Baby's Breath II Substudy: Nicotine Patch as an Adjunctive Intervention to Reduce Secondhand Smoke Among NICU families

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Aim: In line with our current project aimed to reduce secondhand smoke (SHS) exposure in NICU infants' homes, the aim of the substudy is to evaluate the feasibility and potential efficacy of adding nicotine replacement therapy (NRT) in the form of transdermal patches to a motivational intervention targeting NICU families who have a smoker in the home. The majority of smoking cessation research is conducted with motivated quitters who state a desire to quit. However, a few studies have found that providing NRT to unmotivated smokers who are not currently planning to quit was associated with positive smoking outcomes [1, 2]. Thus, we would like to explore the potential for directly targeting smoking cessation regardless of motivation level in a subsample of NICU parents with the ultimate goal of reducing SHS in their homes.

Hypotheses: (1) Providing NRT as part of a comprehensive secondhand smoke program to NICU families will be acceptable and feasible; (2) NRT as part of a comprehensive secondhand smoke intervention will increase smoking cessation rates and decrease SHS exposure in homes of NICU families as compared to education and referral to a smoking cessation quitline.

Methods

Overview. A two group, randomized, controlled substudy (N = 32) will be conducted with parents who are smokers and have a high risk, NICU infant. Similar to the parent study, primary caregivers will be recruited in the NICU and offered to enroll in the SHS sub-study, including randomization to either motivational interviewing and NRT (nicotine patch) or SHS education and referral to a smoking cessation quitline. Two follow-up assessments will be conducted 2 weeks and 1 month post-intervention.

Participants and procedures will largely be the same as the parent study. Altered procedures are noted below.

Participants. Inclusion and Exclusion criteria from the parent study will be retained in this substudy with additional criteria related to the provision of NRT noted in red. The nicotine patch is available over-the-counter and has been used by the general public with minimal problems. Only extreme disease conditions, which should be relatively rare in our population of new, young, parents will be excluded.

Inclusion Criteria: Eligible mothers of any age or ethnic background must: (1) have an infant that is at least 1 week prior to the estimated date of hospital discharge in the NICU at Children's Memorial Hermann Hospital (**CMHH**; ensuring time for the intervention); (2) report that she or her partner smokes at least 5 cigarettes per day, on average, within the 2 months preceding the screening visit; (3) agree to attend intervention sessions; (4) live within 50 miles of our center; and (5) have access to a telephone.

Exclusion Criteria: Mothers will be ineligible for study participation based on the following criteria: (1) severe cognitive, and/or psychiatric impairment, per judgment of NICU and research staff, that precludes cooperation with study protocol; (2) inability to read, write, and speak English; (3) inability or unwillingness to provide signed consent for participation; and (4) inability or unwillingness to meet study requirements for data collection and intervention purposes.

Additional exclusions:

- Within the month immediately preceding the screening visit, use of any form of tobacco or nicotine products other than cigarettes (e.g., e-cigarettes, chewing tobacco, etc.) on 3 or more days within a week if the individual refuses to refrain from such tobacco use during the course of the study.
- Current use of NRT or enrollment (or plans to enroll) in another smoking cessation program in the next 3 months
- Uncontrolled hypertension (SBP greater than 180 or DBP greater than 110).
- History of severe cardiovascular (stroke, heart attack), kidney (e.g. chronic or acute kidney failure) or liver disease, or other unstable disease in the last 3 months.
- History of hypersensitivity or allergic reaction to NRT or similar chemical classes or any component of these formulations (including allergy to latex).

Measures. The baseline measures approved for the parent protocol will remain the same. Post treatment outcomes also will be largely the same, with a few additions, and will be collected at 2 weeks and 1 month post intervention.

Feasibility/acceptability outcomes. Participants will be asked to report on whether or not any patches were used, and if any were used, questions will be asked regarding the # of patches used and acceptability and satisfaction with the patch.

Smoking outcomes will consist of 7-day point prevalence, number of cigarettes smoked per day, number of 24 hour quit attempts, and longest sustained abstinence from cigarettes. Similar to the parent study, the **Timeline Follow-Back** [3], a retrospective structured interview, will be used to obtain continuous data of actual cigarette consumption in the 30 days prior to study enrollment and will also be used at the post intervention timepoints to collect continuous data from the time of intake to the last assessment. Parental **Exhaled Carbon Monoxide** concentration in parts per million will be measured by trained personnel using the EC-50 (Vitalograph, Inc., Lenexa, KS), to indicate recent exposure to tobacco smoke in parts per million (ppm). These monitors are small, hand-held, battery-operated devices with disposable mouthpieces. Two such instruments purchased for the parent study are currently available for use.

Secondhand smoke outcome measures will include reports of home and car smoking bans and the TLFB for secondhand smoke identical to the parent study.

Intervention. The motivational intervention will be similar to the first two sessions of the parent study intervention protocol delivered in the NICU, with additional content related to smoking cessation. In addition, parents will be provided with 2 weeks of 21-mg nicotine patches for each smoker (or 14 mg if smoking less than 10 cigarettes per day per standard medication instructions http://reference.medscape.com/drug/nicoderm-cq-nicotrol-nicotine-transdermal-999319).

Control. The control condition will receive identical educational materials to the control group in the parent study and will also receive a referral to the Texas Tobacco Quitline which provides counseling and 2 weeks of free nicotine patches after enrollment.

Sample size estimation

The primary outcome for this feasibility and preliminary efficacy study is use of the nicotine patch. We estimate that 66.7% intervention and 33.3% control participants will use at least one patch during the

study period. A sample size of 32 will provide 80% power to detect this effect at the .05 probability level.

