RUTGERS
Robert Wood Johnson
Medical School

***Title of Project*:** **Examining Persistence in Smokers with Schizophrenia**

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Funding Source(s): **National Institute on Drug Abuse (NIDA)**

1. Purpose/Specific Aims

This study will modify our existing 8-session, individual counseling treatment manual ("Persistence Targeted Smoking Cessation (PTSC)") to make it more feasible for treating smokers with schizophrenia. We will also test the ability of our new treatment, "Persistence Targeted Smoking Cessation in Schizophrenia (PTSC-S)" to increase task persistence in smokers with schizophrenia.

1.1 Objectives

We will demonstrate that our new treatment "Persistence Targeted Smoking Cessation in Schizophrenia (PTSC-S)" is feasible for treating smokers with schizophrenia and that it increases their task persistence.

1.2 Hypotheses

1. We hypothesize that that at least 80% of participants will rate the intervention as "easy to understand" and "helpful" on a post-intervention exit interview questionnaire.
2. We hypothesize that smokers with schizophrenia receiving our PTSC-S intervention will demonstrate cognitive and behavioral increases in task persistence from baseline to follow-up.

2. Background and Significance

We propose to modify a theory-based smoking cessation intervention (called Persistence-targeted smoking cessation; PTSC) to make it more feasible for treating smokers with schizophrenia. We will include 8 weekly individual counseling sessions and use of the nicotine patch for 10 weeks. We will provide counseling sessions and nicotine patches free of charge to research participants. We will test the feasibility of the intervention and its ability to influence persistence (measured as described in the table in section 4.2). We hope to develop a feasible psychosocial treatment for use in a later randomized controlled trial.

Summary of Proposed Project in Lay Terms and Scientific Terms:

This study is a non-randomized trial of a new psychosocial treatment for smoking cessation (for smokers with schizophrenia) that is based on cognitive behavioral therapy for smoking cessation – a commonly used approach. Participants will receive free weekly counseling (8-weeks) and free nicotine patches (10-weeks). They will complete assessment measures

commonly used in smoking cessation studies. We hope to show that this treatment is feasible in this small pilot study before comparing it to a more established treatment in a future RCT.

3. Research Design and Methods

We will conduct an open trial (N=26) of our 8-session, weekly, individual treatment, (Persistence Targeted Smoking Cessation for Schizophrenia (PTSC-S)). The purpose of this open trial will be to "begin to demonstrate that the intervention alters the targeted mechanism (thus providing an initial proof of principle)." We will measure task persistence via behavioral and cognitive measures administered in counterbalanced order at baseline, after session 3, and at one- and three-months post-quit date. By assessing task persistence at multiple follow-up points, we will be able to examine how many sessions are required to produce an effect (i.e., effect of treatment "dose").

A trained research assistant (who will receive weekly and as-needed supervision from the principal investigator) will pre-screen potential participants on the phone, followed by obtaining informed consent and administering the baseline assessment battery (see Assessment Measures table below). We will divide the baseline assessment battery into two sessions to minimize participant fatigue. Each baseline assessment session will last approximately 90 minutess. We will then provide free, weekly individual counseling sessions for 8 weeks and 10-weeks' worth of the nicotine transdermal patch (an FDA-approved smoking cessation product available over the counter). All sessions will be audio recorded for treatment integrity and supervision.

Questionnaires that are commonly used in tobacco dependence treatment studies will be used in the current study. Women of childbearing age will take a pregnancy test to rule out pregnancy. Carbon monoxide (CO) levels (also commonly collected in tobacco dependence treatment studies) will be assessed with a carbon monoxide monitor and CO reading in parts per million (ppm) will be recorded. The carbon monoxide monitor used will be the *Bedfont Scientific Ltd. Micro+ Smokerlyzer.* The Micro+ Smokerlyzer is a hand-held, battery powered instrument which uses electrochemical technology to sample the gas and a microprocessor to convert the output from the sensor to a carbon monoxide (CO) concentration. The result and menus are displayed on a color LCD and an accompanying buzzer sounds in response to the CO level. The instrument is controlled using a touch screen operation and has a USB link to a computer to download readings.

The Micro+ uses a breath sampling D-Piece with integrated bacterial and viral filter and a one-way valve designed to maximize infection control. Each patient uses a fresh mouthpiece for each breath sample. The D-Piece may be reused or replaced as required.

The patient is asked to hold their breath for a 15 second countdown. This is displayed on the screen of the device. At the end of the breath hold, the patient blows gently into the Micro+ expiring as much of the breath in their lungs as possible. The reading on the device shall rise until the peak reading is held on the display.

