Use of Psychostimulants and Risk of Bipolar Disorder in Children and Adolescents with Attention Deficit/Hyperactivity Disorder

By

Digvijay C Yeola

A thesis submitted in partial fulfillment of

the requirement for the degree of

MASTER OF SCIENCE

IN

PHARMACY

(PHARMACY ADMINISTRATION)

Thesis Option

University of Houston

College of Pharmacy

August 2012

Acknowledgements

It would not have been possible to write this thesis without the help and support of people around me. I would like to acknowledge the advice and guidance of Dr. Hua Chen, committee chairman. I also thank the members of my thesis committee, Dr. Rajender Aparasu and Dr. Michael Johnson for their guidance and suggestions and for all their valuable advice and encouragement. Their valuable suggestion immensely helped me in completion of my thesis.

I also want to thank my friends Shweta, Dhaval, Ruchika, Rohan, Pooja, and Ankit whose critical comments on my research always helped me to lift the quality of my work and whose great company made this graduate program a memorable experience of my life.

I would like to extend my gratitude to my family members for their love, support and understanding during my education.

Abstract

USE OF PSYCHOSTIMULANTS AND RISK OF BIPOLAR DISORDER IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER

Objectives: The aim of our study is to compare effectiveness of psycho stimulants on risk of developing Bipolar Disorder in children and adolescents with ADHD diagnosis.

Methods: This is an observational, retrospective cohort study with longitudinal follow-up of minimum 12 months and maximum up to 4 years and 6 months. The cohort consists of incident ADHD children and adolescents (6-18 years old) and prescription filled for Psychostimulants within 30 days of diagnosis were identified by using files from 2003-2007 from Medicaid Analytic Xtract (MAX). Children and adolescents with prior history of ADHD or/and BD or/and psycho stimulants were excluded. Time to development of bipolar disorder was conducted using survival analysis. Main outcome variable was time to bipolar and status variable was development of BD. Use of psycho stimulants was main independent dichotomous variable. All analysis was conducted using SAS 9.3 with significance level of 0.05.

Results: Out of 3942935 children and adolescents without any history of ADHD and BD, 252388 children and adolescents developed ADHD during July 31, 2003 till December 31, 2006. Out of these Children and adolescents 68173 filled prescription for psycho stimulants within 30 days. Mean age of children and adolescents with ADHD diagnosis was 9.0 years (±3.12). Seventy two percent children were boys, majority (46% of cohort) of them were white by race, were from Texas (43.67%) region. Common co-morbidities were learning conduct disorder (7.8%) followed by adjustment disorder (5.4%) and depression (3.3%). 5029 were diagnosed with bipolar disorder which accounts for 7.37%. The age of onset of ADHD was found to be 9.0 years (±3.12) and that for BD was 10.49 years (± 3.44). Age of onset of BD for those who were

exposed to stimulants and those who filled prescription of stimulants for just one time vs more than one time (12.11±3.60 vs 10.37±3.40 years p =<0.0001). The hazard ratio for children and adolescents with ADHD filled Rx for more than once for stimulant was more (HR 1.583; CI 1.418-1.768; p-<0.001) as compared to those who filled Rx only once for stimulants.

Conclusion: Survival estimates for children and adolescents with ADHD were significantly different for patients filled Rx more than once for psycho stimulants vs patients with one Rx filled (HR 1.583, CI 1.418-1.768; p-<0.001). This study will help physicians to make better-informed decision.

Table of Contents:

Chapter 1

Introduction

Attention Deficit/Hyperactivity Disorder in Children:

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder characterized by developmentally inappropriate levels of inattention and continuous history of hyperactivity, forgetfulness and impulsiveness. The underlying causes of ADHD are not known. Some studies suggest that genetic component and psychosocial factors are involved (Keen 2008). According to DSM IV ADHD can be categorized mainly into 3 classes: predominantly inattentive (ADHD-I), predominantly hyperactive (ADHD-HI) and the combined type (ADHD-C). The combined type (ADHD-C) being the most prevalent (Skounti, 2010; Barbaresi, 2006). Core symptoms of ADHD include: inattention, hyperactivity and impulsivity. DSM IV diagnostic criteria state that symptoms must present for at least 6 months prior to diagnosis.

The prevalence of ADHD in the US was around 3-7% (Keen, 2008; Ambuabunos, 2011; Kim, 2011; Klassen, 2004; Landass, 2011). According to National Survey of Children's health (NSCH) percentage of children aged 4-17 years with a parent-reported ADHD diagnosis prevalence increases from 7.8% to 9.5% during 2003-2007, representing a 21.8% increase (Center for Disease Control and Prevention, 2010). Boys are at a greater risk of developing ADHD compared with girls, with a ratio of about 4:1(Keen, 2008; Schubert, 2010; Hodgkins, 2011; Klassen, 2004). Several studies including National Comorbidity Survey Replication of adults (18-44 years of age) have documented that ADHD is a chronic disorder with onset in childhood and persistence of symptoms into adulthood for approximately 66% of afflicted individuals (Young, 2011; Landass, 2011; Klassen, 2010).

Table 1: ADHD prevalence according to countries

Country	Study	Population	Prevalence
Nigeria	Ambuabunos (2011)	1473 public primary school pupils aged 6-12 years, Cross-sectional prospective study	ADHD prevalence – 7.6% Prevalence in boys – 9.4% Prevalence in girls – 5.5%
Germany	Schubert (2010)	Random sample of insures of the AOK health insurance (6-18 years), cross-sectional retrospective study	ADHD prevalence – 2.21%
Netherland	Hodkings (2011)	13212 children and adolescents (6-17 years) from PHARMCO medical records, observational retrospective study	ADHD Prevalence – 3.7%
Greece	Skounti (2010)	603 school children (6-11 years), Cross-sectional prospective study	ADHD prevalence – 6.0% Prevalence in boys – 8% Prevalence in girls – 3.8%

ADHD posses' considerable impact on quality of life and most patients suffering with ADHD experience functional impairment in academic, family, and social settings (Ambuabunos, 2011;

Klassen, 2010). Compared to people without ADHD, people with ADHD achieve fewer education, are less likely to be employed, and have significantly lower average income. Children with ADHD had significantly lower reading achievement score, more days of absenteeism, higher rate of grade retention and higher rate of school dropouts (Barbaresi, 2010).

Treatment Strategy of ADHD:

The aim of treatment for ADHD is to decrease symptoms, enhance functionality, and improve well-being for the child. Stimulant medications have been the primary medical treatment for ADHD and are recommended in practice guidelines endorsed by the American Academy of Pediatrics and the American Academy of Child and Adolescent Psychiatry (Klassen, 2004; Barbaresi; 2007). Despite its usefulness in the treatment of ADHD, the prescription of this drug has raised public health concerns because of its high abuse potential. It also causes appetite suppression and weight loss (Kim, 2007; Frauger, 2011). FDA found serious cardiovascular adverse events in patients taking standard doses of ADHD medications as well as drug-related psychiatric adverse events, such as delusions, hallucinations, paranoia and mania. Patients with ADHD treated with stimulants showed two fold increases in insomnia, decreased appetite and weight loss which may be a key cause of discontinuation. Another class of drug introduced recently i.e. Atomoxetine (non-stimulant) has demonstrated overall good tolerability. Adverse events associated with use of atomoxetine include dizziness, palpitations, atrial fibrillation, depressive symptom, insomnia, and somnolence (Barbaresi, 2006). Also, one of the major adverse events is increased risk of suicidal ideation (Wigal, 2009).

Co-morbidity is a rule rather than exception for ADHD and often coexists with learning disabilities, conduct disorder, anxiety, depression, bipolar disorder and developmental

coordination disorder, and substance abuse. Bipolar disorder being the most common and has received much attention in literature (Jaworowski et al. 2006, Galender et al. 2008).

Bipolar Disorder:

With lifetime prevalence of 3% - 6.5% for Bipolar spectrum disorder (BD), it is a considered as serious public health concern (Kent and Craddock, 2003; Ghaemi, 2007; Guo, 2007). The term bipolar suggests two phases: a down or depressive phase and an elevated (manic or hypomanic) phase that is episodic in nature. In children, bipolar disorder is described as a severe recurrent mental disorder with continuous, non-episodic irritable mood (Klassen, 2010). Children and adolescents with BD have increased risk of substance abuse and suicidality. Several studies suggested that bipolar disorder has significant morbidity and mortality rates with lower quality of life. The co-morbid condition usually includes psychiatric conditions such as anxiety, alcohol and substance abuse, ADHD and impulse disorder and medical conditions, such as hypertension, diabetes and obesity (Guo, 2007).

Atypical antipsychotics (AAP) and mood stabilizers are the treatment choice for patients with bipolar disorder. The major adverse event associated with the use of atypical antipsychotics is drug induced movement disorder such as extra-pyramidal symptoms. Other adverse events are weight gain, metabolic abnormalities, hyperprolactinaemia, hyperglycemia and sedation (Findling, 2003; Hert, 2011).

Co-morbid ADHD and Bipolar Disorder:

In several studies of children with ADHD and in studies of children with BD, they have documented a bidirectional diagnostic overlap between ADHD and BD. In a study by Biederman et al. (1999), suggested that children and teenagers with ADHD have up to a 10-fold increased

risk for BD. Another study by Tamam et al. (2008) proposed that the rate of ADHD co-morbidity in BD patients is as high as 38–98%. Some researchers have tried to explain possible relationship for co-occurrence of ADHD and BD by 4 potential explanations (Klassen et al. 2004, Singh et al. 2006, Youngstrom et al 2010, and DelBello et al. 2001):

Explanation 1: Bipolar symptom expression leads to over diagnosis of ADHD in BD youth

In children, BD course is rather subcutaneous and erratic with prominent symptoms of irritability, hostility, verbal and physical aggressiveness. Children with BD have a chronic illness with symptoms such as hyperactivity, impulsivity, aggressiveness, distractibility, and emotional lability (Masi 2006, Wozniak, 1995; Geller, 2004).