Data Analysis

The general data analytic strategy will be similar to the parent study, using Frequentist and Bayesian analyses. Bayesian analyses primarily will be employed to determine the probability of benefit of NRT provided directly to smoking parents in the NICU + the behavioral SHS intervention, relative to health education and quitline referral.

Adverse Experiences Associated with Nicotine Replacement Therapy (NRT): All of the commercially available forms of nicotine replacement therapy (NRT), i.e. gum, transdermal patch, nasal spray, inhaler, lozenge and sublingual tablet, are effective as part of a strategy to promote smoking cessation, enhancing long-term abstinence rates as much as 50 to 70%[18]. Recent reports indicate that recommended changes to NRT product labeling by the FDA include a removal of the warning that consumers should not use an NRT product if they are still smoking, chewing tobacco, using snuff or any other product that contains nicotine—including another NRT. The FDA suggests to consumers, "There are no significant safety concerns associated with using more than one over-the-counter (OTC) NRT at the same time, or using an OTC NRT at the same time as another nicotine-containing product—including a cigarette" (http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm345087.htm).

In general, the patch is tolerated well by those who use it. The most frequent side effects reported by those using the patch tend to be mild and include: nausea, redness at the patch site and/or minor swelling, dizziness, difficulty sleeping, rapid heart rate, abnormal dreams, increased blood pressure, headaches, rash and/or itching. A review of adverse effects based on 63 trials of 21 mg NRT did not find evidence of harm from major adverse cardiovascular events, with a slight increased risk for well-known lower-severity events, such as palpitations and arrhythmia [4]. Additionally, a review of safety in patients with cardiovascular disease found no evidence of an increased risk of cardiac events [5].

Breastfeeding mothers who smoke will not be excluded as the nicotine patch is likely less detrimental than smoking cigarettes due to the numerous additional toxins in cigarettes (e.g., carbon monoxide, formaldehyde, benzene) [6]. The American Academy of Pediatrics has stated that breastfeeding and parental smoking are less detrimental to child health than bottle-feeding and parental smoking, and therefore recommend that all mothers breastfeed, regardless of smoking status [7]. Further, data suggest that cotinine levels are lower with NRT relative to smoking cigarettes [8].

Protection Against Risks: NRT formulations, including the nicotine patch, are FDA approved medications for smoking cessation. Our trained research assistants will screen participants for contraindications of the nicotine patch and we will monitor participants for adverse reactions while they are on medication. Questions regarding safety will be referred to our study physician, Dr. Winston Liaw (recently hired Family Medicine faculty member previously on the faculty at Virginia Commonwealth University). Potential participants with medical exclusions will be encouraged to see their physicians and obtain documented clearance for participation in the study and use of NRT.

The typical side effects are not usually serious in nature and often abate within a few days to weeks after starting medication or once the medication is withdrawn. Adverse effects will be assessed at each

of the post-baseline visits. The PI and research staff will monitor participants' complaints of adverse events and, when necessary, adjust the dosage or discontinue medication in consultation with Dr. Liaw.

Potential Benefits of the Proposed Research to Human Subjects and Others:
NRT is an evidence-based treatment for nicotine dependence and has been associated with reductions in smoking, even among unmotivated smokers. We believe that the proposed research will provide preliminary feasibility and efficacy data in support of NRT to increase smoking cessation and reduce SHS exposure and health consequences among NICU patients. Participants may benefit directly through reduction of the health risks posed by smoking as well as SHS exposure in their children. Other members of participant households may experience similar benefits. The risks posed by SHS in children are substantial and well documented, and effective interventions to reduce such exposure in high risk infants could result in significant decreases in adverse health effects and associated costs. If successful, the proposed intervention could be replicated in other settings that would benefit from evidence-based measures to improve the health status of infants and their caregivers. We believe these long-term benefits outweigh the risks involved in using NRT and participating in counseling.

Role of the Principal Investigator

The Principal Investigator will be responsible for knowing the policies of the local IRB (the University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects [**CPHS**]). The PI will adhere to CPHS policies and maintain accurate documentation of CPHS correspondence and reports. The PI is responsible for documentation and handling of all possible study-related adverse events. These include staff training, manual-driven processes, and periodic audit of data collection/entry.

Data Safeguarding and Checking

Drs. Stotts (PI) and Northrup (Project Director/co-I) will closely monitor the data to ensure participants in the study are protected and to ensure their interests are not made secondary to the interests of the scientific investigation. Once a month all key personnel will meet in-person to review study progress and address any impediments. Specifically, this team of conscientious investigators will perform the following activities: (a) review the research protocol and plans for data and safety monitoring; (b) review major modifications to the study proposed by the team prior to implementation; (c) evaluate study progress, including data quality, participant recruitment rates, retention rates, outcome and adverse experience data, and risk-versus-benefit profile; (d) communicate information and recommendations to appropriate persons at the UTHSC-H IRB regarding the assessment of issues or problems and effective resolutions; (e) make recommendations regarding discontinuation of treatment for an individual patient based on adverse experiences; (f) make recommendations to terminate the trial because of safety concerns; (g) protect the confidentiality of the trial data and the results of monitoring.

IRB and Adverse Events Reporting.

Adverse Events (AE) will be recorded by study staff as they occur, reported to the PI and CPHS within 24 hours if determined to be serious. Serious AEs will also be reported immediately (verbally within 24 hours) to co-investigators, and to the sponsor agency. A written report will follow as soon as possible but within no more than three days. The written report will be in the format required by the local IRB

and will contain information regarding the date of the SAE, description of the SAE, severity rating (Grade 1 to 4), assessment of cause, whether the SAE indicates an increased risk for current or future subjects, and whether changes to the informed consent form are necessary.

References

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