PROTOCOL TITLE: Brief Cognitive Behavioral Therapy to Treat Itch Rumination "Itch CBT" in Eczema

Funded by the National Eczema Association

PRINCIPAL INVESTIGATOR:

Amy Paller, MD
Professor
Northwestern University and Lurie Children's Hospital
Department of Dermatology
Feinberg School of Medicine
676 N Saint Clair Street, Suite 1600
Chicago, IL 60611

Anna Fishbein, MD
Assistant Professor of Pediatrics
Ann & Robert H. Lurie Children's Hospital of Chicago
Department of Pediatrics
Feinberg School of Medicine
255 E Chicago Ave, Box #60
Chicago, IL 60611

James Griffith, PhD
Associate Professor
Northwestern University
Department of Medical Social Sciences
Feinberg School of Medicine
625 N Michigan Ave, Floor 27
Chicago, IL 60611

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LIST OF ABBREVIATIONS

AD	Atopic Dermatitis
CBT	Cognitive-behavioral therapy
PROMIS	Patient-Reported Outcomes Measurement Information Systems
IRB	Institutional Review Board
PRO	Patient Reported Outcomes
QOL	Quality of life
PSC-C	Pain Castastrophization Scale for Children adapted for itch
PIQ-C	PROMIS Itch Questionnaire-Children
CDLQI	Children's Dermatology Life Quality Index
NRS	Numeric Rating Scale
POEM	Patient Orientated Eczema Measure

1.0 Objectives

Chronic itch is one of the most difficult to treat symptoms in atopic dermatitis (AD; eczema). Many children with eczema suffer from a chronic focus (rumination) on itch. Cognitive Behavioral Therapy (CBT) intervention is effective in treating rumination on pain in other chronic diseases, and would likely be successful to treat itch in eczema. In this project we will develop an "Itch CBT" intervention specific for itch rumination in eczema. After developing a standard protocol based on input from patients, parents, clinicians and the National Eczema Association, we will then pilot the intervention in our multidisciplinary eczema clinic. The total intervention will last approximately one month. The intervention will consist of four 60-minute telehealth sessions with children and their parent/guardian. The first visit will be done ~60 directly after a telehealth clinic visit to assess areas of difficulty followed by 3 weekly telehealth visits to assess progress and implementation, provide further instruction, and review as necessary. At each time-point, we will assess how much the intervention decreased itch, improved medication adherence, and improved other quality of life concerns (anxiety, depression, sleep, and stigma). Future directions will include making the Itch CBT protocol widely available and securing an NIH grant to broadly test the efficacy.

2.0 Background

Eczema is characterized by chronic itch. Many children develop a chronic focus (rumination) on their itch. Rumination is a maladaptive method of responding to distress, in which the individual thinks obsessively about the source of distress, its possible causes and correlates. The rumination on chronic itch in eczema can have detrimental effects on one's quality of life, as well as induce significant anxiety about when itch will return, how long it will last, and how it will affect physical and social functioning.

Cognitive-behavioral therapy (CBT) is a frontline treatment for rumination, as it focuses on teaching strategies so that the individual can examine distressing thoughts objectively and determine their validity, replace negative thinking patterns with more adaptive thought patterns, and increase the individual's awareness to their problematic thought patterns. Additionally, CBT helps the individual to implement behavioral strategies to cope with possibly anxiety-inducing situations, such as scratching while trying to go to sleep. Through behavioral strategies, such as mindfulness and meditation activities, exposure, or distraction, the individual can learn to function in spite of their physical symptoms and cope more effectively.

We propose to create a protocol for Itch CBT that focuses on itch rumination and anxiety in eczema for children ages 8-17 years. We hypothesize that an Itch CBT intervention is an effective, non-medication based, easy to implement strategy to improve itch in children with eczema. Our first aim was to develop an Itch CBT protocol specific for children with eczema. With the input of children with eczema and their families as to the nature of their symptom-related distress, we created a brief intervention and questionnaire to measure itch-related distress and rumination and a set of cognitive,

behavioral, and relaxation strategies to combat itch rumination. With expert input from the National Eczema Association and our research team, we have formalized a protocol for Itch CBT. In our second aim, we will pilot the protocol in a brief (4 session) intervention as part of an interdisciplinary AD clinic, comparing Itch CBT to usual care (our standard educational handouts).

Because each group will have similar levels of eczema severity and will be receiving the same level of medical care, we will be able to attribute changes over time between the two groups to this mental health intervention. We predict that patients treated with Itch CBT will show significantly less itch and less severe itch, as well as significantly greater quality of life, at follow-up compared to those receiving standard treatment. Predicted secondary outcomes include decreased rumination on itch, sleep disturbance, depression, and anxiety, as well as improved medication adherence, and social/family functioning. This pilot study will allow us to measure itch rumination, its effects on children with AD, and the efficacy of Itch CBT in itch rumination. With this preliminary data, we can apply for NIH funding to provide more extensive evidence for the efficacy of Itch CBT in treating itch rumination; ideally we hope to develop an Itch CBT protocol that can easily be implemented by trained personnel in the clinic setting or even as an online tool for patients. The National Eczema Association is the perfect partner for our research team to help develop and disseminate this intervention.

