Essential Oils for Enhancing of Quality of Life in Autism Spectrum Disorder (ASD)

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INTRODUCTION

Impact and Relevance

Quality of life (QOL) is very often a cause of concern for parents of children with autism spectrum disorder (ASD). This concern may develop as parents observe their children struggle to adapt to the world around them. Children with ASD may become especially agitated when confronted with situations not normally considered challenging for the neurotypical child; and parents of children with ASD learn quickly to avoid potentially volatile situations in order to maintain their child's equilibrium. Comorbid anxiety, with prevalence estimates ranging from 44% to 83% (Johnson et al., 2009; Hollway & Aman, 2011) greatly stresses the ability of the family to engage in enrichment activities. Additionally, anxiety in ASD has been found to be a strong predictor of sleep disturbance (Hollway, Aman, & Butter, 2013) and irregular and delayed sleep may leave the child exhausted, impacting daytime behavior (Meltzer & Mindell, 2006) and QOL in children (Hsiao & Nixon, 2007; Wirell, Blackman, Barlow, Mah & Hamiwka, 2005).

Considerably more impairing, the bidirectional nature of sleep disturbance and anxiety affects QOL, as anxiety may disturb sleep, and a lack of sleep may lead to increased anxiety (Hollway & Aman, 2011). In a report of unpublished data (Hollway, 2012), the investigator found that Emotional Functioning on the Pediatric Quality of Life Inventory (PedsQL) was associated with sleep disturbance in 1583 children with ASD. Out of 12 possible predictors, seven significantly predicted Emotional Functioning [$F(7,1482) = 87.643$, $p < .001$]. The results indicated that the Children's Sleep Habits Questionnaire (CSHQ) subscales, Sleep Anxiety, Bedtime Resistance, and being a poor sleeper in general, contributed to quality of emotional functioning and showed a moderate effect ($R^2 = .293$). This indicated that a moderate proportion of the variance found in the PedsQL Emotional Functioning subscale score was explained by the model (29.3%) (Cohen, 1988).

Sleep problems cause significant family distress (Hiscock & Wake, 2002; Doo & Wing, 2006) and clinicians are utilizing behavioral intervention (BI) first for sleep improvement. For many, this intervention is sufficient for improving sleep quality and quantity (Andersen et al., 2008). However, when BI alone is unsuccessful and sleep problems persist, there are few alternatives from which parents can choose that do not involve pharmacological agents (e.g., melatonin, medication) (Hollway & Aman, 2011a; Hollway & Aman, 2011b). As an adjunct, an essential oil formulation distributed by Young Living Essential Oils may be useful for improving quality of life by increasing sleep quantity and equilibrium without the undesirable side effects associated with medications. A pilot study of essential oils will help us determine whether essential oils are tolerable and effective for improving QOL. This study will provide data to help us decide whether continued study is warranted in a much larger multisite study. The proposed research will contribute new knowledge that could be useful for clinicians. The purpose of this research is to increase the existing knowledge regarding quality of life in children with ASD.

Background and Significance

Aromatherapy has been used as a supplement to decrease stress, anxiety, and to help induce sleep (Hur, Song, Lee, J. & Lee, M., 2014; Lee, Wu, Tsang, Leung & Cheung, 2011). However, there is a paucity of empirical data reflecting its effectiveness for improving quality of life in children with sleep disturbances. The data that are available include studies lacking systematic rigor that are fraught with methodological problems (Hirokawa & Nishimoto, 2012; Hur, Song, Lee, J. & Lee, M., 2014; Lee, Wu, Tsang, Leung & Cheung, 2011; Williams, 2006). Studies of late have introduced massage therapy while simultaneously implementing essential oils (Cetinkaya, B., Basbakkal, Z.; 2013; Satou, et al. 2012; Williams, 2006). In these studies the length of the physical contact during the massage may have influenced the study results and it is difficult to tease out whether it was the physical touch during the massage or the aromatherapy that was increasing relaxation and sleep. Other studies have used aromatherapy in a variety of ways such as the diffusion method, applying the oil directly to a body part (without massaging it in), and adding the oil to a cotton ball and attaching it to a piece of clothing (Ndao et al., 2012; Nord & Belew, 2009). In other studies subjects were not randomized (Hirokawa & Nishimoto, 2012), there was not an adequate placebo (Satou et al., 2013), and the sample sizes were quite small (Hirokawa & Nishimoto, 2012; Williams, 2006). Another problem was the subjective nature of the data collection (parent or subject self ratings). Not surprisingly the results were mixed (Jefarzadeh, Arman & Farahbakhish Pour, 2012; Ndao et al., 2012; O'Flaherty, vanDijk, Alertyn & Millar, 2012; Satou et al., 2013; Williams, 2006; Wu, 2014). Our aim is to systematically evaluate in a pilot study the use of Reconnect Essential Oils to determine if it is effective for increasing QOL, equanimity, and sleep. We intend to enroll 28 study participants in a randomized crossover study of Reconnect Essential Oils and a scented coconut oil comparator. Participants will be randomized to two groups. Group 1 will receive Reconnect for the first 3 months of the study while Group 2 will receive a scented coconut oil comparator. At the end of the 3 month period there will be a one month washout and each group will be crossed over to the opposite condition. We will use parent ratings of QOL and objective measures of relaxation/sleep (actigraph).

Specific Aims/Hypotheses

Our primary aims are to evaluate the feasibility of a larger study and examine preliminary data regarding benefit and tolerability of an essential oil formulation distributed by Young Living Essential Oils, Lehi, UT., for enhancing QOL in children with ASDs. We will develop preliminary data suitable to be submitted in a competitive NIH grant application for a larger multisite study. The proposed study will include a 7-month crossover with two 3-month conditions and a month washout between, with randomly assigned order. The 2 conditions will be a proprietary formula of essential oils and a scented coconut oil comparator. Measures of QOL, equanimity, and sleep health will include parent report on valid and reliable rating scales.

Primary Hypotheses

1. We can recruit 28 participants in 2 years with 85% adherence and 85% retention through both conditions.

2. With essential oils, participants will show significantly improved QOL on the Pediatric Quality of Life Inventory compared to the control condition, with a medium effect size.
3. While receiving essential oils participants will show negligible or no increases in adverse events (AEs), including allergic contact dermatitis, immediate contact reactions (contact urticaria), and photosensitivity, compared to the control condition.

Secondary Mediational Hypotheses

1. With essential oils, compared to the control condition, participants will show significantly improved sleep onset and maintenance on objective and subjective measures (actigraphy; parent sleep diaries, and parent and clinician-rated scales) with a medium effect size, and this will mediate the improvement in QOL.
2. With essential oils, compared to the control condition, participants will display greater equanimity and improvements in mood and daytime behavior on objective and subjective measures (heart rate; parent and clinician rated scale) compared to the control condition and this will mediate the improvement in QOL.

Participant Inclusion/Exclusion Criteria

Inclusion Criteria

Entry criteria are the following:

i. Outpatients between 3 and 9 years of age, inclusive;
ii. Diagnosis of Autism Spectrum Disorder (ASD) by DSM-V;
iii. Total item mean score of $\geq$ 1.5 on PedsQL Inventory;
vi. Care provider who can reliably bring subject to clinic visits and provide trustworthy ratings.

