Study Protocol:
Open-Label Study of N-Acetylcysteine in Children and Adolescents ages 5-17 with Bipolar I, Bipolar II, and Bipolar Spectrum Disorder

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1. BACKGROUND AND SIGNIFICANCE

As highlighted in NIMH Research Roundtables, pediatric bipolar disorder is now recognized as a significant public health concern (J Biederman et al., 2001). Children with bipolar disorder make up the most difficult psychopathologic group with poor functioning and high levels of psychiatric comorbidity, hospitalization and special education services. Aggressive behavior, suicidality and reckless impulsivity are common problems for bipolar youth and some are diverted to the youth criminal justice system (Wozniak & Biederman, 1997). Pediatric bipolar disorder is commonly characterized by high levels of irritability as well as mixed states, that is, concurrent features of both mania and depression. The clinical picture of concurrent depression and mania significantly complicates the diagnosis, course and treatment of pediatric bipolar disorder. The severity of illness associated with pediatric bipolar disorder is so extreme that not treating is usually not a viable option.

Common Pharmaceutical Treatments are Inadequate

Part of the controversy surrounding the diagnosis of bipolar disorder in youth is the concern that children given the diagnosis may be subjected to treatments that are fraught with potentially serious side effects. Children with bipolar disorder are frequently treated with a multitude of medications despite unclear efficacy and inadequate safety data (J. Biederman et al., 1998; Kowatch & DelBello, 2003). Medications such as lithium, which have been the mainstay of pharmacotherapy for bipolar adults, show only moderate effectiveness in children (Kowatch et al., 2000), and side effects of newer atypical antipsychotic agents (e.g. risperidone, aripiprazole, olanzapine and quetiapine) have been found to limit these drugs' utility (Liu et al., 2011).

For several decades, mood stabilizers, including lithium, valproate, and carbamazepine, have been the cornerstone of acute and maintenance therapy for mania in bipolar adults (Sachs, Printz, Kahn, Carpenter, & Docherty, 2000; Sachs & Thase, 2000). Despite various advantages of these compounds including putative neuroprotective effect, there is a gap between drug efficacy in controlled trials and the effectiveness of mood stabilizers in the clinical setting. For example, in controlled and naturalistic trials in children mood stabilizers were demonstrated to be only moderately effective for the treatment of mania (J. Biederman et al., 1998; Geller et al., 1998; Kowatch et al., 2000). In the naturalistic setting, mood stabilizer therapy was associated with a slow onset of action and substantial risk of relapse (J. Biederman et al., 1998). In the controlled trials, there were frequent adverse events, noncompliance, and treatment dropouts (Kowatch et al., 2000; Wagner et al., 2002). In a chart review of our naturalistic experience in the treatment of pediatric bipolar disorder, we documented that the traditional mood stabilizers lithium, valproic acid and carbamazepine, were minimally effective in treating children and adolescents with bipolar disorder (J. Biederman et al., 1998).

In comparison to conventional mood stabilizers, which are limited in their efficacy and carry adverse side effect profiles, more encouraging results have emerged with the use of atypical antipsychotic medications. For years, lithium had been the only agent with FDA approval for bipolar disorder in youth. The atypical antipsychotic medications have been approved by the

Food and Drug Administration (FDA) for use in mania in adults (Perlis, Welge, Vornik, Hirschfeld, & Keck, 2006), and in the case of risperidone and aripiprazole, down to age 10 for children with mania (J. Biederman, McDonnell, et al., 2005; J. Biederman et al., 2007; J. Biederman, Mick, et al., 2005). There is a very real concern, however, regarding the development of weight gain and diabetes in individuals treated with atypical antipsychotic medications (Leslie & Rosenheck, 2004; Lindenmayer, Nathan, & Smith, 2001; McElroy et al., 2004; Meltzer, 2005; Regenold, Thapar, Marano, Gavirneni, & Kondapavuluru, 2002; Rosenbloom, 2002), and tardive dyskinesia remains a risk associated with these treatments (Aggarwal & Burnett, 2013; Gardos & Cole, 1995; J. Kim, Macmaster, & Schwartz, 2014).

In addition to weight gain, risperidone is associated with elevations of the hormone prolactin (J. Biederman, Mick, et al., 2005), which can result in galactorrhea in youth and has unknown effects on pubertal development (Y. K. Kim, Kim, & Lee, 1999; Petty, 1999; Popli, Gupta, & Rangwani, 1998; Turgay, Binder, Snyder, & Fisman, 2002; Wudarsky et al., 1999).

Furthermore, adverse effects and noncompliance may be a more significant problem in children than in adults. Side effects such as weight gain, acne, cognitive impairment, or gastrointestinal distress can make youth self-conscious and non-compliant. Also, adverse effects due to drug-drug interactions or routine blood collection for serum level monitoring increases the risk of refusing medications with the attendant consequences on clinical course and adaptive life. Clinicians and parents would happily turn to alternative treatments were more information available regarding their efficacy and confirming their presumed safety. In the absence of this data, the tenets of evidence based medicine dictate the use of pharmaceutical agents with established efficacy, especially those with approval, despite miserable side effects (Kowatch et al., 2005).

N-acetylcysteine and Psychiatry

Alternative products, including N-acetylcysteine (NAC), may offer a healthy option for treating developing youth with psychiatric disturbance. As bipolar disorder is severely impairing, intervention of some sort is usually necessary. Alternative treatments may be acceptable to a subset of individuals throughout the lifecycle who refuse treatment with conventional agents.

Nutritional products including NAC have demonstrated utility in the treatment of mood disorders. These agents offer the promise of a safe and healthful approach to controlling the symptoms of bipolar disorder in youth. NAC is an acetylated amino acid and a precursor of glutathione. When ingested, NAC increases cysteine levels, leading to the synthesis of more glutathione in the brain; glutathione then acts as an anti-oxidant to reduce oxidative stress, which has been implicated in bipolar disorder and major depression (Magalhaes et al., 2011; Smaga et al., 2012). Ingesting glutathione itself is not helpful, as it never reaches the brain due to poor absorption and rapid metabolism. NAC, however, crosses the blood-brain barrier with ease (Dean, Giorlando, & Berk, 2011; Witschi, Reddy, Stofer, & Lauterburg, 1992).

NAC has an additional role in regulating glutamate levels. The cysteine portion of NAC is a key

player in the transport of glutamate out of the cell. Excessive glutamate levels have been implicated as a possible mechanism of psychopathology in psychiatric conditions. Through a feedback mechanism with astrocytes, this can result in diminished release of glutamate into the extracellular space. Thus, this additional role in regulating glutamate levels may also be therapeutic, as malfunctions in the glutamate system result in consequent excito-toxic damage from activation of the N-methyl-D-Aspartate (NMDA) glutamate receptor.

Coupled with the purported mechanism of action, clinical trials have also provided compelling interest in NAC as an evidence-based treatment for pediatric bipolar disorder. Research has demonstrated the utility of NAC in the treatment of bipolar disorder in adults: both open-label and double-blind, randomized, placebo-controlled trials of NAC have found decreases in depression rating scale scores and improvements in global functioning (Berk, Copolov, Dean, Lu, Jeavons, Schapkaitz, Anderson-Hunt, & Bush, 2008; Berk et al., 2011). NAC has also proven to be safe in pediatric studies: children with autistic disorder have responded well to treatment with NAC without any serious adverse events or side effects (Ghanizadeh & Moghimi-Sarani, 2013; Hardan et al., 2012). NAC has been shown to be helpful in treating a multitude of disorders (OCD; marijuana, nicotine, and cocaine addictions; gambling; skin picking; nail biting; trichotillomania; schizophrenia; autism; and bipolar disorder), suggesting it may address the end of the line pathway targets common to multiple disturbances (Wozniak, in press).

Rationale
Emerging research suggests that NAC may be an effective treatment for bipolar disorder, but there are no published data to date in the pediatric bipolar population. Additional research is needed on NAC's optimal dosing, side effects, and efficacy in treating pediatric bipolar disorder.

