Supplementary Online Content


eFigure. Consolidated Standards for Reporting of Trials Flow Diagram of Participants
eAppendix. Abstinence Period and Positron Emission Tomography (PET)/Computed Tomography (CT) Protocol
eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.
eFigure. Consolidated Standards for Reporting of Trials Flow Diagram of Participants

186 Assessed for eligibility

98 Excluded
   90 Did not meet inclusion/exclusion criteria
   8 Did not initiate the study

88 Randomized

44 Randomized to receive active transdermal nicotine patch

41 Included in analysis

3 Withdrew from study or had unusable PET data

44 Randomized to receive placebo patch

40 Included in analysis

4 Withdrew from study or had unusable PET data

3 Withdrew from study or had unusable PET data

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Participants began smoking/nicotine abstinence two nights prior to the PET/CT session to minimize the impact of nicotine in the body on radiotracer binding. For this abstinence period, participants were monitored as described previously. On the day of PET/CT scanning, participants arrived at 11AM, reported on their abstinence, and had exhaled CO measurements of ≤ 4 ppm to verify at least 36 h of smoking abstinence. At 12PM, bolus-plus-continuous-infusion of 2-FA was initiated, with a mean 147 MBq of 2-FA administered as an intravenous bolus in 5 mL saline over 10 seconds. This same amount of 2-FA was diluted in 60 ml saline, and 51.1 ml was infused over the next 420 min (7.3 ml/h). Participants remained seated in a room adjacent to the PET/CT scanner for the next 4 h to allow the radiotracer to reach a relatively steady state in brain. At 4PM, PET scans were acquired as a series of 10-min frames for the next 3 h, with a 10-min break.

PET/CT scans were obtained with the Philips Gemini TruFlight scanner (Koninklijke Philips Electronics N.V., Eindhoven, the Netherlands), a 3-dimensional PET/CT scanner, operated in non-TOF mode. Reconstruction was done using Fourier rebinning and filtered back projection, and scatter and random corrections were applied. Mean spatial resolution (FWHM) was 5.0 mm (transverse) by 4.8 mm (axial). 2-FA was prepared using a published method. Each participant also underwent an MRI scan of the brain within a week of PET/CT scanning with the same specifications as in prior reports. Blood samples were drawn during PET scanning for determinations of free, unmetabolized 2-FA and nicotine plasma levels, as described previously.

**Vs/fp Calculation**

To determine Vs/fp values, total binding volume of distribution (VT/fP) values were calculated from the seventeen 10-min PET frames, as the ratio CT/(CP·fP) where CT is the mean total decay-corrected concentration of 2-FA in the ROIs, (CP·fP) is the mean decay-corrected concentration of free 2-FA in plasma, and fP is the fraction of free (unbound) 2-FA in plasma. Vs/fp was then calculated as Vs/fp = VT/fP – VND/fP, where VND/fP was the non-displaceable volume of distribution for each ROI determined from prior research. While we recognize that calculating Vs/fp in this manner does not change the overall study statistics (compared to simply using VT/fP), we used this value because it allowed for the most accurate comparison of nAChR availability between smokers in this study and non-smokers from prior research (see Results section). In addition, for scans in which participants had measurable plasma nicotine concentrations, Vs/fp values were corrected for nicotine levels at the time of scanning using the following equation: Vs/fp = (Vs/fP)obs x (1 + I/IC50), where (Vs/fP)obs is the observed value of specific binding volume of distribution, I is the plasma nicotine level at the time of scanning, and IC50 is the plasma nicotine concentration resulting in 50% reduction in Vs/fP. This plasma nicotine correction did not change overall study results.

**eReferences**