Exclusion Criteria

Exclusion criteria are the following:

i. Bipolar disorder by Child & Adolescent Symptom Inventory (CASI, Gadow & Sprafkin, 1997) and clinical interview/history, or major depression accompanied by family history of bipolar disorder;
ii. Children with allergies to essential oils;
iii. Children with seizure disorder/epilepsy;
iv. Significant physical illness (e.g., serious cardiovascular, liver, or renal pathology);
v. Medications specifically given for insomnia and exogenous melatonin, which have the potential to confound study results, within the previous 2 weeks before baseline;
vi. Anticipated changes of doses of medication or other medical treatments or supplements;
vii. Weight less than 10 kg;
viii. Sleep Disordered Breathing (SDB) as defined by a total score of $\geq$ 3 on the CSHQ SDB subscale and parent report;
ix. Nut allergies;
x. Allergy to vanilla;
xi. A substantial trial of essential oil use within the past 6 months (i.e., consistent use for 6 weeks).

METHODS

Study Design

This study will use a double-blind -controlled crossover design with random assignment to order of conditions. The 2 conditions will be Reconnect™, a mixture of essential oils formulated by Young Living (YL) vs. a fragrant appearance-matched coconut-oil comparator. In order to randomize 28 children we anticipate that approximately 36 children will be screened. There will 2 conditions in the crossover design.

Participants will receive Reconnect or scented coconut oil comparator for 3 months following the Baseline visit. At the end of 3 months, participants will be administered all endpoint measures for that condition. Then there will be a 1-month washout prior to the start of the second condition. At the end of the second 3-month condition, participants will again be administered all endpoint measures for that condition. The endpoint assessment for the 2nd condition will be 7 months from original baseline. During the 1st condition participants will be evaluated at 2 week intervals for the first month to assess whether the mode of essential oils application is tolerable (i.e., inhalation or topical application) and to develop graphs of effect on sleep and equanimity over time. During the final 8 weeks of condition one, participants will be seen monthly. During the second condition we will have established that the modes of application are tolerable and subjects will be evaluated at 3 monthly visits. There will be 10 visits to the Center including the Screening and Baseline Visits.

Procedures

All participants must have significant problems with QOL as measured by the PedsQL Inventory, with a total item mean score of $\geq$ 1.5 (i.e., one standard deviation below the normative mean).

At baseline, participants will be randomly assigned to one of two orders of essential oils. The oil will be dispensed at the Baseline visit, and will be administered by both massaging the oil on the feet and the back of the neck in the morning and by the diffusion method in the evening.

In this study, clinical responders will be defined as showing a 30% improvement in the total score of the PedsQL Inventory.

Approximately 50% of children will wear a device known as an actigraph that measures activity level and sleep quality. There will be 6 actigraphs and they will be assigned to participants as they are made available on a first come first serve basis. There may be some participants who are unwilling to wear the actigraph and for those who are tactiley defensive we will not require them to do so. Participants will wear the devices for five consecutive nights, on three separate occasions (i.e., between Screening and Baseline, prior to the End Point of the first 3 month period, and prior to the End Point of the second 3 month period). The small watch-like devices worn on the wrist or ankle will collect activity data and measure body temperature while the participant sleeps. They will yield the following sleep variables: 1) time in bed, 2) total sleep time (from lights out), 3) sleep onset latency, 4) morning waking time, 5) frequency of night

wakings, 6) longest sleep period, and 7) sleep efficiency. This is a reliable method of objective data collection for sleep-wake patterns including timing, continuity, and duration of sleep.

In the proposed study, there will be a primary clinician (the physician) and an independent evaluator. The physician will discuss possible side effects and make dose or administration mode adjustments. The independent evaluator will interview the parents with respect to target improvements (QOL) and make DD-CGAS ratings based on all feedback, including parent rating scales.

Dosing
Each participant will utilize both oil delivery methods: diffusion at night and topical application in the morning. If a participant is unable to tolerate one of these delivery methods, then both the morning and night-time doses can be administered via the same, more tolerable method.

Reconnect™ Directions:
To be applied only by a trusted adult or under adult supervision.

Topical: Apply 1 drop to the back of the neck and 1 drop to the feet. Rub in the oil for 30 seconds to 1 minute. Each bottle has an orifice that allows the oil to be expelled drop by drop. Dilution is not required, except for the most sensitive skin. Apply in the morning.

Aromatic Method: Diffuse one diffuser-full (8-12 drops of oil in water) at night.

1. Home diffuser instructions: Open the water reservoir by lifting the lid. Add room-temperature water (distilled water is recommended) up to the fill line of the reservoir. Do not exceed the fill line.
2. Add 8-12 drops of Reconnect to the water.
3. Replace the lid to cover the water reservoir.
4. Plug in the Home Diffuser and push the power switch to start diffusing.
5. When water runs out, the diffuser will automatically shut off.
6. To cycle through the three-mode power settings, press the power switch quickly: Mode 1: Green light - Constant diffusion Mode 2: Red light - 30 seconds intermittent diffusion Mode 3: Off. Use constant diffusion (green light, mode 1).
7. To turn on/off the ambient LED light, press and hold the power switch for approximately 2 seconds.

Notice: Due to the mist output of the Home Diffuser, use caution on surfaces that are sensitive to water.

Essential Oil
The type of Young Living essential oil we will be utilizing is Reconnect™. Reconnect™ contains the following ingredients: Caprylic/capric triglycerides, Prunus amygdalus dulcis (Sweet almond) oil, Boswellia sacra† oil, Citrus aurantium bergamia† peel oil, Commiphora myrrha oil, Lavandula angustifolia† oil, Pelargonium graveolens† flower oil, Callitris intratropica wood oil, Santalum paniculatum† wood oil, Cananga odorata† flower oil, Cedrus atlantica† wood oil, Aniba rosaeodora† wood oil, Melissa officinalis† leaf oil, Picea pungeons†

branch/leaf/wood oil, Picea mariana leaf oil, Hyssopus officinalis† leaf oil, Rosa damascena† flower oil. The comparison oil is coconut oil with a tiny amount of vanilla, just enough for an aroma. Please see Table 2 for a listing of the ingredients, their current common uses, and potential side effects.

Primary Outcome Measure

Pediatric Quality of Life Inventory (PedsQL) (Varni, Burwinkle, & Seid, 2006). The 23-item PedsQL Generic Core Scales were designed to measure the core domains of health and their impact on the quality of life in children as outlined by the World Health Organization. The four Multidimensional Scales are: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning. The summary scores include a Total Scale Score, a Physical Health Summary Score, and a Psychosocial Health Summary Score. Response choices are in Likert-scale format ranging from 0 to 4 (i.e., 0 = Never, 1 = Almost Never, 2 = Sometimes, 3 = Often, 4 = Almost Always). There are 4 versions of the PedsQL including versions for ages 2-4 years, 5-7 years, 8-12 years, and 13-18 years. We will use the age-normed scale for each child that matches the age the child is expected to be at the end of the first condition; once selected, the same scale will be used throughout that child's participation. To be enrolled participants will have clinically significant problems with quality of life (i.e., total item mean score of $\geq$ 1.5).