2. SPECIFIC AIMS

Specific Aim I: Assessing the efficacy of NAC in the treatment of pediatric bipolar spectrum disorders. Other research suggests that NAC is effective in the treatment of bipolar disorder in adults (Berk, Copolov, Dean, Lu, Jeavons, Schapkaitz, Anderson-Hunt, & Bush, 2008; Berk et al., 2011), but no work has assessed the effectiveness of NAC for pediatric bipolar disorder and associated symptoms. Hypothesis 1: NAC will yield a reduction in the symptoms of pediatric bipolar spectrum disorders, as measured by scores on the YMRS and the Mania Symptoms Checklist.

Specific Aim II: Assessing the side effect profile of NAC. Medications used to treat bipolar disorder in youth are fraught with side effects including sedation, extra-pyramidal symptoms, cognitive clouding, weight gain and diabetes. In contrast, NAC has health benefits. Hypothesis 2: The use of NAC will have few side effects in youth, as measured by the number of adverse events.

3. LENGTH OF STUDY

The study will last up to 15 weeks from the initial phone screen (it could take up to three weeks to schedule and complete the initial screening process). Once subjects have completed the screening process, they will begin the 12-week open-label phase. Subjects will be assessed weekly throughout the study for efficacy and tolerability.

4. SOURCE OF SUJECTS

We will recruit subjects from the pool of existing subjects, patients, and new referrals to the Pediatric Psychopharmacology Program at MGH, as well as through advertising in the local media and online. If a potential subject's clinician ascertains that the patient has an interest in study participation, the clinician will only offer contact information for the study to their patients. The patient can then contact the study coordinator for more information on the actual study. All subjects that enter the study will undergo standard screening and diagnostic procedures.

The majority of subjects referred to our program first participate in our general screening protocol entitled, "Screening Protocol for Children and Adolescents with Bipolar and Bipolar Spectrum Disorder" (Protocol # 2001-P-001247). After participating in this screening protocol, subjects are invited to participate in specific studies based upon eligibility requirements (i.e. age, prior medication efficacy or tolerability).

Subjects who have completed a previous medication trial in our program may be eligible to participate in this study, as described in the Study Design section.

5. SUBJECT ENROLLMENT

All subjects that enter the study will undergo standard screening and diagnostic procedures. Written informed consent will be obtained from subjects' parent/guardian prior to initiation of the study protocol. Subjects aged 7 and older will sign age appropriate assent forms. Subjects ages 14-17 will document their assent on a designated line of the general study consent form. Subjects who turn 18 years old during the trial must re-sign on a designated line in the parent/guardian consent when they reach age of maturity. The study subjects and their parent may take as much time as they feel necessary to consider their participation in the study as well as consult with their family members or physician. Only patients who are not responding to their current treatment regimen will be tapered from their medications to enter this study. Subjects may remain on most current treatments while participating in this study. Participation in this study is voluntary, and subjects may withdraw from the study at any time.

6. SUBJECT SELECTION CRITERIA

A. Inclusion Criteria

1. Male or female subjects, 5-17 years of age.

2. Subjects must have a DSM-5 diagnosis of a bipolar spectrum disorder (type I, II, or Not Otherwise Specified (NOS)), and currently displaying mixed, manic, or hypomanic symptoms according to clinical assessment based on the DSM-5 and confirmed with structured diagnostic interview (Schedule of Affective Disorders and Schizophrenia for School-Age Children - Epidemiological Version (K-SADS-E)).
3. Subjects and their legal representative must have a level of understanding sufficient to communicate intelligently with the investigator and study coordinator, and to cooperate with all tests and examinations required by the protocol.
4. Subjects and their legal representative must be considered reliable.
5. Each subject and his/her authorized legal representative must understand the nature of the study. The subject's authorized legal representative must provide written consent and the subject must provide written assent.
6. Subjects must have an initial total score on the YMRS of at least 15.

B. Exclusion Criteria

1. Investigator and his/her immediate family (defined as the investigator's spouse, parent, child, grandparent, or grandchild).
2. Serious or unstable illness including hepatic, renal, gastroenterological, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, immunologic, or hematologic disease.
3. Uncorrected hypothyroidism or hyperthyroidism.
4. History of sensitivity to N-acetylcysteine, a history of intolerance to N-acetylcysteine or a non-responder after 2 months of treatment at adequate doses as determined by the clinician.
5. Severe allergies or multiple adverse drug reactions.
6. Current or past history of seizures.
7. Active substance abusers, per clinician judgment.
8. Judged clinically to be at serious suicidal risk.
9. Currently displaying psychotic features.
10. Any concomitant medication with primary central nervous system activity other than specified in the Concomitant Medication portion of the protocol.
11. Current diagnosis of schizophrenia.
12. Pregnancy.
13. C-SSRS score ≥ 4.
14. IQ < 70.

7. DESIGN

This will be a 12-week, open-label study of NAC in the treatment of bipolar disorder in children and adolescents. Subjects will include youth ages 5-17 years with a bipolar spectrum disorder (type I, II, or NOS), mixed, manic, or hypomanic state, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition DSM-5 (American Psychiatric Association,

2013). The primary outcome measures will be improvement in manic symptoms as measured by the Young Mania Rating Scale (YMRS) and improvement in depressive symptoms as measured by the Child Depression Rating Scale (CDRS).

Bipolar diagnoses will be made according to the DSM-5 in a clinical evaluation by a Child Psychiatrist and confirmed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children - Epidemiological Version (K-SADS-E)(Orvaschel, 1994). All subjects must have a YMRS score of at least 15. Only patients who are not responding to their current treatment regimen will be tapered from their medications; youth on concomitant psychiatric medications will be permitted to continue those medications as listed in the concomitant medication section.

We will consent and screen 40 subjects to ascertain 20 subjects who complete 12 weeks of open-label treatment. The subject's first visit to the office consists of a meeting with a study clinician who explains the study, obtains informed consent and assent, and administers an abbreviated form of the structured diagnostic assessment (45-90 minutes). After the evaluation with the study clinician, the subjects will undergo a neuropsychological assessment (35-45minutes).

We anticipate that subjects may enter this trial following completion of/withdrawal from other Bipolar Disorder protocols in our office, and that there may be procedural overlap. So as to not burden subjects/parents/guardians with redundant time commitments, we will use the following diagnostic data previously collected:

- If a subject has completed an evaluation with one of the study clinicians and/or the structured assessment within the 12 months prior to entrance into this study, they will not be asked to repeat any overlapping diagnostic procedures. We will use the previously collected data. However, the study clinician will review the interval time period to assess for clinically significant medically or psychiatric history to ensure that the subject meets appropriate study entrance criteria, including a DSM-5 diagnosis of a bipolar spectrum disorder.

- If the subset of scales assessing intelligence (WASI-II/KBIT-2) and cognitive functioning (select WISC/WPPSI-III tasks) in the neuropsychological battery have been completed within 12 months prior to entrance into this study, subjects will not be asked to repeat these procedures. We will use the previously collected data. Study participants (or their parent/guardian) may request the results of their cognitive testing. In this case, the subject will receive a letter providing a basic interpretation of the results and referring the subject (or their parent/guardian) to the department's supervising neuropsychologist for any questions or concerns.

Eligible subjects will be required to come into the office for the following visits: Screening, Baseline (Week 0), Weeks 1-4, Week 8, and the Week 12 final visit. Visits for Weeks 5-7 and 9-11 will be completed by the clinician over the phone; however, if the parent and subject prefer to

come into the office for these visits instead, they may do so. During this time subjects will receive prescriptions from the study doctor for their NAC treatment.

Although every effort will be made to encourage subjects to keep regularly scheduled appointments, in the event that a subject is unable to come into the office within a reasonable timeframe of a scheduled study visit, and the study doctor feels that subject safety will not be jeopardized by doing so, the clinician may conduct the visit with the subject and parent/guardian over the phone; this will ensure that each subject will be continuously monitored by the clinician throughout the course of the study despite unforeseen scheduling circumstances. However, if a subject completes a phone visit instead of a scheduled office visit, the office visit must be made up within two weeks. Neither the Screening visit, nor the Baseline visit, nor the final study visit may be conducted over the phone.

