavior disorder. On studying the predictive value of many risk factors it was found that positive mood

disorder in parents is predictive to development of bipolar disorder in their offsprings, with no difference between unilinial (one parent) and bilineal (both parents).

In another study by (***Henin et al., 2005*****)** SCID-I & KSADS-PL were applied on 117 offsprings of parents with bipolar affective disorder diagnosis and compared to age and sex matched 171 offsprings of parents without bipolar affective or major depressive disorders. The results revealed that offsprings of bipolar parents were at statistically significant higher risk for bipolar affective disorder (33% of at high risk sample), unipolar depressive disorder (50%) with onset before age of 8 years old which could be a predictive factor for subsequent bipolar disorder and significant increase in morbid risk for disruptive behavior disorder (especially ADHD and oppositional defiant disorder). In addition a significant comorbidity between bipolar affective disorder and ADHD (22% of the at high risk sample) with onset of ADHD preceding the bipolar disorder.

In a study by (***Brotman et al., 2007***) first degree relatives of children with bipolar affective disorder were compared to first degree relatives of children with only severe mood dysregulation (subsyndromal presentations) as regard all axis I diagnoses. The study revealed that 71% of the first degree relatives of bipolar children have axis I diagnosis, of those 33.3% were bipolar affective disorder and 40.5% were major depressive disorder. On comparing them with first degree relatives of children with severe

mood dysregulation there were statistically significant association between bipolar relatives and bipolar affective disorder in their children.

The above studies collectively suggest that co-morbidity with ADHD may be a precursor for the later development of BPD. If ADHD is a marker or prodrome for the development of early-onset BPD, the offspring of adults with BPD should show high rates of ADHD. Family studies of offspring of BPD are useful to identify potential prodromal manifestations of BPD. ***(Chang et al., 2000)*** found that 55% of offspring of BPD parents had a DSM-IV Axis I psychiatric disorder, most commonly of them ADHD (28%), major depression or dysthymia (15%), or BPD or cyclothymia (15%). In this study, predictors of BPD in offspring of parents with BPD included early parental symptom onset and parental history of childhood ADHD. Additionally, BPD parents with a history of childhood ADHD were more likely to have children with BPD, but not ADHD.

An overall increased risk for psychopathology in offspring of parents with BPD was also observed in a recent controlled study ***(Henin et al., 2005),*** which concluded that disruptive behavior disorders, anxiety disorders, and early onset depression may be useful markers for the risk of subsequent BPD in high risk samples. In a sample of 36 children, the study also found significantly increased rates of ADHD in children at familial risk for BPD when compared to children without a familial BPD risk, suggesting that ADHD may be an early

manifestation of an impending mood disorder in children of parents with BPD **(*Singh et al., 2006*).**

It was suggested that ADHD and bipolar disorder share an underlying biological etiology (i.e., a common familial or genetic risk or a common underlying neurophysiology). Elevated rates of ADHD in pediatric BPD may be the result of a shared risk factor for both disorders. For example, family studies of children with BPD and ADHD suggest shared heritability. Family studies have been used to clarify the nosology of pediatric BPD, and determine whether co-morbid ADHD and BPD is a familial subtype. Based on this explanation, one would predict a linked familial transmission of ADHD and BPD.

In support of a shared or linked familial transmission of BPD and ADHD, **(*Faraone et al., 2001*)** studied 140 children and 822 of their first-degree relatives, and found that compared with non-ADHD controls, relatives of children with ADHD were at increased familial risk for having ADHD. There was a 5-fold elevated risk for BPD among relatives of probands with BPD but not among probands with ADHD alone, and an elevated risk for major depression with severe impairment in relatives of probands with both ADHD and BPD. This study concluded that comorbid ADHD and BPD is a distinct illness that was associated with high rates of ADHD among the subject's relatives. The study also reported that rates of BPD were increased only among relatives of patients with comorbid ADHD and BPD compared with patients with ADHD alone.

The results of the studies mentioned above are similar to our results in the presence of great association between mood disorder in parents with all its forms as bipolar affective disorder or major depressive disorder and bipolarity in their offsprings. Also studies revealed that the risk is higher in females more than male relatives which could explain the high association between mood disorders in mothers and bipolarity in their children we found in our study. The absence of significant association between fathers and their offsprings in contrast to other studies could be explained by that some fathers in our study were not very willing to cooperate and attend assessment sessions. The mothers were the ones more eager to share and cooperate.

In our study logistic regression was done to assess Predictive factors for pediatric bipolar disorder in ADHD children, the only significant factor was mood disorder in the mother. This result is similar to a study by (***Pavuluri et al., 2006*b)** on 98 referred child aged from 5-18 years old and their first degree relatives, 28 healthy controls, 37 bipolar type I and 33 comorbid BADI & ADHD. On logistic regression bipolar disorder in first degree relatives was a predictive factor for bipolar disorder in their children in BADI group and ADHD comorbid with bipolar group in comparison to healthy controls. There are some difference from our study as we didn't compare BAD to comorbid BAD & ADHD, but we compared ADHD as controls to comorbid cases, also we searched for any mood disorder in both parents yet they only searched

for bipolar disorder in all first degree relatives. Although the results are similar indicating the high predictive value of mood disorder in parents. Also in the Egyptian study by (***yousef et al., 2006***) mentioned earlier they found that family history of mood disorder is a predictive factor for bipolarity in their children supporting our results.

On the other hand we found no significant difference in family history of ADHD in between comorbid bipolar and ADHD children with only ADHD children, which agrees with **(*Yousef et al. 2006*)** they also found no significant correlation. These could be due to that in our study all cases were ADHD at the end with or without comorbid bipolar disorder except for one misdiagnosed case. In addition we didn't use any scales for ADHD in parents only depend on family history which is not very reliable leading to bias in the results.

Finally our study drew some attention that bipolar disorder is actually a valid diagnosis among children that need to be more overlooked to avoid missing or misdiagnosing it. Many factors should concern us before diagnosing a child as only having a severe form of ADHD and shifting to the management plan. One important predictive factor that should never be missed is positive mood disorders in the parents, followed by other minor factors as age of onset of ADHD, severity and other comorbid disruptive behavior disorders.

Limitations and Implications

The strengths and limitations of the study must be put into consideration on interpreting the results.

The strengths include

- A clear strength of the study is that it is one of the few studies in Egypt interested to explore the bidirectional relation between pediatric bipolar disorder and ADHD in an Egyptian sample of children. Also it studied mood disorder spectrum in both parents in correlation to bipolar disorder in their children.

- The use of a comprehensive assessment battery including the gold standard semi-structured clinical interview KSADS-PL for clinical diagnoses of ADHD, bipolar affective disorder and other comorbid disruptive behavioral disorders.

- The use of the child mania rating scale as a screen tool for mania and to differentiate only ADHD cases from comorbid ADHD and bipolar affective disorder.

- This study emphasize the importance of looking for the possibility of pediatric bipolar disorder misdiagnosed

or missed among cases of ADHD especially severe forms. Our goal was to detect such cases for early intervention to improve outcome, promote full recovery aiming to reduce long term disability and cost.

However, some limitations in our study must be taken into account in interpreting the results

- The small sample size, limiting the statistical power of analysis of the results.

- All referred ADHD cases were from 6 to 12 years old, so no adolescents were studied, these could be due to very few number of adolescents in the outpatient clinic with ADHD diagnoses.

- There were 7 shared diagnostic criteria according to DSM-IV between ADHD and bipolar affective disorder leading to over diagnoses of ADHD in the sample and great difficulty in determining whether it is comorbid ADHD and bipolar or simply misdiagnosed cases, yet we tried to overcome that through depending on core symptoms in diagnoses and using other tools as conner's parent rating scale and child mania rating scale, yet no tool is currently available to differentiate only bipolar affective disorder from comorbid ADHD and bipolar disorder.

- The group of referred ADHD cases were heterogeneous, some new cases and others on treatment of different categories.

- During assessment of mood disorder spectrum in parents, the fathers were not very cooperative to attend assessment session and reveal all needed data as mothers which may lead to under evaluation of mood disorders in fathers than mothers.

Conclusion

Our study's main interest is to highlight that pediatric bipolar disorder is a valid diagnosis among children that is under-diagnosed and neglected. We hypothesized that there is a great overlap between pediatric bipolar disorder and ADHD in form of comorbidity or misdiagnosis. Also that the increased percent of bipolar spectrum disorders in parents of ADHD diagnosed children could be an indicator of comorbid or misdiagnosed bipolar disorder.

Thus we investigated the prevalence of misdiagnosed or comorbid bipolar disorder among ADHD children, tried to demonstrate the phenomenology of such cases in comparison to non comorbid children. On the other hand we assessed the prevalence of mood disorders in parents of those children and its predictive value.

We conclude from the previously presented data that pediatric bipolar disorder is highly comorbid with ADHD and that it is under-diagnosed and missed within the context of ADHD. This could lead to more impaired functioning, poor prognosis and less response to prescribed medications or even worsening of the condition on prescribing stimulants or anti-depressants.

The comorbid bipolar and ADHD cases were characterized by earlier age of onset of ADHD, all were combined type of ADHD and more to have comorbid

conduct disorder. The bipolar cases were mainly bipolar I with mixed type more than the manic type followed by bipolar disorder not otherwise specified.

The study concludes that bipolarity in children was correlated to mood disorder in their mothers either in form of major depressive disorder or bipolar spectrum disorder. On studying the predictive value of many factors, mood disorder spectrum in mother was found to have a high predictive value.

Our results go in agreement with other research as regards prevalence of comorbidity, phenomenology of comorbid cases and the importance of mood disorder in parents.

We suggest that the child psychiatrists should be aware of pediatric bipolar disorder and overlook it before simply diagnosing a child as having severe form of ADHD and shifting to the management plan.

Finally we suggest the following:

1. Any ADHD case should be very well investigated to exclude any sub-threshold mood symptoms as irritable or euphoric mood, grandiosity, hypertalkativeness, racing thoughts, decreased need for sleep or hypersexulaity.
2. If any of the above is present it is preferred to apply the KSADS-PL to confirm ADHD and mood disorder

diagnoses as it can diagnose BAD-NOS which is very common and hard to diagnose clinically only.

3. The child mania rating scale is a very helpful and reliable screen tool for mania and helps differentiate it from only ADHD children.

4. Family history of mood disorders in first degree relatives especially parents is a very important predictive factor that need to dig for.

5. The early onset of ADHD, less response or worsening with stimulants and more comorbidities as with conduct disorder should concern us to reassess for bipolar disorder.

6. If a case presented with major depressive disorder and ADHD, it should be assessed and followed up carefully as it could be an index episode of bipolar disorder. Some factors as early onset and family history of bipolar should be taken into consideration before prescribing an antidepressant, altogether with very meticulous follow up.

Summary

There has been increasing recognition of pediatric bipolar disorder (BD) in the psychiatric literature during the past few years. Despite the dramatic increase in the knowledge about pediatric BD, there is still considerable controversy about the clinical presentation, particularly its core symptoms, and hence the prevalence. It should be well considered that the diagnosis of bipolar disorder carries with it several implications that must not be taken lightly, and so assigning a diagnosis of bipolar disorder to a child or teenager should be done carefully. Many factors complicate accurate diagnosis as the unique pattern of comorbidities, especially its overlap with attention-deficit hyperactivity disorder (ADHD) and conduct disorder. Clinically, symptoms of mania can be discounted as severe ADHD or ignored in the context of conduct disorder.

For the past two decades, there has been an ongoing debate regarding the methodology employed to differentially diagnose attention-deficit/hyperactivity disorder (ADHD) and juvenile-onset bipolar disorder (JBPD). Researchers suggest that 57% to 100% of children with juvenile bipolar disorder have comorbid ADHD, while only 11% to 22% of children with ADHD also have juvenile bipolar disorder.

Accurate diagnosis however is of vital importance to avoid inappropriate treatment. In childhood, the

symptoms of Bipolar Disorder can initially look like Attention-Deficit Hyperactivity Disorder (ADHD). It is well known among clinicians that if a child is treated with stimulant or antidepressant medication and there is an underlying undiagnosed bipolar disorder, the medications can induce a manic state with very serious consequences.

Four testable hypotheses might explain the high rates of comorbidity of mania and ADHD: comorbidity is a chance phenomenon, comorbidity is an artifact of overlapping criteria, comorbidity is due to a common diathesis that leaves patients vulnerable to separate illnesses and symptoms of ADHD that precede the onset of bipolar disorder represent a prepubertal expression of illness antecedent to the development of a full affective episode.

The magnitude of this comorbidity, the issue of ADHD– juvenile bipolar disorder symptom overlap and the fact that some authors postulate ADHD as a possible precursor of bipolarity in some children leading to high rates of underdiagnosis or misdiagnosis of pediatric BAD are still controversial issues undergoing further research.

There is great evidence that genetics and heritability play a great role in pediatric bipolar disorder, so studying the family history is of great value on assessing any child for possibility of PBD.

Based on what is mentioned above, the main aims of the study were to investigate the comorbidity and misdiagnosis of pediatric bipolar disorder among ADHD children. Also to study the correlation of positive family history of bipolar spectrum disorders among parents of the children and this comorbidity or misdiagnosis.

Accordingly 60 child aged from 6-16 years old altogether with their both parents were included if having a diagnosis of ADHD in the outpatient clinic, IQ above 80 and without any neurological problems, both sex were included.

The tools used in the study fell into several categories

Tools for diagnosis

1) **The Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime versions (K-SADS-PL) (Ibrahim et al., 2000),** was used for diagnosing ADHD, pediatric bipolar disorder and other comorbid disruptive behavioral disorders.
2) **The child mania rating scale (Pavvuluri et al., 2006a),** was used to diagnose mania and helps differentiate ADHD alone from comorbid manic episode and ADHD yet it can't differentiate co-morbid ADHD and bipolar from only bipolar cases.

3) **Structured Clinical Interview for DSM-IV (SCID I) (El Missery et al., 2003),** was used to diagnose any mood spectrum disorder in both parents.