Diagnosis of co-morbid ADHD and BD remains challenge as several symptoms for ADHD and BD overlap in the DSM-IV where the person appears overly talkative, distractible, and exhibits increased activity, physical restlessness and loss of normal social inhibitions, chronic irritability and distractibility. This may complicate the diagnostic process, response to treatment and clinical prognosis (Biederman, 1996; Klassen, 2004; Zeni. 2009; Tamam, 2008; Taurines, 2010), making it of high clinical and scientific relevance. Some researcher suggests that the high rates of co-occurrence of ADHD and BD may be because of mis-diagnosis.

Explanation 2: ADHD and BD share an underlying biological etiology (i.e., a common familial or genetic risk or a common underlying neurophysiology)

Some researcher tried to explain high co-occurrence of ADHD and BD by familial studies. In a meta-analysis, Faraone el al. reported bidirectional association between BD in parents and ADHD in their offspring, as well as between ADHD in child probands and mania in relatives. Wozniak et al found an elevated risk of BD only in relatives of probands of BD and BD plus

ADHD. Studies like this suggests that early onset of BD and ADHD transmitted together in subgroup of families and represents a distinct diagnostic subtype.

Explanation 3: ADHD is a marker for or a prodromal of early manifestation of pediatric-onset BD

In several studies, it has been observed that the age of onset of ADHD is much earlier as compare to diagnosis of BD in patients with co-morbid ADHD-BD diagnosis (Biederman, 1999; Masi, 2006; Tamam, 2008). Mean age of onset of ADHD was 4-6 years and that of BD was 10-12 years (Masi, 2006; Tillman, 2006). Also, it has been reported in several studies that patients with ADHD had much earlier age of onset of BD (8.1±2.8 vs. 11.1±2.9 years) than otherwise it would occur (Masi, 2006).

Explanation 4: ADHD and associated factors (e.g., psycho stimulants) lead to the onset of pediatric BD

Psychostimuant have long been used in children with ADHD. However, the advent of effective pharmacotherapy has incited concern that these agents may also precipitate mania in children. Apart from precipitation of mania, there is a concern that psycho stimulants may accelerate or cause earlier age of onset of BD. This may result in mania at much early age otherwise would occurred. Reichert et al (2002), postulate that high rate of pediatric BD in the US is related to frequent use of psycho stimulants in youth.

Some studies showed that psycho stimulants had no differences in adverse events in children with complicated and uncomplicated ADHD (Carlson, 1998; Carlson, 2000; Galanter, 2003). Tillman and Galler in their study reported that psycho stimulant exposure is associated with less switching to BD. In contrast, several case reports described stimulant induced mania in patients

with ADHD (Faedda, 2004; Ross, 2006; Kraemer, 2010). In a retrospective study by DelBello, he found that prior exposure to stimulants in 34 hospitalized mania patients lowered the age of onset of BD. In a study by El-Mallakh, reported that children and adolescents with BD showed that those who received prior stimulant had an earlier diagnosis than those who were never exposed. A possible explanation for this may be that stimulants increases dopaminergic neurotransmission which may contribute to mania like symptoms and for precipitates earlier age of onset of BD in patients with chronic use of psycho stimulants. Therefore, it is important to study effectiveness of psycho stimulants in treatment of ADHD and its association with development of Bipolar disorder.

Chapter 2

Literature review

Co-morbidity and Age of Onset:

Reports in pediatric and adult samples document the co-occurrence of Attention Deficit/Hyperactivity Disorder (ADHD) and Bipolar Disorder (BD).

In a 4 year follow up study, Biederman et al (1996) showed BD was diagnosed in 11% of ADHD children at baseline and additional 12% at 4 year follow-up. ADHD children with BD had significantly higher rates of major depression, conduct disorder, oppositional defiant disorder and anxiety disorder. Co-morbidity poses serious risk of psychiatric hospitalization and severely impaired psychosocial functioning.

In a study which included 159 adult outpatients from Cukurova University Medical School. Patient included in this study had diagnosis of BD. All patients were assessed for ADHD in two phases: initial phase where patients were asked to complete Turkish version of current symptoms scale (CSS) and Wender Utah rating scale (WURS-25), followed by psychiatric, clinical and diagnostic interview by staff psychiatrists. Twenty six (16.3%) of 159 patients met diagnostic criteria for adult ADHD. Seventeen (10.7%) of patients met childhood ADHD diagnostic criteria which did not met adult ADHD criteria. Also, this study showed that patients with co-morbid ADHD and BD have earlier age of onset of BD, higher number of hospitalizations and higher number of episodes as compared to patients with only BD (Tamam et al, 2008).

Masi et al in 2006, reported out of 98 clinically referred children with a diagnosis of BD 38 patients had diagnosis of co-morbid ADHD. Bipolar patients with combed ADHD were

predominantly male, younger, and had an earlier age of onset of BD (8.1±2.8 VS 11.1±2.9 years). ADHD-BD patients also showed high rates of co-morbid Oppositional defiant disorder and conduct disorder. ADHD co-morbidity was associated with a greater psychosocial impairment.

In a study by Carlson et al in 2000, they used data from a completed longitudinal study. 75 clinically referred and diagnosed with ADHD children followed for BD diagnosis as young adults. The children were grouped into two groups MAX and MIN based on co-morbid conditions they present at the baseline. Both groups treated with methylphenidate and did not differ in any aspect of treatment experience. They found that ADHD boys with childhood symptoms of mania did not respond differently to methylphenidate than those without and concluded that methylphenidate does not precipitate BD.

In a Multimodal treatment study of children with ADHD, Galander et al. found that out of 270 children with ADHD 61 children fulfilled criterion for mania proxy. They found no treatment response effect as well as any difference in side effects when treated with methylphenidate. Galander et al concluded that children with ADHD and manic symptoms responded similarly to one month methylphenidate treatment without precipitating mania.

In a 6 year prospective follow up study by Tillman et al, he indentified 81 patients with ADHD diagnosis and followed for development of BD assessed at 2 year interval. 28.5% of these patients developed BD at the end of the study. BD diagnosis was confirmed as DSM - IV (manic or mixed phase) with cardinal symptoms (elation & grandiosity) to avoid diagnosis of mania by symptoms that overlap with ADHD symptoms. Significant predictors of switching to BD were more severe baseline CGAS, parental recurrent MDD, and less stimulant use.

Goldsmith et al conducted a systematic literature review on effect of psycho stimulant treatment in patients with ADHD and its association with development of BD or risk of precipitating mania. They concluded that even though children may react to stimulants with mania or psychosis, the risk is very low. They also reported that treatment with stimulant may even be protective against development of BD.

Faedda et al. conducted a chart review of 82 children meeting modified criteria for BD. The aim of this review was to evaluate risk and timing of operationally defined treatment emergent mania (TEM) following pharmacologic treatment. Out of these 57 (69%) had been prescribed a mood elevating agent at least once. Out of these 57, 33 (57%) met the criteria for TEM. Use of stimulant caused TEM in 18% of children.

In a case report by Ross GR, he reported that a child (7 year old) with ADHD started with methylphenidate treatment after confirming symptoms at home, school and tutoring environment. The dose was increased to 40 mg/day at which he showed beneficial effect. At age of 8 years and 3 months, he showed new symptoms of mania. Author concludes that though stimulants are highly beneficial in reducing ADHD symptoms it may cause mania at high doses and these symptoms resolve within 2 days after discontinuation of stimulants.

Delbello et al conducted a retrospective analysis on 34 adolescents (12-19 years), hospitalized with mania and assessed by WASH-U-KSADS. These patients were systematically reviewed for prior stimulant use and age of onset of BD. Twenty one of 34 (62%) bipolar adolescents had history of stimulant use. He found that bipolar patients with history of stimulant exposure prior to the onset of BD had an earlier age of onset of BD (10.7±3.9 years) compared to those without stimulant treatment (13.9±3.7 years).

Table 2: Bidirectional overlap between ADHD and BD

Reference	Sample	Age range (or mean) in years	Findings (Rate of Co-morbidity)
Butler et al., 1995	270 consecutively admitted inpatient Children and adolescents		28% of sample met criteria for ADHD; 68% of ADHD children met criteria for affective disorder, of whom 22% had BPD
Wozniak et al., 1995	262 clinically referred prepubertal children to psychopharmacology clinic; 43 with mania, 164 with ADHD, 84 non-ADHD controls	<12 (7.9 for manic, 8.8 for non-manic ADHD)	98% of children with mania had ADHD and 20% of the ADHD group met criteria for mania
Dilsaver et al., 2003	104 prepubertal children referred to community mental health clinic with presumed ADHD	5–11; mean ¼ 8.3	60% mood disorder; 12.5% mania; 41% met modified criteria for mania
Wozniak et al., 2004	280 boys/girls referred for study on ADHD; 109 with unipolar depression, 43 with BPD 128 with non-affective	7.8 (unipolar); 6.5 (BPD)	15% BPD; 39% unipolar depression. Higher rates of co-morbid psychiatric