3.0 Hypothesis and Specific Aims

Hypothesis: Our overall hypothesis is that a brief CBT intervention to treat itch rumination is an effective adjunctive strategy to improve itch in AD.

Aim 1: Develop and refine a brief, user-friendly, easily deployable CBT intervention to treat itch rumination (Itch CBT) for pediatric AD. We will conduct semi-structured interviews of 20 patient/parent dyads to tailor a CBT rumination intervention for itch in AD to determine the best cognitive and behavioral strategies to implement in Itch CBT. Both open- and close-ended questioning will be used to allow for patient suggestions for new material, as well as input on proposed materials and strategies.

Aim 2: Determine the efficacy of the itch rumination intervention in reducing distress related to AD and itch, as well as correlates of AD that affect quality of life, such as social concerns and sleep disturbance. Preliminary data will also be collected to determine the validity of a child and parent-proxy questionnaire designed to measure rumination on itch in AD.

4.0 Inclusion and Exclusion Criteria

4.1 Inclusion Criteria:

1. Moderate to severe atopic dermatitis [assessed by Patient Oriented Eczema Measure (POEM) score of >-8 OR NRS itch score of >= 4].

2. English speaking (restriction of PROMIS measure).
3. Age 8-17 years.
4. Currently receiving treatment at Lurie Children's Hospital for atopic dermatitis.
5. Parent or guardian available to participate in protocol.
6. For Aim 2, Have sufficient technology (e.g., cell phone, computer, tablet, etc.) that can be used to access Zoom conference technology for telemedicine visits.

4.2 Exclusion Criteria:
1. Inability to comprehend and complete questionnaires.
2. History of intellectual disability or psychosis.
3. For Aim 2, enrollment in Aim 1.

5.0 Procedures Involved

5.1 Overall Study Design

The overall study design is to develop a brief CBT intervention tailored to itch rumination via qualitative methods, including creating an interview guide with closed- and open-ended questions for stakeholders concerning itch-related distress and rumination. From these interviews, the itch rumination CBT will be created to address common fears and anxiety around itch, ruminative thoughts concerning itch, and other correlates associated with lowered quality of life in AD. This intervention will then be tested in a pilot RCT to compare the brief CBT intervention to usual care. Although therapists will not be blinded to intervention group, the research assistant assessing and analyzing outcomes with patients and their caregiver will be blinded to which intervention they received. Figure 1 summarizes our interventional model of CBT Itch.

Figure 1. Model of Improving Itch in atopic dermatitis using the "CBT Itch" Intervention

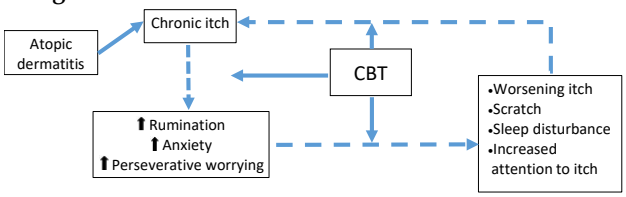

Figure Caption. Chronic itch leads to anxiety, rumination, and worry about symptoms, in turn leading to sleep disturbance and a continued focus on itch sensations. By reducing rumination, anxiety, and worry, CBT can perturb these maladaptive processes leading to less itch, less attention to itch, and better sleep. *Dotted lines indicate the hypothesized relationships improved by CBT.*

Target Population: A convenience sample of children (8-17 years) with moderate-severe AD (and one parent) will be recruited from our group's multidisciplinary AD clinic.

Patients are referred into this clinic through several "recruitment sites." The diverse racial and ethnic demographics are summarized in Table I. The age group is chosen because all measures are validated in this age group, and cognitive interventions are easiest to implement in this narrow age group for a pilot study. Future work would expand to younger age groups.

Table I. Racial and Ethnic Demographics of Recruitment Sites

Recruitment Sites	African-American	Hispanic	Caucasian	Asian	Other
Clark-Deming Outpatient	36%	46%	15%	3%	<1%
Uptown Clinic	38%	35%	13%	9%	5%
La Rabida Hospital	74%	11%	8%	unknown	6%
Northbrook Lurie Outpatient	2%	7%	80%	6%	5%
Lurie Children's Outpatient	9%	23%	47%	4%	17%

A strength of this application is the volume and diversity of patients seeking treatment at the interdisciplinary pediatric allergy/dermatology clinic Lurie Children's Hospital, allowing for a wide range of racial, ethnic, and socioeconomic diversity.

