NHLBI 5R01HL123609-05

Treating Caregiver Depression to Improve Childhood Asthma: Impact and Mediators

Protocol and Statistical Design

NCT02809677

September 8, 2021

3. Research Strategy

3.1. Significance

Asthma prevalence, morbidity, and mortality remain high despite a tremendous increase in knowledge about the pathogenesis of asthma and new medications. A staggering 7.2% of Americans have asthma.[1] Well over 4000 Americans die each year from asthma,[2] and asthma accounts for over 1.5 million emergency room visits and 500,000 hospitalizations each year.[3] Health-related expenditures for asthma are over $12.7 billion per year in the United States (US).[4] In the past three decades, the prevalence of asthma has increased by 75%,[5] asthma-related hospitalizations have increased by over 70%, and asthma-related mortality rates have doubled.[6] The highest prevalence of asthma and asthma-related morbidity and mortality is in low-income,[7-9] inner-city,[9-11] minority communities,[7-10, 12-14] and this is especially true for children.[15] In the US, 9% of children have asthma,[16] and asthma is the most common chronic illness affecting children.[17] Asthma prevalence and morbidity remain a significant public health concern for children, despite a tremendous increase in knowledge about the pathogenesis of asthma and new medications. We suggest that a barrier to progress in the field is that the impact of depression on asthma adherence and outcomes is underappreciated. ***The goal of our project is to begin to close this gap in the scientific knowledge base by examining the impact of the treatment of caregiver depression on childhood asthma.***

3.1.a. Depression is common in asthma patients and is associated with negative asthma outcomes. Depression is associated with increased asthma-related morbidity, mortality, and unscheduled service utilization. Adults and children with asthma have higher levels of depressive symptoms than controls and persons with most other medical illnesses.[18] When present, depression is associated with unfavorable asthma outcomes, including medication non-adherence, increased frequency of emergency room visits, hospitalizations, unscheduled visits for asthma,[19] and even asthma-related death.[20] Youth with asthma have an almost twofold higher prevalence of comorbid anxiety and depressive disorders compared to controls.[21] Brown (PI) found that 30% of children with asthma had scores on the Children's Depression Rating Scale-Revised consistent with major depressive disorder (MDD) (see section 3.3.a.iii), which was associated with a greater number of hospitalizations for asthma in the year before.[22] Miller and Wood (PIs) have shown that depressive symptoms are associated with increased asthma severity[23] and with compromised pulmonary function in children with asthma.[24]

Depression and other psychiatric disorders are also common in *caregivers* of children with asthma, and are associated with poor outcomes in the child including greater use of acute care resources. Wade et al. found that 50% of 1628 caregivers of children with asthma had significant psychiatric symptoms based on Brief Symptom Severity (BSI) Global Severity scores.[25] Leao et al.[26] reported that the prevalence of depression was over twice as high among mothers of children with asthma as in mothers of non-asthmatic children (Odds Ratio [OR] 2.74), and that depression was more common in mothers of children with persistent asthma than intermittent asthma (OR 2.77). Similar findings were reported by Szabo et al.[27] Thus, depression is not only common in asthma caregivers, but related to the severity of the child's asthma.

While it is likely that having a child with severe asthma contributes to caregiver depression, there is also evidence that caregiver depression, in turn, contributes to poor asthma control in the child. Otsuki et al.,[28] using a path analysis, observed that in inner-city African American families, maternal depression at baseline predicted the child's asthma symptoms 6 months later, but baseline asthma symptoms in the child did not predict the development of maternal depression.

Caregiver depression, when present, is associated with increased use of unscheduled asthma-related services by the child. Weil et al. found that asthma caregivers with BSI scores indicating significant psychopathology were twice as likely to report an asthma-related hospitalization by the child in the past 9 months, as those with scores below the cutoff.[29] Bartlett et al.[30] found that 47% of mothers of children with asthma had clinically significant levels of depressive symptoms. Mothers with high levels of depression were 40% more likely to report an emergency room visit by the child in the following 6 months than were mothers with lower depressive symptom severity. Other reports suggest that in addition to increased asthma service utilization by the child, caregiver depression is associated with lower caregiver self-efficacy, lower quality of life, fewer symptom-free days and nights, as well as greater use of as needed bronchodilators by the child.[31, 32] Brown, Miller and Wood (PIs) examined 175 caregivers of children hospitalized with asthma.[33] A total of 26% had a current depressive episode and 22% had an anxiety disorder (section 3.3.a.i). Caregiver depression was associated with a 50% increase in unscheduled visits and anxiety with a 43% increase in asthma-related hospitalizations.[33] ***These findings suggest that caregiver depression may influence asthma outcomes rather than be solely a consequence of the asthma symptoms, but no study to date has definitively tested this hypothesis. Our proposed study will do so by treating caregiver depression with antidepressants to see if the child's asthma subsequently improves. Affirming that caregiver***

depression actively impacts asthma outcomes would extend the knowledge base of factors influencing asthma outcomes, and provide clinically relevant scientific knowledge.

3.1.b. Treating maternal depression to improve child outcomes. A study of physically healthy children demonstrated that improvement in maternal depression with antidepressant treatment improved functional status and reduced the child's depression and anxiety.[34] This supports the idea that maternal depression compromises child emotional function, and that it is possible to improve child's function by treating the depressed mother. We conducted, what is, to our knowledge, the only caregiver depression intervention study in pediatric asthma (section 3.3.a.ii). In this pilot study, antidepressant treatment of the caregivers (n = 8) was associated with improvement in depressive symptoms in the caregiver, accompanied by reduction in the child's unscheduled visits and improvement in asthma symptoms.[35] Strong associations were observed between changes in caregiver depression and the child's asthma symptoms (r = 0.78), asthma-related quality of life (QOL) (r = -0.85) and peak flow (r = -0.93). Findings from this pilot study suggest that treating the caregiver's depression may be important in improving asthma-related outcomes in the child. ***Our study aims to test this hypothesis. If affirmed, this could significantly change clinical practice in pediatric asthma and improve pediatric asthma outcomes.***

3.1.c. Mediators of the relationship between caregiver depression and child asthma outcomes. Another critical barrier to progress is that most research, to date, has focused on associations between caregiver depression and asthma, without examining how these associations are mediated. In order to develop effectively targeted child asthma interventions, it is necessary to know not only whether caregiver depression contributes to poorer asthma control in the child, but *how* it affects asthma control. Much of the research in this area focusing on "*how"* has been conducted by Drs. Wood and Miller (PIs). Lim, Wood and Miller[36] demonstrated that maternal depression predicted depression and anxiety in the child which, in turn, predicted worse asthma disease activity. More recently these investigators replicated this finding and extended it to fathers.[37] Furthermore, Miller and Wood's findings show how the child's depression may impact asthma through emotion and stress-related pathways (autonomic dysregulation),[38] while others have shown the impact of child's stress on asthma-related immune dysregulation.[39] ***Our proposed study will test the proposition that improvement in the child's anxiety and depression may mediate the effect of improvement in caregiver depression on the child's asthma, thus, providing knowledge that may inform future scientific theory and clinical practice.***

Adherence is a key factor in determining child asthma outcomes,[40] and is highly influenced by family context.[41, 42] Kub et al.[32] reported a relationship between maternal depression and the use of as-needed rescue medications (bronchodilators), suggesting poor adherence to controller medications in depressed mothers. Furthermore, a longitudinal study of low-income African American children, showed an association between caregiver depression and poor adherence.[43] Treatment adherence is critical for asthma control. Bender et al. noted that adherence in pediatric asthma is inadequate and that there is relatively little agreement on how to correct the problem.[44] ***Our study will test the proposition that medication adherence may be an additional mediating pathway by which caregiver depression impacts child asthma, thus, contributing scientific knowledge about causes of poor adherence and how to improve adherence.***