Tools to assess intelligence and attention profile

Wechsler Intelligence Scale for Children (WISC) Arabic version **(Ismail and Melekia, 1999).**

Tools to assess severity of ADHD symptoms

Conner's Parent Rating Scale –revised –long version (CPRS-L) **(El Seikh et al.,2003).**

The procedural protocol for conducting this study involved referral of ADHD children fulfilling the inclusion criteria for psychiatric interview. An informed consent was taken then followed by assessment of IQ using *Wechsler Intelligence Scale* to make sure IQ above 80. Then Conner's parent rating scale was applied to assess symptom severity, these two scales were done by the clinical psychologist. This was followed by applying the KSADS-PL to confirm diagnosis of ADHD, determine which type, to diagnose mood disorders and search for other co-morbid disruptive behavioral disorders. Then the CMRS was applied to search for any missing cases with a manic episode, and differentiate ADHD from ADHD and comorbid manic episodes.

For the parents full family history of ADHD or Mood Disorders was verified. The structured clinical interview for DSMIV axis I disorders (SCID-I) clinical version, the section of mood disorders was applied on them to detect any form of mood disorders.

The results of the study were obtained using the statistical package of the SSPS version 16. The statistical process performed were the Pearson chi square test, the student's t-test, the paired t- test and multiple logistic regression analysis.

The main findings in the Study Were

As regards the demographic data,

The present study revealed that 85% of the sample were males and 15% were females which go with abundant research showing ADHD to have male predominance.

The age range in our study is 6-12 years old which is the most susceptible age for detecting ADHD, with mean age 8.03 which is similar to the mean age of ADHD children referred from outpatient clinics in many studies which is 8.6- 8.7. The mean age of onset of ADHD was 4.45.

In our study the majority are suffering from the combined type of ADHD 76.6% and 18.4% predominantly inattentive type and 5% predominantly hyperactive type.

The mean total IQ was average 99.2 ± 9.46. There were 78.3% newly diagnosed cases not on treatment, 11.7% on Ritalin and 10% on other medications (anti-epileptics and anti-psychotics).

As regards the comorbidity and misdiagnosis of PBD,

There were 23.3% comorbid ADHD and pediatric bipolar disorder, only one case 0.6% was misdiagnosed as ADHD in a previous manic episode and came presenting with BAD currently depression.

As regards the phenomenology of the bipolar cases,

They were predominantly males 86.7% and 13.3% were females. The mean age was 7.46 and mean age of onset was 4.8±1.6. The mean total IQ was within average 104.78.

The mean age of onset of ADHD in comorbid cases was earlier than non comorbid group with statistical significance.

All comorbid cases were ADHD combined type. The conner's parent rating scale revealed that non comorbid ADHD were more impaired on cognitive subscale than comorbid group may be due to higher total IQ, they were less impaired on social problem subscale. Otherwise no other differences were found.

The bipolar cases are 53.3% BADI, 20% are manic and 33.3% are mixed. Also 40% are BAD NOS and 6.7% are BAD II.

The comorbid group has 58.8% additional comorbidity with oppositional defiant disorder and 21.4% comorbid conduct disorder.

As regards the parents,

The results revealed 23.3% of the mothers have positive mood spectrum disorder on SCID-I in form of major depressive disorder, bipolar affective disorder and cyclothymia. There is significant association between positive mood spectrum disorders in mothers and bipolarity in their children.

Only 6.67% of fathers have positive mood spectrum disorder on SCID-I in form of major depressive disorders, bipolar affective disorder and cyclothymia. There is no significant association between positive mood spectrum disorders in fathers and bipolarity in their children.

For The predictive factors for possible bipolar comorbidity in ADHD cases using multiple logistic regression analysis. The only significant is positive mood spectrum disorders in the mother.

From the above results we concluded that pediatric bipolar disorder in common among children and in comorbidity with ADHD. So we suggest that child psychiatrists should be aware of pediatric bipolar disorder and overlook it before simply diagnosing a child as having severe form of ADHD.

At the end we suggest some points to avoid missing any bipolar child within the context of ADHD, any ADHD case should be very well investigated to exclude any sub-threshold mood symptoms as irritable or euphoric mood,

grandiosity, hypertalkative and racing thoughts, decreased need for sleep or hypersexulaity. If any of the above is present it is preferred to apply the KSADS-PL. The child mania rating scale is a very helpful and reliable screen tool for mania and helps differentiate it from only ADHD children. Family history of mood disorder in first degree relatives especially parents is a very important predictive factor that need to dig for.

During the follow up of treatment plan if there is less response or worsening with stimulants and more comorbidities as with conduct disorder we should reassess for bipolar disorder. If a case presented with major depressive disorder and ADHD, it should be assessed and followed up carefully as it could be an index episode of bipolar disorder. Some factors as early onset and family history of bipolar should be taken into consideration before prescribing an antidepressant, altogether with very meticulous follow up.

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المراجع العربية

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الملخص العربى

لقد أصبح هناك زيادة في معدلات ظهور الاضطراب الوجدانى ثنائي القطب فى الاطفال خلال السنوات القليلة الماضية , وبالرغم من الزيادة المضطردة في معرفتنا به ألا أنه لازال هناك جدلاً عن الصورة الأكلينيكية للمرض و خصوصاً أعراضه الأساسية.

وهناك العديد من العوامل التي تؤثر على التشخيص الدقيق مثل شكل الأعراض المتلازمة والتي قد تتداخل مع فرط الحركه و نقص الانتباه أو العدوانية أو الاضطرابات السلوكيه.

وعملياً يمكن لأعراض الهوس أن تغفل في فرط الحركه و نقص الانتباه الشديد أو تهمل أذا كانت في سياق اضطرابات السلوك الشديدة مما يؤدي الى صعوبه فى تشخيص مثل هذه الحالات.

وفي أخر عقدين كانت هناك مناقشات وجدل عن الطرق المستخدمة في التشخيص التفريقي بين فرط الحركه و نقص الانتباه والاضطراب الوجدانى ثنائى القطب ، ووجدت الأبحاث أن 57%- 100% من الأطفال المصابين بالاضطراب الوجدانى ثنائى القطب يكون مصاحبا مع فرط الحركه و نقص الانتباه, بينما من 11%-20% من الأطفال المصابين بفرط الحركه و نقص الانتباه يكون مصاحبا مع الاضطراب الوجدانى ثنائى القطب.

أن التشخيص الدقيق له أهمية قصوى في تفادي العلاج الغير مناسب لأن في سن الطفولة اعراض الاضطراب الوجدانى ثنائي القطب تكون مشابهة لأعراض فرط

الحركه و نقص الانتباه ومن المعروف جيداً للمعالجين أن الأطفال الذين يعالجون بالمنشطات أو مضادات الاكتئاب مع وجود الاضطراب الوجدانى ثنائي القطب الغير مشخص قد يزيد من سوء حالة الهوس او ظهور اعراض الهوس في الاطفال ذوى الاستعداديه للمرض.

وهناك أربع نظريات تم اختبارها قد توضح المعدل المرتفع للمصاحبه بين الهوس و فرط الحركه و نقص الانتباه:-

- المصاحبه قد تكون صدفة.
- أن هناك تداخل للمعايير الخاصه بتشخيص المرضين.
- وجود الاستعداديه المشتركه للأصابة بالمرضين.
- أعراض فرط الحركه و نقص الانتباه التي تسبق بداية الاضطراب الوجداني ثنائي القطب قد تمثل صوره سابقه لما قبل بلوغ المرض والتي قد تتطور إلى نوبة كاملة شديدة فيما بعد.

وشدة هذه الأعراض مع موضوع تداخل فرط الحركه و نقص الانتباه مع الاضطراب التوجداني ثنائي القطب تسببت أن بعض الناشرين بدأ يسلم بأن وجود معدلات عالية من التشخيص الخاطئ للأضطراب الوجدانى ثنائي القطب مازال محلا" للجدل و يحتاج المزيد من الأبحاث.

أيضا هناك أدلة قوية على أن العامل الوراثي يلعب دوراً كبيراً في الأضطراب الوجداني ثنائي القطب لذلك فدراسة التاريخ العائلي المرضي يعد من النقاط الهامه في تحديد الأطفال القابلين للإصابة به.

الفرضية:

صمم هذا البحث لمحاولة إثبات الفرضيه ان مرض الاضطراب الوجدانى ثنائى القطب فى الاطفال غير مشخص بنسب سليمه لتعدد اوجه التداخل و المصاحبه بينه و بين مرض فرط الحركه و نقص ا لانتباه. أيضا وجود نسب عاليه من الاضطرابات المزاجيه فى والدى الاطفال المصابين بالاضطراب الوجدانى ثنائى القطب مما قد يساعد على لفت الانتباه لوجود اضطراب وجدانى مصاحب او غير مشخص.

ومما سبق فأن الأهداف الأساسية للدراسة كانت في:-

- بحث المصاحبه والتشخيص الخاطئ بين الاضطراب الوجداني ثنائي القطب و فرط الحركه و نقص الانتباه في الأطفال.
- المصاحبه والتشخيص الخاطئ وعلاقتها بالتاريخ الإيجابي للاضطرابات المزاجيه في الآباء.

وبالتالي تم دراسة 60 طفل في المرحلة العمرية من 6-16 سنة المحولين من العيادات الخارجيه بتشخيص فرط الحركه و نقص الانتباه مع آباؤهم. معدل الذكاء كان فوق 80 وليس لديهم اي امراض عصبيه. كانت الدراسة تشمل الذكور والإناث.

الاختبارات و الأدوات المستخدمة للتشخيص:-

- مقياس K-SADS وتم استخدامه لتشخيص فرط الحركه و نقص الانتباه والاضطراب الوجداني ثنائي القطب وأى امراض أضطرابات السلوك الاخرى.
- مقياس الهوس لدى الأطفال استخدم لتشخيص الهوس وتفريقه عن المصاحبه مع فرط الحركه و نقص الانتباه من عدمه.
- تم عمل مقابلات باستخدام SCID-I واستخدم لتشخيص الاضطرابات المزاجية في الآباء.

أدوات تحديد الذكاء والأنتباه:

- اختبار مقياس وكسلر للذكاء النسخة العربية.
- مقياس كونر للأعراض البعدية لمرض الحركة المفرطة و نقص الانتباه بواسطة الأهل.

الاجراءت البحثيه:

أخذ الموافقة من ذوى المرضى المقيمين على رعايتهم وكذلك المرضى الذين تنطبق عليهم الشروط السابقة على اجراء البحث عليهم وسوف يتم اعطائهم الايضاحات عن هدف اجراء البحث مع ذكر أن المعلومات التي سوف تجمع عنهم سرية حتي فى حالة نشر البحث مع وجود فرصة لانسحابهم من الدراسة وقتما يشاءون دون إبداء أسباباً.

الأطفال المختارين للدراسة سوف يطبق عليهم الاتى:

- يحولون الي الاخصائى النفسي لعمل اختبار وكسيلر للذكاء, اذا كان اكثر من 80 يتم عمل مقياس كونر للأعراض البعدية لمرض الحركة المفرطة و نقص الانتباه بواسطة الأهل.
- يتم تطبيق KSADS للتأكد من التشخيص السليم لمرض فرط الحركه و نقص ا لانتباه وتحديد نوعه و تشخيص اي اضطرابات مزاجيه مع البحث عن أي اضطرابات سلوكية مصاحبة.
- يلي ذللك عمل CMRS للبحث عن أي حالات هوس قد تفقد والتفريق بين مرض فرط الحركه و نقص الانتباه وبين نوبات الهوس لأنها صعبة جداً نظراً لوجود العديد من الاعراض المشتركة.
- بالنسبة للآباء تم عمل مقابلات لهم باستخدام SCID-I مع تطبيق الجزء الخاص بالاضطرابات المزاجية.

النتائج التي تم الحصول عليها

باستخدام البرنامج الاحصائي SSPS (الحزم الاحصائية للعلوم الاجتماعية النسخة الـ 16).

وأظهرت النتائج الوصفيه للدراسه التالى:

- وجدت الدراسة أن 85% من العينة كانت ذكوراً و15% أناثاً وهذا يتماشى مع الأبحاث العديدة التي تقول بأن مرض فرط الحركه و نقص الانتباه سائد في الذكور.

- وجدت الدراسة أن الفئة العمرية كانت من 6-12 سنة وهو السن الأكثر عرضة لتشخيص فرط الحركه و نقص الانتباه وبمتوسط عمري 8.3 سنة وهو مشابه لعمر الأطفال المصابين فرط الحركه و نقص الانتباه والمحولين من العيادات الخارجية في عدة دراسات وكان متوسطهم من 8.6- 8.7 سنة ومتوسط العمر لبداية ظهور فرط الحركه و نقص الانتباه كان 4.45 سنة.

- وقد وجدنا في الدراسة أن الأغلبية كانت تعاني من النوع المركب لفرط الحركه و نقص الانتباه بنسبة 76.6 %.

- وكان متوسط معدل ذكاء 99.2.

- وجدت الدراسة أن 78.3% كانت حالات جديدة لا تخضع للعلاج وأن 11.7% كانوا يعالجون بالريتالين وأن 10% كانت تعالج بأدوية نفسية أخرى.

المصاحبه و سوء التشخيص:

- وجدت الدراسة أن 23.3% كانت فرط الحركه و نقص الانتباه مصاحب مع اضطراب وجدانى ثنائي القطب وحالة واحدة فقط بنسبة 6.% تم تشخيصها خطأ

فرط الحركه و نقص الانتباه في نوبة هوس سابقة جاءت باضطراب وجدانى ثنائي القطب فى نوبه اكتئاب.

- وجد ان حالات الاضطراب الوجداني ثنائي القطب سائدة في الذكور بنسبة 86.7% والأناث بنسبة 13.3% وأن متوسط العمر كان 7.46 سنة وعمر بداية المرض كان 4.8 ±1.6 ومتوسط معدل الذكاء كان 104.

- متوسط العمر في بداية ظهور فرط الحركه و نقص الانتباه في الحالات المصاحبه كان أقل من الحالات الغير مصاحبه وكانت 3.46 ± 8. وكل الحالات المتلازمة كانت من النوع المركب.