Other Measures for Establishing Study Inclusion Criteria

Autism Diagnostic Observation Schedule (ADOS) (Rutter et al., 2004). The ADOS is an investigator-based assessment that places the child in naturalistic social situations demanding specific social and communication responses. Behaviors are coded in the areas of social communication, social relatedness, play and imagination, and repetitive behaviors. The ADOS provides a DSM- based algorithm for the diagnosis of ASD. The ADOS will be administered by a research-reliable clinician if it has not already been done by a reliable administrator.

Child and Adolescent Symptom Inventory (CASI) (Gadow & Sprafkin, 2004). We will use the CASI to evaluate children ages 3 to 9 years of age for symptoms of common childhood psychiatric disorders. The CASI will aid ruling out exclusionary psychiatric disorders. Based on DSM-IV diagnostic criteria, this scale assists clinicians by providing useful diagnostic information from parents. The inventory offers both criterion-related cut-off scores and norm-based scores for determining symptom severity (low, moderate, or high, based on parent ratings.

Exploratory Dependent Measures in addition to PedsQL

Developmental Disabilities – Children's Global Assessment Scale (DD-CGAS) (Wagner et al., 2007). The DD-CGAS is a reliable instrument for measuring global functioning of children with developmental disorders in treatment studies. We will use the DD-CGAS to characterize children's impairment on the following four domains: Self Care, Communication, Social Behavior, and School/Academic. In addition, this scale also includes a series of descriptive "bands" to characterize global functioning in children with pervasive developmental disorders from "extreme and pervasive impairment" through "superior functioning."

Parent Stress Index (PSI) (Abidin, 1995). The PSI is used to evaluate the degree of stress in the

parent-child relationship. The Short Form is composed of 36 items taken from the full length PSI and is completed in 10-15 minutes. Child characteristics in the full scale include Distractibility/Hyperactivity, Adaptability, Reinforces Parent, Demandingness, Mood, and Acceptability. Parent measures include Competence, Isolation, Attachment, Health, Role Restriction, Depression, and Spouse. The PSI is used for early identification of dysfunctional parent-child interactions, parental stress, and family functioning. It may be used for parents of children up to 12 years, but it is primarily intended for parents of children 0-3 years. It yields a Total Score and three domain scores. Parents rate each of the 36 items on a 5-point scale (1 = strongly disagree, to 5 = strongly agree). The 90^{th} percentile of the Total PSI score represents a clinically significant level of parenting stress (i.e., total score of $\geq$260). The PSI will be a secondary outcome.

Children's Sleep Habits Questionnaire (CSHQ) (Owens, Spirito, & Mcguinn, 2000). The abbreviated CSHQ is a valid measure of sleep problems with good psychometric properties. The CSHQ was designed for use in children 3 to 7 years of age. It includes 33 items and is rated retrospectively over the previous week by parents to screen for the most common sleep problems. The CSHQ incorporates items related to eight key sleep domains. The eight subscales include: (1) bedtime resistance (2) sleep onset latency, (3) sleep duration, (4) anxiety around sleep, (5) night awakenings, (6) sleep disordered breathing, (7) parasomnias and (8) morning waking/daytime sleepiness. A Total Score of 41 or greater on the CSHQ 33 items has been reported to be an appropriate clinical cut-off for identifying sleep problems in children. In a recent study of the participants in the Autism Treatment Network 75% of the participants analyzed had a CSHQ score of 41 or higher (Hollway, Aman, and Butter, 2013). The Abbreviated CSHQ will be used to determine whether a child has a clinically significant sleep problem and will be a secondary (mediational) outcome measure of the study.

Parent Sleep Diary (Thomas & Burr, 2009). A parent/caregiver diary documenting overall information about participant sleep-wake behavior patterns, will be implemented. Caregivers will record "time in bed," time asleep," "time awake after sleep onset," and "number of nighttime awakenings." The diary will be used in conjunction with the CSHQ rating scale to collect caregiver estimates of sleep efficiency. These data will be evaluated for their reliability when compared to our objective measure of the sleep, the Motion-logger Micro Watch. The sleep diary will be distributed to the caregiver at the end of each visit to be filled in at home each morning.

The Autism Anxiety Scale (AAS)(Aman, Scahill, Lecavalier, and Sukodolsky, 2013). Investigators from OSU, Emory University, and Children's Hospital of Philadelphia (CHOP) are engaged in developing what will be the definitive instrument for measuring anxiety in children with autism spectrum disorders (NIMH grant "Toward outcome measurement of anxiety in youth with autism spectrum disorders"). This project uses the Children and Adolescent Symptom Inventory's (CASI) anxiety items as its nucleus. But investigators have expanded the scale's content following a review of the literature and conducting 6 focus groups with parents of children with ASD. In a few months the instrument will be empirically derived and the shape or structure will be decided by factor analysis, and the composition will be decided by electrophysiological measures. This scale will likely become the standard for use in randomized clinical trials. We are fortunate to be allowed to use an early version of this cutting-edge scale. The AAS, in addition to the abbreviated CSHQ, will be a secondary (meditational) outcome measure of the study.

*Aberrant Behavior Checklist (ABC).*The ABC is a 58-item parent-report measure with five subscales: 1) Irritability (includes agitation, aggression and self-injurious behaviors, 15 items); 2) Social Withdrawal (16 items); 3) Stereotypies (7 items); 4) Hyperactivity (16 items); and 5) Inappropriate Speech (4 items), (Aman et al., 1985a; Aman et al. 1985b; Aman et al., 1987, Brown, Aman, & Havercamp, 2002). Psychometric characteristics of the ABC range from satisfactory to very good (Aman et al.,1985b). The ABC has been commonly used in research on children with ASD and is highly sensitive. Its parent-rated five subscales will be used to explore whether the use of Reconnect Essential Oils is associated with behavior changes during the day. We will evaluate the ABC to assess irritability levels and improvement over the course of the study. The ABC will be an exploratory outcome measure.

Social Responsiveness Scale (SRS) (Costantino et al., 2003). This 65-item rating scale measures the severity of autism spectrum symptoms as they occur in natural social settings. Completed by a parent or teacher in 15 to 20 minutes, the SRS provides a clear picture of a child's social impairments, assessing social awareness, social information processing, capacity for reciprocal social communication, social anxiety/avoidance, and autistic preoccupations and traits. It is appropriate for use with children from 4 to 18 years of age. Sensitive and reliable across a wide range of symptom severity, the SRS can be used as a screener in clinical or educational settings, an aid to clinical diagnosis, or a measure of response to intervention. SRS scores are particularly helpful in identifying Autism, Asperger's Disorder, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), and Schizoid Personality Disorder of Childhood.

Short Sensory Profile (SP) (Dunn, 1999). The Short Sensory Profile is a 38-item caregiver questionnaire and score sheet designed for use in screening and research protocols. The items on the *Short Sensory Profile* are grouped into three major sections: sensory processing, modulation, and behavioral and emotional responses. In a recent report it was found that sensory sensitivities were related to sleep difficulties in children with ASD (Hollway, Aman, Butter, 2013). We will use the SP to track sensory sensitivities which may be related to avoidance behavior that interferes with family QOL, over the course of the study. The SP will be an exploratory measure.