Based on the literature reviewed above, a model of two possible pathways linking caregiver depression to asthma symptoms and service utilization by the child is provided in Figure 1. We propose that improvement in caregiver depression results in improved asthma medication adherence and decreased anxiety/depression in the child, both of which contribute to improved asthma control and quality of life and decreased unscheduled service utilization. We include quality of life in our outcome measures because an essential purpose of asthma control is to ensure that the children thrive in their everyday lives.[45]

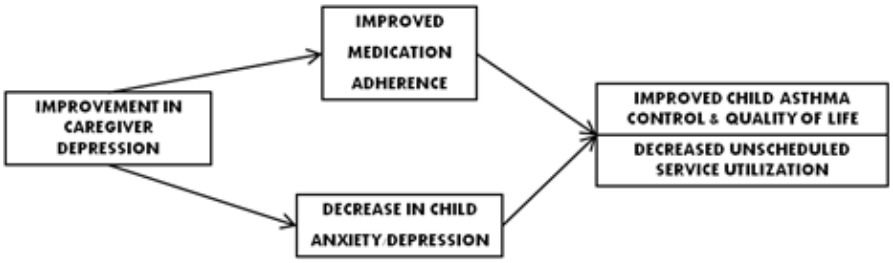


Fig. 1: Hypothesized pathways by which improvement in caregiver depression contributes to improved child asthma

Based on the literature reviewed above, we propose a longitudinal study in which we will follow depressed caregivers treated with antidepressant medications and their children with asthma every 4 weeks for 52 weeks to determine if improvement in caregiver depression is associated with subsequent improvement in the child's asthma. We will assess whether improved asthma outcomes is due to improved adherence, reduced child anxiety/depression or both. We will use an established antidepressant algorithm to guide treatment. The findings of this

study will lay the groundwork for a future clinical trial of a multi-modal intervention targeting caregiver depression and the mediating pathways of adherence and child stress and depression.
3.1.d. Summary of significance: The results of the proposed study may lead to a very different, and more efficacious, way of conceptualizing childhood asthma treatment in clinical practice, and thus improve outcomes and reduce morbidity. In addition, the algorithm-based antidepressant treatment approach we chose lends itself to primary care-based intervention, which makes such an intervention widely accessible.

3.2. Innovation: The *clinically* innovative aspect of this study is the attempt to improve childhood asthma outcomes by treating caregiver depression. If the finding supports the hypothesis that treating caregiver depression improves asthma outcomes, then, as discussed above, this approach may lead to a very different way of conceptualizing asthma treatment in clinical practice. The most *methodologically* innovative part of the study is using a repeated measures longitudinal design with cross-lagged panel modeling (CLPM) to statistically test whether the improvement of caregiver depression precedes and predicts subsequent child asthma improvement. To our knowledge, this method has not been used in asthma outcomes research. The *scientifically* innovative part of the proposal is identifying mediating pathways by which the effect of improvement in caregiver depression is transmitted to asthma improvement in the child. We will examine not only *if* caregiver depression impacts the child's asthma, but also *how* it makes this impact, by examining mediating pathways. Such specific knowledge has not been sought, to date, in previous studies. Finally, most studies focus on either adherence *or* stress and emotions as factors affecting asthma control. Our study will look at both potential pathways concurrently in order to examine their relative and joint contributions to asthma outcomes. This overall approach may offer a powerful new way of conceptualizing future outcomes research in asthma and in other physical and psychiatric diseases.

3.3. Approach
3.3.a. Preliminary Studies: The contact PI (Dr. Brown) has had four NIH grants, several foundation and industry grants, and a grant from the State of Texas on asthma patients. An ongoing R18 from National Heart, Lung, and Blood Institute (NHLBI) by the contact PI examines the treatment of depression in adults with asthma. Drs. Wood and Miller (PIs) have collaborated with him on many of these earlier studies. Their own Child and Family Asthma research program has been steadily funded by three National Institute of Mental Health (NIMH) grants for studies highly relevant to the current proposal. These studies demonstrated, in laboratory-based stress paradigms, pathways by which caregiver depression, negative parenting, and child stress and depression contribute directly to child asthma disease activity. All of the PIs' research staff members also have experience with this research population. Three prior studies of the contact PI (Dallas), and four by the other PIs (Buffalo), which are directly pertinent to the proposed study, are highlighted below.
3.3.a.i. Pilot Study 1: Psychiatric Symptomatology and Disorders Are Common in Caregivers of Children with Asthma: We examined the prevalence of psychiatric symptoms and disorders and their relationship to asthma-related service utilization in caregivers of Dallas children hospitalized for asthma.[33]
Methods: Caregivers (n = 175 enrolled over approximately 15 months) were assessed during the child's asthma hospitalization. Number of asthma-related hospitalizations, emergency room visits and unscheduled clinic visits in the past 12 months were quantified. The BSI, an assessment of psychiatric symptoms including somatic, anxiety and depression subscales, and the Mini International Neuropsychiatric Interview (MINI),[46] a structured clinical interview for psychiatric disorders, were administered.
Results: Mean age of the caregivers was 34.2 ± 7.3 years, and 96% were women. Both depressive (26%) and anxiety disorders (22%) were common. Caregivers with clinically significant elevations in the anxiety or depression BSI subscales reported more asthma-related hospitalizations for the child in the past 12 months than did caregivers with lower BSI scores (all $p < 0.05$). Asthma-related hospitalizations correlated with BSI total ($r = 0.20$, $p \leq 0.01$), anxiety ($r = 0.21$, $p < 0.01$), and depression ($r = 0.16$, $p \leq 0.05$) subscale scores. Caregiver psychiatric diagnosis of an anxiety disorder (n = 36) was associated with 43% more asthma-related hospitalizations (2.0 ± 2.5 vs. 1.4 ± 1.2, $p < 0.05$) in the child while current caregiver depression (n = 44) was associated with 50% more unscheduled clinic visits (3.0 ± 3.4 vs. 2.0 ± 2.6, $p < 0.05$).
Significance: This study demonstrates that the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)-defined psychiatric disorders, particularly depressive disorders, are common in asthma caregivers and associated with a greater frequency of asthma-related service utilization by the child. The study also supports feasibility by demonstrating that we can enroll large numbers of caregivers in a research study.
3.3.a.ii. Pilot Study 2: Antidepressant Treatment of Caregivers of Children with Asthma Improved the Child's Asthma: This pilot study, conducted in Dallas, examined the impact of antidepressant treatment on the caregiver's depression and the child's asthma.[35]
Methods: Eight currently depressed asthma caregivers (6 women and 2 men, mean age of 35.8 ± 6.6 years) were enrolled in this intervention study with monthly assessments for 6 months, and received algorithm-based

antidepressant treatment. The children were 5 boys and 3 girls with a mean age of 9.8±3.8 years. Caregiver depressive symptoms were assessed with the Hamilton Rating Scale for Depression (HRSD)[47] and Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR).[48] Spirometry was obtained and asthma symptoms quantified using the Pediatric Asthma Symptom Scale (PASS). Hospitalizations, emergency room visits, and unscheduled clinic visits were also assessed.

Results: Caregiver depressive symptoms and the child's asthma symptoms improved significantly (Table 1). Emergency Room (ER) and unscheduled visits decreased with substantial effect sizes, but did not reach statistical significance because of the small sample size. ***Reduction in caregiver HRSD scores correlated strongly with change in peak expiratory flow (r = -0.93, p = 0.002), PASS (asthma symptoms) scores in the child (r = 0.78), as well as quality of life in the caregiver (r = -0.85, p = 0.007).***

Table 1. Caregiver Depressive Symptoms, Caregiver and Child Quality of Life, Child Asthma Symptoms, and Asthma-related Service Utilization Before and During Antidepressant Treatment

Assessment	HRSD (Caregiver)	QIDS-SR (Caregiver)	PASS (Child)	Asthma Related Hospitalizations (per month)	ER Visits (per month)	Unscheduled Clinic Visits (per month)
Baseline Exit	20.9 ± 5.8 15.5 ± 7.9	13.9 ± 3.9 10.9 ± 4.9	19.4 ± 9.9 13.3 ± 8.0	0.13 ± 0.06 0.11 ± 0.17	0.30 ± 0.21 0.16 ± 0.18	0.34 ± 0.39 0.14 ± 0.18
Significance	p = 0.08	p = 0.03	p = 0.05	p = 0.76	p = 0.06	p = 0.07
Effect size (Cohen's *d*)	0.84	0.68	0.68	0.16	0.72	0.66

Significance: ***Findings from this pilot study suggest that antidepressant treatment was associated with improvement in caregiver depression as well as reduction in asthma symptoms and service utilization for the child.*** In addition, the study demonstrates a strong relationship between change in caregiver depressive symptoms and the child's asthma. These findings suggest that improvement in depressive symptoms in caregivers may be associated with improved outcomes related to the child's asthma.

