In Vivo Evidence for β2 Nicotinic Acetylcholine Receptor Subunit Upregulation in Smokers as Compared to Nonsmokers with Schizophrenia

Supplemental Information

Regulatory Approvals

This study was conducted with the approval of the institutional review boards of the Yale University School of Medicine and the Veterans Affairs Connecticut Healthcare System. The use of the radioactive isotope was approved by the Yale Radiation Safety Committee. Magnetic Resonance Imaging (MRI) was performed with the approval of the Yale Magnetic Resonance Research Center. The radiotracer was administered under IND 61,156.

Consent Process in Schizophrenia Patients

Before signing the consent form, subjects had several meetings with study staff where detailed information was provided to ensure that they understood the study and were suitable candidates. Subjects were required to pass a questionnaire about the key risks of the study. Parents and family and non-research clinicians were involved in the process when available. The patient’s primary clinician (i.e. non-research clinician) was required to assent to patient’s participation.

Inclusion/Exclusion Criteria for Schizophrenia Patients

Only subjects with a primary diagnosis of schizophrenia were included. A structured clinical interview for DSM-IV (SCID) to verify the primary diagnoses of schizophrenia (or lack thereof for comparison group) was conducted. In addition, for the schizophrenia group, information collected by clinical evaluation, SCID data, review of the medical record and contact with the patient’s clinician was used to confirm the diagnosis. Subjects with a diagnosis of substance abuse within the past month or substance dependence (with the exception of nicotine...
or caffeine) within the past 6 months prior to screening evaluation were excluded. Smoking status was confirmed by plasma cotinine levels > 150 ng/mL, urine cotinine levels > 100 ng/mL, and carbon monoxide (CO) levels > 11 parts per million at baseline. Nicotine dependence was evaluated using the Fagerström Test for Nicotine Dependence (1).

**General Screening for Both Groups**

Lifetime history of and current substance use disorders was ascertained by psychiatric interview, chart review (only in schizophrenia patients), SCID, 30-day Timeline Follow Back and urine toxicology.

Subjects were screened for any MRI exclusions, such as ferrous metal in the body, cardiac pacemaker or severe claustrophobia. If a potential subject had any experience working with metal or had any eye injury involving metal, orbital x-rays were performed.

Nicotine dependence was evaluated with the Fagerström Test for Nicotine Dependence (1). Smoking status at screening was verified by a plasma cotinine level > 150 ng/ml, urine cotinine level > 100 ng/ml, and CO level > 11 ppm at baseline. Nonsmoking status was ascertained by self-report, plasma cotinine level < 15 ng/ml, breath CO levels < 8 ppm at baseline and scan day, and urine cotinine levels < 50 ng/ml.

The schizophrenia group was also screened to ensure clinical stability, which included a chart review and review of medications and evaluation by a research psychiatrist. Subjects who were deemed clinically unstable as evidenced by recent psychiatric hospitalization or emergency room visits, increase in clinic visits due to psychiatric symptoms, homicidality, suicidality, and/or grave disability were excluded. Subjects needed to be taking stable doses of antipsychotic medications for at least 12 weeks.
Description of Contingency Management

Contingency management has been shown to reduce cigarette smoking in smokers with schizophrenia in several short-term studies (2-4). Several methods have been used to monitor smoking behavior to verify smoking abstinence in contingency management studies. Breath carbon monoxide levels which have a short half life, reflect only recent smoking and therefore require frequent breath testing to confirm continuous abstinence (5). Urine, plasma or salivary levels of cotinine, a principal metabolite of nicotine have also been used to monitor abstinence (6); cotinine has a longer half-life (16 hours) than carbon monoxide. In this study we used the combination of daily carbon monoxide and urinary cotinine monitoring in real-time and plasma collected for cotinine levels were assayed later.

Smokers with schizophrenia received escalating payments according to the schedule tabulated below. Subjects were told that the payments were for being hospitalized to achieve and maintain abstinence from smoking. However, subjects were told that if they showed evidence of having smoked (breath carbon monoxide level ≥ 11 or urine cotinine level > 200 ng/ml) on the day of the SPECT scan, the scan would be cancelled and they would not be paid for the scan day. Furthermore, if they were unable to abstain they were also told that they would be discharged from the study.

Table S1. Contingency Management For Smokers with Schizophrenia

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Day #1</th>
<th>Day #2</th>
<th>Day #3</th>
<th>Day #4</th>
<th>Day #5</th>
<th>Day #6</th>
<th>Day #7</th>
<th>Total Scan</th>
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<tbody>
<tr>
<td>Smoking As Usual</td>
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<td>Outpatient</td>
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<td>$100</td>
<td>$125</td>
<td>$150</td>
<td>$300</td>
<td>$800</td>
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</tbody>
</table>

In rare instances the abstinence period could be extended because of technical difficulties with the camera, delays in shipping of the tracer, availability of scan slots or availability of inpatient beds days. In such instances, subjects are paid additional according to the $25/day escalation schedule.
Supplemental References