Participants in the active and control conditions will be matched for age, gender, and disease severity. All participants will be compensated $25 for each visit for their time and to cover the cost of transportation. Inclusion and exclusion criteria are listed above in the previous section.

5.2 Aim 1 Study Design

Step 1: Conduct Qualitative Interviews to Develop Itch CBT

The CBT for itch rumination protocol and measure will be derived from qualitative (semi-structured) interviews with patients and families with AD from the interdisciplinary clinic at Ann & Robert H. Lurie Children's Hospital, as well as via expert input from the study team. Qualitative interviews will be one-on-one with the patient and caregiver separately and will begin with open-ended questions to avoid biasing the participants with our own preconceptions of their needs. Example questions will include "When are you [your child] thinking about the itch most?" and "What would help take your mind off the itch?". After open-ended questions, we will present participants with our conceptualization of itch rumination to ensure it accurately reflects their experiences, as well as questions adapted from the PCS-C for itch to determine whether these questions accurately reflect their experiences of itch rumination. Participants will also be presented with various options and directed questions about their preferences for strategies to cope with itch rumination. Options for discussion will include behavioral strategies, such as pleasant activities to distract from the itch; cognitive interventions, such as self-questioning to de-escalate catastrophizing the itch (e.g. "The itching will never stop" and fears of the itch returning); and relaxation strategies, such as progressive muscle relaxation and diaphragmatic breathing when distraction is not possible, such as during the night. These strategies are the primary

interventions of CBT and have been found particularly beneficial in treating physical difficulties, such as chronic pain [25].

For Aim 1, 20 patient-parent dyads (40 participants) of children with moderate/severe AD will be recruited for qualitative interviewing with a research assistant to provide feedback on the concept of itch rumination and therapeutic techniques to be included in CBT for itch rumination. Sample size for the interviews is based on our study team's experience conducting qualitative research in support of protocol development and clinical health research. To ensure that qualitative findings are representative, research must 1) include key characteristics of the population thought to influence the outcomes of interest in the study sample; 2) confirm that the concepts are adequately described by study participants; and 3) bring participants into the study until no new themes, or relevant concepts, are obtained. This point of redundancy is known as theoretical saturation [54,55]. It has been suggested that 20 patient-parent dyads is generally adequate to reach saturation [56-58].

Step 2: Develop and refine the Itch CBT protocol.

Qualitative data from Step 1 will be analyzed systematically using a constant comparative approach [59]. Trained coders will independently generate a preliminary list of emergent themes [60]. Next, the coders will meet to discuss initial thoughts, insights, and observations for the development of initial coding categories. Through a systematic analysis process, analysts will continually refine themes by collapsing redundant and removing irrelevant themes and suggested treatments. Once no new categories have emerged, coding dictionaries will be developed for the remaining analysis [61]. We will construct a saturation grid to track themes as they emerge and determine when no new relevant information is obtained. Coded data will be summarized and the most important themes in terms of prevalence and/or impact will be identified. These themes, data representing the themes in the words of patients and families, will form the basis for the Itch CBT intervention.

The study team and key stakeholder (National Eczema Association) will then meet and agree to the best protocol to target and address themes related to itch rumination generated during qualitative interviews. The result of Aim 1 will be a standardized protocol that can be tested in Aim 2.

5.3 Aim 2 Study Design

Step 3 Implement CBT Itch compared to usual care in a RCT.

Based upon the interviews conducted in Aim 1, patients with atopic dermatitis reported significant concerns in addition to preoccupation with itch and scratching, specifically regarding social difficulties, anxiety, sleep challenges, and difficulty with concentration. Thus, the treatment was expanded to address these multiple areas of concern. Additionally, parents of patients reported significant concerns about scheduling office appointments because of absences from work and school due to multiple appointments for medical providers. For this reason, it was decided that the primary method of intervention would be provided via telemedicine.

We plan to recruit 24 patient-parent dyads (48 total participants) stratified by child's age (*n* =6: 8-12, *n* = 6: 12-17 years) to the CBT itch rumination intervention. Usual care will be provided to 12 AD patients, matched on gender and itch severity. Itch severity will be based on the NRS Itch Severity score. Potential participants will be recruited from Lurie Children's Dermatology and Allergy Departments. If patients have an upcoming clinic (or remote clinic visit) scheduled, they will be contacted prior to their clinic visit by a study coordinator/provider and will be provided with a brief description of the study to determine interest in order to allow patients to schedule sufficient time for study activities following their clinic appointment. If patients do not have an upcoming clinic visit, they will be contacted by phone by a study coordinator/provider and given a brief description of the study. If interested, participants will be screened using the inclusion/exclusion criteria (see Screening Questionnaire). If eligible, patients will be e-consented to the study using REDCap e-consent procedures by a study coordinator. A study coordinator will email a link to the e-consent form to the participant and then thoroughly explain the study, allowing time for participants to ask questions. If participant is still interested, they will be instructed to sign the e-consent form using the link. After participants have been e-consented, they will be randomized to one of the study conditions (usual care vs. CBT). Following e-consent, participants will be emailed a copy of their signed e-consent form. Following their clinic appointment, all participants will complete study questionnaires (see Table of Assessments below).