- مقياس كونرللمصابين بفرط الحركه و نقص الانتباه كانوا أكثر ضعفاً في مقياس الأدراك عن المجموعات المصاحبه للاضطراب الوجدانى وقد يكون ذلك بسبب معدل الذكاء وكانوا أقل ضعفاً في المشاكل الاجتماعية وماعدا ذلك لم نجد أي اختلاف.

- المجموعات المشخصه بفرط الحركه و نقص الانتباه و اضطراب وجدانى كانت فيها 58% مصاحبه مع اضطراب العناد و 21.4% مصاحبه مع اضطراب المسلك.

- وبالنسبة للآباء كانت 23.3% من الأمهات مصابين باضطرابات مزاجيه ما بين اكتئاب شديد أواضطراب وجداني ثنائي القطب أواضطرابات مزاجية دورية . ووجد ان هناك دلالات مهمة ما بين الاضطرابات المزاجيه للامهات واصابة اطفالهم بالاضطراب الوجدانى ثنائى القطب.

- فقط 6.67% من الآباء كانوا لديهم اضطرابات مزاجيه ما بين اكتئاب شديد أواضطراب وجداني ثنائي القطب ولكن ليست هناك دلائل على ارتباط ذلك باصابة أطفالهم بالاضطراب الوجدانى ثنائى القطب.

- وبالنسبة للعوامل الاستباقية للتنبؤ بمصاحبه الاضطراب الوجدانى في حالات فرط الحركه و نقص الانتباه باستخدام تحليل الانحدار فكانت الاهمية فقط لأصابة الأمهات باضطرابات مزاجيه.

ومن النتائج السابقة يمكن القول بأن الاضطراب الوجداني ثنائي القطب قد يكون شائعاً في الأطفال ومصاحبا لفرط الحركه و نقص الانتباه.

لذلك تقترح الدراسة بأن يكون اخصائي الأطفال النفسي واعياً ومدركاً ومتفهماً لاضطراب الوجداني ثنائي القطب ويفحص ويراقب جيداً قبل أن يشخص أن هذا الطفل يعاني من شكل حاد من أشكال فرط الحركه و نقص الانتباه ومن ثم تحويله إلى العلاج.

وفي النهاية تقترح الدراسة بعض النقاط لتفادي اغفاء أي حالات اضطراب وجدانى في الأطفال في سياق حالات فرط الحركه و نقص الانتباه.

لذلك فأي حالة من حالات فرط الحركه و نقص الانتباه لابد من فحصها بعناية فائقة لاستبعاد أية أعراض مزاجية في بدايتها مثل التوتر الشديد أو الأحساس بالنشوة والسعادة أو العظمة أو كثرة الكلام أو الأفكار المتزاحمه أو قلة الحاجة إلى النوم أو الانشغال المفرط بافكار او سلوكيات جنسيه. وعند وجود أحد هذه الأعراض يفضل تطبيق K-SADS.

ومقياس الهوس للأطفال مفيد جداً وفعال ويساعد في تفرقتها عن أطفال فرط الحركه و نقص الانتباه فقط.

التاريخ العائلي لاضطرابات المزاجيه في أقارب الدرجة الأولى وخصوصاً الآباء هو عامل تنبؤي مهم جداً يجب البحث عنه.

ومن خلال متابعة خطة العلاج إذا وجدنا أن الاستجابة كانت اقل مما هو متوقع لابد من أعادة تقييم الحاله مرة اخرى.

وعند وجود حالة تعاني من الاكتئاب مع فرط الحركه و نقص الانتباه لابد من متابعتها بعناية لأنها قد تكون مؤشر على نوبة اضطراب وجدانى. بعض العوامل مثل البداية المبكرة للمرض والتاريخ العائلي للأضطرابات المزاجيه لابد من أخذها في الحسبان قبل وصف مضادات الاكتئاب مع متابعة وعناية شديدة.

المناقشه و الاستنتاج:

بمقارنه نتائج هذا البحث بالدراسات المختلفه. تماثلت نتائج البحث مع الدراسات فى الكثير من الجوانب مثل نسبه المصاحبه بين فرط الحركه و نقص الانتباه و الاضطراب الوجدانى.

أيضا البدايه المبكره لفرط الحركه و نقص الانتباه في الحالات المصاحبه عن فرط الحركه و نقص الانتباه فقط, وجود ارتباط بين اضطرابات المزاج فى الامهات و

الاضطراب الوجدانى في اطفالهم ووجود فرص اعلي للمصاحبه مع اضطراب المسلك.

هناك اختلاف فى بعض النقاط مثل عدم وجود ارتباط بين اضطرابات المزاج فى الاباء و الاضطراب الوجدانى في اطفالهم.

التوصيات

توصيات بحثيه:

- تكرار هذه الدراسه علي عينه اكبر و اكثر تمثيلا, متضمنه المراهقين.
- الحاجه الى مقايس اكثر سهوله فى الاستخدام لتشخيص الاضطراب الوجداني و تفرقته عن فرط الحركه و نقص الانتباه.
- دراسات اكثر عن الاضطراب الوجداني في الاطفال, و العوامل الوراثيه الخاصه به.

توصيات اكلينيكيه:

- زياده الوعى العام للاطباء بوجود الاضطراب الوجداني كتشخيص قائم فى الاطفال.
- الحاجه الى التشخيص المبكر للاضطراب الوجداني لمنع تبعات عدم التشخيص و العلاج.
- وجود برامج علاجيه للاضطراب الوجداني متضمنه الاسره كجزء هام فى التقيم, العلاج و اعادة التأهيل للطفل.

Chapter (I)

Pediatric Bipolar Disorder

Bipolar disorders were once considered to be quite rare in children and adolescents. However, there is a growing body of scientific evidence to suggest that they are prevalent more than once believed. There has been increasing recognition of pediatric bipolar disorder (PBD) in the psychiatric literature during the past 10 years. In the United States, the prevalence in outpatient clinics increased 40-fold between 1994 and 2003 **(Moreno et al., 2007).** Despite the dramatic increase in the knowledge about pediatric BD, there is considerable controversy about the clinical presentation, particularly its core symptoms, and hence the prevalence **(Pavuluri et al., 2005).**

The diagnosis of bipolar disorder carries with it several implications that must not be taken lightly, and so assigning a diagnosis of bipolar disorder to a child or teenager should be done carefully. A clinician working with such cases is faced with a variety of difficulties in the assessment process as sub-syndromal states in children and teenagers and high rates of co-morbidity, besides difficulties in the implementation of the treatment plan **(Findling et al., 2002).**

On the other hand inadequate treatment may deny a child or adolescent effective prophylaxis against future episodes and protection against ensuing complications, such as substance abuse, conduct disorder, or suicidal behavior. In spite of these pressing dangers, the current knowledge about treating bipolar disorder in this age group is still limited **(Steele and Fisman, 1997).**

Epidemiology of pediatric bipolar disorders

Very few epidemiological studies have assessed the prevalence of childhood bipolar disorder, so there is limited information about the occurrence of this condition. Bipolar disorder presents in a wide variety of ways in children and adolescents. This may be one of the reasons why there are so few epidemiological data regarding juvenile bipolarity when compared to what is known about adults with bipolar disorders **(Findling et al., 2002).**

Retrospective studies in adults with BAD have reported that as many as 60% experienced the onset before 20 years of age, and 10%–20% reported the onset before 10 years of age. The initial presentations, however, are usually depressive symptoms or full depressive episodes, with only 20% to 24% of adults having early-onset BD initially presenting with mania (**Pavuluri et al., 2005).**

The data existing suggests that BAD I is not the most common in children and teenagers. It appears that BAD-NOS is the most common form. Although no extensive epidemiological data are available, it seems as if the male

to female ratio for patients aged 5-17 years is approximately 2:1 **(Findling et al., 2002).**

Risk factors for pediatric bipolar disorder

In the adult literature, twin, adoption, and family history studies support a strong genetic component, with a four to six fold increased risk of the disorder in first degree relatives of affected individuals **(Nurnberger and Foroud, 2000).** Although more controversial, the presence of severe disruptive disorders (symptoms that suggest ADHD accompanied by uncontrollable temper outbursts or rage) in the context of family history of BD may be associated with increased risk of BD **(Pavuluri et al., 2005).**

Youths with cyclothymia or BD type II and prepubertal major depressive disorder seem to be at high risk of BD type I. Approximately 20% of youths with major depression go on to experience manic episodes by adulthood (Similar to findings in adults, factors that predict the eventual development of mania in depressed children and adolescents include very early onset before age 13 a depressive episode characterized by rapid onset, psychomotor retardation, bodily concerns, decreased concentration and psychotic features; a family history of affective disorders, especially bipolar disorder; and a history of mania or hypomania after treatment with antidepressants) **(McClellan et al., 2007).**

The Clinical features

The clinical presentation of this disorder in the pre-adolescent and early adolescent age groups is greatly debated, although mid to late adolescent onset BD is considered similar to that of adult BD. A key question is whether children with a pre-pubertal and early adolescent bipolar I disorder phenotype (PEA–BP-I) have the same illness as their adult counterparts. This question arises because of the greater severity, longer current episode, preponderance of mania, and high rates of ultradian rapid cycling and co-morbid attention- deficit/hyperactivity disorder (ADHD) in child mania in prospective and retrospective studies. In most but not all studies, children with BP-I resemble the most severely ill adults with BP-I, of whom approximately 20% also have long episodes and rapid cycling, fueling interest in whether they are the same disorder **(Pavuluri et al., 2005)**.

Difficulties in the diagnosis

There are several reasons why bipolar spectrum may be difficult to diagnose accurately in children and adolescents. First of all, the acceptance that bipolar disorder can occur in children. One of the causes that pediatric bipolar disorder is very debatefull is the atypicality of the clinical picture. This is presented in form of that the most common mood disturbance is severe irritability and prolonged aggressive outbursts of temper, not euphoria. Although these outbursts are episodic there is chronic irritability or anger. Besides the clinical picture is not episodic but chronic rapid cycling , mixed state and therefore many children do not have the currently

required DSM-IV duration of symptoms to fulfill diagnosis for bipolar I disorder or bipolar II disorder **(Akiskal, 2002)**.

The Limitations of the DSMIV in diagnosis of pediatric bipolar disorder as there is continued debate over the appropriateness of DSM-IV criteria for classifying BD in children and young adolescents (**Biederman et al., 2000; Findling et al., 2001).** For example identifying episode onset and offset can be difficult because many children with BD present with frequent daily mood swings that have been occurring for months to years. Children with BD often present with a mixed or dysphoric picture characterized by frequent short periods of intense mood lability and irritability rather than classic euphoric mania **(Findling et al., 2001).**

The developmental issues influencing the clinical picture of bipolar disorder in youths, the difficulties children and adolescents have in verbalizing their emotions. The high rates of co morbid disorders including multiple anxiety disorders, conduct disorder, oppositional defiant disorder, and ADHD may account for the complexity and current controversies in diagnosing children and adolescents with bipolar disorder (**Birmaher, 2007).**

How to accurately diagnose pediatric bipolar disorder and overlap the obstacles?

It is important to interview, at minimum, the child and one parent. Ideally, both parents will attend the evaluation.

First:

- Assess \identify mood states:
  Depressed (sad or irritable)
  Manic (euphoric or irritable)
  Mixed
  Euthymic
- Characterize mood states:
  Spontaneous or precipitated
- Assess the longitudinal course
- Assess time course of other symptoms (co-morbidity)
- Rule out general medical condition (endocrinal disturbance or neurological conditions)
- Rule out drug induced mood states
- Take a detailed family history
- Assess environmental factors **(Findling et al., 2002)**

Second:

The Symptom Thresholds can be used as follow, when ascertaining the presence or absence of manic symptoms; it is recommended that clinicians use the FIND (frequency, intensity, number, and duration) strategy in diagnosis.

The FIND guidelines for the diagnosis of BPD include:

- Frequency: symptoms occur most days in a week.

- Intensity: symptoms are severe enough to cause extreme disturbance in one domain or moderate disturbance in two or more domains.
- Number: symptoms occur three or four times a day.
- Duration: symptoms occur 4 or more hours a day, total, not necessarily contiguous **(Kowatc et al., 2005).**

The symptomatic description

Core symptoms,

Euphoric /Expansive Mood. It is one of the cardinal symptoms; it is a distinguishing factor in BAD. It is crucial that the clinician obtain a detailed history, with many examples that include the context (if there was an environmental trigger for the euphoria or not?).

Grandiosity. It is another core symptom; Pathological grandiosity typically exceeds a child's normal fantasy or imagination for his or her age.

Decreased Need for Sleep. It is important to distinguish decreased need for sleep from more common forms of insomnia that result in fatigue the next day. A school age child sleeps from 9 to 11 hours per night in average. To meet this manic criterion, a child's sleep should be decreased by 2 or more hours per night for his or her age without evidence of daytime fatigue (**Kowatc et al., 2005)**.

Racing Thoughts. Racing thoughts are impairing when they occur so frequently that the child cannot keep his or her daily activities on track. To ascertain flight of ideas, ask whether topics of discussion change rapidly, in a manner quite confusing to anyone listening.

Pressured Speech. Children who are excited, nervous, or angry often speak rapidly. This is a transitory phenomenon and not a sign of mania. Some children always talk a lot, particularly those diagnosed with ADHD. For such children, a change from baseline functioning is critical to count pressured speech as a symptom of mania. Additionally, manic, children may be loud, intrusive, and difficult to interrupt (**Kowatc et al., 2005).**

Psychosis. In addition to core symptoms of mania, psychotic symptoms, including hallucinations and delusions, are frequently present in children with BD **(Geller et al., 2002 ; Kafantaris et al., 2001).**

Suicidality. Although not a core symptom of mania, children with BPD are at extremely high risk of suicidal ideation, intent, plans, and attempts during a depressed or mixed episode or when psychotic (**Geller et al., 2002 ; Lewinsohn et al., 1995).**

<u>Non specific symptoms,</u>

Irritable mood. Irritability is common in childhood psychopathology. Children with major depressive disorder, oppositional defiant disorder, pervasive

developmental disorder (PDD), anxiety disorders schizophrenia, and ADHD routinely experience irritable moods. Manic irritability sometimes can be differentiated from other causes of irritability by its episodic and extreme nature. Children with BPD who experience irritability frequently have extreme rages or affective storm, over trivial matters. Aggressive and/or self-injurious behavior often accompanies this irritability.