3.3.a.iii. Pilot Study 3: Depressive Symptoms are Common in *Children* with Asthma, and They May Impact Asthma-related Service Utilization: This pilot study examined depressive symptoms in ***children*** with asthma, *not* their caregivers.[22]

Methods: Participants were recruited during visits at a Dallas asthma clinic. Inclusion criteria included a physician diagnosis of asthma, and ages 6-17. Demographic and medical information was obtained from the patient and guardian, treating physician, and medical record including age, gender, current medications, number of hospitalizations, ER visits, and oral steroid courses in the past year. In addition, the current Forced Expiratory Volume (FEV_1) % predicted was obtained from routine spirometry on the day of clinic visit. The valid and standardized Children's Depression Rating Scale, Revised (CDRS-R)[49] was administered. Participants were divided by FEV_1% predicted (> 80 vs. $\leq$ 80), inhaled steroid dose (high dose vs. medium/low dose/none based on NHLBI guidelines),[50] oral steroid use, and number of hospitalizations or ER visits in the past 12 months.

Results: A total of 46 children with asthma were enrolled (63% male, mean age 9.9 $\pm$ 2.8 years). Eighty-six percent of children were on medium or high doses of inhaled corticosteroids. Forty-one percent of children had FEV_1% predicted < 80% despite taking inhaled corticosteroids. In this population of children with asthma 14 (30%) had CDRS-R scores with the range of likely, very likely, or almost certain depression. Higher mean CDRS-R scores were found in children with a hospitalization in the past year (64.2 ± 9.1 vs. 56.9 ± 12.5, p = .03, Cohen's *d* = 0.67).

Significance: These data demonstrate that depression was common in the children and was associated with hospitalization in the past year. Thus, they suggest that one possible pathway by which maternal depression may affect a child's asthma is through the child's own depression.

Drs. Miller and Wood (PIs) report four studies below from the Buffalo site directly pertinent to the current proposal.

3.3.a.iv. Pilot Study 4: Relationship between Maternal Depression, and Depression and Asthma Control in the Child: This study examined the relationship between maternal depression and child depression and asthma disease activity mediated by parenting and medication adherence. A sample of 242 children (59% male) with asthma, aged 7 to 17, participated with their mothers. Maternal depression was assessed by the Beck Depression Inventory (BDI), and parenting was observed and rated during family interaction tasks using the Iowa Family Interaction Rating Scale (IFIRS), a widely used valid rating scale. Child depression and anxiety were assessed by the Child Depression Inventory (CDI), the CDRS-R, and the Speilberger State Trait Anxiety Inventory for Children (STAIC). Asthma disease activity was assessed according to NHLBI guidelines, and medication adherence was evaluated with Bender's validated 24-hr recall method (Childhood Asthma Management Program Continuation Study, CAMPCS). Structural equation modeling indicated that maternal depression predicted child depression and anxiety (B = .39, p < .001) and, in turn, child depression and anxiety mediated associations between maternal depression, negative parenting and asthma disease activity (B = .36,

$p < .001$). Medication adherence did not mediate the link from maternal depression to disease activity.[51]

3.3.a.v. Pilot Study 5: Replication of Pilot Study 4 with Fathers and Mothers: Using the same methodology as above, Wood replicated this study with co-habiting fathers and mothers of children with asthma aged 7-17 (n = 106, 65% male). Structural Equation modeling showed that the path from maternal depressive symptoms to child depression and anxiety through mothers' parenting behaviors was significant, Chi Square (32, *N* 106) = 57.50, $p < .004$; incremental fix index (IFI)= .89, comparative fit index (CFI) = .87, root mean square error of approximation (RMSEA) = .09; and in turn, child depression and anxiety predicted asthma disease activity ($B = .28$, $p < .05$). Paternal depressive symptoms were linked to child asthma disease activity only through the effect of inter-parent negativity (B=.32, p<.01*)* on maternal parenting of the child.[52]

Significance: These two studies illustrate possible mediating pathways by which caregiver depression impacts the child's asthma by way of depression in the child.

3.3.a.vi. Pilot Study 6: Relationship Between Child Stress and Emotions with Asthma and Airway Function: Miller (PI) developed a laboratory film stress protocol to test autonomic mechanisms by which child depressive emotions impact airway function in asthma. Miller chose the film "E.T., the Extraterrestrial" because of its ecological validity in evoking emotional responses to situations similar to those experienced by children with asthma, e.g. family stress, separation and loss, illness, and fear of death. A preliminary study of 24 children with asthma assessed the effects of the film stress on continuous heart rate, heart rate variability (HRV), oxygen saturation, and pulmonary function (FEV_1). FEV_1 was associated with emotional and physiological (HRV) reactivity and decreased pulmonary function in response to the movie,[53] especially during sad/hopeless scenes.[24]

3.3.a.vii. Pilot Study 7: Airway Reactivity in Depressed Children with Asthma: Using the same film stress methodology, the effect of child depression/autonomic nervous system (ANS) dysregulation on airway function was demonstrated in a study of depressed (D) and non-depressed (ND) children with asthma (N = 171). The D group, in comparison with the ND group, showed significantly greater vagal activation in response to the family distress/loss scene ($p < .03$); the E.T. dying scene ($p < .003$); and the E.T. death scene ($p < .03$). The ND group showed consistent sympathetic activation ($p < .04$), whereas the D group showed vagal activation ($p < .03$). Furthermore, the D group showed robustly and significantly higher airway resistance compared with the ND group ($p < .001$). Finally, vagal bias (vagal vs. sympathetic activation) was associated with respiratory resistance ($r = 0.39$, $p < .004$).[38] These findings are consistent with Miller's autonomic dysregulation theory of the effect of depression on pulmonary function which posits that depression is accompanied by a preponderance of vagal over sympathetic activation, which is problematic for asthma because cholinergic/vagal activation is one mechanism of airway constriction.[54]

Significance: These studies demonstrate a psychobiologic stress pathway by which the child's depression affects asthma. This is a plausible mediating pathway by which caregiver depression affects child asthma.

3.3.a.viii. Summary of Findings from Preliminary Studies and the Literature: 1) Our pilot studies show that we can successfully enroll and retain caregivers and children with asthma in research studies. 2) Our pilot data suggest that psychiatric disorders, especially depression, are very common in caregivers of children with asthma. 3) Caregiver depression is associated with more severe childhood asthma and greater service utilization. 4) The literature and Miller and Wood's preliminary studies suggest that caregiver depression contributes to worse asthma in the child, possibly mediated through stress/depression pathways. 5) The literature suggests that poor adherence is also a likely mediator between caregiver depression and child asthma. 6) Based on our pilot data, treatment of depression in the caregiver was associated with improvement in caregiver depression and a reduction in asthma symptom severity and service utilization by the child.

Given these findings, a study of caregivers and their children with asthma is proposed. **We will test these hypotheses: 1) Improvement in caregiver depression leads to subsequent improvement in the child's asthma control, quality of life, and service utilization. 2) Improved adherence and/or decreased child anxiety/depression mediates the effect of improved caregiver depression on child asthma outcomes.** To test these hypotheses depressed caregivers will be offered algorithm-based antidepressant treatment by the research psychiatrists, and the impact of changes in caregiver depression on asthma in the child will be examined for 52 weeks (1 year). Mediating pathways linking caregiver depression and the child's asthma will be examined.