Randomization Procedures: Participants will be randomized to one of two groups: (1) Itch CBT or (2) Usual care. Randomization will occur on a 1:1 ratio and within strata, which are gender (male vs. female) and Itch Numerical Rating Scale (4-6 vs. 7-10). Participants will be randomized to treatment based on a predetermined list within each strata created using the *blockrand* package of R. Randomization will occur by blocks, with varying block sizes, in accord with recommended methods for RCTs. The randomization key will be linked to a unique study ID number, as well as to a treatment condition (Itch CBT vs. Usual Care). Participants will be aware that there are different arms they can be assigned to and will know which randomization group they are assigned.

For participants randomized to the Usual Care Arm:

Participants randomized to the Usual Care arm of the study will receive eczema educational materials that are typically provided by their health care provider after a clinic (or telehealth) visit. Examples include an eczema action plan that is created by the provider with the patient and includes daily skincare as well as special skincare instructions for eczema flares, handouts on recommendations for dry skin, etc. Participants in the Usual Care arm will complete the same schedule of study surveys (see Table of Assessments below) as participants randomized to the CBT arm.

For participant randomized to the CBT Arm:

Participants randomized to the CBT arm of the study will be contacted by their study therapist to complete an initial telehealth assessment (see Assessment Interview document) about understanding of AD, adherence to medication, strategies they use to

cope with itch, social concerns, mood and anxiety concerns related to AD, sleep concerns, and areas of functional impairment due to AD.

Following their assessment, families will be instructed on how to download a free version of the Zoom application onto their internet-capable personal device, with specific details on how to connect for follow-up telehealth visits. Resources will be provided to families for technical support. Therapists will then follow up with participants for three sessions on a weekly basis via telehealth on Northwestern Zoom, which is encrypted to increase security and privacy. Sessions will include instruction on mindfulness-based activities, behavioral interventions to improve adherence, action planning during flares, and coping mechanisms to help cope with social challenges (see CBT Supplemental Materials). Participants will review the session with their parents, in conjunction with their therapist, and be given homework to complete for the following week. Following each therapy session, participants will complete study surveys via REDcap and at 4 weeks following the intervention. Participants will have up to 2 weeks to complete the follow-up questionnaires.

Table of Assessments for Children:

Assessments:	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Follow-Up**
Itch Rumination Questionnaire - Child	**X**			**X**	**X**
Stigma Short-Form	**X**			**X**	**X**
PROMIS Pediatric Profile – Anxiety & Depression	**X**			**X**	**X**
PROMIS Sleep – Child	**X**			**X**	**X**
PROMIS Pediatric Itch	**X**			**X**	**X**
VAS Dose	**X**	**X**	**X**	**X**	**X**
POEM	**X**			**X**	**X**
Child's Derm Life Quality Index (CDLQI)	**X**			**X**	**X**
Mood NRS	**X**	**X**	**X**	**X**	**X**
Itch Severity VAS	**X**	**X**	**X**	**X**	**X**
PROMIS Positive Affect	**X**			**X**	**X**
PROMIS Meaning and Purpose SF	**X**			**X**	**X**

Table of Assessments for Parents/Guardians:

Assessments:	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Follow-Up**
Itch Rumination Questionnaire - Parent	**X**			**X**	**X**

Parent Proxy Pediatric Itch – Short Form 1 (2+6)	**X**	**X**	**X**	**X**	**X**
PROMIS Parent Proxy – Anxiety & Depression	**X**			**X**	**X**
PROMIS Parent Proxy— Positive Affect	**X**			**X**	**X**
PROMIS Sleep - Parent	**X**			**X**	**X**
VAS Dose	**X**	**X**	**X**	**X**	**X**
Itch Severity VAS	**X**	**X**	**X**	**X**	**X**
Five Facet Mindfulness Questionnaire SF	**X**			**X**	**X**
PROMIS Family Relationships	**X**			**X**	**X**

5.4 Statistical Analysis Plan – Aim 2

Because this a clinical trial, our primary statistical approach will be a response profile analysis. In this model, the effect of treatment and other variables are used predict the outcome over time, but an influence of treatment is not posited for pre-treatment assessments. This method is recommended for analyzing clinical trials. We will include participants using the intent-to-treat criterion, in which all randomized participants are included in the analysis. All aspects of this clinical trial will be reported in accord with CONSORT guidelines. Although the response profile analysis will be our primary approach, we will also explore alternative approaches. Latent growth curve models use all available data (i.e., they do not discard observations with missing data) and provide valid inferences in the presence of missing outcome data under the missing at random (MAR) assumption.