Distractibility. For distractibility to be considered a manic symptom, it needs to reflect a change from baseline functioning, needs to occur in conjunction with a ''manic'' mood shift, and cannot be accounted for exclusively by another disorder, particularly ADHD.

Increase in Goal-Directed Activity/Psychomotor Agitation. Whereas increased goal-directed activity is relatively specific to mania, psychomotor agitation is common. Therefore, increased goal-directed activity is more informative than psychomotor agitation in diagnosing mania. For example, children with ADHD are frequently full of energy and activity. For this symptom to count toward a diagnosis of mania, the level of activity or agitation has to be more than what is typically seen in the child with ADHD. Children or adolescents who are hypomanic may be fairly productive, but if their mania progresses, they may become increasingly disorganized and nonproductive (**Kowatc et al., 2005).**

Excessive Involvement in Pleasurable or Risky Activities. Children with BPD are often hypersexual. It is

important to rule out sexual abuse or exposure to sexually explicit materials or behaviors as a possible cause of hypersexual behavior in any child, including one with BPD. Adolescents may seek out sexual activity multiple times in a day **(Geller et al., 2002).**

The clinical forms of bipolar disorder in children and adolescents

A framework for classification of pediatric Bipolar Disorder spectrum into subtypes was introduced by **Leibenluft et al. (2003).** They suggested defining pediatric BD into ''narrow,'' ''intermediate,'' and ''broad'' phenotypes.

The narrow phenotype is attributed to those that meet the full DSM-IV diagnostic criteria for mania or hypomania, including the duration criterion of 7 and 4 days, respectively, and have the hallmark symptoms of elevated mood or grandiosity, but excludes those diagnosed based on irritable mood alone.

The second is the intermediate phenotype and consists of two sub-phenotypes, the first of which describes patients presenting symptoms of euphoria, elation or grandiosity, as well as other hypomanic symptoms, although the duration of the episodes is

generally less than that established by the DSM-IV to define a hypomania crisis. The other intermediate phenotype describes patients presenting no euphoric or grandiose behavior, although such patients present increased irritability and other long-lasting hypomanic symptoms. Patients in these intermediate phenotypes are often diagnosed with unspecified hypomania.

The Broad Phenotype includes children who have explosive rages, aggression, hyperarousal, hyperactivity, distractibility and chronic mood disturbance but meet neither DSM-IV symptom nor duration without the hallmark symptoms of elated mood or grandiosity. The BAD-NOS category in DSMIV corresponds to the intermediate and broad phenotypes **(Leibenluft et al., 2003).**

The pediatric bipolar spectrum

There are no great differences from adult bipolar except for some points:

Bipolar disorder not otherwise specified (NOS): This term is used for cases that do not meet full criteria for other bipolar diagnoses. This term also has been recommended to describe the large number of youths who receive a diagnosis of bipolar disorder who do not have the classic adult presentation**.** A recent study found that youths with BD-NOS, operationalized as elated mood plus two DSM-IV BD symptoms or irritability plus three DSM-IV BD symptoms, at least 4 hours of symptoms in a 24-hour period, and lifetime of 4 days total of symptoms,

showed levels of severity, comorbidity, and family history that were comparable with those of youths with BD types I and II **(Birmaher et al., 2006).**

At follow-up, youths with BD-NOS showed longer time to recover and a shorter time to recurrence than youths with other types of BD, perhaps because they had more chronic subsyndromal presentations that may prove to be more resistant to treatment. Moreover, approximately 25% of youths with BD-NOS converted to BD type I or II. These results are important because a great proportion of children and adolescents are being classified as BD-NOS because they do not fulfill the DSM-IV requirements for BD types I and II **(Leibenluft et al., 2003).**

Definitions currently used in the juvenile bipolar literature, but not provided in DSM-IV-TR, include the following

- **Complex cycling** to describe the presence of short cycles embedded within a more prolonged cycle or episode.

- **Ultrarapid cycling:** Ultrarapid cycling refers to brief, frequent manic episodes lasting hours to days, but less than the 4-day prerequisite for hypomania. **Geller et al. (2000)** define ultrarapid cycling as having 5 to 364 cycles per year.

- **Ultradian cycling:** Ultradian cycling refers to repeated brief (minutes to hours) cycles that occur daily. **Geller**

et al. (2000) use the definition of greater than 365 cycles per year**.**

The course of pediatric bipolar disorder

In identifying the course of pediatric bipolar disorder, it is very important to differentiate between different forms of recovery. There are syndromatic recovery, symptomatic recovery and functional recovery.

Retrospective studies **(Werry et al., 1991**) and naturalistic longitudinal studies of children and adolescents with BAD **(Birmaher et al., 2006; Carlson et al., 2000, 2002; Geller et al., 2004; Jairam et al., 2004; Lewinsohn et al., 1995; Strober et al., 1995)** have reported that 40%–100% will recover in a period of 1–2 years. Of those patients who recovered, however, approximately 60%–70% showed recurrences in an average of 10–12 months. The rate of functional recovery is much lower than the rate of syndromatic and symptomatic recovery. So sub- threshold bipolar symptomatology was associated with significant impairment and dysfunction. Also many children did not attain euthymia with continuing depressive symptoms in the absence of manic symptomatology **(Pavuluri et al., 2005)**.

Within the syndromal symptoms, subjects with BP-I spent significantly more weeks with syndromal mania and mixed symptoms than those with BP-NOS, and subjects with BP-II spent significantly more time with depressive symptoms than those with BP-I and BP-II. Within the subsyndromal symptoms, BP-NOS subjects spent

significantly more weeks with subsyndromal mania and mixed symptoms compared with BP-I subjects, and BP-II subjects spent significantly more time with subsyndromal depression than BP-I and BP-NOS subjects **(Birmaher et al., 2006).**

Although recovery from the index episode was observed in approximately two thirds of subjects, half of them had at least one full syndromal recurrence. Subjects with BP-I and BP-II recovered from their index episode and had recurrence more frequently than those with BP-NOS. In contrast, subjects with BP-NOS had a more protracted illness, but once they recovered from their index episode, they took a longer time to recur than those with BP-I and BP-II **(Birmaher et al., 2006).**

A recent study found that youth with BAD-NOS, showed levels of severity, comorbidity, and family history that were comparable with those of youths with BD types I and II**.** At follow-up, youths with BAD-NOS showed longer time to recover and a shorter time to recurrence than youths with other types of BAD, perhaps because they had more chronic subsyndromal presentations that may prove to be more resistant to treatment **(Birmaher et al., 2006)**.

Other investigators have diagnosed these youths as having BAD with very rapid cycling or chronic BAD and reported that these children have poor prognosis **(Pavuluri et al., 2005).**

A retrospective interview of a large sample of adult BD indicated that approximately 30% experienced very early onset (age younger than 13 years) and approximately 40% experienced early onset (ages 13–18 years). Earlier onset was associated with greater rates of anxiety and substance abuse disorders, more recurrences, shorter periods of euthymia, and higher incidence of suicide attempts and violence. Also, approximately 20%–30% of depressed children, particularly those with psychosis, a family history of BD, and/or pharmacologically induced mania eventually develop BD **(Geller et al., 1994; Strober and Carlson, 1982; Yung and McGorry, 1996).**

Many important factors affect the morbidity of the illness in this age group, including early age of first onset of mood disturbance, long duration, fluctuating course, high familial loading for mood and other psychiatric disorders, and high rates of comorbid disorders, particularly attention deficit/ hyperactivity disorder, disruptive behavior, and anxiety disorders (**Birmaher et al., 2006).**

Low maternal warmth predicted faster recurrence after recovery from mania, and psychosis predicted more weeks ill with mania or hypomania. Furthermore, some studies, but not all, have reported that subjects of low socioeconomic status, rapid cycling, mixed episodes, co-morbid disorders, and family conflicts have a worse prognosis. Still additional studies evaluating the risk and protective factors with larger samples of children and adolescents with bipolar spectrum disorders are needed

(Birmaher et al., 2006; Carlson et al., 2002; Geller et al., 2004; Lewinsohn et al., 1995; Strober et al., 1995).

Genetic basis in pediatric bipolar disorder

There are several lines of evidence to suggest heritability in pediatric BD. Although twin, adoption, and molecular genetic studies have established heritability in adult BD, such studies are lacking in the pediatric population.

Genetic studies pertaining to pediatric BD can be discussed within two categories: familial studies (top-down studies examining the offspring of parents with BD and bottom-up studies estimating the prevalence of BD among relatives of children with BD) and molecular genetics studies **(Pavuluri et al., 2005).**

Family studies of juvenile bipolar disorder

High-Risk or Top-Down Studies Offspring of bipolar probands provide a rich source for identifying prodromal forms of the disorder. Studying populations at high risk of BD raises the possibility of discovery of biological and phenomenological markers. One phenomenological marker of pediatric BD appears to be the combination of mood disorder and behavioral problems **(Chang et al., 2003).**

A meta-analysis of studies conducted before 1997 found offspring of parents with BD to be at 2.7 times higher risk of developing any psychiatric disorder and at

four times higher risk of developing a mood disorder than are children of parents without psychiatric illness. One of the largest studies among them (No = 72 offspring) reported significantly more psychopathology (60% versus 25%), in particular, disruptive disorders and depression, in the offspring of parents with BAD as compared with the offspring of normal controls**.**

In a study by **Birmaher et al.** offsprings aged 6 to 18 years old who have parents with BADI and II disorders in comparison to control group was found to have 14 fold increase in rates of bipolar spectrum disorders and 2 to 3 fold increase in any mood or anxiety disorders. The offsprings had onset of bipolar episodes during childhood and mostly bipolar NOS type and to lesser degree depressive episodes. Also 85% of the children had other comorbid disorder mainly anxiety disorders, disruptive behavior disorders as ADHD **(Birmaher et al., 2009).**

In a paper dealing with children at risk for bipolar disorder, **Henin et al.** used structured diagnostic interviews to compare offsprings of parents with diagnosed bipolar disorder and gender matched offsprings of parents without bipolar disorder or major depression. Compared to offspring of parents without mood disorders, high-risk youth had elevated rates of unipolar and bipolar mood disorders anxiety and disruptive behavior disorders, as well as significantly more impaired global assessment of functioning (GAF) scores, higher rates of psychiatric treatment, and higher rates of placement in special education classes. These

findings extend the literature on high risk children of BPD parents and support the hypothesis that offspring of parents with bipolar disorder are at significantly increased risk for developing a wide range of severe psychiatric disorders and accompanying dysfunction. They also suggest that early disruptive behavior and anxiety disorders, as well as early-onset depression may be useful markers of subsequent bipolar disorder in high-risk samples (**Henin et al., 2005**).

Unfortunately, the majority of studies of children at high risk are limited by small sample sizes, lack of longitudinal follow-up, inclusion of a group of parents with heterogeneous diagnoses (bipolar and unipolar), failure to control for parental co-morbid disorders, lack of normal controls, retrospective assessments, offspring assessments not conducted blind to parental diagnosis, no direct assessment of offspring, lack of analysis of developmental and parental psychiatric disorder influences on the child's psychopathology, lack of standardized assessments of psychopathology and family psychiatric history, no measurement of the effects of environmental stresses, and no evaluation of the presence of sub-syndromal symptoms **(Pavuluri et al., 2005).**

As regard bottom up studies (familial risk) they provide most of the genetic evidence of early-onset bipolar illness. Several studies have shown a strong link between early age at onset and risk of BD among first-degree relatives of youths with BD as compared with relatives of youths with schizophrenia and unipolar major depressive

disorder and normal controls. Furthermore, earlier onset of BD is associated with greater familial loading of BD. Relatives of adolescents with subsyndromal symptoms of BD also have increased family history of BD, comparable with those with the full syndrome **((Pavuluri et al., 2005).**

In summary, family studies and segregation analyses show clear familiality of early-onset bipolar disorder at levels that may exceed those of late-onset bipolar disorder. Furthermore, this familiality of the disorder appeared from initial studies to be due to at least some genetic influence. These findings have led some authors to suggest a greater genetic role in early-onset cases, and to regard them as more genetically homogeneous **(Smoller and Finn, 2003).**

It should be taken in consideration that bipolar disorder might occur earlier fueled by a cohort effect or iatrogenic causes. The cohort effect describes a phenomenon where an illness begins earlier in successive generations due to a combination of genetic susceptibility and environmental factors. Iatrogenic is a term used to describe medical conditions that are exacerbated by medical treatments. An example would be the use of anti-depressants and stimulants in pediatric patients **(Scheffer, 2002).**

Molecular Genetics Studies

The age at onset of bipolar disorder has been recognized for some time as a potentially important marker for disease severity and possibly a more

substantial genetic basis. Initial studies clearly supported this possibility, especially in the degree to which early onset was found to predict the amount of familial aggregation of the disease. **Tsuang and Faraone (1990)** reviewed 16 family studies, assessing the age at onset of mood disorders. They found an elevated risk for mood disorders among relatives of probands who experienced an early onset of their mood disorder versus relatives of those with later onset. This was true for both bipolar disorder and unipolar depression. But, because these studies defined early and late onset by dichotomizing the age at onset in either early or mid-adulthood, their relevance to juvenile-onset bipolar disorder was not clear **(Faraone et al., 2003).**

Subsequent work has addressed this issue using samples strictly ascertained for juvenile-onset bipolar disorder**. Neuman et al. (1997)** observed a similar pattern, in which relatives of pediatric-onset bipolar patients were more than twice as likely to have bipolar disorder than were relatives of later-onset patients. Such observations led these authors and others to posit a greater genetic role in early-onset cases and to regard them as more genetically homogeneous **(Faraone et al., 2003).**

The focus of molecular genetics in pediatric BD has focused on allelic associations with the disorder. Brain derived neurotrophic factor (BDNF) is heavily expressed in human brain and has increased expression beginning in young adulthood relevance to child psychiatry of differential BDNF expression by age is not yet known.