Repetitive Behavior Scale – Revised (RBS-R) (Lam & Aman, 2007). The RBS-R is a 43-item self-report questionnaire that is used to measure the breadth of repetitive behavior in children, adolescents, and adults with Autism Spectrum Disorders. The RBS-R provides a quantitative, continuous measure of the full spectrum of repetitive behaviors. The RBS-R consists of six subscales including: Stereotyped Behavior, Self-injurious Behavior, Compulsive Behavior, Routine Behavior, Sameness Behavior, and Restricted Behavior that have no overlap of item content. This permits differential identification and scoring of discrete varieties of repetitive behaviors. Participants are asked to read a list of behaviors and choose a score that best describes how much of a problem the behavior has been. Behaviors are rated on a 4-point scale: 0-Behavior does not occur, 1-Behavior occurs and is a mild problem, 2-Behavior occurs and is a moderate problem, 3-Behavior occurs and is a severe problem. We will use the RBS-R to assess repetitive behaviors and improvement over the course of the study.

Swanson, Nolan, and Pelham Version IV Parent Rating Scale (SNAP-IV). The SNAP-IV ADHD and ODD sections include the 18 DSM-IV symptoms of ADHD (9 hyperactive/impulsive items

and 9 inattention items) and eight symptoms of ODD (Oppositional Defiant Disorder) on a 0-3 metric; it can be downloaded from www.adhd.net. We will use the SNAP-IV to assess ADHD and ODD symptoms and improvement over the course of the study.

Objective Measure of Sleep

Motionlogger Micro Watch (Ambulatory Monitoring). The Motionlogger Micro Watch includes basic sleep estimation with simultaneous environmental data collection. A range of recording capabilities exist including four validated sleep algorithms and a suite of circadian rhythm analyses. The software package allows for quick easy download of actigraph data. Study participants will wear the actigraph on five consecutive nights between the Screen and Baseline Visits, between Visit 5 and 6 and again between visits 9 and 10.

Safety Measures

Laboratory Tests. On three separate occasions during the study participants will have blood drawn and laboratory tests will be conducted to assess any changes in test values since the Screening Visit. Blood and urine will be collected at the Screen Visit, at the Endpoint of the first phase (Week 12), and at the Endpoint of the last phase (Week 28). The following tests will be run on the blood samples: ALT, AST, total and direct bilirubin, creatinine, CRP, IL-6, and CBC. The following tests will be run on the urine samples: standard urinalysis, to evaluate protein, PH, glucose, ketones, nitrites, appearance, color, specific gravity, and bacteria.

Adverse Events (AEs). To minimize the risk, subjects will be systematically monitored. AEs, vital signs, including resting BP, will be evaluated at each visit throughout all phases of the study. When the treating clinician elicits an AE, it will be documented on a case report form, regardless of suspected relationship to the essential oil. For all AEs, the investigator will obtain sufficient information to determine the onset, course, and outcome of the AE. If a subject has experienced an AE, the subject may return to the site for an unscheduled visit at the PI's discretion. If any of these AEs are serious and/or unexpected, the site PI will contact the Sponsor and notify the IRB as appropriate.

Potential AEs include sun sensitivity due to the Bergamot in the essential oil, possibly gynecomastia in pre-pubescent males due to the lavender oil in the essential oil, and skin irritation at the application site.

Sample Characteristics

Demographic Profile. This will be completed by the parent / caregiver at screening to document basic demographic information (parent education, occupation, and marital status).

Cognitive / Developmental Measures. Depending on the age and functioning level of the child, the Stanford-Binet Intelligence Scales; 5th Edition abbreviated battery (Nagle & Bell, 1993) or Mullen Scales of Early Learning AGS Edition will be administered (Mullen, 1995). These are the two cognitive/developmental measures used in the Autism Treatment Network and our other projects. We will evaluate level of cognitive functioning to characterize our sample. The IQ test results will be used to characterize our sample via mean and standard deviation.

Social Validity

Consumer Satisfaction Questionnaire. The Consumer Satisfaction Questionnaire will be filled in by parents at the end of both the first condition and the second. This questionnaire will be used to determine parents level of satisfaction with the study conditions and procedures. The Consumer Satisfaction Questionnaire (CSQ) speaks to feasibility of a larger study, which is one of the study's aims.

Masking Questionnaire. The Making Questionnaire will be completed by parents and by a study clinician at Visit 10 (Week 28). This questionnaire will be used to determine whether parents and clinicians can guess the oils that parents received during the first and last 3 months of the study and why. This questionnaire will provide information about the efficacy of masking essential oils treatments that may be useful for future studies.

Data Analytic Plan

The primary goal of this double-blinded randomized pilot study is to establish the feasibility of a full-scale study by evaluating (1) recruitment (retention and adherence), (2) safety, (3) and preliminary evaluation of the effect on the clinical outcomes. The primary outcome is QOL. Chief secondary outcomes are CSHQ, AAS and PSI. Exploratory outcomes include DD-CGAS, ABC SRS, RBS and Actigraphy.

Data analysis will be primarily comparing Reconnect to the control condition. For drop-outs, we will do a terminal evaluation and evaluate whether it is related to study oils or procedures or to some unrelated issue (e.g., moving away), and report the pattern of drop out. If more subjects drop out at a very early stage (week 1 or 2) than expected based on our experience, we will consider recruiting additional subjects to insure 28 subjects experiencing both conditions.

Demographic and recruitment information will be summarized. Frequency tables will be used to summarize toxicity and tolerability based on type, severity, and attribution of the adverse events during each condition. Clinical outcomes will be plotted and summarized for all subjects over time by individual and condition. Data summaries for missing and outlying data will be distributed and reviewed. Visual displays will be generated and presented to investigators in order to identify any outliers or other problems that could be missed by summary statistics. The categorical outcomes will be tabulated for each condition. The effect sizes of the changes of these clinical outcomes after 12 weeks will be estimated, using Cohen's definition, for each condition. Each phase will last for a total of 12 weeks. The effect size of active vs control condition will be calculated as the differences of the mean improvements between conditions, divided by pooled standard deviation of the improvements from the two groups.

Sample size and Randomization

This randomized crossover pilot study will have 28 subjects randomized into 2 orders of condition with a block size of 4 initially, then block size of 2 as the sample size nears

completion. Considering up to 15% early drop outs due to reasons not related to essential oils, we plan to randomize up to 33 subjects.

With 28 participants in this crossover study and using the participants as their own controls we estimate that we will be able to detect statistical significance with an effect size **of 0.8.** In addition, we will compare the changes of the clinical outcome variables between Reconnect and control conditions by testing the interaction of condition and time based on a linear mixed model for repeated measurement, with conventional alpha of 0.05 for the primary outcome. In order to protect against Type 2 error in this pilot study, we will not correct for multiple tests.

Study Time Line

Study Timeline. The time-line for the study appears in Figure 1. The first several months will be used to obtain IRB approvals and create Case Report Forms or source documents. The next 19 months will be used for participant recruitment, supplementation, and assessment. Finally, the last 3 months will involve data analysis and manuscript writing.

