

Protocol Title: A controlled trial of citalopram added to methylphenidate in youth with severe mood dysregulation

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Total requested accrual

160 Patients (separately describe patient groups)

Youth with bipolar disorder

0 Volunteers

Project Uses Ionizing Radiation: ☒ No ☐ Yes (attach *RSC/RDSC* documentation)

☐ Medically-indicated only

☐ Research-related only

☐ Both

IND/IDE ☒ No ☐ Yes (attach *FDA* documentation)

Drug/Device/# _____

Sponsor: _____

Durable Power of Attorney ☒ No ☐ Yes

Multi-institutional Project ☒ No ☐ Yes

Institution _____ FWA # _____

Date of IRB approval _____ (attach *IRB* documentation)

Data and Safety Monitoring Board ☐ No ☒ Yes

Technology Transfer Agreement ☒ No ☐ Yes

Agreement type and number _____ Expiration Date _____

Confidential Disclosure Agreement ☒ No ☐ Yes

Samples are being stored ☒ No ☐ Yes

Table of Contents

Section	Page
I. Précis	4
II. Introduction/ Scientific Rationale and Hypothesis	5
III. Subjects	8
A. Inclusion criteria	8
B. Exclusion criteria	8
IV. Study Design and Methods	9
A. Study overview	9
B. Recruitment	9
C. Screening methods	10
D. Study design	10
E. Study procedures	11
F. Termination procedures	13
G. Follow-up procedures	14
V. Risks/ discomforts	15
VI. Subject monitoring	17
VII. Outcome measures	17
VIII. Statistical Analysis	18
IX. Human Subjects Protection	19
A. Subject selection	19
i. Statement of equitability	
B. Justification for inclusion of children	19
C. Safeguards for Vulnerable Populations	19
D. Justification for use of placebo and medication withdrawal	19
E. HPSU team participation	20
F. Qualifications of investigators	20
X. Benefits	20
XI. Summary/classification of risk	21
XII. Consent documents and process	21
XIII. Data and Safety monitoring	23
XIV. Quality Assurance	24
XV. Adverse event reporting	24
XVI. Alternatives to participation or alternative therapies	24
XVII. Privacy	24
XVIII. Confidentiality	25
XIX. Conflict of Interest/ Technology Transfer	25
XX. Compensation	25
XXI. Pharmaceutical Information	25
XXII. References	30
XXIII. Attachments/Appendices	
A. Flow sheets (Figures 1)	Attached
B. Appendix B: CTDB Description	Attached
C. Recruiting advertisements	to be appended for IRB
XXIV. Consent forms	

- | | |
|--|------------------------|
| A. Consent form for patient's parent or guardian | to be appended for IRB |
| B. Assent form for patient | to be appended for IRB |

I. PRECIS

i. Objective: To test the efficacy of citalopram plus methylphenidate vs. placebo plus methylphenidate in decreasing irritability in youth with severe mood dysregulation.

ii. Study population: Youth ages 7-17 with severe mood dysregulation (SMD). SMD is characterized by non-episodic, impairing irritability (defined as increased reactivity to negative emotional stimuli at least 3 times/week and angry or sad mood, most days, most of the time, noticeable to others) and hyperarousal (three of: distractibility, intrusiveness, pressured speech, racing thoughts, agitation, insomnia), with onset before age 12 for at least a year. Many of these children receive the diagnosis of bipolar disorder (BD) in the community, although they do not meet DSM-IV criteria for BD because of the lack of distinct manic episodes.

iii. Design: Medication withdrawal, followed by a 5-week dose stabilization phase of methylphenidate and an 8-week double-blind, placebo-controlled treatment trial of citalopram plus methylphenidate vs. placebo plus methylphenidate. There will also be optional open treatment at the end, so that all patients have the opportunity to have a total of up to 10 weeks of citalopram plus methylphenidate. The target dose of citalopram will be 20-40 mg/day.

iv. Outcome measures: The primary outcome measures will be the Aberrant Behavior Checklist Irritability subscale and the CGI-I.

II. INTRODUCTION/SCIENTIFIC RATIONALE AND HYPOTHESIS

Few effective treatments are available for children with severe irritability (Brotman et al in press); developing such treatments is important given the prevalence of severe mood dysregulation (see below for definition) and disruptive mood dysregulation disorder in clinical (Martin et al in press), as well as epidemiological (Althoff et al 2016; Copeland et al 2013; Brotman et al 2006) samples. Moreover, high levels of childhood irritability predict increased risk for suicidality (Pickles et al 2010; Conner et al 2004) and functional impairment in adulthood (Copeland et al 2014; Stringaris et al 2009; Vidal-Ribas et al 2016). Although irritability is among the most common reasons that children are brought in for psychiatric care, pharmacological studies for irritability are only beginning to emerge.

There are no solidly established treatments for severe mood dysregulation. One unblinded study of stimulants (Blader et al 2016), and one double blind placebo controlled trial in adults used selective serotonin reuptake inhibitors (SSRIs) (Coccaro et al 2009; Kim et al 2016) and suggested potential benefit. One small double blind placebo controlled trial of divalproex also has appeared (Blader, et al 2009). The use of antipsychotics in youth has been increasing over the past several decades (Olfen et al 2015), which are non-specific, associated with significant health risks, and side effect burden (Correll & Blader 2015). Using atypical antipsychotic agents, one open trial (Kreiger et al 2011) and one using a randomly assigned, double blind design (Gadow et al, 2014) suggested short term, limited benefit in the treatment of aggression and irritability. Indeed, reviews continue to call for more randomized controlled trials in youth with severe irritability (Benarous et al 2017; Tourian et al 2014).

A. Severe Mood Dysregulation

The term “Severe Mood Dysregulation (SMD)” identifies a group of children and adolescents presenting with a pattern of prominent, chronic, extreme irritability. This entity, occurring in more than 3% of children and adolescents in the community (Brotman et al., 2006), was identified in the context of research on pediatric bipolar disorder (BD). SMD was identified in an attempt to facilitate research on the long-debated nosological status of youth with chronic severe irritability as a potential phenotype related to BD (Leibenluft, Charney, Towbin, Bhangoo & Pine, 2003). The core clinical characteristics of SMD are persistent, non-episodic irritability/anger or sadness, symptoms of hyper-arousal, and increased reactivity to negative emotional stimuli in the form of temper outbursts. The unbroken course of symptoms of SMD contrasts with the episodic nature of BD (Leibenluft et al., 2003). SMD must begin before age 12, persist for at least a year, and cause significant impairment. Children with SMD meet criteria for several DSM-IV disorders, with rates of ADHD and ODD in excess of 80%; high rates of anxiety (63.3%), and moderate rates of lifetime major depressive disorder (20%) (Brotman et al., 2007). Importantly, despite only moderate concurrent or past comorbidity with MDD, two longitudinal community studies each found that children with SMD faced high risk for depressive disorders but not BD in early adulthood (Brotman et al., 2006; Leibenluft et al. 2006).

Beyond these longitudinal data, other research distinguishes SMD from DSM-IV BD. Children with BD are significantly more likely to have a parent affected with BD, compared to those with SMD (Brotman et al., 2007). Moreover, children with BD and SMD differ in the neural processing of some, although not all, affective stimuli (Dickstein et al., 2007, Guyer et al., 2007, Rich et al., 2007).

Whilst converging evidence from clinical course, family history, and pathophysiology differentiate SMD from BD, many children with chronic irritability may be receiving the diagnosis of BD in the community, although they do not have discrete episodes and thus do not meet DSM-IV criteria for the illness. A recent study (Moreno et al., 2007) found that annual rates of BD in the clinic have increased 40-fold in less than a decade. The increase has occurred most markedly in boys with comorbid ADHD, characteristics of SMD. Furthermore, data from children screened at the NIMH-IRP for Protocols 00-M-0198 and 02-M-0021, show that the majority of children meeting criteria for SMD are classified as BD in the community, whilst only about 20% of children referred to our studies with a community diagnosis of BD meet diagnostic criteria for the disorder.

These findings have significant treatment implications: to the extent that youth with SMD suffer from DSM-IV ADHD, anxiety disorders, and/or depression (Brotman et al., 2007, Brotman et al., 2006), the indicated treatment is Serotonin Reuptake Inhibitors (SSRIs) and/or stimulants, two medications that are relatively contraindicated in BD because of concerns about precipitating mania (Baumer et al., 2006, Goldberg et al., 2007). The only controlled trial in SMD, conducted under our protocol 02-M-0021, compared lithium, effective in BD, to placebo; the trial found no evidence for efficacy of lithium treatment. This, too, suggests an important difference between SMD and BD, while further emphasizing the need for research on therapeutics in SMD. Our experience screening youth for inclusion in 02-M-0021 indicates that a large majority of SMD patients are treated for their putative BD with antipsychotic and/or mood stabilizing medication. Both classes of medication are used conventionally to treat BD and are associated with relatively serious adverse effects. The inferior response of many SMD patients to these agents illustrates the need for more effective treatments beyond those typically used in BD. Indeed, in our experience, youth with SMD appear to be receiving medications that are both ineffective and have a higher side-effect burden than the first-line medications previously shown to benefit their DSM-IV diagnoses (i.e., ADHD, anxiety, depression). The latter treatments have been avoided in the community, due to fears of exacerbating symptoms of BD, while data from our group suggest that most of these youth do not, in fact, exhibit symptoms warranting the diagnosis of BD. Thus, major questions remain on best treatment practices for SMD. In youth with SMD, treatments appropriate for BD may provide minimal benefit and high side-effect burden; treatments appropriate for non-BD mood, anxiety, or disruptive behavior disorders have typically been avoided, but may provide benefit. The potential public health significance of addressing these questions becomes clear when considering the high prevalence of SMD in the community (3.2%, Brotman et al., 2006).