Preclinically, BDNF has been implicated in numerous mood-relevant neurobiological actions (antidepressant drug response and the neuroprotective action of lithium), and thus it was hypothesized to be a good candidate for investigation in bipolar disorders **(Geller et al., 2004)**. Also the *Val66* allele (found at the amino acid position 66 in exon 1 of the BDNF gene on chromosome 11p13) is a functional variant in both human and preclinical studies **(Egan et al., 2003).**

Geller et al. 2004 examined the commonly studied Val/Met amino acid variant and showed preferential transmission of the brain-derived neurotrophic factor val66 alleles in children with prepubertal and early adolescent BD **(Geller et al., 2004).**

Geller and Cook (1999) have studied genetic transmission of the serotonin transporter–linked promoter region short and long alleles using the transmission disequilibrium test. They found no evidence of such an association. These results concurred with the meta-analysis of adult studies **(Craddock et al., 2001)** but differed from another pediatric BD sample that showed significantly more short serotonin transporter alleles **(Ospina-Duque et al., 2000)**. The catechol- O-methyltransferase, a dopamine-metabolizing enzyme, lacked linkage disequilibrium with ultradian rapid cycling pediatric BD **(Geller and Cook, 2000).** This is in opposition to findings documented in adult studies **(Craddock et al., 2001).** This could be the result of phenotypic differences, inadequate sample sizes, or developmental influences on

gene expression. Given that the genes of interest, such as the serotonin transporter, are abundantly expressed in limbic regions (critical for affect regulation), they are considered a good candidates for further study **(Faraone et al., 2003).**

Several researchers have suggested that BD is associated with genetic anticipation defined as an apparent tendency of certain diseases to appear at earlier age at onset and with increasing severity in successive generations. This was indicated by trinucleotide repeats (CAG/CTG) coding for polyglutamine tracts **(Geller et al., 2004).**

Evidence is emerging that polyglutamine is in fact linked to neurotoxicity, although the specific mechanisms that underlie this association remain to be established. **Scrambler et al. (1992)** found that pediatric BD was significantly associated with microdeletion of chromosome 22, possibly representing a susceptibility gene for pediatric BD. Although results are pointing to strong familial transmission in the early-onset variant of BD, there are no reliable indicators of genetic risk and efforts toward further exploration have just begun **(Faraone et al., 2003).**

The use of genetic studies in early intervention

The identification of prodromal BD in children and adolescents would mean the possibility of early intervention and prevention of the full expression of BD in these children. To develop intervention strategies for

bipolar offspring, it is helpful to use a model for BD development. One elegant model of the development and progression of BD is the kindling model as applied to mood disorders, as proposed by **Post (1992).** In this model, psychosocial stressors interact with genetic predisposition predominantly at the outset of the disorder. These stressors may affect neurobiological change that not only leads to affective episodes but may also create vulnerability to future episodes.

Thus, prevention of this trajectory would involve either increasing the neurobiological buffer to withstand these stressors (by pharmacotherapy or psychotherapy) or by actually decreasing the amount or intensity of the stressors. From a psychosocial standpoint, early intervention could therefore consist of family therapies to improve dysfunctional family interactions, psycho-education to parents regarding parenting skills and early signs of BD to monitor, or direct psychotherapy with the at risk child to increase his or her ability to cognitively and emotionally handle stress. These interventions also may not carry as much concern as using pharmacological agents that have uncertain effects on the developing central nervous systems; however, these psychosocial interventions may be difficult to implement and their efficacy in preventing BD development may be difficult to study **(Chang et al., 2003).**

The second approach involves pharmacologically appropriate medications that would first treat subsyndromal symptoms, such as mood or ADHD

symptoms, adequately without furthering the progression to BD. For example, antidepressants may be relatively poor choices to treat depression or anxiety symptoms in bipolar offspring due to the risk of directly causing a manic episode **(Chang and Ketter, 2001).** Second, proposed medications should be able to hinder, or even reverse, the neurobiological progression toward BD as hypothesized by the kindling model. There are some early data suggesting that lithium and certain anticonvulsants may have neuroprotective qualities **(Manji and Chen, 2002 ; Young et al., 2002).**

Therefore, these agents, who are already being used to treat BD, may be good candidates for study in bipolar offspring cohorts. Caution should be exercised, however, in implementing pharmacologic early intervention in symptomatic bipolar offspring at this point. Some prodromes may be self limiting and not progress to BD, and effects of certain medications on the developing brain are still not well understood **(Gottesman and Erlenmeyer-Kimling, 2001).**

Management of Pediatric Bipolar Disorder

Pharmacotherapy research has a critical role in enriching clinical practice. However, the pediatric pharmacotherapy studies often suffer from small numbers, open trials, intangible methods that do not lend themselves to enroll seriously ill patients, and worst of all, too slow behind the actual clinical experience acquired through trial and error.

There have been few prospective studies on the efficacy and safety of psychotropic medications in the treatment of pediatric BAD. Given the paucity of studies involving youths, no psychotropic medications have been approved for pediatric BD by the U.S. Food and Drug Administration except lithium carbonate.

Some treatment guidelines arose out of a need first voiced by members of the Child and Adolescent Bipolar Foundation (CABF), who noted that clinicians are in desperate need for guidelines regarding how to best manage such cases **(Kowatch et al., 2005)**.

Acute Phase Medication Treatment for BPD

Two treatment specific algorithms were developed for acute phase treatment of BPD-I in children and adolescents, manic or mixed, depending on whether the child presented with or without features of psychosis.

Both treatment algorithms consist of six potential stages of treatment. For all the treatment stages described below, when a child does not respond to treatment, it is important to consider factors frequently associated with non-response such as misdiagnoses, poor adherence to treatment, presence of comorbid disorders (ADHD, substance abuse, anxiety disorders), and exposure to environmental and biological stressors **(Kowatch et al., 2005).**

Algorithm I: BPD-I, manic or mixed, acute without psychosis

- **Monotherapy**

Monotherapy with the traditional mood stabilizers lithium, divalproex, and carbamazepine and the atypical antipsychotics olanzapine, quetiapine, and risperidone was determined to be first-line treatment. However, the majority recommended lithium or divalproex as the first medication choice for non psychotic mania.

- **Monotherapy with augmentation**

For children who have had a partial (moderate to minimal) improvement in initial monotherapy, it was recommended that an augmenting agent can be used. There is some evidence to support augmentation strategies for children and adolescents with manic or mixed episodes combining lithium and divalproex before combination treatment with an atypical antipsychotic for non psychotic mania is recommended.

- **Alternate monotherapy**

For those children who had no response to the initial monotherapy agent or who had intolerable side effects, monotherapy with one of the medications not tried is recommended **(Kowatch et al., 2005)**.

- **Combination vs monotherapy**

When a child with a mixed or manic episode has tried two monotherapy agents without success. It is recommended that to reduce the likelihood of side effects and to increase compliance, selection of monotherapy agents not tried before would be a reasonable clinical choice. If failed the possible medication combinations are lithium plus divalproex, lithium plus an atypical antipsychotic (olanzapine, quetiapine, or risperidone), divalproex plus an atypical antipsychotic, or carbamazepine plus an atypical antipsychotic.

Children who had no response or a partial response to augmentation with a monotherapy agent, or who had no response or a partial response to a combination of two mood stabilizers. Possible combinations of three mood stabilizers include lithium plus divalproex plus olanzapine, lithium plus divalproex plus quetiapine, lithium plus divalproex plus risperidone, carbamazepine plus lithium plus olanzapine, carbamazepine plus lithium plus quetiapine, or carbamazepine plus lithium plus resperidone can be used **(Kowatch et al., 2005)**.

- **Alternate monotherapy**

Trials of alternate monotherapy with oxcarbazepine, ziprasidone or aripiprizole. Although there is past clinical experience (level D) with typical antipsychotics, the atypical antipsychotics have the advantage of a more tolerable side effects profile. Although lamotrigine has received U.S. Food and Drug Administration approval for long-term maintenance treatment of BPD-I in adults **(Bowden et al., 2003),** there are no data available about its use for manic episodes in youths. Therefore, not recommend for treatment of acute manic episodes in children and adolescents.

- **Electroconvulsive therapy or clozapine**

For youths who did not show a positive response or who experienced intolerable side effects to all the treatments, clozapine for children and adolescents is recommended, and treatment with ECT is recommended for adolescents only. Case reports of the effectiveness of ECT in the treatment of acute mania in adolescents **(Rey and Walter, 1997)** have been reported. In case series, clozapine has been effective in the treatment of children and adolescents with BPD. There were insufficient data to recommend one treatment over the other **(Kowatch et al., 2005).**

<u>Algorithm II: BPD-I, manic or mixed, acute with psychosis</u>

- **Mood Stabilizer Plus Atypical Antipsychotic**

For children with BPD-I, manic or mixed with psychosis, it was recommended that initial treatment should be a combination of a traditional mood stabilizer (lithium, divalproex, or carbamazepine) and an atypical antipsychotic.

- **Augmentation**

For children whose symptoms do not respond to a mood stabilizer plus an atypical antipsychotic, a combination treatment with three medications is recommended, based on clinical experience. In this case, lithium plus divalproex plus an atypical antipsychotic or lithium plus carbamazepine plus an atypical antipsychotic would be the treatment regimen.

- **Other Mood Stabilizer Plus Atypical Antipsychotic**

If a child's symptoms fail to respond or the child has intolerable side effects from the medication used previously, then the combination of medications not tried is recommended.

- **Augmentation**

If a child has a partial improvement augmentation is recommended, based on clinical experience. For example, lithium plus divalproex plus an atypical antipsychotic would be the treatment combination.

- **Mood Stabilizer Plus Alternate Atypical Antipsychotic**

If a child's symptoms fail to respond treatment with lithium plus divalproex plus an atypical antipsychotic or to lithium plus carbamazepine plus an atypical antipsychotic, substitution of an alternate atypical antipsychotic is recommended.

- **Combination of Two Mood Stabilizers Plus Atypical Antipsychotic**

For children whose symptoms have not responded to treatment with lithium and two atypical antipsychotic trials, divalproex and two atypical antipsychotic trials, or carbamazepine and two atypical antipsychotic trials, combination treatment of two mood stabilizers plus an atypical antipsychotic is recommended, based on clinical experience. In this case, lithium plus divalproex or carbamazepine plus an atypical antipsychotic would be the treatment regimen.

- **Alternate Monotherapy Plus Atypical Antipsychotic**

If medications used all fail, then alternate monotherapy (oxcarbazepine) plus an atypical antipsychotic is recommended, based on clinical experience.

- **ECT or Clozapine**

For children and adolescents who have not responded to combinations of treatment with three medications, clozapine is recommended. ECT is recommended for adolescents only **(Kowatch et al., 2005)**.

<u>Acute Phase Treatment for BAD-I, Depressed</u>

Because there are no prospective studies in children and adolescents for the treatment of BPD-I depressed, it was agreed that there was insufficient evidence to develop a treatment algorithm. Based on data available on adults with bipolar depression treated with lithium **(Zornberg and Pope, 1993)**, lithium was recommended as a treatment option for bipolar depression in children and adolescents.

Studies in depressed youths have shown that cognitive behavioral therapy (CBT) and interpersonal psychotherapy are efficacious for the acute treatment of depression (**Birmaher et al., 2000; Mufson et al., 1999)**.

Newer agents

Lamotrigine is effective in adult bipolar depression, rapid cycling BPD, and prophylaxis of mood episodes in adults with BPD. Data in children with BPD are limited. Lamotrigine carries a black box warning from the U.S. Food and Drug Administration that children younger than the age of 16 are at increased risk of Stevens- Johnson syndrome. However, more recent data suggest that the incidence of serious rash in children taking lamotrigine may be 1 in 10,000. Nevertheless, more data on lamotrigine use in children with BPD are needed before a consensus recommendation can be made **(Kowatc et al., 2005)**.

The maintenance / continuation phase

The basic goals of maintenance treatment include prevention of relapse and recurrence, reduction of

subthreshold symptoms, suicide risks, affective cycling, and mood instability, reduction of vocational and social morbidity, and promotion of wellness. At present, it appears that the agents that help patients get well are the same ones that keep them well.

Unfortunately, there is a paucity of prospective randomized maintenance studies. The results of one trial suggest that in young patients with BPD who achieve syndromal remission with combination of lithium and divalproex sodium therapy, maintenance monotherapy treatment with either lithium or divalproex sodium appears equally effective. Unfortunately, the use of either lithium or divalproex monotherapy treatment in this patient group was associated with a relatively rapid median time to relapse **(Findling et al., 2003).**

In a prospective case series, **Strober et al. (1990)** found that continuation of lithium decreased the 18-month relapse rate from 92.3% to 37.5% in 37 adolescents diagnosed with BPD. Because pediatric BPD appears to be a chronic condition with a high risk of relapse, it was recommended that maintenance treatment studies are a high priority. Due to the possibility that drug monotherapy may not be associated with optimal long-term symptomatic control; future maintenance studies should compare combination pharmacotherapy with single drug treatment.

There is also limited information regarding how long treatment for BPD should be maintained in young

patients. It was recommended that medication tapering or discontinuation should be considered if the patient has achieved remission for a minimum of 12 to 24 consecutive months. For less severely ill patients or in patients for whom a diagnosis is less clear, a briefer treatment period may be indicated. The risk associated with a potential relapse should be compared with the risk associated with continued pharmacotherapy. Patients for whom greatest caution should be taken are those with a history of suicidal behavior, severe aggression, and/or psychosis. It was acknowledged that for many patients, long-term or even lifelong pharmacotherapy might be indicated.

The consensus was that there appear to be several factors that might place a youth at higher risk of relapse during discontinuation of pharmacotherapy, as a greater length of illness, and a higher number of episodes before stabilization. If medications are to be reduced in a patient with BPD, it was recommended that medications should be tapered and not abruptly discontinued, the taper should occur at a time that would be associated with the lowest possible risk of dysfunction/ poor outcomes, and the environment be stable with adequate monitoring systems in place so that prodromal mood symptoms of relapse can be readily detected **(Kowatch et al., 2005)**.