Table 3. Study Timeline (24 months)

	Year 1				Year 2			
Month	0-3	4-6	6-9	9-12	0-3	3-6	6-9	9-12
Activity	Preparation	Recruiting, Assessment, Oil Use						Completion

(Training on actigraphy ; IRB, Teleforms)

(Data analysis, manuscript writing, progress reports)

REFERENCES

Abidin, R. *Parenting stress index* (three editions) Psychological Assessment Resources, Inc, Odessa, FL (1983, 1990, 1995).

Abidin, R.R. *Parenting stress index short form* Pediatric Psychology Press, Charlottesville, VA (1990).

Aman MG, Singh NN, Stewart AW, Field CJ. (1985a). Psychometric characteristics of the Aberrant Behavior Checklist. *American Journal of Mental Deficiency, 89,* 492-502.

Aman, M.G., Singh, N.N. Stewart, A.W., & Field, C, J. (1985b). The Aberrant Behavior Checklist rating scale for the assessment of treatment effects. *American Journal of Mental Deficiency, 89,* 485-491.

Anders, T.F., Iosif, A., Schwichtenberg, A.J., Tang, K., Goodlin-Jones, B.L. (2011). Six-month sleep-wake organization and stability in preschool-age children with autism, developmental delay and typical development. *Behavioral Sleep Medicine 9*, 92-106.

Andersen, I.M., Kaczmarska, J., McGrew, S.G., Malow, B.A. (2008). Melatonin for insomnia in children with autism spectrum disorders. *Journal of Child Neurology, 23*, 482-485.

Arnold, L. E. , Aman, M.G., Martin, A., Collier-Crespin, A., Vitiello, B., et al. (2000). Assessment in a multisite clinical trial of patients with autistic disorder: Autism RUPP Network, Research Units on Pediatric Psychopharmacology. *Journal of Autism and Developmental Disorders, 30*, 99-111.

Brogen, L., Brogen, I., Thorell, L. (1998). Defense Mechanism Test and electrodermal activity. *Perceptual and Motor Skills, 87*, 279-290

Brown, E. C., Aman, M. G., & Havercamp, S. M. (2002). Factor analysis and norms on parent ratings with the Aberrant Behavior Checklist Community for young people in special education. *Research in Developmental Disabilities, 23*, 45-60.

Cetinkaya, B., Basbakkal, Z. (2012). The effectiveness of aromatherapy massage using lavender oil as a treatment for infantile colic. International Journal of Nursing Practice, 18, 164-169.

Chattopadhyay, P.K., Bond, A.J., Lader, M.H. (1975). Characteristics of galvanic skin response in anxiety states. *Journal of Psychiatric Research, 12*, 265-270.

Constantino, J.N., Davis, S.A., Todd, R.D., Schindler, M.K., Gross, M.M., Brophy, S.L., Metzger, L.M., Shoushtari, C.S., Splinter, R., Reich, W. (2003). Validation of a brief quantitative measure of autistic traits: Comparison of the Social Responsiveness Scale with the Autism Diagnostic Interview – Revised. *Journal of Autism and Developmental Disorders, 33* (4), 427-433.

Doo, S, & Wing, Y. (2006). Sleep problems of children with pervasive developmental disorders; correlation with parent stress. *Developmental Medicine & Child Neurology, 48*, 650-655.

Dunn W. (1999).The Sensory Profile manual. San Antonio TX: The Psychological Corporation.

El Shiekh, M. & Ariswalla, D.D. (2011). Children's sleep skin conductance level and mental health. *Journal of Sleep Research, 20*, 326-337.

Gadow, K. D., & Sprafkin, J. (1997). *ADHD Symptom Checklist–4 manual*. Stony Brook, NY: Checkmate Plus.

Goel, N., Kim, H., Lao, R.P. (2005). An olfactory stimulus modifies nighttime sleep in young men and women. Chronobiology International, 22(5), 889-904.

Gotham, K., Risi, S., Pickles, A., & Lord, C. (2007).The Autism Diagnostic Observation Schedule: Revised algorithms for improved diagnostic validity. *Journal of Autism Disorders, 37*, 613-627.

Hare, D.J., Jones, S., Evershed, K. (2006). Objective investigation of the sleep-wake cycle in adults with intellectual disabilities and autistic spectrum disorders. *Journal of Intellectual disability Research, 50*, 701-710.

Hirokawa, K., Nishimoto, T. (2012). Effects of lavender aroma on sleep quality in healthy Japanese students. Perceptual and Motor Skills 114 (1), 111-122.

Hiscock, H., & Wake, M. (2002). Randomized Controlled trial of behavioral infant sleep intervention to improve infant sleep and maternal mood. *British Medical Journal, 324*, 1062-1065.

Hollway, J.A., (Unpublished manuscript). Dissertation Research: Correlates and risk markers for sleep disturbance in participants of the Autism Treatment network.

Hollway J.A. & Aman, M.G. (2011a). Pharmacological Treatment of Sleep Disturbance in Developmental Disabilities: A review of the literature. *Research in Developmental Disabilities, 32*, 939-962.

Hollway, J.A., Aman, M.G. (2011b). Sleep correlates of pervasive developmental disorders: A review of the literature. *Research in Developmental Disabilities, 32,* 1399-1421.

Hollway, J.A., Aman, M.G., Butter, E. (2013). Correlates and risk markers for sleep disturbance in participants of the Autism Treatment Network. *Journal of Autism and Developmental Disorders.* DOI 10.1007/s10803-013-1830-y.

Hur, M.H., song, J.A., Lee, J., Soo Lee, M. (2014). Aromatherapy for stress reduction in healthy adults; a systematic review and meta-analysis of randomized clinical trials. Maturitas. Http://dx.doi.org/10.1016/j.maturitas.2014.08.006

Hyde, M., O'Driscoll, D.M., Binette, S., Galang, C., Tan, S., Verginis, n., Davey, M., Horne, R. (2007). Validation of actigraphy for determining sleep and wake in children with sleep disordered breathing. *Journal of Sleep Research, 16*, 213-216.

Jafarzadeh, M., Arman, S., Farahbakhsh Pour, F. (2013). Effect of aromatherapy with orange essential oil on salivary cortisol and pulse rate in children during a dental treatment: Randomized controlled clinical trial.

Johnson, K.P., Giannotti, F., Cortesi, G. (2009). Sleep patterns in autism spectrum disorders. Child and *Adolescent Psychiatric Clinics of North America 18*, 917-928.

Johnson, C.R., Turner, K., Foldes, E., Malow, B.A., & Wiggs, L. (2012). Comparison of sleep questionnaires in the assessment of sleep disturbances in children with autism spectrum disorders. *Sleep Medicine, 13,* 795-801.

Lam, K.S.L. and Aman, M.G. (2007). The Repetitive Behavior Scale-Revised: independent validation in individuals with autism spectrum disorders. *Journal of Autism and Developmental Disorders, 37(5)*: 855-866.

Lee, Y., Wu, Y., Tsang, H.W.H., Leung, A.Y., Cheung, W.M. (2011). A systematic review on the anxiolytic effects of aromatherapy in people with anxiety symptoms. Journal of Alternative and Complementary Medicine, 17(2), 101-108.