A research assistant will provide instructions on how to use the CO monitor and will record the results at baseline and followup appointments. A research therapist will do so during the 8 counseling sessions. The study PI is accountable for the device.

3.1. Duration of Study

Participants will be active in the study for approximately 4 months. We anticipate completing data collection activities within 24 months.

3.2 Study Sites

Participants will be daily smokers primarily from central New Jersey. Participants will attend treatment at our Addiction Psychiatry office at 317 George St., Suite 105, New Brunswick, NJ. We will also recruit participants from several University Behavioral Health Care (UBHC) locations, including: New Brunswick, Piscataway, Monmouth Junction, and Edison. If it proves more convenient for participants to receive counseling at UBHC locations, we will provide services in those locations instead of at our George Street office.

3.3 Sample Size Justification

26 participants will be enrolled.

We will enroll 26 smokers from the local area. We will collect demographic data that will allow us to compare this sample to the general population of smokers. This is a non-randomized, pilot, feasibility study so a power analysis is not applicable to this study design.

3.4 Subject Selection

3.4.1 Inclusion Criteria

- Must be between 18 – 64 years old
- Must indicate commitment to quitting smoking in the next 30 days
- Must smoke at least 5 cigarettes (including those labeled "little cigars") per day for past 6-months
- Expired breath carbon monoxide (CO) > 5 to ensure daily cigarette use
- Must score < 8 (or <7 for women) on the Alcohol Use Disorders Identification Test
- Must score less than 3 on the 6-month Drug Abuse Screening Test-10
- Must provide a negative urine drug screen for cannabis, cocaine, or opiates (Note: Participants with a positive screen for opiates may participate with proof of prescription for opiates.)
- Must have a diagnosis of Schizophrenia or Schizoaffective Disorder on SCID-I
- Psychiatric illness must be stable, as indicated by no hospitalizations in previous 8 weeks, and a stable psychotropic medication regimen including a stable antipsychotic dose for 8 weeks
- Must have a working phone (for feasibility of follow-up and for ability to receive optional SMS text messages)

3.4.2 Exclusion Criteria

- Must <u>not</u> be currently receiving tobacco dependence treatment counseling
- Must <u>not</u> currently be taking varenicline (Chantix),
- Must <u>not</u> be taking bupropion (Zyban/Wellbutrin) to quit smoking
- Must <u>not</u> be taking any nicotine preparations (gum, lozenge, patch, spray, inhaler) daily over the last 10 days
- Must <u>not</u> report myocardial infarction in the past year, unstable angina pectoris, , or significant cardiac arrhythmia (including atrial fibrillation) in the past 90 days.
- Must <u>not</u> be pregnant, breastfeeding, or planning on becoming pregnant in the next 4-months. Women who can become pregnant may be included if using effective birth control

- Must not have pending legal matters with potential to result in jail time
- Must not be planning on moving outside local area in next 3-months

Participants answering "yes" to any item on the "Nicotine Patch Contraindications Form" will meet with an Addiction Psychiatrist for follow-up and approval for the study. The Addiction Psychiatrist will document this assessment in signed progress notes.

Justification of exclusion of any sub-segment of the population: Children will not be included in the study because young children are unlikely to be daily smokers and the nicotine patch (which will be used in this study) is not currently FDA approved for children. All participants must be at least 18 years old to participate in this study.

4. Study Variables

4.1 Independent Variables or Interventions

We will provide 8-weeks of free counseling to participants. Study therapists will utilize the "Persistence-Targeted Smoking Cessation-Schizophrenia (PTSC-S)" manual developed by Dr. Steinberg, which is based on cognitive behavioral therapy. PTSC-S is an 8-session, individual, smoking cessation counseling strategy that focuses heavily on using cognitive behavioral therapy targeted at disputing automatic thoughts that may reduce task persistence for smokers with schizophrenia. While disputing automatic thoughts will be the focus of each session, skill building and support will also be included. Participants will be asked to complete homework assignments between sessions – including keeping a daily thought record to monitor automatic thoughts that may put them at risk for smoking. A daily thought record is a commonly used cognitive behavioral therapy homework assignment in which participants practice identifying and evaluating their thoughts. Participants will also track their daily cigarette use and nicotine patch use for homework. Participants will use commonly used, established measures to provide brief assessment information at the end of each session (i.e., nicotine dependence, tobacco use, nicotine lozenge use, nicotine craving, and nicotine withdrawal).