	ADHD		disorders in BPD versus unipolar depression and their relatives
Biederman et al., 2005	121 children and adolescents with ADHD referred by a pediatric primary care clinic	6–17; mean ¼ 11.9	44% with any co-morbid psychiatric disorder; 7% BPD
Kessler et al., 2005	36.3% of sample of 3,197 adults found to have adult ADHD, retrospectively assessing predictors or modifiable risk factors for adult persistence of ADHD	18–44	Co-morbidity for 17 DSM-IV diagnoses is associated with childhood ADHD; 8.4% distribution of BD in childhood onset ADHD, 37% prevalence of ADHD in co-morbid subsample
Chang et al., 2000	60 offspring of at least 1 parent with BPD given structured interviews to establish prodromal signs of and risk factors for childhood BPD	11.1; mean parental age of onset of BPD = 10.7	55% offspring of BD had axis-I diagnosis; 28% had ADHD; 15% BD (88% of these children had Co-morbid ADHD). Diagnosis of BPD in offspring was

			related to parental earlier-onset mood symptoms and childhood-onset ADHD
Kowatch et al., 2000	42 outpatients with BPD randomly assigned to 6 weeks open treatment with lithium, divalproex sodium, or carbamazepine	11.4; age at onset of BPD symptoms 7.1; prepubertal 6.1; post-pubertal 8.1, Age at stimulant therapy: 6.9, prepubertal 6.4, post-pubertal 7.9	71% sample had ADHD; 85% of prepubertal sample with ADHD versus 50% post-pubertal sample ($p < 0.03$)
Findling et al., 2003	90 youth with diagnosis of BPD I or BPD II, with a history of hypomanic or manic symptoms in the preceding 3 months prospectively studied open-label combination therapy with lithium and divalproex	5–17	68 (75.6%) met diagnostic symptom criteria for ≥1 Co-morbid psychiatric diagnoses. ADHD and disruptive behavioral disorders were the leading co morbidities, with 64 (71%) subjects meeting diagnostic criteria for ≥1 of these disorders

Perlis et al., 2004	1,000 consecutive adult bipolar patients retrospectively studied to determine effect of age of onset of mood symptoms to clinical course, co-morbidity, functional status, and quality of life	Age of onset: very early (<13), early (13–18), adult (>18)	Rates of ADHD: 20.4% very early, 7.6% early, 5.7% adult, ($p < 0.0001$, pair wise comparisons between groups)
DelBello et al., 2004	10 manic and 10 euthymic adolescents with BD compared to 10 healthy controls in performance of a parametric task of sustained attention	16 (euthymic, manic); 15 (healthy controls). Age of onset of affective illness: 10.8 (euthymic); 11.0 (manic)	40% ADHD in euthymic, 20% ADHD in manic ($p < 0.2$). Manic and euthymic BD patients do not exhibit attentional dysfunction compared to healthy Adolescents; medication exposure and co-morbid.
Nierenberg et al., 2005	1,000 consecutive adults with BPD assessed for lifetime ADHD, retrospective course of BPD, current mood state, and prevalence of other co morbidities compared in	18–44; mean with ADHD ¼ 37.8; mean without ADHD ¼ 40.9	Lifetime prevalence 9.5% of co-morbid ADHD. Patients with BPD and ADHD had onset of mood disorder ~ 5 years earlier. Co-morbidity predicted worse BPD course,

	groups with and without lifetime co-morbid ADHD		increased rates of other co-morbid
Patel et al., 2005	27 bipolar I adolescents hospitalized for depressive episode	12–18; mean ¼ 15.6	52% had disruptive behavioral disorders; 22% had ADHD

Table 3: Co-morbidity and Age of onset of BD

Reference	Method	Findings
Biederman et al (1999)	Systematic medical chart review of 38 patients with diagnoses of ADHD and BD, reviewed over multiple visits for improvement and prescription patterns	9.8±3.5 years, Mean age of onset of ADHD (2.9±1.9 yrs), Mean age of onset of BD (5.4±3.9 yrs)
Tamam et al (2007)	159 patient with BD diagnosis, interviewed for presence of childhood ADHD, ADHD diagnosis made by structured clinical interview for DSM IV	10.7% - childhood ADHD, Age of onset of BD – With co-morbid ADHD – 19.8(5.8) Without co-morbid ADHD – 25.7(8.9)

Masi et al (2006)	38 patients (13.7±3.0 years) diagnosed with BD by K-SADS-PL	ADHD Age of onset (AAO)- 3.7±1.1 year BD AAO (co-morbid ADHD)- 8.1±2.8years BD AAO (no co-morbid ADHD)- 11.1±2.9 years)
Carlson et al (2000)	Patients (6-12 yrs) with ADHD and on methylphenidate treatment data from a longitudinal study, risk of developing mania	No difference in response to treatment and mania symptoms
Galander et al (2003)	Reanalyzed data from Multimodal treatment study of Children with ADHD with and without mania symptoms, treatment with methylphenidate for 1 month	ADHD with and without mania did not respond differently and no side effects, 1.4% in mania group developed BD vs. 1% (p=0.056)
Tillman et al (2006)	81 subjects (9.7±2.0 years) from outpatient visits identified with ADHD, followed for 6 years for development of BD, factors predicting switch from ADHD to BD	28% developed BD at end of study, Mean AAO for ADHD – 4.5±1.5 years, Mean AAO of BD – 11.4±2.1 years, Significant factors were severe baseline CGAS (p=0.004) and less stimulant use (p=0.033)

DelBello et al (2001)	34 adolescents hospitalized for BD, history of stimulant treatment and age of onset of BD	Patient with history of stimulant treatment AAO of onset of BD – 10.7±3.9 years vs. 13.9±3.7 years

K-SADS-PL- Schedule for affective disorder and schizophrenia for school aged children, present and lifetime version,

Currently available literature, especially on use of psycho stimulants and their risk of developing BD in children and adolescents with ADHD are largely based on clinical experience and small studies. There are no retrospective studies performed on nationally representative data. Due to scarcity of prospective randomized studies and chronic nature of co-morbidity, it is important to devise an appropriate treatment strategy to treat ADHD symptoms without precipitating mania.

In the proposed study, we will conduct a retrospective cohort study using the Medicaid Analytic eXtract (MAX) data from 4 US states to determine time to bipolar development in children and adolescents diagnosed with ADHD and on psycho stimulant treatment. The cohort for this study will be incident children and adolescent diagnosed with ADHD.

With this consideration, the aim of our study is to compare effectiveness of psycho stimulants on risk of developing Bipolar Disorder in children and adolescents with ADHD diagnosis.

Objectives:

Specific Aim 1

To determine age of onset of Bipolar Disorder in children and adolescent with Attention Deficit Hyperactivity Disorder.

Specific Aim 2

To compare the survival benefit of Psycho stimulants with a Cox proportional hazards regression.

Chapter 3

Methods

Data Source:

Data used for the purpose of this study was Medicaid analytic extract (MAX), which is a centralized collection of state Medicaid claims maintained by the Centers for Medicare and Medicaid Services (CMS) for the years 2003-2007 (latest available). MAX is a person-level dataset which contains information that allows ascertainment of longitudinal outpatient drug use, outpatient service use, expenditures, hospitalization, long-term care residency, and other services (e.g. physical therapy). MAX derives data from the Medicaid Management Information System (MSIS) and undergoes editing by CMS before release to researchers. US states used this electronic data records to report quarterly Medicaid eligibility and claims data to CMS. Diagnoses and procedures are coded to the International Classification of Disease, ninth revision, and clinical modification (ICD-9 CM) and/or to the Current Procedural Terminology, fourth edition (CPT-4). Medications in the MAX pharmacy file are coded to national drug codes (NDC).

MAX data contains five files namely:

a) Personal Summary record (PS) file: includes information on enrollees' demographics, annual and monthly Medicaid eligibility and managed care enrollment.
b) Inpatient record (IP) file: includes information on hospital encounters, claims and their payments.

c) Other record (OT) file: includes information on encounters other than inpatient hospital, long term care and pharmacy by enrollees.
d) Prescription drug record (RX) file: includes information on drugs and other services provided by pharmacy for each recipient.
e) Long Term Care services (LT) file: includes information on services provided in long term care institutions for each recipient.

For the purpose of this study we used four files namely: PS file, IP file, OT file and Rx file. Apart from this, Lexi-medication file used for linking NDC to ascertain drug names, strengths and dosage forms.

Because it is difficult to analyze data from all 50 states and District of Columbia, we used MAX data from the four states with largest Medicaid enrollment of children and adolescents (California, Illinois, New York and Texas) & also these states are representative of overall US population geographically. We used data from calendar years 2003-2007, the most recent available.

Study Design:

This was an observational, retrospective cohort study with longitudinal follow-up of minimum 12 months and maximum up to 4 years and 6 months. The cohort consists of incident ADHD children and adolescents (6-18 years old) from fiscal year 2003 till fiscal year 2006, from Medicaid data files. A six month wash out period (1 Jan'03 to 31 June'03) was allowed to confirm all incident cases with ADHD and no history of BD. Children and adolescents with diagnosis of ADHD and who filled prescription within 30 days from the date of diagnosis formed our cohort. Patients with prior psychostimulant exposure i.e. before diagnosis of ADHD

were excluded from the cohort. Index date was the first psychostimulant prescription filled after the ADHD diagnosis. Patients were followed for minimum of 12 months from the index date and maximum of four and half years. Those patients who were not eligible for entire follow up period were censored at their lost to follow up.