Lindstrom, E.M., Öhlund, L.S., Lindström, L.F., Öhman, A. (1991). Symptomatology and electrodermal activity as predictors of neuroleptic response in young make schizophrenic patients. *Psychiatry Research, 42,* 145-158.

Moon, E.C., Corkum, P., Smith, I.M. (2011). Case Study: A case series evaluation of a behavioral sleep intervention for three children with autism and primary insomnia. *Journal of Pediatric Psychology*, 37, 47-54.

Mullen, E. M. (1995). Mullen Scales of Early Learning (AGS ed.). Circle Pines, MN: American Guidance Service Inc.

Nord, D., & Belew, J. (2009). Effectiveness of the essential oils lavender and ginger in promoting children's comfort in a perianesthesia setting. Journal of Periansesthesia Nursing, 24(5), 307-312.

Ndao, D.H., Ladas, E.J., Cheng, B., Sands, S.A., Snyder, K.T., Garvin, J.H. & Kelly, K.M. (2012). Inhalation aromatherapy in children and adolescents undergoing stem cell infusion: results of a placebo-controlled double-blind trial. Psycho-Oncology, 21, 247-254.

O'Flaherty, L.A., vanDijk, Alertyn, R., Millar, A. (2012). Aromatherapy massage seems to enhance relaxation in children with burns: An observational pilot study. Burns, 38, 840-845.

Owens, J.A., Spirito, A., Mcguinn, M. (2000). The children's sleep habits questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. *Sleep 23*, 1043-1051.

Prince, J. B., et al. (1996). Clonidine for sleep disturbances associated with attention-deficit hyperactivity disorder: a systematic chart review of 62 cases. *Journal of the American Academy of Child and Adolescent Psychiatry, 35,* 599-605.

Reed, H.E., Mcgrew, S.G., Artibee, K., Surdkya, K., Goldman, S.E., Frank, K., Wang, L., Malow., B.A. (2009). Parent-based sleep education workshops in autism. *Journal of Child Neurology, 24*, 936-945.

Reid, M. J., Walter, A. L., & O'Leary, S. G. (1999). Treatment of young children's bedtime refusal and nighttime wakings: A comparison of "standard" and graduated ignoring procedures. *Journal of* Abnormal Child Psychology, 27, 5-16.

Roid, G.H. (2003). *Stanford-Binet Intelligence Scale, Fifth Edition*. Itasca, IL: Riverside Publishing.

Rutter. M., Le Couteur, A., & Lord, C. (2004). *Autism Diagnostic Observation Schedule (ADOS): Manual*. Multi-Health Systems Inc. (MHS).

Sadeh, A., Hauri, P.J., Kripke, D.F., Lavie, P. (1995). The role of actigraphy in the evaluation of sleep disorders. *Sleep, 18*, 288-302.

Satou, T., Chikama, M., Chikama, Y., Hachigo, M., Urayama, H., Murakami, S., Hayashi, S., Koikem, K. (2013). Effect of Aromatherapy Massage on Elderly Patients Under Long-Tem Hospitalization in Japan. The Journal of Alternative and Complementary Medicine, 19(3), 235-237.

Shakibaei, F., et al. (2008). Effect of trazodone on sleep bruxism in children and adolescents 6-18 years of age, a pilot study. *Journal of Research in Medical Sciences, 13*, 29-33.

Simonds, J.F., & Parraga, H. (1982). Prevalence of sleep disorders and sleep behaviours in children and adolescents. *Journal of the American Academy of Child Psychiatry, 21*, 383-388.

So, K., Buckley, P., Adamson, T.M., Horne, R.S. (2005). Actigraphy correctly predicts sleep behavior in infants who are younger than six months, when compared with polysomnography. *Pediatric Research, 58*, 761-765.

Sprafkin, J., et al. (1984). Reliability and validity of a DSM-III-based checklist for disruptive behavior disorders. Unpublished data. Reported in Gadow and Sprafkin (1994*), Child Symptom Inventories manual.* Stony Brook, NY: Checkmate Plus.

Thomas, K.A., Burr, R. L. (2009). Accurate Assessment of Mother & Infant Sleep: How many diaries are required? *MCN 34, (4),* 257-260.

Turner, K.S., & Johnson C.R. (2012). Behavioral interventions to address sleep disturbance in children with Autism Spectrum Disorders: A review. Topics in Early Childhood Special Education, published on line 24 May 2012. DOI:10.1177/0271121412446204.

Vriend, J. L., et al. (2011). Behavioral Interventions for Sleep Problems in Children WithAutism Spectrum Disorders: Current Findings and Future Directions. *Journal of Pediatric Psychology, 36,* 1017-1029.

Varni, J.W., Burwinkle, T.M., & Seid, M. (2006). The PedsQL™ 4.0 as a school population health measure: Feasibility, reliability, and validity. Quality of Life Research, 15, 203-215.

Wagner, A., Lecavalier, L., Arnold, L. E., Aman, M. G., Scahill, L., Stigler, K. A., Johnson, C. R., McDougle, C. J., Vitiello, B. (2007). Developmental disabilities modification of the Children's Global Assessment Scale. *Biological Psychiatry, 61,* 504-511.

Wiggs, L., & Stores, G. (1996). Severe sleep disturbance and daytime challenging behaviour in children with severe learning disabilities. *Journal of Intellect & Disability Research, 40,* 518–528.

Wiggs, L., & Stores, G. (1998). Behavioural treatment for sleep problems in children with severe learning disabilities and challenging daytime behaviour: Effect on sleep patterns of mother and child. *Journal of Sleep Research, 7,* 119-126.

Wiggs, L., & Stores, G. (1999). Behavioural treatment for sleep problems in children with severe learning disabilities and challenging daytime behavior: Effect on daytime behaviour. *Journal of Child Psychology & Psychiatry & Allied Disciplines, 40*, 627-635.

Wiggs, L., & Stores, G. (2004). Sleep patterns and sleep disorders in children with autistic spectrum disorders: Insights using parent report and actigraphy. *Developmental Medicine & Child Neurology, 46,* 372-380.

Williams, T.I. (2006). Evaluating Effects of Aromatherapy Massage on Sleep in Children with Autism: A pilot study. Advance Access Publications, 3(3), 373-377.

Wu, J., Cui, Y., Yang, Y., Kang, M., Jung, S., Keun Park, H., Yeun, H., Jang, W., Lee, S., Kwak, Y.S., Eun, S. (2014). Modulatory effects of aromatherapy massage intervention on electroencephalogram, psychological assessments, salivary cortisol and plasma brain-derived nerurotrophic factor. Complementary Therapies in Medicine, 22, 456-462.

Zahn, T.P., Abate, F., Little, B.C., Wender, P.H. (1975). Minimal brain dysfunction, stimulant drugs, and autonomic nervous system activity. *Archives of General Psychiatry, 32*, 381-387.