B. Serotonin Reuptake Inhibitors and SMD

As noted above, SMD youth have high rates of current irritability and anxiety, as well as high lifetime rates of MDD, three problems previously shown to be targeted by SSRIs. Despite only moderate evidence of efficacy in pediatric MDD, SSRIs are considered the first-line treatment for this syndrome (McClellan, Kowatch & Findling, 2007), with a recent meta-analysis demonstrating that both children and adolescents achieve significantly better overall response to SSRIs than placebo after 12 weeks of treatment (Hetrick, Merry, McKenzie, Sindahl & Proctor, 2007). SSRIs are also the medication of choice in pediatric anxiety disorders (Connolly & Bernstein, 2007) with several placebo-controlled studies demonstrating their benefit (Wagner et al., 2004, RUPP, 2001, Birmaher et al., 2003). Here,

the effect size is larger than seen in MDD, further suggesting the possible utility of SSRIs in SMD, given the very high rates of anxiety in SMD youth. Moreover, data from SSRI trials in both pediatric MDD and anxiety suggest that SSRIs target irritability in children, core features of SMD. In light of these observations, the absence of data on the utility of SSRIs in SMD appears quite remarkable.

Data in adults also suggest the potential utility of SSRIs in the treatment of irritability (Bond, 2005). Specifically, RCTs indicate that SSRIs improve anger symptoms in adults presenting with anger concomitant to MDD (Bond, 2005; Fava et al., 1996; Fava et al., 1993). Similar findings emerge in Borderline Personality Disorder, associated with extreme levels of anger (Binks et al., 2006).

Use of SSRI's in youth with SMD introduces concerns about increased suicidal thinking and medication-induced switching into mania. Recently, the FDA imposed a "black-box" warning for increased suicidal thinking in youth treated with SSRI's. Data from the FDA indicate that the risk, while statistically significant in large samples, is quite small, roughly 2%, in absolute magnitude. On initial review, there was concern about particularly high rates of adverse outcomes with paroxetine and venlafaxine. However, more detailed analysis suggests that rates of adverse behavioral effects are similar for all SSRIs (Hamad et al., 2006). Importantly, the level of clinical monitoring that our subjects will receive far exceeds standard care and the recommendations by the FDA as part of the black-box warning.

Regarding SSRI-induced mania, data from our lab, cited above, suggest that there may be significant, fundamental pathophysiological differences between SMD and BD. Therefore, it has not been established that youth with SMD have the elevated risk for SSRI-induced mania shown by BD youth. In addition, data in adults suffering from bipolar depression treated with SSRIs suggest that the rate of manic switches is low (Amsterdam & Shults, 2005; Nemeroff et al., 2001) and may be equal to that observed with placebo (Gijsman, Geddes, Rendell, Nolen & Goodwin, 2004).

Five SSRIs have been used to treat anxiety or MDD in children and adolescents, although only three are viable for treatment of SMD. Considerable data document efficacy with fluoxetine. However, fluoxetine's long half-life is a concern because any severe adverse effects could persist for weeks after stopping it. Similarly, paroxetine seems a less desirable choice because high rates of adverse outcomes have been reported (Keller et al., 2001). This leaves fluvoxamine, sertraline, and citalopram. Studies in pediatric anxiety document efficacy for fluvoxamine, and there are relatively few data for sertraline or citalopram. The opposite applies to MDD, where positive RCTs have used citalopram or sertraline but not fluvoxamine. Given the prominence of depressive symptoms in the presentation and subsequent outcome of youth with SMD, available data provide support for considering either citalopram or sertraline. Ultimately, one can justify the choice of citalopram over sertraline because the former shows greater pharmacological specificity and fewer drug-drug interactions.

C. SMD, comorbidity with ADHD, and treatment with stimulants

As noted above, approximately 90% of those with SMD meet DSM-IV criteria for DSM-IV ADHD (Brotman et al., 2007) and preliminary evidence suggests that impairing sub-threshold symptoms of ADHD are present in the rest. In this protocol, all patients will receive treatment with methylphenidate, to target these symptoms, which will then be

supplemented by the addition of citalopram vs. placebo, to determine the degree to which citalopram provides benefits for mood and anxiety symptoms, beyond placebo. Based on our experience treating SMD youth openly and in the context of the lithium trial conducted under 02-M-0021, we have concluded that ADHD symptoms are so prominent in this population that it will be difficult to discern improvement in other domains (specifically, irritability) without first treating their ADHD. Indeed, given the effectiveness of stimulant medication and its use as a first line to treat ADHD symptoms (Pliszka, 2007), we routinely offer this treatment to youth with SMD. Thirty-four of 52 (65%) children we have treated at the NIH were placed on stimulant medication (3/34 received only atomoxetine) at discharge. No adverse events were encountered during their open treatment with these agents during inpatient hospitalization or day treatment. In our experience, treatment with methylphenidate (MPH) is well-tolerated in youth with SMD, and their ADHD symptoms respond. Our experience is consistent with data from two studies (one placebo-controlled) indicating that, among children with ADHD and mood symptoms similar to those of SMD (e.g., “mania-like symptoms” or “multi-morbid ADHD”), the response of their ADHD symptoms to methylphenidate is as robust as that of youth with ADHD but no mood symptoms (Galanter et al., 2003; Carlson et al., 2003). Indeed, in youth with ADHD, data indicate that irritability may even be decreased somewhat by treatment with stimulants (Carlson et al., 2000; Galanter et al., 2003).

Specific Aim:

To demonstrate that citalopram plus methylphenidate will be more effect than placebo plus methylphenidate in decreasing irritability in youth with SMD.

Primary Hypothesis:

SSRIs will reduce irritability and be well tolerated in children and adolescents with SMD who are treated concurrently with stimulant medication.

III. Subjects

Description of Study Population:

Up to 160 children age 7-17 who are diagnosed with SMD will be recruited in order to reach a total of 80 randomized participants. Those who withdraw or are withdrawn prior to randomization will be replaced.

A. Inclusion criteria (all must be met): These are based on the criteria for severe mood dysregulation (SMD) outlined in Leibenluft et al., 2003.

1. Ages 7-17
2. Abnormal mood (specifically, anger, sadness, and/or irritability), present at least half of the day most days, and of sufficient severity to be noticeable by people in the child’s environment (e.g. parents, teachers, peers).
3. Hyperarousal, as defined by at least three of the following symptoms: insomnia, agitation, distractibility, racing thoughts or flight of ideas, pressured speech, intrusiveness
4. Compared to his/her peers, the child exhibits markedly increased reactivity to negative emotional stimuli that is manifest verbally and/or behaviorally. For example, the child responds to frustration with extended temper tantrums (inappropriate for age and/or

precipitating event), verbal rages, and/or aggression toward people or property. Such events occur, on average, at least three times a week

5. Criteria 2, 3, and 4 are currently present and have been present for at least 12 months without any symptom-free periods exceeding two months.

6. The onset of symptoms must be prior to age 12 years.

7. The symptoms are severe in at least in one setting (e.g. violent outbursts, extreme verbal abuse, assaultiveness at home, school, or with peers). In addition, there are at least mild symptoms (distractibility, intrusiveness) in a second setting.

8. Currently in treatment with a psychiatrist for the symptoms.

9. The child is failing his/her treatment. To meet this criterion:

- i. The child's current CGAS score must be ≤ 60 .
- ii. The child's psychiatrist/treater must agree that the child's response to his/her current treatment is no more than minimal. According to this criterion, it would be clinically appropriate to change the child's current treatment.
- iii. On the basis of record review and interviews with child and parent, the research team agrees that the child's response to his/her current treatment is no more than minimal.
- iv. The child has a score of > 12 on the irritability subscale of the Aberrant Behavior Checklist.

B. Exclusion criteria:

1. As assessed in the mania section of the K-SADS-PL, the individual exhibits any of these cardinal bipolar symptoms in distinct periods lasting more than 1 day, and therefore meets criteria for bipolar disorder not otherwise specified:

- i) Elevated or expansive mood
- ii) Grandiosity or inflated self-esteem
- iii) Decreased need for sleep
- iv) Increase in goal-directed activity (this can result in the excessive involvement in pleasurable activities that have a high potential for painful consequences)

2. Meets criteria for schizophrenia, schizophreniform disorder, schizoaffective illness, more than mild PDD, or PTSD.

3. Meets criteria for substance use disorder in the three months prior to randomization.

4. IQ < 70

5. The symptoms are due to the direct physiological effects of a drug of abuse, or to a general medical or neurological condition.

6. Currently pregnant or lactating, or sexually active without using a barrier method of contraception.

7. Failed an adequate trial (defined as four weeks of consecutive treatment at the minimally effective) or severe ill effects while on citalopram (at least 20 mg) or escitalopram (at least 10 mg).

8. Hypersensitivity or severe adverse reaction to methylphenidate

9. A history of serious adverse reactions (psychosis, severely increased activation compared to baseline) to methylphenidate or amphetamines.

10. Any chronic medical condition that requires medications that are contraindicated with SSRIs or methylphenidate, or any serious chronic or unstable medical disorder.
11. Medical contraindications to treatment with SSRI or stimulant (e.g. liver, seizure, renal, platelet disorder).
12. NIMH employees and staff and their immediate family members will be excluded from the study per NIMH policy.

IV. STUDY DESIGN AND METHODS

A. Study overview

This is a double-blind study of methylphenidate plus placebo vs. methylphenidate plus citalopram in pediatric patients with SMD. The study consists of four phases (Phases 1-4, Fig. 1): medication withdrawal (duration flexible), medication-free period (one week), initiation of optimal methylphenidate dose (five weeks), and an add-on trial of randomly-assigned citalopram vs. placebo (in addition to methylphenidate; 8 weeks). There will also be optional open treatment at the end (Post Trial Open Treatment, Fig. 1). The duration of the latter will be such that all patients have the opportunity to have a total of up to 10 weeks of citalopram. The target dose of citalopram will be 20-40 mg/day, titrated using a fixed-flexible design. With such a design, dose is increased to 40 mg unless symptoms remit or adverse effects occur. The primary outcome measures will be the Aberrant Behavior Checklist Irritability subscale and the CGI-I. The blind will be broken after each patient's treatment. Children will be invited to also enroll in 02-M-0021, which provides for structural and functional MRI scanning, MEG scanning, behavioral testing, and longitudinal follow-up.