Vital signs (blood pressure, pulse, temperature), height, and weight will be measured at every office visit. A urine drug screen will be performed for all subjects aged 12 and over at the screening visit. For female subjects who have begun menstruating, a urine pregnancy test will be performed at the screening visit, followed by a serum pregnancy test if the urine test is positive. If a participant has a positive serum pregnancy test, the study doctor will inform the subject, and she will not be able to take part in the study. The decision whether to inform the parent of these results will be made by the physician based on the participant's age and maturity level and the requirements of the law, unless the participant agrees to parental notification.

Those subjects who terminate study participation before the completion of the study will be asked to complete all tasks scheduled to take place on the final study visit at the time of study discontinuation; however, if the subject refused to complete any portions of the cognitive assessment at baseline, or if the subject was not yet exposed to the study treatments, it is possible that we will not ask him/her to complete these tasks at endpoint, per clinician judgment. Medication compliance for the study will be assessed at each study visit after Baseline.

Dosing

We plan to treat subjects with the following dose:

<u>Subjects ages 5-12</u>
Week 1: 900mg po daily
Weeks 2+: 900mg po QAM, 900mg po QPM

<u>Subjects ages 13-17</u>
Week 1: 900mg po daily
Week 2: 900mg po QAM, 900mg po QPM
Weeks 3+: 1800mg po QAM, 900mg po QPM

In Weeks 3-12 for subjects ages 13-17, we will encourage twice per day dosing, but we will

permit daily dosing if needed for adherence.

The rationale for the NAC dosing is based on two pilot clinical trials and one case report indicating that oral dose of NAC in the range of 800-2700mg is well-tolerated in children (Ghanizadeh & Derakhshan, 2012; Ghanizadeh & Moghimi-Sarani, 2013; Hardan et al., 2012). Hardan and colleagues' (2012) use of increasing doses of NAC in the range of 900-2700mg appears to have been more efficacious than Ghanizadeh's and Moghimi-Sarani's (2013) dosing of 1200mg per day. Therefore, we decided upon an age-appropriate forced titration dosing within the 900-2700mg range, which has been shown to be safe for children.

PharmaNAC brand was chosen to supply the NAC tablets due to its palatability and ease of administration. Younger subjects have difficulty swallowing pills, but PharmaNAC tablets offer the advantage that they dissolve in water and do not require that subjects swallow pills. This brand of NAC has been used in previous studies (Hardan et al., 2012; Miller & Angulo, 2014) and has excellent reliability of content. The Principal Investigator has successfully used this brand of NAC in clinical practice.

The supplements will be stored in our research pharmacy and delivered to the Pediatric Psychopharmacology Unit, where a clinician will dispense them. Subjects are instructed to return unused tablets. Pill counts will be reviewed each visit to ensure compliance.

Concomitant Medications

A detailed past and present treatment history will be taken as part of initial evaluation. Patients who are partially responding to current psychotropic medication yet continue to have symptoms of mania and depression will be permitted to continue on their current regimen, provided that the patient's regimen remains the same throughout the study. Patients treated with these medications must be on a stable dose for at least one month prior to study entry. No new medications (except for the use of the benzodiazepine lorazepam listed below) or alterations to the current regimen may be initiated throughout the duration of study participation.

Only patients with a poor response to their current medication treatment will be advised to consider a taper off their medications for entry into the study. No patient will be tapered from medication that is useful to him or her.

The use of the benzodiazepine lorazepam is permitted during the study for exacerbation of symptoms of agitation. Patients may not exceed a dosage of 2mg lorazepam per day and lorazepam is permitted for a maximum of 3 days during the study. Any greater need for lorazepam will be considered evidence of poor treatment response and grounds for drop from the study.

Additionally, participants who are on a stable dose of ADHD medications may continue on that dose throughout the study. However, no new medications for ADHD or alterations to the current

ADHD regimen may be started throughout the duration of participation in the study, per clinician judgment.

Non-pharmacological treatments such as individual, family or group therapy will be allowed if they were in place before the patient joined the study. The patient's therapy regimen must remain the same throughout the study. No new non-pharmacological treatments may be initiated after study participation has begun.

Washout Period

Medication washout may be recommended by our clinicians on a case-by-case assessment, considering the duration on drug, the dose, the adverse effects associated with the treatment, and potential effects of stopping that medication/treatment. Only subjects not responding to current treatment will be tapered from medication. No subject on a useful treatment will be tapered from medication for entry into this study. The referring or study clinician will monitor medication tapers in agreement with the research subject and his/her legal guardians. Our office does not take over care for the patient, but remains available during this time period. The washout schedule will be discussed with the subject's family as well as the current provider.

Typically a 7-day washout period is recommended for antidepressant medications and atomoxetine (with the exception of Prozac requiring 14 days). Mood stabilizers/atypical antipsychotics are generally washed out over the course of 7 days, while stimulants are discontinued in 2 or 3 days.

Screening Visit (Week 99)

Before any participant can start the study, the study clinician will discuss the details of the study with the participant and his/her parent/guardian. Before starting the screening process, the study clinician will obtain informed consent from the parent or guardian and assent from the child subject. Assent will be obtained, in writing, from each child aged 7 or older who, in the opinion of the Investigator, is capable of providing assent based on his/her age, maturity, and psychological state. When assent is not obtained, the Investigator will document his/her rationale in the research records.

After the consent/assent form is signed, we will do the following:

- Review medical and health questions with the participant and his/her parents/guardians. (For example, "Does your child have a history of any medical conditions such as diabetes or hypertension?")
- Obtain psychiatric history and administer the YMRS, the CDRS, the HAM-D, the C-SSRS, and the K-SADS-E mania and depression modules to determine that subject meets the diagnostic criteria of a current DSM-5 bipolar spectrum disorder (mixed, manic, or hypomanic) and has an YMRS score ≥ 15.

All exclusionary and inclusionary criteria will be reviewed. Appropriate patients will undergo:

- Assessment battery (CBCL, SAICA, FES)
- Cognitive evaluation (IQ and cognitive function [subtests of the WASI-II or KBIT-2, the WISC-IV or WPPSI-III])
    - Select WPPSI-III subtests will be used in the place of the WISC-IV processing speed subtest for children younger than 6 years.
    - The KBIT-2 will be used in the place of the WASI-II to assess IQ in children younger than 6 years.
- Physical exam
- Vital Signs (blood pressure, pulse, temperature), height, and weight
- Urine pregnancy test (for females who have begun their period)
- Urine drug screen (for subjects age 12 years and older)

The above may take place over two visits over the course of three weeks, if necessary. All are to be completed prior to the Baseline Visit. Any subjects requiring medication washout must be tapered off this medication prior to Baseline Visit as indicated in the washout section. Patients who do not meet all the criteria for enrollment after these assessments will be discontinued.

Baseline Visit (Week 0)

Subjects must continue to meet all inclusionary and exclusionary criteria at this visit

- The study clinician will ask the parents/guardians questions about their child's symptoms of bipolar disorder
- Study clinician will administer additional scales: the ADHD Rating Scale and BPRS
- The parent and subject will complete
- Vital signs (blood pressure, pulse, temperature), height, and weight
- Subjects will receive study treatment

Weekly Visits (Weeks 1 through 12)

Weekly study visits will have a visit window of 7 +/- 2 days to facilitate scheduling.

During these visits:

- The study clinician will ask the parents/guardians questions about their child's symptoms of bipolar disorder
- The study clinician will also ask if the participant is having any side effects and if they have taken any other medications since the last visit
- Blood pressure, pulse, height, weight, and temperature will be obtained (unless it is a phone visit week)
- At the last visit (or at time of drop from study) al subjects will undergo repeat cognitive evaluation.