4.1.1 Drug or Device Interventions

We will give participants a 10-week supply of the nicotine transdermal patch (an FDA-approved, over-the-counter medication) to be used starting on their Quit Date. Although the nicotine patch is commercially available without a doctor's prescription, Co-I Dr. Jill Williams (an addiction psychiatrist) will provide medical monitoring during this study. Consistent with the product insert, participants will be instructed to use one nicotine patch daily, and to apply it upon awakening at about the same time each day. Subjects will be instructed to vary the site of application of the patch daily to minimize any skin irritation. They will use the 21mg patch for the first 8-weeks, then 2-weeks of the 14mg patch.

4.2 Dependent Variables or Outcome Measures

Assessment measures: See table below

Concept	Measure	B/L	Weekly	QD	Session 8	3-mo. Post QD
DEMOGRAPHICS	Smoking History & Demographics Questionnaire (includes National Health and Nutrition Examination Survey (NHANES) items)	*X*				
TOBACCO USE	Fagerström Test for Nicotine Dependence (Heatherton et al., 1991)	*X*				
	Timeline Followback (TLFB; Sobell & Sobell, 2000)		*X*	*X*	*X*	*X*
	Current Tobacco Use – $ spent, menthol use, night-time smoking	*X*				
	Expired Breath Carbon Monoxide (CO)	X	X	X	X	X
	Brief WISDM	X				
NRT USE	Self-reported use of patch – including visual inspection of patch		*X*	*X*	*X*	*X*
	NRT side effects		*X*	*X*	*X*	*X*
	Nicotine patch contraindications form	*X*				
CRAVING AND WITHDRAWAL	Wisconsin Smoking Withdrawal Scale (Welsch et al., 1999)	*X*	*X**	*X*	*X*	
MOTIVATION TO QUIT SMOKING	ICT – Change Measure (includes self-efficacy) (Miller & Johnson, 2008)	*X*		*X*	*X*	
	Quitting Fatigue			*X*	*X*	*X*
	Commitment to Quitting Smoking Scale (CQSS)	*X*		*X*	*X*	
ANHEDONIA	Temporal Experience of Pleasure Scale (Gard et al., 2006)	*X*		*X*	*X*	*X*
	Snaith - Hamilton Pleasure Scale (Snaith et al., 1995)	*X*		*X*	*X*	*X*
	Tripartite Pleasure Inventory (Leventhal, 2010)	*X*		*X*	*X*	*X*
TASK PERSISTENCE	Mirror Tracing	*X*		*X*	*X*	X
	Breath-holding	*X*		*X*	*X*	X
	Temperament and Character Inventory—Persistence Scale (TCI-P)	*X*		*X*	*X*	*X*
	2-item Task Persistence Measure	*X*		*X*	*X*	X
	Distress Tolerance Scale (DTS)	*X*		*X*	*X*	X
	Sustained Divided Attention Task	*X*		*X*	*X*	X
	Thoughts About Smoking Questionnaire	*X*		*X*	*X*	X
	Daily Habits Questionnaire	*X*				
SUBSTANCE USE / MENTAL HEALTH ISSUES	Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 2001)	*X*				
	6-month Drug Abuse Screening Test – 10 (DAST-10; Skinner, 1982)	*X*				
	Urine drug screen (for cannabis, cocaine, opiates)	*X*				
	SCID-RV for DSM 5 - Modules A, B, and C	*X*				
	Brief Symptom Inventory (BSI; (Derogotis, 1975)	*X*				
	CES-D	*X*	*X*	*X*	*X*	*X*
INTERVENTION INTEGRITY / FEASIBILITY	Exit interview		*X*	*X*	*X*	
	Study created integrity measure	*We will confirm treatment integrity throughout the study*				

*Wisconsin Smoking Withdrawal Scale will be administered before sessions 4 through 8

4.4 Risks of Harm

There is a risk of discomfort associated with nicotine withdrawal for patients who are quitting smoking. The nicotine patch (an FDA-approved medication) is well tolerated; however there are potential side effects that may arise when using the patch. Each patient will discuss these side effects with their therapist. If questions arise as a result of the patch,

one of the study co-investigators is an Addiction Psychiatrist who will be available to provide patients with information regarding their side effects.

There is a risk that participants' confidentiality could be violated. To reduce the risk of violating confidentiality, several steps will be taken. Only IRB approved members of the research team will have access to the data. The research staff collecting the data will bring the data to the PI within 24 hours of it being collected. Data will only be accessed when coded, entered, or audited. The PI will maintain responsibility for safe data storage. All data will be stored in locked cabinets within locked rooms. Based on these procedures, we anticipate that the risk to confidentiality is very low.