B. Recruitment

Patients will be recruited nationwide through mailings to selected physicians, internet postings on the NIMH website, announcements in newsletters, contacts with support groups, and postings to listservs. Travel expenses for the patient and accompanying parent will be reimbursed. Travel and lodging assistance will be available for every-other-weekend visits for one parent while the patient is hospitalized.

Recruitment efforts for minority subjects will be enhanced with additional measures. Current recruitment strategies will continue because of the widespread nature of the current outreach into the community which will expose the study to minority as well as majority populations due to the diverse nature of the Washington DC metropolitan area. As noted, increased attempts ought to be made in the hopes of enrolling a more diverse population. Outreach is currently planned into very rural communities. A concerted effort will also be made to highlight this study to the Latino population in Montgomery County through the Up County Latino network. Relationships can also be strengthened with the adult bipolar disorder researchers at NIMH, which also runs a Hispanic Initiative program, with the goal of cross-referrals. Additional efforts can be increased with outreach and presentations in Prince George's county and other local areas with increased diversity samples. Local adoption support agencies often service international adoption families, and specific outreach will be made to these agencies.

NIH Employees and staff will not be directly recruited by or through their supervisors or co-workers to participate in this study.

C. Screening methods

Preliminary Screening: Consent forms and other information about the study will be mailed to prospective participants who express interest. Prospective subjects will be screened initially by a clinician, who will use a semi-structured telephone interview to assess the child's clinical course and treatment history. After the initial telephone interview, appropriate records (medical, psychiatric, etc.) will be requested for individuals deemed to be potential candidates, and the patient's treating psychiatrist will be consulted.

On-Site Screening (one-two days): After the preliminary screening, those youth who appear to qualify for inclusion will be invited to NIMH for a comprehensive medical and psychiatric evaluation under the MAP omnibus Screening Protocol 01-M-0254 (P.I. Dr. Carlos Zarate). Parents and children will participate in clinical and semi-structured psychiatric interviews (K-SADS-PL). Parents and patients will also receive the standardized interview module that we developed to identify children who meet the criteria outlined in Appendix A. Parents will complete the Autism Screening Questionnaire, the Social Responsiveness Scale (SRS), and the Children's Communication Checklist, so that children with probable PDD can be identified and, if symptoms are severe, excluded from the protocol. At the end of these assessments, a consensus decision will be reached as to whether or not the child meets inclusion criteria.

D. Study design

The anticipated duration of the study (exclusive of open treatment at the end) is approximately 12-15 weeks, depending on the time required for medication discontinuation (Figure 1). This time frame includes five phases: 1) medication withdrawal (duration flexible, depending on the patient's medication at admission), 2) medication free period (one week), 3) open treatment with methylphenidate (up to 5 weeks), 4) a randomized trial of citalopram plus methylphenidate vs. placebo plus methylphenidate (8 weeks), and 5) open treatment as indicated in preparation for return to community care. Specifically, those patients who responded to citalopram will be offered an additional 2 weeks of open treatment. For those who received placebo and they and their parents wish to have an open trial of citalopram, we will offer 8 weeks of initiation and open outpatient citalopram treatment, followed by an additional 2 weeks, if they respond. In this way, all study participants will have the opportunity to receive a total of 10 weeks of citalopram treatment. Patients who did not respond to citalopram, or those who do not wish to have a trial of this medication, will be offered 2-4 weeks of open treatment with the medication(s) that, in the treatment team's judgment, are most likely to benefit the child.

Medication withdrawal, the medication-free week, the methylphenidate open trial, and initial dose stabilization using citalopram/placebo will occur while patients are either hospitalized or attending the Behavioral Health Day Treatment Center. The decision between these two treatment settings will depend on whether children live locally and on their clinical status. We considered restricting the medication withdrawal phase of the study only to an inpatient trial. However, previous experience suggests that recruitment will be facilitated, increasing feasibility, by offering both inpatient and Day Treatment options. Moreover, our prior experience also suggests that the similarities between these two options,

in terms of overall level of care or supervision provided and the opportunities for staff observation of the patient, are much greater than the differences. During the 8-week citalopram/placebo trial and subsequent open treatment, patients can be hospitalized, in day treatment, or outpatients, according to what is clinically appropriate. This decision will be made based on the child's current clinical status, previous history, and living situation. We considered limiting this to inpatient or day treatment, but believe that this option would involve an unnecessary degree of restriction for the patients, including an extended time away from home. We also wish to adhere to the clinical guideline that children should be treated in the least restrictive setting capable of meeting their needs. For those subjects who live locally and are too unstable to conduct the trial as an outpatient, the option of day treatment or hospitalization is available. For those who live outside the metropolitan area and are too unstable for outpatient care, hospitalization will be available. In addition, patients who begin the trial as outpatients but whose clinical status deteriorates can be re-hospitalized or enter day treatment and continue in the trial. However, those patients who are stable enough to do so will be allowed the less restrictive alternative of outpatient status. For outpatients, close monitoring will be provided via telephone contact and clinic visits, as detailed below, and an on-call physician will be available.

E. Study procedures

At the beginning of the study, children will be evaluated to determine whether their clinical needs during the medication withdrawal, medication-free, methylphenidate, and dose stabilization phases are best met with day treatment (this is an option only for those who live within a 50 mile radius of the NIH Clinical Center) or inpatient treatment. They will be admitted to either the Day Treatment or Pediatric Behavioral Health Unit at the NIMH and gradually withdrawn from their medication, as clinically tolerated, over a 1 to 6 week period. The Day Treatment Center is on the child psychiatry inpatient unit; the hours are approximately 8:00 a.m.-4:00 p.m. five days a week. Day treatment patients whose clinical status deteriorates can be hospitalized and continue in the protocol.

Upon admission to the hospital or Day Treatment program, patients will receive a physical examination. Blood will be drawn for CBC, thyroid and liver function tests, HIV and Hepatitis B testing, and electrolytes. Urine will be obtained for urinalysis, toxicology screen, pregnancy (in pubertal girls) and creatinine clearance, and an EKG will be performed.

The duration of the medication withdrawal phase will depend on the pharmacological agents and doses the patient has been receiving prior to admission. However, this phase will not exceed 8 weeks. We will draw on our considerable prior experience with medication withdrawal among pediatric bipolar patients, as implemented in protocols 00-M-0198 and 02-M-0021. Thus, each patient's withdrawal schedule will be tailored to their regimen and the duration will be guided by clinical considerations. In general, stimulant and antidepressant medication will be tapered more rapidly than will mood stabilizing and antipsychotic medications. However, exceptions are expected such as when children are receiving antidepressants associated with withdrawal symptoms (e.g. paroxetine) which will be tapered more gradually than other antidepressants or agents with very long half-lives (e.g. aripiprazole). The medication withdrawal phase will continue until the patient has been free of medication for 5 half-lives in order to eliminate the direct effects of any current psychotropic agents on mood symptoms. At the end of the medication withdrawal phase, all patients will have a one-week medication-free period to assure elimination of all

psychotropic medications. All patients will be concurrently enrolled in protocol 02-M-0021 and some research tasks may be obtained during the medication-free period under this concurrent protocol.

After medication withdrawal, patients will be given methylphenidate 5, 10, 15, or 20 mg at 8 AM and 1 PM or the equivalent in an extended release form. The treating clinicians will have up to 5 weeks to determine the optimal dose. The maximal dose will be 80 mg or 2 mg/kg whichever is smaller. Clinical worsening will be defined as a rating of "8" ("much worse") or greater on the CGI-I, or a clinically significant adverse event. Those experiencing significant worsening or significant improvement ("2" or "very much improved") will be withdrawn from the study, stabilized clinically (as needed) and discharged to care in the community. All patients will be invited to enroll in 02-M-0021 and participate in the longitudinal follow-up study, even if they are ineligible for randomization.

Those children who, on stimulant medication, still meet inclusion criteria will be randomized to receive add-on citalopram or placebo using double-blind procedures in a 1:1 ratio. While all patients will undergo the citalopram/placebo dose stabilization phase while hospitalized or in day treatment, at the beginning of this dose stabilization phase a preliminary decision will be made as to whether the patient is likely to undergo the subsequent 8-week citalopram/placebo trial as an inpatient, day treatment patient, or outpatient. The patient's research physician, primary NIMH clinician who performs mood ratings, and nursing staff will be blind to treatment assignment.

The duration of the citalopram/placebo trial is 8 weeks. The goal for citalopram will be to reach a dose between 20 and 40 mg/d. The dose of citalopram/placebo will begin at 5 mg daily and increase to 10 mg after five doses. Thereafter, dosage will increase by 5 mg every 5 days until reaching 20 mgs (Day 15). After one week at 20mg/d (Day 22), patients will be discharged to outpatient or Day Treatment status if clinically appropriate. Outpatients will be seen in clinic on approximately Days 29 and 43 and will be contacted routinely by a clinician on the alternate weeks, so that there is weekly clinical contact. On approximately Day 29, when the child is seen in clinic, a dose of 30 mg/d may be prescribed if clinically appropriate, and two weeks subsequently (when the child is seen in clinic on approximately Day 43) the dose may be increased to 40 mg if clinically appropriate. The maximum dose for the study will be 40 mg. Patients in both the placebo and treatment groups will receive study pills once daily. Dosage adjustments will be also be made as needed to minimize side-effects.