Study Discontinuation

Subjects may drop at any time due to patient preference, physician decision, need for psychiatric hospitalization, or a poor response to treatment. Poor response to treatment will be measured by a CGI-bipolar score that is 2 points higher (more severe) than baseline for 2 weeks in a row or a YMRS score that is 30% higher than baseline for 2 weeks in a row, which may lead to drop from the study as determined by the clinician. Initial and emergent suicidality will be assessed weekly through administration of the Columbia Suicide Severity Rating Scale (C-SSRS). Subjects scoring 4 or higher will be dropped from the study. In addition, drop from study will occur at clinician discretion for lack of efficacy, non-compliance with treatment or inability to tolerate study treatment.

Subjects will receive three months of optional pro bono clinical care visits (one appointment per month) with a study doctor at the completion of the study, or if they are required to discontinue for the above reasons. These appointments must take place within three months of the subject's final study visit. No research data will be collected at these follow-up visits. The three months of follow-up care are a courtesy that is offered to help find long-term care. Subjects will receive referrals to clinicians in their communities.

Subjects who fail to return medication for two consecutive office visits, fail to keep study appointments, or are non-compliant (less than 70% compliance for two weeks or longer) may be dropped from the study. These study subjects will be given a referral to clinicians in their area.

If a subject becomes pregnant or is found to be abusing substances during the study, he or she will be discontinued from the study and given a referral, as well.

If a subject would like us to forward their clinical history to his/her primary care physician, or a new clinician, we will forward any pertinent information. If a subject who has come from the clinic of the investigator happens to drop out of the study, he or she will return to his or her treating physician.

Audio Recordings

For quality control purposes, the rating scales completed during office visits may be recorded. The PI will use these recordings to monitor quality control and inter-rater reliability in this study. Each recording will be coded with patient initials and number to maintain confidentiality. These recordings will be stored in a password-protected database.

Data Collection

Data will be collected using StudyTRAX. StudyTRAX is an electronic data capture system that streamlines data collection and management and ensures data integrity. StudyTRAX software allows researchers to design and implement study surveys for collected, story, retrieving, and

manipulating data electronically.

Participants and/or research staff will enter survey responses into electronic assessment forms, using computer terminals at the research site. The responses will then be transmitted securely via an encrypted connection and stored in a secured database. Electronic data capture obviates the need for subsequent data entry by staff, thus minimizing human error. However, it is still possible that rating scales will be collected in paper form in the case that StudyTRAX is not working or unavailable.

8. ASSESSMENTS (see Table 1)

A. K-SADS-E (Epidemiologic Version)

- We will collect information for psychiatric diagnoses in children with study relevant modules of the KSADS-E (Epidemiologic Version)(Orvaschel, 1994).
- This is a widely used, semistructured, diagnostic interview with established psychometric properties. Study staff can effectively administer it in 45 to 90 minutes, although more complex cases may require additional time. This assessment will be administered by a study clinician.
- For all children, psychiatric data will be collected from the primary caretaker. All children and primary caregivers will be seen in direct clinical interview with a trained member of study staff.
- The mania and depression modules will be administered prior to the baseline visit to ensure entry criteria are met.
- The subject's parent/guardian will also be asked a series of background information questions regarding the subject's age, sex, education history (tutoring, placement in special classes, repeated grade), intactness of family of origin, and psychological and psychiatric treatment history, including past and current therapy and medication for emotional, behavioral, and attentional problems. In addition, questions about occupation and level of education of the subject's parents will be asked to determine socioeconomic status; this information will be entered on the study-specific form ("Background Information/KSADS face page").

B. Child Behavior Checklist-Parent Form (CBCL)

- The CBCL (T.M. Achenbach, 2000; T. M. Achenbach & Dumenci, 2001) is a standardized assessment of child behavior problems and social competence. Due to its extensive use and available norms, it provides us with an effective method of comparing our sample with others in the literature.
- The CBCL records, in standardized format, the behavioral problems and competencies of children aged 4 to 18, as reported by their parents/guardians.
- The CBCL is scored on the recently revised social competence and behavior problem scales of the Child Behavior Profile. A T-score above 70 is considered to be a clinically meaningful indicator of childhood psychopathology.

- Administered at beginning of study to characterize the groups and ensure their similarity.

C. Social Adjustment Inventory for Children and Adolescents (SAICA)

- The SAICA (John, Gammon, Prusoff, & Warner, 1987) is a semi-structured interview of the child or parent that measures social functioning in children 6 to 18 years old.
- Content areas assessed include activities, peer relations, family relations, and academic performance. A total score is then calculated as the arithmetic mean of all global rating scores.
- We will administer this scale to parents/guardians at beginning of study and endpoint to assess the impact of treatment on social functioning. We will administer this scale for all subjects, including 5 year olds.

D. Family Environment Scale (FES)

- As an additional measure of the family environment, we will use the Moos Family Environment Scale (FES) (Moos, 1985)
- The FES assesses the quality of interpersonal relationships among family members. This scale consists of 90 true-false items to be completed by the parents. This measure permits an assessment of the degree of stress in the family environment and of parental discord.
- Administered at beginning of study to characterize the groups and ensure their similarity.

E. Global Assessment of Functioning (GAF)

- The GAF (American Psychiatric Association, 1994) will assess global functioning using a scale from 1 (worst) to 100 (best). Guidelines and examples of how to use this scale are provided with the scale.
- This clinician rated scale will be used at baseline visit to characterize the sample, at each of the 12 weekly visits to assess change, and at endpoint, to assess the impact of treatment on global functioning.

F. Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)

- A 15-item rating scale to assess the degree of life enjoyment and satisfaction for children (Endicott, Nee, Yang, & Wohlberg, 2006).
- We will administer this scale to parents/guardians at baseline and endpoint.

G. Neuropsychological Tests/Cognitive Evaluation

- **IQ Testing:** At study beginning, subjects will complete a brief cognitive screen. The scales we will use meet the demand for quick reliable measures of intelligence in clinical, educational and research settings. These tests will provide estimates of verbal and nonverbal ability respectively, as well as the direct measure of Full Scale IQ. This portion of the cognitive evaluation will take approximately 30 minutes to complete. In the unlikely event that a subject's estimated IQ is below 70, the subject will not be eligible to participate in the study. Depending upon the subject's age, the cognitive screen will consist of:
    - **Subjects age 5:** Verbal Knowledge, Riddles, and Matrices subtests of the

Kaufman Brief Intelligence Test, Second Edition (KBIT-2)(Kaufman & Kaufman, 2004)
- **Subjects ages 6-17:** Vocabulary and Matrices subtests of the Wechsler Abbreviated Scale of Intelligence (WASI-II)(Wechsler, 2011)

❖ **Cognitive Functioning Testing:** At screening and endpoint, to evaluate the impact of treatment on cognition, we will assess basic intellectual and cognitive functions purported to be deficient in patients with bipolar disorder. Cognitive deficits that have been observed in bipolar disorder may reflect dysfunction in the frontal subcortical circuits that support aspects of attention, executive functions processing speed, memory, and learning (Bearden, Hoffman, & Cannon, 2001). The neuropsychological battery we have developed to assess these functions includes both published clinical measures with large, normative samples and experimental measures with strong empirical evidence of validity. This neuropsychological battery, which has been used widely in clinical trials and family studies in our office, has been well-tolerated. The testing will take approximately 15 minutes to complete. The age-appropriate testing will include:
- **Subjects age 5:** Symbol Search and Coding subtests of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) (Wechsler & Sattler, 2002) to measure processing speed
- **Subjects ages 6-16:** Digit Span and Symbol Coding subtests from the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) (Wechsler, 2003) to measure working memory and processing speed
- **Subjects age 17:** Digit Span and Symbol Coding subtests from the Wechsler Adult Intelligence Scale (WAIS-IV)(Wechsler, 2008)

The working memory scale will be omitted for subjects who are 5 years of age, as we do not have an age-appropriate scale available.