The primary outcome measures will be the NRS Itch Severity and the CDLQI. All other questionnaires will be used as secondary outcome measures.

Primary outcomes:

1. NRS Itch Severity
2. CDLQI

Secondary outcomes:All other questionnaires listed above.

6.0 Data Management

All of the data will be collected at Lurie Children's hospital and saved on a secure research server that is maintained by Northwestern University. Survey data will be maintained within Northwestern University's secure REDCap system. Only members of the authorized study team will have access to these systems.

Protected health information (PHI) necessary for study management (subject name and email addresses) is separated from the study data and non-PHI clinical data. This

provides additional data security to prevent unauthorized access or release of PHI. Subjects will be given a unique subject ID and that will be the link between PHI data and non-PHI clinical data. PHI will be marked appropriately in REDCap so data will not be exported with identifiers. Any review of data outside of the IRB-approved research team will be done only using de-identified data and/or summary tables or figures once the appropriate data use agreements are in place.

Data Storage for project

The team will create a central database for storage of data on the FSM research server within the Department of Medical Social Sciences. Data will be deidentified with a separate coded identifier list with subject IDs.

7.0 Risks and Benefits to Subjects

7.1 Risks:

Because the study procedures take the form of interviews, there are no safety risks to consider in this study. Participation in this study does not involve any physical or emotional risk to participants beyond that of everyday life.

Interviews and Questionnaires: Interview participants and/or those completing questionnaires can choose to not answer a question, skip a question, request a break, or to stop/leave the interview/focus group at any time. Breaks will also be offered to participants throughout the interview. There is a very small risk of loss of confidentiality. Every measure to safeguard the information will be taken by the research team, including keeping all identifying in a locked cabinet and/or password-protected and keeping all questionnaire data de-identified using a study ID number.

Audio Recordings: There is a risk of loss of confidentiality with the audio recordings. Audio recordings will be destroyed after the study team has reviewed all interview notes and confirmed they are complete. In the interim, audio recordings will be kept in a secure, locked area to ensure access is only granted to the authorized research personnel.

7.2 Benefits:

Participants may not have any direct benefit from being in this research study but taking part in this research study may enable investigators to create a comprehensive pool of items that fully describe the patient experience with AD and itch. It is possible that participants randomized to the CBT arm may receive direct benefit in the form of decreased symptom/symptom bother from the intervention being tested in this study.

Compensation for Arm 2:

Participants randomized to the CBT arm will be paid up to a maximum of $130 for their participation over the course of the study. Participants randomized to the Usual Care arm will be paid up to a maximum of $90 for their participation. Participants will be paid according to the following schedule:

	Payment for Assessments (Usual Care arm **AND** CBT arm)	Payment for Therapy Visits (CBT arm **ONLY**)
Visit 1	$20	$10
Visit 2	$10	$10
Visit 3	$10	$10
Visit 4	$20	$10
Follow-up visit	$20	$0
Bonus (for completing all assessments)	$10	$0
Total per subject	$90	$40

Participants will be paid at the end of the study or when they are withdrawn/drop-out. Participants will only be paid for the portions of the study that they complete. Payment will be in the form of e-gift cards emailed to participants within 2-4 weeks of completing their participation in the study.

8.0 Ethical Considerations

8.1 Human Subjects Protection

A periodic review must be submitted to the IRB at least once a year. The IRB must be notified of completion of the study. After study completion or termination, a final report must be provided to close the study. The investigator must maintain an accurate and complete record of all submissions made to the IRB, including a list of all reports and documents submitted. Adverse events must be submitted promptly to the IRB per IRB guidelines. At least once per year, the IRB must review and give written approval in order to continue the study. This trial will be conducted in accordance with Good Clinical Practices and the Declaration of Helsinki.

8.2 Consent Form

Prior to study entry, a written parental consent form must be obtained. Assent will be also obtained from subjects participating who are 12 years and older. A copy of the consent and assent form will be retained in the appropriate study file.

8.3 Protocol Amendments

All changes must be submitted to the IRB. Protocol modifications that impact subject safety or the validity of the study must be approved by the IRB before initiation.

8.4 Retention of Records

Food and Drug Administration and Good Clinical Practice guidelines require that an Investigator retain subject identification codes, subject files, and source data for the maximum period of time permitted by the hospital, institution, or private practice, but not less than 15 years after the completion or discontinuation of the trial.

8.5 Use of Information and Publication

The Principal Investigator, sub-investigators may publish the results of this study in conjunction will appropriate scientific and medical personnel.