During the treatment trial, a patient's level of care (inpatient, day treatment, outpatient with weekly clinical contact) will be determined on clinical grounds by the treatment team. There will be a physician on call for the study at all times should parents need to contact staff. Outpatients or day treatment patients whose clinical status deteriorates so that they require hospitalization will be admitted for clinical stabilization, but they will not be discontinued from the trial. If they continue to deteriorate in the hospital they will be withdrawn from the trial and treated clinically until they can be safely transferred to care in the community.

For both inpatients and outpatients, every other week ratings will consist of the CGI-I, Aberrant Behavior Checklist (ABC), CGAS, CDRS, combined WASH-U-K-SADS and Young Mania Rating Scales, Brief Psychiatric Rating Scale for Children (BPRS-C) (where

positive psychotic symptoms are noted), Pediatric Anxiety Rating Scale (PARS), the Treatment Emergent Symptom Scale, blood pressure, pulse, and weight. The Treatment Emergent Symptom Scale will be administered by a different clinician than the one who completes clinical rating scales. For both inpatients and outpatients, the primary clinician will make a best-estimate rating on each scale, based on direct interview of the child, and on interview with parent (in the case of outpatients and day treatment patients) and/or nurses (in the case of inpatients and day treatment patients). Inpatients and day treatment patients will also be rated weekly by nurses using the Overt Aggression Scale, and the Direct Observation Form, and ward teachers will complete the Conners 10-item Abbreviated Teachers Rating Scale (ABTRS) on school days and the 39-item Conners Teacher Rating Scale (CTRS) weekly. Research data will be collected and stored using the NIH Clinical Trials Survey System (CTSS) and the Clinical Trials Database (CTDB). This allows parents and children to log in to a secure, password-protected website and directly enter responses to questionnaires and checklists, or enter their responses while at NIH using a wireless-device interface to access the NIH-intranet secure CTDB. The security features and operation of CTDB are described in Appendix D.

Those patients who are treated as inpatients will be confined to the grounds of the NIH, unless approved to travel off the grounds by the medical staff. If patients are approved to travel off the NIH grounds, a staff member or adult relative must accompany them.

E. Termination procedures

Throughout the study, the Principal Investigator will request that an independent evaluator, not connected to the protocol, review any case that shows clinical worsening, or a serious clinically significant adverse event. Clinical worsening during the washout period is defined as a CGI-I rating of “8” (“much worse”) or greater for two consecutive weeks, and during the randomized period as a rating of “8” (“much worse”) or greater, or a drop in the CGI-I rating of 2 or more points, for three consecutive weeks. This CGI-I will compare current function to the more impaired of two “baseline” ratings (one baseline rating is obtained prior to admission, the other after cessation of medication). As discussed in more detail below, comparing current function to the more impaired of these two baseline ratings allows us to not terminate a patient whose condition may have worsened in the course of the hospitalization but who is still functioning at a level superior to that prior to his/her entry into the study. In addition, use of lorazepam PRNs in excess of 4 mg/d for more than one day will prompt review by an independent evaluator. Results of the review will be discussed with the patient and his/her family. As always, families are free to discontinue the trial at any point. Also, independent evaluations may be requested by the research team or by the HSPU team (via a member attending the weekly multidisciplinary meetings).

If clinical worsening occurs, the one week medication-free phase may be shortened and the child advanced more rapidly to randomized treatment. Clinical worsening will be defined as above.

An independent evaluator may recommend a range of actions. Worsening during the period when medication is being discontinued may lead to truncation of the washout period and passage to the randomized period, or more frequent monitoring. Worsening during the randomized period may lead to removal from the study, closer monitoring and re-assessment, or continuation without further changes. In all cases, the subject’s safety will be the first priority; a conservative standard will be applied in deciding whether a child should continue

in the study. Only after a patient is removed from the study will the blind be broken. At this point, appropriate clinical care will be provided to stabilize and return the patient to the community psychiatrist who provided care prior to the subject's enrollment in the trial. Treatment will be guided by what is considered "best clinical interest." A patient who received only placebo will be offered an open trial of citalopram.

In our opinion, it is reasonable to allow children who are "much worse" to have a review of their course rather than immediate removal from research. In our experience, it is common for children with SMD to have brief but severe occurrences of explosive behavior, anxiety, or angry mood. These behaviors and mood shifts are sufficient to influence weekly ratings, and sometimes occur in response to events quite remote from the unit and patient (e.g. marital disputes, an absent parent suddenly surfacing, etc). Accordingly, a period of observation is needed to determine whether the observed deterioration will persist and, in that sense, is clinically meaningful. If subjects were discharged from the trial immediately, there is a significant risk that we will exclude unnecessarily children undergoing typical fluctuations associated with their condition. Indeed, these children may be among those who are most likely to benefit from the treatment being studied.

In addition, this design allows for clinical judgment and consideration of circumstances to enter into the decision to remove subjects from the protocol. This averts resorting to an "automatic ejection clause" that eclipses clinical judgment when considering the overall severity of the patient's condition, hospital course to date, parents' concerns, or alternative monitoring or unit procedures that might support a patient who is having difficulties. Our experience is that independent evaluations are a better mechanism for protection of subjects' care and interests than restrictive "no alternative" procedures.

Finally, we have found that, for some children, a "honeymoon period" results in less impairment early in the hospitalization (even when children are off medication) than later, during the randomized phase. Thus, during the randomized phase a patient can decline to a level of functioning below that seen earlier in their hospital course, but no more severe than that observed by the family prior to admission. Therefore, the rating procedures allow the patient's clinical condition during the trial to be compared, not just to their level of function when off medication, but also to their level of function at home, prior to entry into the study.

In addition to stopping the study because a child's clinical condition deteriorates, the investigators may withdraw a child from the study if his/her symptoms during medication tapering or the treatment trial interfere with his/her ability to cooperate, or if the patient's behavior threatens his/her safety and that of others. Symptoms leading to withdrawal may include anxiety, psychosis, or conduct problems. Finally, voluntary withdrawal is always an option for a child or parents. We do not plan to study any children off protocol.

F. Follow-up procedures

After an 8 week trial of citalopram plus methylphenidate vs. placebo plus methylphenidate, the blind will be broken for each participant. The rationale for doing so is that, in this severely impaired population, it is important for families to know immediately whether or not each patient has received citalopram (and, if they did receive active treatment, how they responded) in order to guide clinical treatment for each individual in as timely a fashion as possible. Those children who received placebo will be offered open treatment

with citalopram (see below) or other appropriate agents as determined by staff and with the agreement of the patient's family. Those who received citalopram and did not respond will be treated clinically with the goal of achieving sufficient stability to be discharged from the study to the care of a psychiatrist in the community. This period of stabilization will generally last 1 to 4 weeks.

Open citalopram treatment will be provided to responders and to individuals who fail to respond to placebo. Open citalopram treatment will be provided for both ethical reasons (i.e., to allow those patients who got randomized to placebo to receive treatment with active medication) and because it would be useful to obtain additional data on potential adverse events, even if those data are uncontrolled. The duration for all participants who wish to receive citalopram would be 10 weeks. Specifically, for responders, open treatment will be provided for up to 2 weeks, and it is anticipated that they will be discharged during the course of this open treatment. Those who failed to respond to placebo during the blinded trial will be invited to receive open treatment with citalopram for 8 weeks followed by up to 2 weeks of additional open treatment if they respond. While some of the initial 8 weeks of citalopram treatment may be as an inpatient or day treatment patient, it is anticipated that these patients will be discharged to outpatient status during the final 4 weeks of open treatment, if not sooner.

During the open treatment phase, patients will be monitored in the same manner as during the placebo-controlled trial, with every other week clinic visits (and phone calls on alternate weeks) for outpatients and close monitoring for day treatment patients and inpatients. All patients will receive ratings every other week, as during the controlled trial. During and following the open phase of the trial, all outpatients will be in the care of a psychiatrist in their community, with whom we will establish contact when care is transferred. During the open citalopram trial, other medications will be allowed as dictated by the child's clinical needs and their safety in combination with citalopram.

While children are being treated clinically at the NIH (i.e. after they have completed the treatment trial but are not yet sufficiently stable for discharge from the study), data from clinical rating scales will be recorded and may subsequently be published as uncontrolled data. However, treatment decisions will be guided only by what is in the best interest of the patient, with the goal being achieving stability as soon as possible. All children on citalopram will receive an electrocardiogram, CBC with differential, electrolytes, and hepatic panel, before discharge from the study.

As noted above, all participants who enroll in this study will be invited to co-register in protocol 02-M-0021 and are eligible to participate in our longitudinal follow-along study of SMD.

G. Management of Data and Samples:

a. Storage

Every necessary step will be taken to prevent identification of study participants or violations of confidentiality of the data and some data will be securely stored in the NIH CTDB (appendix B). Samples are not stored or shared. Saved data include behavioral, clinician-, parent- and self-ratings, measures of mood, and side effects. Data will be stored in secure servers at NIH and only study investigators will have access to stored data.

Future use: After the study has ended, the data will be stored for future use and will only be accessible to study investigators. Information will be stored using a confidential code, stripped of all identifiers, and data will be treated only as groups. All data entered into a database will appear only in coded form. The IRB will be informed of any future use of this data subsequent to termination of the protocol.

b. Data and sample sharing plan

This protocol is not subject to the Genomic Data Sharing (GDS) policy.

Data may be shared with collaborating laboratories at NIH or outside of NIH and/or submitted to NIH-designated repositories and databases if consent for sharing was obtained. Repositories receiving data from this protocol may be open-access or restricted access.