Efficacy Measures

The primary efficacy measures are the mean change from baseline to endpoint in the Young Mania Rating Scale (YMRS) total score and the Children's Depression Rating Scale (CDRS). These will be administered by the clinician at all visits.

A. Young Mania Rating Scale (YMRS)

❖ The YMRS (Young, Biggs, Ziegler, & Meyer, 1978) consists of 11 items rated on a scale from 0 (symptom not present) to 4 (symptom extremely severe).
❖ Items 5, 6, 8, and 9 are rated on a scale from 0 (symptom not present) to 8 (symptom extremely severe). These items assess irritability, speech, content and disruptive/aggressive behavior) and are given extra weight in the overall score.
❖ The YMRS score ranges from 0-60. Questions are asked about the last week. This scale is generally accepted as the main outcome measure in studies of pediatric bipolar disorder and is linked directly to the core symptoms of mania.
❖ Collected at the Screening Visit, Baseline Visit (only subjects with a YMRS score of 15 or greater, but not above 40, are included), at each of the weekly visits and at endpoint to

assess the impact of treatment on manic symptoms.

B. Children's Depression Rating Scale (CDRS)

- The CDRS (Poznanski, Freeman, & Mokros, 1985) is modeled after the Hamilton Depression Rating Scale for adults, but includes questions relevant to youth, such as questions about school, family and peer functioning.
- This is a clinician-rated instrument with 17 items scored on a 1 to 5 or 1 to 7 scale. A rating of 1 indicates normal, thus the minimum score is 17. The maximum score is 113. Scores of 20-30 suggest borderline depression. Scores of 40-60 indicate moderate depression.
- This scale is generally accepted as the main outcome in studies assessing childhood depression and is linked directly to the core symptoms of depression.
- Collected at all visits.

C. Hamilton Depression Rating Scale (HAM-D)

- The HAM-D is a clinician rated instrument that measures the severity of depressive symptoms.
- This is a clinician-rated instrument with 21 items scored on a 0 to 4 scale.
- Collected at all visits.

As secondary measures to assess severity and improvement relative to baseline for mania, depression and common comorbid conditions, we will use other measures including: a DSM-IV Mania Symptom Checklist; the Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale; the Brief Psychiatric Rating Scale (BPRS); and the NIMH Clinical Global Impression scale (CGI) (Severity, Improvement and Efficacy Index) for mania, depression, Bipolar Disorder overall, ADHD, Oppositional Defiant Disorder and Anxiety. Most of these scales will be administered at baseline visit, at each of the weekly visits and at endpoint by the clinician to assess the impact of treatment on ADHD, anxiety, and to have other measures related to the impact of treatment on bipolar disorder. We will also have the subject's parent/guardian complete the Social Responsiveness Scale (SRS) and the Behavior Rating Inventory of Executive Function – Parent Form (BRIEF) at the Baseline Visit and Week 12 visit.

A. DSM-IV Mania Symptom Checklist

- This Checklist is adapted from the DSM-IV mania diagnostic criteria with items for each symptom of mania. Each item is scored 0 to 3 ranging (0=never or rarely; 1=sometimes; 2=often; 3=very often).
- Collected at baseline visit, at each of the weekly visits and at endpoint as an additional measure of manic symptoms.

B. Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale

- The ADHD Rating Scale is an 18-item scale with 1 item for each of the 18 DSM-IV ADHD symptoms. Each item is scored 0 to 3 (0=never or rarely; 1=sometimes; 2=often; 3=very often).

- Collected at baseline visit, middle and endpoint to assess the impact of treatment on ADHD symptoms, which often co-occur with pediatric bipolar disorder.

C. Brief Psychiatric Rating Scale (BPRS)

- The Brief Psychiatric Rating Scale (BPRS) is a common scale used to assess overall psychopathology (Overall & Pfefferbaum, 1982). The scale consists of 18 items; each rated on a scale from 1 (symptom not present) to 7 (symptom extremely severe).
- Collected at Baseline Visit and at endpoint to assess the impact of treatment on depression, anxiety hallucinations and unusual behavior, which often co-occur with pediatric bipolar disorder.

D. Social Responsiveness Scale (SRS)

- The SRS is a 65 item rating scale completed by the parent or guardian. This scale measures the severity of autism spectrum symptoms as they occur in natural social settings.
- Collected at Screening and Endpoint visits as assessment of symptoms and capacities associated with social interaction.

E. NIMH Clinical Global Improvement scale (CGI)

- The CGI is a measure of illness severity adapted for specific disorders. It allows rating of mania, depression and overall bipolar disorder illness, as well as other conditions frequently comorbid with bipolar disorder.
- The severity score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). The improvement score ranges from 1 (very much improved) to 7 (very much worse).
- Collected at Baseline Visit, at each of the weekly visits and at endpoint as an accepted measure of clinician rated improvement to assess the impact of treatment on bipolar disorder and other comorbid conditions.

F. Behavior Rating Inventory of Executive Function – Parent Form (BRIEF)

- The BRIEF is an 86-item rating scale to assess level of executive function deficits (Roth, Isquith, & Gioia, 2004). It is completed by the subject's parent/guardian.
- Collected at Baseline Visit and at the Week 12 visit for subjects who complete the study.

G. MGH Autism Spectrum Disorder Rating Scale (MGH-ASD-RS-I)

- This is a 37-item scale that asks informants to rate subjects on their social competence and abilities on a Likert scale from 0 to 6.
- Collected at Baseline and Endpoint visits.

Safety Measures

- Adverse Experiences: to record any adverse health events experienced during the study along with duration, severity, cause, remedy, and outcome.

- Columbia Suicide Severity Rating Scale (C-SSRS): to assess initial and emergent suicidality.

9. DATA ANALYSIS

A. Statistical Analysis

Considering our open-label single group design, we will rely on comparisons of the participants' performances at baseline (week 0) prior to the initiation of treatment relative to their scores at the last assessment (week 12). Thus, statistics for paired samples will be utilized. This design largely protects against the bias introduced by confounding factors. That is, since the same participants are tested on two occasions, all static confounding factors are perfectly balanced, and can have no impact on the findings. Bias can still result from time-varying factors that are not associated with the outcomes, but we are confident that any such factors will have a minimal impact on this study, considering the duration of the trial. Specifically, we will employ Wilcoxon signed rank tests for continuous or discrete outcome measures, and McNemar's test for binary outcomes. These tests are free from assumptions regarding the distribution of the outcome variables, which is appropriate since the scales we are proposing to utilize are not considered to have Gaussian distributions, and will not be amenable to parametric methods.

B. Power

As this is a single-arm, open-label study designed to demonstrate effectiveness and safety of NAC, formal power analyses are not warranted. For the purposes of an approximate power calculation, we used the two-sample t-tests as a proxy for the power of a Wilcoxon signed rank test. We used the responses we have observed in previous trials of other atypical neuroleptics to estimate effect sizes for the primary outcome measure (the Young Mania Rating Scale). Small and large effect sizes are estimated as mean reductions of 5 and 15 points, respectively. With 20 subjects and alpha set at 0.05, we estimate power to be 0.99 to detect small effects in YMRS scores (with a SD of 5) over the 12-week trial.

10. SAFETY

Consistent with good clinical practice, safety will be monitored by each subject's study clinician at each study visit. This clinician will be available 24 hours a day by page. The Principal Investigator will supervise all study activities including ratings, reported adverse events, laboratory tests, and vital signs. Subjects will be monitored for adverse events at each visit and adverse events will be recorded on an Adverse Events Form. Treatment-emergent adverse events will be monitored through changes in vital signs. All adverse events will be reported according to PHRC guidelines. Blood pressure, pulse, height, weight, and temperature will be recorded at each office visit.