9.0 References

1. Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermatol.* Jan 2011;131(1):67-73.
2. Koinis-Mitchell D, Craig T, Esteban CA, Klein RB. Sleep and allergic disease: a summary of the literature and future directions for research. *The Journal of allergy and clinical immunology.* Dec 2012;130(6):1275-1281.
3. Chamlin SL, Mattson CL, Frieden IJ, et al. The price of pruritus: sleep disturbance and cosleeping in atopic dermatitis. *Archives of pediatrics & adolescent medicine.* Aug 2005;159(8):745-750.
4. Hon KL, Leung TF, Wong KY, Chow CM, Chuh A, Ng PC. Does age or gender influence quality of life in children with atopic dermatitis? *Clinical and experimental dermatology.* Nov 2008;33(6):705-709.
5. Camfferman D, Kennedy JD, Gold M, Martin AJ, Lushington K. Eczema and sleep and its relationship to daytime functioning in children. *Sleep medicine reviews.* Dec 2010;14(6):359-369.
6. Sack R, Hanifin J. Scratching below the surface of sleep and itch. *Sleep medicine reviews.* Dec 2010;14(6):349-350.
7. Weisshaar E, Dalgard F. Epidemiology of itch: adding to the burden of skin morbidity. *Acta dermato-venereologica.* 2009;89(4):339-350.
8. Elman S, Hynan LS, Gabriel V, Mayo MJ. The 5-D itch scale: a new measure of pruritus. *The British journal of dermatology.* Mar 2010;162(3):587-593.
9. Tey HL, Yosipovitch G. Targeted treatment of pruritus: a look into the future. *The British journal of dermatology.* Jul 2011;165(1):5-17.
10. Senra MS, Wollenberg A. Psychodermatological aspects of atopic dermatitis. *The British journal of dermatology.* Jul 2014;170 Suppl 1:38-43.
11. Jauregui I, Ortiz de Frutos FJ, Ferrer M, et al. Assessment of severity and quality of life in chronic urticaria. *Journal of investigational allergology & clinical immunology.* 2014;24(2):80-86.
12. Palermo TM, Eccleston C, Lewandowski AS, Williams ACdC, Morley S. Randomized controlled trials of psychological therapies for management of chronic pain in children and adolescents: an updated meta-analytic review. *PAIN®.* 2010;148(3):387-397.
13. Palermo T, Eccleston C, Goldschneider K, Larkin McGinn K, Sethan N, Turner H. Assessment and management of children with chronic pain. *Am Pain Society.* 2012.
14. Morley S, Eccleston C, Williams A. Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. *Pain.* 1999;80(1-2):1-13.
15. Li JC, Fishbein A, Singam V, et al. Sleep Disturbance and Sleep-Related Impairment in Adults With Atopic Dermatitis: A Cross-sectional. *Dermatitis : contact, atopic, occupational, drug.* Aug 31 2018.
16. Sanders KM, Akiyama T. The vicious cycle of itch and anxiety. *Neurosci. Biobehav. Rev.* Apr 2018;87:17-26.