Data will be stripped of identifiers and may be coded (“de-identified”) or unlinked from an identifying code (“anonymized”). When coded data is shared, the key to the code will not be provided to collaborators, but will remain at NIH. Data may be shared with investigators and institutions with an FWA or operating under the Declaration of Helsinki (DoH) and reported at the time of continuing review. Sharing with investigators without an FWA or not operating under the DoH will be submitted for prospective IRB approval. Submissions to NIH-sponsored or supported databases and repositories will be reported at the time of Continuing Review. Submission to non-NIH sponsored or supported databases and repositories will be submitted for prospective IRB approval.

Required approvals from the collaborating institution will be obtained and materials will be shipped in accordance with NIH and federal regulations.

V. RISKS/DISCOMFORTS

General: By agreeing to participate in this study, subjects will be temporarily forgoing the opportunity to receive routine clinical care in the community. The potential disadvantages of this will be clearly explained to all patients, along with their options for receiving optimal pharmacotherapy and psychotherapy in the community. Patients will also be told that citalopram is available with a physician’s prescription in the community; however, it has no FDA approval for use in children or for the treatment of anxiety.

Screening evaluation: All participants will be screened under the MAP Screening Protocol (01-M-0254, P.I. Dr. Carlos Zarate). Risks and benefits of screening are detailed in that protocol.

Treatment Trial: Patients could experience worsening of symptoms while tapering medications or during the treatment trial whether they are on placebo or citalopram. During the medication withdrawal and initial dose stabilization phases, all patients will be either in day treatment or hospitalized so that they can be monitored closely. Nursing staff will maintain the patient’s safety at all times. In our experience withdrawing children and youth with severe mood dysregulation from medication since 2001, none of 40 patients showed clinical deterioration during the taper phase to a degree that required reinstating

pharmacological treatment and cessation of efforts to discontinue medication. Two of 25 patients who were randomized were withdrawn because of clinical deterioration. While on the Behavioral Health Unit, roughly 20 of 45 patients (44%) who discontinued medication improved compared to their preadmission baseline and no longer meet criteria for randomization. The Pediatric Behavioral Health Unit has developed expertise in supporting children during medication tapering and when children are medication free. They have expertise in supporting patients in a way to minimize the need for restraints or quiet room use.

Almost half of the SMD children enrolled in 02-M-0021 have a history of psychiatric hospitalization, so for many the experience will not be unfamiliar to them. Indeed, patients who have been hospitalized in the community generally find our inpatient unit to be more pleasant than other hospital settings, because of its small size and high staff:patient ratio. Provision will be made for parents to visit their children frequently throughout the hospitalization and this will be strongly encouraged by nursing staff. Weekly consultations with parents, either in person or on the telephone, will be conducted in order to answer questions and to discuss their child's progress during the trial. In addition, children will be allowed to telephone their parents daily, and a variety of activities will be provided to make the child's stay at NIMH more enjoyable. Schooling will be provided year-round by teachers who are particularly adept at educating children with severe psychiatric illnesses.

Citalopram is generally well-tolerated in both children and adults, including by medically ill patients taking multiple concomitant medications. Side effects that were noted in randomized trials to exceed incidence rates of more than 5% or were double the rate observed among patients receiving placebo included (Micromedex®): dry mouth, sweating increased, tremor, nausea, diarrhea, dyspepsia, vomiting, abdominal pain, general fatigue, fever, arthralgia, myalgia, somnolence, insomnia, anxiety, anorexia, agitation, dysmenorrhea, libido decreased, and yawning. As is standard practice for treatment with any SSRI, staff, patients and family will be alerted to risks for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. As noted in the Introduction, FDA data suggest that youth treated with SSRIs have a significantly increased risk for suicidal ideation, compared to those treated with placebo, but the absolute risk remains small. Having said that, the rate in youth with SMD is unknown, so patients will be observed closely.

Because of the primary route of elimination is via the liver, we will exclude patients with liver enzyme elevation (two-fold increase over upper limits of normality) or a history of liver disease. Risks of bleeding are also reported and we will exclude any patients with abnormal baseline CBC or who require routine use of non-steroidal anti-inflammatory drugs that decrease coagulation..

Citalopram is metabolized by liver enzyme cytochrome P450III A4 (CYP3A4) and IIC19 (CPY2C19). One advantage of citalopram is that it has been relatively immune to drug-drug interactions that elevate or depress levels of other SSRIs. The manufacturer of citalopram has not reported significant drug-drug interactions, except for NSAIDs as noted above. We do not anticipate use of triptan drugs such as sumatriptan with citalopram in this study but such interactions could be anticipated and will be watched for during the trial; we

will exclude individuals with a history of migraine who require triptan agents for relief of migraine symptoms.

Adverse medication effects could prolong hospitalization. If patient and family decline further hospitalization at NIH or wish to leave NIH despite being unstable, then they may choose inpatient admission at another facility. In that case they or their insurance company will be responsible for costs associated with the hospitalization. The staff will work to stabilize the patient to a level that allows for a safe transfer to another facility if the family chooses. Involuntary psychiatric hospitalization is not an option at NIH, and if such commitment is necessary, transfer to an appropriate institution will be facilitated.

Patients may find the repeated administration of the rating scales to be unpleasant or boring.

VI. SUBJECT MONITORING

During the medication withdrawal, medication-free, and dose stabilization phases, patients will be on the Pediatric Behavioral Health Unit (in day treatment or inpatient) and will be monitored very closely by nursing staff. On the Unit, events that require holds or quiet room use will be closely tracked and assessment of the clinical treatment plan will be reviewed subsequent to each event. Patients and families are informed about the quiet room, “as needed medication,” and policy governing holds/restraints at the consent signing and during the orientation to the Pediatric Behavioral Health Unit. Furthermore, parents are informed by nursing staff after each event whenever a hold, quiet room use, or PRN medication are needed. In addition, the HSPU will provide ongoing monitoring throughout the study.

VII. OUTCOME MEASURES

We will have two primary outcome measures, one of which will be used as a continuous measure and the second of which will be treated categorically. These primary outcome measures will be the Aberrant Behavior Checklist—Irritability Subscale (ABC-I), which will be treated continuously, and the Clinical Global Improvement Scale (CGI-I), which will be treated categorically. As described in the Background section, irritability is the most hallmark symptom of SMD. In addition, since it is also important to determine how citalopram impacts on the patient’s overall severity of illness and to ascertain a frequently-used global designation of “responder” status, we will use the CGI-I, which is the most commonly used outcome measure in pediatric psychopharmacology trials. The baseline for the CGI-I ratings will be the measure obtained at the end of the medication withdrawal phase, just before the dose stabilization phase begins, as described in more detail above.

VIII. STATISTICAL ANALYSIS

To test the hypothesis that citalopram plus methylphenidate (MPH) will be more effective than placebo plus MPH in treating irritability associated with severe mood dysregulation, we will compare reductions from baseline scores on the ABC-I after 8-weeks of double-blind therapy to the ABC-I score before the start of therapy. Specifically, random effects regression will be used to contrast study groups for continuous measures. For continuous measures, each dependent measure (Y_j) is predicted by the following model: $Y_j = \mu + \alpha_j + \beta_1 T + \beta_2 I + \beta_3 T \times I + \epsilon_{ij}$ where I indicates treatment status; j indexes subjects; T indexes time (for repeated measures); α_j is a random effect for the intercept of the j th subject; μ is the

average slope; β_{3j} is a random effect for the slope of the j th subject; 4 is treatment status; 5 is the difference in slopes over time between the two groups specified in 4. Z is the effect of possible covariates and ϵ_{ij} is the random effect for error. To assess the efficacy of citalopram plus MPH, we will test the significance of a group (citalopram+MPH vs. placebo+MPH) by time interaction. The level of significance will be $p < .05$. This analytic plan also will be used for any secondary outcome measures that can be treated continuously. Specifically, in addition to the primary measure, the impact of citalopram+MPH vs. citalopram + placebo on the secondary measures of CDRS, YMRS, SCAR-H and PARS scores will also be assessed.

For our categorical analysis, a responder analysis will be performed to compare the proportion of subjects in each treatment group who met the response criteria. Response rates will be analyzed using logistic regression, with the principle study hypothesis being that rates of response will be greater in the citalopram+MPH vs. the placebo+MPH cell. This hypothesis is tested as the main effect of treatment group on CGI category (responder vs. non-responder). Response will be defined as a CGI rating of 1 (completely well) or 2 (much improved).

In all analysis, the intent-to-treat principle will be used, such that all available data from all randomized subjects will be included. Subjects who have a baseline measure and at least one other post-baseline rating will be included in the analysis.

The number of subjects withdrawn from the study prior to randomization will be reported in the publication resulting from this trial, along with the reasons for their withdrawal.

Sample size estimation

We assume a response rate of 60% to citalopram+MPH and 20% to placebo+MPH. While, on the surface, this might seem like a somewhat large clinical difference, when SSRIs are highly effective in pediatric conditions, such as pediatric anxiety disorders, effect sizes of this magnitude are typically found. Since there are no treatment trials in SMD targeting irritability, the placebo response rate is based on the MTA, a large treatment trial in ADHD using stimulants (Greenhill et al., 2001; Galanter et al., 2003). Assuming power=0.8 and a two-tailed alpha= 0.05, a sample size of 80 (40 in each group) is needed. However, of course, in the event that the response to SSRIs in SMD is more similar to that in pediatric MDD than pediatric anxiety, power will be less than 0.8.

Our experience with a previous treatment trial in this population suggests that roughly 50% of participants may not reach the point of randomization because of behavioral improvement, withdrawal from the study because of homesickness, or intolerance of medication discontinuation. Thus we are anticipating enrolling 160 children in order to ascertain 80 who will be randomized.

IX. HUMAN SUBJECTS PROTECTION

A. Subject selection

i. Statement of equitability

Every attempt will be made to recruit participants nationally from all racial and ethnic groups. Our past experience is that most participants come from our longitudinal studies of pediatric bipolar disorder and reflect disproportionate representation of Caucasian children. We currently have 88 percent Caucasian individuals, 8 percent African Americans, and 2 percent Asian individuals in our cohort, with 2 percent whose race was not reported.