Study Design:

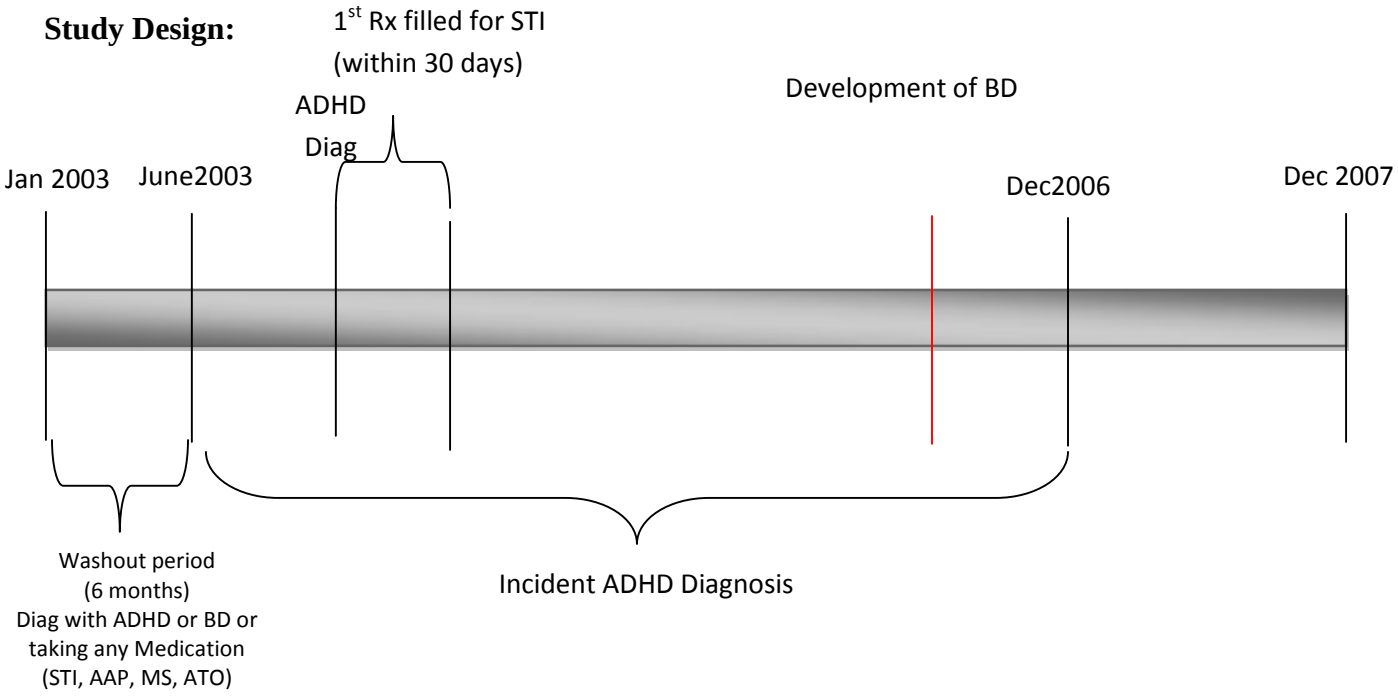

Fig 1: Study design for the study

Study Population:

All children under age 6 with family income at or below 133% of the federal poverty level that satisfy certain asset requirements are eligible for Medicaid. Children between age 6 and 19 in families at or below 100% of the federal poverty level are also eligible if they were born after September 30, 1983.

ADHD cohort:

All children and adolescents with at least one outpatient visit for Attention Deficit Hyperactivity Disorder (ADHD) from 1st July 2003 to 31st Dec 2006 were included in the cohort. Children and adolescents with prior diagnosis of ADHD or BD or taking medication i.e. psycho stimulants, atomoxetine, mood stabilizer and antipsychotics between periods Jan 2003 to June 2003 were excluded from the cohort. Also, patient with psychostimulant exposure before diagnosis of ADHD were excluded from the cohort. All diagnoses were made by using ICD-9 CM codes. For ADHD ICD-9 CM code used was 314.xx. This national cohort of all ADHD children and adolescents is referred as the ADHD cohort.

Inclusion Criteria for our study:

All children and adolescents between ages 6 to 18 with at least one outpatient visit from 1st July 2003 to 31st Dec 2006 were included in the study.

Children and adolescents diagnosed with ADHD and prescription filled for psycho stimulants within 30 days of diagnosis were included.

Exclusion Criteria for our study:

All children and adolescents with diagnosis of ADHD and/ or BD between 1 Jan 2003 to 31st June 2003 were excluded from the study. Also, children and adolescents with prescription for any medication (psycho stimulants, antipsychotics, mood stabilizers) from 1 Jan 2003 to 31st June 2003 were excluded.

Also, patient with prior history of psycho stimulants were excluded.

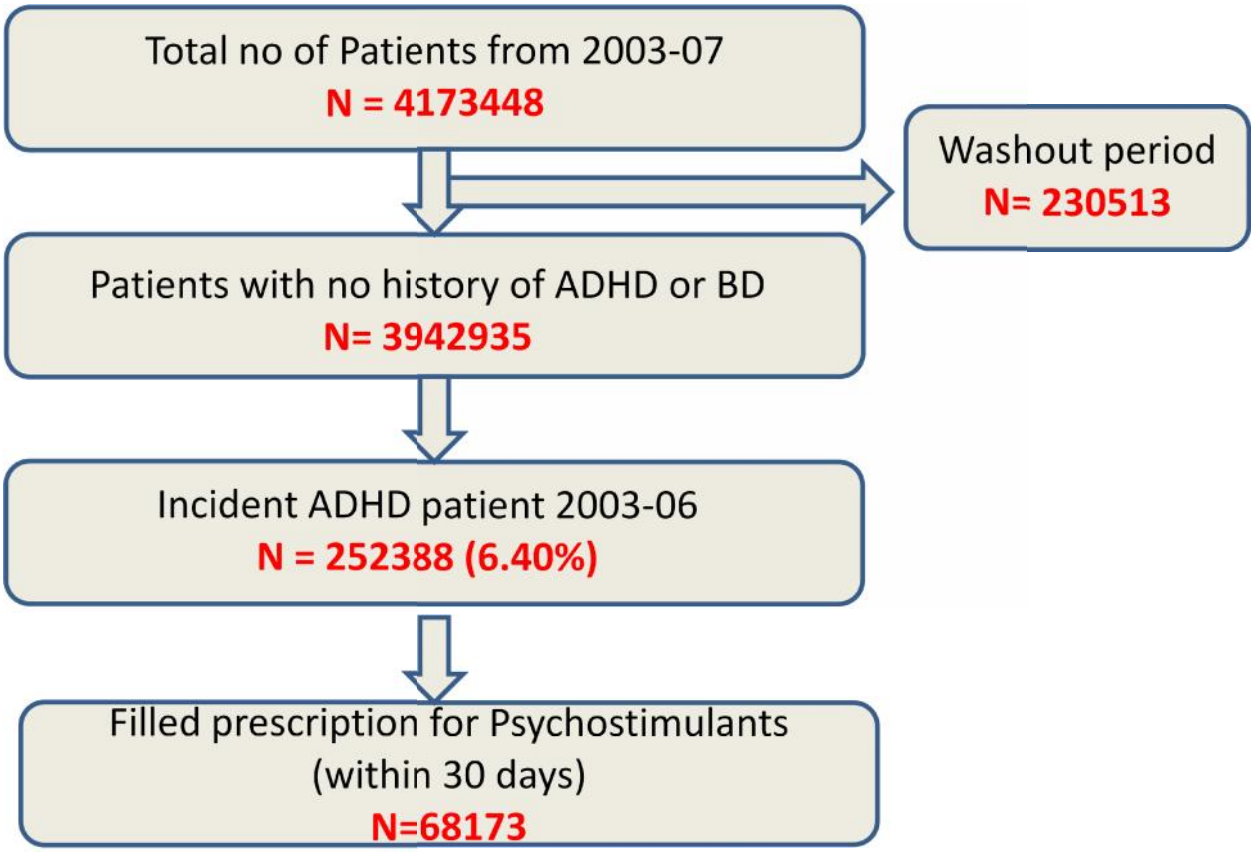

Figure 2: Derivation of the study sample

Operational Definition of Variable:

Outcome:

Diagnosis of Bipolar Disorder in children and adolescents was the outcome of interest in the study, as survival benefit from psychostimulant treatment in patients with ADHD diagnosis. Development of BD up to December 31, 2007 was determined by using OT files.

The outcome variable was coded as 1, if patient develops Bipolar disorder during study period, otherwise coded as 0.

Time to Event (Development of Bipolar Disorder):

Time to event is defined as the length of time period between the index date and the date of 1st diagnosis of Bipolar Disorder.

The variable is kept as continuous variable (in days).

Treatment:

Children and adolescents diagnosed with ADHD and with more than one prescription filled for psycho stimulants from date of diagnosis of ADHD till December 31, 2007 were identified by using prescription records and a coded as 1, otherwise coded as 0.

Covariates:

A) Socio-demographic Factors:

Age:

It has been observed in studies that age is important predictor of development of BD in patients with ADHD. It has been observed that the patients developed BD earlier when treated with psycho stimulants. Age, a continuous variable was converted to categorical variable. Age was calculated at the first diagnosis of ADHD.

Age: 0 ≤ 12 years

1 > 13 years

Gender

As observed in studies that boys are about four times at risk for development of ADHD, this variable was controlled in our final model. Gender variable in dataset is characterized as:

- Male
- Female

Race

The model was also adjusted for the race of the patient. The variable was characterized as:

- Whites
- Blacks
- Others

State

The model was also adjusted for the state where patient belongs from. The state variable was characterized as:

- California
- Illinois
- New York
- Texas

B) Clinical Factors:

Co-morbidities

The model was adjusted for all psychological co-morbidities. The diagnostic information from OT files used to code co-morbidities for the cohort. The details of all the co-morbid conditions are given in Appendix B. The OT files were checked for any co-morbid

condition using ICD-9 CM codes 6 months prior to the ADHD diagnosis date. All the variables were made as dichotomous variable.

Co-morbidities Included in model were:

- Adjustment disorder
- Anxiety
- Autism
- Conduct disorder
- Depression
- Schizophrenia
- Tic disorder

C) Treatment Factors:

The model was adjusted for following co-medications:

Use of other medication can be a major confounder in the assessment of survival function in ADHD patients treated with psycho stimulants. The pharmacy records were checked for the prescription fills of any medication 6 month prior to ADHD diagnosis date. All the variables were made dichotomous.