Table 1. Schedule of Measures for the use of Essential Oils in Children with Autism Spectrum Disorder to improve Quality of life

	Screen Visit 1	Wk0 V2 BL	Wk2 V3	Wk4 V4	Wk8 V5	Wk12 V6	Wk16 V7 BL (2)	Wk20 V8	Wk24 V9	Wk 28 V10
	Actigraphy	Begin Cond 1			Actigraphy	End Cond 1 Begin WO	Begin Cond 2		Actigraphy	End Cond 2
Laboratory Analysis	X					X				X
Informed Consent	X									
CASI	X									
Pediatric Quality of Life Inventory	X					X				X
Parent Stress Index		X				X				X
CSHQ/Sleep Interview	X	X	X	X	X	X	X	X	X	X
Autism Anxiety Scale (AAS)	X	X	X	X	X	X	X	X	X	X
DD-CGAS		X				X				X
Demographics	X									
DSM-V Interview	X									
ADOS	X									
IQ Test (SB-5 or MSEL)	X									
Physical Exam	X									X
Vital Signs; Height, Weight	X	X	X	X	X	X	X	X	X	X
Medical/Psychiatric History/Medication History	X									
Pre-existing conditions	X	X								
Adverse Events, skin exam			X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X
Aberrant Behavior Checklist (ABC)		X				X				X
Repetitive Behavior Scale-Revised (RBS-R)		X				X				X
Short Sensory Profile		X				X				X
Social Responsiveness Scale-2		X				X				X
SNAP-IV	X					X				X
Parent Satisfaction						X				X
Masking Questionnaire										X
Actigraph	X (T)	X (D)			X (T)	X (D)			X (T)	X(D)

Note: Schedule based on 12 weeks in each of 2 conditions with 1-month washout between, with two biweekly then two monthly visits in first condition and four monthly visits in the second condition.

Table 2. Ingredients of Reconnect formulation of essential oils, their uses/actions, and potential side effects.

Reconnect™ Ingredient	Uses	Safety	Chemical Composition	Citations
Prunus amygdalus dulcis (Sweet Almond) oil	Protects skin's barrier function and keeps it from drying - used in body lotions, face creams, and body oils; anti-inflammatory and pain relieving	CIR approved as safe for topical application; absorbs slowly through skin; completely digested if taken orally; non-irritating and non-sensitizing in any concentration ****Nut/almond allergies**	Oleic acid (62-86%), Linoleic acid (20-30%), other fatty acids, α-tocopheral, arginine, phytosterols, polyphenols	Almond oil (prunus amygdalus dulcis) – the universal skin oil (n.d.). *Bio G Cosmetics.* Web.
Boswellia sacra oil	"Frankincense." Perfumes and skin care; edible. Potential anti-depressant. Studies suggest it may have cancer-killing properties and improve osteoarthritis.	Not CIR or FDA approved, but widely used and appears to be well tolerated	Acid resin (56%), gum (similar to gum arabica) (30-36%), 3-acetyl-β-boswellic acid, α-boswellic acid, incensole acetate, phellandrene	Martin, N. (n.d.). Sacred Frankincense Essential Oil - The Original Oil Given to Baby Jesus? *Experience-Essential-Oils.com.* Web.
Citrus aurantium bergamia peel oil	Helps with heartburn, gas, insomnia, mild depression, and upset stomach (Martin).	FDA approved as a Food Additive and generally regarded as safe, but not recommended for children < 5 years old and can result in skin irritation, particularly from frequent usage or UV light exposure (Martin).	α-pinene, myrcene, limonene, α-bergaptene, β-bisabolene, linalool, linalyl acetate, nerol, neryl acetate, geraniol, geraniol acetate and α-terpineol (Bergamot)	Bergamot essential oil information (2014). *Esoteric Oils CC.* Web. Martin, N. (n.d.). The Benefits of Bergamot include Easing Stress from Mind & Body! *Experience-Essential-Oils.com.* Web.
Commiphora myrrha oil	Helps clear colds, bronchitis, cough by removing mucus; used for chapped skin, eczema, skin ulcers, ringworm, skin wounds	Non-toxic, non-irritating, and non-sensitizing	α-pinene, cadinene, limonene, cuminaldehyde, eugenol, m-cresol, heerabolene, acetic acid, formic acid	Myrrh essential oil information (2014). *Esoteric Oils CC.* Web.

Lavandula angustifolia oil	Natural antibiotic, anti-depressant, sedative; promotes healing and stimulates the immune system (Worwood 1990); Pain relief, antiseptic, stress and anxiety relief, burns and insect bites, aromatherapy ("Lavender Oil").	Topical application can sometimes cause irritation; likely safe in food and possible safe in medicinal amounts; **disrupts hormones in pre-pubertal boys and can result in gynecomastia** (abnormal breast growth) (Henley 2007)	Linalool (51%) and linalyl acetate (35%) mostly. Other components include α-pinene, limonene, 1,8-cineole, cis- and trans-ocimene, 3-octanone, camphor, caryophyllene, terpinen-4-ol and lavendulyl acetate ("Lavender Oil")	Henley, D.V. (2007) Prepubertal Gynecomastia Linked to Lavender and Tea Tree Oils. N Engl J Med. 356(5), 479-485. "Lavender Oil." Wikipedia. Wikimedia Foundation (2014). Web. Worwood, V.A (1990) *The Fragrant Pharmacy*. London: Macmillan.
Pelargonium graveolens flower oil	Antidepressant, anxiolytic, astringent, diuretic	Generally regarded as safe and approved as a food additive by the FDA; non-toxic, non-irritant and generally non-sensitizing	α-pinene, myrcene, limonene, menthone, linalool, geranyl acetate, citronellol, geraniol and geranyl butyrate	Rose geranium essential oil information (2014). *Esoteric Oil CC*. Web.
Callitris intratropica wood oil	Fragrances; helps with arthritis and asthma	No contraindications found; generally regarded as safe	Guaiol, guaienes, selinenes, guaiazulene, eudesmols, furnanones	Rose, Jeanne. *375 Essential Oils and Hydrosols*. Berkeley, CA: Frog, 1999. 51. *Blue Cypress Essential Oil*. AromaWeb. Web.
Cananga odorata flower oil	Antidepressant, aphrodisiac, hypotensive, sedative; helps with oily skin, anxiety, tension, and fear	Non-toxic, non-irritating, and in most cases non-sensitizing, but sensitivity has been reported and headaches and nausea can result from excessive use.	Linalool, geranyl acetate, caryophyllene, p-cresyl methyl ether, methyl benzoate, benzyl acetate, benzyl benzoate and other sesquiterpenes.	Ylang-ylang essential oil information (2014). *Esoteric Oil CC*. Web.
Aniba rosaeodora wood oil	Anti-depressant, mildly analgesic, antiseptic, aphrodisiac; helps with headaches	Non-toxic, non-irritating, non-sensitizing; generally regarded as safe	α-pinene, camphene, geraniol, neral, geranial, myrcene, limonene, 1,8-cineole, linalool, benzaldehyde, linalool oxides and a-	Rosewood essential oil information (2014). *Esoteric Oil CC*. Web.