B. Justification for inclusion of children

As detailed in Section II, severe mood dysregulation is an extremely impairing illness for which there are few effective treatments. Therefore, many youths with the illness continue to suffer significant impairment. Current treatment lore that these children have a variant of Pediatric Bipolar Disorder has left clinicians wary of giving stimulants and/or SSRIs to patients for symptoms of ADHD or anxiety, respectively, in the belief that these agents will precipitate mania. There is a need for research using standard agents. Since the target population for these treatments is children and adolescents with severe mood dysregulation, it is essential to conduct controlled trials in a well characterized population.

C. Safeguards for vulnerable populations and sensitive procedures

Protections for NIH employees, staff and family members participating in this study include 1) assuring that the participation or refusal to participate will have no effect, either beneficial or adverse, on the subject's employment or position at the NIH, 2) giving employees and staff who are interested in participating the "NIH Information Sheet on Employee Research Participation" prior to obtaining consent, and 3) assuring that there will be no direct solicitation of employees or staff.

D. Justification for use of placebo and medication withdrawal

A stimulant-only (placebo+MPH) arm in this trial is justified because of the limited data concerning treatment efficacy of any agent in children with severe mood dysregulation. The dearth of knowledge on therapeutics is particularly problematic in light of the fact that children with SMD suffer considerable morbidity and impairment and are seen commonly in treatment settings, where they are treated with a variety of psychotropic agents. Indeed, we anticipate that the typical child referred for the study will be receiving treatment with multiple medications with significant side effect risks, none of whose efficacy has been tested in a systematic fashion. As specified above, patients who experience clinical worsening during the treatment trial will be terminated from it early and will receive either an open trial of citalopram or other appropriate clinical care. Of the 40 children we have withdrawn from medication under protocol 02-M-0021, two had worsening of symptoms to the point of requiring removal from research and roughly 50% were clinically improved during the medication-free period compared to pre-admission baseline ratings.

Our prior experience suggests that a medication-free period provides the unusual opportunity to observe children during a phase where their psychiatric symptoms cannot easily be attributed to effects from ongoing treatments, providing insights on diagnosis and on capacities that could not be observed under heavy medication. Thus, the superior diagnostic assessment that the drug-free period provides is essential. For example, approximately 25% of the 40 patients we have withdrawn from medications were diagnosed with conditions following medication-free observation not evident at the initial assessment. Indeed, since the patients who enter our discontinuation study are not doing well and often are on many medications, there are legitimate questions as to whether their symptoms are influenced by treatment with antipsychotics or "mood stabilizers," both of which are commonly prescribed in this population.

E. HSPU team participation

We value the support of the HSPU in our studies. Following IRB guidelines, we are requesting that the HSPU provide consent/assent monitoring and ongoing oversight during the inpatient/Day Treatment portions of the study for all participants. Once patients are discharged to the outpatient portion of the study, we would involve the HSPU on a case-by-case basis.

F. Qualifications of investigators

The principal and co-investigators are well qualified to conduct this investigation.

Dr. Argyris Stringaris, MD, PhD is a Child and Adolescent Psychiatrist and the Unit Chief of the Mood, Brain & Development Unit (MBDU). He is an internationally recognized expert in the pathophysiology of mood disorders. He has broad and deep experience working with children and adolescents with mood disorders or other serious psychiatric illnesses in a clinical research context. He will be obtaining consent for the protocol.

Dr. Ellen Leibenluft is an internationally recognized expert on all aspects of pediatric bipolar disorder. Her broad experience has focused on the presentation, course, mechanisms, and treatment of the disorder. She also has extensive clinical and research experience in the course and treatment of bipolar disorder in adults. She is the Chief of the Section on Mood Dysregulation and Neuroscience (SMDN) in the Emotion and Development Branch in the Mood and Anxiety Disorders Program.

Dr. Daniel Pine is an internationally recognized expert in pediatric neuroscience and child and adolescent psychiatry. He has conducted many treatment trials for childhood onset anxiety disorders and depression, and has vast experience in all aspects of pediatric psychiatric research. He was previously a lead investigator for the Research Units in Pediatric Psychopharmacology for studies of anxiety in children and adolescents and is Chief of the Emotion and Development Branch..

Dr. Kenneth Towbin is board-certified in adult and in child and adolescent psychiatry and has been Chief of Clinical Child and Adolescent Psychiatry in the Mood and Anxiety Disorder Program since its inception. Dr. Towbin is currently staffed in the Emotion and Development Branch and has been the primary clinician for all inpatients treated by SMDN including medication discontinuation studies of pediatric bipolar patients and a placebo-controlled trial of lithium in those with Severe Mood Dysregulation. Dr. Towbin has exceptionally strong experience working with children with bipolar disorder or other serious psychiatric illnesses in a clinical research context.

Chana Engel, CRNP-PMH has experience working with adults and children with serious psychiatric disorders who works full time with the Emotion and Development Branch.. She will be performing routine clinical assessments (e.g. physical examinations, interpreting laboratory data, KSADS, clinical assessment for suicide) for patients entering or in the protocol. She will also provide direct care and clinical monitoring of patients in the study. She will be obtaining consents.

Holly Yokum, MSW is a licensed clinical Social Worker with decades of experience working with adults and children with bipolar spectrum disorder. She works full time in the Section on Mood Dysregulation and Neuroscience. She will be obtaining clinical ratings and performing clinical assessment of patients entering the protocol. She will not be obtaining consents for the study.

Gerald Overman, Pharm.D, BCPP Clinical Pharmacy Specialist NIH CC Pharmacy Dept provides consultative assistance to the program and to Dr. Towbin. Dr. Overman will provide oversight of the process of delivering coded capsules to the unit and consultation to Dr. Towbin on matters related to medication tapering schedules, pharmacokinetics of stimulants, and liaison with the Pharmacy Department. He will not be obtaining consent for this protocol

Wanda Wheeler, MSW is a licensed clinical Social Worker and who works full time in the Section on Mood Dysregulation and Neuroscience. She will be obtaining clinical ratings and performing clinical assessment of patients entering the protocol. She will not be obtaining consents for the study.

Mollie Davis, MSW is a licensed clinical Social Worker and is credentialed through the Clinical Center Social Work Department. She has extensive experience working with adults and children with a variety of psychiatric disorder. She is a contractor working full time in SMDN. She will be obtaining clinical ratings and performing clinical assessment of patients entering the protocol. She will not be obtaining consents for the study.

Cheri McNeil, PsyD is a licensed clinical Psychologist who is credentialed in the NIH Clinical Center as a licensed independent practitioner and works full time for SMDN. She has extensive experience working with adults and children with a variety of psychiatric disorders. She will be obtaining clinical ratings and performing clinical assessment of patients entering the protocol. She will not be obtaining consents for the study.

X. BENEFITS

It is reasonable to expect that some patients may benefit from citalopram+MPH or from MPH alone. The weight of the evidence favors prospect of benefit. Of course, we cannot predict which patients will benefit, so subjects who enter the trial must be informed of the possibility that they will see no direct personal benefit from participation. The research evaluations performed in this investigation, including laboratory assays and neuropsychological testing, are not designed to benefit study participants.

The overall results of the study may provide information leading to new treatments for SMD and may be of benefit to others.

XI. SUMMARY/CLASSIFICATION OF RISK

The risks associated with citalopram+MPH administration can be classified as a minor increment over minimal risk, with a prospect of direct benefit to participants. As such, enrolling children into this study is ethically permissible, despite a greater-than-minimal-risk classification, since children entering in the study have severe illness and the potential for direct benefit. As reviewed in Section II, these standard drug treatments for SMD are often ineffective, and individual patients will only be included in the current study if their ongoing treatment is ineffective. In addition, if citalopram is effective in reducing symptoms of irritability this would have a significant public health impact and reduce the suffering of many children with this constellation of symptoms. Overall, risk in this study is categorized as more than minimal risk with the prospect of direct benefit.

XII. CONSENT DOCUMENTS AND PROCESS

The consent process will be conducted by one of the physician investigators or Ms. Engel, and the Human Subjects Protection Unit (HSPU) will be present to oversee the

procedure and assure protection of the interests of the subjects and their families. HSPU will also provide on-going subjects monitoring during hospitalization.

Subjects and their legal guardians will be informed that this is the first systematic investigation of citalopram as a treatment for symptoms in SMD in young patients, and that no one knows if it will be helpful. Because there have been no previous studies of citalopram in SMD, subjects and guardians will also be told that there is a chance that the medication could worsen their mood symptoms, although we think this unlikely. Subjects and guardians will be informed of the possibility and encouraged to discuss any concerns. All subjects and guardians also will be fully informed about the side-effects of citalopram and MPH. They will be reminded that alternative and potentially effective treatments exist for symptoms of SMD.

Following these explanations, if subjects and their guardians wish to enroll in the citalopram/placebo trial, the study will be described in detail, the consent document reviewed, and subjects and guardians will have an opportunity to have their questions answered before being asked to sign three identical copies of the consent form. Children and adolescents will be asked to sign assent forms that describe the study in age-appropriate language. They will be informed that they have true decision-making authority, and withholding assent means they will not continue in the study. Parents and children will be informed that they may withdraw their consent/assent at any time and for any reason. Investigator and witness will then sign the consents/assents, and one copy of each form will be returned to the study participants, another filed in the subject's research folder, and the third will be entered into the NIH medical record.

Consent for participation of minors will be obtained from parents/legal guardians. If the parents are married, written consent may be obtained from one parent only. If the parents are not married, written consent will be obtained from: 1) the custodial parent if only one parent has legal custody, or 2) from both parents if they share legal custody for medical decision-making. For unmarried parents, signature of one parent will also suffice if the other parent is deceased, unknown, incompetent, or not reasonably available. When signature of both parents is required, written consent will be obtained in-person from at least one parent. When the second parent is unable to attend the consent process conference in person, the following telephone process to obtain written consent will be used.