3.3.b. Overview and rationale of study design: We propose a one-year, repeated measures, within-subject design to examine the impact of improved caregiver depression on child asthma outcomes. A CLPM for longitudinal data will be fit using a maximum likelihood structural equation model (SEM) in order to explore longitudinal mediation between asthma outcomes (asthma control, spirometry, QOL) and depressive symptoms. CLPM will test whether caregiver improvement preceded child asthma improvement, and SEM will test whether improved adherence and/or decreased child anxiety/depression mediated the effect. We considered a randomized control trial, but it would not be ethically acceptable to withhold medication from caregivers diagnosed with MDD for the proposed one-year duration of the study. It is unlikely that potential

participants in the study would find this acceptable. Furthermore a controlled design is not necessary since we are not testing the efficacy of antidepressants for depression, but rather the impact of improvement on caregiver depression on the child.

3.3.c. Experimental Procedures: Depressed caregivers will be identified using two methods. At the Buffalo and Dallas sites, clinicians at clinics specializing in childhood asthma will inform caregivers that we are doing a study to try to figure out how best to help children with asthma and their caregivers, and will ask the caregivers if a research coordinator can ask them some screening questions related to depression and their child's asthma. If they agree, then a research coordinator at the clinic will introduce themselves, provide a brief, scripted description of the study, and, after obtaining verbal permission, will ask the caregiver questions from a 2-item questionnaire[55] for current depression (assessing depressed mood and anhedonia) (Appendix 1). Caregivers who screen negatively (not likely depressed) will be debriefed and thanked for their willingness to be screened. Caregivers with a positive response to either screening question will be given additional information about the study. The aims of the study will be clearly presented. The study will be framed in the context of developing more comprehensive assessment and treatment of stress-related conditions with the goal of improving the caregiver's and child's QOL and the child's asthma management. At this point potential caregivers who are interested in the study will complete an IRB-approved informed consent process, and an appointment will be scheduled for a full baseline assessment. In order to ensure recruitment from the broadest possible population of children with asthma, an additional method of recruitment will be used at the Dallas site. This approach will be through a very large database in the Parkland Hospital Community Oriented Primary Care (COPC) clinics. Using methods employed in prior IRB and HIPAA office-approved studies using this system, caregivers of children with an asthma diagnosis and within the study age range will receive a letter by mail describing the study and providing contact information. This recruitment letter has been presented to the Community Advisory Panel (CAP) at Parkland for evaluation, and the feedback from the community members has been incorporated into the wording of the recruitment letter. If no response is received in 2 weeks, then the research coordinator will call the caregiver and ask if they might tell the caregiver about this study. If they decline, no further contact will be made. If they express interest and answer "yes" to one of the 2-item depression screening questions above, then an appointment will be scheduled to obtain written consent and for a complete baseline assessment.

The baseline assessment will take approximately 2.5 hours and will consist of a 45-60 minute structured clinical interview (SCID) using DSM-4 criteria to establish psychiatric diagnoses, depression, quality of life, and other assessments (see Table 2 for a complete list), as well as information about number of asthma-related hospitalizations, ER visits, and unscheduled clinic appointments by the child within the preceding 12 months as assessed by caregiver report (and confirmed through medical records when possible). Caregivers not meeting criteria for the intervention study will be paid for the initial assessment, informed of any psychiatric disorders identified (e.g. a psychiatric disorder other than MDD) and, when appropriate, given referral information. Caregivers with current MDD and meeting all inclusion criteria will be offered algorithm-based depression pharmacotherapy for 52 weeks. If a caregiver does not elect to participate in the algorithm-based treatment, they will remain eligible to enroll in the study and will receive referral information for an alternative depression treatment (e.g., psychotherapy) from a study psychiatrist. The caregiver will be still eligible to enroll in pharmacotherapy during a later stage of the study and will be advised by a study psychiatrist if they elect this option. Furthermore, participants who are currently receiving or plan to receive treatment for depression (e.g. medication, psychotherapy) by a healthcare provider outside of the study may also participate. In these cases the participants will receive all of the assessments and physician evaluation but will not receive algorithm-based treatment as part of the study. This protocol modification should improve enrollment by allow potential participants who prefer psychotherapy or want to receive antidepressant care from their PCPs to enroll. Given the inclusion, exclusion and discontinuation criteria, as well as the careful monitoring during the study this change should not adversely impact the safety profile of the study. The change is scientifically sound because the aims of the study are related to relationships between depressive symptom changes in the caregiver and asthma control in the child regardless of the method by which the changes were achieved. A total of 196 caregivers will be enrolled. A modified and simplified version the Texas Medication Algorithm Project (TMAP) MDD guidelines (Appendix 2) will be utilized to guide treatment. Caregivers and children will be assessed every four weeks (weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52) with additional phone assessments 2 weeks after medication changes to assess for adverse events, medication side effects, or suicidality, and to confirm the next clinical appointment. Follow-up assessments will take approximately 1.5 hours including psychiatrist assessment and quality of life, asthma adherence, anxiety and depression questionnaires administered by a research team member. Caregivers will be assessed by a study psychiatrist at appointments for medication management. Caregivers will be paid $60 for the baseline visit and assessments every 4 weeks (weeks 4-52). Children will be paid $20 at each visit. Bus, rail, or taxi expenses will be reimbursed if these transportation methods are needed. Both caregivers and children will be paid using a UT Southwestern issued

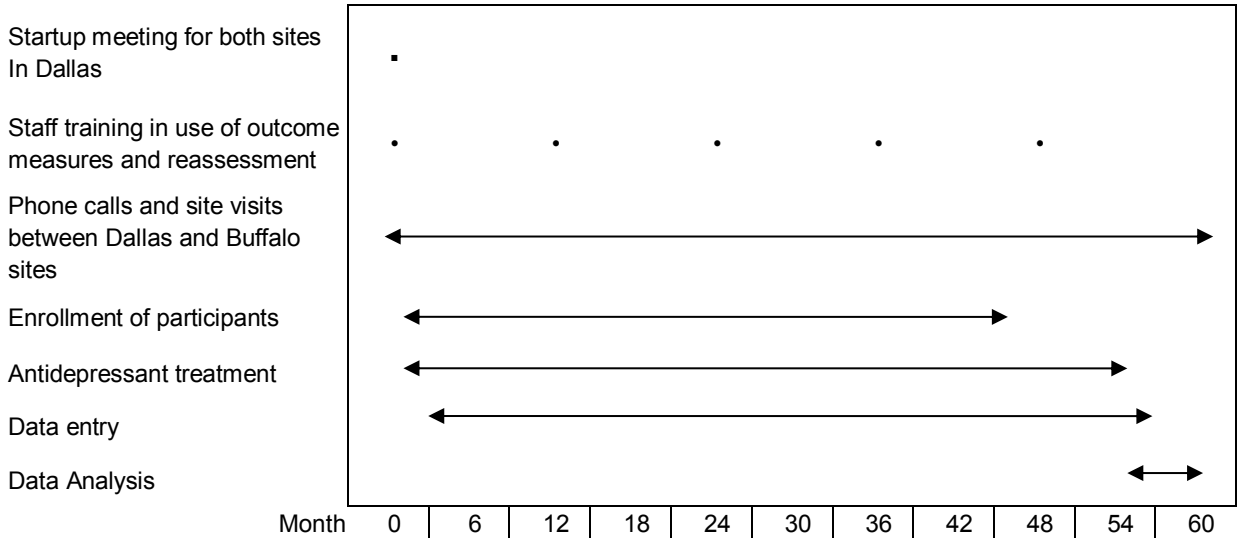
Greenphire ClinCard, which can be used as a credit or debit card. Caregivers who are consented and come to our clinic for a baseline assessment but not meet all of the entry criteria will be given $20 for their time and inconvenience. This smaller payment reflects the generally shorter time required when a participant does not qualify for the study because the assessments stop at the point that an exclusion criterion is identified.