In addition, emotional and environmental factors may trigger relapses or recurrences. These include sleep deprivation, stress, and negative cognitions. For these reasons, psychotherapeutic interventions that include the

family may be helpful in solidifying treatment gains **(Kowatch et al., 2005).**

Treatment of co-morbid psychiatric disorders

Most children and adolescents with BPD have other coexisting (co-morbid) psychiatric disorders, particularly ADHD, oppositional defiant disorder, conduct disorder, anxiety disorder, and, during adolescence, substance abuse. In this section, the treatment of these comorbid disorders is described. However, it is important to emphasize that there are very few controlled studies for the treatment of comorbid disorders in youths with BPD.

Before treating the comorbid disorder, it is important to first stabilize the symptoms of BPD. Once the bipolar symptoms are stabilized, the need for treatment of comorbid disorders should be reviewed. If the symptoms of the comorbid condition are negatively affecting the child's psychosocial or academic functioning, then treatment is warranted **(Kowatch et al., 2005)**.

Psychotherapy as CBT has been found to be helpful for the treatment of depression, anxiety, and obsessive-compulsive disorders **(Gaynor et al., 2003),** and interpersonal psychotherapy is effective for the treatment of major depression in teens **(Mufson et al., 1999).** In contrast to some medications, psychosocial therapies do not generally cause mood dysregulation and can therefore be used without the risk of aggravating bipolar symptoms.

Although it is important to treat most of the impairing comorbid symptoms as soon as possible, it is best to begin treatment for each comorbid disorder sequentially, one at a time after the BPD has been adequately treated. It is recommended to introduce medications one at a time, if possible, to observe the benefits and side effects of each agent **(Kowatch et al., 2005)**.

Role of Psychosocial Therapy

Once a child with BPD is stable on medication and is capable of learning new skills, it may be useful, if available, to pursue evidence-based therapy. It includes psychoeducation (teaching parents and children information about BPD, its symptoms and course, and treatment) as well as skill building, especially communication and problem solving in regard to symptom management, emotion regulation, and impulse control **(Fristad et al., 2003; Miklowitz, 2002; Pavuluri et al., 2004).** Therapeutic techniques used are based in part on family systems interventions and cognitive-behavioral interventions.

A therapeutic alliance is essential when working with families of children with BPD. For a child to benefit from therapy, they must be comfortable talking with the therapist. Sometimes forcing a child to attend therapy has the potential to do more harm than good, turning a child off to the process of therapy, which may inhibit its use at a later stage in life. If the child does not wish to attend therapy, parents can still benefit greatly from sessions

with a professional who can help them to recognize symptoms, learn problem solving skills to manage symptoms, and develop stress reduction strategies necessary for family preservation **(Kowatch et al., 2005).**

Chapter (II)

Attention Deficit Hyperactive Disorder

ADHD is considered the most researched and commonly diagnosed psychiatric disorder of childhood. It is characterized by a triad of symptoms (hyperactivity, inattention, and/or impulsivity) that cause impairment in the child's social, educational, relational, occupational, and self-sufficiency roles.

Estimates suggest that ADHD occurs in 3% to 7% of school-age children and is three times more common in boys. Theories suggest that boys are more likely to receive a diagnosis of the hyperactive subtype since they are more likely to exhibit aggressive, externalizing types of behaviors. Girls are more likely to receive a diagnosis of the inattentive subtype **(Stein et al., 2004).**

What causes ADHD?

Over the last few decades, scientists have come up with possible theories about what causes ADHD. Some of these theories have led to dead ends, some to exciting new avenues of investigation.

Environmental Agents

Studies have shown a possible correlation between the use of cigarettes and alcohol during pregnancy and risk for ADHD in the offspring of that pregnancy.

Another environmental agent that may be associated with a higher risk of ADHD is high levels of lead in the bodies of young preschool children. Since lead is no longer allowed in paint and is usually found only in older buildings, exposure to toxic levels is not as prevalent as it once was. Children who live in old buildings in which lead still exists in the plumbing or in lead paint that has been painted over may be at risk **(Braun et al., 2006).**

Brain Injury

One early theory was that attention disorders were caused by brain injury. Some children who have suffered accidents leading to brain injury may show some signs of behavior similar to that of ADHD, but only a small percentage of children with ADHD have been found to have suffered a traumatic brain injury **(Keenan et al., 2008).**

Food Additives and Sugar

It has been suggested that attention disorders are caused by refined sugar or food additives, or that symptoms of ADHD are exacerbated by sugar or food additives. In 1982, the National Institutes of Health held a scientific consensus conference to discuss this issue. It was found that diet restrictions helped about 5 percent of children with ADHD, mostly young children who had

food allergies. A more recent study on the effect of sugar on children, using sugar one day and a sugar substitute on alternate days, without parents, staff, or children knowing which substance was being used, showed no significant effects of the sugar on behavior or learning **(Wolraich et al., 1985).**

In another study, children whose mothers felt they were sugar-sensitive were given aspartame as a substitute for sugar. Half the mothers were told their children were given sugar, half that their children were given aspartame. The mothers who thought their children had received sugar rated them as more hyperactive than the other children and were more critical of their behavior (**Hoover and Milich, 1994).**

Genetics

Family, twin and adoption studies have traditionally been used to examine whether ADHD runs in families and is genetically influenced. Family studies show that the biological relatives of probands with ADHD display higher rates of ADHD than relatives of controls. The relative risk of ADHD in first degree relatives is between 4 and 9% **(Faraone et al., 2000; Chen et al., 2008).** Disorders can cluster in families because of shared environment as well as genes. Thus twin and adoption designs are needed to separate these effects.

Twin studies have primarily focused on dimensionally defined ADHD. There have been numerous published studies from across the world showing that

ADHD symptoms are highly heritable and that is most of the individual variation in ADHD scores is attributable to genetic influences **(Thapar et al., 2006; Faraone et al., 2005)**. Shared environmental influences that result in greater twin similarity for a given phenotype do not appear to be important. Non-inherited influences must however contribute, as genetic factors do not account for 100% of the phenotypic variation in ADHD. This "left over" non-shared environment variance could be explained by measurement error, random effects including those that are biological (e.g. epigenetic effects) as well as environmental factors that make twins different.

The findings of all the published adoption studies are consistent with those of twin studies in demonstrating the importance of genetic influences in ADHD. All of these studies show that adopted children are more similar to their biological relatives than to their adoptive relatives on measures of ADHD. In summary, there is consistent evidence of a strong genetic contribution to ADHD from family, twin and adoption studies and it is clear that ADHD is also influenced by non-inherited factors (gene environment interaction) **(Thapar and Stergiakouli, 2008).**

Clinical picture

For a diagnosis of ADHD, the child must exhibit hyperactive, inattentive, and/or impulsive symptoms before the age of 7 years. There is lack of empiric support for this established age criterion, however, and it has been criticized as overly restrictive. Nevertheless, ADHD

remains a common childhood diagnosis given to children with uncomplicated forms of the disorder as well as to others with severe disability and comorbidity (depression, conduct disorder, and oppositional defiant disorder) **(Barkley, 2004).**

The symptoms of ADHD will appear over the course of many months, often with the symptoms of impulsiveness and hyperactivity preceding those of inattention, which may not emerge for a year or more. Different symptoms may appear in different settings, depending on the demands the situation may pose for the child's self-control.

When the child's hyperactivity, distractibility, poor concentration, or impulsivity begin to affect performance in school, social relationships with other children, or behavior at home, ADHD may be suspected. But because the symptoms vary so much across settings, ADHD is not easy to diagnose. This is especially true when inattentiveness is the primary symptom **(Johnson et al., 2005)**.

According to the most recent version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR), there are three patterns of behavior that indicate ADHD. These are the **predominantly hyperactive-impulsive type** (that does not show significant inattention), the **predominantly inattentive type** (that does not show significant hyperactive-impulsive behavior) and the **combined type** (that displays both inattentive and

hyperactive-impulsive symptoms). The two most common subtypes of ADHD are the combined type, where impairment is due to inattention and hyperactivity/ impulsiveness (also known as hyperkinetic disorder), and the inattentive type, where impairment is caused by inattention alone. About 3–5% of primary school aged children have ADHD, with approximately 1.5% having the combined type **(Vance, 2008).**

Two important issues that must be taken into consideration in diagnosing ADHD are symptoms mimicry and co-morbidity.

As regarding symptoms mimicry, Problems of hyperactivity, impulsivity, and inattention can be caused by various conditions other than ADHD. Although the topography of the behaviors displayed by the child may be similar, the underlying causal factors may differ. These include various psychological disorders, physical illnesses or conditions, and contextual influences.

Both child anxiety and depressive disorders can result in problems in concentration and symptoms of inattention, as well as increased levels of activity in some instances. Likewise, children with histories of physical or sexual abuse or those who have been exposed to parental violence may display post-traumatic stress symptoms, which may be reflected in clinically significant problems of inattention. The behavioral disorganization that can occur in such cases may also result in increased levels of activity that, without adequate assessment, can be confused with ADHD symptoms.

Furthermore, with the preschool child, it can sometimes be difficult to distinguish between ADHD and the non compliant behaviors associated with early oppositional defiant disorder. Distinguishing between ADHD, mental retardation, and certain pervasive developmental disorders also can pose a challenge because of the problems of inattention and disorganization of behavior that may be seen in each of these conditions. Appropriate diagnosis in such instances is best accomplished by considering the total clinical picture and contextual influences rather than simply those behaviors commonly seen as core symptoms of ADHD **(Johnson et al., 2005).**

Attention Deficit Hyperactivity Disorder (ADHD) often occurs with other disorders, referred to as its *co-morbidities.* Research shows that two-thirds of children diagnosed with ADHD have at least one additional mental-health or learning disorder. ADHD and its co-morbidities present extra challenges to affected individuals, educators, and health care providers. So it is important to screen every child with ADHD for other disorders and problems.

The comorbidity between ADHD and learning disabilities was found to range between 17-38%. Many more show significant school-related difficulties, such as lowered levels of achievement, grade repetitions, school failure, and behavioral problems that interfere with classroom learning. When studying the comorbidity with

reading difficulty twin studies proved genetic influences especially with the inattentive symptoms **(Willcutt et al., 2000).**

About 60% of clinically referred children with ADHD show evidence of oppositional defiant disorder. Approximately 30 to 50% of children with ADHD go on to display more serious forms of antisocial behavior, consistent with a clinical diagnosis of conduct disorder. Between 25 and 40% of clinically referred children with ADHD show evidence of some type of anxiety disorder. This is especially true for younger children and those with ADHD whose problems are primarily reflected in inattention rather than hyperactive/impulsive behavior **(Johnson et al., 2005).**

Familial risk analysis detected that ADHD and major depression share common familial vulnerabilities **(Bidermen et al., 1991).** Of clinically referred children with ADHD, 40 to 50% are likely to show evidence of some sort of mood disorder (usually major depressive or dysthymic disorder). Although depressive disorders can result from various factors, there is speculation that some child depressive disorders may develop as a result of the social, academic, and other impairment resulting from ADHD. Findings regarding comorbidity with child/adolescent bipolar disorder are less clear, although it has been suggested that the degree of overlap between ADHD and bipolar disorder is on the order of 11 to 22%. In addition those with comorbid ADHD and bipolar disorder show

substantially higher rates of early substance abuse problems.

Likewise, children with ADHD have been shown to display comorbid Tourette's syndrome or other tic disorders. Here, the number of children with ADHD who develop Tourette's syndrome is thought to be on the order of 7%. Clinical studies have suggested that 40 to 50% of those diagnosed with Tourette's show comorbid ADHD, with the development of ADHD typically preceding the onset of Tourette's symptoms. Several other clinical characteristics also are correlates of ADHD as speech and language disorders, as well as delayed motor coordination, frequent somatic complaints, health problems such as upper respiratory infections and allergies, sleep difficulties, and increased risk for accidents of various types. Indeed, it has been suggested that almost 50% of children with ADHD can be considered accident-prone **(Johnson et al., 2005).**

Patterns of correlates and comorbid conditions also differ as a function of ADHD course and characteristics. Children with inattentive-type ADHD are more likely to display internalizing symptomatology, learning disorders, and speech/language problems compared with those with hyperactive/impulsive or combined subtypes. Furthermore, children with early onset ADHD tend to display more comorbid aggressive symptoms, whereas those with later onset ADHD are more likely to have comorbid anxiety or depressive conditions. Comorbid conditions may differ across the lifespan as with certain

disorders such as substance use disorder emerging more during adolescence and early adulthood.

The nature of the relationship between ADHD and comorbid conditions is also important to consider when developing treatment goals. Some comorbid conditions, although not resulting directly from ADHD, may be related to the natural consequences of ADHD-related problem behavior. For instance, in some cases of comorbid depression, depressive features can result from increases in negative responses from peers and adults who witness or experience a child's ADHD-related behavior or behavior resulting from comorbid conditions. In such instances, it is possible that the amelioration of ADHD symptoms may lead to more positive social interactions, and, in turn, support improvements in depressive symptoms without targeting depression directly. Alternative treatments of depression may be required when the child's depression results from other factors. As can be seen, effective treatments for children with ADHD and associated comorbidities are likely to be multimodal and multidisciplinary in nature and necessarily more extensive and complex than treatments for children with "uncomplicated" ADHD **(Johnson et al., 2005).**

Management of ADHD: Treatment strategies

There is insufficient evidence to identify which child with ADHD will respond to psychosocial or drug treatments. All cases of ADHD should be initially treated with psychosocial interventions alone. This is usually sufficient for milder cases, while moderate to severe cases

of ADHD need medication in conjunction with psychosocial interventions. Often psychiatric referral is indicated to optimize the complex mix of medication, targeted psychosocial and specific specialist services that are needed to maximize learning and development. These services include Speech therapy for speech and language disorders **(Taylor et al, 2004 ;Pliszka, 2007).**

The MTA, 1999 (the Multimodal Treatment Study of Children with Attention Deficit Hyperactivity Disorder) included 579 elementary school boys and girls with ADHD, who were randomly assigned to one of four treatment programs: medication management alone, behavioral treatment alone, a combination of both or routine community care.

In each of the study sites, three groups were treated for the first 14 months in a specified protocol and the fourth group was referred for community treatment of the parents choosing. All of the children were reassessed regularly throughout the study period. An essential part of the program was the cooperation of the schools, including principals and teachers. Both teachers and parents rated the children on hyperactivity, impulsivity, and inattention, and symptoms of anxiety and depression, as well as social skills.