17. Stein TR, Sonty N, Saroyan JM. "Scratching" beneath the surface: an integrative psychosocial approach to pediatric pruritus and pain. *Clinical child psychology and psychiatry.* Jan 2012;17(1):33-47.
18. Hedman-Lagerlof E, Bergman A, Lindefors N, Bradley M. Exposure-based cognitive behavior therapy for atopic dermatitis: an open trial. *Cognitive behaviour therapy.* Sep 7 2018:1-11.
19. Wittkowski A, Richards HL. How beneficial is cognitive behaviour therapy in the treatment of atopic dermatitis? A single-case study. *Psychology, health & medicine.* Aug 2007;12(4):445-449.
20. Dass K, Petrusan AJ, Beaumont J, Zee P, Lai JS, Fishbein A. Assessment of sleep disturbance in children with allergic rhinitis. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology.* Apr 2017;118(4):505-506.
21. Yarbrough KB, Neuhaus KJ, Simpson EL. The effects of treatment on itch in atopic dermatitis. *Dermatol. Ther.* Mar-Apr 2013;26(2):110-119.
22. Mochizuki H, Schut C, Nattkemper LA, Yosipovitch G. Brain mechanism of itch in atopic dermatitis and its possible alteration through non-invasive treatments. *Allergology international : official journal of the Japanese Society of Allergology.* Jan 2017;66(1):14-21.
23. Nascimento SS, Oliveira LR, DeSantana JM. Correlations between brain changes and pain management after cognitive and meditative therapies: A systematic review of neuroimaging studies. *Complement. Ther. Med.* Aug 2018;39:137-145.
24. Patel T, Ishiuji Y, Yosipovitch G. Nocturnal itch: why do we itch at night? *Acta Derm Venereol.* 2007;87(4):295-298.
25. Palermo TM. *Cognitive-behavioral therapy for chronic pain in children and adolescents.* Oxford University Press; 2012.
26. Turner JA, Mancl L, Aaron LA. Brief cognitive-behavioral therapy for temporomandibular disorder pain: Effects on daily electronic outcome and process measures. *Pain.* 2005/10/01/ 2005;117(3):377-387.
27. Kendall PC, Hudson JL, Gosch E, Flannery-Schroeder E, Suveg C. Cognitive-behavioral therapy for anxiety disordered youth: a randomized clinical trial evaluating child and family modalities. *Journal of consulting and clinical psychology.* 2008;76(2):282.
28. James AA, Soler A, Weatherall RR. Cognitive behavioural therapy for anxiety disorders in children and adolescents. *Cochrane database of systematic reviews.* 2005(4).
29. James AC, James G, Cowdrey FA, Soler A, Choke A. Cognitive behavioural therapy for anxiety disorders in children and adolescents. *Cochrane Database of systematic reviews.* 2013(6).
30. Watkins ER. *Rumination-focused cognitive-behavioral therapy for depression.* Guilford Publications; 2018.
31. Sezibera V, Van Broeck N, Philippot P. Intervening on persistent posttraumatic stress disorder: Rumination-focused cognitive and behavioral therapy in a population of young survivors of the 1994 genocide in Rwanda. *Journal of Cognitive Psychotherapy.* 2009;23(2):107-113.
32. Barlow DH, Farchione TJ, Sauer-Zavala S, et al. *Unified protocol for transdiagnostic treatment of emotional disorders: Therapist guide.* Oxford University Press; 2017.
33. Ellard KK, Fairholme CP, Boisseau CL, Farchione TJ, Barlow DH. Unified protocol for the transdiagnostic treatment of emotional disorders: Protocol development and initial outcome data. *Cognitive and Behavioral Practice.* 2010;17(1):88-101.
34. Farchione TJ, Fairholme CP, Ellard KK, et al. Unified protocol for transdiagnostic treatment of emotional disorders: a randomized controlled trial. *Behavior therapy.* 2012;43(3):666-678.

35. Verhoeven EW, de Klerk S, Kraaimaat FW, van de Kerkhof PC, de Jong EM, Evers AW. Biopsychosocial mechanisms of chronic itch in patients with skin diseases: a review. *Acta Derm Venereol.* 2008;88(3):211-218.
36. Mochizuki H, Lavery MJ, Nattkemper LA. Impact of Acute Stress on Itch Sensation and Scratching Behavior in Atopic Dermatitis Patients and Healthy Controls. Jun 26 2018.
37. Backhaus J, Hohagen F, Voderholzer U, Riemann D. Long-term effectiveness of a short-term cognitive-behavioral group treatment for primary insomnia. *European Archives of Psychiatry and Clinical Neuroscience.* 2001;251(1):35-41.
38. Hong J, Buddenkotte J, Berger TG, Steinhoff M. Management of itch in atopic dermatitis. *Semin. Cutan. Med. Surg.* Jun 2011;30(2):71-86.
39. Lyons JJ, Milner JD, Stone KD. Atopic dermatitis in children: clinical features, pathophysiology, and treatment. *Immunol. Allergy Clin. North Am.* Feb 2015;35(1):161-183.
40. Jafferany M. Psychodermatology: a guide to understanding common psychocutaneous disorders. *Prim. Care Companion J. Clin. Psychiatry.* 2007;9(3):203-213.
41. LeBovidge JS, Elverson W, Timmons KG, et al. Multidisciplinary interventions in the management of atopic dermatitis. *The Journal of allergy and clinical immunology.* Aug 2016;138(2):325-334.
42. Schut C, Weik U, Tews N, Gieler U, Deinzer R, Kupfer J. Psychophysiological effects of stress management in patients with atopic dermatitis: a randomized controlled trial. *Acta Derm Venereol.* Jan 2013;93(1):57-61.
43. Chida Y, Steptoe A, Hirakawa N, Sudo N, Kubo C. The effects of psychological intervention on atopic dermatitis. A systematic review and meta-analysis. *Int. Arch. Allergy Immunol.* 2007;144(1):1-9.
44. Arkwright PD, Stafford JC, Sharma V. Atopic dermatitis in children. *The journal of allergy and clinical immunology. In practice.* Jul-Aug 2014;2(4):388-395.
45. Chiu CPY, Griffith JW, Lenaert B, Raes F, Hermans D, Barry TJ. Meta-analysis of the association between rumination and reduced autobiographical memory specificity. *Memory (Hove, England).* May 16 2018:1-12.
46. Barry TJ, Lenaert B, Hermans D, Raes F, Griffith JW. Meta-Analysis of the Association Between Autobiographical Memory Specificity and Exposure to Trauma. *Journal of traumatic stress.* Feb 2018;31(1):35-46.
47. Schoofs H, Hermans D, Griffith JW, Raes F. Self-discrepancy and reduced autobiographical memory specificity in ruminating students and depressed patients. *Cognition & emotion.* 2013;27(2):245-262.
48. Raes F, Griffith JW, Van der Gucht K, Williams JMG. School-based prevention and reduction of depression in adolescents: A cluster-randomized controlled trial of a mindfulness group program. *Mindfulness.* 2014;5(5):477-486.
49. Van der Gucht K, Griffith JW, Hellemans R, Bockstaele M, Pascal-Claes F, Raes F. Acceptance and commitment therapy (ACT) for adolescents: outcomes of a large-sample, school-based, cluster-randomized controlled trial. *Mindfulness.* 2017;8(2):408-416.
50. Paller AS, McAlister RO, Doyle JJ, Jackson A. Perceptions of physicians and pediatric patients about atopic dermatitis, its impact, and its treatment. *Clinical pediatrics.* Jun 2002;41(5):323-332.
51. Fishbein AB, Mueller K, Kruse L, et al. Sleep disturbance in children with moderate/severe atopic dermatitis: A case-control study. *J Am Acad Dermatol.* Feb 2018;78(2):336-341.
52. Fishbein AB, Vitaterna O, Haugh IM, et al. Nocturnal eczema: Review of sleep and circadian rhythms in children with atopic dermatitis and future research directions. *The Journal of allergy and clinical immunology.* Nov 2015;136(5):1170-1177.