Co-medications included in the model were:

- Atomoxetine
- Atypical Antipsychotics
- Mood stabilizers
- Others

Statistical Analysis:

Descriptive statistics were used to summarize demographic and clinical characteristics of children and adolescents diagnosed with ADHD according to their treatment with psycho stimulants. Crude rates for development of Bipolar Disorder were calculated as number of patients as a percentage of total patients diagnosed with ADHD as well as those on treatment. Methods of analysis for specific objectives are described below:

Specific Aim 1

To determine age of onset of Bipolar Disorder in children and adolescent with Attention Deficit Hyperactivity Disorder.

Descriptive statistics were performed to determine the age of onset of BD in patients with ADHD.

Specific Aim 2

To compare the survival benefit of Psychostimulants with a Cox proportional hazards regression.

Survival of individuals treated with or without psycho stimulants was determined by modeling time to bipolar development in days while controlling for socio-demographics, clinical factors and treatment factors in Cox proportional hazards model.

The Cox Proportional Hazards model:

The most common approach for comparing the effectiveness of treatment is to use statistical method that can compare treatment in the basis of their ability to delay the time to an outcome such as hospitalization or mortality after the treatment. In our study, aim was to find out the time to bipolar development in patients with ADHD treated with and without psycho stimulants. For the analysis of this type of time-to-event data, the statistical method most widely used is Cox proportional hazards regression (Aydemir et al, 1999). Traditionally it has been done by modeling the probability of outcome as a function of treatment and pre-treatment variables (Bodnar et al, 2004) in a model such as Cox ph model. The equation for Cox model can be written as follows:

$h (t|X) = h_0 (t) \exp (x_1\beta_1+\ldots+ x_p\beta_p)$

$h_0 (t)$ = baseline hazard

$X = (x_1,.., x_p)$ = predictor variables including treatment

Here the baseline hazard function does not involve time (t) but does involve X while the exponential function involves X but doesn't involve (t). So the Xs are in this model are referred as time-dependent variables. Cox model is a semi-parametric model because the baseline hazard is an unspecified function. The model assumes that hazard of one individual is proportional to hazard of another individual and the proportionality constant is independent of time. This is also known as PH assumption.

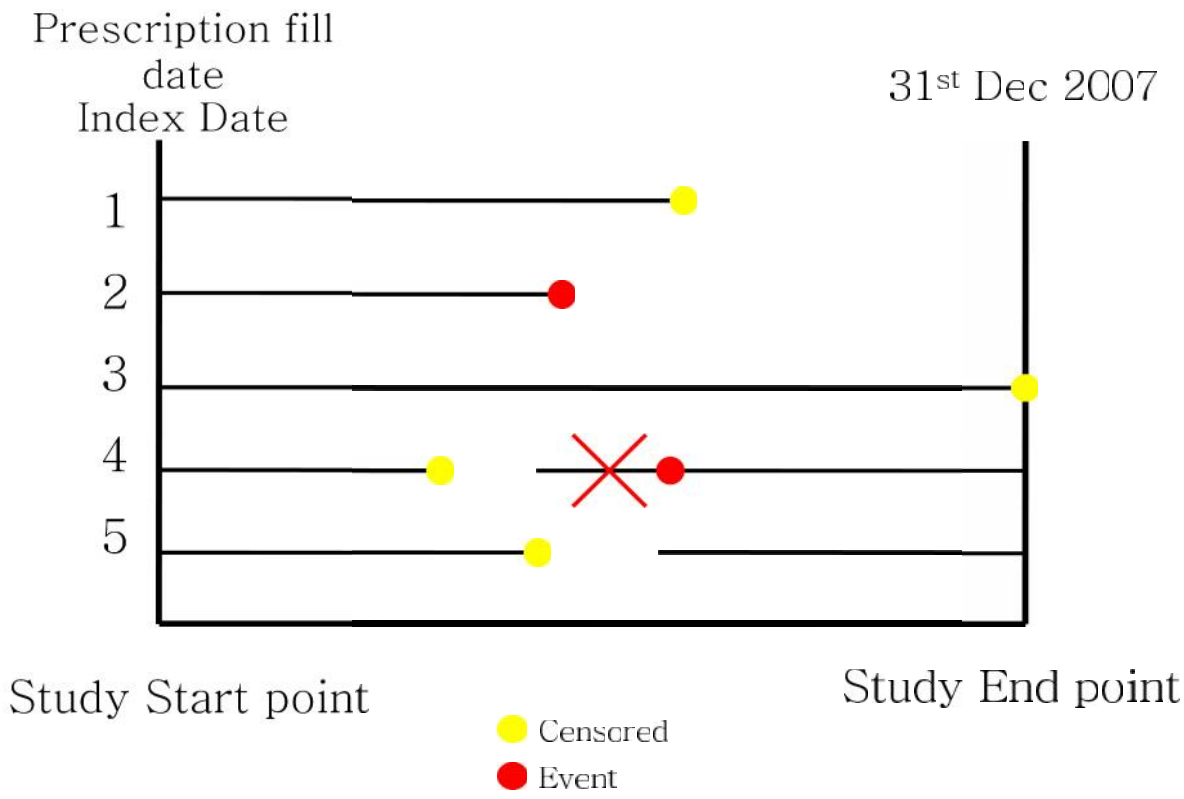

Figure 3: Censoring technique used in Survival Analysis

In our Cox model, patients without the outcome till December 31, 2007 were right censored at that date (Patient 2). Patients who were not eligible for entire period of follow up were censored at last eligible day (Patient 1, 3 and 5). Patient who experienced event were censored at their BD diagnosis date (Patient 2). Those patients who had BD diagnosis but were lost to follow up before BD diagnosis and again entered into study were censored at their 1st exit (patient 4). For such patient event was not occurred.

Unadjusted mortality for users vs. non-users of psycho stimulants were calculated by using Kaplan Meier curve and with use of log rank test. Adjusted hazard ratios were obtained from the regression modeling, after adjusting for covariates listed above.

All analyses were conducted using SAS® (version 9.3, SAS Institute, Cary, NC). SAS procedures PROC LIFETEST, PROC PHREG and PROC LOGISTIC were used to perform statistical analysis.

Chapter 4

Results

Cohort Formation:

Out of total 4173448 children and adolescents ages between 6 to 18 years were identified from MAX data from 2003-2007. Out of these 230513 children and adolescents were excluded because of any or all of following reasons:

a) Children and adolescents with diagnosis of ADHD during period Jan 1, 2003 to Jun 31, 2003
b) Children and adolescents with diagnosis of Bipolar Disorder during period Jan 1, 2003 to Jun 31, 2003
c) Children and adolescents who were exposed to Atypical Antipsychotics, Mood stabilizers, Atomoxetine or/and Psychostimulant during period Jan 1, 2003 to Jun 31, 2003

This was done to ensure all incident ADHD patients with any prior history of BD. Out of 3942935 children and adolescents without any history of ADHD and BD, 252388 children and adolescents developed ADHD during July 31, 2003 till December 31, 2006. Out of these Children and adolescents 68173 filled prescription for psycho stimulants within 30 days. Thus our final cohort was made up of 68173 children and adolescents who were diagnosed with ADHD.

Descriptive statistics:

Treatment:

Out of 68173 ADHD children and adolescents, 88% (n=60046) filled more than one prescription for psychostimulant and 12% (n=8127) filled only one prescription.

Socio-demographic Factors:

Mean age of children and adolescents with ADHD diagnosis was 9.0 years (±3.12). Approximately 84% of these were below age 13 years. Seventy two percent children were boys out of total cohort. Majority (46% of cohort) of them were white by race. Most of the ADHD children and adolescents were from Texas (43.67%), followed by Illinois (20.93%), California (18.92%), and New York (16.49%).

Clinical Factors:

Co-morbidities: In general children and adolescents with ADHD burdened with co-morbidities with around 19.44% of the cohort having one or other co-morbidity. Conduct disorder was the most frequent co-morbid condition with 7.80% of the children and adolescents. Adjustment disorder (5.38%), Depression (3.34%), and Learning Disorder (4.36%) were some of the other frequently reported co-morbidities.

Treatment Factors:

Co-Medication: Highest used co medication was atypical antipsychotics (1.50%), followed by atomoxetine (1.43%) and other (1.28%).

Following table shows demographic characteristics of cohort.

Table 4: Demographic Characteristics of children and adolescents diagnosed with ADHD and receiving stimulants

Characteristics	**Only 1 Rx filled for Stimulants (n=8127)**		**> 1 Rx filled for Stimulants (n=60046)**		**Total**		**P-value**
	N	%	N	%	**N**	**%**	
Age in years (Mean±SD)	10.21±3.42		8.85±3.14		**9.0±3.14**		<0.0001
Age category							<0.0001
< 13 years	5918	10.33	51389	89.67	**57307**	**84.05**	
≥ 13 years	2209	20.33	8657	79.67	**10866**	**15.15**	
Sex							0.0011
Female	2353	12.58	16353	87.42	**18706**	**28.39**	
Male	5744	11.67	43693	88.33	**49467**	**71.61**	
Race							<0.0001
White	3163	9.97	28573	90.03	**131376**	**46.55**	
Black	1920	13.82	11976	86.18	**13896**	**20.38**	
Others	3044	13.50	19497	86.50	**22541**	**33.06**	

State								<0.0001
	Texas	3470	11.66	26295	88.34	**29765**	**43.66**	
	California	2014	15.61	10885	84.39	**12899**	**18.92**	
	Illinois	1484	10.40	12784	89.60	**14268**	**20.93**	
	New York	1159	10.31	10082	89.69	**10082**	**16.49**	
Clinical Factors Co-morbidities								
Adjustment Disorder		371	10.12	3294	89.88	**3665**	**5.38**	0.0006
Anxiety		175	13.32	1139	86.68	**1314**	**1.93**	0.1146
Autism		57	22.01	202	77.99	**259**	**0.38**	<0.0001
Conduct Disorder		596	11.21	4722	88.79	**5318**	**7.80**	0.0943
Depression		345	15.13	1935	84.87	**2280**	**3.34**	<0.0001
Learning Disorder		336	11.30	2637	88.70	**2973**	**4.36**	0.2865
Schizophrenia		9	27.27	24	72.73	**33**	**0.05**	0.0129
Tic Disorder		12	23.53	39	76.47	**51**	**0.07**	0.0166
Treatment Factors								
Mood Stabilizers		58	11.29	465	88.71	**523**	**0.77**	0.5559
Atypical Antipsychotics		138	13.45	888	86.55	**1026**	**1.50**	0.1277
Atomoxetine		118	12.14	854	87.86	**972**	**1.43**	0.8321
Others		105	12.01	769	87.99	**874**	**1.28**	0.9322

Main Results:

Objective 1:

The age of onset of ADHD was found to be 9.0 years (±3.12). For the first objective, i.e. to determine the age of onset of BD in patients with ADHD we found in our cohort age of onset of BD was 10.49 years (± 3.44). We also calculate the age of onset of BD for those who were exposed to stimulants and those who filled prescription of stimulants for just one time vs. more than one time (12.11±3.60 vs 10.37±3.40 years p =<0.0001).