3.3.c.i. Inclusion/Exclusion Criteria

Inclusion Criteria: Primary Caregivers (defined as the adult who is primarily responsible for the child's asthma management): Male or female, ages 18 to 70, primary asthma caregiver of the child, currently meeting criteria for MDD (based on DSM-4 depression symptoms for at least 2 weeks and causing clinically significant distress or impairment in social, occupational, or other important areas of functioning) based on a SCID interview. Child: Male or female, ages 7-17 years who have a diagnosis of ***persistent asthma*** as classified by either of the following criteria: **A.** requirement for treatment with daily controller medication; or **B.** symptoms of persistent asthma in children not on a daily controller medication: 1. Daytime symptoms two or more days per week; 2. Rescue bronchodilator use two or more times per week; 3. Nocturnal symptoms two or more nights per month; or 4. Two or more oral steroid bursts in the last year.[56]

Exclusion Criteria: Caregivers: Severe cognitive impairment that could impair their ability to provide informed consent; member of a vulnerable population (incarcerated, pregnant or breastfeeding women); women of childbearing age who will not use acceptable methods of birth control or abstinence during the study; severe psychiatric disorder in addition to MDD that should be a primary focus of treatment (e.g. severe and disabling eating or anxiety disorders); treatment refractory depression defined as failing ≥ 3 adequate trials of antidepressants (≥ 4 weeks at a therapeutic dose); electroconvulsive therapy or repeated transcranial magnetic stimulation during the current episode; depression as part of bipolar disorder or schizophrenia or schizoaffective disorder, or current depression secondary to substances or general medical condition, or with psychotic features or accompanied by severe obsessive compulsive disorder (OCD), or high risk for suicide defined by multiple recent suicide attempts (> 2 in the past year) or any attempt in the past month, or current suicidal ideation with a well-formed plan or intent. Child: Severe cognitive impairment that could impair their ability to provide informed consent; high risk for suicide defined by multiple recent suicide attempts (≥ 2 in the past year) or any attempt in the past month, or current suicidal ideation with a well-formed plan or intent; severe or life-threatening medical illness, such as other serious cardiopulmonary conditions (e.g. congenital heart disease, cystic fibrosis, alpha-1-antitrypsin disease) or cancer, which would confound the assessment of asthma, anxiety, depression or QOL; severe psychiatric illness, such as autism, bipolar disorder, schizophrenia or current drug/alcohol abuse/dependence. If an eligible caregiver presents with more than one child meeting inclusion criteria for the study, only one child, randomly selected, will be enrolled.

Figure 2. Timeline for Study



3.3.c.ii. Participant Enrollment: Dallas: The Dallas pediatric asthma clinic (Dr. Neaville) that will be used for enrollment has 459 current active patients in the age range proposed for the study and 174 new patients in this age range each year. Given these numbers, if 26% of caregivers have current MDD (as in our pilot study) then over a 4 year enrollment period, we will have 300 eligible participants. To enroll 98 participants, 33% of these will need to agree to participate. We realize that enrollment is challenging in any clinical research study.

Furthermore, MDD rates could be lower than in our pilot, and participation rates could be less than 33%. Therefore, to augment enrollment at the Dallas site, we will use the Parkland COPC database to identify and contact potential participants. As of September 4, 2013, this database had 3500 children with asthma in the age range with 707 new patients entering the system each year. If, as in our pilot study, 26% of caregivers have current MDD, this potentially provides 1645 potential participants. Thus, if 6% of potential participants agreed, we could enroll 98 over 4 years. A study by Drs. Tiro and Persaud (co-Is) using this database to recruit girls ages 11-18 in a study about the human papilloma virus (HPV) vaccine employed similar recruitment methods to those in the proposed study. In this study from February and December 2011, the investigators evaluated 2160 Parkland COPC patient records, of which 875 (40.5%) appeared to be eligible. Of these 875, a total of 337 (38.5%) were enrolled. About 1.4% of recruitment letters were returned due to an incorrect address, in which case recruitment calls were still attempted. Over 3000 recruitment calls were made, with patient contact attempted an average of 3.7 times per patient. The 538 patients who did not complete the pre-clinic survey had the following study outcomes: unable to contact (19.1%), wrong number/out of order (10.7%), maybe later (14.2%), not eligible (11.4%), no-shows (9.8%), and not interested (6.5%). These data suggest that the database is a useful method for recruiting research participants and will supplement recruitment from the asthma clinic.

Buffalo: The Buffalo pediatric asthma service (Dr. Lehman, co-I) that will be used for enrollment is a three-site practice with a diverse patient demographic. The main clinic site is an inner-city clinic attached to the Women and Children's Hospital of Buffalo. In addition, there is a suburban satellite clinic and a suburban/rural satellite clinic. The Buffalo pediatric asthma service has 1160 patients in the age range proposed for the study and 315 new patients in this age range each year. Given these numbers, if 26% of caregivers have current MDD (as in our pilot study), then over a 4 year enrollment period the site will have 547 eligible participants. To enroll 98 participants, 18% of these will need to agree to participate.

Participant retention: We will use established methods for recruiting and retaining populations over long periods of time. Drs. Wood and Miller have used these methods throughout their multi-visit studies and obtained excellent retention statistics (95% completion of a 6 week study). Dr. Brown (PI) was an investigator on TMAP, a large multisite study using treatment algorithms for one year in patients with psychiatric illnesses in a similar fashion as the proposed study. In the MDD module of TMAP, retention was 100% at 3 months, 99.5% at 6 months, 83.2% at 9 months and 75.9% at 12 months. To maximize retention in the proposed study, multiple contact numbers (home, cell, work, family, friends), mailing addresses, and e-mail addresses will be obtained. Participants will be compensated appropriately for participation, transportation, time, and effort. Participants will have contact with research staff every 2-4 weeks either by phone or in person to keep them engaged in treatment. Participants are in the study for 52 weeks even if they miss some appointments, and we will collect as much data from each participant as possible. It is noteworthy that our data analytic procedures have robust methods of dealing with missing data. In addition, we propose enrolling 196 participants, rather than the 175 needed based on a power analysis, to allow for some early attrition.

3.3.c.iii. Medication: Caregivers with current MDD will be offered antidepressant treatment from a research psychiatrist at no cost for 52 weeks. All medications used will be FDA-approved for MDD. The antidepressants and augmenting agents selected are widely used. We will provide these to the participants at each visit. This method of dispensing medications is different than in clinical practice where a patient would receive the medication at a pharmacy. We propose to use this method to enhance medication adherence and optimize internal validity of the study. Adherence to medication will be assessed by pill counts. We will use a simplified version of the TMAP MDD algorithm that has been adapted for this study. The algorithm is flexible because participants will potentially enter the study with different treatment histories. The doses of antidepressant will be titrated upward, to the FDA-approved maximum if needed, with the goal of achieving depression remission or full response. If the participant is already taking an antidepressant, they will remain on the prescribed medication until the first evaluation stage required by the algorithm and the doctor will assess how well the medication is working at that stage. If this is the first depressive episode and during the course of the study the participant's depression symptoms improve to the point at which they may no longer require medication, the doctor can evaluate if subject should be tapered off the medication. This would only be after at least 6 months of full remission of symptoms. At any time, the subject is free to decide to discontinue taking medication but can remain in the study under the study doctor's care. This decision will be fully discussed with the study doctor for safety reasons. After 12 weeks a change of medication or augmentation can be performed depending upon level of response. This process is repeated at weeks 24 and 36 at which time additional augmentation strategies are allowed. The

objective is to provide active treatment with careful monitoring of depressive symptoms using remission as the goal. For additional medication and algorithm information see Appendix 2. Due to the known side effect profiles of these medications, ECGs and blood tests will be performed in the study as deemed necessary by clinician judgment.