The results of the study indicated that long-term combination treatments and the medication-management alone were superior to intensive behavioral treatment and routine community treatment. And in some areas anxiety, academic performance, oppositionality, parent-child

relations, and social skills the combined treatment was usually superior. Another advantage of combined treatment was that children could be successfully treated with lower doses of medicine, compared with the medication only group **(Vance, 2008).**

Psychosocial interventions

Appropriate psychosocial interventions include positive reinforcement of desired behaviors (including token systems), penalties for undesired behaviors, and contingency contracts for older children and adolescents. Learning techniques to self manage stress and group social skills training have also proven helpful **(Vance, 2008).**

Dexamphetamine and methylphenidate

The psychostimulants dexamphetamine and methylphenidate remain the primary effective drug treatments for ADHD. They do not differ in effectiveness or adverse effects, although individual patients may appear to respond better to one than to the other. These drugs decrease ADHD symptoms, improve cognitive deficits (for example, attention, memory and working memory), decrease academic and social impairments due to ADHD, improve quality of life for children and their families, and increase adherence and learning from psychosocial interventions. These effects were evident in short-term (4–6 weeks) and long-term (1–2 years) controlled trials **(Vance, 2008)**.

Psychostimulant medications are thought to work by increasing the functional activity of dopamine and noradrenaline through inhibiting their presynaptic uptake. These actions appear to facilitate compensatory brain neural networks that promote more situation-appropriate cognitions, emotions and behavior in a child with ADHD **(Vance et al., 2007).**

The clinical effects of dexamphetamine and methylphenidate last for 3–4 hours on average, necessitating 2–3 times daily dosing. Modified-release formulations of methylphenidate are available with the primary advantage of once-daily dosing which aids adherence. The medication can be taken every day during the week with a break on weekends. This is an option that some families may prefer because of mild adverse effects (for example mild initial insomnia) or for ideological reasons (they want their child to use the least amount of medication possible) **(Vance, 2008).**

About the use in preschoolers, Results from the short-term, open-label, run-in and double-blind, crossover studies do show that MPH is effective in preschoolers with ADHD **(Greenhill et al., 2006).** The mean optimal dose of MPH was found to be 0.7 ± 0.4 mg/kg/day, which is lower than the mean of 1.0 mg/kg/day found to be optimal in the MTA study with school-age children. Eleven percent of subjects discontinued MPH because of adverse events. Also relative to the MTA study, the preschool group showed a higher rate of emotional adverse events, including irritability, and proneness to

crying. The conclusion was that the dose of MPH (or any stimulant) should be titrated more conservatively in preschoolers than in school-age patients, and lower mean doses may be effective. A pharmacokinetic study was done showed that preschoolers metabolized MPH more slowly than did school-age children, perhaps explaining these results **(McGough et al., 2006).**

Key adverse effects are all dose-dependent and can be managed through subtle dose reduction. Appetite suppression and initial insomnia are the most common adverse effects, along with nervousness, dysphoria, nausea and headache early in treatment. Motor or vocal tics and growth retardation can occur. Rarer adverse effects are vomiting, rash, dizziness, weight loss and irritability **(Vance, 2008).**

Atomoxetine

Atomoxetine is the current second-line treatment for ADHD. It is a potent reuptake inhibitor of noradrenaline at the presynaptic terminal and is of some benefit for children with ADHD in the short and long terms. It has been approved for use in children (6 years of age and older), adolescents, and adults with ADHD. It has a longer duration of action than psychostimulant medication and can be helpful during the evening and sleep as well as during the day. Its adverse effects profile is similar to psychostimulant medication. Initial insomnia, appetite suppression, irritability and nervousness are the most common adverse effects along with nausea and headache.

There is a precaution that atomoxetine may increase the risk of suicidal ideation **(Banaschewski et al., 2004)**.

Alternative pharmacotherapy for ADHD

Antidepressants

Bupropion is an antidepressant with agonistic effects mainly on noradrenergic and to a lesser extent dopaminergic system. Its serotonergic properties are even less pronounced. In a four-centre, double-blind, placebo-controlled trial in 109 children aged 6-12 years, **Conners et al.** demonstrated that bupropion reduced hyperactivity and aggression in a group of children with conduct and attention problems. The effects, however, were somewhat less robust than the meta-analyses of standard stimulant drug effects **(Conners et al., 1996).** In an open-label study in 24 adolescents with comorbid ADHD and depression, **Daviss et al.** reported that bupropion sustained-release (SR) was effective for both conditions, yet they also suggested vigilance for medication- induced irritability and bipolarity when using bupropion SR in depressed ADHD patients **(Daviss et al., 2001).**

Some side effects that may discourage the use of Bupropion in children as severe skin rash has been reported to associate with its use in child psychiatric cases. It can also aggravate tics in children with comorbid ADHD and tic disorder. The risk of drug induced seizures relative to other antidepressants is increased by 0.4% with

possible link to high doses and a previous history of seizure **(Biederman and Spencer, 2000).**

Venlafaxine, an antidepressant with both serotonergic and noradrenergic properties, has been investigated as a possible alternative treatment in ADHD. It has no significant affinity for muscarinic, cholinergic, histaminic, or alpha-1- adrenergic receptors. It has a short half-life and is given in divided doses. Some small open-label studies suggest that venlafaxine may be an effective medication (50 –75% response rate in completers; 25% dropout due to side effects) in the treatment of the core symptoms of ADHD in children, adolescents, and adults. Its side effects include irritability, insomnia, and gastrointestinal disturbance **(Banaschewski et al., 2004).**

Two open-label studies of fluoxetine in a total of 51 children and adolescents with ADHD suggested that fluoxetine may be beneficial in the treatment of ADHD, but the effectiveness of selective serotonin reuptake inhibitors (SSRI) in the treatment of core ADHD symptoms is not supported by clinical experience. Considering the lack of comparison trials, the role of the SSRIs in the treatment of ADHD remains unclear. A small number of studies with MAOIs suggested that both irreversible and reversible MAOIs may improve ADHD symptoms.

Imipramine, a tricyclic antidepressant, is a current third-line treatment for ADHD, although it is being virtually phased out of routine clinical practice. It is

similar to atomoxetine although it has significant potential for cardiac adverse effects, mainly cardiac arrhythmias and/or conduction defects **(Vance, 2008).**

Clonidine

Clonidine, is a central adrenergic agonist that reduces the presynaptic release of noradrenaline. It can be used when other options are ineffective or contraindicated. It targets not only ADHD but also tics, insomnia and explosivity. It can be used in combination with methylphenidate giving better results than being used alone. The most problematic side effect is sedation which usually decreases after 8 weeks. Guanfacine another alpha agonist has advantage over it as less sedating. Clonidine decreases the hyperactivity/ impulsiveness symptoms more than inattention at low doses, while there is some evidence of improved attention at higher doses **(Vance, 2008 ; Palumbo et al., 2008).**

Neuroleptic drugs

Atypical antipsychotics (for example, risperidone) have limited benefit on core ADHD symptoms and unreliably improve cognition. However, they can be of benefit when there is severe co-occurring aggression or irritability/affective instability. Specialist assessment is required before these medications are prescribed, given the potential for drug interactions and effects on the psychosocial treatments being applied **(Vance, 2008).**

Antiepileptics

The prevalence of symptoms consistent with attention deficit/ hyperactivity disorder (ADHD) in children with epilepsy has been observed to be in the range of 12 to 39% in epidemiological studies. The prevalence of ADHD, thus, is higher in children with epilepsy than the 3 to 5% that would be expected from the rates of ADHD in the general population. Here the use of antiepileptic can be one of the important lines of treatment **(Bauchner, 2000 ; Dunn et al., 2003).**

Valproate is being prescribed with increasing frequency for epileptic children who have ADHD. It has been shown to be effective in treating severe disruptive behavior disorders, including explosive behavior in children**.** Side effects include weight gain, loss of appetite, trembling hands, polycystic ovary and hepatotoxicity **(Bauchner, 2000 ; Dunn et al., 2003).**

Carbamazepine, has been successfully used in some cases of ADHD. Meta-analysis using weighted variables revealed a significant positive correlation between duration of treatment and positive outcome. In three double-blind studies, it was found that carbamazepine was a safe and effective treatment for children with features of ADHD when compared to placebo and showed an effect size equivalent to that of stimulant treatment. Several adverse effects such as sedation, rash, agranulocytosis, and hepatotoxicity also discourage the use of carbamazepine in children with ADHD **(Silva et al., 1996).**

Chapter (III)

The overlap between ADHD and pediatric bipolar disorder

For the past two decades, there has been an ongoing debate regarding the methodology employed to differentially diagnose attention-deficit/hyperactivity disorder (ADHD) and juvenile-onset bipolar disorder (JBPD). Bipolar disorder can be difficult to diagnose in children. Accurate diagnosis, however, is of vital importance to avoid inappropriate treatment. In childhood, the symptoms of Bipolar Disorder can initially look like Attention Deficit Hyperactivity Disorder (ADHD) and/or unipolar depression. It is well known among clinicians that if a child is treated with stimulant or antidepressant medication and there is an underlying undiagnosed bipolar disorder, the medications can induce a manic state with very serious consequences **(Papolos and Papolos, 2002).**

Researchers suggest that 57% to 100% of children with juvenile bipolar disorder have comorbid ADHD, while only 11% to 22% of children with ADHD also have juvenile bipolar disorder. Other researchers suggest that the younger the child when bipolar disorder is diagnosed, the more likely ADHD is to be present also **(Kent and Craddock, 2003).**

Some clinicians and researchers have questioned these comorbidity figures, suggesting that they can be explained by overlapping symptoms, confusion of normal developmental behaviors, and/or shared genetic vulnerabilities. Others argue that manic symptoms are not being adequately differentiated from hyperactive symptoms. Some have suggested that children with comorbid juvenile bipolar disorder and ADHD have a familial subtype of bipolar disorder **(Compton et al., 2006)**.

The relationship between attention deficit hyperactivity disorder (ADHD) and bipolar disorder is unclear. Studies examining the rates of ADHD in bipolar patients consistently show higher than expected rates. Four testable hypotheses might explain the high rates of comorbidity of mania and ADHD, comorbidity is a chance phenomenon, comorbidity is an artifact of overlapping criteria, comorbidity is due to a common diathesis that leaves patients vulnerable to separate illnesses, and symptoms of ADHD that precede the onset of bipolar disorder represent a prepubertal expression of illness antecedent to the development of a full affective episode **(Sachs et al., 2000)**

ADHD and bipolar disorder are listed as separate diagnoses in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR);* however, the diagnostic criteria overlap, making the differential diagnosis problematic. Although the accuracy of diagnosis among these disorders has been investigated

for years, it has become increasingly relevant as growing numbers of children with severe emotional and behavioral difficulties are identified **(Compton et al., 2006).**

Limited diagnostic criteria make overlapping symptoms even more difficult to interpret. In fact, the *DSM-IV-TR* does not provide distinct diagnostic criteria for juvenile bipolar disorder. At least seven of the DSM-IV criteria used to diagnose ADHD are commonly shared with bipolar disorder as it presents in childhood:

- Easily distracted by extraneous stimuli.
- Difficulty sustaining attention in tasks or play.
- Restlessness as if driven by a motor.
- Often talks excessively.
- Difficulty waiting turn.
- Blurts thoughts out.
- Often have difficulty organizing tasks.

By resolving the diagnostic dilemma and providing prophylactic pharmacotherapy, practitioners can reduce the psychiatric and psychosocial morbidity associated with juvenile bipolar disorder. Medications commonly used to treat ADHD, such as psychostimulants, atomoxetine, and antidepressants, may be ineffective for children with juvenile bipolar disorder and may even exacerbate bipolar symptoms or trigger mania resulting in an earlier onset of bipolar disorder **(Post et al., 2004 ; Reichart and Nolen, 2004).**

The magnitude of this comorbidity, the issue of ADHD– juvenile bipolar disorder symptom overlap and the fact that some authors postulate ADHD as a possible precursor of bipolarity in some children are still controversial issues undergoing further research. These specific features of pediatric BD often contribute to the underdiagnosis or misdiagnosis of pediatric BAD. For example, many children with juvenile mania are frequently misdiagnosed as having ADHD with comorbid Conduct disorder **(Soutullo et al., 2005).**

How to differentiate through the symptoms profile?

It was suggested that the symptoms that can best differentiate ADHD and prepubertal bipolar are euphoric mood, grandiosity, racing thoughts and decreased need for sleep, and the symptoms least to differentiate are irritable mood, accelerated speech, distractibility and increased energy **(Geller et al., 2002).**

Mood

Euphoria, or elation, is a key distinguishing factor in bipolar disorder. Although all children are at times giddy or silly in appropriate environments consider a threshold of appropriateness when making a bipolar diagnosis. Families should perceive the giddiness, inappropriate laughter, and elevated mood of children with mania as disturbing and inappropriate. Children with primary

ADHD do not show inappropriately elevated mood. In fact, their failures often make these children dysphoric **(Scheffer and Apps, 2005).**

Speech

Pressured speech seen in BAD is known by that speech is powered by a flight of ideas and shifting topics that may have little relationship to each other. ADHD may talk too much and too loudly but they can be redirected and their verbal delivery can be slowed by a request from the listener. This same request to a child with Bipolar Disorder may cause him to pause for about two seconds only. If pressured speech occurs with other challenges associated with Bipolar Disorder, it is a good idea to assess if it is an aspect of hypomania and thus indicative of the Bipolar presentation **(Wagner, 2000).**

Behavior

Grandiosity can be confusing to evaluate in children but is often a core symptom in bipolar disorder. All children sometimes say self-inflating things, but those with pathologic grandiosity cross the threshold into the dysfunctional belief that they are better, stronger, smarter, or more talented than others. Children with grandiosity may act inappropriately on their beliefs, such as by telling adults what to do or engaging in risky daredevil acts with no concern for their safety. Children with ADHD are not

usually grandiose. Instead, they often become demoralized and develop poor self-esteem from negative feedback about their behavior.