53. Fishbein AB, Lin B, Beaumont J, Paller AS, Zee P. Nocturnal Movements in Children with Atopic Dermatitis have a Timing Pattern: A Case Control Study. *Journal of the American Academy of Dermatology.* Apr 16 2018.
54. Cutcliffe JR. Methodological issues in grounded theory. *Journal of advanced nursing.* Jun 2000;31(6):1476-1484.
55. Bowen GA. Naturalistic inquiry and the saturation concept: a research note. *Qualitative Research.* February 1, 2008 2008;8(1):137-152.
56. Weiss RS. *Learning from strangers: The art and method of qualitative interview studies.* Simon and Schuster; 1995.
57. Dworkin SL. Sample size policy for qualitative studies using in-depth interviews. Springer; 2012.
58. Morse JM. Determining sample size. Sage Publications Sage CA: Thousand Oaks, CA; 2000.
59. Glaser B, Strauss AL. *The Discovery of Grounded Theory.* Chicago: Aldine; 1967.
60. Rothman M, Burke L, Erickson P, Leidy NK, Patrick DL, Petrie CD. Use of Existing Patient-Reported Outcome (PRO) Instruments and Their Modification: The ISPOR Good Research Practices for Evaluating and Documenting Content Validity for the Use of Existing Instruments and Their Modification PRO Task Force Report. *Value Health.* 2009;12(8):1075-1083.
61. Patrick DL, Burke LB, Gwaltney CJ, et al. Content Validity—Establishing and Reporting the Evidence in Newly Developed Patient-Reported Outcomes (PRO) Instruments for Medical Product Evaluation: ISPOR PRO Good Research Practices Task Force Report: Part 1—Eliciting Concepts for a New PRO Instrument. *Value Health.* 2011;14(8):967-977.
62. Irwin DE, Stucky BD, Thissen D, et al. Sampling plan and patient characteristics of the PROMIS pediatrics large-scale survey. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* May 2010;19(4):585-594.
63. Lewis-Jones M, Finlay A. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. *British Journal of Dermatology.* 1995;132(6):942-949.
64. Forrest CB, Meltzer LJ, Marcus CL, et al. Development and validation of the PROMIS Pediatric Sleep Disturbance and Sleep-Related Impairment item banks. *Sleep.* Jun 1 2018;41(6).
65. Cohen J. Statistical power analysis for the behavioral sciences. 2nd. Hillsdale, NJ: erlbaum; 1988.
66. McHugh RK, Murray HW, Barlow DH. Balancing fidelity and adaptation in the dissemination of empirically-supported treatments: The promise of transdiagnostic interventions. *Behaviour research and therapy.* 2009;47(11):946-953.
67. Conaughton RJ, Donovan CL, March S. Efficacy of an internet-based CBT program for children with comorbid High Functioning Autism Spectrum Disorder and anxiety: A randomised controlled trial. *Journal of affective disorders.* Aug 15 2017;218:260-268.
68. Ebert DD, Zarski AC, Christensen H, et al. Internet and computer-based cognitive behavioral therapy for anxiety and depression in youth: a meta-analysis of randomized controlled outcome trials. *PloS one.* 2015;10(3):e0119895.