Table 2. Assessment Schedule (Baseline + 13 assessments)

Instrument	Respondent	Wk 0	Wk 4 – 48	Wk 52	Time
2-SRSD	Caregiver	X			3 min
SCID	Caregiver	X			45-60 min
HRSD	Caregiver	X	X	X	15 min
QIDS-SR_{16}	Caregiver	X	X	X	10 min
STAI	Caregiver	X	X	X	15 min
PACQOL	Caregiver	X	X	X	10 min
PRD-III	Caregiver	X	X	X	5 min
UPT*	Caregiver	X	X	X	1 min
ECG*	Caregiver	X	X	X	5 min
Blood panels*	Caregiver	X	X	X	5 min
CAMPCS	Caregiver & Child	X	X	X	5 min
PSS	Caregiver & Child	X	X	X	5 min
CVLT/CVLT-C	Child	X			20 min
CASI	Child	X	X	X	10 min
Relatedness Scale	Child	X	X	X	5 min
SCARED	Child	X	X	X	10 min
CDI Full Length	Child	X	X	X	15 min
PAQOL	Child	X	X	X	15 min
ACT/cACT	Child	X	X	X	3 min
Spirometry	Child	X	X	X	5 min
Debriefing Interview	Caregiver & Child			X	30 min
COVID-19 Interview	Caregiver		X	X	5 min

**these tests will be performed as clinically indicated based on physician judgment. UPT will be performed at Wk 0 and again as clinically indicated.*

3.3.d. Assessments and Outcome Measures

***3.3.d.i. Psychiatric diagnoses*:** The SCID for DSM-4 Clinician Version (SCID-CV) is a fairly brief version of the SCID that assesses Axis I disorders in DSM-4 including MDD, dysthymic disorder, bipolar disorders, schizophrenia, anxiety disorders, eating disorders, and drug/alcohol abuse/dependence. ***3.3.d.ii. Depression and anxiety measures*:** A 2-item self-report screening tool for depression (2-SRSD) taken from the Primary Care Evaluation of Mental Disorders Procedure (PRIME-MD) screening interview will be used to detect suspected cases of depression among asthma clinic caregivers.[55] This instrument had better sensitivity (96%) than either the Center for Epidemiologic Studies Depression Scale (CES-D) (93%) or BDI (89%) in identifying depression as defined by structured clinical interview in a general medical clinic.[55] Specificity of the 2-SRSD was 57%. A positive answer to either 1) "During the past month, have you often been bothered by feeling down, depressed, or hopeless?" or 2) "During the past month, have you often been bothered by little interest or pleasure in doing things?" will be considered a possible case of depression and qualify for further assessment. Dr. Brown has used this screening tool in prior studies including an ongoing NHLBI-funded study in adults with asthma. The HRSD (17-item version)[47] is an observer-rated measure of depressive symptomatology. The HRSD will be given at every visit. Because of its wide use for many decades, the HRSD will be the primary measure of caregiver depressive symptoms in the study. The QIDS-SR[48] is a validated 16-item self-report scale that assesses depressive symptom severity. Scores of ≤ 7 are considered normal, 8-12 suggest mild depressive symptoms, 13-16 moderate depressive symptoms, 17-20 moderate to severe depressive symptoms, and ≥ 21 severe depression. The use of these two depression instruments allows us to assess changes in both clinician-rated and self-reported depressive symptoms and their relationship to asthma outcomes. Perceived Stress Scale (PSS) is a 10 question self-report measure validated in middle school children and adults, and available in both English and Spanish. This instrument will be administered to the caregiver and the child at each visit, and will allow for detection of changes in stress levels that are not as severe as depression and anxiety. Research coordinators will assist younger children, if necessary, by helping them read and understand the questions. The Relatedness Questionnaire is a validated 17-item questionnaire completed by the child regarding his or her primary caregiver. It will assess the quality of the child's self-reported relationship with the caregiver.[57] Screen for Child Anxiety Related Disorders (SCARED) is a 41-item self-report scale, validated in

both English and Spanish. This scale has 3-point response options and assesses children's anxiety level within the last 3 months.[58] The Children's Depression Inventory Full Length (CDI Full Length) is a 27-item self-report scale designed to assess depression in children and validated in both English and Spanish.
The COVID-19 Interview is intended to take into account the impact of the COVID19 pandemic on the factors under study in our research. One goal is to assess whether caregiver depression and child asthma control worsened after the onset of the COVID19 pandemic. We will accomplish this by comparing the severity of caregiver depression and the degree of control of the child's asthma in the months before the COVID19 to the caregiver severity depression of and control of child's asthma during the COVID19. This is data that is collected under the currently approved study protocol. In addition, one of our IRB approved research staff and/or a study psychiatrist will ask the caregivers to report on the perceived impact of COVID19 on their own emotional state and functioning, and on the emotional state and asthma control in their child.
***3.3.d.iii. Quality of Life*:** The Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQOL)[59] measures the problems that the parents of children with asthma experience as a result of their child's asthma. There are 13 questions in 2 domains (activity limitations and emotional function) that were selected on the basis of their importance to the parents themselves. The questionnaire is self-administered and has 7-point response options. Pediatric Asthma Quality of Life Questionnaire (PAQOL)[59] measures problems that children experience as a result of their asthma. It has 23 items in 3 domains (symptoms, activity limitations, emotional function); 3 of the activity questions are "patient-specific" and identified by the patient at the beginning of the study. Items were selected on the basis of their importance to the children themselves. The questionnaire has 7-point response options and takes approximately 10 minutes to complete. California Verbal Learning Test (CVLT-II or CVLT-C for children under 16 years of age) is a validated assessment that measures episodic verbal learning and memory, and is sensitive to the effects of inhaled corticosteroids that many child participants with asthma take daily. CVLT consists of 16 nouns read aloud to the participant in one-second intervals over five learning trials. After each trial, participants are asked to recall as many words as the can in any order.
***3.3.d.iv. Asthma Severity, Control and Outcomes*:** Asthma outcome measures to be used in this study will adhere to the recommended asthma clinical research core outcome measures recently proposed by the NIH's Asthma Outcomes Workshop.[60] We will incorporate information on asthma exacerbations, healthcare utilization, pulmonary function, quality of life, composite control scores, and asthma symptoms into our outcome measures. Exacerbations will be assessed by caregiver report at each study visit. Exacerbation outcomes will include systemic steroid courses, asthma-specific hospitalizations, asthma-specific emergency department visits/urgent care visits, and asthma-specific intensive care unit admissions/intubations since the last appointment. Healthcare utilization relating to each child's asthma will be assessed, including asthma-specific hospitalizations, asthma-specific emergency department visits/urgent care visits, asthma-specific outpatient visits, and asthma-specific medication use. The number of asthma-specific hospitalizations, emergency department visits and unscheduled clinic appointments by the child in the prior year and during the 1 year of the intervention will be assessed by caregiver report using a calendar to facilitate recall. This information will be supplemented with data obtained directly from the child's hospital, primary physician/asthma specialist, and pharmacy records.

Spirometry data, including % predicted of FEV_1, forced vital capacity (FVC), and FEV_1/FVC ratio will be collected on the child at all study visits using a portable spirometer (EasyOne Plus, NDD Medical Technologies, Inc. Andover, MA).

As a measurement of asthma control, the Asthma Control Test (ACT) will be administered to children ages 12+ at each caregiver depression study visit and the Childhood Asthma Control Test (cACT) will be administered to children ages 5-11.[61, 62] The ACT and cACT tools represent a continuum of asthma control assessment tools across childhood age ranges. In both tools, a score of > 19 signifies controlled disease and scores of ≤ 19 signifies uncontrolled asthma. Thus, the scores can be combined in the data analysis.