	Only 1 Rx filled	>1 Rx filled	Total	P-value
Age of Onset of ADHD	10.21±3.41	8.85±3.05	9.0±3.12	<0.0001
Age of Onset of Bipolar	12.11+3.60	10.37±3.40	10.49±3.44	<0.0001

Objective 2:

In our cohort of 68173 patients, 5029 were diagnosed with bipolar disorder which accounts for 7.37%. 11.90% (n=8224) of those who filled prescription for psychostimulant only once during follow-up and 88.10% (n=60869) filled prescription for psychostimulant more than once during follow-up. Out of those who filled Rx only once 344 (4.23%) developed BD at the end of study vs. 4685 (7.80) for those who filled Rx more than once.

Unadjusted Association:

For examining the unadjusted association between the exposure, stimulants and outcome, development of bipolar disorder, Kaplan-Meier method was used. The KM curve obtained is shown in figure. Log-rank test was conducted for differences in survival experience with stimulants vs. non-stimulant users. Log-rank test showed that survival experience for those who filled Rx once vs. more than once users was statistically significantly different (p = <0.0001).

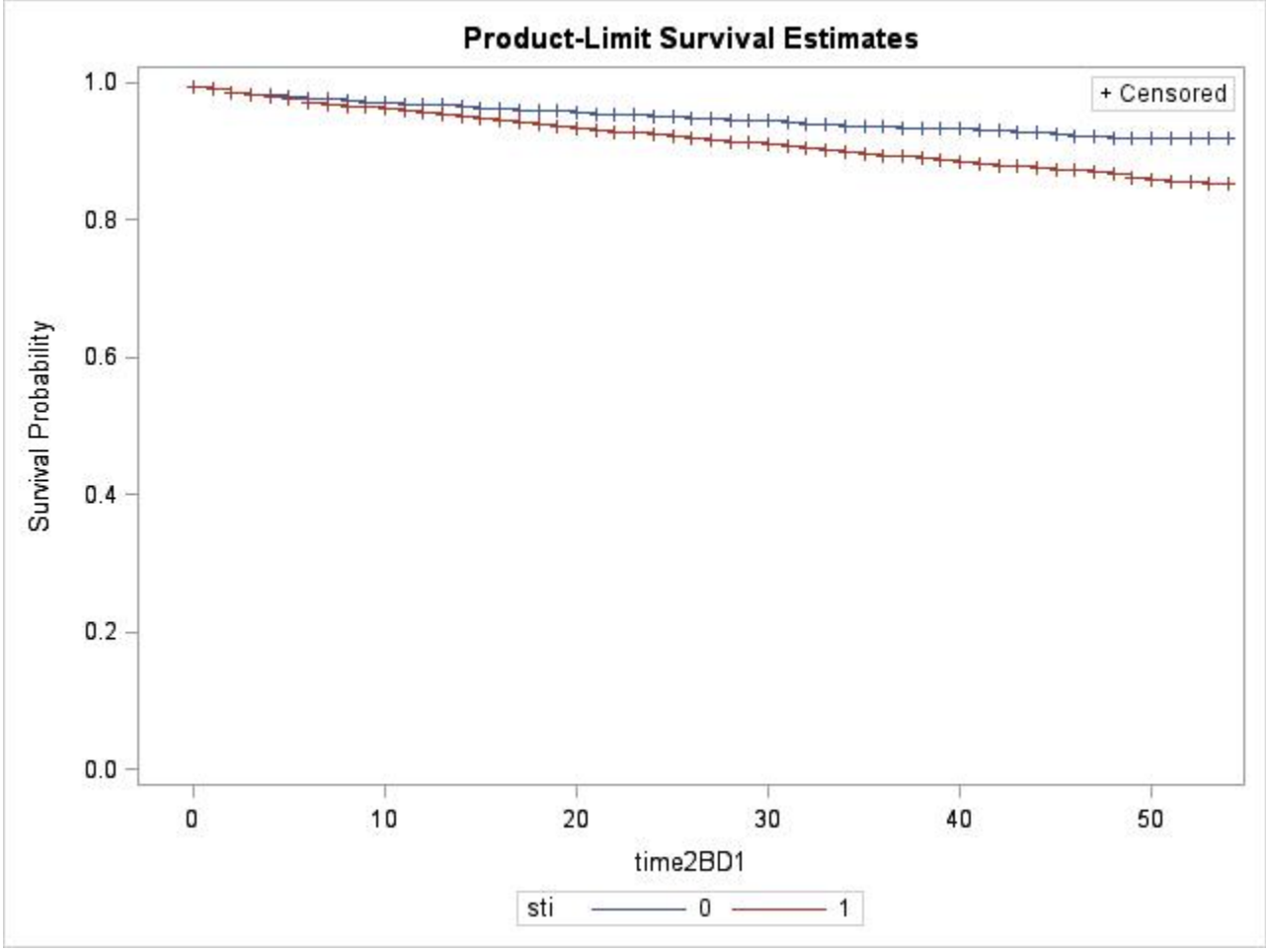

Figure 4: Kaplan Meier Curve

Adjusted Association:

For the second objective, a Cox proportional hazards regression model was constructed for time to bipolar development for patients with one Rx filled and more than one Rx filled for stimulants. Children and adolescent with ADHD and only one Rx filled for stimulants was kept as a reference group. The model was adjusted for sociodemographic factors included age at diagnosis of ADHD, sex, race and state. Major classes of drugs that are used for treatment of ADHD and bipolar are also controlled for in the model. Co medications included in the model were atypical antipsychotics, mood stabilizers, atomoxetine and others. The data on co-morbid conditions were obtained from OT files. All psychological conditions which include a total 8 conditions were included in the model. These conditions are adjustment disorder, anxiety, conduct disorder, depression, learning disorder, schizophrenia, tic disorder, and autism.

Table 6: Cox proportional hazard regression model for determining time to development of Bipolar Disorder

Variable		Hazard ratio	95% C.I.	P-value
Treatment				
	Only 1 Rx filled	Reference		
	>1 Rx filled	1.583	1.418-1.768	<0.0001*
Age				
	< 13 years	Reference		
	≥ 13 years	1.424	1.327-1.527	<0.0001*
Sex				
	Female	Reference		
	Male	0.929	0.875-0.988	0.0182*
State				
	Texas	Reference		
	California	0.639	0.589-0.694	<0.0001*
	Illinois	0.832	0.772-0.896	<0.0001*
	New York	0.616	0.565-0.672	<0.0001*
Race				
	Whites	Reference		
	Blacks	0.982	0.915-1.053	0.6091
	Others	0.750	0.700-0.804	<0.0001*

Co-morbidities				
Adjustment Disorder	No	Reference		
	Yes	1.532	1.390-1.689	<0.0001*
Anxiety	No	Reference		
	Yes	1.339	1.148-1.563	0.0002*
Autism	No	Reference		
	Yes	1.318	0.894-1.944	0.1628
Conduct Disorder	No	Reference		
	Yes	1.401	1.284-1.529	<0.0001*
Depression	No	Reference		
	Yes	1.665	1.487-1.865	<0.0001*
Learning Disorder	No	Reference		
	Yes	0.755	0.652-0.874	<0.0001*
Schizophrenia	No	Reference		
	Yes	0.733	0.303-1.772	0.4899
Tic Disorder	No	Reference		
	Yes	0.526	0.132-2.107	0.3646
Treatment				
Atypical Antipsychotic	No	Reference		
	Yes	2.291	1.974-2.659	<0.0001*
Mood Stabilizers	No	Reference		
	Yes	1.432	1.154-1.778	0.0011*
Atomoxetine	No	Reference		
	Yes	1.191	0.978-1.450	0.0822

Others	No	Reference		
	Yes	1.402	1.166-1.687	0.0003*

After controlling for all covariates, the hazard ratio for children and adolescents with ADHD filled Rx for more than once for stimulant was more (HR 1.583; CI 1.418-1.768; p-<0.001) as compared to those who filled Rx only once for stimulants. Hazard for adolescent patients (age > 13 years) was 1.42 times as compared to children (age <13 years) (HR= 1.424, CI 1.327-1.527; p-<0.0001). Children and adolescents from Illinois and Ney York are less likely to develop BD as compared to Texas State with HR of 0.639 and 0.832 respectively. Children and adolescents with race other than white and blacks are less likely to develop BD as compared to whites (HR 0.750; CI 0.700-0.804; p-<0.0001). Children and adolescents with ADHD and other psychiatric co-morbidities like Adjustment disorder, Anxiety, Conduct disorder, Depression are more likely to develop BD as compared to those without such co-morbidities. Patients with learning disorder as co-morbid condition are less likely to diagnosed with BD. Patients taking any medication i.e. Atypical antipsychotics, mood stabilizer or others are more likely to develop BD.