HANDLING OF UNEXPECTED OR ADVERSE EVENTS

Response to new or unexpected findings and to changes in the study environment:

The study team will meet on a quarterly basis while participants are in the study. The team will monitor the study according to the guidelines specified in the study protocol and the operating procedures established at the initial meeting, unless the team determines during the course of the trial that modification of the guidelines is in the best interest of the study and its participants. Such a decision may be based on new information that emerges during the course of the study (e.g., publication of the results of a similar trial), realization of inappropriate initial study assumptions, or the occurrence of an unanticipated scenario.

Identifying, managing, and reporting adverse events:

There is a risk of discomfort associated with nicotine withdrawal for patients who are quitting smoking. The nicotine patch (an FDA-approved medication) is well tolerated; however there are potential side effects that may arise when using the patch. Each patient will discuss these side effects with their therapist. If questions arise as a result of the patch, one of the study co-investigators is an Addiction Psychiatrist who will be available to provide patients with information regarding their side effects.

The research staff member who observes or is notified of a possible adverse event will notify the Principal Investigator within 24-hours. Events which are 1) Unexpected in terms of nature, severity or frequency, given the research protocol, IRB-approved informed consent document, product labeling and other sources of information, and given the characteristics of the subject population being studied, 2) Related or possibly related to participation in the research, and 3) Potentially place the research subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized will be reported to the IRB in a written Unanticipated Problems/Adverse Events In Human Subjects Research Report. If these events are deemed "serious," we will report within one week of discovery. If not, we will report within two weeks of discovery. In addition, if a death occurs within 30 days of the intervention, whether or not it was deemed study related, we will report within 24-hours of discovery.

Any item listed on the Adverse Events Log that is deemed to be of more than mild severity will be discussed with the Addiction Psychiatrist within 7 days of the study appointment at which the research staff learned of it. The Addiction Psychiatrist will document this "Moderate" or "Severe" AE and the recommended action, if any, in signed progress notes.

The Principal Investigator will meet with research staff to discuss the impact of participation upon patients. If concerns are reported, the Principal Investigator will discuss modification of the research procedures with the research team, and request IRB approval of proposed

changes (if any). We believe that this level of monitoring is commensurate with the degree of risk to participants.

Adverse events will be reviewed weekly at research meetings, followed by completion of a separate progress note inserted into the participant's binder. Each adverse event will now have a space to indicate the date a progress note was made. The AE list and related progress notes will be on a different color paper than the rest of the chart to ensure that proper attention is paid.

Emergency care:
Participants will be instructed to call 911 if they experience a medical emergency and Acute Psychiatric Services (APS) at 855-515-5700 if they experience a psychiatric emergency. The research assistant will administer a depression measure at the beginning of each session. If there is an indication that the patient is experiencing serious depression, the therapist will inform the patient and communicate concerns with the PI. The patient will be counseled accordingly and provided with appropriate emergency contact information.

4.5 Potential for Benefit

The benefits of taking part in this study include access to high-quality, smoking cessation treatment based on empirically supported psychosocial approaches. If participants quit smoking, they will experience health benefits; however, they may receive no direct benefit from taking part in this study.

5. Subject Recruitment and Enrollment Considerations

5.1 Subject Recruitment

The project will take place at our Rutgers offices in New Brunswick, NJ, located in the building next to a large University Behavioral Health Care outpatient clinic that serves more than 500 clients with a diagnosis of schizophrenia or schizoaffective disorder annually. We will recruit smokers from Rutgers University Behavioral Health Care, from private psychiatric intensive outpatient treatment providers, from the community via our website and local flyers, and via Rutgers listservs. Potential participants will call our offices for a telephone pre-screen. If potentially eligible, they will be offered a more in-depth in-person screening after providing informed consent. If all inclusion criteria are met, they will be invited to participate. This is an urban area with a large low-income population and therefore a greater proportion of smokers than the average of 14.8% in the state of New Jersey. Previous studies have given us the necessary experience with Rutgers listservs, websites, Craigslist, and use of flyers and brochures to maximize recruitment.

5.2 Consent Procedures

Participants will read a consent form or will have the consent form read to them before signing it. A trained research assistant (who will receive weekly and as-needed supervision from the principal investigator) will pre-screen potential participants on the phone, followed by obtaining informed consent and administering the baseline assessment battery. Trained research staff will proactively ask participants to describe the research study to them in their own words to ensure that participants understand the consent form. If there is any doubt of competence to consent, the individual will not be enrolled.