The Composite Asthma Severity Index (CASI) will be obtained on the child at baseline and at all study visits.[63] CASI was developed by the National Institutes of Health–supported Inner City Asthma Consortium (ICAC) and includes five domains: day symptoms and albuterol use, night symptoms and albuterol use, controller treatment, lung function measures, and exacerbations. The CASI tool has been validated to assess asthma severity in children between 6 and 20 years of age. Because it combines domains of impairment and treatment level to assess asthma severity, the CASI score remains steady through changes in standard guidelines-based asthma care (i.e. step-up or step-down asthma controller therapy). Therefore, it has utility in assessing response to new asthma treatment/intervention modalities such as our proposed intervention, which may not only alter asthma symptoms but the requirement for asthma controller treatments as well.[63]
3.3.d.v. Adherence: CAMPCS medication adherence interview is a brief 9-item clinician-rated scale assessing controller medication adherence in the past week that can be administered over the phone or in person.[64] The CAMPCS interview, along with its specific manner of presentation, has established reliability and validity.[65] The interview shows impressive sensitivity to asthma inhaler adherence, assessed via electronic monitoring.[66]

3.3.d.vi. Medication Side Effects and Adverse Events: Antidepressant side effects and adverse events will be inquired about at each clinic and phone visit. In addition, The Psychobiology of Recovery in Depression III - Somatic Symptom Scale (PRD-III),[67] a 24-item side effects rating scale developed for a longitudinal depression study at the University of Pittsburgh, will be utilized to formally assess somatic complaints. The PRD-III covers a wide range of common medication side effects and can be quickly and easily administered by a clinician. Dr. Brown has used this scale in numerous prior studies. Spirometry results at each visit will be also used to evaluate whether the children need to follow up with their primary care provider or the emergency room. Dr. Lehman has designed a safety protocol to ensure that if any of the following signs/symptoms are present, then a child needs to be referred to the medical doctor or the emergency services: albuterol use prior to the study visit more closely spaced than every 4 hours, child's FEV_1 on spirometry is 50% predicted or less, caregiver is concerned that child's is experiencing a significant asthma attack. Additionally, the children will be immediately referred to 911/emergency room for transport in presence of the following: child can't talk without gasping/losing breath, child is hunched forward with deep breathing, chest/neck pull is during each breath, nostrils flaring (open wide) during each breath, lips or fingertips look blue.

3.3.e. Assessment Training

Staff members are already familiar with the assessments from prior or ongoing research projects at the Dallas and Buffalo sites. We will schedule formal training in the instruments for research staff from both sites in Dallas prior to participant enrollment. For the psychiatric diagnosis and mood and anxiety scales, we will arrange training through the UT Southwestern Psychiatry Clinical Research Infrastructure (P-CRI) by David Morris, Ph.D. Dr. Morris is a highly experienced trainer for almost all commonly used psychiatric symptom scales and performs this role in the ongoing multisite NIMH Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) study. A mock patient will be interviewed. Intraclass Correlation Coefficients (ICC) will be calculated and additional training will be provided, when needed, for individual raters with scores outside the acceptable range. The goal will be an ICC of at least 0.8. The most recent assessment of Dr. Brown's research team showed an ICC of 0.98 on the HRSD. Dr. Wood will provide training on the use of the CAMPCS, PACQOL, PAQOL questionnaires, which she has used extensively in previous studies. Training in the use of asthma-related outcomes, including the CASI and portable spirometer, will be conducted by Dr. Lehman. Research coordinators at the Dallas site already use a portable spirometer in an ongoing NHLBI-funded study examining the effect of antidepressant treatment on adult asthma. However, to assure proper use of the spirometer, reassessment of proper spirometry use will take place on site (Drs. Lehman-Buffalo, Dr. Khan-Dallas) every 4 months. Retraining and reassessment for other scales will be conducted on an annual basis.

Rater Blinding: We propose to have different raters assess the child's asthma symptoms and the caregiver's depression. Each rater will be blinded to the data obtained by the other rater. Participants will be instructed to not discuss the results with the other rater or the raters among themselves. This procedure is proposed to maximize the objectivity of the ratings of the outcome variables and minimize any biases or assumptions based on the hypotheses of the study. One outcome measure (CAMPCS) will use adherence feedback from both caregiver and child. Since this is an outcome related to the child's asthma management, this assessment will be administered by the staff member performing ratings on the child, and this staff member will be blind to the caregiver mood ratings and scores.

3.3.f. Data Management: A highly experienced data manager from the UT Southwestern P-CRI will set up the database, and monitor and advise the research team throughout the study. The data manager has managed data in much larger multisite depression research studies (e.g. TMAP, STAR*D). At the beginning of the study, a database format will be designed by the Dallas-based data management team in collaboration with Dr. Wood in Buffalo. A manual containing that format will be transmitted to Buffalo, and Dr. Wood will supervise its implementation and maintenance. Data will be maintained at the site of collection (Dallas or Buffalo). However, de-identified data (containing a study ID number but not name, SS#, or DOB) that will be used in the data analysis (e.g. depressive symptoms, asthma control) from the Buffalo site will be sent electronically to the Dallas site on a weekly basis. These data will be reviewed each week by the Dallas monitor and any errors or inconsistencies will be discussed. A data monitor from both the Dallas and Buffalo sites will review data charts and corresponding digital database content weekly and provide feedback to the PIs and research staff on data quality and recommend remediation, if necessary. To assure consistency and accuracy between sites, the data monitor from the Dallas site will travel to Buffalo every 6 months to review the data collected (e.g. charts) at the Buffalo site. The data will be checked for errors or inconsistencies, extreme values, and missing data which will be discussed and resolved.

3.4. Statistical Analyses

Aim 1. Determine if improvement in depressive symptoms in caregivers of children with asthma predicts subsequent improvement in the child's asthma control. A CLPM for longitudinal data will be fit using a maximum likelihood SEM in order to explore reciprocal causation between asthma outcomes and depressive symptoms with lagged effect. A separate model will be constructed for each asthma outcome (e.g. CASI, ACT, steroid bursts). The full CLPM with all cross-lagged paths will test if both the asthma outcomes and depressive symptoms predict each other at subsequent visits. For each full model, paths will connect the value of the depressive symptom score (e.g. HRSD) at each visit to the asthma outcome (e.g. CASI) at each subsequent visit (e.g. 4 weeks later, 8 weeks later). Another set of paths will connect the asthma outcome at each visit to the HRSD at each subsequent visit. The full model will be compared to reduced models containing either the first set of paths or the second set. We hypothesize that the model with the first set of paths will provide a better fit than the second set. The models will be compared on goodness of fit criteria, a non-significant X^2 p-value .05 or more, fit indices .90 or more, RMSEA .05 or less, and significant path coefficients.[68-75] Extensive overviews of the use of this CLPM for longitudinal data analyses are given by Cole and Maxwell and MacKinnon.[70, 75] We will follow Cole and Maxwell's[70] guidelines for testing the proposed causal relationship, caregivers' depressive symptoms preceding child's asthma outcomes, with longitudinal data using SEM software *Mplus*. We will control for variables that might impact depressive symptoms or asthma response including age, gender and race/ethnicity. The primary analysis for this aim will use CASI scores for the child and caregiver HRSD scores. The HRSD is a widely used clinician-rated depression scale while the CASI scores take into account both asthma symptoms and asthma medication use to treat symptoms. Similar analysis will be conducted using the QIDS-SR as the depression measure and STAI as a caregiver anxiety measure. ACT scores and steroid bursts will be used as well as CASI scores in the analysis.

Aim 2. Determine if improvement in depressive symptoms in caregivers of children with asthma predicts reduced unscheduled asthma-related service utilization. Separate analyses will be done for each event (ER visits, hospitalizations and unscheduled appointments). The dependent variable will be a count of the number of times the event occurred during the 52 week study period. This number will be converted to events per month to adjust for subjects who do not complete 52 weeks. The independent variables will be caregiver depressive symptoms as measured by HRSD along with site, baseline depressive symptoms, baseline asthma symptoms, and season of the year. Other baseline demographic and clinical variables (such as child's age) will be added if they improve the fit of the final model. Because the dependent variable is accumulated over the study period, caregiver HRSD will also be summarized over the study period for each subject by computing a seasonally adjusted slope of change over time during the 52 week study. All participants with two or more post-baseline HRSD measurements will be included in the analyses. Count data typically follow a Poisson distribution. Therefore, a generalized linear mixed model with Poisson link function will be used (SAS Proc GLIMMIX). Intercepts will be random effects. If an excessive number of subjects have zero events and the Poisson distribution is not appropriate (which often occurs with count data), then we will consider negative binomial models, zero-inflated Poisson models, and hurdle models. At times caregiver depression may get worse, despite treatment. Therefore, we will examine whether increases in caregiver depressive symptom severity predicts worse child asthma outcomes. The same model used above will be used here except that an indicator variable will be added to indicate if caregiver HRSD scores worsened or stayed the same during the study (zero or positive slope) versus improved (negative slope). The addition of this indicator variable will allow the relationship between change in HRSD and utilization events to differ for those who worsen or stay the same versus those who improve. This aim will be tested by the significance of this additional indicator variable. The primary analysis for this aim will use HRSD scores and ER visits (sensitive to the intervention in Pilot Study #2 and an important clinical outcome). However, similar analysis will be conducted using the QIDS-SR and STAI in place of the HRSD, and using unscheduled clinic visits and hospitalizations.