Chapter 5

Discussion, Strengths and Limitations

Discussion:

In our study, prevalence of ADHD was found to be 6.4%, which is consistent with previous studies from United States. Though, the rate of Bipolar in patients with ADHD was found to be 7.37%, which is far less from the literature. Also, the rates of co-morbid conditions observed in our study were far less from the literature. The reason for such low prevalence of BD and low rates of co-morbid conditions in our cohort might be that most of the previous studies used data from psychiatric clinics (Biederman, 2005; Delbello, 2001; Wozniak, 1995). Hence, patient may be severely ill compared to our study population where the population is more general.

Age of onset of Bipolar Disorder:

Age of onset of Bipolar disorder was found to be 10.5 years (±3.44), which is consistent with literature. The age of onset of BD in patients filled Rx more than once for psycho stimulants was much lower than age of onset of BD in patients with one Rx filled (10.37±3.40 vs. 12.11±3.60, p- <0.0001). Also, we found that age of onset of ADHD for patients filled Rx more than once for psycho stimulants was much earlier than those patients with one Rx filled (8.85±3.05 vs. 10.21±3.41; p- <0.0001). To confirm these findings we also performed survival analysis, to determine the association between stimulant use and risk of developing Bipolar disorder.

Survival estimates for children and adolescents with ADHD were significantly different for patients filled Rx more than once for psycho stimulants vs. patients with one Rx filled (HR 1.583, CI 1.418-1.768; p-<0.001). These results are consistent with previous literature where

several case reports suggests than use of psycho stimulants leads to earlier onset of bipolar disorder in patients with ADHD. Probable explanation for this can be that psycho stimulants causes increase in dopamine neurotransmission which may lead to mania like symptoms or earlier onset of BD. So, our hypothesis that children and adolescents with ADHD and treated with stimulants will have earlier age of onset for BD compared to non users is accepted. Still the question of treatment of such patients remains a challenge. As untreated patients may complicate the condition and treatment with stimulants may lead to BD. Hence, it is very important to devise an appropriate treatment strategy for treating ADHD symptoms.

Also, other important predictors for development of Bipolar disorder were age, sex, race, state, co-morbidities and co-medication. Geographic differences are of significance as results showed high rates of stimulant prescription as well as development of bipolar disorder for Texas region as compared to other states. Patients with co-morbidities showed increase risk of developing BD. Such children and adolescents might be severely ill and hence at greater risk of development of BD.

Strength and Limitations:

Our study possesses several unique strengths. Our cohort of children and adolescents with ADHD was an adequate representation of the patients population in day to day life hence our findings are generalizable than previous studies. To our knowledge this was the first study conducted on a nationally representative sample to determine use of psycho stimulants and risk of developing Bipolar disorder in children and adolescents with ADHD. Also, the study used advanced method to compute survival of users and non-users of stimulants.

Our study also has some limitations. Firstly, the severity of children and adolescents was not taken into account as the data does not provide any information on severity. Also, physician attributes are important in deciding treatment strategy and also can affect diagnosis decision for a particular patient. This information was also not available.

Implications:

Our study examined the effect of psychostimulant on development of bipolar and found association between use of stimulants and earlier onset of BD. It showed that those patients who discontinued use of psycho stimulants are less likely to develop BD.

Clinically, our study assessed real-world situation and adds to the very limited literature on comparative effectiveness of psycho stimulants and risk of development of BD and helps physicians to make better-informed decision. From past literature showed concern about prescribing psycho stimulants to ADHD children, our study confirms that clinician should be careful while prescribing psycho stimulants to Children and adolescents with ADHD.

Future Research:

This study assessed the association between stimulant exposure and risk of developing Bipolar in ADHD children and adolescents which showed use of stimulant causes earlier development of BD. Further studies examining effectiveness of atomoxetine in patients with ADHD, without precipitating mania is warranted as atomoxetine is non-stimulant.

References:

Aman MG, Binder C, Turgay A Risperidone Effects in the Presence/Absence of Psychostimulant Medicine in Children with ADHD, Other Disruptive Behavior Disorders, and Subaverage IQ. *J Child and Adolescents Psych* 2004;14:243-254.

Ambuabunos EA, Ofovwe EG, and Ibadin MO. Community survey of attention-deficit / hyperactivity disorder among primary school pupils in Benin City, Nigeria. *Annals of African Medicine.* 2011;10(2):91-96.

Barbaresi WJ, Katusic SK, Colligan RC, et al. Long-Term School Outcomes for Children with Attention-Deficit/Hyperactivity Disorder: A Population-Based Perspective. *J Dev Behav Pediatr,* 2007; 28:265-273.

Barbaresi WJ, Katusic SK, Colligan RC, et al. Long-Term Stimulant Medication Treatment of Attention-Deficit/Hyperactivity Disorder: Resultsfrom a Population-Based Study. *J Dev Behav Pediatr,* 2006; 27:1-7.

Barbaresi WJ, Katusic SK, Colligan RC, et al. Modifiers of Long-Term School Outcomes for Children with Attention-Deficit/Hyperactivity Disorder: Does Treatment with Stimulant Medication Make a Difference? Results from a Population-Based Study. *J Dev Behav Pediatr*. 2007; 28:274–287.

Benjamin E, Salek S, et al. Stimulant atypical antipsychotic interaction and acute dystonia. *J. Am. Acad. Child Adolesc. Psychiatry* 2005; 44:6.

Biederman J, Faraone S, Mick E. Attention deficit hyperactivity disorder and juvenile mania: An overlooked co-morbidity? *J Child and Adolescents Psych* 1996; 35(8): 997-1008.
Biederman J, Mick E, Prince J, Systematic review of the pharmacologic treatment of comorbid Attention deficit hyperactivity disorder in youth with Bipolar Disorder. *J Child and Adolescents Psych* 1999; 9:247-256.

Biederman J, Monuteaux MC, Kendrick E et al. The CBCL as a screen for psychiatric co-morbidity in pediatric patients with ADHD. Arch Dis Child 2005; 90: 1010–1015.
bipolar disorder in clinically referred children. J Am Acad Child Adolesc Psychiatry 1995; 34: 867–876.
Butler SF, Arredondo DE, McCloskey V. Affective co-morbidity in children and adolescents with attention deficit hyperactivity disorder. Ann Clin Psychiatry 1995; 7:51–55.
Carlson GA., Kelly KL. Manic symptoms in psychiatrically hospitalized children-What do they mean? J Aff Dis. 1998; 51: 123-135.

Carlson GA., Loney J., Salisbury H., et al. Stimulant treatment in young boys with symptoms suggesting childhood mania: A report from a longitudinal study. J Child Adol Psychopharm. 2000; 10(3): 175-184.

Centers for Disease Control and Prevention. Racial/Ethnic Disparities and Geographic Differences in Lung Cancer Incidence - 38 States and the District of Columbia, 1998–2006. MMWR 2010;59(44):1433-1472.

Chang K, Nayar D, Howe M, et al. Atomoxetine as adjunct therapy in the treatment of Co-morbid ADHD disorder in children and adolescents wit h bipolar I or II disorder.

Chang KD, Steiner H, Ketter T. Psychiatric phenomenology of child and adolescent bipolar offspring. J Am Acad Child Adolesc Psychiatry 2000; 39: 453–460.

DelBello MP, Adler CM, Amicone J et al. Parametric neurocognitive task design: a pilot study of sustained attention in adolescents with bipolar disorder. J Affect Disord 2004; 82 (Suppl.): 79–88.

DelBello MP, Soutullo CA, Hendricks W, et al. Prior stimulant treatment in adolescents with bipolar disorder: association with age at onset. *Bipolar Disorders* 2001: 3: 53–57

DelBello MP, Soutullo CA, Hendricks W., et al. Prior stimulant treatment in adolescents with bipolar disorder: association with age at onset. Bipolar Disorders. 2001; 3: 53-57.

Dilsaver SC, Hernderson-Fuller S, Akiskal HS. Occult mood disorders in 104 consecutively presenting children referred for the treatment of attention-deficit/hyperactivity disorder in a community mental health clinic. J Clin Psychiatry 2003; 64: 1170–1176.

Dodson WW. ADHD and Bipolar Disorder 2000. ADDvance Magazine.

Faedda GL., Baldessarini RJ., Glovinsky IP., et al. Treatment emergent mania in bipolar disorder: A retrospective case review. J Aff Disorder. 2004; 82: 149-158.

Findling R, Short E, McNamara N, et al. Methylphenidate in the treatment of children and adolescents with Bipolar Disorder and ADHD. *J Am Acad Child Adolescents Psych* 2007; 46(11): 1445-1453

Findling RL, McNamara NK, Gracious BL et al. Combination lithium and divalproex sodium in pediatric bipolarity. J Am Acad Child Adolesc Psychiatry 2003; 42: 895–901

Frauger E, Pauly V, Natali F, et al. Patterns of Methylphenidate Use and Assessment of its Abuse and Diversion in Two French Administrative Areas Using a Proxy of Deviant Behaviour Determined from a Reimbursement Database Main Trends from 2005 to 2008. *CNS Drugs*. 2011; 25(5):415-424

Galanter CA., Carlson GA., Jensen PS., et al. Response to methylphenidate in children with attention deficit disorder and manic symptoms in the multimodal treatment study of children attention deficit disorder titration trial. J Child Adol Psychopharm. 2003; 13(2): 123-136.