Sharing of data will be done under a waiver of informed consent if a participant previously signed a consent form that did not have information on sharing or if the consent form provided options for sharing and the participant did not ask that his/her data not be shared. For coded/linked data shared under a waiver of informed consent, those using the shared data will not contact or attempt to contact the participant unless the IRB approves such contact. Waiver of consent to share these data meets the criteria set out in 45 CFR 46.116(d):

- The research involves no more than minimal risk to the subjects. The sharing and additional use of data does not present more than minimal risks to previous participants.
- The waiver or alteration will not adversely affect the rights and welfare of the subjects. Data will have personally identifying information removed and will be coded or completely unlinked from any identifying code.
- The research could not practicably be carried out without the waiver or alteration. Long term storage and complete data require the submission of these data. Understanding

of the disease or condition being studied cannot be generated without broad contributions to the research effort.

- We will have been unable to contact those for whom coded data are being used under this waiver. In the unlikely event that such participants make contact with us, we will provide them with information about the waiver and research use of their data.

Three attempts will be made to reach former minor participants before determining that they are unavailable. The waiver applies only to those whose parents signed a version of the consent form that was silent on sharing and who cannot be reached for re-consent. The waiver does not apply to those whose parents explicitly declined sharing/additional uses of the data or who requested recontact before deciding. The waiver does not apply to those who were contacted as adults but declined to sign a consent form

Telephone Consent Procedures:

The unavailable parent will be provided with a copy of the consent form, usually by fax, email, or hard copy. Once the consent form is received, an Investigator authorized to obtain consent will arrange for a telephone call with the parent in the presence of a witness to review the study and the consent form and to answer any questions. If the parent cannot arrange for a witness in his/her location, the consenting investigator will have a witness present at NIH during the teleconference. Once the parent agrees to his/her child's participation, the parent and witness (if present with the parent) will sign and date their copy of the consent form. The Investigator will enter a note documenting the consent process in the Medical Record. The 2nd parent will return their signed copy to the Investigator. Once the copy with the parent signature is received, the Investigator and witness (if present at NIH) will sign and date the 2nd parent consent form, place the original copy with all signatures in the Medical Record, retain a copy for research records, and mail a copy to the parents. The telephone consent process will be documented in the medical record.

Verbal assent will be obtained from minor participants who are old enough to understand the nature of the study and its implications, but are too young to provide a signature. Written assent will be obtained from minors older than age seven whenever possible. Dissent will be respected in children of all ages. The assent process will be documented in the medical record.

Consent for NIH employees and staff will not be obtained by coworkers.

XIII. DATA AND SAFETY MONITORING

a. Data and safety monitor

Data and safety will be monitored by the Principal Investigator.

b. Data and safety monitoring plan

The PI will review data and safety parameters at least annually. The PI will document the data and safety review in the research records and at the time of continuing review.

c. Criteria for stopping the study or suspending enrollment or procedures

The study (or the study-specific procedure) will be stopped if there is any Serious Adverse Event related to the research. The PI and IRB will determine if changes are needed for the research to continue or if it will be closed. Any changes required as

conditions for resuming the research must be submitted as an amendment and IRB-approved before the changes can be implemented.

XIV. QUALITY ASSURANCE (QA)

a. Quality assurance monitor

Quality assurance will be monitored by the PI, the research team and the NIMH Office of Regulatory Oversight (ORO).

b. Quality assurance plan

ORO monitors intramural research studies to ensure compliance with GCP, organizational policies and regulations. Audit frequency is determined by the ORO SOP based on the study level of risk. Results of ORO audits are provided to the PI, the Clinical Director and the CNS IRB. This study will undergo audits at least once every three years and for cause.

XV. ADVERSE EVENT REPORTING

The Principal Investigator is responsible for detecting, documenting, and reporting unanticipated problems, adverse events (AEs), including serious adverse events (SAEs), and deviations in accordance with NIH policy, IRB requirements, and federal regulations. Relatedness to the research of all serious adverse events will be determined by the PI in consultation with the Clinical Director (CD) of NIMH.^[11]^[SEP]

Serious unanticipated problems, serious adverse events (including deaths) that are not unanticipated problems, and serious protocol deviations will be reported to the IRB and CD as soon as possible and in writing not more than 7 days after the PI first learns of the event, unless immediate reporting is waived for specific serious adverse events as noted below. Unanticipated problems and serious deviations will be reported on the NIH “Problem Report Form.” Serious Adverse Events will be reported on the “Serious Adverse Event Report Form.” Not serious unanticipated problems and not serious deviations will be reported to the IRB and CD as soon as possible and in writing on the NIH Problem Report Form not more than 14 days after the PI first learns of the event.

All adverse events, deviations, and unanticipated problems will be summarized and reported at the time of Continuing Review.

XVI. ALTERNATIVES TO PARTICIPATION OR ALTERNATIVE THERAPIES

Antidepressants (TCAs, MAOIs, SSRIs), mood stabilizers (lithium, carbamazepine, lamotrigine and valproate), atypical antipsychotics (e.g. risperidone, olanzapine, quetiapine) and psychotherapies (e.g. CBT) could be efficacious for SMD. Before being considered for this study, subjects will be reminded that these treatments are available to them in the community. This approach will assure that subjects are clearly informed of the standard care before being exposed to the risks of citalopram or MPH.

XVII. PRIVACY

All research activities will be conducted in as private a setting as possible.

XVIII. CONFIDENTIALITY

Every necessary step will be taken to prevent identification of study participants or violations of confidentiality of the data. Information will be stored using a confidential code and data will be treated only as groups. All data entered into the NIH CTDB database will appear only in coded form. Members of the research team will have access to these coded data. Only staff directly involved in the care of each subject will have access to clinical documents that contain identifying information. This will include research assistants, clinical staff, and the study psychiatrist. Please see Appendix B for a description of data security of CTDB.

All research activities will be conducted in as private a setting as possible.

XVIX. CONFLICT OF INTEREST/TECHNOLOGY TRANSFER

There is no conflict of interest involved with this study beyond the professional benefit from academic publication or presentation of the results.

XVX. COMPENSATION

Subjects will not be compensated for participation in the Stimulant + Citalopram trial. Compensation is provided for research activities completed during the medication trial period as follows:

	Amounts
Ratings (weekly)	\$10
Total	\$120-180

Employees and staff who participate during work hours must have permission from their supervisor. NIH employees must either participate outside of work hours or take leave in order to receive compensation.

XVXI. PHARMACEUTICAL INFORMATION

A. Source, formulation, and preparation

1. Citalopram or placebo capsules

Citalopram 5mg capsules or matching placebo capsules will be manufactured by Murty Pharmaceuticals, Inc under current Good Manufacturing Practice (cGMP) regulations.

1.a Open Label Citalopram

Citalopram HBr is an orally administered selective serotonin reuptake inhibitor (SSRI) with a chemical structure unrelated to that of other SSRIs or of tricyclic, tetracyclic, or other available antidepressant agents. Citalopram HBr is a racemic bicyclic phthalane derivative designated (±)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, HBr with the following structural formula:

The molecular formula is C₂₀H₂₂BrFN₂O and its molecular weight is 405.35. Citalopram HBr occurs as a fine, white to off-white powder. Citalopram HBr is sparingly soluble in water

and soluble in ethanol. Citalopram hydrobromide is available as tablets or as an oral solution. Citalopram 10 mg tablets are film-coated, oval tablets containing citalopram HBr in strengths equivalent to 10 mg citalopram base. Citalopram 20 mg and 40 mg tablets are film-coated, oval, scored tablets containing citalopram HBr in strengths equivalent to 20 mg or 40 mg citalopram base. The tablets also contain the following inactive ingredients: copolyvidone, corn starch, croscarmellose sodium, glycerin, lactose monohydrate, magnesium stearate, hypromellose, microcrystalline cellulose, polyethylene glycol, and titanium dioxide. Iron oxides are used as coloring agents in the beige (10 mg) and pink (20 mg) tablets. Citalopram oral solution contains citalopram HBr equivalent to 2 mg/mL citalopram base. It also contains the following inactive ingredients: sorbitol, purified water, propylene glycol, methylparaben, natural peppermint flavor, and propylparaben.

2. Methylphenidate

Ritalin hydrochloride, methylphenidate hydrochloride USP, is a mild central nervous system (CNS) stimulant, available as tablets of 5, 10, and 20 mg for oral administration. Methylphenidate hydrochloride is methyl α -phenyl-2-piperidineacetate hydrochloride. Methylphenidate hydrochloride USP is a white, odorless, fine crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular weight is 269.77. Inactive Ingredients. Ritalin tablets: D&C Yellow No. 10 (5-mg and 20-mg tablets), FD&C Green No. 3 (10-mg tablets), lactose, magnesium stearate, polyethylene glycol, starch (5-mg and 10-mg tablets), sucrose, talc, and tragacanth (20-mg tablets).

B. Pharmacology

1. Citalopram:

The single- and multiple-dose pharmacokinetics of citalopram are linear and dose-proportional in a dose range of 10-60 mg/day. Citalopram has a mean terminal half-life of about 35 hours and is metabolized in the liver primarily via N-demethylation, deamination, and N-oxidation to less lipophilic compounds which are more readily excreted by the kidney (Milne & Goa, 1991; Sweetman, 2000). With once daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of citalopram in plasma, based on the half-life, is expected to be 2.5 times the plasma concentrations observed after a single dose. The tablet and oral solution dosage forms of citalopram HBr are bioequivalent (Product Information, Celexa®).