Poor response to treatment will be measured by a CGI-bipolar score that is 2 points higher (more severe) than baseline for 2 weeks in a row or a YMRS score that is 30% higher than baseline for

2 weeks in a row, which may lead to drop from the study as determined by the clinician. Subjects with individual YMRS item scores of 8 on Item #8 (Content), or scores greater than 6 on Disruptive-Aggressive Behavior for 2 weeks in a row will be dropped from the study. In addition, drop from study will occur at clinician discretion for worsening of clinical course, non-compliance with treatment or inability to tolerate study treatment. Finally, the Columbia Suicide Severity Rating Scale (C-SSRS) will be administered weekly to assess initial and emergent suicidality in subjects. Subjects with scores of 4 or higher on the C-SSRS will be dropped from the study.

Having treated hundreds of bipolar patients, we are aware that this is a group of very highly disturbed children at risk for psychosis, suicide and disruption in the family. Although it is unlikely that these risks will be exacerbated by the protocol, we will be vigilant regarding the potential for patient decompensation or dangerousness to self or others. In the execution of research protocols, our primary concern is always the safety of the research participant. Dr. Wozniak has extensive experience in working with youth with severe psychopathology in clinical trials and in designing and implementing safety plans in these trials. Also, Dr. Wozniak is expert in the diagnosis and treatment of pediatric bipolar disorder and high-risk pediatric psychiatry patients in clinical settings. Given the especially unstable nature of bipolar spectrum subjects, we are available to handle clinical emergencies with subjects and their families at any time: at the time of visit, whether in person or over the phone, as well as between visits.

If needed, emergency evaluation and referral is available through coverage by the clinician-investigators on this study and through the Acute Psychiatry Service (APS) at the MGH. All subjects will have access to a 24 hour a day, 7-day week coverage provided by Dr. Wozniak or her designated substitute by pager for psychiatric emergencies. As part of the Massachusetts General Hospital, all research subjects can access the Acute Psychiatry Service (APS) in the emergency room at any time of the day or night. The APS is a well-staffed 24 hour/7 day per week emergency service for psychiatric emergencies.

11. CONFIDENTIALITY

All research-related records, initiated as a result of a subject's participation in this study that reveal the subject's identity, will remain confidential except as may be required by law. Subjects will only be contacted regarding future studies if they indicate that they are interested in being contacted by initialing in the specific section of the consent form.

If subjects agree on the Consent Form, we may share subjects' information with others within our research group for future research on emotional dysregulation or other related conditions. We will label all subjects' study materials with a code instead of their names. The study doctor will not share the key to code names with researchers outside of this institution.

12. MONITORING AND QUALITY ASSURANCE

The Principal Investigator is responsible for monitoring the safety and data of this trial. The PI will monitor adherence to the protocol, subject participation (e.g. tolerance to medication, drop-out rates, etc.), the risk-benefit ratio, and all Adverse Events throughout the course of the study. The IRB will be informed of any serious adverse events occurring during the trial. If at any time during the study more than 10% of the patients have had a serious adverse event, the study will be stopped. The primary concern of the investigators of this study is the safety of the subjects.

13. RISKS AND DISCOMFORTS

Potential side effects are few and will be monitored for throughout the research study. Consent forms will clearly list potential medication side effects. Since NAC is a derivative of a naturally occurring amino acid, it appears to have a low potential for unwanted side effects or negative effects on the child's growth and development. Although NAC is generally well tolerated, animal (but not human) subjects have developed pulmonary hypertension with high doses. Seizure with NAC has been reported in an accidental overdose of 39,207mg NAC in a 30-month-old girl, more than 10 times the dose she should have received. Seizure has not been reported with recommended dosing (Bailey, Blais, & Letarte, 2004)**.**

The most common side effects reported with use of NAC are gastrointestinal. Other less common side effects that have been reported include fatigue, nervousness, vivid dreams, heartburn, pruritus (without rash), and headaches (Berk, Copolov, Dean, Lu, Jeavons, Schapkaitz, Anderson-Hunt, Judd, et al., 2008; Ghanizadeh & Moghimi-Sarani, 2013; Gray et al., 2012; Hardan et al., 2012; Mardikian, LaRowe, Hedden, Kalivas, & Malcolm, 2007). Serious side effects are uncommon.

Other Adverse Events

Problems and side effects not listed above and not known at this time could occur. Subjects will be told of any changes in the way the study will be done and any newly discovered risks to which they may be exposed.

Answering detailed questionnaires may create a mild degree of inconvenience or emotional upset for the subjects. Interviewers will be trained to support the subjects who raise such concerns, and the PI will be available to respond to any concerns or to answer other questions about the study (available by pager 24 hours per day). All of the information about participants will be treated confidentially. Subjects may refuse to answer any of these questions.

Having treated hundreds of bipolar patients, we are aware that this is a group of very highly disturbed children at risk for psychosis, suicide and disruption in the family. Although it is unlikely that these risks will be exacerbated by the protocol, we will be vigilant regarding the potential for patient decompensation or dangerousness to self or others. In the execution of research protocols, our primary concern is always the safety of the research participant. Given the especially unstable nature of bipolar patients, we will be available to the study staff and to

patients and their families to handle clinical emergencies. The Massachusetts General Hospital has an active and well-staffed psychiatric emergency service that will be available to subjects if needed. This study has clearly defined exit criteria to ensure the safety of participants.

Protection Against Risk

Subjects' confidentiality will be protected throughout the study. Information about subjects and their families will be stored in research files identified only by a code. The code key connecting the participant's names to identifying information will be kept in a separate, secure location. Data in databases is similarly identified only by coded ID number and is password-protected. Data will not leave our institution in any form that would identify individual subjects or families. The information collected in our assessments and treatment outcome rating scales will not become part of the individual's hospital medical record. In the case that serious psychopathology (suicidality, homocidality, psychosis) is uncovered in the course of the research study, the Principal Investigator or appointed proxy will be immediately contacted by the clinician. All efforts will be made to alert parents of the subject and, if necessary, treating clinicians, of the circumstances to enable the subject to secure appropriate treatment. If needed, emergency evaluation and referral will be available through coverage by the clinician-investigators on this study and through the Acute Psychiatry Service (APS) at the MGH. The APS is a well staffed 24 hour/7 day per week emergency service for psychiatric emergencies. Subjects who do not respond to the study treatments will be dropped from the study using clear drop criteria ("patients may drop at any time due to patient preference, physician decision, need for psychiatric hospitalization or a poor response to treatment. Poor response to treatment leading to drop from the study will be measured by a CGI-mania score that is 2 points lower (more severe) than baseline for more than 2 weeks in a row, a YMRS score that is 30% higher than baseline for more than 2 weeks in a row"), or a C-SSRS score of 4 or higher.

14. POTENTIAL BENEFITS

To the Subject

The study will offer rapid access to treatment and provide subjects with a free detailed psychiatric and cognitive evaluation. Subjects will be provided with a potentially useful treatment, which has low risks associated with it.

To Others

The study will further our understanding of the treatment of bipolar disorder in children by testing a novel treatment, N-acetylcysteine. This study will also be useful in the testing of specific hypotheses about the efficacy of alternative treatments.

Importance of the Knowledge to be Gained

Little is known about the treatment of pediatric bipolar disorder, despite the fact that it is recognized as a significant public health concern. This study will further our knowledge regarding potentially useful treatments. As parents are often concerned about the effect of pharmaceutical agents on growth and development, this study examines the efficacy of a safe, alternative treatment that will be appealing to parents and children, due to its safety profile and benign side effect profile. From a scientific perspective, this study also furthers our understanding of the role of NAC in psychiatric disorders.