5.2 Subject Costs and Compensation

Participants will be paid $100 through the duration of the study. They will receive $40 at the baseline assessment ($10 for first baseline session, $30 for second baseline session), $10 at the Quit Date assessment, $30 at session 8, and $20 at the 3-months post-quit date assessment.

6. *Data Handling*

As this study is primarily a feasibility study, our data analysis plan will primarily comprise descriptive statistics such as mean (sd) sessions attended and percent of participants reporting 3-months post quit-date abstinence. We need to collect all of this data in order to demonstrate that our PTSC treatment manual is generalizable to a population of smokers with schizophrenia. We need to examine changes in relevant variables such as self-reported cigarette and medication use, withdrawal, smoking urges, and mechanisms of change in order to evaluate the efficacy of our treatment.

Data collection:

The majority of data will be collected through face-to-face interview. A research assistant will read the questions to the participants while they read along from their own copies of the measures to maximize participant comprehension. If participants are unable or unwilling to attend a follow-up appointment at our Rutgers RWJMS offices, a research assistant will meet the participant off-site, in a public location agreeable to the participant such as a local public library. If off-site appointments are also impossible, we will conduct telephone interviews. Data will be stored at the Division of Addiction Psychiatry; 317 George Street; Suite 105; New Brunswick, NJ 08901. Only the IRB-approved research team will have access to the research data.

Data entry, editing and management, including handling of data collection forms, different versions of data, and data storage and disposition:

To reduce the risk of violating confidentiality, several steps will be taken. Only IRB approved members of the research team will have access to the data. The research staff collecting the data will bring the data to the PI within 24 hours of it being collected (data are collected on secure laptops and/or in file folders identified only by participant ID number). The research team shares the same office space at 317 George Street in New Brunswick. Data will only be accessed when coded, entered, or audited. The PI will maintain responsibility for safe data storage. All data will be stored in locked cabinets within locked rooms in the Division of Addiction Psychiatry, 317 George Street, New Brunswick, NJ.

All computer files will be kept on computers requiring login and complex passwords for entry, and all files with identifying information will have the extra protection of a password to open that individual file. The individual participant's personal information, including name and contact numbers, will be kept separate from their study data and linked only by a study number assigned by the PI. The master link between the study number and patient contact information will be destroyed once all data is collected and checked for accuracy. The confidential binder containing telephone screen forms will be shredded and properly discarded after 12 months of study completion. Participant names will not be used in any publications or papers derived from this study.

Limitations of study:

Because this is a pilot feasibility study, our sample size is relatively small and the generalizability of our findings should therefore be interpreted with caution.

7. Statistical Analysis

We will review all data quarterly.

To address hypothesis 1 that participants will rate the PTSC-S as "easy to understand" and "helpful" during a post-intervention exit interview, we will do the following:

a) Calculate the percentage of participants who rate the intervention as "easy to understand" and "helpful" and test whether this percentage exceeds 80% using a one-sample test of binomial proportion (Rosner, 2010)

b) Explore which participant characteristics tend to be associated with positive or negative views of this intervention, by examining bivariate association (e.g., chi-square test for discrete categorical characteristics and two-sample t-test for continuous measurements) and logistic regression analysis

To address hypothesis 2 that smokers with schizophrenia receiving our PTSC-S intervention will demonstrate cognitive and behavioral increases in task persistence (measured by mirror tracing, breath-holding, 2-item persistence self-report, Sustained Attention Test, and Thoughts About Smoking Questionnaire), we will do the following:

a) Calculate and plot summary statistics to explore the cross-sectional and longitudinal distributions of persistence scores
b) Use paired t-tests to probe for changes in task persistence from baseline to end-of-counseling (session 8), followed by mixed model analysis with persistence scores as the dependent variable and time as the independent variable
c) Construct linear contrasts to evaluate changes in persistence scores from baseline to end-of-counseling (session 8). If the normality assumption is violated, we will apply the necessary variable transformations

8. Reporting Results

8.1 Individual Results

Participants will not be provided with individual study results.

8.2 Aggregate Results

Aggregate results such as average number of sessions attended, proportion of participants obtaining abstinence from smoking, and cigarettes smoked per day may be reported in peer reviewed scientific conference presentations, peer-reviewed scientific publications, or peer-reviewed NIH grant applications.

8.3 Professional Reporting

Study results may be presented to the scientific community via peer reviewed manuscripts and presentations at scientific conferences. They will also be included in peer-reviewed NIH grant applications.

9. Bibliography

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