Sleep

Decreased need for sleep is the hallmark symptom of mania that is absent in other psychiatric disorders. Children with bipolar disorder may need 1 or more hours less sleep or deny needing sleep at all. Use age-appropriate amounts of sleep as a standard. A 24-hour sleep history can easily assess decreased need for sleep. Determining the daytime fatigue by self-report or observation by parents or teachers, then ascertaining if there are periods of days with less fatigue. Many bipolar youth have a nearly continuous decreased need for sleep. Children with ADHD often have difficulty settling at night, which delays their falling asleep. The sleep history will likely show that once asleep they sleep well for an appropriate amount of time or are fatigued during the day **(Scheffer and Apps, 2005).**

Temper tantrum

In Bipolar Disorder, rage is present from an early age. Once it is engaged, it is unstoppable. It will go on for over half an hour. It can be violent, and it often results in exhaustion and rage state specific amnesia **(Popper, 1989).**

ADHD children will get enraged because of frustration or simple hot temperedness. ADHD children do not rage on a consistent basis as do children in the

mixed state of aggressive depression seen in BAD. And they do not generally get pleasantly energized by it nor do they experience state specific amnesia of what they did when enraged. It is important to identify the severity of a child's rage.

The other aspects of Bipolar Disorder such as the nighttime hyperarousal pattern and anempathy

There are some additional challenges that bipolar children typically have that ADHD don't. Nighttime hyperarousal is sometimes seen in ADHD and is usually a medication side effect or the inability of the person to calm the sense of ADHD "driveness." The Bipolar child comes alive at night when his brain levels of serotonin, are at a 24 hour low. Many Bipolar children are anempathetic. They do not understand the feelings of others and may show shallow affect themselves **(Kovacs and Pollack, 1995).**

Psychotic symptoms

The child with affective illness, on the other hand, may experience visual hallucinations that are very disturbing **(Hendren, 2000).**

Family history

A meticulous study of the family history is very important for making the ADHD bipolar distinction. Children with bipolar disorder often have the condition in their immediate family, siblings, parents, grandparents, especially if they are diagnosed at an early age. This is an indication that affective disorder may exist in the family

line. If it does, there is a high probability that it will be passed on **(Goodwin and Jamison, 1990).**

Table (1): Core symptoms: Pediatric bipolar disorder vs. ADHD (Scheffer and Apps, 2005).

Core symptoms	***Pediatric bipolar disorder***	***ADHD***
Euphoria/giddiness	*Excessive*	*Appropriate to situations*
Irritability	*Severe & intense, often accompanied by tantrums*	*Occasional, may be caused by medication "wear off"*
Self-esteem	*Grandiose*	*Demoralized*
Sleep patterns	*Decreased need for sleep*	*Difficulty settling at night*
Speech patterns	*Pressured, fragmented with flight of ideas*	*Energetic & quick*
Thought processes	*Racing thoughts Psychosis can occur*	*No racing thoughts*
Sexual disinhibition	*Present*	*Age appropriate*
Attention	*Distractible*	*Distractible*

Activity level	*High energy, on the go, multiple projects, creative, high risk behavior*	*Hyperactive, multiple projects Impulsive*
Disruptive behaviors	*Can become aggressive*	*Intrusive & active*
Response to psycho stimulants	*Poor or worsen symptoms*	*Good*

Neuropsychological findings as a tool of differentiation

As regards Attention deficit hyperactivity disorder, executive dysfunction is one of the cognitive deficits which have been suggested. Executive function is the ability to maintain an appropriate problem solving set to attain future goals. An executive function (EF) deficit theory of ADHD, has been proposed by several researchers. Executive functions include set shifting and set maintenance, interference control, inhibition, integration across space and time, planning and working memory. In neuropsychology, executive functions are described as the performance on tasks that patients with frontal lobe lesions do badly on.

Persons with ADHD have been found to exhibit deficits in most of EF abilities. In the review on executive functions in children with ADHD, **Pennington and Ozonoff** found that 15 out of 18 studies have established a significant difference between ADHD patients and

controls on one or more executive functions measures. He then concluded that the most consistently impaired measures are Tower of Hanoi, Matching Familiar Figure test, Stroop test, and measures of inhibition. The main cognitive model linking executive deficit to the behavioral symptoms of ADHD is that three cardinal symptoms of ADHD (hyperactivity, inattention and impulsivity) can be reduced to deficit in inhibition which is one of the executive functions **(Pennington and Ozonoff, 1996**; **Barkley, 1997.)**

Moreover, it has been proposed that these children have some impairment in frontal lobe functions. In a review on studies of frontal lobe functions in children with ADHD**, Barkley et al**. found that most of these tests assess the ability of response inhibition. It is believed that these tests are mediated by the frontal lobes, particularly, the orbital–prefrontal and medial prefrontal areas and their rich connections to the striatum **(Barkley et al, 1992).** Wisconsin Card Sorting test, Stroop test, Matching Familiar Figures test, Tower of Hanoi, and Tower of London are several neuropsychological tests used to assess executive functions. Planning and organizing are the two executive functions believed to be impaired in children with ADHD. Tower of London is one of the neuropsychological tests which measures planning and problem solving. In a study by **Tehrani-Doost et al.** it was found that ADHD children have impairment in executive functions including response inhibition and planning **(Tehrani-Doost et al., 2007).**

Some of the current research has examined neuropsychological variables in childhood onset bipolar disorder. **Pavuluri et al.** found that children diagnosed with bipolar disorder demonstrated impaired ability on tests of attention, executive functioning, working memory, and verbal learning. Children with bipolar disorder and co-morbid ADHD did worse on tests of attention and executive functioning than those with bipolar disorder alone (**Pavuluri et al., 2006b).**

McClure reported that children with bipolar disorder did less well than a comparison group of children on tests of pragmatic use of language and facial expression recognition as well as on a test that required response flexibility **(McClure et al., 2005).** Dickstein also found that children with bipolar disorder were more impaired than a group of controls on tests of attention set shifting and visuospatial memory **(Dickstein et al., 2004).**

Dickstein et al. used the Revised Physical and Neurological Examination for Soft Signs (PANESS) to compare attention deficit hyperactivity disorder (ADHD) and BPD children for neurological examination abnormalities (NEAs) with normal controls (NC). Their goal was to help disentangle whether pediatric BPD is associated with a unique pathophysiology that is distinct from that of ADHD. They found that while ADHD subjects were impaired on repetitive task reaction time, BPD subjects were impaired on sequential task reaction time, irrespective of the comorbidity with ADHD. This differential pattern of NEAs by diagnosis suggests

pathophysiologic differences between ADHD and BPD in children. Repetitive motor performance requires inhibition of non relevant movements; ADHD subject's impairment in this domain supports the hypothesis that ADHD involves a core deficit of frontostriato-basal ganglia neurocircuitry. In contrast, BPD subject's impaired sequential motor performance is consistent with behavioral data showing impaired attention set shifting and reversal learning in BPD subjects **(Dickstein et al., 2005).**

Doyle et al. compared the neuropsychological and academic functioning of youth with and without DSM-IV bipolar disorder to examine whether cognitive deficits found in youth with bipolar disorder are accounted for by comorbidity with ADHD. Subjects were 57 youth with BPD and 46 non mood disordered controls assessed on a battery of clinical neuropsychological measures that included subtests from the WISC-III, the Stroop, the Wisconsin Card Sorting Test, the Rey-Osterreith Complex Figure, an auditory working memory continuous performance test (CPT), a measure of verbal learning and the WRAT-III achievement test.

Results showed that BPD was associated with impairments on subtests reflecting sustained attention, working memory and processing speed, even after controlling for ADHD. Decrements of moderate effect sizes were found for measures of interference control, abstract problem solving and verbal learning but did not meet criteria for statistical significance. Considering the

well known functional implication of neuropsychological deficits, this study calls for more work on how to help identify and treat such deficits in youth with BPD **(Doyle et al., 2005).**

Importance of the dual diagnosis, ADHD & pediatric bipolar disorder

Classic ADHD symptoms occur in most bipolar children as well. Why not just diagnose these children with bipolar disorder and leave out ADHD as an additional diagnosis? One reason is that treatment may be ineffective if the possibility of ADHD is not also considered. Most children who have bipolar disorder and who could also have ADHD are treated for bipolar disorder first. If the symptoms of distractibility and impulsivity improve, then the diagnosis of ADHD would be dropped. However, in a number of cases, distractibility and impulsivity remain a problem even when there is effective treatment for bipolar disorder. The classic ADHD symptoms need to be treated in these cases as well **(Papolos and Papolos, 2006).**

Thus, at the beginning of treatment, all potential diagnoses should be considered, and many of these children will be diagnosed with comorbid ADHD. The higher percentages are found in studies of younger, prepubertal cases and in studies of patients at university psychiatry clinics, where more difficult cases are likely to seek treatment **(Papolos and Papolos, 2006).**

Another reason to consider a dual diagnosis is that the degree of distractibility and impulsivity is sometimes more severe and pervasive than if there were only one disorder. For example, impulsivity for ADHD usually does not lead to daredevil acts the way it does for bipolar children. Likewise, bipolar children without ADHD usually only have episodic impulsivity when they are in a manic phase. However, in dual diagnosis cases, the impulsivity is usually persistent throughout the day and to a high degree, not occurring just when the child is manic. Likewise, distractibility does not occur just when the child is in the manic phase. It is persistent throughout the day.

Many of the most commonly used diagnostic inventories employed by mental health professionals to diagnose ADHD include symptoms that would be indistinguishable from the most common symptomatic profiles observed in children with bipolar disorder. Therefore, since attention problems, motor disinhibition, and organizational deficits are part of both conditions, it is difficult to make a clear diagnosis. If a clinician diagnoses according to strict DSM-IV criteria, and there are symptoms of mania present also, than, as mentioned earlier, both bipolar disorder and ADHD must be diagnosed as co-occurring disorders **(Papolos and Papolos, 2006).**

In a study by **Biederman, (2000)** maintains that there is a serious lack of knowledge among diagnosticians about how to diagnose the presence of Bipolar Disorder. It points

to research on the kindling effect of depression to show how misdiagnosis can hurt a child. The kindling effect is seen in the damage the brain incurs as it is weakened by depression over time. The first depression may be bad, but because it has happened, the next one is worse. If a child presents with a mixed-state, rapid cycling early onset bipolar disorder and is misdiagnosed as severe ADHD and given stimulants, he may be thrown into a manic episode, or the misdiagnosis can result in that the child not receiving medical treatment for the depression, so ignoring this problem makes it worse **(Biederman, 2000)**.

Goodwin and Jamison (1990) assert that 15 to 20% of those with bipolar disorder suicide. The misery that these people experience makes ADHD looks comfortably tolerable. Misdiagnosis of the child with bipolar disorder can do great damage because it not only cuts him off from help appropriate to his illness, but sets the stage for his isolation from the community. This is a tragedy preventable with the right diagnosis at the right time **(Goodwin and Jamison, 1990).**

The Effect of ADHD Comorbidity on Response to Treatment in Youth with Mania

Pediatric bipolar disorder course is chronic, protracted, and dysfunctional. The syndromatic recovery occurs, but functional remission & euthymia did not remit. The two main classes of medications which can be used

effectively with bipolar children with ADHD are the atypical antipsychotics and the mood stabilizers. The atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, clozapine, and the chemically different aripiprazole) are preferred over the older antipsychotics, because they usually are easier to tolerate due to their relatively few side effects. They also help reduce agitation, irritability and impulsivity, of bipolar children. There are some possible problematic side effects, such as weight gain and fatigue **(Gottlieb and Shoaf, 2006)**.

The mood stabilizers include carbamazepine, lamotrigine, lithium, and valproic acid. None of these medications has been approved by the FDA for the use with mania in children under the age of 13, but clinicians are finding that either a mood stabilizer or an antipsychotic medication is helpful in reducing the manic symptoms in children **(Gottlieb and Shoaf , 2006)**.

One question which has not yet been resolved in the treatment of children with bipolar disorder and ADHD is whether to start with an atypical antipsychotic medication or a mood stabilizer. Sometimes, an antipsychotic is tried first, and in other cases, a mood stabilizer is used first. It is recommended to start with an antipsychotic in cases where there are rapid shifts of mood in a single day **(Gottlieb and Shoaf , 2006)**.

For many of the children who have bipolar disorder and ADHD, neither a mood stabilizer alone nor an

antipsychotic alone seems to resolve all of the problems. Each seems to manage some of the behaviors in many of these children, but there often continue to be some impulsivity and attention problems. In one small study of bipolar adolescents, some of whom had also been diagnosed with ADHD and some of whom had not, **Strober et al. (1998)** reported that those teenagers with a history of ADHD did not improve as much on lithium as the group with bipolar disorder. About a third of the dual diagnosis cases did not respond to lithium, whereas only ten percent of teens with bipolar disorder alone did not respond.

In another preliminary study with a small number of cases, the effectiveness of an atypical antipsychotic (risperidone) was evaluated in dual diagnosis cases **(Frazier et al., 1999)**. The antipsychotic medication was effective for manic symptoms, but not for ADHD symptoms. Sometimes treatment with two or more medications is necessary for children and adolescents who have bipolar disorder and ADHD. For some children, when a mood stabilizer helps only in part and there continue to be problems with impulsivity and behavioral problems, the addition of an atypical antipsychotic is effective **(Gottlieb and Shoaf , 2006)**.

Recent studies with adolescents have supported the combination of mood stabilizer and atypical antipsychotic for treatment of adolescent mania **(Kafantaris et al., 2001; DelBello et al., 2002).** In other children with ADHD and bipolar illness, stimulant medication may be gradually

added to treat distractibility, if that symptom continues, once there has been successful treatment of mood problems with the appropriate mood stabilizer and/or antipsychotic. Depending on the response, the ADHD medications can become a part of the treatment regimen **(Biederman et al., 1999).**

Children and adolescents with bipolar illness and ADHD usually remain on their medications for several years. In a maintenance treatment study for pediatric bipolar disorder, patients who were maintained on lithium had a significantly lower relapse rate than patients who were not maintained on lithium (**Strober et al., 1990).** When children or adolescents with bipolar disorder have been without symptoms for several years, the mood stabilizer and/or antipsychotic medication can be tapered gradually over several months and then discontinued. If symptoms recur, then the medications should be restarted once more **(Gottlieb and Shoaf, 2006)**.