Table 1
Schedule of Events

Visit	99[1]	0[2]	1	2	3	4	5	6	7	8	9	10	11	12
Consenting														
Parental Consent & Child Assent	**X**													
Procedures														
Physical Examination	**X**													**X**
Vital Signs, Height, Weight	**X**	**X**	**X**	**X**	**X**	**X**				**X**				**X**
Cognitive Tasks														
Cognitive Tasks: IQ Measures (WASI-II or KBIT-2)	**X**													
Cognitive Tasks: EF Measures (WISC-IV or WPPSI-III)	**X**													**X**
Clinician Assessments/Rating Scales														
Clinician K-SADS-E (MDD, Mania)	**X**													
YMRS	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Mania Symptom Checklist		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
CGIs (Mania, Depression, Anxiety, ADHD, ODD, BPD)		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
CDRS	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
HAM-D	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
CSSRS	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
ADHD Rating Scale		**X**						**X**						**X**
BPRS		**X**						**X**						**X**
GAF		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse Events		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Concomitant Medications		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Parent Assessments/Rating Scales														
K-SADS Face Page	**X**													
CBCL	**X**													
FES	**X**													
SAICA	**X**													**X**
PQ-LES-Q		**X**												**X**
BRIEF Parent		**X**												**X**
SRS	**X**													**X**
MGH-ASD-RS-I		**X**												**X**

[1] 99 – Screening visit(s)

[2] 0 – Baseline visit

15. REFERENCES

Achenbach, T. M. (2000). *Manual for the Child Behavior Checklist/1-1/2-5*. Burlington, VT: ASEBA.

Achenbach, T. M., & Dumenci, L. (2001). Advances in empirically based assessment: revised cross-informant syndromes and new DSM-oriented scales for the CBCL, YSR, and TRF: comment on Lengua, Sadowksi, Friedrich, and Fischer (2001). *J Consult Clin Psychol, 69*(4), 699-702.

Aggarwal, S., & Burnett, P. (2013). Tardive dyskinesia with atypical antipsychotics in youth. *Australas Psychiatry, 21*(5), 507-508. doi: 10.1177/1039856213492864

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)*. Washington, D.C.: American Psychiatric Association.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (5th ed.)* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Bailey, B., Blais, R., & Letarte, A. (2004). Status epilepticus after a massive intravenous N-acetylcysteine overdose leading to intracranial hypertension and death. *Ann Emerg Med, 44*(4), 401-406. doi: 10.1016/S0196064404005451

Bearden, C. E., Hoffman, K. M., & Cannon, T. D. (2001). The neuropsychology and neuroanatomy of bipolar affective disorder: a critical review. *Bipolar Disord, 3*(3), 106-150; discussion 151-103.

Berk, M., Copolov, D., Dean, O., Lu, K., Jeavons, S., Schapkaitz, I., . . . Bush, A. I. (2008). N-acetyl cysteine as a glutathione precursor for schizophrenia--a double-blind, randomized, placebo-controlled trial. *Biol Psychiatry, 64*(5), 361-368. doi: 10.1016/j.biopsych.2008.03.004

Berk, M., Copolov, D. L., Dean, O., Lu, K., Jeavons, S., Schapkaitz, I., . . . Bush, A. I. (2008). N-acetyl cysteine for depressive symptoms in bipolar disorder--a double-blind randomized placebo-controlled trial. *Biol Psychiatry, 64*(6), 468-475. doi: S0006-3223(08)00500-3 [pii]
10.1016/j.biopsych.2008.04.022

Berk, M., Dean, O., Cotton, S. M., Gama, C. S., Kapczinski, F., Fernandes, B. S., . . . Malhi, G. S. (2011). The efficacy of N-acetylcysteine as an adjunctive treatment in bipolar depression: an open label trial. *J Affect Disord, 135*(1-3), 389-394. doi: 10.1016/j.jad.2011.06.005

Biederman, J., Birmaher, B., Carlson, G. A., Chang, K. D., Fenton, W. S., Geller, B., . . . Weller, E. (2001). National Institute of Mental Health Research Roundtable on Prepubertal Bipolar Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry, 40*(8), 871-878.

Biederman, J., McDonnell, M. A., Wozniak, J., Spencer, T., Aleardi, M., Falzone, R., & Mick, E. (2005). Aripiprazole in the treatment of pediatric bipolar disorder: A systematic chart review. *CNS Spectrums, 10*(2), 141-148.

Biederman, J., Mick, E., Bostic, J., Prince, J., Daly, J., Wilens, T., . . . Faraone, S. (1998). The naturalistic course of pharmacologic treatment of children with manic-like symptoms: A systematic chart review. *J Clin Psychiatry, 59*(11), 628-637; quiz 638.

Biederman, J., Mick, E., Spencer, T., Doyle, R., Joshi, G., Hammerness, P., . . . Wozniak, J. (2007). An open-label trial of aripiprazole monotherapy in children and adolescents with bipolar disorder. *CNS Spectr, 12*(9), 683-689.

Biederman, J., Mick, E., Wozniak, J., Aleardi, M., Spencer, T., & Faraone, S. V. (2005). An open-label trial of risperidone in children and adolescents with bipolar disorder. *J Child Adolesc Psychopharmacol, 15*(2), 311-317. doi: 10.1089/cap.2005.15.311

CANTABeclipse Test Administration Guide. (2004). Cambridge: Cambridge Cognition Limited.

Dean, O., Giorlando, F., & Berk, M. (2011). N-acetylcysteine in psychiatry: current therapeutic evidence and potential mechanisms of action. *J Psychiatry Neurosci, 36*(2), 78-86. doi: 10.1503/jpn.100057

Endicott, J., Nee, J., Yang, R., & Wohlberg, C. (2006). Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q): reliability and validity. *J Am Acad Child Adolesc Psychiatry, 45*(4), 401-407.

Gardos, G., & Cole, J. O. (1995). The evaluation and treatment of neuroleptic-induced movement disorders. *Harv Rev Psychiatry, 3*(3), 130-139.

Geller, B., Cooper, T., Sun, K., Zimerman, B., Frazier, J., Williams, M., & Heath, J. (1998). Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. *Journal of the American Academy of Child & Adolescent Psychiatry, 37*(2), 171-178.

Ghanizadeh, A., & Derakhshan, N. (2012). N-acetylcysteine for treatment of autism, a case report. *J Res Med Sci, 17*(10), 985-987.

Ghanizadeh, A., & Moghimi-Sarani, E. (2013). A randomized double blind placebo controlled clinical trial of N-Acetylcysteine added to risperidone for treating autistic disorders. *BMC Psychiatry, 13*, 196. doi: 10.1186/1471-244X-13-196

Gray, K. M., Carpenter, M. J., Baker, N. L., Desantis, S. M., Kryway, E., Hartwell, K. J., . . . Brady, K. T. (2012). A double-blind randomized controlled trial of N-acetylcysteine in cannabis-dependent adolescents. *Am J Psychiatry, 169*(8), 805-812. doi: 10.1176/appi.ajp.2012.12010055

Hardan, A. Y., Fung, L. K., Libove, R. A., Obukhanych, T. V., Nair, S., Herzenberg, L. A., . . . Tirouvanziam, R. (2012). A randomized controlled pilot trial of oral N-acetylcysteine in children with autism. *Biol Psychiatry, 71*(11), 956-961. doi: 10.1016/j.biopsych.2012.01.014

John, K., Gammon, G. D., Prusoff, B. A., & Warner, V. (1987). The Social Adjustment Inventory for Children and Adolescents (SAICA): Testing of a new semistructured interview. *J Am Acad Child Adolesc Psychiatry, 26*(6), 898-911.

Kaufman, A. S., & Kaufman, N. L. (2004). *Kaufman Brief Intelligence Test, Second Edition (KBIT-2)*. Circle Pines, MN: AGS Publishing.

Kim, J., Macmaster, E., & Schwartz, T. L. (2014). Tardive dyskinesia in patients treated with atypical antipsychotics: case series and brief review of etiologic and treatment considerations. *Drugs Context, 3*, 212259. doi: 10.7573/dic.212259

Kim, Y. K., Kim, L., & Lee, M. S. (1999). Risperidone and associated amenorrhea: a report of 5 cases. *Journal of Clinical Psychiatry, 60*(5), 315-317.

Kowatch, R. A., & DelBello, M. P. (2003). The use of mood stabilizers and atypical antipsychotics in children and adolescents with bipolar disorders. *CNS Spectr, 8*(4), 273-280.