			terpineol	
Picea mariana (Spruce) leaf oil	Helps with arthritis, infections, and pain; supports the immune system	FDA approved Food Additive and Flavoring Agent; non-toxic and generally safe but could result in skin irritation	Pinenes, limonene, boryl acetate, tricyclene, phellandrene, thujone	Martin, N. (n.d.). Spruce Essential Oil offers Support for Muscles and the Immune System! *Experience-Essential-Oils.com.* Web.
Hyssopus officinalis leaf oil	Used in cooking; medicinally used as a cough suppressant and expectorant; helps with nervous exhaustion and grief	Contains thujone which stimulates the CNS and can cause seizures as the oil, even in low doses, in children; otherwise non-irritating and non-sensitizing	α-pinene, camphene, β-pinene, sabinene, myrcene, limonene, pinocamphone, isopinocamphene, γ-terpineol, 1,8-cineole and thujone	Woolf, A. (1999). Essential Oil Poisoning. *Clinical Toxicology,* 37(6), 721-727.
Rosa damascena flower oil	Helps with dry skin/eczema, asthma, heart arrhythmia, high BP; anti-depressant, sedative, laxative, aphrodisiac, anxiolytic	Non-toxic, non-irritating, and non-sensitizing	300+ compounds, but main ones are citronellol, phenyl ethanol, geraniol, nerol, farnesol, stearpoten, α-pinene, myrcene, limonene, menthone, and linalool (Rose)	Woolf, A. (1999). Essential Oil Poisoning. *Clinical Toxicology*, 37(6), 721-727. Rose geranium essential oil information (2014). *Esoteric Oils CC.* Web.
Santalum paniculatum (Royal Hawaiian Sandalwood) wood oil	Perfume, meditation, relaxation; Helps chapped skin, scars, and stretch marks; anti-inflammatory, a disinfectant, diuretic, and anti-depressant; said to help with insomnia, bug bites, headaches, depression	May cause skin irritation and should be diluted.	100% steam-distilled pure Sandalwood oil from Hawaiian trees (organic compounds not specified)	"Royal Hawaiian Sandalwood Essential Oil Santalum Paniculatum." *Hana Naia Aromatherapy*. Hana Naia LLC, 2014. Web.
Caprylic/capric triglycerides	Ester derived from Coconut oil; Good solvent and emollient, acts as a	Skin exposure shows very low toxicity and no potential for skin/eye irritation/sensitization; FDA approved as a food additive and CIR approved for cosmetic use	Derived from coconut oil and glycerin	"Caprylic/Capric Triglycerides." *Truth in Aging*. Truthinaging.com, 2013. Web.

	carrier for fat-soluble vitamins; used in cosmetics: hair products, dyes, sunscreen, deodorants, make-up			
Cedrus atlantica (Cedarwood) wood oil	Acne, arthritis, coughing, dermatitis, bronchitis, stress	No special precautions indicated	Atlantone, caryophyllene, cedrol, cadinene	"Atlas Cedarwood Essential Oil." *AromaWeb*. AromaWeb, LLC, 2014. Web.
Melissa officinalis leaf oil	Antidepressant, sedative, antispasmodic, hypotensive; helps with nausea, headaches	Non-toxic, but could be irritating or sensitizing so should be diluted and not used on sensitive skin	Tannins, eugenol, terpenes, citronellal, octyl benzoate, linalool, nerol, etc	"Melissa Essential Oil (a.k.a. Lemon Balm Essential Oil) Information." *Esoteric Oils*. Esoteric Oils CC, 2014. Web.
Picea pungens (Idaho blue spruce) branch/leaf/wood oil	Relax the mind and muscles, relieve muscle tension, cleanse minor skin irritations	FDA approved as a Food Additive, so generally safe	45-55% monoterpenes (mostly α-pinene and limonene); 3-12% sesquiterpenes	"Idaho Blue Spruce Essential Oil." *Aromatherapy Living with Young Living Essential Oils*. Young Living Essential Oils, 2012. Web.

Table 3. Ingredients of coconut oil scented with 0.5% vanilla absolute oil, their uses/actions, and potential side effects.

Scented Coconut Oil Ingredient	Uses	Safety	Chemical Composition	Citations
Vanilla Absolute Oil	Found in Madagascar. Used primarily as a fragrance.	A solution of 10% vanillin diluted in petrolatum resulted in occasional contact allergy. In a study by Hausen, no positive reactions to vanillin were found.	Primary constituents include vanillin, vanillic acid, and p-hydroxybenzaldehyde	"Certificate of Analysis: Vanilla Absolute." *Eden Botanicals*. Eden Botanicals, 2015. Web. Wöhrl, S., Hemmer, W., Focke, M., Götz, M. and Jarisch, R. (2001), The significance of fragrance mix, balsam of Peru,

				colophony and propolis as screening tools in the detection of fragrance allergy. British Journal of Dermatology, 145: 268–273. doi: 10.1046/j.1365-2133.2001.04345.x Hausen BM. Contact allergy to balsam of Peru. II. Patch test results in 102 patients with selected balsam of Peru constituents. Am J Contact Dermat. 2001;12(2):93–102. [PubMed]
Coconut Oil	Used as a flavoring in foods. Added to some pharmaceuticals and cosmetics. Commonly rubbed on the skin.	Populations of people that consume large quantities of coconut oil show no adverse effects. According to the FDA, "There is no evidence in the available information on coconut oil, peanut oil, and oleic acid that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public as they are now used in paper and cotton packaging material for food at levels now current or as they might reasonably be expected to be used for such purposes in the future."	Composed of 92% saturated fatty oils.	Thampan, P.K., Glimpses of coconut industry in India, Coconut Development Board, Cochin 1988. Krishna, G., Rah, G., Bhatnagar, A. S., Kumar, P., & Chandrashekar, P. Indian Coconut Journal. "Coconut Oil: Chemistry, Production and Its Applications - A Review." 2010. "Select Committee on GRAS Substances (SCOGS) Opinion: Coconut Oil (packaging)." U.S. Food and Drug Administration, Apr. 2013. Web. 02 Jan. 2015.

Human Subjects considerations

Participants:
Participants are 28 children age 3-9 with autism spectrum disorder and excessive anxiety and sleep disturbance. Although we are not treating autism, this population is especially prone to impaired QOL due to sleep problems and anxiety, and is the population for which OTC essential oils are most often used by consumers without adequate test of benefits and safety. Careful evaluation of this practice has been requested by parents of children with autism.

Risks:
Essential oils themselves are generally regarded as safe and are routinely used by the public. One of the purposes of this pilot study is to check whether this assumption is valid. The main known risk/discomfort is from the blood draws, with possible bleeding, bruising, or infection. The ratings pose some time/effort burden for parents and the usual confidentiality risks apply. Although uncommon, skin irritation with topical administration or breast enlargement in boys is a potential side effect of a few ingredients of Reconnect (See Table 2).

Minimization of risk:
Numbing cream will be offered for blood draws, which will be done by experienced phlebotomists. The usual security for personal health information will be used, with locked files accessible only to CITI-trained and HIPAA-trained research staff and password-protected electronic data. Time/effort burden will be partially compensated by payment. All families will be given phone numbers of the PIs and coordinator to reach in the event of some unexpected adverse event. Potential skin sensitivity and potential male breast enlargement will be checked for at each visit by a physician, who may discontinue the oils or switch mode of administration based on clinical judgment.

Ethnic & Sex Composition of sample:
The sample is expected to reflect the ethnic proportions of central Ohio. Sex ratio is expected to mirror that of the autism population, 4:1 boys. Both males and females will be included in the study.