Aim 3. Determine if improvement in depressive symptoms in the caregivers of children with asthma predicts improvement in asthma-related QOL in the caregiver and child. We will use the same approach outlined above under Aim 1 above but substituting the quality of life measure (PAQOL and PACQOL) in place of the asthma control measure.

Aim 4. Examine medication adherence and child anxiety/depression as possible mediators transmitting the effect of decreased caregiver depression on asthma control and unscheduled service utilization. The goal of Aim 4 is to validate the following relationships:

Caregiver HRSD (1) → medication adherence or child anxiety/depression (2) →child asthma outcomes (3)

The relationship between (1) and (3) is considered in Aim 1. For Aim 4, two sets of CLPM analyses, (1) → (2) and (2) → (3), will be done independently as described for Aim 1. The first set of analyses will determine if caregiver HRSD improvement (1) precedes child adherence (CAMPCS scores) and ~~a~~nxiety/depression

improvement (SCARED, CDI-Full Length scores) (2). Separate models will be fit for adherence and anxiety/depression. The second set of analyses will determine if child adherence and anxiety/depression improvement (2) precedes child asthma outcome improvement (3). Separate models will be fit relating adherence to each asthma outcome and relating anxiety/depression to each asthma outcome (6 models altogether). Similar analysis will be conducted replacing the HRSD with the caregiver scores on the QIDS-SR and STAI.

Missing Data: The analyses described here for the Primary Aim and Secondary Aim 2 will make use of data from all available subjects, even subjects with some missing data. Also, these models are unbiased if the missing data are missing at random (MAR).[76] However, in case the MAR assumption is not satisfied, we will investigate the effect of dropouts on the final results by introducing a variable into the models to indicate whether the patient dropped out or completed.[71] If this dropout status variable is significant, then sensitivity analyses will be done to determine the possible effects of dropouts on the final results.[72-74, 76, 77] The impact of missing data in the structural equation models will be assessed by using full information maximum likelihood.[78]

Power: No data exist on which to base a power analysis. However, the hypothesis tests used here involve testing regression coefficients. To obtain an approximate idea of the power of our tests, we can refer to the test of a regression coefficient that can be detected with 80% power given a sample of 175. If we conservatively assume 10 predictors for the Primary Aim and Secondary Aim 2, then an effect size of $f^2 = 0.10$ could be detected. This effect size is classified as small ($f^2 = 0.02$) to medium ($f^2 = 0.15$) according to Cohen.[69] In the full model for Secondary Aims 1, 2 and 3 there are 13 measurement occasions and approximately 200 paths; however, the hypotheses to be tested involve the 78 paths between each visit and each later visit. Given this number of predictors to be tested, an effect size of 0.31 could be detected with 80% power. This effect size is classified as medium ($f^2 = 0.15$) to large ($f^2 = 0.35$) according to Cohen.[69]

3.5. Design Considerations

Why target MDD? MDD is a common and disabling disorder. Our data and the literature support a relationship between caregiver depression and asthma outcomes in the child. Anxiety disorders were also common in Pilot Study #1 and associated with unscheduled service utilization. However, in this study, 53% with an anxiety disorder also had MDD. Many of the antidepressants that will be used in the study (e.g. SSRIs, SNRIs) are also effective treatments for most anxiety disorders. Thus, by including MDD, we also include and treat anxiety disorders. The outcome measures are different for each anxiety disorder (e.g. panic, specific phobia) which would further complicate a study focusing on specific anxiety disorders. However, we will use a general anxiety symptom assessment tool (STAI) in the study. Thus, for both the internal and external validity of the study we elected to target MDD, allow co-occurring anxiety disorders, and exclude only those with an anxiety disorder that should be the primary focus of clinical treatment (e.g. severe OCD).

Why target asthma? 1) Childhood asthma is a major public health concern. 2) Asthma symptoms are influenced by mood and emotions in both the child and caregiver. 3) We have substantial pilot data and an extensive track record relevant to the proposed study. 4) In addition to reasons 1-3 which were also discussed earlier in the application, it is important to note that asthma is a pulmonary disease that is, at least partially, reversible and is influenced by medication adherence. Therefore, it is reasonable to expect to observe a positive effect on asthma control with an intervention that improves treatment adherence. Finally, it is important to note that the findings from the proposed study could have implications beyond asthma treatment. Positive findings could lead to the testing of similar approaches in other common illnesses (e.g. diabetes).

Why was algorithm-based treatment selected? A randomized, placebo-controlled antidepressant trial was considered but rejected, in part because of the relative strengths of a clinical trial versus the experimental longitudinal within subject design described above in section 3.3.b. In addition, a lengthy placebo-controlled antidepressant trial would raise both safety and ethical concerns. Most importantly, our interest is not whether antidepressants work for MDD (this is already established) but whether improvement in caregiver depression has an impact on the child's asthma. A placebo-controlled design is not needed to observe a range of depression responses.

Non-pharmacologic interventions were considered. Brief interventions for depression are generally associated with small effect sizes.[79] Psychotherapy, while potentially very effective, requires more frequent and longer visits than pharmacotherapy. Another alternative design that we considered was treatment of the child's depression. Our pilot data suggest high rates of depression in the children with asthma as well as their caregivers. However, we rejected this approach because 1) of concerns regarding the safety of antidepressant treatment in children, 2) literature suggests that the impact of depression in children with asthma on asthma outcomes is largely mediated through caregiver depression,[36] and 3) a large depression study conducted as part of the STAR*D project observed that treatment of maternal depression was effective in treating depression in the child.[80] These findings suggest that a study addressing caregiver depression would have the greatest

clinical impact. Finally, an algorithm-based antidepressant treatment is desirable because it lends itself to primary care settings.

Why a 52-week period of antidepressant treatment? We observed positive changes in the child's asthma symptoms at 6 months in Pilot Study # 2. However, it may take some time for improvement in caregiver depression to result in improvement in the child's asthma control. In addition, to assess differences in relatively infrequent events (e.g. emergency care), 52 weeks may be needed. A period of 52 weeks 1) allows a preliminary determination of the impact of depression treatment on unscheduled service utilization, 2) allows a reasonable assessment of changes in the child's asthma control, and 3) allows us to assess the child's asthma through all four seasons.

Will a range of changes in depression symptom severity be observed? Available data suggest that a range of degrees of improvement and time to improvement will be observed. Participants will receive state-of-the-art depression care. A concern might be that if depressive symptoms were quickly and fully ameliorated in all of the participants, the study would have little ability to assess relationships between improvement in depression and asthma outcomes. However, available data suggest that many people receiving sequential depression treatment remain symptomatic. Antidepressant effectiveness trials conducted in clinical practice settings suggest remission (virtual absence of symptoms) of 15% to 35% in primary and specialty care.[81-84] In the STAR*D study, remission rates were 36.8%, 30.6%, 13.7%, and 13.0% for the first, second, third, and fourth acute treatment steps. In those achieving remission, 90% continued to have some residual depressive symptoms after 12 months.[85] These findings suggest that while the cumulative percentage achieving remission increased through treatment steps, the percentage remitting at each step decreased.

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