Absorption and Distribution

Following a single oral dose (40 mg tablet) of citalopram, peak blood levels occur at about 4 hours. The absolute bioavailability of citalopram was about 80% relative to an intravenous dose, and absorption is not affected by food. The volume of distribution of citalopram is about 12 L/kg and the binding of citalopram (CT), demethylcitalopram (DCT) and didemethylcitalopram (DDCT) to human plasma proteins is about 80% (Kragh-Sorensen et al., 1981; Milne & Goa, 1991; Sweetman, 2000).

Metabolism and Elimination

Following intravenous administrations of citalopram, the fraction of drug recovered in the urine as citalopram and DCT was about 10% and 5%, respectively. The systemic clearance of citalopram was 330 mL/min, with approximately 20% of that due to renal clearance.

Citalopram is metabolized to demethylcitalopram (DCT), didemethylcitalopram (DDCT), citalopram-N-oxide, and a deaminated propionic acid derivative (Milne & Goa, 1991; Oyeaug & Ostensen, 1984; Overo, 1982). In humans, unchanged citalopram is the predominant compound in plasma. At steady state, the concentrations of citalopram's metabolites, DCT and DDCT, in plasma are approximately one-half and one-tenth, respectively, that of the parent drug. *In vitro* studies show that citalopram is at least 8 times more potent than its metabolites in the inhibition of serotonin reuptake, suggesting that the metabolites evaluated do not likely contribute significantly to the antidepressant actions of citalopram. *In vitro* studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of citalopram.

2. Methylphenidate

Absorption and Distribution:

For regular methylphenidate (oral), time to peak concentration is 1 h to 2 h and the distribution (Vd) is 6 L/kg with protein binding of 10% to 33% (Kimko et al., 1999). Following administration of 0.3 mg of methylphenidate per kg of body weight (mg/kg) the blood concentration in children is 10-18 nanograms per mL (Kimko et al., 1999). Peak plasma concentrations showed marked variability between subjects (Kimko et al., 1999). Dose-proportionality was demonstrated in peak plasma concentrations and area under the concentration-time curve (AUC) values for all brands of methylphenidate. Time to Peak Concentration is 1 to 3 hours (Dayton et al., 1970).

Metabolism and Elimination:

Metabolism is via deesterification into metabolites alpha-phenyl-piperidine acetic acid (PPA, ritalinic acid). Excretion is primarily via the kidneys. 78% to 97% is eliminated via the kidneys with less than 1% is unchanged and approximately 80% is excreted as PPA. Fecal elimination occurs for 1% to 3%. The elimination half life is 3 h for methylphenidate and 3-4 hours for ritalinic acid.

C. Toxicity

Side effects of citalopram and methylphenidate are also reviewed in Section V.

Toxicity Criteria

1. Citalopram

In clinical trials of citalopram, there were reports of citalopram overdose, including overdoses of up to 2000 mg, with no associated fatalities. During the post-marketing evaluation of citalopram, citalopram overdoses, including overdoses of up to 6000 mg, have been reported. As with other SSRI's, a fatal outcome in a patient who has taken an overdose of citalopram has been rarely reported.

Symptoms most often accompanying citalopram overdose, alone or in combination with other drugs and/or alcohol, included dizziness, sweating, nausea, vomiting, tremor,

somnolence, and sinus tachycardia. In more rare cases, observed symptoms included amnesia, confusion, coma, convulsions, hyperventilation, cyanosis, rhabdomyolysis, and ECG changes (including QTc prolongation, nodal rhythm, ventricular arrhythmia, and one possible case of torsades de pointes).

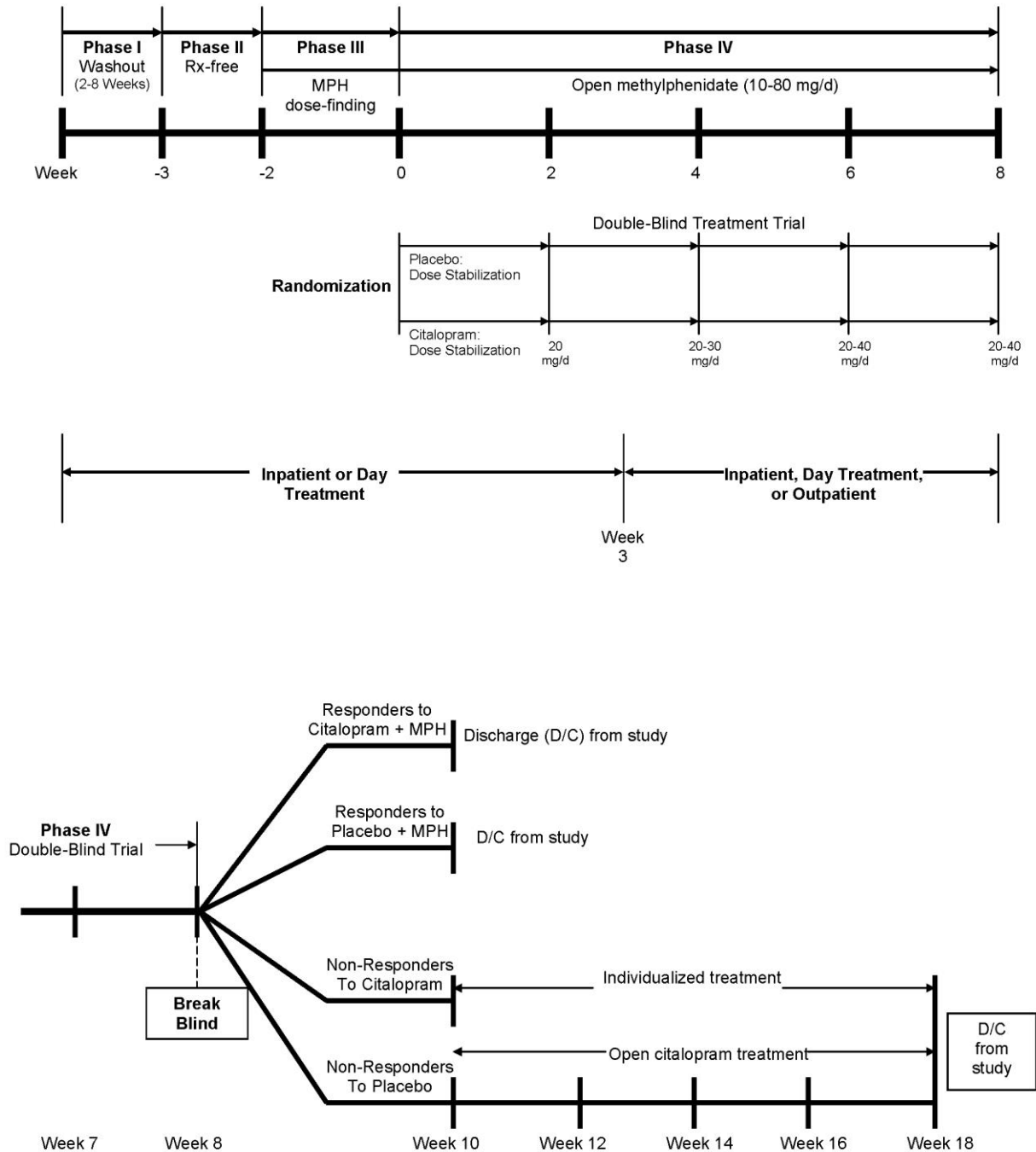
2. Methylphenidate

In overdose with methylphenidate, agitation, tachycardia and lethargy were commonly reported following unintentional exposure to immediate-release methylphenidate in children. CNS toxic effects may range from restlessness, uncontrolled movements, agitation, irritability, confusion and insomnia to marked hyperactivity, seizures, hypertension and coma following severe exposure. Although infrequent, death has been reported following overdose. Effects appear to be dose-dependent. Severe toxicity has been reported in adolescents and adults following intentional methylphenidate misuse.

D. Administration

See Section IV E.

Double-blind trial of citalopram plus methylphenidate vs. placebo plus methylphenidate in youth with severe mood dysregulation (Phases 1-4)



Appendix B: CTDB

The Clinical Trials Database Project (CTDB) assists Investigators with the management of natural history and clinical trial research projects. Associated with the project are two major components: (1) a set of information technology systems based upon industry standard technologies and best practices (e.g. Java, XML, UML); and (2) a team of support staff that assist investigators with designing and executing research projects.

The CTDB is a web-based application that supports flexible data capture, and reporting. The system is hosted at the NIH in Bethesda, MD. It is accessible via the Internet through the NIH firewall, on both Mac and Windows based computers. An Oracle relational database is utilized to capture and secure data entered through the web interface.

The web interface is organized in to areas for system administration, protocol design, data collection, and reporting. The primary features of the system include the following:

- System Administration functions to secure electronic patient data, and allow PIs to control staff access to confidential clinical information.
- Protocol design tools that allow researchers to customize the system for each protocol, including creating data collection instruments, intervals, barcode labels, and collaborative tools, as well as to record patient demographics.
- A Question Library that serves as a central repository for researchers to build protocol forms and share common vocabularies.
- Multi-Site capabilities allow investigators to become the coordinating center for a geographically dispersed trial.
- Data collection tools (e.g., double-key data entry) to ensure the integrity of patient response data.
- The Clinical Data Mart – an ancillary system that integrates patient data and allows for data analysis across multiple protocols.
- A Reporting tool that allows researchers to directly query patient response data and facilitates IRB and DSMB reporting.
- The Clinical Trial Survey System (CTSS) – an ancillary web-based application, accessible outside the NIH, that allows patients to remotely respond to clinical questionnaires.
- A Bio-specimen management module that allows users to create custom locations and track the biospecimens collected during trials. The results of bio-specimen analysis may also be seamlessly integrated using this module.

Collectively, the CTDB project currently supports 170 research protocols across 10 Institutes at NIH: NICHD, NIMH, NINR, NIDDK, NIDCR, CC, NIEHS, NIAMS, NHGRI, and NHLBI. The project has assisted researchers consolidate datasets for over 300 scientific publications.

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