Galender CA, Leibenluft E, Frontiers between Attention Deficit Hyperactivity Disorder and Bipolar Disorder. *Child Adolesc Psychiatric Clin N Am* 2008; 325-346

Galender CA, Leibenluft E, Frontiers between Attention Deficit Hyperactivity Disorder and Bipolar Disorder. *Child Adolesc Psychiatric Clin N Am* 2008; 325-346

Geller B, Tillman R, Craney JL, Bolhofner K. Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. Arch Gen Psychiatry 2004; 61: 459–467.

Goldsmith M., Singh M., and Chang K. Antidepressants and psycho stimulants in pediatric population: Is there an association with mania? Pediatric Drugs. 2011; 13(4): 225-243.

Guo J, Keck P, Li H et al. Treatment costs related to bipolar disorder and comorbid conditions among Medicaid patients with Bipolar Disorder. *Psych Services* 2007; 58(8): 1073-1078

Hassan A, Agha S, Langley K et al. Prevalence of bipolar disorder in children and adolescents with attention-defecit hyperactivity disorder. *B J Psych* 2011; 198: 195-198

Hert MD, Dobbelaere M, Sheridan EM, et al. Metabolic and endocrine adverse effects of second-generation antipsychotics in children and adolescents: A systematic review of randomized, placebo controlled trials and guidelines for clinical practice. *European Psychiatry* 2011;26:144–158.

Hodgkins P, Sasane R, and Meijer WM. Pharmacologic Treatment of Attention-Deficit/Hyperactivity Disorder in Children: Incidence, Prevalence, and Treatment Patterns in The Netherlands. *Clinical Therapeutics*. 2011;33(2):188-203.

Jaworowski S, Benarroch F, and Gross-Tsur Concomitant Use of Atomoxetine and OROS Methylphenidate in a 10-Year-Old Child Suffering from Attention-Deficit/Hperactivity Disorder with Co-morbid Bipolar Disorder and Tourette Syndrome. *J Child and Adolescents Psych* 2006;16:365-370.

Keen D and Hadjikoumi I. ADHD in children and adolescents. *Clinical Evidence*. 2008;10:312.

Keshen A, Carandang C. Acute dystonic reaction in an adolescent on resperidone when concomitant stimulant medication is discontinued. *J Child and Adolescents Psych* 2007; 17(6): 867-869.

Kessler RC, Adler LA, Barkley R et al. Patterns and predictors of attention-deficit/hyperactivity disorder persistence into adulthood: results from the National Comorbidity Survey Replication. Biol Psychiatry 2005; 57: 1442–1451.

Kim J, Mutyala B, Agiovlasitis S, et al. Health behaviors and obesity among US children with attention deficit hyperactivity disorder by gender and medication use. *Preventive Medicine*. 2011;52: 218–222.

Klassen AF, Miller A, and Fine S. Health-Related Quality of Life in Children and Adolescents Who Have a Diagnosis of Attention-Deficit/Hyperactivity Disorder. *Pediatrics.* 2004;114:e541.

Klassen LJ, Katzman MA, Chokka P, et al. Adult ADHD and its comorbidities, with a focus on bipolar disorder. *Journal of Affective Disorders* 2010; 124 :1–8.

Kowatch RA, Suppes T, Carmody TJ et al. Effect size of lithium, divalproex sodium, and carbemazepine in children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2000; 39: 713–720.

Kraemer M., Uekermann J., Wiltfang J, et al. Methylphenidate induced psychosis in adult attention deficit/hyperactivity disorder: Report of 3 new cases and review of the literature. Clinical Neuropharm. 2010; 33(4): 204-206.

Kronenberger WG, Giauque AL, Lafata DE, et al. Quetiapine Addition in Methylphenidate Treatment-Resistant Adolescents with Co-morbid Attention-Deficit/Hyperactivity Disorder, Conduct/Oppositional-Defiant Disorder, and Aggression: A Prospective, Open-Label Study. *J. Child Adolesc. Psychiatry* 2007; 17:334-347

Landaas ET, Johansson S, Halmoy A, et al. Bipolar disorder risk alleles in adult ADHD patients. *Genes, Brain and Behavior* 2011; 10:1-6.

Nierenberg AA, Miyahara S, Spencer T et al. Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder co-morbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. Biol Psychiatry 2005; 57: 1467–1473.

Nivoli AM, Murru A, Goikolea JM. New treatment guidelines for acute bipolar mania: A critical review. *J. Affect. Disord* 2011;10.015

Patel NC, DelBello MP, Bryan HS et al. Open-label lithium for the treatment of adolescents with bipolar depression. J Am Acad Child Adolesc Psychiatry 2006; 45: 289–297.

Penzner JB, Dudas M, Saito E. Lack of Effect of Stimulant Combination with Second-Generation Antipsychotics on Weight Gain, Original Article Metabolic Changes, Prolactin Levels, and Sedation in Youth with Clinically Relevant Aggression or Oppositionality. *J. Child Adolesc. Psychiatry* 2009; 19:563-573

Perlis RH, Miyahara S, Marangell LB et al. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Biol Psychiatry 2004; 55: 875–881.

Rader R, McCauley L, Callen EC. Current strategies in the diagnosis and treatment of childhood Attention deficit hyperactivity disorder. *American Family Physician* 2009; 79(8): 657-665.

Rader R, McCauley L, Callen EC. Current strategies in the diagnosis and treatment of childhood Attention deficit hyperactivity disorder. *American Family Physician* 2009; 79(8): 657-665.

Radigan M, Lannon P, Roohan P. Medication Patterns for attention deficit hyperactivity disorder and comorbid psychiatric conditions in a Low-income population. *J Child and Adolescents Psych* 2005; 15(1): 44-56

Reichart CG, Nolen WA. Earlier onset of bipolar disorder in children by antidepressants or stimulants? An hypothesis. J Aff Dis. 2004; 78: 81-84.

Ross RG. Psychotic and manic like symptoms during stimulant treatment of attention deficit hyperactivity disorder. Am J Psychiatry. 2006; 163(7): 1149-1152.

Scheffer RE, Kowatch RA, Carmody T, et al. Randomized, Placebo-Controlled Trial of Mixed Amphetamine Salts for Symptoms of Co-morbid ADHD in Pediatric Bipolar Disorder After Mood Stabilization With Divalproex Sodium. *Am J Psychiatry* 2005; 162:58–64

Schubert I, Koster I, Lehmkuhl G. The Changing Prevalence of Attention-Deficit/ Hyperactivity Disorder and Methylphenidate Prescriptions. *Dtsch Arztebl Int.* 2010; 107(36):615–21.

Schubert I, Koster I, Lehmkuhl G. The Changing Prevalence of Attention-Deficit/ Hyperactivity Disorder and Methylphenidate Prescriptions. *Dtsch Arztebl Int.* 2010; 107(36):615–21.

Singh MK, DelBello MP, Kowatch RA, et al. Co-occurrence of bipolar and attention-deficit hyperactivity disorders in children. Bipolar Disord 2006: 8: 710–720

Skounti M, Giannoukas S, Dimitriou E, et al. Prevalence of attention deficit hyperactivity disorder in school children in Athens, Greece. Association of ADHD subtypes with social and academic impairment. *Atten Def Hyp Disord*. 2010;2:127–132.

Tamam L, karakus G, Ozpoyraz N, Comorbidity of adult attention deficit hyperactivity disorder and bipolar disorder: prevalence and clinical correlates. *Eur Arch Psychiatry Cli Neurosci* 2008; 258:385-393

Taurines R, Schmitt J, Renner T, et al. Developmental co-morbidity in attention-deficit/hyperactivity disorder. Atten Def Hyp Disord 2010; 2:267–289

Tillman R., and Geller B. Controlled study of switching from attention deficit hyperactivity disorder to prepubertal and early adolescent bipolar I disorder phenotype during 6-year prospective follow-up: Risk, rate and predictors. Development and Psychopathology. 2006; 18: 1037-1053.

Waxmonsky JG, Waschbusch DA, Akinnusi O, et al. A Comparison of Atomoxetine administered as once vs twice daily on the school and home functioning of children with attention deficit/ hyperactivity disorder. *J Child Adolescents Psych*, 2011; 21:21-22

Wigal SB. Efficacy and Safety Limitations of Attention-Deficit Hyperactivity Disorder Pharmacotherapy in Children and Adults. CNS Drugs 2009; 23(1): 21-31

Wozniak J, Biederman J, Kiely K, Ablon JS, Faraone SV, Mundy E. Mania-like symptoms suggestive of childhoodonset

Wozniak J, Spencer T, Biederman J et al. The clinical characteristics of unipolar versus bipolar major depression in ADHD youth. J Affect Disord 2004; 82 (Suppl.): 59–69.

Wozniak JB, Biedeman J. A pharmacological approach to the quagmire of co-morbidity in juvenile mania. *J Am Acad Child Adolesc Psychiatry* 1996; 35(6):826-828.

Yanofski J The dopamine dilemma: Using Stimulants and Antipsychotics Concurrently. Psychiatry (Edgemont) 2010;7(6):18–23

Young JL, Sarkis E, Qiao M, et al. Once-Daily Treatment With Atomoxetine in Adults With Attention-Deficit/Hyperactivity Disorder: A 24-Week, Randomized, Double-Blind, Placebo-Controlled Trial. *Clin Neuropharm* 2011;34: 51-60.

Youngstrom EA, Arnold LE, Frazier TW, et al. Bipolar and ADHD Comorbidity: Both Artifact and Outgrowth of Shared Mechanisms. *Clin Psychol* 2010 December 1; 17(4): 350–359

Zeni CP, Tramontina S, Ketzer CR et al. Methylphenidate Combined with Aripiprazole in Children and Adolescents with Bipolar Disorder and Attention-Deficit=Hyperactivity Disorder: A Randomized Crossover Trial. *J Child and Adolescents Psych* 2009;19:553-561