Kowatch, R. A., Fristad, M., Birmaher, B., Wagner, K. D., Findling, R. L., & Hellander, M. (2005). Treatment guidelines for children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry, 44*(3), 213-235.

Kowatch, R. A., Suppes, T., Carmody, T. J., Bucci, J. P., Hume, J. H., Kromelis, M., . . . Rush, A. J. (2000). Effect size of lithium, divalproex sodium, and carbamazepine in children and adolescents with bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 39*(6), 713-720.

Leslie, D. L., & Rosenheck, R. A. (2004). Incidence of newly diagnosed diabetes attributable to atypical antipsychotic medications. *Am J Psychiatry, 161*(9), 1709-1711.

Lindenmayer, J. P., Nathan, A. M., & Smith, R. C. (2001). Hyperglycemia associated with the use of atypical antipsychotics. *J Clin Psychiatry, 62*(Suppl 23), 30-38.

Liu, H. Y., Potter, M. P., Woodworth, K. Y., Yorks, D. M., Petty, C. R., Wozniak, J. R., . . . Biederman, J. (2011). Pharmacologic treatments for pediatric bipolar disorder: a review and meta-analysis. *J Am Acad Child Adolesc Psychiatry, 50*(8), 749-762 e739. doi: 10.1016/j.jaac.2011.05.011

Magalhaes, P. V., Dean, O. M., Bush, A. I., Copolov, D. L., Malhi, G. S., Kohlmann, K., . . . Berk, M. (2011). N-acetylcysteine for major depressive episodes in bipolar disorder. *Rev Bras Psiquiatr, 33*(4), 374-378.

Mardikian, P. N., LaRowe, S. D., Hedden, S., Kalivas, P. W., & Malcolm, R. J. (2007). An open-label trial of N-acetylcysteine for the treatment of cocaine dependence: a pilot study. *Prog Neuropsychopharmacol Biol Psychiatry, 31*(2), 389-394. doi: S0278-5846(06)00357-5 [pii]
10.1016/j.pnpbp.2006.10.001

McElroy, S. L., Kotwal, R., Malhotra, S., Nelson, E. B., Keck, P. E., & Nemeroff, C. B. (2004). Are mood disorders and obesity related? A review for the mental health professional. *J Clin Psychiatry, 65*(5), 634-651, quiz 730.

Meltzer, H. Y. (2005). The metabolic consequences of long-term treatment with olanzapine, quetiapine and risperidone: are there differences? *Int J Neuropsychopharmacol, 8*(2), 153-156.

Miller, J. L., & Angulo, M. (2014). An open-label pilot study of N-acetylcysteine for skin-picking in Prader-Willi syndrome. *Am J Med Genet A, 164A*(2), 421-424. doi: 10.1002/ajmg.a.36306

Moos, R. (1985). Family Environment Scale. In J. V. Mitchell (Ed.), *The Ninth Mental Health Measurements Yearbook* (Vol. 1, pp. 573-575). Lincoln, NE: Buros Institute of Mental Measurements, University of Nebraska.

Orvaschel, H. (1994). *Schedule for Affective Disorders and Schizophrenia for School-Age Children Epidemiologic Version* (5th Edition ed.). Ft. Lauderdale: Nova Southeastern University, Center for Psychological Studies.

Overall, J. E., & Pfefferbaum, B. (1982). The Brief Psychiatric Rating Scale for Children. *Psychopharmacol Bulletin, 18*(2), 10-16.

Perlis, R. H., Welge, J. A., Vornik, L. A., Hirschfeld, R. M., & Keck, P. E., Jr. (2006). Atypical antipsychotics in the treatment of mania: a meta-analysis of randomized, placebo-controlled trials. *J Clin Psychiatry, 67*(4), 509-516.

Petty, R. G. (1999). Prolactin and antipsychotic medications: mechanism of action. *Schizophrenia Research, 35 Suppl*, S67-73.

Popli, A., Gupta, S., & Rangwani, S. R. (1998). Risperidone-induced galactorrhea associated with a prolactin elevation. *Annals of Clinical Psychiatry, 10*(1), 31-33.

Poznanski, E., Freeman, L., & Mokros, H. (1985). Children's depression rating scale-revised. *Psychopharmacology Bulletin, 21*(4), 979-989.

Regenold, W. T., Thapar, R. K., Marano, C., Gavirneni, S., & Kondapavuluru, P. V. (2002). Increased prevalence of type 2 diabetes mellitus among psychiatric inpatients with bipolar I affective and schizoaffective disorders independent of psychotropic drug use. *J Affect Disord, 70*(1), 19-26.

Rosenbloom, A. L. (2002). Increasing incidence of type 2 diabetes in children and adolescents: treatment considerations. *Paediatr Drugs, 4*(4), 209-221.

Roth, R. M., Isquith, P. K., & Gioia, G. A. (2004). Brief-A^{tm} Self report form: Psycholigcal Assessment Resources, Inc.

Sachs, G. S., Printz, D. J., Kahn, D. A., Carpenter, D., & Docherty, J. P. (2000). Medication Treatment of Bipolar Disorder 2000: Institute for the Advancement of Human Behavior, Inc. and Expert Knowledge Systems, LLC.

Sachs, G. S., & Thase, M. E. (2000). Bipolar disorder therapeutics: maintenance treatment. *Biological Psychiatry, 48*(6), 573-581.

Smaga, I., Pomierny, B., Krzyzanowska, W., Pomierny-Chamiolo, L., Miszkiel, J., Niedzielska, E., . . . Filip, M. (2012). N-acetylcysteine possesses antidepressant-like activity through reduction of oxidative stress: behavioral and biochemical analyses in rats. *Prog Neuropsychopharmacol Biol Psychiatry, 39*(2), 280-287. doi: 10.1016/j.pnpbp.2012.06.018

Sweeney, J. A., Kmiec, J. A., & Kupfer, D. J. (2000). Neuropsychologic impairments in bipolar and unipolar mood disorders on the CANTAB neurocognitive battery. *Biol Psychiatry, 48*(7), 674-684.

Turgay, A., Binder, C., Snyder, R., & Fisman, S. (2002). Long-term safety and efficacy of risperidone for the treatment of disruptive behavior disorders in children with subaverage IQs. *Pediatrics, 110*(3), e34.

Wagner, K. D., Weller, E., Carlson, G. A., Sachs, G., Biederman, J., Frazier, J., . . . Bowden, C. L. (2002). An Open-Label Trial of Divalproex in Children and Adolescents with Bipolar Disorder. *Journal of the American Acadamey of Child and Adolescent Psychiatry, 41*(10), 1224-1230.

Wechsler, D. (2003). *Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV)*. San Antonio, TX: The Psychological Corporation.

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV)*. San Antonio, TX: NCS Pearson, Inc.

Wechsler, D. (2011). *Wechsler Abbreviated Scale of Intelligence - Second Edition (WASI-II)*. Bloomington, MN: NCS Pearson, Inc.

Wechsler, D., & Sattler, J. M. (2002). *WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence*. San Antonio, TX: PsychCorp.

Witschi, A., Reddy, S., Stofer, B., & Lauterburg, B. H. (1992). The systemic availability of oral glutathione. *Eur J Clin Pharmacol, 43*(6), 667-669.

Wozniak, J. (in press). Alternative and Complementary Treatments. In A. Yildiz, P. Ruiz & C. Nemeroff (Eds.), *Bipolar Book: History, Neurobiology, and Treatment*. New York: Oxford University Press.

Wozniak, J., & Biederman, J. (1997). Childhood mania: insights into diagnostic and treatment issues. *Journal of the Association for Academic Minority Physicians, 8*(4), 78-84.

Wudarsky, M., Nicolson, R., Hamburger, S. D., Spechler, L., Gochman, P., Bedwell, J., . . . Rapoport, J. L. (1999). Elevated prolactin in pediatric patients on typical and atypical antipsychotics. *Journal of Child and Adolescent Psychopharmacoly, 9*(4), 239-245.

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry, 133*, 429-435.